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ECONOMIC EVALUATION

COLORECTAL CANCER SCREENING: EFFICIENCY AND EFFECTIVENESS

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SUMMARY

The cost-effectiveness of a series of mutually exclusive colorectal cancer screening programmes with varying screening interval and target group are analysed. Costs and effects for 60 possible screening programmes are simulated on the basis of data collected from a randomized trial initiated in 1985 in Funen County, Denmark. The screening test applied is the unhydrated Hemoccult-II. The analysis identifies six efficient programmes with cost-effectiveness estimates ranging from 17 000 to 42 500 Danish kroner (DKK) per life-year. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — screening; colorectal cancer; cost-effectiveness; economic evaluation; model simulation

INTRODUCTION

It is possible today to detect some types of cancer at an early and yet asymptomatic stage. In many western countries screening programmes for breast cancer and cervical cancer have been introduced in order to save lives and treatment costs.

In the county of Funen, Denmark, a systematic screening programme for cervical cancer was introduced in 1989 and at the beginning of 1994 a screening programme for breast cancer was launched. No screening programme for colorectal cancer has been introduced, but a randomized study initiated in August 1985 is currently running with the aim of evaluating costs and benefits of screening every second year with the unhydrated Hemoccult-II (H-II) test. Similar projects are running in Nottingham, UK[1] and Burgundy, France. In some countries, such as Japan[2] and the USA,[3] the screening test has received much clinical support and screening programmes for colorectal cancer have been introduced. Moreover, in Germany and Austria population screening for colorectal cancer has been performed since the 1970s.[4]

The causes of colorectal cancer are complex and primary prevention is not possible. However, secondary prevention by early detection and treatment of asymptomatic colorectal cancers can potentially reduce mortality. The present conventional treatments are not satisfactory in that 60% of colorectal cancer patients die within the first 5 years of detection,[5] so an improvement in these mortality figures would be welcome. A possible way of introducing secondary prevention could be administering the H-II test to a relevant population. Although the H-II test has a relatively low sensitivity for colorectal cancer, it has other features that make it suitable as a screening test. It has a high specificity, it is convenient and easy to administer for the individual and it is inexpensive.

This paper will evaluate the cost-effectiveness of colorectal cancer screening programmes on the

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basis of the preliminary results of the Danish randomized study. Since there is no reason to believe that this programme has an optimal choice of screening interval and invited target population, costs and effects will be estimated for a total of 60 alternative programmes where the target population and the screening interval are altered. This is made possible by adopting a model originally developed by Day and Walter.[6] This model is a statistical model, which on the basis of information collected from existing screening programmes estimates the effects of alternative screening programmes where variables such as target group and screening interval are altered. Performing cost-effectiveness analyses over a range of possible programmes should give valuable input into future decision making on this issue.

Data, methods and assumptions used in the analysis are described, followed by a presentation of results. A sensitivity analysis is performed in order to emphasize the vital parameters of the model and the model is validated through comparison of results of the present analysis with the results of other simulation models. A discussion follows where the focus is on both the strengths and weaknesses of the model.

DATA, METHODS AND ASSUMPTIONS

Data

A randomized population study was initiated in 1985 in the County of Funen, Denmark.[7–9] Support for the study was obtained from the local administration and the Danish Medical Research Council, the Danish Cancer Society and several private funds; 30 967 persons were offered screening and 30 966 were selected as controls by random allocation among the 14 000 inhabitants in the county between 45 and 74 years of age. The Hemoccult-II test (H-II) is offered every 2 years. From the randomized study, information on cancers detected per screening round per age group (prevalence) and information on cancers surfacing between screening rounds per age group (interval incidence) were collected.

The main outcome of the randomized study was that the colorectal cancer mortality, including deaths from complications linked to colorectal cancer treatment, over a study period of 10 years, was significantly reduced in the screening group [mortality ratio 0.82 (0.68–0.99)] Kronborg *et al*.[10] This result was used in this analysis assuming that the survival improvement is due to early detection by screening alone. There was no statistical significance between the number of cancers occuring in the test group relative to the control group. Hence the improved survival is attributable to the early detection of cancers and not to the avoidance of cancers due to adenoma follow-up (although such an effect is likely to surface in the future). For a more detailed description of the study and its results, see Ref. 10.

