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Screening for Colorectal Cancer

AFTER CARCINOMA of the bronchus, colorectal cancer kills more people than any other malignancy in the developed Western world. Currently, more than 24 000 new cases and 17 000 deaths from the disease are being reported in England and Wales annually [1]. Prognosis is largely determined by the extent of spread of the disease at presentation, corrected 5-year survival figures of 30–40% reflecting that the majority of patients still present with lymph node or distant metastases [2]. Slight improvements in survival have been matched by an increasing incidence of the disease in Great Britain so that death rates have changed little for 40 years. Public health measures to reduce disease incidence require a greater understanding of aetiological (probably largely dietary) factors as well as a willingness by the population to accept changes in lifestyle. They are unlikely to have any impact for decades. While recent reports of perioperative radiotherapy and chemotherapy are encouraging for Dukes' B and C tumours, currently the most promising potential method for improving disease prognosis would seem to be screening for asymptomatic early stage disease.

The basis for screening relates to the biology and natural history of the disease. There is widely accepted evidence that most colorectal cancers slowly develop in stepwise fashion from normal mucosa through enlarging adenomatous polyps to localised surgically curable malignancy, eventually culminating in disseminated incurable disease [3, 4].

The process of screening aims to preferentially detect large adenomas and early cancers by the investigation of certain asymptomatic individuals selected from a large population by a positive screening test, their treatment leading to both a reduction in mortality from colorectal cancer as well as a decrease in its incidence.

The incidence of colorectal cancer increases exponentially with age, those over 50 years old making up only 37% of the population yet accounting for 95% of cases and more than 96% of deaths [1]. To be cost-effective, screening needs to be applied to this older age group (average risk) unless other risk factors for colorectal cancer apply. Of particular interest among high-risk groups are those with genetically determined cancer. The recognition of phenotypic markers (hypertrophy of the retinal pigment epithelium and mandibular osteoma) for familial adenomatous polyposis (FAP) as well as the recent availability of linked DNA markers has allowed for greatly improved prediction of level of risk for family members. However, this condition represents only 1% of all colorectal cancer cases. A recent endoscopic study of 640 relatives of 34 patients with sporadic colorectal neoplasia suggests that 19% of all colorectal neoplasias might be genetically determined [5]. It may be that appropriate genetic markers, determined from a simple blood test, will be able to stratify a population at average risk into those with a particularly high risk who could be offered screening and those at lower risk where risk outweighs benefit. The principle of stratifying broad risk groups is illustrated by a longitudinal study of 1618 patients with rectosigmoid adenomas followed for a mean of 14 years—those with tubular adenomas < 1 cm (43% of the series) were found to be at no increased risk of subsequent colon cancer in contrast to those with larger, more villous polyps [6].

A screening test should be inexpensive, rapid and simple and is not intended to be diagnostic, those with positive tests requiring further evaluation. The use of symptom questionnaires is ineffective because colorectal symptoms are common and poorly predictive and because the presence of symptoms may signify more advanced disease. Digital rectal examination will detect no more than 10% of cancers while rigid sigmoidoscopy will adequately visualise only the distal 16 cm [7] allowing detection of, at most, 40% of all colorectal cancers. The method is further disadvantaged by the fact that it is unpleasant and inconvenient. However, an uncontrolled study of 26 000 subjects undergoing rigid sigmoidoscopy found 58 cancers, 81% of which had no evidence of lymph node or distant metastasis, with 90% 15-year survival [8]. Furthermore, a recent case–control study of the efficacy of screening sigmoidoscopy in the setting of regular health checks has shown a significant 70% reduction in death from rectosigmoid (but not colon) cancer [9]. Following a simple enema, fibreoptic flexible sigmoidoscopy (FOS) allows

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direct examination of the distal 30–60 cm, where 70% of cancers and large adenomas are found. Though more costly, it is better tolerated than rigid sigmoidoscopy and yield is significantly greater [7]. Logistic problems of population screening by this means may be overcome by training nurse or GP endoscopists in the use of the shorter and safer 35 cm endoscopes. Colonoscopy is the gold standard for assessment of large bowel mucosa but it is a labour-intensive, expensive examination with a serious complication rate (perforation and haemorrhage) of 0.2% precluding its use in population screening. It is the means of surveillance of choice for high-risk patients, particularly those with long-standing ulcerative colitis and those from hereditary non-polyposis syndrome kindreds. The ability to carry out snare polypectomy at the same time as diagnosis makes it particularly suited as the secondary investigation of subjects with positive faecal occult blood (FOB) tests.

In 1971, Greegor reported 12 cases of 'silent' colon cancer detected by the use of guaiac impregnated slides [10]. Since then, guaiac-based FOB tests, in particular Haemoccult^{R} (Rohm Pharma), have become the most widely evaluated means of population screening for colorectal cancer. The test detects the peroxidase-like activity of haematin in faeces. A significant drawback is the interference from ingested animal haemoglobin and from certain vegetables (broccoli, cauliflower, parsnip) containing naturally occurring peroxidases. While normal blood loss from the gastrointestinal tract is approximately 1 ml per day, Haemoccult will detect losses of 10 ml per day or more in 67% of cases [11]. Because of substantial overlap between normal and pathological bleeding, this allows for reasonable test sensitivity without resulting in large numbers of false positive results and hence low specificity. By specifically detecting human haemoglobin, immunological tests avoid the problem of dietary interference and are potentially more sensitive. False-positive reactions from upper gastrointestinal tract bleeding (because of rapid digestion of haemoglobin in the stomach and small bowel) are also less likely although this may be offset by higher detection rates of innocent perianal bleeding. These tests are being simplified and warrant further investigation.

