Effect of subject age on costs of screening for colorectal cancer

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Abstract

Study objective—The aim was to estimate costs and yields of faecal occult blood screening and rescreening for colorectal cancer, for differing age cohorts.

Design—Cost and clinical data were used as the basis for modelling the expected costs, and cost savings, resulting from the treatment of screen detected cancers, as compared with cancers detected by symptomatic presentation.

Setting—Data were derived from the MRC screening trial currently in progress in Nottingham.

Participants—Approximately 140 000 subjects, age 50–79 years, were randomly allocated to a test (screened) and a control (unscreened) group.

Main results—The net costs of detecting and treating a cancer following colorectal screening fall as the age of the target population increases, owing principally to the increasing incidence of the disease with age. Generally, the marginal detection and treatment cost falls for all age groups with the first screening round, but rises considerably with the second. If allowance is made for cancers prevented as a result of early detection and excision of adenomas, the costs of screening are substantially reduced for all age groups.

Conclusions—Assuming a cost per QALY (quality adjusted life year gained) equivalent to that derived for the breast cancer screening programme, and a QALY gain from colorectal screening of one year, three screens, each separated by two years, appear economically justified for populations aged 60 years and above. Expected gains from cancer prevention make two screens justifiable for those between 45 and 59 years of age.

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As a contributor to cancer related mortality in Europe and North America, cancer of the large bowel is second in significance only to lung cancer.1 However, if carcinomas can be detected and treated at a sufficiently early (and generally presymptomatic) stage, improvements in survival rates and in patient life expectancies may be anticipated.2 In recent years, the development of faecal occult blood testing and endoscopic investigation has made the mass screening of asymptomatic individuals a practical possibility, and several randomised controlled screening trials are currently under way. Research in the USA has suggested that one in four new cases of colorectal cancer will occur in people with a family history of the disease, a small fraction of this subgroup occurring in individuals with genetic disorders such as familial polyposis.3 Age also appears to represent the dominant risk factor, as evidenced by incidence rates for symptomatic colorectal cancer. In England and Wales, for example, incidence rises from 20 cases per 100 000 for those aged 45–49 years to in excess of 400 per 100 000 for those aged 80 years and above.4 Accordingly, the age range of subjects selected for colorectal cancer screening trials is generally from 45 or 50 years up to 75 years. This range is determined by considerations of incidence (lower age limit) and the ability to undergo treatment (upper limit).

To date, the economic evaluation of colorectal screening in terms of subject age has been neglected—the only published report indicates that beginning screening at age 40 rather than 50 years of age would be likely to produce little benefit but would double the cost of a lifetime screening programme.5 However, age effects have been considered in other screening applications, and with significant findings. Opportunistic cholesterol testing, for example, has been costed at £200 per quality adjusted life year gained (QALY) for men, aged 40 to 69 (with diet therapy), but at £14 150 per QALY for men aged 25 to 39.6 An evaluation of breast cancer screening for women aged 40–49 years has also been conducted, predicting increases in life expectancy for those screened but at very considerable cost.7

The present paper is based on data from the colorectal screening trial presently under way in Nottingham, England.8 To date, this trial has recruited approximately 140 000 subjects in its control and study groups, making it by far the largest randomised controlled colorectal screening trial currently in operation. The aims of this paper are, first, to provide an order of magnitude estimate of the costs of detecting and treating a cancer by colorectal screening for different age ranges and, second, to assess the benefits which would have to result to make the implementation of colorectal screening economically justifiable.

Methods

Were mass screening for colorectal cancer for the 45–75 year age range to be introduced into the United Kingdom, it would involve the recruitment of approximately 17 million subjects. We shall assume that the screening protocol would be broadly similar to that employed in the Nottingham trial, and that the results of this trial may be generalised to the population at large.
Thus, screening targets would be issued with a Haemoccult™ faecal occult blood test which they would be asked to complete by depositing stool samples collected over a number of days on guaiac impregnated paper. Samples would be returned to the test centres for development. The addition of a reagent produces a characteristic colour change in the presence of occult blood in the stool, itself an indicator of bowel abnormality. Subjects with positive test results would receive a confirmatory diagnostic investigation, principally colonoscopy. Initially, the Nottingham trial experimented with both three day and six day occult blood testing, although, for reasons which will become clear shortly, it now employs only three day tests. Compliant subjects would be offered three day faecal occult blood retesting every two years, as has occurred throughout the trial.

