

Population based endoscopic screening for colorectal cancer

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We propose that there should be a national colorectal cancer screening programme in the UK, and that there is a good case to base it on a single flexible sigmoidoscopy (FS) at approximately 60 years of age, possibly supplemented by faecal occult blood testing (FOBT) after age 60 years, predominantly for the detection of early proximal cancers.

CASE FOR SCREENING

There is no longer doubt that screening is an effective method of reducing colorectal cancer (CRC) incidence and mortality rates. The US Preventive Services Task Force¹ recently reviewed the evidence and gave a grade A recommendation that all men and women over the age of 50 years should be screened for CRC. In the UK, the Department of Health has demonstrated its commitment to CRC screening by funding a national demonstration pilot to assess the feasibility and acceptability of FOBT in the general population.² Together with the MRC it is also funding a randomised trial of a single FS screen offered at around age 60 years with colonoscopy for those found at FS to have high risk adenomas. The trial recently reported³ that FS is acceptable, feasible, and safe but has yet to report on the magnitude and duration of efficacy. The FOBT pilot was completed in mid-2002 and results are due to be presented to ministers in early 2003. Colonoscopy is not considered a feasible option for mass screening in the UK because of the personal commitment required of the screenee, the risks of perforation, and manpower issues.

GOAL FOR SCREENING: PREVENTION IS BETTER THAN EARLY DETECTION

The FOBT regimen under consideration in the UK is the *unrehydrated* guaiac test, offered biennially between the ages of 50 and 69 years. In two European trials^{4,5} this regimen produced a 15–18% reduction in CRC mortality rates. Case control studies, which allow estimates of the maximum effect achievable assuming complete compliance, show that FOBT and FS reduce CRC mortality rates by a similar proportion (approximately 35%).^{6,7} Importantly, the effect of a single FOBT in protecting against the diagnosis of a fatal CRC appears to abate after two years whereas the effect of a single FS examination lasts at least 10 years. Therefore, FOBT must be repeated at least every two years while FS is effective when offered very infrequently. We have suggested that it needs to be done only once if offered at approximately 60 years of age.⁸

The most important advantage of FS is its ability to *prevent* CRC through detection and treatment of adenomas, the precursor of most CRC. The

evidence comes from several large case control⁹ and cohort^{10,11} studies and a small Norwegian trial.¹² The reduction in CRC incidence seen after 18 years in the US trial of *rehydrated* FOBT¹³ was almost certainly due to the very high rate of colonoscopy resulting from the low specificity of the test. (In this trial, 38% of the annually and 28% of the biennially screened groups had at least one colonoscopy for a positive test.) No reduction in CRC incidence has been observed in European trials which used the unrehydrated FOBT, probably because cumulative colonoscopy rates were much lower (approximately 4%).

Prevention has advantages over early cancer detection. Firstly, the costs of the screening programme can be offset against avoided treatment costs (surgery, adjuvant chemo- and radiotherapy), imaging investigations, and clinical follow up. CRC is an expensive disease to manage and is set to become more costly with the introduction of new imaging, adjuvant, and palliative regimens. It has been suggested that FS screening may even be cost saving in the long term.¹⁴

Screening for cancer induces more anxiety than screening for premalignant lesions. While there have been no direct comparisons of FOBT and FS, work on cervical screening suggests that anxiety on receiving an abnormal result is lessened when people are given a leaflet explaining that cancer is unlikely.¹⁵ Such reassurance cannot be given with FOBT because 10% of people with a positive test result will be found to have cancer.

COMPLIANCE AND ACCEPTABILITY

Compliance rates with a single FS have been reported to vary between 39% and 50% in the UK.¹⁶ When FS and FOBT are offered together, attendance rates have been low,^{16,17} possibly because of confusion about the role of each test in that situation. Evidence that higher uptake rates with a single FS screen are achievable in a programme comes from Norway¹² and Northern California (Selby J, personal communication) where they are above 70%. Maximum effectiveness with FOBT screening requires long term regular screening. FOBT offered biennially between 50 and 69 years of age represents 10 opportunities to fail to comply. Studies show that approximately 60% will do the test once but less than 40% will complete all tests offered.^{4,18} If FOBT screening is started at age 50 years, when CRC incidence rates are low, it is likely that compliance rates will have fallen by age 60 years (five rounds later) when cancer incidence is increasing. It might be better to start after age 60 years to detect the cancers (mainly proximal) not prevented by a prior FS screen.