Danish national registry data on the incidence of colorectal cancer by sex and gender from the period 1983–87[5] were also used in the model simulations. Incidence rates from the control group of the randomized study could have been used, but the population data were chosen owing to the greater sample size.

Model

The model, originally developed by Day and Walter,[6] is a statistical model which, on the basis of screening data from existing screening programmes, estimates the sensitivity of the test used (assuming that the sensitivity is independent of disease stage) and the average time period in which the cancer is detectable by the test, but yet asymptomatic (the average sojourn time). Input into the model are the prevalence and interval incidence data collected from the screening programme on Funen. These data form the basis on which the sensitivity rate of the H-II test and the average sojourn time are estimated by an iterative algorithm that satisfies maximum likelihood criteria subject to distribution assumptions. The strength of the model is hence that the core variables, sojourn time and sensitivity, are estimated within the model on the basis of screening data and not required as input variables.

These estimates, along with age-dependent incidence rates, are subsequently input into a simulation process, where the number of cancers detected per age group at each screening round are estimated for hypothetical screening programmes with varying screening intervals and target groups.

The number of true positive cancers detected at each screening round is estimated by the model. Other effects are also estimated using the experi-

ence of the Danish project: 1% of the participating population are assumed to have a false-positive H-II test. These will be referred to a diagnostic test: colonoscopy and/or x-ray. Moreover, the observed age-dependent incidence of adenomas was used to estimate the number of persons who were offered a colonoscopy including adenoma removal and subsequently included in a follow-up programme. It is assumed that the follow-up programme entails colonoscopy every 3 years until the age of 75. The age-dependent adenoma incidence is assumed to be constant across screening intervals of 1, 2 and 3 years. This assumption seemed justified since in the Danish study there was no observed decline in adenoma incidence rates across screening rounds (holding age constant).

The observed age- and sex-dependent participation rates in the randomized study were used in the model. The overall participation rate was 67.3% for first-time participants and 93.5% at subsequent screening rounds. Individuals who refuse to participate in former screening rounds are not invited to subsequent screening rounds. In the cost-effectiveness analysis, the target groups are the relevant age groups in the Funen population.

Outcome measure

The outcomes of the screening programmes are measured in number of gained life-years relative to the nul-option of no screening. The cost-effectiveness analysis is based on model estimates of number of cancers detected at each screening round. The improved survival rate in the test group is a result of early detection and can be explained by a survival rate of 84.3% amongst patients with cancers detected by the screening test. The survival rate in the control group is 48.5%. This indicates that 35.8% of the cancer patients, whose cancers were detected by the screening test, survive due to the early detection. A conservative estimate of 30% was used in the present analysis. In this analysis it is assumed that the excess survival rate amongst the individuals whose cancers are detected by screening is constant and independent of screening interval. This may be an unrealistic assumption, since it is probable that cancers will be detected at a later stage when the screening interval is long and at earlier stages when the screening interval is short. It has not been possible to estimate such an effect in the present model, since the only data available are those collected from a screening programme using a 2 year interval. However, the effect of an increase/decrease in screening interval on survival amongst screen detected cancers will most likely be relatively slight owing to the short sojourn time of colorectal cancer.[11]

The effect of adenoma removal on cancer incidence and survival is as yet uncertain. Hence it has been necessary to make some assumptions based partly on data from the literature. The Danish study indicated that over time only around 60% of the adenomas detected through the screening programme would have otherwise gone undetected.[10] In the Funen trial 173 adenomas were detected in the control group compared with 413 in the screened group, of which 143 adenomas were detected through clinical indications. Hence the clinically detected adenomas were reduced by *ca* 20% in the test group over this relatively short observation period. Since adenomas have a long latency period, the reduction in clinically detected cancers due to screen detection will most likely increase over time.

