Colorectal cancer screening

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Clin Med 2006;6:453–6

Background

Colorectal cancer (CRC) is the second most common cause of cancer deaths in developed countries, with 35,000 new cases and 16,000 deaths in the UK in 2004 (Fig 1).[1] There have been significant improvements in CRC survival over the last decade (5-year survival is now about 50%) but the UK still lags behind the USA and most of Western Europe. One of the main reasons is late presentation; early-stage tumours (TNM stage I/II) have a good to excellent five-year survival (65–95%) with surgery alone, but in the UK only about 40% of colorectal cancers are diagnosed at early stages.[1]

In 2004, the Secretary of State for Health announced his intention to introduce population screening for CRC in 2006.[2] This decision was based on the results from pilot schemes in Scotland and Warwickshire which offered CRC screening with faecal occult blood tests (FOBt) to almost half a million people, demonstrating that population screening was reproducible and feasible.[3] This article discusses the details of the UK screening programme and the data supporting its conception and implementation (Table 1).

Screening trials and statistical data (Table 2)

Faecal occult blood test

CRC screening with FOBt, followed by colonoscopy for a positive test, fulfils the modified Wilson-Jungner criteria for a screening test.[4,5] The UK screening programme is based on the results of two large randomised controlled trials (RCTs) of CRC screening with FOBt in the 1990s and the subsequent UK FOBt pilot study. Each RCT involved 50,000–150,000 subjects aged over 45 years. This information is summarised in Table 3. There are other screening modalities but none has been subjected to RCTs (although these are now underway).

American study. Annual or two-yearly rehydrated FOBt was performed in 46,551 subjects aged 50-80.[6] There was a 33% and 21% reduction in CRC mortality over 13 years for annual and two-yearly screening respectively. The authors cited increased detection of early-stage cancers as the probable reason for the improved outcomes.

Danish study. Two-yearly, un-rehydrated FOBt (with dietary restrictions) was offered to ~31,000 patients.[7] Of the ~14,000 patients originally recruited in this study, ~31,000 were also entered as a control group (and were not screened), while the remainder were not entered into the protocol. There was 67% uptake for the initial FOBt in the group offered screening, with 90% of those undergoing repeat screening. Similar rates of cancer were detected in the screening and control groups but the CRC mortality ratio was 0.82 (95% confidence interval (CI) 0.68–0.99) in favour of screening after eight years follow-up.

UK study. The largest trial of FOBt (in Nottingham) recruited 150,000 individuals, half of whom were randomised to be invited for two-yearly unhydrated FOBt screening (without dietary restrictions).[8] There was a 60% uptake in

