Review Article

Screening for colorectal cancer

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Introduction

Colorectal carcinoma is the third commonest cause of death from malignant disease in England and Wales – approximately 25,000 deaths in 1992. The incidence of the disease appears to be increasing while there has been a slow decline in mortality since 1985.4 The result has been a relatively constant annual mortality from colorectal cancer throughout the Western world over the last 30 years. The aim of colorectal cancer screening is to reduce this mortality by both preventing its development and by detecting its presence at a stage when curative resection is possible.

Screening for colorectal cancer is justified on the premise that prognosis is mainly related to the extent of tumour spread at the time of diagnosis2,3 and diagnosis when the tumour is at a less advanced stage may offer the best hope of reducing the mortality. For a screening programme to be effective, the disease in question must be common, the epidemiology and natural history of the condition known and a screening test be available which detects the condition while symptomatic. Similarly, the screening test should be simple, acceptable to the patient and clinician, sensitive, specific, safe and, preferably, cheap. Finally, the investigation and treatment of positive test results should be effective, readily available and cost-effective.

Around 1970 several procedures were introduced which changed the management of colorectal cancer – colonoscopy, colonoscopic polypectomy and modern techniques of cancer surgery4 – enabling screening for colorectal cancer to be undertaken using simple and inexpensive faecal occult blood (FOB) testing.5

Epidemiology and natural history

Colorectal cancer is a major problem in most developed countries. During the period 1980–1984 recorded mortality from all member states shows that the average annual number of colorectal deaths in European Community residents was over 85,000.6 Similarly, in the USA, there are approximately 60,000 deaths and 152,000 new cases reported annually.7 In the UK it is the second commonest cause of death from malignant disease coming after lung cancer in men and women.8

As mentioned above, survival rates have improved slightly over recent decades, 5-year relative survival of all registered cases diagnosed in 1971 being 30%,9 and of all cases registered in 1979–1981 being 35%.10 It has been calculated that a 50 year old person has a 5% risk of having colorectal cancer by the age of 80 and a 2.5% risk of dying from it.11

The natural history of the disease is continuing to be elucidated as the genetic changes underlying the development of malignancy are discovered. It is believed that the majority of colorectal cancers arise from adenomas, evidence supporting this argument including firstly, the demonstration that polyps sometimes contain sites of adenocarcinoma12 and, secondly, the incidence of both adenomas and carcinomas increase in parallel with age. Cancer of the large bowel is a disease of older people (except in the rare familial form), the risk doubling with every decade over 40 years.13 The incidence of adenomas also increases with age. Adenomas are common only in countries with a high incidence of colorectal cancer.14

However, only a minority of adenomas progress to cancer formation. Necropsy studies of asymptomatic patients show that the prevalence of adenomas in Britain is 34% in 50–60 years olds, rising to 40–60% in the over-75s. However, the prevalence of cancers in age-matched asymptomatic patients is only 1.6% and 3%.15

Is it possible to predict which adenomas will progress? In a retrospective study, Stryker et al. suggested a cumulative risk of polyp progression at 5 years, 10 years and 20 years of 2.5%, 8% and 24%, respectively.16 There appear to be three indices which relate to possible progression –
histological characteristics, size and the degree of dysplasia. The villous adenoma is the most likely to transform, along with polyps greater than 2 cm in diameter and those exhibiting severe dysplasia. Eide calculated the annual risk of an adenoma converting to a carcinoma to be 0.25% for all adenomas, 3% for adenomas greater than 1 cm, 17% for villous adenomas and 37% for villous adenomas with severe dysplasia.17

The recent advances in genetic research provide perhaps the strongest evidence supporting the adenoma – carcinoma progression. The discovery of the gene for familial adenomatous polyposis, known as APC, has provided direct evidence for a genetic cause for the development of polyps. Similarly, somatic mutations in the APC gene have been demonstrated in colorectal cancer tissue in patients with no known heritable syndrome.18,19 Further support comes from identification of ki-ras oncogene mutations which occur in premalignant adenomas as well as carcinomas and a series of genetic mutations have been suggested as necessary before malignant invasion occurs.20

In summary, colorectal cancer is a common condition with a significant burden of illness and is an important cause of mortality. Its natural history suggests that detection at an early stage or in its precancerous stage should improve outcome, meeting the criteria to make screening effective.

Three principle tests have been used to screen for colorectal cancer – digital rectal examination, faecal occult blood tests (FOBT) and sigmoidoscopy. While digital examination is an easy test, it is of minimal value for screening since the majority of tumours are out of reach of the examining finger21 and soft polypoid tumours may be difficult to feel.