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Debate

Advantages of flexible sigmoidoscopy for colorectal cancer screening

- Detects adenomas, precursors of cancer.
- Reduces incidence and therefore morbidity.
- By preventing disease, costs of screening can be offset against avoided treatment costs.
- Takes only five minutes and there is an immediate result.
- Small polyps can be removed during screening.
- Very low complication rate.
- Infrequent examination.
- High attendance rates.
- Can be performed by nurses.

The FS screening regimen in the UK trial is quick, taking only 4–5 minutes, and an immediate result is available for most screenees; it is safe, with only one perforation in 50 000 FS^{3 19}; it is efficient in that screening and polypectomy can be achieved on a single visit in 95% of individuals³; and it minimises the need for subsequent colonoscopy. The 5% who are offered a colonoscopy are those whose screen detected polyps have characteristics which indicate a higher risk of proximal cancer.²⁰ With FOBT, a 1–2% positivity rate at each screening round results in a cumulative colonoscopy rate across the 50–69 year age range of 10–20% among compliers. Reducing the age range, by starting FOBT at 60 years, would decrease the cumulative positivity rate and also increase cost effectiveness.²¹

We can now predict that there will be manpower problems with whatever form of screening is selected. Nurses and non-specialist medical endoscopists can perform screening FS as well as gastroenterologists,²² but they are currently in short supply. Both FS and FOBT will put pressure on already stretched colonoscopy services, so it is essential to address these issues now. This will require training new endoscopists (medical and non-medical) and retraining established endoscopists to meet the rigorous standards required of a screening programme. The rewards would be great. The dramatic reductions in incidence rates of cancers of the sigmoid colon and rectum over the past 15 years in the USA have been attributed to sigmoidoscopy and polypectomy.²³ During this same time period in the UK, CRC incidence rates have remained unchanged.²⁴

Our aim in the UK must be to eradicate CRC rather than to increase, through earlier detection, the duration of the cancer experience and thereby the physical and psychological burden of suffering from the disease. Ultimately, it might be cost effective to exploit the long benign phase in CRC development using DNA markers in stool, which have the potential to be both sensitive and specific for precancerous lesions with high malignant potential. In the meantime, a policy based on a single FS at approximately 60 years of age offers the best prospect in the UK.

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ANTAGONIST

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POPULATION SCREENING FOR COLORECTAL DISEASE: A MUST DO?

Colorectal cancer is the second commonest cause of cancer death in the Western world and the median five year survival from this terrible disease remains at approximately 40%. In the UK approximately one third of cases still present as emergencies with intestinal obstruction or perforation

One method of reducing the mortality of this disease is through earlier diagnosis but the symptoms and signs of bowel cancer are often non-specific and therefore earlier diagnosis is unlikely to occur through increased awareness or patient education alone.

Colorectal cancer is an ideal disease for population screening: it is common, has a well recognised premalignant precursor lesion (the adenoma), and treatment of the premalignant condition reduces the risk of cancer.¹ Several case control studies and four randomised trials have shown that population screening for colorectal cancer reduces disease specific mortality. One large trial has also shown that population screening can reduce the incidence of this disease.² Overall, the cost effectiveness of screening for colorectal cancer compares favourably with other cancer screening strategies (that is, breast and cervical).³

The case for screening for colorectal cancer is increasingly compelling and with the launch of the National Pilots in Scotland and Warwickshire the politicians appeared convinced too! Over 12 months later, with the pilots nearing completion and preliminary data from the MRC Flexible Sigmoidoscopy study, another difficult decision looms.

WHICH SCREENING TEST SHOULD WE USE?

