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ECONOMIC EVALUATION

FAECAL OCCULT BLOOD SCREENING FOR COLORECTAL CANCER: IS IT COST-EFFECTIVE?

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SUMMARY

Recently published evidence from two large-scale clinical trials conducted in England and in Denmark suggests that faecal occult blood screening for colorectal cancer significantly reduces mortality. However, before screening can be advocated as part of national health policy, its cost-effectiveness must be demonstrated. The English screening trial has been the subject of a detailed economic evaluation over the past 10 years. In this paper, cost-effectiveness estimates of screening are presented, based on cost and outcome data combined in a mathematical model developed from the trial's clinical findings. The estimates of cost per quality-adjusted life-year gained from colorectal cancer screening show the procedure to be of similar cost-effectiveness to breast cancer screening in the short term. Over the longer term, however, the estimates for colorectal cancer screening appear superior. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — colorectal cancer; cost-effectiveness; cost-utility; economic evaluation; faecal occult blood test; mathematical model; screening

INTRODUCTION

From the point of view of health care policy, colorectal cancer meets the World Health Organization's requirements for suitability for mass population screening.[1] Colorectal cancer is clearly an important health problem, being the second most common cause of cancer mortality, after lung cancer, in North America and the majority of countries of Western Europe.[2] It has a defined natural history with recognized early stages, including a pre-malignant adenoma phase.[3] Surgical treatment at the early stages of malignancy has been shown to be effective in improving survival rates.[4] An inexpensive and acceptable test for the presence of the faecal occult blood (FOB) associated with both malignant and benign lesions has become available,[5] a test which may be re-applied to the population at reasonable intervals. Parallel advances in fibre-optic endoscopy have facilitated the accurate confirmatory diagnosis of positive FOB tests.

The recently-published evidence from two large-scale European randomized controlled trials (RCTs) strongly supports the view that routine FOB screening is effective in reducing mortality.

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The English trial,[6] based in Nottingham, and the Danish trial,[7] based in Odense, were each initiated in the early 1980s and have employed essentially similar protocols. In both cases, asymptomatic subjects were drawn from the general population and randomly allocated to study and control groups of approximately equal size. Between them, the two trials recruited more than 200 000 subjects. Those in the study groups were offered Haemoccult FOB tests biennially and positive test results were investigated by colonoscopy. On the basis of mean periods of follow-up of approximately 8 and 10 years, respectively, each trial reported statistically significant reductions in cumulative colorectal cancer mortality in their study groups, in comparison with their controls, of the order of 15 and 18%, respectively. Neither trial managed to demonstrate an overall significant survival increase although, given that deaths from colorectal cancer accounted for only 3.2% of combined trial mortality, such a result is unsurprising.

By itself, evidence of effectiveness in reducing disease-specific mortality is insufficient to justify the implementation of a national mass population screening programme. It is obvious that any mortality reductions which might result from screening can only be obtained at some positive cost. In all health care systems, resources are scarce and might, in principle, be allocated to any one of a number of competing health care ends. Therefore, to be deemed a priority from the point of view of public health care policy, any new programme must prove itself to be not simply effective but cost-effective in relation to other possible programmes. Assessments of the potential cost-effectiveness of FOB screening have already been undertaken,[8,9] although these were not based on RCT evidence. In the case of the Nottingham trial, a parallel economic evaluation has been conducted over the past 10 years and this paper presents the results of the evaluation.

METHOD

Economic evaluations may be conducted in any one of a number of ways, two important and defining characteristics being form and viewpoint.[10] With respect to form, we have chosen to present our evaluation results in terms of 'additional cost per quality-adjusted life year (QALY) gained' as a result of screening according to the Nottingham trial protocol. The analysis is thus technically one of cost-utility, rather than cost-effectiveness. With respect to the viewpoint or frame of reference, the costs included in our estimates comprise all those likely to be incurred by the UK National Health Service (NHS) in colorectal cancer detection and treatment, whereas the benefits — survival gains — accrue to patients. Both the chosen form and the chosen viewpoint are relatively common in UK economic evaluations,[11] although our choices were guided principally by one specific consideration. Cost-utility and cost-effectiveness are relative rather than absolute concepts and any one evaluation therefore requires a comparator. The UK breast cancer screening programme seemed to us to represent the most obvious comparator for colorectal cancer screening and we therefore chose the same form and viewpoint as used in that programme's evaluation.[12] Although debate persists over the merits or otherwise of discounting survival gains in economic evaluations,[13,14] the expected gains in our study were discounted at the same rate as costs, again following the approach of the breast cancer evaluation.