It was furthermore assumed that only the large adenomas (≥ 1 cm in diameter) were at risk of developing into cancers. In the study the proportion of large adenomas was 70%. According to Stryker *et al.*,[12] the cumulative risk of diagnosis of cancer at an adenoma site (for adenomas ≥ 1 cm) is 2.5, 8 and 24% over follow-up periods of 5, 10 and 20 years, respectively. All these figures were used in the model to estimate the number (and timing) of cancers avoided owing to the detection of adenomas. The age-dependent incidence rates are adjusted for this decrease. The relative risk of colorectal carcinoma due to detection of and follow-up of adenomas was assumed to be 0.57, according to previous estimates.[13] The mortality risk of cancers that develop during the course of the adenoma follow-up programme was assumed to be the same as for screen-detected cancers.

The reduced mortality rate in the screened population is converted to number of life-years gained which is the outcome measure in the cost-effectiveness analysis. Life-years gained are estimated by identifying how many lives are saved in each 5 year age group and multiplying these by their average life expectancy (adjusted for mean lead time). Gained life-years are not quality adjusted since it has been shown that recovery

entails close to perfect health.[14] Although avoidance of cancers due to adenoma detection may improve quality of life in the period in which the patient would have suffered from the illness, this effect was ignored, since it was judged that the main outcome of the screening programme is life extension.

Costs

The costs included in the analysis are the costs incurred by screening in excess of the costs of the nul-option of no screening. All costs are in 1993 prices. Every person in the target group receives an H-II test at a cost of 9 DKK (1 DKK≈0.15 US$) for the test and 11.50 DKK in mailing costs. In total a cost of 20.50 DKK is initiated for each invitation. If the invited individual chooses to participate an extra cost of 8.00 DKK is initiated for test analysis (it was estimated that a laboratory technician could analyse 12 H-II tests per hour). If the test is found to be positive due to adenomas, false positives or true positives, colonoscopy is performed in 96% of the cases and/or an x-ray examination is performed in 7% of the cases. Colonoscopy is estimated to cost 1000 DKK. The cost of emptying the bowels is based on 4 nurse-hours, whereas the colonoscopy itself costs ¾ clinician hours, 1 nurse-hour plus depreciation of machinery and cost of materials. The cost of an x-ray was estimated at 460 DKK based on the cost of 1 clinician-hour, 1 nurse-hour and materials (contrast and antropin). All positives are offered a consultation with a physician at a cost of 100 DKK. This is an average cost across all positives. Every participant receives a letter informing them of the result of the test, a consultation is offered if the patient has further enquiries prior to the diagnostic test.

In addition to variable costs, the following fixed costs per year were estimated based on the average yearly costs incurred over the initial 8 years of the trial: computer assistant 16 800, software 150 000, offices 36 000 and inventory 6000 DKK. Hence it is assumed that costs of software, offices and inventory are independent of the size of the programme whereas costs of coordinator and secretaries are assumed to vary with number of invited persons per screening round. These costs are included as a mark-up of 19.65 DKK per invitation, corresponding to the calculated mark-up at the fourth screening round in the Danish study.

Trial evidence has shown that treatment costs of screen-detected cancers do not differ significantly from the treatment costs of symptomatic cancers.[15–17] Since the introduction of screening programmes has no effect on the costs of treatment, these could be left out of the analysis. One could argue that the treatment of screen-detected cancers takes place earlier in time incurring a cost because of the increase in present value. The lead time, however, is estimated at 2.1 years,[11] making this effect minimal.

The detection af adenomas incurs the cost of an initial colonoscopy and the subsequent follow-up programme. For those patients who avoid developing a cancer, there are cost savings due to avoided treatment. A cancer avoided will initiate a future saving of 119 500 DKK. The cost of a hospital day on the surgical ward is estimated at 4250 DKK (calculated by the administration, Odense University Hospital) and the average number of bed-days is 28 for a cancer patient. These future savings are discounted back to present time at a discount rate of 5%.

The viewpoint chosen for this analysis is that of the National Health Service. Hence, only direct treatment costs are considered. Disutilities such as time costs and anxiety involved in participating, as well as the disutility involved in complications following possible perforation of the colon during a colonoscopy (the mortality risk is included in the calculated survival rate), are not included in the analysis. The possible process disutilities experienced in connection with colonoscopy and the H-II test are also omitted and so are the potential benefits the participants may experience through relief and gratitude in connection with a negative test. Omitted also is the potential gain in production due to reduced morbidity from avoiding a cancer. Measurement of these indirect and intangible costs and benefits should however be focus for further research.