Since Gregor's proposal for the use of a home test involving guaiac-impregnated paper slides,22 five large trials have been set up to evaluate the effectiveness of screening by FOBTs. The commonest type of FOBT employed is the Haemoccult test, a slide preparation of guaiac gum which relies on the peroxidase activity of haematin to catalyse the phenolic oxidation of the substrate. Based on unrehydrated tests performed 2-yearly, the sensitivity of this test in the various trials has ranged from 48% to 75%23–25 while the specificity can be as high as 99%.23

### Controlled trials – results (Table I)

The first trial to report4 mortality data was a non-randomized study which systematically assigned participants to screening or a control group. This study showed a 43% reduction in mortality in the screened group after 10 years of follow-up. This reduction, however, failed to reach statistical significance due to an inadequate number of deaths from colorectal cancer.

The three European randomized population trials23,24,26 have all reported interim results. The Swedish trial randomly divided 27,700 participants aged 60–64 years into test and control groups, and rescreened the test group after a mean interval of 20 months. The compliance in the study was 66% at the first screen and 58% at the second. Investigation of 322 subjects with a positive test result revealed 16 cancers and 58 individuals with one or more adenomas at the first screen. In the interval between screens, 26 carcinomas presented symptomatically in the screened group and 16 in the control group. The rescreen revealed 19 carcinomas and 92 adenomas in the test group compared with two carcinomas and one adenoma in the control group. There was no statistical difference between the Dukes' staging of the carcinomas, 46% of the screened group having stage A or B tumours compared with 40% of the control group.

### Table I Randomized controlled trials of Haemoccult testing in screening for colorectal cancer

<table>
<thead>
<tr>
<th></th>
<th>Nottingham, England</th>
<th>Goteborg, Sweden</th>
<th>Fuhnen, Denmark</th>
<th>Burgundy, France</th>
<th>New York, USA*</th>
<th>Minnesota, USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort size</td>
<td>155,000</td>
<td>52,000</td>
<td>62,000</td>
<td>94,000</td>
<td>22,000</td>
<td>48,000</td>
</tr>
<tr>
<td>Positivity rate (%)</td>
<td>2.1</td>
<td>1.9†</td>
<td>1.0</td>
<td>2.1</td>
<td>1.7</td>
<td>2.4†</td>
</tr>
<tr>
<td>Compliance</td>
<td>54%</td>
<td>65%</td>
<td>67%</td>
<td>52%</td>
<td>75%§</td>
<td>90%§</td>
</tr>
<tr>
<td>Predictive value (%)</td>
<td>50</td>
<td>22</td>
<td>57</td>
<td>31</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Dukes' A cancers (%)</td>
<td>Screened group: 52</td>
<td>50</td>
<td>51</td>
<td>52</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Test group: 30</td>
<td>30</td>
<td>27</td>
<td>n/a</td>
<td>35</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Control group: 13</td>
<td>12</td>
<td>9</td>
<td>n/a</td>
<td>27</td>
<td>35</td>
</tr>
</tbody>
</table>

*Trial included rigid sigmoidoscopy in both arms of trial; †non-rehydrated Haemoccult slides; ‡rehydrated Haemoccult slides; §subjects recruited were volunteers rather than identified from Practice lists and then randomized.
In the light of these inconclusive results, the trial has been extended to 51,477 participants and further results are awaited.

The Danish study randomly allocated 61,938 participants aged 50–74 to the screening and control groups. The rescreening interval was approximately 2 years. Sixty-seven per cent of those invited completed the first screen and 93% of those initially screened completed the second test. There were 215 positive test results at the first screen with 37 carcinomas and 86 adenomas detected compared with 159 positive tests at the rescreen with a further 13 carcinomas and 76 adenomas detected. During the follow-up, 40 interval cases and 39 non-responders presented with a carcinoma compared with a total of 115 carcinomas in the control group. The screened group showed a statistically significant earlier Dukes' stage than the controls (59% stage A or B in the screened group compared with 45% in the control group). The estimated death rate from colorectal cancer was 1.2 per 1,000 persons in the screening group versus 1.6 per 1,000 persons among controls, a trend which does not reach statistical significance ($P = 0.16$).

The largest of the randomized studies is taking place in Nottingham where 155,034 persons aged 50–74 years have been randomly allocated to test and control groups. Rescreening has been carried out at 2-yearly intervals. The average initial compliance 54%. At the initial screen 842 of the tests were positive and further investigation detected 91 cancers and 305 persons with adenomas. At the first rescreen, the compliance was 78% and revealed 54 carcinomas, and 139 patients with adenomas while the second rescreen (compliance 88%) revealed a further 25 carcinomas and 77 people with adenomas. There was a significantly greater number of screened people with less advanced tumours than among the controls (56% Dukes' A or B compared with 46%) and this was also found to be the case on rescreening (62% Dukes' A and B). This difference in the proportion of early Dukes' stage carcinomas between the screen-detected and control groups accords with the findings of the Danish trial. The Nottingham study also reported fewer emergency procedures, unresectable tumours and fixed tumours in the screened group.

