

Healthcare innovation can be a long and tortuous process – close to 40 years in the case of national screening for colorectal (bowel) cancer. The first studies to suggest that population screening using the faecal occult blood test (FOBT) might reduce colorectal cancer deaths were conducted in the mid-1970s. Three large randomised control trials, each lasting eight to 10 years and involving close to a third of a million volunteers, followed. By 1996, when the last of these was published, the principle that population screening using FOBT is effective in reducing colorectal cancer deaths by 15–18% was established. Government commitment to a national bowel cancer screening programme was included in the NHS *Cancer Plan*, published in 2000. A pilot scheme at two sites, one in England (West Midlands) and the other in Scotland (Grampian, Tayside and Fife) was initiated in 2001, and positive evaluation of the pilot in 2003 allowed health secretary John Reid to announce in 2004 that a national bowel cancer screening scheme would be rolled out across the country from April 2006. Although a little later than scheduled, the roll out process began towards the end of last year and, if all goes according to plan, by 2010 all those living in England aged 60–69 will be offered FOBT (with follow-up colonoscopy if FOBT-positive) every two years. Similar schemes in Scotland and Wales are planned. Just as national screening for bowel cancer is at last becoming a reality, FOBT methodology is emerging as a potentially contentious issue. The randomised trials and pilot schemes on which recommendation for national screening was based were conducted using a guaiac-based FOBT. This is the chosen method for national screening. Accumulating evidence suggests that newer immunochemical methods might be more appropriate. The latest study to highlight superior performance of immunochemical FOBT over guaiac-based FOBT is recently published (*Gut* 2007; **56**: 210–4). The authors of this study, in common with other experts, argue that immunochemical FOBT, rather than the chosen guaiac FOBT, should be the tool for population screening.

Colorectal cancer screening

The large bowel comprises the colon (ascending colon, transverse colon, descending colon, sigmoid colon) and rectum. Although colorectal (bowel) cancer can occur at any site from the caecum (first portion of the ascending colon) to the anus, it occurs most commonly in the final (distal) portion of the bowel that includes the sigmoid colon and rectum.

After lung and breast cancer, colorectal cancer is the third most common malignant disease in the UK, with an annual incidence around 35,000. There has been an unexplained gradual increase in annual incidence over the past 30 years.

It is a disease that predominantly affects the elderly, with around 80% of patients aged over 60 years at the time of diagnosis. Males are at slightly higher risk. The condition currently accounts for close to 16,000 UK deaths each year.

A LONG NATURAL HISTORY

Nearly all colorectal cancers are adenocarcinomas, originating from the glandular epithelium that lines the internal (luminal) surface of the large bowel. A multistep process occurring over many years marks the change from normal epithelium to colorectal cancer. The first visible signal of this change is the adenomatous polyp (adenoma; Fig 1). This is an abnormal but benign growth on the luminal surface of the bowel measuring between 1 mm and 1–2 cm.

Around 20% of the adult population harbour these small growths, the vast majority without ill effect. However, an estimated 5% of adenomas undergo malignant transformation to colorectal cancer. Progression from adenoma to cancer is slow and may take as long as 10–15 years. Larger adenomas (>10 mm) carry greater risk of malignant transformation. Removal of malignantly transformed adenomas prevents colorectal cancer.

As long as colorectal cancer is diagnosed early while it remains localised to the surface (mucosal and submucosal) layers of

the bowel wall, surgical treatment is usually curative (five-year survival around 90% and 10-year survival not substantially less). At the other extreme, most cases of advanced disease with full penetration of the bowel wall and metastasis to distant organs are associated with a five-year survival of just 2%.

The problem is that the few non-specific signs and symptoms of colorectal cancer – change in bowel habit, abdominal pain, rectal bleeding, and anaemia – are usually not present in the early stages, and often ignored or not recognised later. Whatever the reason, most (60%) patients are diagnosed when the disease is in a relatively advanced state and the chances of long-term survival are much reduced (Table 1). Overall, at the current time, around half of patients die during the five years following diagnosis.

SCREENING FOR COLORECTAL CANCER

Diagnosis of colorectal cancer is achieved by colonoscopy. A colonoscope is a flexible fibre-optic instrument inserted via the anus to a previously emptied and cleaned bowel. It allows visual inspection of the entire bowel wall for the presence of both colorectal cancer and precancerous disease (eg large adenomas). The design of the instrument permits surgical removal of adenomas and the biopsy of malignant tissue. Histopathological examination of the recovered biopsy tissue is necessary for confirmation of colorectal cancer.

Although colonoscopy is theoretically the most effective screening tool available, it is prohibitively expensive, logistically impractical and associated with unacceptably high risk of adverse effects for first-line, low-risk population screening. However, as a second line test, colonoscopy is an essential component of the screening process.