Cost-effectiveness

It is assumed that the size and the age and sex distribution of the invited population are constant over time and equal to the population size and distribution of 1993 in Funen County. Each screening programme is assumed to run for a period of 36 years. All costs and effects are based

on screening an unscreened population. Hence in the initial years after a programme's introduction the cancer detection rate will be higher, whereafter it will fall to a constant rate. A long running period of 36 years was chosen in order to simulate the cost and effects of a screening programme that is introduced in a population on a permanent basis. Simulating the costs and effects of a programme soon after implementation would overestimate the cost-effectiveness of the programme. Costs and gained life-years incurred by the screening programmes are calculated over lifetime and costs as well as effects are discounted by 5% annually to present value. The estimations assume that no screening has taken place before the introduction of the screening programme.

The cost-effectiveness analysis is performed on a series of screening programmes for colorectal cancer in which screening interval and target population are varied. All programmes are mutually exclusive since the costs and effects of each programme are calculated subject to no other screening activity. Analysis is performed on screening intervals of 3, 2, 1.5 and 1 year, since it was considered that specific outcomes of the Danish study could only be generalized to screening programmes with alternative screening intervals of 2 years $\pm$ 1 year. These intervals are each combined with a range of mutually exclusive target groups: 70–74, 65–74, 65–69, 60–64, 60–69, 60–74, 55–59, 55–64, 55–69, 55–74, 50–54, 50–59, 50–64, 50–69 and 50–74 years, giving a total of 60 combinations and hence 60 simulated screening programmes. The effect of screening 45–49 year olds was not simulated because the data on adenoma incidence of this group were considered uncertain owing to small numbers. The number of cancers found in this age group was also very low, implying that it is not cost-effective to screen this age-group. The remaining age intervals were chosen on the basis of national incidence data, which show that colorectal cancer incidence is very low before the age of 45–50 years, whereafter the risk gradually increases with age.

Sensitivity analysis

A general sensitivity analysis on clinical as well as cost parameters is performed. Sensitivity analysis is performed on the following variables: cost of H-II test, cost of colonoscopy, effect of adenoma follow-up and excess survival rate. Moreover, the effect of leaving effects undiscounted is analysed along with the effect of including future unrelated health care costs. Subsequently, the effect on cost-effectiveness of widening the scope from that of the national health care perspective to that of the social perspective is discussed.

RESULTS

Estimates of sensitivity and sojourn time

Prevalence and interval incidence data from the randomized study on Funen and also national registry data on the population incidence of colorectal cancer formed the input into the estimation of the two core parameters; the sensitivity of the H-II test and the average sojourn time.

The results of the maximum likelihood estimation based on the screening data from the Danish study, assuming that the sojourn time is exponentially distributed, are an estimated sensitivity of the H-II test of 62.1% and an estimated average sojourn time of 2.1 years.[11] When the estimates for the sensitivity and the average sojourn time are entered into the model along with age- and gender-specific incidence rates and also defined screening interval and target group, the model can estimate the prevalence of colorectal cancers per screening round. For more information on the model and a more detailed description of the parameter estimations, see Gyrd-Hansen *et al.*[11,18]

Costs and gained life-years

The estimated prevalences per screening round are subsequently transformed into gained life-years by multiplying number of cancers detected at each screening round by the excess survival rate and further multiplying these saved lives by the age specific life expectancy (adjusted for lead time). The costs are estimated on the basis of these model predictions and also assumptions made on the occurrence of false positives and adenoma incidence.

Efficiency and cost-effectiveness

In Fig. 1 the 60 hypothetical screening programmes are plotted according to the estimated costs involved in setting up and running the programme and the estimated life-years gained as a result of this specific screening programme. A line is drawn between the points that lie to the south east, indicating the screening programmes that save most life-years at each level of costs. This provides an efficiency curve on which lie the efficient screening programmes. The screening programmes south-west of this curve are dominated and hence inefficient, since there will always exist an alternative screening programme, which gains more life-years at the same or less cost. Choosing an inefficient screening programme is never an optimal strategy, so in the following we focus on the characteristics of the efficient screening programmes only.

