

Invited review

Screening for colorectal cancer

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SUMMARY

Colorectal cancer is one of the commonest fatal malignancies in the Western World. Recent evidence suggests that the disease is preventable. This review examines the relative strengths of the different strategies proposed for population-based colorectal cancer screening programmes. Full colonoscopic examination of the large bowel, particularly in subjects with a family history of colorectal carcinoma or adenoma, may be a cost-effective method of screening.

INTRODUCTION

Cancer is the most significant health event in our society. In addition the diagnosis of cancer remains the most feared in our community with enormous psychological effects on patients, their families and friends.

Screening programmes to prevent cancer are well established in breast, cervical, testicular and prostate cancer but is less accepted for gastrointestinal cancer. This might be explained by patient's reluctance to discuss G.I. symptoms but it is essential that patients don't die of embarrassment.

Several criteria have been put forward for successful screening. Screening should be directed towards diseases which are relatively common in the population. The condition to be screened should have a high morbidity and mortality, it should be identified at an early or pre-symptomatic stage by a suitable screening test and earlier treatment at a pre-symptomatic stage should benefit the affected patient. In addition, a screening program for disease would need to be cost-effective.

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COLORECTAL CANCER SCREENING

Colorectal cancer is an ideal disease to be screened. It is the second most common cancer after lung and is the most common fatal malignancy in non-smokers. Colorectal cancer arises from a benign process, an adenoma or a polyp. A polyp is probably present for 10-20 years before it becomes malignant. Not all polyps become cancerous and it is not possible to predict with certainty which ones carry a malignant potential. However, in general, if polyps are multiple or larger than 1cm in diameter malignant change is more likely to occur.¹ The finding of a polyp in the distal colon increases the chances of finding a polyp or cancer in the proximal colon.² Furthermore, although distal hyperplastic polyps have been considered to be of little significance, there is data to suggest that their presence also increases the risk of developing a cancer in the proximal colon.² If polyps are detected they can be removed by colonoscopic polypectomy. The knowledge that colorectal cancer starts as a benign process has stimulated an interest in screening to prevent colorectal cancer. In addition, numerous studies have shown that if colorectal cancer is detected early it can be cured.

There are many guidelines approved by national cancer and gastroenterological societies.^{3,4} Standard recommendation include annual testing for faecal occult blood (FOB) and flexible sigmoidoscopy every 5 years after the age of 50 years for persons at average risk of colorectal cancer. This has been approved for reimbursement by insurers in the US. Screening with the use of colonoscopy was approved for reimbursement only for those at high risk for colorectal cancer. Randomised controlled clinical trials have shown that screening programmes based on faecal occult blood (FOB) testing are effective in reducing colorectal cancer mortality. Biennial FOB testing over a 10-year period reduced colorectal carcinoma mortality by 15% and 18% in two European population based trials.^{5,6} In the Minnesota trial, annual testing of

volunteers aged between 50 and 80 years reduced mortality by 33%.⁷ The mortality data from an ongoing fourth European trial are awaited. Meta-analysis of all trials to date indicates that mortality is reduced by approximately 16% in those randomised to screening.⁸ Furthermore, a recent US study indicates that screening with FOB is cost effective. The cost of lifetime screening for a cohort of individuals 50 years of age is in the region of \$10,000 per life-year saved.⁹ This figure is well below the commonly used limit of \$40,000 per life-year saved, below which a screening intervention is considered cost-effective.

There are, however, a number of problems with FOB testing which may limit its use in population based screening programmes. The true sensitivity of the technique may be as low as 30%.¹⁰ Furthermore, efforts to increase sensitivity in the Minnesota trial by rehydrating specimens prior to testing resulted in an unacceptably high false positive rate without any gain in the number of cancers detected.⁷ Compliance with FOB testing is also a problem. In the two European population-based studies only about 60% of eligible subjects participated in the first screen.^{5,6} In addition, although FOB screening might be expected to detect adenomas, all three published trials showed that screening had no effect on cancer incidence. In all cases reduced mortality was secondary to earlier detection and treatment of established colorectal cancers in the screened population.¹¹

Screening for stool markers more accurate than faecal occult blood could improve screening outcomes and there is a strong biological rationale for targeting DNA alterations exfoliated from neoplasms.¹² DNA is released continually into the faecal stream. The DNA comes from the neoplasm itself and exfoliation from cancer is much greater than normal mucosa. Genetic alterations are potential targets for assays. DNA is stable in transit and storage.¹² Recovered faecal DNA can be amplified a billion-fold by polymerase chain reaction before it is measured. Targeting single mutations of the K-ras oncogene with this technique can detect 50% of colorectal cancers. Diagnostic accuracy can be improved if multiple cancer-associated mutations are assayed.^{12,13} The technique can detect some but not all polyps.¹² Methods that can reliably detect polyps as well as cancer are needed if this approach is to be accepted.