The cost-utility estimates were calculated using a mathematical model of the screening process and cancer progression.[15] The primary clinical data for this model were derived from the accumulated results of the trial, supplemented, where necessary, by literature values. The primary cost data derived from a series of audits of resource usage for trial subjects which had been conducted for each stage of the screening and treatment process — invitation and FOB testing, diagnosis and investigation, treatment and follow-up. For example, an early goal of the economics research programme was to model the likely resource costs of employing the Nottingham protocol, involving Haemoccult FOB tests and the colonoscopic investigation of positives, in a real-world context.[16] In turn, these cost estimates rested on assessments of the cost of diagnostic procedures.[17] We subsequently initiated a study to evaluate the hospital costs of treatment by cancer stage within the two trial arms.[18]

The administrative structure of the Nottingham screening protocol is outlined in Fig. 1. Subjects drawn from a target population aged between 50 and 74 years were sent FOB tests with invitations to complete and return. Those complying and testing positive were offered a second test to be

completed under a specified regime of dietary restriction (the Haemoccult test is known to be sensitive to the presence of peroxidase in, for example, red meat). Of this group initially testing positive, those remaining positive at the second FOB test proceeded to investigation, whilst those now testing negative were offered a third FOB test. Those exiting from the screening protocol without treatment were returned to the screening pool, to be re-invited on a biennial basis.

The mathematical model of the screening process is semi-Markovian and encompasses the following possibilities for disease progression. In theory, the screening of asymptomatic subjects might be expected to reveal the presence of:

(i) a pre-symptomatic cancer or adenoma which, without screening, would have become clinically detected;
(ii) a slowly-developing adenoma or carcinoma which, in the absence of screening, would never have been detected in the subject's lifetime;
(iii) adenomas which would not have progressed to carcinomas;
(iv) no abnormality, such subjects remaining in the screening cohort until exit or death.

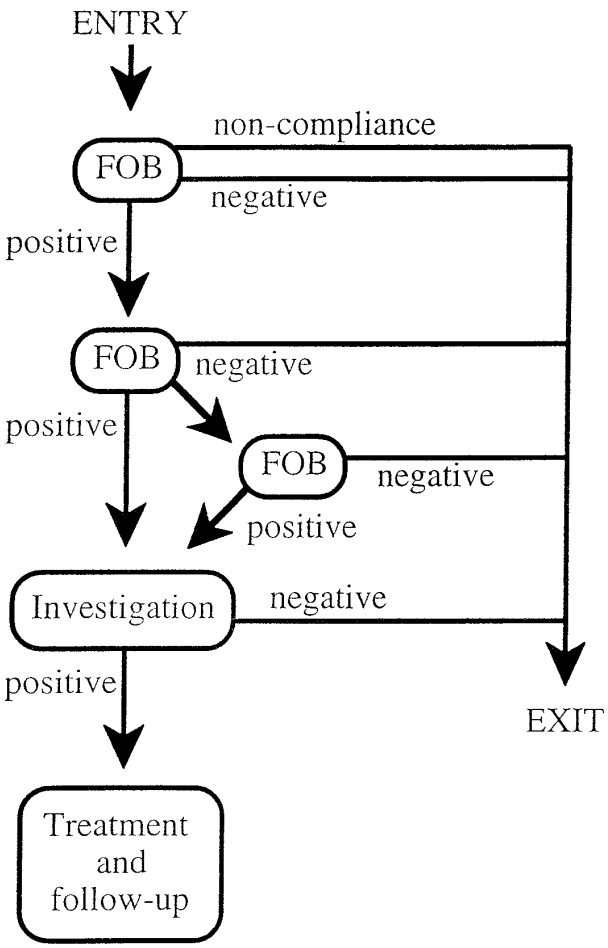

Figure 1. Nottingham screening protocol.