The slope of the efficiency curve is clearly increasing at an increasing rate indicating that the extra life-years gained as one moves up this curve become more expensive. The costs rise markedly when intensifying the screening programme, whereas the increase in effect is decreasing. The cost of the last life-years gained can be read off the slope of the curve at the point representing the screening programme in question and is calculated by dividing the extra costs involved in the expansion of the screening programme with the extra life-years which the expansion contributes. These costs per life-year are in the following labeled incremental costs and presented in Table 1.

In Table 1, the average costs and incremental cost of the six efficient programmes, i.e. the set of programmes with increasing incremental cost-effectiveness ratios, are presented. The estimated incremental costs per life-year gained of the identified efficient programmes range from 17 000 to 42 500 DKK. The highest incremental cost occurs when expanding the programme from screening the 55–74 year olds every year (E) to include also the 50–54 year olds in the programme (F). The cost of the extra 474 life-years is 42 500 DKK per life-year.

Sensitivity analysis

A sensitivity analysis provides an assessment of

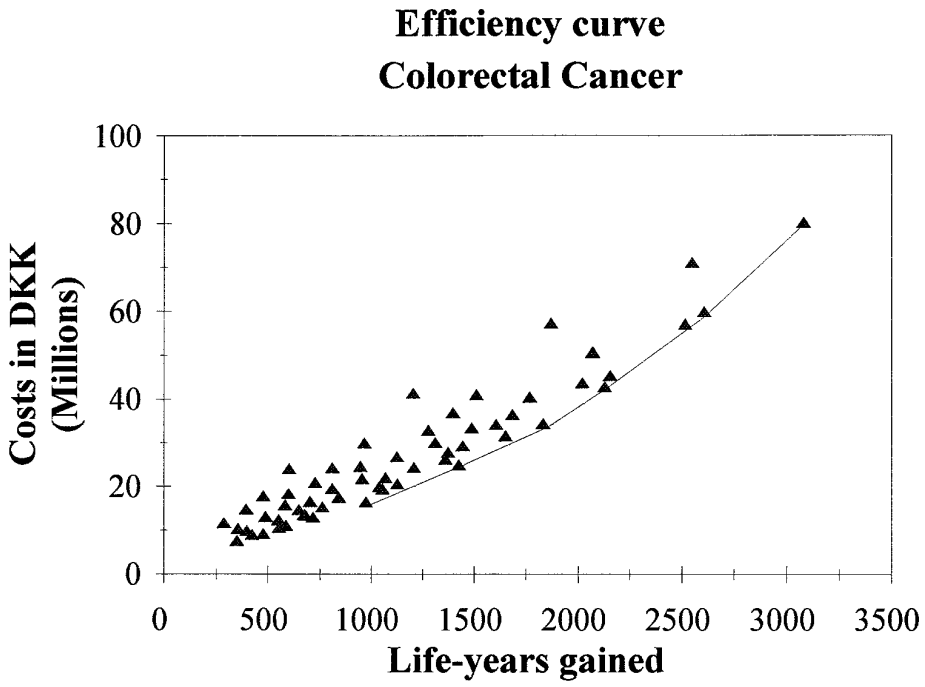

Figure 1. Alternative screening programmes for colorectal cancer plotted according to costs and effects incurred over a period of 36 years. Costs and effects are discounted by 5%. A curve is drawn connecting the efficient programmes.

Table 1. Costs and effects of efficient screening programmes for colorectal cancer (all costs in 1993 DKK)

Programme	Total costs	Life-years gained	Cost per life-year	Incremental cost per life-year
(A) Every 2 years, 65–74 year olds	16 558 000	974	17 000	17 000
(B) Every 2 years, 60–74 year olds	25 080 000	1425	17 600	18 896
(C) Every 2 years, 55–74 year olds	34 422 800	1831	18 800	23 012
(D) Every 1.5 years, 55–74 year olds	43 005 800	2129	20 200	28 802
(E) Every year, 55–74 year olds	59 961 000	2607	23 000	35 471
(F) Every year, 50–74 year olds	80 106 000	3081	26 000	42 500

Table 2. Incremental cost for efficient programmes when parameter values are varied (all costs in 1993 DKK)

Programme	Cost of H-II test 20 DKK	Cost of colonoscopy 3000 DKK	No cancers avoided	Excess survival = 20%
A	19 740	23 830	19 310	25 310
B	22 380	29 380	22 970	26 210
C	27 760	34 830	27 210	33 240
D	33 940	43 750	34 770	40 060
E	42 620	53 130	42 730	49 740
F	50 780	61 730	49 430	59 430

the robustness of the results presented above and may furthermore help to identify estimates and assumptions to which results are sensitive such that future research can focus on improving these.