Since FOB tests have limitations, complementary use of flexible sigmoidoscopy has been recommended. Retrospective case-controlled studies provide the best evidence that sigmoidoscopy prevents colorectal carcinoma. Selby et al studied 261 patients who had died of this

disease. Only 9% had undergone sigmoidoscopy compared with 24% of 868 age and sex matched historical controls.¹⁴ The adjusted odds ratio of 0.41 implies that sigmoidoscopy reduces the risk of death from carcinoma "within reach of the scope" by about 60%, a conclusion supported by two other case-controlled studies.^{15,16} The sensitivity of sigmoidoscopy for left sided lesions is high. Prospective studies indicate a sensitivity of at least 90% for left sided polyps with significant neoplastic potential (adenoma > 1cm). Furthermore, screening is likely to be cost effective. In a cohort of individuals 50 years of age sigmoidoscopy carried out at 3 to 10 year intervals has been estimated to cost \$8,000 to \$20,000 per life-year saved, well below the \$40,000 cut-off⁹ (vide supra).

Paradoxically, the best argument against screening sigmoidoscopy may be its predicted efficacy. If 60% of cancers "within reach of the scope" can be prevented, why not examine the entire colon and prevent this percentage of all colonic carcinomas? The case for screening by colonoscopy is strong. One large US study showed a 75-95% reduction in the incidence of colorectal cancer in individuals undergoing regular colonoscopy with polypectomy compared to historical controls.¹⁷ Recent data from a large group of asymptomatic individuals undergoing screening colonoscopy provides further support for the use of this modality in preference to sigmoidoscopy. Colonoscopy detected a high incidence of adenomas and carcinomas in this group with one third of significant advanced lesions present in the right colon.¹⁸ Flexible sigmoidoscopy as a screening method is as illogical as screening one breast in a breast screening mammography. Furthermore, recent data comparing colonoscopy with radiological techniques of imaging the entire large bowel shows it to have a far superior sensitivity for detecting significant colorectal lesions.^{19,20} The recognition of flat adenomas as cancer precursors may further increase this advantage.²¹

Three potential problems with screening colonoscopy may be envisaged; high cost, possible low compliance with the test and procedure related complications. However, data modelled on a cohort of 50 year old individuals indicates that although colonoscopy is more expensive than either FOB testing or sigmoidoscopy it may still be a cost effective screening technique (estimated cost \$9,000 to \$22,000 per life-year saved).⁹ Compliance may be a real problem; in one study, less than 15% of medical personnel invited by mail to undergo a screening colonoscopy accepted the offer.²² Clearly public education will be required. Procedure related mortality is in fact low, with 1-3 deaths per 10,000 examinations and

might be expected to be even lower in a relatively young and fit "screening" population.³

The age of onset and interval of colonoscopic screening remain controversial. Based on current knowledge of the demographics of colorectal carcinoma and the chronobiology of the adenoma-carcinoma sequence, it has been proposed that an initial colonoscopy be carried out at age 50 years with repeat colonoscopy at 3 years if adenomas are detected and successfully removed. Repeat colonoscopy at 10 years may be appropriate if initial colonoscopy is normal.³

In the European context, population-based colonoscopic screening has huge cost implications for government. It may be more appropriate to try and increase the yield of significant lesions on screening colonoscopy (and, therefore, increase the cost-effectiveness) by targeting high-risk groups. Such subjects can be readily identified on the basis of family history. Individuals with a single first degree relative under 60 years of age with a colonic polyp or carcinoma have a 1:10 lifetime risk of developing a colorectal carcinoma. With two affected relatives the risk rises to 1:6. Therefore, relatives of patients under 60 years of age with known adenomas or carcinomas could be offered screening colonoscopy. In view of the natural history of the disease it would seem reasonable to commence screening at an age 10 years younger than the age of onset of disease in the index case. Indeed, it may be appropriate to have two screening strategies running in parallel with screening colonoscopy for high risk individuals identified on the basis of family history and annual FOB testing for individuals at average risk. For the high-risk group a detailed family history taken at an initial clinic visit would allow definition of families requiring genetic counselling and genetic testing on the basis of recognised criteria.²⁴ The case for screening colonoscopy is particularly strong in familial forms of colorectal carcinoma. Proximal cancer is more common in these cases and the prognosis is generally good.²³

Colorectal cancer is a common, fatal disease. An overwhelming body of evidence implies that the disease is preventable. On the basis of this evidence, the setting up of some form of population-based screening programme may reasonably be considered mandatory in Western societies.

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