Viable trial data currently exist for three screening rounds. These comprise data relating to (1) subject compliance—the proportion of tests issued which are completed and returned for development; (2) positive rate—the proportion of completed tests which prove positive on development; (3) the cancer yield, from which may be derived the detection rate (yield per test completed). These data form parameters for a model previously developed, from which the average variable costs of cancer detection by screening in a population of asymptomatic individuals may be estimated. This model employs 1989–1990 costs of labour, capital, and disposables employed in faecal occult blood testing and follow up investigation, based on an “average” Family Health Service Authority (FHSAs) area of 75,000 target individuals. The FHSAs, we assume, would form the basic building blocks of a national screening programme.

As originally constructed, the model generated gross costs of cancer detection by screening, to which must be added, for present purposes, the expected costs of cancer treatment. We have used a treatment cost equivalent to 17 days of inpatient stay, an estimate determined by an earlier Nottingham study. Of particular relevance in the present context, however, are net costs. The alternative to detection by screening is the detection by symptomatic presentation, which would require both a confirmatory diagnostic investigation and a course of treatment similar to that employed under the screening protocol, albeit at some point in the future. As the time interval between the development of a cancer and its symptomatic presentation is not known with certainty, we have estimated these latter costs assuming both a two year and a five year presentation lag, ie, the costs of future symptomatic presentation and treatment have been discounted over these time intervals. The net cost of detection and treatment by screening is accordingly the difference between (1) gross detection and treatment costs incurred in the present, and (2) discounted future investigation and treatment costs.

Faecal occult blood screening is capable of detecting two forms of neoplasia, adenomas, which are benign tumours, and carcinomas, which are malignant. The significance of this property of the test lies in the accepted belief that a high proportion of colorectal cancers arise in adenomas, and that an adenoma therefore possesses some finite probability of becoming malignant over time. During investigative colonoscopy, adenomas may be excised as part of the procedure, at minimal additional cost. The routine excision of adenomas detected during screening therefore implies that screening has an important role in cancer prevention.

A model has been developed of adenoma malignancy probabilities over time using published data on the long term follow up of adenomas in excess of 1 cm in diameter. Thus, for example, it has been shown that an adenoma patient with a 20 year life expectancy has a 25% chance of developing a malignancy in the adenoma. Using trial data on adenoma yield by five year age cohort, it is thus possible to model the number of cancers likely to develop within the expected lifetimes of the patients. Yield can therefore be reinterpreted as cancers both detected and prevented and costs calculated in a manner equivalent to that for detection alone. The prevention variant also makes an additional allowance for cost savings on all future investigations and treatments which would have been required, had the adenomas been allowed to develop and present as cancers.

Results
The trial data relevant to our cost estimates appear in table I. They were originally collected for five year age cohorts and then pooled into the three age ranges, because the very low prevalence of neoplasia gives rise to yields in five year cohorts too small to demonstrate statistical significance. The data show that compliance increases with each screening round and that it peaks in the middle of the target population age range. Both positive tests and detection rates increase with age, but decrease as the number of rescreens increases. These findings are broadly in agreement with those of the Danish trial which has a similar protocol to that employed in Nottingham.

With respect to the initial three day screen, differences in the number of cancers detected in the three age ranges are statistically significant ($\chi^2$ at 5%). More cancers, in other words, are detected in older age ranges, as would be expected from the symptomatic incidence data presented earlier. For six day testing, the ≥70 years yield is significantly different from the other two age ranges. The difference between the 45–59 age range and the other two is significant (at 0.5%) in the first rescreen. Relatively fewer additional cancers are accordingly detected by rescreening the younger age group. The inclusion of prevented cancers does not affect the significance of the differences between yields except in one respect—the yield difference for the first two age groups on the initial screen now becomes insignificant.