Several studies and programmes around the world to evaluate screening with the chemical FOB test, Haemoccult, confirm its potential [12–16]. They appear to have similar rates of positive reactions for unrehydrated slides (1.0–2.4%), similar predictive values for neoplasia (22–58%) and a significant shift towards Dukes' stage A cancers (50–53% in the screened group vs. 9–13% in the control group for the European studies). Furthermore, the high proportion of Dukes' A tumours is maintained during later rounds of screening when the majority of the slow growing prevalent cancers will already have been diagnosed. All data indicate an improved sensitivity for cancers after rehydration (addition of a drop of water to the slide before development) but, because of loss of specificity when the tests are rehydrated (positive rate 6.1–10.2%) [12, 13], this practice is not cost-effective. Sensitivity can only be measured indirectly by assessing the proportion of cancers presenting in the interval between tests and is estimated at 50–70%, the rectum and caecum being the sites where cancers are most likely to be missed. Complete evaluation of the colon is necessary and has been achieved in more than 90% of cases within the trials. It is disturbing that, in a large, media-advertised mass screening programme in Cleveland, Ohio, of 1356 patients whose physicians responded to a questionnaire relating to further investigation of their Haemoccult-positive patients, 35% did not undergo either colonoscopy or barium enema [17] illustrating the need for physician as well as patient education. Survival data is only available for two studies. In New York, a 43% reduction in mortality from colorectal cancer after 10 years of follow-up was observed in the screened group who differed from the controls only in being offered the Haemoccult test. However, the groups were non-randomly allocated, limiting the conclusions that can be drawn from this study [14]. The randomised controlled study from Funen in Denmark has reported an 18% reduction in deaths from colorectal cancer in the test (58 deaths) compared with control (71 deaths) groups but this failed to reach statistical significance [15]. More prolonged follow-up is necessary for all the European studies. No data on reduction in disease incidence following polypectomy can be expected in the near future but it is encouraging that the adenoma yield is high in all studies. While more than 90% of prevalent adenomas are smaller than 1 cm, 63% of those detected by screening in Nottingham (8/1000 screened) have been larger than 1 cm [16]. The US Congress Office of Technology Assessment (OTA) has constructed a model of the cost-effectiveness of annual FOB test screening in a population from the age of 65 years using data and assumptions that were unfavourable towards screening. They found that it would prevent approximately 23 000 cases of colorectal cancer and provide 45 000 added years of life to that population of 2.1 million [18].

Even if screening is shown to be effective, the magnitude of the effect must be sufficiently great to justify the cost to the nation. Mathematical models have provided estimates of cost-effectiveness and cost-benefit [19]. Ransohoff has suggested that it would cost $1200 million to screen the American population over the age of 50 [20] while the cost per cancer detected by Haemoccult in the Nottingham study has been estimated at less than £2700 [21], a figure which compares favourably with the costs of cancer detection by cervical smear or mammography. The more important figure of cost per life-year saved awaits publication of mortality data, though OTA have estimated the cost at $35 000, similar to the cost per year of life gained by breast cancer screening [18]. Psychological morbidity associated with colorectal cancer screening has so far recieved scant attention.

While Canada and most European countries have made no recommendations on colorectal screening, five national US expert groups have suggested annual FOB testing and 3–5-yearly flexible sigmoidoscopy for their population over 50 years. These differences reflect the different criteria for judging the available evidence. Protagonists argue that those people seeking regular health checks should be screened because the disease is common and lethal and the indirect evidence for benefit (interim data from the large randomised controlled trials) is substantial. Critics point out the medical risks and costs of screening which cannot be justified until an unequivocal mortality benefit has been shown [20].

Research into alternative serum, faecal or urine markers, possibly genetic, of the disease is required. Appropriate immunological FOB tests require assessment in representative populations. Since most interval cancers are left-sided, adding flexible sigmoidoscopy to Haemoccult screening may increase sensitivity and specificity for cancer detection. However, although the yield of adenomas would substantially increase, the majority would be smaller than 1 cm, leaving the problem of whether and how to survey them. Furthermore, the procedure is costly, time-consuming and may not be acceptable to the public. Another approach may be to offer a single colonoscopy at the age of 60. Because only 8% of adenomas > 1 cm progress to invasive

disease over 10 years [21], a clean colon at this age might mean that no further follow-up is needed. For high-risk group screening, the most pressing need is for methods to accurately quantify an individual's risk of subsequent cancer. Genetic markers may be useful in this respect. Screening may then be tailored according to individual risk either by changing the age at which screening starts, the frequency of testing or finally by employing more sensitive tests, either alone or in combination. The converse of this may be the identification of a population subset with a particularly low risk of the disease who do not need to be screened at all.

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Cathepsin D in Breast Cancer: A Tissue Marker Associated with Metastasis

BREAST CANCER kills via its metastatic potential and removal of a primary tumour is not always sufficient to cure a patient who may develop distant metastasis. Tumour size and node invasiveness are the most potent classical prognostic markers for predicting tumour aggressiveness. However, in 20–30% of node-negative patients, breast cancer will relapse and new predictive markers are required to help in making treatment decisions[1].

10 YEARS OF RESEARCH ON CATHEPSIN D IN ONCOLOGY

The first biologically active molecular markers used were oestrogen receptors (ER) and progesterone receptors which are now routinely assayed in the cytosol of primary tumours. Since about 30% of oestrogen receptor-positive tumours are unresponsive to hormone therapy, our laboratory searched for better hormone responsiveness markers and found a 52 kD protein secreted by metastatic breast cancer cell lines and

Editorial dedicated to the memory of William McGuire (San Antonio), a pioneer in the field of prognostic markers in breast cancer, who died on 25 March 1992.
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