For all four possibilities, the screening programme entails net costs, although survival benefits would only be expected in case (i).

The model itself comprises three sectors. The first begins by calculating the expected number of cancers occurring in a reference (unscreened) population with a given age/sex distribution and yields the expected number of life years lost from normal life expectancy as a result of the disease. Following the imposition of the screening modality, estimates are then made of the reduction in annual disease incidence occasioned by screening. Such a reduction will come about as a result both of cancer detection at earlier stages and adenoma excision, which prevents the subsequent onset of cancer in a proportion of cases. Again, expected life years lost under the screening modality are calculated and, from these combined results, year-by-year survival gains from screening are estimated.

Disease incidence by stage thereafter determines expected treatment costs over time.[18,19] This first sector also estimates the number of cancers and adenomas detected in each screening round, and also the number of subjects passing through to subsequent rounds. These outputs of the first sector drive the calculations in the remaining two. The second sector calculates the year-by-year costs of screening, diagnostic investigations, polypectomy and adenoma surveillance, whilst the third calculates the costs of detecting and treating lifetime-latent cancers, those detected by screening but which would not have presented symptomatically during the expected lifetime of the subject.

Whilst the life-year gains as a result of screening are modelled from the trial data, the quality of life element of the QALY outcome measure was the subject of empirical investigations.[20,21] The QA estimate produced was within the range identified in the evaluation of breast cancer screening for women aged above 50 years.

Being based upon (and thus consistent with) trial data, the model, at the simplest level, permits cost-utility estimates to be made within the actual duration of subject follow-up thus far reported. Such estimates are presented below. However, the mathematical structure of the model provides the flexibility to simulate likely outcomes beyond the fixed parameters of the trial and the results of such simulations are also reported. First, the demographic structure of the UK, indicated by the 1991 Census, differs slightly from that of the trial population. For example, relative to the former, the older age groups are marginally under-represented. The results were accordingly re-estimated for a population with the UK's demographic structure, as this would be the realistic assumption were a national programme to be implemented. Second, the reported trial results are naturally truncated; not all subjects initially recruited had exited from the screening age range at the time of report. Our next simulation therefore entailed modelling the cost-effectiveness of screening up until the time when all subjects initially invited could be assumed to had died from colorectal cancer or from other causes.

Finally, the previous simulations follow the trial results with respect to compliance, which was observed to decline with screening rounds. It is difficult to assess, however, how compliance with an advertised and fully-operational national screening programme over the longer term could be expected to behave. Having been established since the late-1980s, our comparator — breast cancer screening — currently achieves 78% compliance in the Trent region[22] and it therefore seems reasonable to expect any future national colorectal programme to achieve higher compliance than that actually achieved in the trial context. Accordingly, we re-estimated the cost-utility results using different compliance rate assumptions.

RESULTS

Table 1 presents the cost-effectiveness (cost-utility) results for five related simulations, expressed as costs and outcomes per 100 000 subjects. Simulation 1 rests squarely on the reported trial results.[6] It presumes the screening of subjects aged between 50 and 74 years, using the sex-specific age distribution of the trial population and the reported age-sex-specific compliance rates for the initial screen. Costs and outcomes accruing beyond the reported follow-up period are not included. For simulation 2, the total population assumes the age/sex distribution for the general UK population (1991 Census), although compliance rates are as for the trial. Simulation 3 follows simulation 2, except that now lifetime costs and outcomes are considered. On publication of the trial results, no subject had received more than six screening invitations. However, with an upper age limit for screening set at 74 years and a mean life expectancy for women of approximately 80 years, it would be theoretically possible for a person of 50 years of age to be offered up to 13 biennial invitations and to be followed over some 30 years in total. Older subjects would face correspondingly few offers and could be subject to shorter periods of follow-up.

