Should organised faecal occult blood test screening be established?

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Received 9 August 2001; accepted 10 October 2001

Key words: colorectal cancer, faecal occult blood, screening

Introduction

Clinical trials conducted in the Nottingham (UK), Funen (Denmark) and Minnesota (USA) using faecal occult blood testing (FOBT) showed evidence that population-based screening with FOBT could reduce mortality from colorectal cancer (CRC) [1–3]. At first glance, these results could be interpreted as positive signals for implementing large-scale screening programmes using FOBT. Faecal occult blood testing was proposed for screening in the 1970s, when fibre-optic endoscopic techniques were in development, and CRC incidence was rising. Since then, endoscopic technologies have constantly improved and become much more widely available. Furthermore, significant advances have been made in the knowledge of the biology and in the medical management of CRC. Therefore, one should be cautious with results from FOBT trials, and examine carefully how these trials relate to the changing epidemiology of CRC, and the advent of new screening techniques. Hereafter, we list seven arguments that should be considered before the implementation of screening programmes based on FOBT.

1. FOBT screening has a modest impact on CRC mortality

Reductions in CRC mortality achieved by the immense Nottingham, Funen and Minnesota trials were modest, in the order of 15% to 21%, and 10–18 years of follow-up were carried out before statistically significant differences were seen between intervention and control groups. This modest impact on CRC mortality is mainly due to the known low sensitivity of FOBT. Translated in absolute terms, these figures indicate that for 1000 persons invited for FOBT screening once every 2 years for 10 years, one death due to CRC would be avoided [4].

2. Efficacy of FOBT is lower than reported by published trials because of the ‘disease awareness’ effect

In FOBT trials, not all of the reduction in CRC mortality was attributable to the FOBT itself, but also to better medical attention given to those subjects who complied with the screening test. This statement comes from the observation that in the Nottingham and Funen trials [1, 2], mortality due to interval CRC in intervention groups was lower than mortality due to CRC in control groups. Because of its low sensitivity, interval CRCs were more numerous than screen-detected CRC in subjects who accepted at least one FOB test, and interval CRCs were detected at an earlier stage than CRC diagnosed in the control group (Table 1). The latter observation is surprising, since one would not expect interval cancers to be detected earlier than in the absence of a screening test. In the Nottingham and Funen trials, control subjects received normal medical care. In contrast, physicians and perhaps many subjects in the intervention group were aware that they were part of a clinical study, and most physicians did not ignore the fact that they were trying to detect interval cancers with a test known for its low sensitivity. Therefore, it is highly probable that among screened subjects, more attention was paid to any symptom that might suggest the eventual presence of interval CRC, leading to more precocious diagnosis and lower mortality.

In contrast, in the Minnesota trial, similar to subjects being allocated to the two intervention arms, control subjects were contacted annually about their vital status or about eventual diagnosis of CRC or colonic adenoma [5]. As a consequence of similar medical attention being paid to all subjects, survival was similar for interval CRCs and for CRCs diagnosed among control subjects [5]. One can calculate that the ‘disease awareness’ effect probably accounted for one-quarter of the impact of biennial FOBT on CRC mortality, and thus CRC mortality reductions achieved in the Nottingham and Funen trials were 11% to 14% rather than 15% to 18% (calculations available upon request).
One could argue that disease awareness is part of the screening process and its eventual effects should thus be attributed to the screening procedure. This argument does not hold, since the evaluation of the efficacy of a screening test in a randomised trial should not be influenced by factors dependent on the trial design, such as the modalities of follow-up of subjects according to their allocation in the intervention or in the control group.

### 3. FOBT affects CRC incidence marginally

Colorectal polyps rarely bleed, and thus FOBT is not very sensitive for detecting the presence of polyps. However, it can detect some of the large polyps that are more likely to bleed, and also to become cancerous. After 18 years, the Minnesota trial obtained a 17% reduction in CRC incidence [4].