Despite its limitations, the faecal occult blood test (FOBT) is considered the most suitable first-line screening test. Colorectal

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cancers and precancerous adenomas can bleed, so the presence of occult (hidden) blood in faeces is a non-specific indicator of both conditions. Not all cancers or adenomas bleed, and some bleed intermittently, so a negative FOBT cannot be used to exclude either condition. A positive result is the trigger for colonoscopy referral.

Screening with FOBT reduces colorectal cancer mortality in two ways: through prevention, by removal of bleeding precancerous adenomas at colonoscopy; and cure, by early identification of bleeding colorectal cancers, and subsequent surgery.

FAECAL OCCULT BLOOD TEST METHODOLOGY

Most products available for detection of occult blood in faeces are based on one of two methods. The oldest are the guaiac-based FOBT (g-FOBT) methods. These exploit the pseudoperoxidase activity of the haem moiety of haemoglobin present in blood. The test involves smearing a faecal sample on guaiac-impregnated filter paper and adding hydrogen peroxide. Any haem/haemoglobin present reacts with peroxide, releasing oxygen that causes colourless guaiac to turn blue. Certain foods (eg red meat, fruits) and medications have pseudoperoxidase or peroxidase activity that can give rise to false-positive results. Bleeding at any point in the gastrointestinal (GI) tract can give rise to a positive g-FOBT result.

The alternative immunological FOBT (i-FOBT) method is based on detection of haemoglobin using monoclonal antibodies that react only with intact human haemoglobin. The main advantage of the i-FOBT method is its specificity for intact human haemoglobin. There is no dietary or medication interference. Only haem, not intact haemoglobin, is present in faeces in cases of GI tract bleeding above the large bowel, so the method is specific for colorectal bleeding. The agglutination reaction that defines a positive i-FOBT result is more easily interpreted (less prone to operator bias) than the colour change that defines a positive g-FOBT result.

FRENCH COMPARISON

The most recently published study (*Gut* 2007; 56: 210–4) to compare the effectiveness of i-FOBT and g-FOBT as screening tools for colorectal cancer was conducted in Calvados, an area in Normandy, France. A screening programme using g-FOBT (Hemoccult II), targeting all those aged 50–74 years, was already up and running when the study was conceived in 2004. All 11,333 patients targeted for screening between 1 June 2004 and 30 June 2005 were invited to join the study, and 10,804 agreed. In addition to providing faecal samples for g-FOBT (Hemoccult II) testing, study participants collected additional faecal samples for i-FOBT.

The i-FOBT method chosen for study was

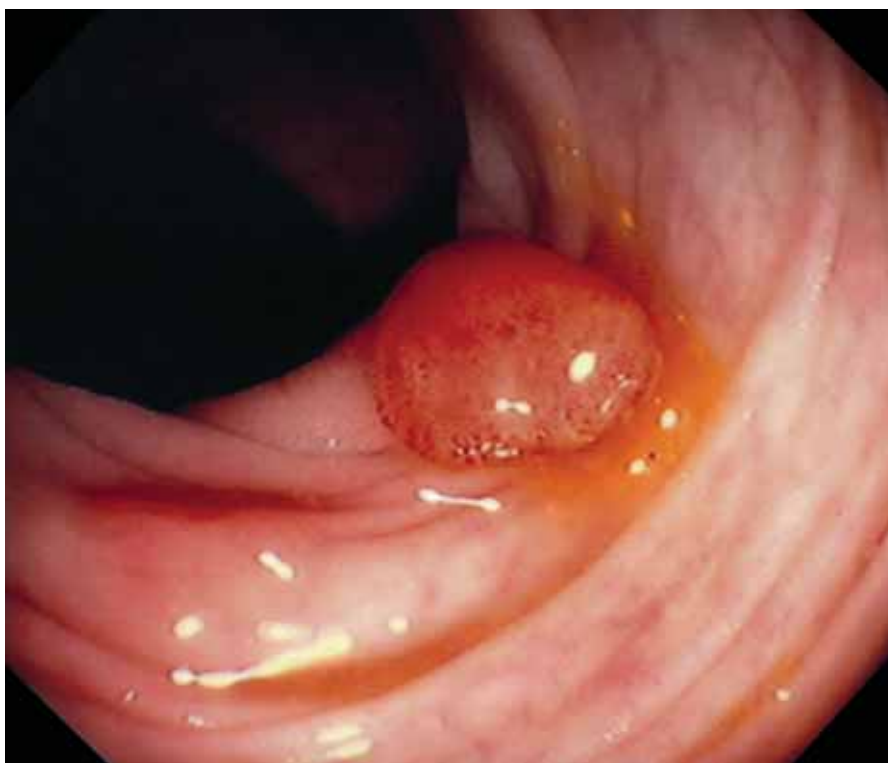


Fig 1. Colonoscopic view of an adenomatous growth in the gastrointestinal tract.