The Minnesota Colon Cancer Control Study,$^{27}$ has recently reported the first statistically significant reduction in mortality from colorectal cancer by FOBT screening. In a prospective randomized trial, 46,551 participants were assigned to screening once a year, every 2 years or to a control group. Compliance within the study was very good with 75.2% of annual and 78.4% of biennial screenings completed. There were 1,002 cases of colorectal carcinoma detected over the 13-year period of follow-up and 320 deaths attributed to this cause, with a cumulative annual mortality rate of 5.88 per 1,000 in the annually screened group and 8.33 per 1,000 in the biennially screened group compared with the control group rate of 8.83 per 1,000. These results show a 33% decline in mortality in the annually screened group compared with the control group. There is also a decline in mortality in the biennially screened group compared to the control but this does not reach statistical significance.

While this study appears to vindicate supporters of colorectal screening programmes, there are several important points to consider. Firstly, the screening programme was interrupted for 3 years and then recommenced when, at that stage, the power of the study was too low to show a statistically significant result. There was both a higher incidence and higher mortality from colorectal cancer in the biennially screened group early in the study which Mandel and colleagues admit could have resulted from a chance imbalance in the randomization procedure. This was followed by the 3-year hiatus in screening and therefore it is impossible to know whether chance influenced the biennially screened group at this stage.

Secondly, and more importantly from the screening point of view, this study utilized rehydrated Haemoccult slides which resulted in a better sensitivity (92.2%) than non-rehydrated slides but a much lower specificity (90.4%). The practical effect of using this technique was a much higher rate of colonoscopy – 38% of the annually and 28% of the biennially screened participants underwent at least one colonoscopy. It could be argued that with over one-third of participants undergoing at least one colonoscopy in the 13-year period, the study demonstrates the value of screening by colonoscopy!

A third comment relates to the positive predictive value for the detection of cancer. In the Minnesota study, the positive predictive value is 2.2% compared with 17% in the Danish study, 4.6% in the Swedish study (who also used rehydrated Haemoccult), 10% in the Nottingham study and 7.5% in the New York study. Thus it can be seen that rehydrating Haemoccult slides significantly reduces the positive predictive value for the test with a consequent increase in the cost of diagnostic investigation.

There are other problems with Haemoccult as a screening test. Red meat and peroxidase-containing vegetables such as tomatoes and bananas may give false-positive results therefore dietary restriction for 3 days prior to the test is sometimes recommended.

When the Nottingham study introduced dietary restriction the rate of positive results fell from 3.4% to 1.3%.
Newer faecal occult blood tests

Since the original Haemoccult test was developed, alternative FOB tests have been produced such as more sensitive peroxidase-based tests, immunochemical tests specific for haemoglobin and heme--porphyrin assays. The more sensitive peroxidase-based tests improve the detection of neoplasia but have a lower specificity.\textsuperscript{28--31} The heme--porphyrin assay, HemoQuant, detects blood loss throughout the gastrointestinal tract and, although provisional results were encouraging,\textsuperscript{32} subsequent studies have been disappointing.\textsuperscript{33,34} The immunological tests have the theoretical advantage that they should only detect blood lost into the large bowel, since any blood lost into the upper tract will have lost the immunologically reactive site recognized by the antibody by the time the blood reaches the large bowel by digestion.

In the most recent work to date, St John et al. compared Haemoccult with a newer peroxidase-based test, HemoccultSENSA, HemeSelect (an immunological test) and HemoQuant both in symptomatic patients and in participants of a colorectal screening programme. The sensitivities for these tests in patients with known colorectal malignancies were 88.8%, 93.5%, 97.2% and 71.0%, respectively. Their results demonstrate significantly better positive rates with the HemoccultSENSA and HemeSelect tests than with Haemoccult (their specificities were comparable). Due to the expense of immunological testing, it is suggested that a two-tier testing strategy be adopted, with slides being prepared for both HemoccultSENSA and HemeSelect, but the HemeSelect slide only being developed if the HemoccultSENSA test was positive. Evaluation of this proposal showed that it would have detected the single carcinoma in the screened participants but would have missed seven out of 13 large adenomas.