### 4. Acceptability of FOBT

FOBT is not well accepted by most people, and participation levels outside the context of randomised trials rarely exceed 30%, with low adherence (i.e. subjects rarely attend more than one screening round) [7]. Hence, it is not necessarily the case that modest gains observed in FOBT trials could be replicated in areas where acceptance of FOBT is low. For obtaining participation rates around 50% to 60%, much effort must be devoted to motivation of the target population, with intense information and invitation–reinvitation procedures, or with strong commitment of general practitioners (GPs) [8, 9]. It is doubtful that such efforts would be easy to replicate in other areas and maintained in the long term.

### Table 1. Dukes’ A colorectal cancers in the Nottingham [1] and Funen [2] trials

<table>
<thead>
<tr>
<th></th>
<th>Origins of colorectal cancers in screening group</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Subjects with ≥1 screening test</td>
</tr>
<tr>
<td></td>
<td>Screen detected</td>
<td>Interval</td>
</tr>
<tr>
<td>Nottingham trial [1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>75253</td>
<td>44838</td>
</tr>
<tr>
<td>All CRCs</td>
<td>885</td>
<td>236</td>
</tr>
<tr>
<td>Number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dukes’ A</td>
<td>178 (20)</td>
<td>97 (41)</td>
</tr>
<tr>
<td>Dukes’ B</td>
<td>286 (32)</td>
<td>71 (30)</td>
</tr>
<tr>
<td>Dukes’ C</td>
<td>211 (24)</td>
<td>51 (22)</td>
</tr>
<tr>
<td>Dukes’ D</td>
<td>191 (22)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Not known</td>
<td>19 (2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>( P ) valueb</td>
<td>&lt; 0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( P ) valuec</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Funen trial [2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>30 967</td>
<td>20 672</td>
</tr>
<tr>
<td>All CRCs</td>
<td>481</td>
<td>138</td>
</tr>
<tr>
<td>Number (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dukes’ A</td>
<td>105 (22)</td>
<td>53 (38)</td>
</tr>
<tr>
<td>Dukes’ B</td>
<td>164 (34)</td>
<td>52 (38)</td>
</tr>
<tr>
<td>Dukes’ C</td>
<td>90 (19)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Dukes’ D</td>
<td>98 (20)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Not known</td>
<td>24 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>( P ) valueb</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( P ) valuec</td>
<td>0.001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Subjects allocated to the screening group but who were never screened with the FOB test.

\( \chi² \) test for percentage of Dukes’ A CRCs compared with controls.

\( \chi² \) test for trend compared with Dukes’ distribution among controls.

CRC, colorectal cancer.
5. FOBT is less efficient than screening tests for other cancers

Participation rates in organised screening programmes with pap smear test for cervical cancer and mammography for breast cancer usually exceed 60%, with false-negative results at 25% to 35%. International experience and recommendations suggest that higher numbers of false-negative results should prompt revision of screening programmes, or in the case of cervical cancer adoption of adjunct screening methods. In view of these requirements, why would one accept large-scale use of the FOBT test, which is not well accepted and misses >50% of CRC? In addition, in the longer term, the numerous interval CRCs are likely to shake the confidence of the general public in FOBT screening.

6. CRC mortality trends will be marginally affected by FOBT screening

Decreasing trends in mortality from CRC have already taken place in many parts of the world. A general decline in CRC mortality is noticeable since the 1950s and 1960s in the UK, Germany, France, the USA and Canada [10–12]. Possible reasons for the decline are multiple: changes in diet patterns, occasional removal of polyps, declining incidence, earlier diagnosis and improved management of CRC. It is difficult to know which of these factors accounts for the observed decline in mortality. Earlier detection encompasses various methods, from physicians and patients giving more attention to early symptoms of the eventual presence of CRC to sporadic screening tests in asymptomatic subjects using one or a combination of available screening methods. It is possible that the widespread use of FOBT would accelerate the decline, but it will be the use of more sensitive screening methods, able to detect the majority of cancerous lesions at an early stage, or lesions before they have evolved in cancer, that are likely to make the biggest difference and lead to substantial reductions in mortality from CRC.