Magstream1000–Immudia/RHPA, manufactured in Japan by Fujirebio. In principle, the immunochemistry involved is the same as other immunological methods in that it detects human haemoglobin using human haemoglobin antibodies raised in animals (in this case rabbits). However, the detection of agglutination is modified to allow automated reading of haemoglobin concentration using the Magstream1000 instrument. Agglutination takes place in small V-shaped wells of microtitre plates, into which samples and reagents are pipetted.

The instrument is able to process a 96-well plate (ie 96 samples) in eight minutes. The manufacturer states that cut-off haemoglobin concentration for a positive occult blood result is 20 ng/mL, but the singular advantage of the system, which was exploited in this study, is that any haemoglobin concentration, so long as it exceeds the detection limit of the assay system, can be chosen to define a positive result.

Of all 10,673 study participants for whom both g-FOBT and i-FOBT test results were available, the vast majority (9787) were, as

expected, negative by both methods. The study focused on the remaining 886 who had a positive result by g-FOBT and/or i-FOBT using the manufacturer's cut-off (>20 ng/mL haemoglobin). Among these 886 there were 260 positive g-FOBT results and 733 positive i-FOBT results. This gives a positivity rate among the population (10,673) tested of 2.6% for g-FOBT and 6.9% for i-FOBT, reflecting the increased sensitivity of i-FOBT for the detection of occult blood in faeces.

All 886 patients with a positive FOBT (either g-FOBT or i-FOBT) were referred for colonoscopy. In the event 175 did not attend, and for technical reasons colonoscopy data were lacking in a further 67. Colonoscopy of the remaining 644 revealed that in 350 cases there was no evidence of neoplastic disease, and thus the FOBT was falsely positive (so far as colorectal cancer is concerned) in these subjects. Evidence of neoplastic disease was found in the remaining 294. Of these, 124 had low-risk small adenomas (<10 mm); 149 had precancerous disease (large adenomas) and 21 had colorectal cancer. The positive FOBTs in the 170 patients with precancerous lesions and colorectal cancer are the 'true' positive results. These are the people who FOBT screening is designed to identify.

Using the manufacturer's cut-off (20 ng/mL), analysis of results demonstrated that i-FOBT was 50% more sensitive in detecting colorectal cancer and 256% more sensitive in detecting precancerous disease than was g-FOBT. Overall, i-FOBT detected three times as many advanced neoplasms (either cancer or precancer) as did g-FOBT. However, this clear advantage is offset by an increase in the number of false-positive cases, because, while

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Table 1. Prognosis depends on Dukes' stage at the time colorectal cancer is diagnosed.

Dukes' stage (modified)	% of patients at diagnosis	% survival at 5 years
Stage A Cancer localised to inner surface of bowel wall. No lymph node involvement	11	>90
Stage B Deep penetration of the bowel wall. No lymph node involvement	34	70
Stage C Full penetration of bowel wall and spread to local lymph nodes	26	35
Stage D Cancer spread to distant organs (eg liver, lung)	29	<5

sensitivity improved, specificity decreased, compared with g-FOBT. The authors calculated that if i-FOBT replaced g-FOBT, for every additional case of cancer or precancerous disease detected, the number of false-positive results increases by 2.2.

The quantitative nature of the i-FOBT method used in this study allowed the authors to calculate the effect of increasing the haemoglobin concentration threshold on sensitivity and specificity of the test. The data were re-analysed using two further cut-off values (>50 ng/mL and >75 ng/mL) to define a positive i-FOBT result.

Clearly, the higher the cut-off limit, the lower the sensitivity for detection of occult

blood. The positive rate fell from 6.9% (cut-off >20 ng/mL) to 3.3% (cut-off >50 ng/mL) and 2.4% (cut-off >75 ng/mL). Clearly, some false positives will be among the positives that go undetected as a result of increasing the cut-off threshold, so there is a trade-off here: decreased sensitivity for increased specificity.

When a positive i-FOBT was defined as haemoglobin concentration >50 ng/mL, i-FOBT was still able to detect just over twice as many advanced neoplasms (cancer and precancer) as was g-FOBT, but now the number of false-positive cases (specificity) was the same as for g-FOBT. When the threshold was increased to >75 ng/mL, i-FOBT detected a little under twice as many

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advanced neoplasms as did g-FOBT, and there were a third fewer false-positive cases than were obtained using g-FOBT. At this threshold, then, sensitivity and specificity achieved with the i-FOBT method were higher than those achieved with g-FOBT.

This study adds to the accumulating weight of evidence indicating that i-FOBT is superior to g-FOBT as a screening tool for colorectal cancer. If i-FOBT were adopted, results suggest that more cases would be detected and fewer healthy people would be subjected to unnecessary colonoscopy and the anxiety associated with an equivocal screening result.

The i-FOBT method chosen for this study has a particular advantage in that it is not prone to operator bias and is eminently suited to the high throughput that national screening demands. ■