In simulation 3, age/sex-specific compliance rates in rounds beyond the trial period were assumed to continue to decline at the same rate as within the trial period. However, simulation 4 assumes that compliance falls to a plateau at round 4 (after 6 years) and is constant thereafter. For simulation 5, we investigated the effects of the initial compliance rates being higher and we have used the rates identified in the Danish trial as initial values. This trial achieved approximately 70% compliance overall in the first round.[23,24] Thereafter, compliance is assumed to fall by 10% for each subsequent round.

When total programme costs are dis-aggregated under expenditure category, only minor variations in proportion (< 1%) are evident between males and females. Under a no-screening scenario in simulations 1 and 2, cancer treatment costs comprise approximately 93% of total costs, the reminder being incurred due to adenoma removal and surveillance. Under simulations 3–5, cancer treatment costs become relatively more important (around 97% of total costs). With the introduction of screening, cancer treatment costs comprise 75–81% of total programme costs under the five simulations, of which costs of treatment for lifetime latent cancers amount to 3–5%. Adenoma treatment and follow-up continues to absorb 5–6% of total costs and FOB testing and investigation accounts for the remainder. As might be expected given the compliance assumptions, the proportion of test and investigation

Table 1. Costs (£, 1995–96) and outcomes (QALYs) for a cohort of 100 000 subjects

		No screening		Screening		Effect of screening		
Simulation	Sex	Total cost	QALYs lost	Total cost	AQLYs lost	Additional cost	QALY gain	Cost per QALY gained
1	Males	3 584 805	3097	5 048 143	2840	1 463 338	257	5685
	Females	3 766 250	3655	5 360 928	3333	1 594 678	322	4951
2	Males	3 733 468	3144	5 191 758	2887	1 458 290	257	5665
	Females	3 919 876	3750	5 511 926	3417	1 592 051	332	4791
3	Males	7 430 307	5217	8 608 945	4642	1 178 638	576	2047
	Females	8 055 650	6715	9 345 505	5774	1 289 855	941	1371
4	Males	7 430 307	5217	8 754 783	4595	1 324 476	623	2127
	Females	8 055 650	6717	9 524 538	5687	1 468 888	1030	1426
5	Males	7 430 307	5217	9 461 913	4307	2 031 605	911	2231
	Females	8 055 650	6717	10 111 505	5498	2 055 855	1219	1686

Table 2. Sensitivity analysis (percentage change from simulation 3 results)

Variation	Sex	Total net costs	Life-years lost	CE ratio
FOB cost increased by 10%	Males	2.8	0.0	2.8
	Females	2.9	0.0	2.9
Colonoscopy cost increased by 10%	Males	0.5	0.0	0.5
	Females	1.9	0.0	1.9
Double the cost differential between treating	Males	–6.9	0.0	–6.9
early- as opposed to late-stage cancer	Females	–9.2	0.0	–9.2
Annual screening	Males	28.7	33.2	–3.3
	Females	25.8	26.8	–0.8
Survival following early-stage detection	Males	0.0	–4.3	4.5
falls by 10%	Females	0.0	–1.7	1.7
Survival gains discounted at 3%	Males	0.0	72.6	–42.1
	Females	0.0	101.8	–50.4
FOB test sensitivity increased by 10%	Males	3.6	11.3	–6.9
	Females	2.1	9.9	–7.1
FOB test specificity falls by 10%	Males	104.1	–0.5	105.1
	Females	115.5	–0.3	116.2

costs in the total is highest in simulation 5 (20%, male/female average) and lowest in simulation 3 (13%).

Using base estimates from simulation 3, we undertook a sensitivity analysis, to judge the likely impact of plausible changes in key parameter estimates on the cost-utility estimates. These results are presented in Table 2. We thought it appropriate to examine the effects of changes in test and investigation costs and also in the cost premium resulting from early- as opposed to late-stage treatment. Both the English and the Danish trials reported relatively high rates of interval cancers in their study groups, of the order of 28 and 31%, respectively. An interval case is defined as one where the patient records a negative test result but subsequently presents symptomatically prior to the next offer of a test. The two principal factors behind the interval rate are less than perfect test sensitivity and rapid disease progression. It is therefore reasonable to argue that screening at more frequent intervals would be expected to increase the yield of screen-detected cancers, although at increased cost.[25] We accordingly consider the possibility of annual rather than biennial screening, which follows the protocol of a contemporary French trial.[26]

We also re-estimated simulation 3 allowing both for poorer survival gains from detecting cancer at an early stage and for the effect of

discounting benefits at a lower rate than for costs (3% as opposed to 6%). In view of the development work currently being undertaken with a view to improving the predictive quality of the FOB test,[27] we also investigated the effects of changes in FOB sensitivity and specificity.