7. Establishment of a FOBT screening programme may hinder the development of more efficient screening programmes for CRC

Most countries experience considerable difficulties in deciding whether or not to organise or support nationwide screening programmes. Usually, these difficulties relate to the costs of such programmes, and to the human and material resources necessary for their proper functioning in the long term. If significant efforts are devoted to the organisation of a FOBT screening programme, then the arrival of a newer, more efficient screening method may well be hindered. As a consequence, populations where large-scale FOBT screening is instituted as a ‘gold standard’ will probably not benefit from reductions in CRC mortality as large as those expected if more sensitive methods are used.

New techniques for CRC screening

New techniques are now proposed or under investigation for early detection of CRC, including endoscopic techniques [13] and detection in stools of molecular alterations that indicate the presence of malignant processes in the large bowel [14].

Endoscopic techniques would be able to detect >90% of cancers and large polyps within reach of the endoscope [13]. Colonoscopy would detect twice as many CRCs as sigmoidoscopy, as the entire colon would be explored [15, 16]. Several prospective studies now provide evidence that colonoscopy combined with polypectomy may result in a 66% to 90% decrease in CRC incidence after 6–13 years [17–19]. Although one must be cautious with results from observational studies aimed at assessing efficacy of screening technologies, data available so far indicate a 60% to 80% decrease in CRC mortality among those subjects who underwent a sigmoidoscopy [20, 21]. According to these results, an endoscopic examination of the bowel once every 10 years would be sufficient to achieve this reduction. One study using Surveillance, Epidemiology, and End Results (SEER) data in the USA suggested that colonoscopy and polypectomy were the major factor responsible for the declining CRC incidence and mortality of CRC observed in that country since 1986 [22].

One should be cautious, however, with the available efficacy data on colonoscopic screening, as these data were obtained from selected subsets of the general population, and not from true population-based studies. The Funen and the Nottingham FOBT trials were population-based randomised trials [1, 2], while the Minnesota trial was conducted in volunteers [5]. Hence, data from FOBT trials and colonoscopic screening are not readily comparable. However, a reasonable approximation would be that with a 50% compliance rate to a single colonoscopic screening (that is the compliance to the initial FOBT test observed in the Nottingham and Funen trials), compared with FOBT screening, one could expect at least a doubling in the reduction of CRC mortality in <10 years.

Colonoscopy is often presented as an expensive technique that is not without risk. In expert hands, routine colonoscopy has an overall complication rate of 0.3% (e.g. perforation, side effects due to sedation, bleeding of removed polyp) [16]. These complication rates are likely to decrease as modern endoscopic techniques allow steadily easier, safer and cheaper colonoscopy [13, 23, 24]. It is not impossible that the cost-effectiveness of colonoscopic screening would compare favourably with the cost-effectiveness of FOBT screening since, first, reductions in CRC mortality would most probably be much higher, and secondly, the cost of colonoscopies would be offset by savings from having to treat fewer patients with CRC, or treating patients with an earlier stage of CRC [13].
Acceptability of colonoscopy remains low [7]. However, accepting a single colonoscopic screening at 50 or 60 years of age would likely reduce the probability of the patient suffering and/or dying from CRC more than accepting a single FOBT screening. The safety and acceptability of colonoscopy should be enhanced by virtual colonoscopy [25]. This novel non-invasive imaging technology consists of thin section, helical computed tomography (CT) of the colon. These sections are used to generate high resolution, two-dimensional axial images. Virtual colonoscopy holds the promise of enabling colonoscopy to be performed without an endoscope, and seems better accepted than conventional colonoscopy [26].

Conclusion

In our opinion, the data available on CRC screening efficacy suggests that FOBT is not the appropriate method for screening for CRC. We do not see the relevance of mobilising millions of men and women for a screening procedure that will have little impact on their likelihood of dying of CRC. It is probable that its use (alone or in conjunction with flexible sigmoidoscopy) should be limited to subjects not willing to undergo colonoscopic screening.

Randomised trials testing the efficacy of colonoscopy and polypectomy will be difficult, as these techniques are offered to steadily larger numbers of subjects. Hence, public health efforts should probably now be directed towards projects promoting colonoscopic screening in selected populations where good cancer and mortality registries are installed, so that the impact on CRC incidence and mortality can be evaluated.

References