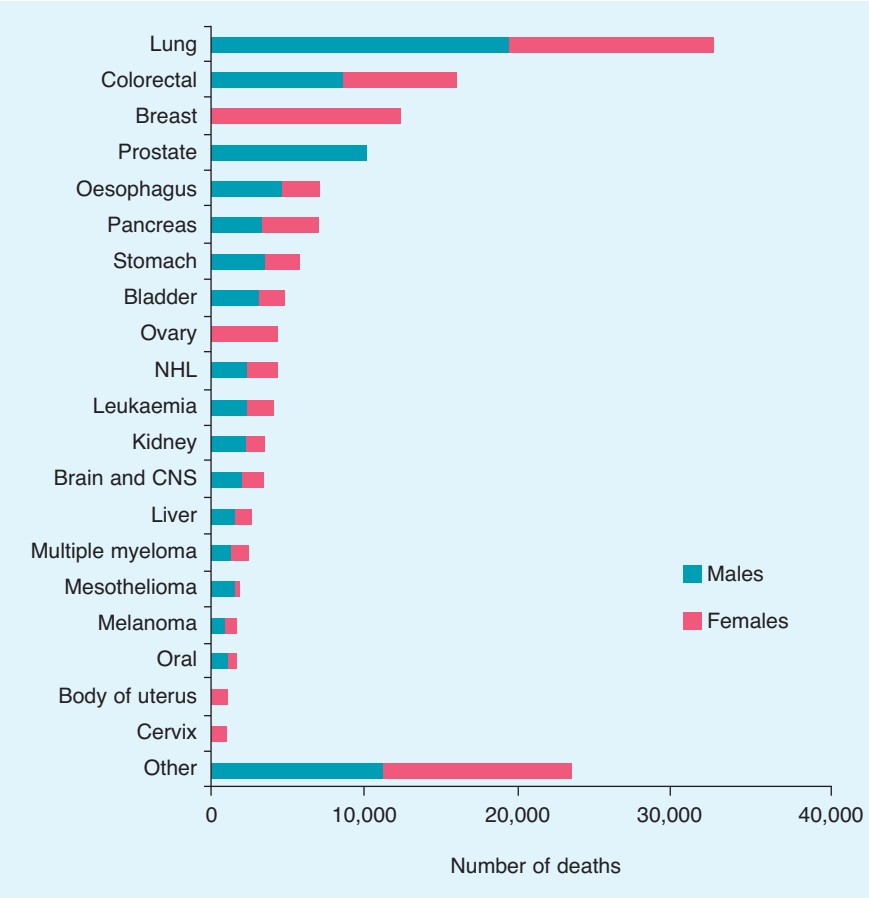

Fig 1. The number of deaths attributed to the 20 most common causes of cancer in the UK, 2004. CNS= central nervous system; NHL = non-Hodgkins's lymphoma. Reproduced, with kind permission, from Cancer Research UK website.[1]

Table 1. The UK screening programme for colorectal cancer (due for implementation in 2006).

- 2-yearly FOBt testing (guaiac-based; 6 test wells) for all men and women aged 60-69 years registered with a GP
- Regional screening hubs will post FOBt kits directly to individuals
- FOBt kits will be unhydrated with no dietary restrictions necessary
- If strongly positive (5–6+), offered nurse-led clinic appointment and colonoscopy
- If weakly positive (1–4+), offered repeat test with dietary restriction
- Expected uptake about 60%, with a 2% positive FOBt rate and 87% attendance for colonoscopy if positive
- Uptake rates have been lower in subjects from the Indian subcontinent, in areas of high deprivation and in men (particularly younger men)
- Will lead to an initial extra 300 colonoscopies per 250,000 population screened per year

FOBt = faecal blood test; GP = general practitioner.

Table 2. Screening modalities for colorectal cancer (CRC).

		Population			
Modality	Ref.	Total	Screened	Advanced neoplasia/CRC at colonoscopy	Mortality reduction (%)
FOBt	6	46,551	31,000	N/A	33
FOBt	7	140,000	31,000	N/A	18
FOBt	8	152,850	75,000	N/A	15
FOBt	3	486,355	259,402	12% CRCs if +ve 30% adenomas if +ve	Pending
FS	10	2,885	2,885	70% advanced neoplasia	–
FOBt & FS	10	2,885	2,885	76% advanced neoplasia	–
FS	9	354,262	57,254	5–6% advanced neoplasia/CRC	Pending
Colonoscopy	In progress				
CTC	Ongoing				

CTC = computed tomographic colography; FOBt = faecal blood test; FS = flexible sigmoidoscopy; N/A = not applicable (these are screening programmes designed to reduce mortality).

those invited to receive screening and 893 cancers were detected (20% Duke's stage A). In the control group, 856 cancers were detected (11% Duke's stage A). Screening reduced the CRC mortality by 15% (ratio 0.85, 95% CI 0.74–0.98).

The discrepancy between the American and European results was explained by the use of mainly rehydrated tests and increased screen frequency in the American study, which significantly increased the colonoscopy rate (ca 40%).

Flexible sigmoidoscopy

Baseline results from the UK flexible sigmoidoscopy (FS) screening trial have been published.[9] Of the 350,000 subjects asked whether they would attend FS screening, 55% agreed and were randomised to screening or no screening (1:2 ratio). There was a 71% attendance for FS; 5% of these subjects were found to have high-risk features at FS (>3 adenomas, adenoma >1 cm, villous histology, severe dysplasia or cancer) and were referred for colonoscopy. FS was found to be safe and well tolerated. Distal adenomas and cancer were found in 12.1% and 0.3%, respectively, and proximal adenomas and cancer in 18.8% and 0.4%.