Finally, it should be noted that both cancer and adenoma yields from six day and three day faecal occult blood testing on the initial screen are not significantly different from one another, reinforcing the conclusions of an earlier study. Moreover, the screening model has previously shown that six day screening costs are 24%, higher than those of three day screening. Accordingly, the six day screening option will not be considered further.
Table I  Nottingham trial data

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Tests sent</th>
<th>Compliance rate (°)</th>
<th>Cancers detected</th>
<th>Positive rate (°)</th>
<th>Detection rate (per 1000)</th>
<th>Adenomas detected</th>
<th>Cancers prevented</th>
<th>Prevention detection rate (per 1000)</th>
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<tr>
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Initial screen (3 day)

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<th>Tests sent</th>
<th>Compliance rate (°)</th>
<th>Cancers detected</th>
<th>Positive rate (°)</th>
<th>Detection rate (per 1000)</th>
<th>Adenomas detected</th>
<th>Cancers prevented</th>
<th>Prevention detection rate (per 1000)</th>
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<th>Adenomas detected</th>
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<th>Positive rate (°)</th>
<th>Detection rate (per 1000)</th>
<th>Adenomas detected</th>
<th>Cancers prevented</th>
<th>Prevention detection rate (per 1000)</th>
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<tr>
<td>All ages</td>
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</table>

Second rescreen (3 day)

It is conventional among economists to appraise the relative merits of health care interventions on the basis of the ratios of costs incurred to benefits obtained. At present, no definitive benefit or outcome measure to cover all interventions has become accepted, although the use of QALYs has been increasing in recent years. The merits of the QALY remain the subject of considerable debate18-22 and several alternative outcome measures exist.23 This having been said, the United Kingdom breast cancer screening programme was evaluated using QALYs as the outcome measure, and was implemented nationally on the strength of a per QALY of £3304 (1983-4 prices).24 As breast cancer screening would seem to be a natural comparator for colorectal cancer screening, the QALY measure will also be employed as an outcome measure in the remainder of this analysis. Thus we assume that, at prices updated to 1989-90, £4000 per QALY (or lower) would be deemed an acceptable cost for the implementation of colorectal screening. In other words, if it costs £2000 to detect and treat a colorectal cancer by screening, then at least six months of "full quality" life must be gained in order for the programme to be deemed worthwhile.

Table II presents the net costs of detecting and treating, and of detecting, preventing and treating, a cancer, by age cohort, for each of the three screening rounds. Each cost is presented as a range, determined by the assumption of a two year and a five year presentation lag (lower and higher figures, respectively). Against each cost is displayed the QALY gain necessary for colorectal screening to produce benefit/cost ratios at least equal to those of the breast cancer programme. As may be seen, costs are consistently lower for older age groups. For detection alone, the marginal cost of detecting and treating a cancer via screening falls slightly with the first rescreen for all age ranges (except the >70 year group), but rises considerably with the second. Note that the cost for the second rescreen of the youngest age group is undefined, as no cancers were detected in this group. The costs of detection and prevention together are very much lower than for detection alone, owing both to the higher overall cancer yields and economies on future treatment costs. In this case, marginal cost increases with the number of rounds for all age ranges.

**Discussion**

The Nottingham screening trial is continuing and will not be in a position to publish data on survival or QALY gains until the mid-1990s. A full evaluation of colorectal screening must therefore await these results. However, given the data in table II, it is evident that, for subjects aged 60 years and over, the necessary gains are considerably less than one QALY per case of disease detected for the initial screen and the first rescreen, and approximately 1.5-5 QALYs for the second. Allowing for cancer prevention in addition to detection reduces the necessary QALYs to below one or for all ages and for each of the three screening rounds (with the exception of the second rescreen for the youngest age group). The results of a widely cited mathematical model of cancer screening25 suggest that a policy of faecal occult blood testing at two year intervals, starting at age 50 years, increases the life expectancy of those who would develop colorectal cancer by 1.3 years. Care should be taken in interpreting these data since they are based on data drawn from a wide variety of sources of varying dependability. Nevertheless, if the predicted health benefit is of the magnitude suggested then colorectal cancer screening will cost (using the most unfavourable estimates) approximately £1370 and £1600 per life-year gained for the initial and first rescreen rounds respectively, rising to £2870 for the third
round. The sharp increase in cost beyond the first rescreen is grounds for believing that the time interval for this later round might profitably be extended to increase yield.

In terms of identifying the most efficient age group to screen, the effects of cancer prevention by adenoma excision are extremely important. Ignoring this effect would mean that it would be considerably harder to justify screening those younger than 60 years of age on economic grounds, especially beyond the first rescreen. In particular, no cancers have been detected in those aged under 50 years in either the Nottingham or the Danish trial, and a Swedish trial report has advocated 55 years as a lower age limit in view of low incidence at younger ages.26 Given the longer life expectancy of the younger group, however, there is a correspondingly higher probability that excised adenomas of 1 cm or more in diameter would have become malignant within their lifetimes. The importance of this effect naturally lessens as the age at which the adenoma is excised increases.