The debate over which screening test to use encapsulates some of the major issues in the provision of healthcare in the 21st century (especially in the National Health Service). Major technological advances are occurring at an increasing rate, but manpower and finance for today's technology are severely limited.

Although there are many potential screening tests for colorectal cancer, ones which are serious contenders for population screening are stool based tests or endoscopy. Of these, only faecal occult blood (FOB) testing has been thoroughly evaluated. FOB testing has been used in at least five case control studies⁴⁻⁸ and four large randomised trials.⁹⁻¹² Endoscopic screening shows promise, but so far no endoscopic screening study has shown a reduction in mortality or incidence in a randomised population based setting. Can a

national screening programme using endoscopy be launched without such data?

The pros and cons of FOB testing and endoscopic screening are summarised in table 1.

ENDOSCOPY

Endoscopic screening is essentially a choice between colonoscopy (examining the whole colon) and flexible sigmoidoscopy (examining the left half of the colon). Colonoscopic screening is good for high risk groups, such as those patients with hereditary non-polyposis coli and adenomatous polyposis coli. Its ability to undertake full colonic examination and simultaneous polypectomy is a major benefit, making it both a diagnostic and therapeutic tool. However, these abilities and benefits do not necessarily make it the most appropriate population based screening tool. Population screening by colonoscopy would be very expensive both in terms of direct costs and the complications such a programme would undoubtedly yield.

In the UK we have neither the manpower nor the necessary facilities to undertake colonoscopic screening for the average risk population. Population screening by colonoscopy would require a doubling of our endoscopy facilities and manpower. In addition, the standard of colonoscopy in the UK appears to be very variable and although steps are being taken to address this, we are a long way from providing a uniformly high quality diagnostic colonoscopy service.¹³

The complications which would arise from screening using colonoscopy would be unacceptable. Our calculations, based on published complication rates, suggest that colonoscopic screening of the UK population at age 60 years would probably lead to over 500 severe haemorrhages, over 150 perforations, and 50 deaths each year (table 2). Complications on this scale would rapidly lead to failure of the screening programme.

Taking all this into account we believe that population screening by colonoscopy is a non-starter in the UK for the foreseeable future.

By contrast, the US literature is increasingly supporting colonoscopic population screening.¹⁴⁻¹⁶ Screening on a private basis (albeit through insurance companies) may skew the data, by directing resources at the "worried well". Nevertheless, several case control studies have shown a reduction in colorectal cancer incidence and mortality following polypectomy.^{17, 18} Testing in a randomised controlled setting is still awaited.

While endoscopic screening by colonoscopy may be a non-starter in the UK, flexible sigmoidoscopy (FS) screening has some appeal although the evidence to confirm its ability to reduce the mortality of the disease is still some way off.

Debate

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Table 1 Pros and cons of the three main screening modalities

| | Faecal occult blood (unhydrated, Haemoccult) | Flexible sigmoidoscopy | Colonoscopy |
|--|--|---|--|
| Setting | Home | OPD endoscopy | Endoscopy |
| Bowel prep | No (diet restriction possible) | Self admin enema | Full bowel prep |
| Sedation | No | No | Yes |
| Staff | Tester | Nurse | Physician, nurse, pathologist |
| Duration of procedure | — | 5 minutes. Longer in novices | 15–20 minutes. Longer in novices |
| Day off work | No | No | Yes |
| Success rate | Predictive value for CRC of positive FOB: 5–10% ³¹ | 2% return due to inadequate bowel prep ³² | Completion rate in 79% of all cases ³³ |
| Sensitivity for cancers or polyps >1 cm | Cancers 50%, ³¹ polyps 17–46% ³⁴ | 95% cancer and high risk polyps ³⁵ | 95% cancer and high risk polyps ³⁵ |
| Specificity for cancers or polyps >1 cm | Cancers 98% ³¹ | 100% ³⁶ | 100% ³⁶ |
| Cost (1999) of individual test | \$5 (2001), ³⁷ £14.3 ³⁸ | \$99 (2001) ³⁷ ; £96 (1998) ³⁹ | \$380 (2001) ³⁷ £138 (1998) ³⁹ |
| Incremental cost effectiveness ratios compared with no screening (per year of life saved) 1998 | \$12 667 ³ \$9705 ⁴⁰ (annual non hydrated FOB) | \$16 786 ³ (annual non-hydrated FOB plus FS every 5 years) | \$20 418, ³ \$10 983 ⁴⁰ (colonoscopy every 10 years) |
| Therapeutic (ability to remove polyps) | No | No | Yes (increases cost slightly) |
| Large intestine visualised | Ability to screen right sided pathology | Rectum, sigmoid colon, and possibly descending colon | Whole large intestine |