The starting age for screening in Nottingham, 50 years, was established at the beginning of the trial, essentially on clinical grounds and simulation 3 accordingly follows a cohort comprising individuals aged ≥50 years until death. Figure 2 presents the cost-utility results of screening cohorts of 100 000 individuals, starting at ages below and above 50 years.

DISCUSSION

Four specific points may be made with respect to the results presented in Table 1. First, the effect of the departure of the trial's age–sex distribution from that of the UK population is evidently insubstantial, with only a minor difference in the cost-effectiveness ratios being apparent (simulations 1 and 2). Second, the results appear relatively insensitive to our differing assumptions regarding compliance (simulations 3–5). As we had earlier anticipated,[28] increased compliance increases cancer yield and survival gains, although at the expense of additional detection, treatment and follow-up costs and the effects appear largely compensatory. Third, for all simulations, the screening of females is more cost-effective than that of males, essentially owing to their longer life expectancy. Finally, and possibly of the greatest significance, lifetime cost-effectiveness ratios are noticeably superior to those obtained over the limited period of the trial (comparing simulations 2 and 3). Such a result is to be expected, given the nature of the screening process. Costs accrue in the short term whilst survival gains accumulate over a far longer period and the analysis of the truncated results (simulation 2) naturally understates expected yield relative to costs.

The sensitivity results of Table 2 point to the importance of both the cost and the predictive quality in the FOB test. FOB cost doubling, for example, would raise the cost-effectiveness ratios by around 30%. As had been observed earlier, high specificity in FOB testing is evidently imperative to avoid the otherwise-considerable costs of investigation of false positives.[29] The ratios themselves are clearly sensitive to the choice of