The CRC detection rates by FS were similar to those in the UK FOBt trial but 62% of cancers were Duke's stage A (*v* 20% in the FOBt trial). This appears promising and may reduce CRC mortality by 30% in the screened group. The final data on the impact of FS on CRC mortality are keenly awaited.

FS examines only the recto-sigmoid area so there are concerns that proximal lesions are missed. Two studies demonstrated that, although proximal advanced adenomas or cancers are relatively uncommon in the absence of distal lesions (2–3%), FS would miss 52%[10] and 66%[11] of these proximal lesions in men and women, respectively. FS and FOBt combined was studied in 2,885 asymptomatic individuals.[12] FS alone detected 70.8% of advanced adenomas or cancers; the addition of FOBt increased the detection rate to 75.8%, amounting to a 'miss rate' of 24%. However, all this must be considered against the fact that FOBt might detect only 30-50% of CRCs.

Colonoscopy

Colonoscopy is regarded as the gold standard for colonic examination. Not only does it allow complete and reliable examination of the entire colon but also offers the option to remove adenomas, thus dramatically reducing the risk of CRC.[13] It has been shown to detect advanced adenomas or cancers in 10% of asymptomatic subjects, aged 50–75.[10] CRC screening using colonoscopy has not been subjected to a large randomised trial.

There are a number of concerns regarding colonoscopy as the screening modality:

1 Screening is conducted in apparently healthy subjects and there is a small but appreciable associated complication rate (perforation rate ca 1:800 and 1:1500 require hospitalisation following a bleed).[14] Colonoscopy was also considered a possible contributory factor in six deaths (following ca 9,000 colonoscopies) although no patient died as a direct result of the procedure.[14]

2 An audit of colonoscopy services in the UK[14] demonstrated a 57% completion rate (defined as full colonoscopic evaluation to caecum), well short of the 90% target.[15] Measures are now in place to ensure adequate training and appraisal of colonoscopists to meet this target.[15,16]

Table 3. Evaluation of screening modalities (as first-line test).

- Screening with FOBt reduces CRC mortality by 15–33%
- FS detects earlier stage cancers than FOBt but may have a lower uptake rate
  - results of the UK FS screening trial are awaited (due June 2008)
  - combined FOBt and FS may still miss 24% of cancer
- Colonoscopy as the 'first-line' tool is three times the cost of FOBt and twice the cost of FS
  - availability, cost and safety issues make it unlikely to be used as a 'first-line' screening tool in the UK
- CTC is equal (may be superior) to colonoscopy for large polyps
  - sensitivity is reduced for smaller polyps; operator-dependent
  - not recommended for screening at present; useful if colonoscopy fails
  - may have a role as technology improves, seen as more acceptable by patients

CRC = colorectal cancer; CTC = computed tomographic colonography; FOBt = faecal blood test; FS = flexible sigmoidoscopy.

3 The cost of colonoscopy as the first-line screening test is three times that of FOBt and twice that of FS.[17] A prospective randomised trial of colonoscopy versus FOBt in CRC screening is being undertaken[18] but this is unlikely to influence plans for CRC screening in the UK.

Computed tomographic colography

Computed tomographic colography (CTC) produces both two-dimensional axial images and three-dimensional endoluminal 'virtual' images. Practical and theoretical advantages of CTC over colonoscopy include safety, patient tolerability and the ability to 'look behind' mucosal folds, which is difficult with colonoscopy.

Several trials with CTC have shown its superiority to air-contrast barium enema[19] and conventional axial CT.[20] CTC detects 53–91% of lesions smaller than 10 mm, but sensitivity reduces dramatically for smaller polyps.[19,21,22] However, in a more recent study CTC sensitivity for polyps below 10 mm was 94%, which is at least as good as with optical colonoscopy (88%).[23] Furthermore, with the advent of faecal 'tagging' and digital subtraction imaging, full bowel preparation may no longer be required for CTC which may improve acceptability. Trials are underway comparing CTC and colonoscopy but there are currently no plans to use CTC as the primary screening modality.

