Overview of colorectal cancer screening

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Screening

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It is well established by randomised controlled trials that screening for colorectal cancer (CRC) using guaiac faecal occult blood tests (gFOBTs), and, by implication, the newer faecal immunochemical tests (FITs) for haemoglobin can reduce disease specific mortality by means of early detection[1]. In addition, it been shown that endoscopic screening in the form of flexible sigmoidoscopy can not only reduce mortality from CRC, but also, by the detection of adenomas, it is an effective means of reducing disease incidence[2]. Both modalities are now employed in the UK for population screening, and the older gFOBT is now being replaced by FIT.

FIT has advantages over gFOBT in that it is specific for human haemoglobin, it is easier to do and therefore associated with higher participation rates and it is quantitative so that the threshold for triggering a colonoscopy can be set at a level that is in keeping with current colonoscopy capacity[3]. When the FIT threshold is set at the same analytical sensitivity as gFOBT (i.e. produces the same positivity rate in the population) it performs better that gFOBT in the detection of adenomas[4], thus enhancing the screening programme's ability to prevent colorectal cancer.

In terms of clinical impact, the screening programme has increased the proportion of CRCs diagnosed at an early stage. In a mature gFOBT programme, which consists of a combination of prevalence and incidence screening, around 35 % of screen-detected cancers are diagnosed at stage A as opposed to 11% in the symptomatic population[5]. Indeed in the region of 16 % of screen-detected cancers are polyp cancers, and are completely removed by colonoscopic polypectomy, usually at the same time as the colonoscopy organised in response to a positive gFOBT or FIT result. Flexible sigmoidoscopy screening also picks up early cancers, but its main strength lies in its ability to identify adenomas[2].

One result of this screening activity is to present the endoscopic and surgical services with an increasing number of early cancers and polyps, many of the latter being complex, and challenging for both endoscopists and pathologists. Thus, although this has significant advantages in terms of survival it adds to the clinical dilemmas that SPECC was set up to address. In addition, of course, it results in a degree of overdiagnosis i.e. some patients will be diagnosed with disease from which they were never destined to die.

Screening programmes in the UK are not perfect; the sensitivities at which gFOBT and FIT operate in order to avoid overwhelming the colonoscopy services mean that there are a significant number of interval cancers[5], which, in the vast majority of cases, are undoubtedly cancers that were missed by the most recent screening test. For this reason, there is worldwide interest in developing tests for CRC that are more sensitive and specific than those in current use.

Of course, colonoscopy as a screening test is highly sensitive (few false negatives) and specific (false positives are extremely rare). However, problems with using colonoscopy in this context are that it is expensive, requires excellent bowel preparation, demands a large,

highly skilled workforce, is associated with relatively low uptake in the general population and carries a measurable morbidity and mortality. Because of these uncertainties, although colonoscopy is widely employed as an "on demand" screening test, especially in North America, its utility in population screening is currently being tested in at least four RCTs, which will take several years to report[6]. CT colography has also been promoted for population screening[7], but has failed to gain traction as a first line test.

Given the imperfections of blood in stool tests and endoscopy, a great deal of effort has gone into developing novel tests. Identification of mutated DNA in faeces shed from the surface of cancers and polyps has long been attractive, and indeed, a test that combines a panel of such markers with FIT has been marketed and approved by the FDA[8]. However, although this is more sensitive than FIT, it is less specific, and, it has been argued that, by altering its threshold parameters, FIT alone can perform just as well[9]. Blood tests have also been developed, such as those for DNA hypermethylation markers[10], but again, none have been shown to outperform FIT. One of the most promising avenues is the study of volatile organic compounds, stimulated initially by the finding that dogs can be trained to recognise patients harbouring CRC by smelling breath or faeces[11], but a clinically viable process has yet to be developed. The development of colon capsule endoscopy may also add to the screening armamentarium with time[12].

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