In the absence of "gold standard" data on the number of cancers missed on screening, faecal occult blood test sensitivity may be calculated by assuming that all cancers presenting symptomatically in the two years following a negative test result were actually present at screening. The sensitivity of the three day HaemoccultTM as estimated from two year follow up data is presented in Table III, the overall sensitivity across all three rounds being 69-6%. Sensitivity appears to decrease with the number of screening rounds, and this result is to be expected. The initial screen clears many of the prevalent asymptomatic cancers in the population, possibly those of a slow growing nature. Rescreen results are progressively more heavily based on incident cancers, a larger proportion of which will be aggressive, fast growing tumours more likely to present as "interval" cases, i.e., between screening rounds. Comparable results cannot be presented for adenomas, owing to the absence of any assessment of adenomas missed by screening. One study,27 however, has shown that sensitivity is positively associated with adenoma size, implying that HaemoccultTM is more likely to detect the adenomas with the higher probability of becoming malignant.

The employment of a more sensitive faecal occult blood test would have beneficial effects on average costs for all age ranges, by virtue of higher yields.9 Indeed, the Swedish colorectal trial has experimented with the rehydration of occult blood tests prior to development, a technique shown to enhance sensitivity at the expense of specificity.20 Owing to the concomitant rise in the cost of unnecessary investigations, however, average detection costs are higher than for a regimen using non-rehydrated tests.28 The use of more sensitive faecal occult blood tests in place of HaemoccultTM may be possible in the future, although at present their higher costs do not compensate for their higher yields.29

A strategy not considered so far involves extending the target range into age groups outside the 45-75 year limits specified in the Nottingham protocol. For the under 45 population, adenomas of 1 cm or more in diameter would stand a very high chance of eventually becoming malignant. However, data from necropsy studies are presently insufficient to judge whether the likely yield would justify the costs incurred. Subjects over 75 years of age have too short a life expectancy to benefit greatly from adenoma excision—for age 75-79 years the probability of preventing a cancer is 6%, and for 80-84 year olds, 4%, according to the model employed above. Although cancer incidence increases dramatically in these age groups, the probability of someone of this age surviving a colonic resection correspondingly diminishes.30,31 It should be remembered that the necessary life-year gains quoted above are the average gains necessary per case; every operative death increases the necessary gain in the survivors. Screening this older age group may also encounter the problems of poor participation as noted earlier.

In the introduction, familial connection with an individual with colorectal cancer was cited as an established factor in selecting subjects for screening. Although not specifically investigated in this paper, this too is likely to have a bearing on the selection of the age range of the population targeted for screening. If, as has been suggested,32 first degree asymptomatic adult relatives of large bowel cancer patients face a considerably increased risk of developing the disease, then the average cost of detecting a cancer by screening this particular high risk population would fall. The study cited reports an average detection cost of approximately 30% when screening a familial risk group as opposed to a control group without such risk. Significantly, the former recruited subjects from the age of 35 years, the latter from the age of 50 years, thereby supporting a case for screening younger age ranges in circumstances of known familial risk.

Conclusion
Assuming that the detection and treatment of presymptomatic cancers as a result of screening is capable of generating one additional life-year of full quality, a programme of screening for those aged 60 years and over—two rounds separated by two years—appears justifiable in economic terms. The screening of the under 60s would only be justified with higher gains in life expectancy, while a second rescreen would only be economic for those aged 70 years and above. Taking account of cancers prevented, however, the screening of the 45-60 age group becomes viable, as does a second rescreen for the 60-69 age group.

This research was conducted within the Nottingham colorectal cancer screening trial, codirected by Professors J D Hardcastle and J O P Chamberlain (Institute for Cancer Research). The trial is funded by the Medical Research Council.

Table III  Sensitivity of faecal occult blood testing (%)

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Initial screen</th>
<th>First rescreen</th>
<th>Second rescreen</th>
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<tr>
<td>45-59</td>
<td>75.0</td>
<td>44.4</td>
<td>0.0</td>
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<td>All ages</td>
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Cost of screening for colorectal cancer