Another interesting feature of this study was the failure to demonstrate any difference in the ability of Haemoccult to detect left- and right-sided lesions. The sensitivity of Haemoccult for detecting carcinomas proximal to the splenic flexure was 89.3% compared with 88.6% for lesions at or distal to the splenic flexure. This contrasts with the Nottingham data where 81% of tumours in the descending and sigmoid colon were detected but Haemoccult only had a sensitivity of 45% for rectal carcinomas, and 47% for carcinomas of the caecum or ascending colon.\textsuperscript{35}

Further support for an immunological FOB test comes from a study performed in Brighton and Guildford\textsuperscript{36} where Haemoccult and HemeSelect were directly compared in an asymptomatic population. Both tests were completed by 1,489 subjects with 1.1% Haemoccult positive and 9.7% HemeSelect positive. Nine cancers were detected by HemeSelect but only one of these was Haemoccult positive. Similarly, 49 patients with adenomas were identified, 48 were HemeSelect positive but only eight were Haemoccult positive. While this study confirms the greater sensitivity of HemeSelect, its lower specificity results in a greater number of investigations with the concomitant increase in the cost of screening and risk of complications. Further data are required to prove the benefits of changing to a newer faecal occult blood test before the use of either HaemoccultSENSA or HemeSelect can be supported.

To summarize, screening by FOBTs leads to the detection of less advanced Dukes' stage tumours with better prognostic features. One randomized trial has shown a significant reduction in mortality and it remains to be seen whether the European trials confirm these findings. Newer FOBTs have a higher sensitivity for the detection of both carcinomas and adenomas but their lower specificities have important implications for the potential cost of public screening programmes.

Sigmoidoscopy as a screening technique

Sigmoidoscopy has not been popular as a screening technique due to the medical input required and the inconvenience and discomfort to the patient. A uniphase screening programme was initiated by the Memorial Sloan-Kettering Hospital who reported their results in 1960.\textsuperscript{37} Cancers were diagnosed in 58 patients out of 26,126 individuals who underwent sigmoidoscopy, a detection rate at the initial screen of 0.002. The majority of these tumours were at an early stage and 5-year patient survival was 88%.

More recently, the Kaiser Permanente Multiphasic Evaluation Study reported its results for screening sigmoidoscopy.\textsuperscript{38} Members of the medical care programme were randomized to a group who were actively encouraged to schedule annual health checkups or a control group who were not so encouraged. The study group subjects had both a lower cumulative incidence (4.3 versus 6.7 cases per 1,000 persons) and a better stage distribution (86 versus 54% Stage B or better) than non-encouraged controls for colorectal cancers arising within reach of the sigmoidoscope. However, there was only a small difference between the two groups in their exposure to sigmoidoscopy (30% in the screened group and 25% in the control group) and it was concluded that the difference in mortality was too great to be accounted for purely by screening sigmoidoscopy.

In a retrospective case-control study,\textsuperscript{39} previous exposure to sigmoidoscopic screening was compared in subjects who had died of rectal cancer with
a general population sample. Eight point eight per cent of the case group had undergone sigmoidoscopy in the preceding 10 years compared with 24.2% of the control group, suggesting screening by rigid sigmoidoscopy reduces the risk of developing colorectal cancer within the next 10 years by over two-thirds. The design of this study has been criticized due to selection bias in the case group but the study contained an internal control, tumours above the reach of the sigmoidoscope occurring with equal frequency in the two groups.

The development of flexible sigmoidoscopy has focused attention on this technique as a possible solution to the poor sensitivity of Haemoccult and the limited examination possible with a rigid endoscope. Data from the Nottingham and Danish studies suggest that over 70% of screen-detected tumours are within reach of the flexible sigmoidoscope and it has been suggested that combining flexible sigmoidoscopy with a FOBT would result in a more realistic sensitivity for the detection of colorectal carcinoma for a screening programme.

In the Nottingham study, 15 of 22 interval cases presenting within 2 years of screening were in the rectum and sigmoid colon; if all these cases had been detected by sigmoidoscopy at the time of screening, the sensitivity of combined FOBT and sigmoidoscopic screening would have been 93% — a gain of 18% over the sensitivity of FOBT alone.

Again, there are some unanswered questions. How many of the interval cancers arise de novo in the interval between screening and are not actually detectable endoscopically at the time of FOBT screening? While the specificity of sigmoidoscopy should be 100%, can it be assumed that the sensitivity will also approximate 100%? What effect will the addition of sigmoidoscopy have on compliance rates? In an attempt to answer some of these questions, a European Multicentre Randomised Control Trial has been initiated to compare colorectal screening by FOBT with screening by combined FOBT and flexible sigmoidoscopy — the results are eagerly awaited.

References

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