The cost of the H-II test is set at 9 DKK in the model corresponding to the actual price of the test in the randomized trial. Since there is always uncertainty of the developments in the price markets when demand increases if universal screening is recommended, it was considered important to calculate the cost-effectiveness of the programmes should the test become more expensive. The higher price was set at 20 DKK. The change in price resulted in higher incremental costs of the programmes, but the efficient programmes remained the same. The incremental costs of the efficient programmes are listed in Table 2. The incremental cost of programme A is calculated relative to the nul-option of no screening (the incremental cost of a programme relative to no screening equals the average cost of that programme). The effect of the price increase is a rise in incremental cost per life-year of between 16% (programme A) and 19% (programme F).

The cost of colonoscopy was estimated at 1000 DKK in the present analysis. This is similar to the estimate of Walker *et al.*[19] but a lower estimate than that used in the OTA report[20] and Eddy's analysis,[21] where the cost of colonoscopy lies in the 3000 DKK range. The reason for this discrepancy may be country variations in cost levels or possibly different cost estimation methods. A sensitivity analysis was performed in order to see what effect a change in this cost variable would have on cost-effectiveness. There was no change in the efficient programmes due to this alteration, but cost-effectiveness was increased by between 40% (programme A) and 45% (programme F). In other words, a 10% increase in the cost of colonoscopy will induce an increase in incremental cost per life-year of between 1.3 and 1.5%.

As stated earlier, there is some uncertainty involved in estimating the effects of adenoma removal and follow-up. We therefore chose to analyse the effect on cost-effectiveness if there was no reduction in incidence of cancer due to adenoma detection. Incident cancers found in the follow-up programme were still considered to have an improved survival rate similar to that of screen-detected cancers. The effect of this change induced an increase in incremental costs of 13–16%. The list of efficient programmes remained unchanged.

The excess survival rate of screen-detected cancers was in this analysis set at 30%, a value that is lower than that found in the Danish study. A conservative estimate was used to take account of possible increases in mortality due to complications following colonoscopy. This could be a potential result if the colorectal cancer screening is introduced nationwide and less experienced clinicians have to perform colonoscopies. The effect of screening programmes may vary due to different treatment regimes across countries, so we thought it of interest to estimate effects at an excess survival rate of only 20%. The results are

given in Table 2 and show an increase in incremental cost per life-year of between 40% (programme F) and 49% (programme A). A 1% decrease in the excess survival rate will hence give rise to an increase in incremental costs of between 4 and 4.9% depending on the proportion of life-years gained that are a consequence of avoided cancers.

When simulating the effect of the hypothetical programmes under ultra-pessimistic assumptions, i.e. introducing all the changes listed in Table 2, the programmes listed in Table 1 still remain on the efficiency curve. The incremental costs are now substantially higher, ranging from 43 470 DKK (programme A) to 118 220 DKK. Moderate programmes such as programmes C and D incur incremental costs of 66 190 and 85 632 DKK.

The savings in future treatment costs due to avoided cancers is estimated to be 119 000 DKK based on an average cost of a hospital bed-day. At best an incremental cost estimate should have been used, which might have given a smaller cost figure. Hence we estimated the effect of reducing the cost savings to 60 000 DKK. This 50% decrease resulted in a 5–6% increase in cost per life-year.

A pessimistic scenario was simulated where the H-II test costs 20 DKK, colonoscopy 3000 DKK, no cancers are avoided by adenoma follow-up and the excess survival rate is as low as 20%. In this case the incremental costs range from 43 470 to 118 220 DKK, with moderate programmes such as programmes B and C incurring incremental costs of 57 130 and 66 190 DKK.

Life-years have not been adjusted for quality of life. Whynes *et al.*[14] have evaluated the quality of life following surgery for colorectal cancer and found that a quality of life coefficient for surviving patients lies within the range 0.948–0.981. Adjusting the effects for quality of life would result in a maximum increase in average cost per life-year of 5.5%.