Key Points

Colorectal cancer (CRC) is the second most common cause of cancer deaths in the UK

The five-year survival is related to the stage at presentation

Faecal occult blood testing (FOBt) has been shown to reduce CRC mortality by 15–33% and is cost-effective

Flexible sigmoidoscopy and colonoscopy are also likely to be effective

The NHS will offer CRC screening with FOBt for subjects aged 60–69

KEY WORDS: colonoscopy, colorectal cancer, computed tomographic colography, faecal occult blood, flexible sigmoidoscopy, public health, quality-adjusted life year, screening

Surrogate faecal markers

There is increasing interest in surrogate faecal markers for CRC. *Faecal calprotectin* (FC) is a neutrophil-specific cytosolic protein and, since CRC often produces a local inflammatory reaction from which neutrophils are shed, elevated levels are detectable in faeces.[24] Early studies showed promise but prospective and population studies have not fulfilled this potential. In population screening, FC performed less well than FOBt (67% *v* 75% sensitivity) and had poorer specificity.[25]

Faecal DNA analysis has been used to detect a combination of known tumour-associated genetic mutations (eg k-ras, TP53, BAT26, APC) from stool with sensitivities of 53–71% in CRC patients.[26,27] Although faecal DNA detection outperformed FOBt in population screening (51.6% *v* 12.9% invasive cancers),[28] because of its high cost and fairly low positive predictive value it is not yet viable for widespread use.

Screening in high-risk groups

Although distinct from population screening, patients at high risk constitute an appreciable proportion of primary and non-specialist secondary care attendances. Summarised from published guidelines by the British Society of Gastroenterology[29] and the American Cancer Society,[30] this group includes those with:

- a past personal or significant family history of CRC
- inflammatory bowel or endocrine conditions that are known risk factors for CRC
- known or suspected inherited genetic defects.

Guidelines for polyp follow-up are also available, but this constitutes surveillance (rather than screening). Patients with a family history of CRC are encountered relatively frequently in non-specialist settings. The British guidelines are summarised in Table 4.

Cost-effectiveness

The National Institute for Health and Clinical Excellence recommends interventions as cost-effective if they cost less than £30,000 per quality-adjusted life year (QALY). CRC screening with FOBt costs £2,600–£6,000 per QALY and is thus cost-effective.[3] Economic analyses of other screening modalities such as FS and colonoscopy indicate that they are also cost-effective, but these analyses are highly dependent on various assumptions and also on patient compliance which varies widely (Table 2). However, the figures are broadly comparable with other screening programmes, for example mammography (ca £3,000/QALY) and cervical cancer screening with liquid-based cytology (£9,000–10,000/QALY).

Table 4. Colorectal cancer (CRC) screening in patients with a family history of CRC.[29]

- Patients with a family history of CRC who are eligible for screening include *only* those:
  - with one FDR under 45 years at diagnosis
  - with two FDRs of any age
- For patients with more than two FDRs with CRC, referral to clinical geneticist recommended (possible HNPCC or familial polyposis)
- No other family history is considered eligible but individual cases are considered
- Colonoscopy performed at first consultation or age 35–40, whichever is the later
- If negative, further colonoscopy at age 55

FDR = first-degree relative; HNPCC = hereditary non-polyposis colorectal cancer.
Reproduced with kind permission from the British Society of Gastroenterology.[29]

Conclusions

Colorectal cancer screening with FOBt has been shown to be effective in reducing CRC mortality in large randomised trials and is cost-effective. Other modalities of screening (FS, colonoscopy, CTC) currently being evaluated in RCTs are also likely to be effective. The optimal screening test has not yet been determined but, as the effectiveness of a screening programme is dependent on compliance, patient preference may determine the overall decision. The NHS has decided to offer FOBt screening and this will be implemented from 2006 onwards.

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