CRC, colorectal cancer; FOB, faecal occult blood; FS, flexible sigmoidoscopy.

The large MRC multicentre trial of FS¹⁹ has recently completed recruitment. Early data have shown that population screening by this modality is safe and yields sufficient polyps and cancers to make it a worthwhile screening tool. However, data on the effect on mortality in this trial are not due until 2005.

A conceptual difficulty with FS screening is that it is analogous to mammographic screening of only one breast! A small proportion of screened patients will have lesions beyond the reach of the FS (resulting in “missed lesions”). While the advocates of FS screening minimise this risk, citing “marker polyps” as their salvation, it remains a medicolegal minefield if such a screening modality were introduced. Evidence of a shift in the site of colorectal cancer and an increase in the proportion of right sided and transverse colon lesions only fuels this anxiety.^{20–22}

The facilities and manpower investment required for population screening by FS are substantial and they raise three other issues:

(i) In order to minimise the cost of introducing FS screening, “a one off” FS examination is proposed to be offered to the population at age 50 years. This is in contrast with an annual or biennial FOB test (likely to be offered to the population from ages 50 to 70 years). The “one off” strategy has several additional merits over and above making the cost of the two programmes comparable:

- (a) FS is more sensitive than FOB for cancers and polyps (table 1).
- (b) In an average risk population, a polyp probably takes 10–20 years to grow to a size where malignant transformation becomes a possibility.

However, introducing such a “one off” programme is likely to cause outrage among those who fall outside the age cut off at the time of commencement. If the “one off” age is 50 years, there may be a discontented cohort of several million who just missed out. A similar ageist policy caused problems in the breast screening programme.

(ii) The second major issue with FS is the proportion of patients who need referral for colonoscopy because of small polyps found on FS. The initial MRC study data found a 5% referral rate for colonoscopy. This is 2.5× the rate in the Nottingham FOB trial where a 2% colonoscopy referral rate required two extra colonoscopy lists per week. Extrapolating the published FS data,¹⁹ up to five extra colonoscopy lists per week in each hospital would be needed to meet the demand from screening patients. Even if one assumes funding will be available, there are too few endoscopists and endoscopy nurses to meet such demands. Furthermore, rolling out FS screening from trial to clinical practice will almost certainly necessitate nurses and technicians performing these examinations and it is widely recognised that nurses are more scrupulous in detecting small polyps than doctors, so potentially pushing the colonoscopy rates up even further. The cut off

Table 2 Complications of colonoscopy and flexible sigmoidoscopy

| | Rate/1000 procedures | | No of cases per year in a UK national screening study of once only screening at age 60 years | |
|------------------------|----------------------|-------|--|----|
| | C | F | C | F |
| Respiratory depression | 5 | — | 858 | 0 |
| Severe haemorrhage | 3 | 0.3 | 514 | 51 |
| Perforation | 1 | 0.025 | 171 | 4 |
| Mortality | 0.3 | 0.15 | 51 | 25 |

C, colonoscopy; F, flexible sigmoidoscopy. Some of the data are extrapolated from the FS trial¹⁹; colonoscopy rates from standard texts.