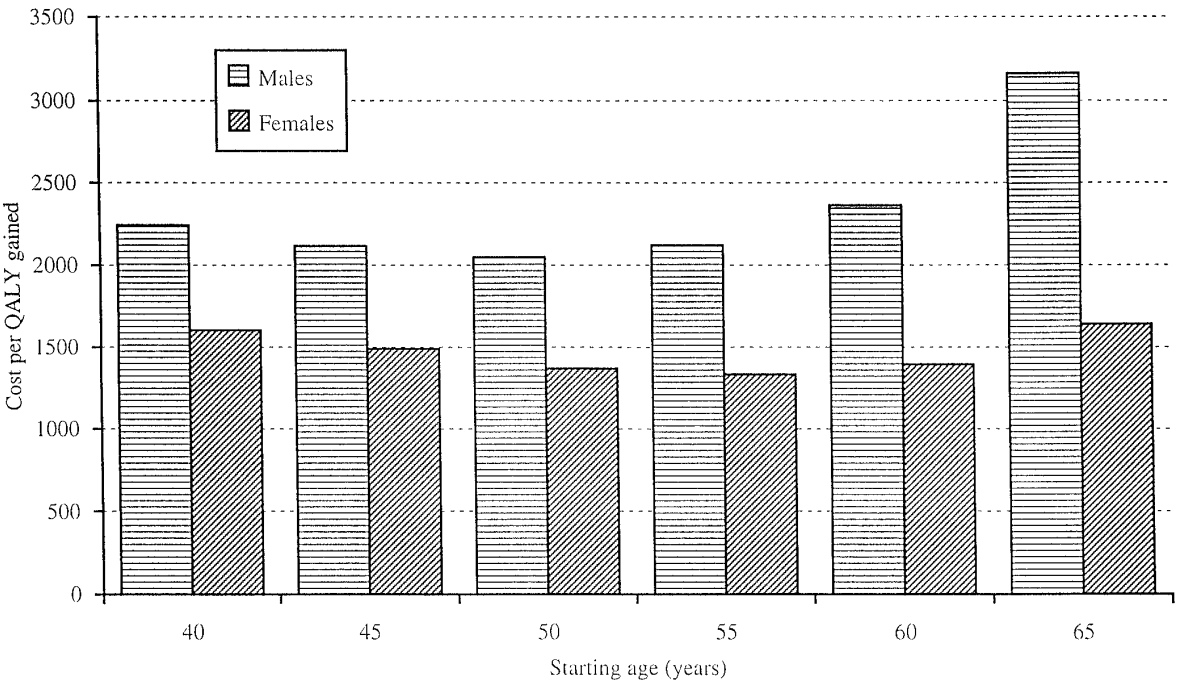

Figure 2. Cost per QALY gained via screening from different starting ages, by gender (using simulation 3 parameters).

differential discount rates, a result unsurprising in view of the lengthy time period over which the cohort's survival gains accrue. Cheaper early-stage treatment evidently offers scope for cost economies, although whether this is likely to be practicable within an operational programme remains unclear.[18]

Whilst we should have anticipated that the impact of annual screening would be to increase both cost and yield over the biennial approach, it is interesting that it does so in roughly equal measure. Similarly, Fig. 2 shows that the cost-utility estimates only vary within a range of around 20% over starting ages in the 40–60 years range. The intuition behind these results is that, for the lower starting ages, the net costs of the screening programme are higher and, although cancer yield is low, the preventive potential of adenoma detection and excision is considerable. At the higher ages, expected net screening costs are lower whilst cancer prevalence and yield are much greater, although the potential to effect substantial survival gains by early detection falls as the starting age increases. This having been said, considerable caution must be exercised in the interpretation of the sensitivity results for simulations which depart radically from the Nottingham protocol. We have little primary information on the likely impact on long-term compliance of more frequent screening, different entry ages or the public's perception of test efficacy, with the result that the model's assumptions might well be inappropriate. For example, although we have already established that regular compliance (serial adherence) over the first five screening rounds in Nottingham is strongly associated with social class, experience of illness and attitudes towards preventive medicine more generally,[30] a US study has observed that positive test results are likely to result, somewhat perversely it might be felt, in falling serial adherence to a screening programme.[31]

The Forrest Report's economic evaluation of breast cancer screening produced an estimate of cost per QALY gained of around £3500 in 1984 prices or around £6000 in 1995 prices. Our cost-effectiveness estimates for colorectal cancer screening over the trial period are slightly lower than this figure; for the lifetime simulations, they are noticeably superior. Three caveats must be noted, however. First, the Forrest evaluation itself has been the subject of criticism.[32,33] Second, neither our nor the Forrest evaluation incorporated indirect costs, including psychological costs associated with anxiety. Third, our cost-effectiveness estimates from the trial evidence have made no allowance for certain cost factors which are likely to be entailed by a fully operational system. Prior to implementation, for example, a mass screening programme would require substantial additional capital investment in endoscopy facilities nation-wide, as well as training for staff. Presumably, a call–recall system, analogous to that employed for breast cancer screening, would have to be developed and maintained and such a system would add considerably to the unit costs of screening.

It must be stressed that the Nottingham trial protocol which we have evaluated represents only one of a number of feasible screening models for potential practical application. For example, as a result of continued innovation in the field, the Haemoccult test is now simply one amongst many possible methods of detecting faecal occult blood and the use of one of these newer tests might be contemplated in the mass screening context. This having been said, research suggests that Haemoccult used according to the Nottingham protocol continues to remain one of the most cost-effective methods of FOB testing.[29,34,35] Again, it will be noted that the screening protocol (Fig. 1) makes no formal attempt to re-invite non-compliers with FOB screening. Experimental re-invitation strategies have been tested within the trial, however, and suggest that 10–15% additional compliance can be obtained as a result, although naturally at some additional cost.[28] In a similar vein, the case for detecting colorectal cancer by mass screening using one-off sigmoidoscopy, rather than regular FOB testing, has recently been argued[36] and a major RCT of this modality is currently under way in the UK.

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