Assuming 572 000 people are aged 60 years in the UK; 50% responding to an invitational letter (enrichment), subsequently being eligible, with 60% actually attending the screening test. A total of 171 600 cases would be undergoing the screening test at the age of 60 years; 5% of those with flexible sigmoidoscopy would need colonoscopic intervention (8580); 5% of colonoscopies would need completion double contrast barium enema (8580).

point at which colonoscopy becomes necessary is therefore a crucial issue, and one which remains to be resolved.²³

(iii) Finally, a further worry about FS screening is the issue of compliance. While in the MRC study compliance was cited at approximately 60%, overall compliance was only 40%. Investigators enriched their study group by randomising only those who expressed interest in the trial (response to postal questionnaire). Only two thirds of those who expressed interest and were randomised to FS actually turned up and underwent the investigation. FOB screening trials achieved population compliance rates of 35–50% in the general population²⁴ and >60% in clinical trials.²⁵

FAECAL OCCULT BLOOD TESTING

All four randomised population based studies showing that an FOB testing programme saved lives used a guaiac based test (usually Haemocult). Haemocult, with its specificity of 98% and sensitivity of only 50% (table 1), could lead to a label of “old technology” but it is tried and tested. Indeed, the current National Pilots in Warwickshire and Scotland are using this type of test.

FOB testing is painless, relatively inexpensive, and has no complications of its own. It also complies well with the WHO criteria of a screening tool: “a screening test should be inexpensive, rapid, and simple, and is not intended to be diagnostic; those with positive tests require further evaluation”.²⁶ When using Haemocult or a similar test, only 2% of the screened population would need further evaluation (normally by colonoscopy).¹¹ This modality therefore places much less strain on under resourced endoscopy units than population screening by endoscopic means. Of those 2% who need endoscopy, approximately 40% will have pathology identified; mostly adenomas, some carcinomas, and a few incidental findings such as inflammatory bowel disease.

More modern stool based tests are immunologically based (for example, Haemensa) and have a better sensitivity than their guaiac based counterparts.²⁷ These tests can also have an element of controlled sensitivity, using automated test reading devices, which is attractive. Even more promising, but some way off, are the stool based gene array tests, identifying mutations in the APC gene and others.²⁸ Multi-target assay panels, with the capability to identify many point mutations, have been successful on freezer archived stools.²⁹

Further support for an FOB testing programme comes from the fact that we know we can do it and we know it works. The current National Pilots are using the tried and tested FOB test (Haemocult), and the health economic data show that it will be as cost effective as either breast or cervical screening—costing approximately \$13 500 per added year of life.³⁰ If better tests come along in the future, the programme would provide an excellent test bed for their use and, if successful, they could easily be rolled out into the programme when appropriate.

COMBINED ENDOSCOPIC AND FOB SCREENING

As mentioned above, “once only” FS has its merits but may cause resentment among those

who are above the age at inception. Combining the “one off” FS screen at age 50 years with FOB screening for 60–70 year olds may be politically expedient and from the data available scientifically sensible. The expense of combined modality screening would be more than either FS or FOB screening alone but combining the tests may yield more right sided lesions and may be worth investigating in a trial setting.

WILL THE PUBLIC ACCEPT SCREENING FOR BOWEL CANCER?

Unless a screening programme is accepted and uptake by the population is over 50%, the benefits of screening for the population are likely to be outweighed by the costs of implementing the programme.

Screening for bowel cancer has been handicapped by the taboo surrounding anything to do with bowels in general. Neither the FOB tests nor FS are pleasant tests, FOB requires the individual to do the test whereas FS allows the individual to be more passive but the test is more invasive (table 1).

Compliance with FOB may be slightly better than for FS. If a National Programme was introduced, compliance rates for either could be expected to increase as the public become more educated and aware of colorectal cancer.

CONCLUSIONS

Screening for bowel cancer works—it reduces the mortality from this awful disease and costs about the same as established screening programmes for breast and cervical cancer. If we are serious about improving outcome for colorectal cancer, screening for this disease ought to be high on our list of priorities.

At the present time population screening for colorectal cancer by FOB testing is the only modality which has been shown to be safe and effective. We should use the National Pilots as a model from which to roll out a nationwide programme, starting by introducing an FOB screening programme and reviewing the technology used as more evidence becomes available. Some centres could be used to pilot new screening technologies and different screening regimens such as “once only” FS and combined FS/FOB regimens.

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