Discounting effects is a controversial issue within health economics. For a discussion see for example Hillmann and Kim.[22] In the present analysis we tested whether leaving effects undiscounted incurs any major changes in conclusions. The result was some changes in the list of efficient programmes. Programmes A, B, C and F still remained efficient, whereas programmes D and E were replaced by two new programmes: screening the 50–74 years olds every 2 and 1.5 years, respectively.

Another controversial issue is that of whether future resource use of unrelated diseases should be included in the analysis. For a discussion of this issue, see Gold *et al.*[23] and also three recent publications in *Journal of Health Economics*.[24–26] Because of the practical concerns and unresolved theoretical issues surrounding the inclusion of health care costs for unrelated illness in added years of life, Gold *et al.* recommend that analysts use their discretion in including or excluding these costs. We were interested to see what effect the inclusion of these costs would have on overall cost-effectiveness of colorectal cancer screening. Including estimates of health care costs as a function of age[27] resulted in significantly higher incremental costs lying in the range 42 800–63 800 DKK and the list of efficient programmes was altered markedly. Since health care costs per life-year rise with increasing age, the younger age-groups become relatively more competitive. Only programmes C and F remained efficient. The list of efficient programmes are in this case 55–69 year olds every 2 years, 55–74 year olds every 2 years, 50–74 year olds every 2 years, 50–74 year olds every 1.5 years and 50–74 year olds every year.

If the scope of the evaluation is instead that of society rather than the national health care sector, the inclusion of future unrelated health care costs should be accompanied by future consumption. Using similar estimates on consumption over lifetime as those applied by Meltzer,[25] we measured the effect on prioritization between programmes when this cost element was included. The effect is interesting: for the age-group which is of interest in this evaluation, a decrease in general consumption neutralizes the effect of increased health care costs, when costs and effects are discounted by 5% p.a. The result of including future health care costs in addition to non-medical costs was hence an unaltered list of efficient programmes. There was, however, a general increase in cost per life-year over all programmes of approximately 79 000 DKK (ranging from 77 000 to 81 000 DKK), entailing a maximum incremental cost of 123 500 DKK.

The scope of the cost-effectiveness analysis presented here is limited to including direct costs incurred by the national health care sector. Such a limited scope could potentially result in non-optimal resource allocation, but in this specific case the national health care sector perspective does not bias the list of efficient programmes

significantly. As shown above, inclusion of future costs of consumption and health care will entail no alterations in the list of efficient programmes. Likewise, inclusion of costs to participants is unlikely to produce changes to the list of programmes, or increase the absolute magnitude of the cost-effectiveness ratios. Since there is no tradition of applying consumer charges for participation in screening programmes in Denmark, cost of participation would involve time and travel costs only. Since the H-II test has the advantage of being administered in the home by the participant him- or herself, the cost of travel is zero and the cost of time is likely to be of a smaller magnitude.

Indirect costs of morbidity, i.e. friction costs and time costs of informal carers, should in principle be included in the evaluation, as should the gain in production due to reduced morbidity from avoiding a cancer. Indirect costs of morbidity due to cancer treatment are likely to be much the same for screen-detected cancers as for clinically detected cancers, but in the case of detection of precursors there will be some savings in morbidity costs. The effect of including these morbidity costs did, however, have a negligible effect on cost-effectiveness, the reason being that a smaller fraction of the total number of lives saved by the screening programme is saved due to adenoma removal. Moreover, these cancers are avoided approximately 15 years from present time, causing the net present value of potential cost reductions to be relatively small.

Meltzer,[25] amongst others, argues that indirect costs of mortality, i.e. production loss, should be included in the cost-effectiveness analysis, but we do not support the idea. The argument against inclusion of production loss in cost-effectiveness is twofold. First, Meltzer fails to discuss what elements are included in quality-adjusted life-years. If individuals value own time when judging the value of a health state, including earnings on the cost side of the cost-effectiveness fraction would entail double counting of the value of production. Second, even in the case that one could argue for inclusion of production loss, we believe that the friction cost method should be applied rather than the human capital approach, since most western societies suffer from high unemployment rates, making the workforce replaceable. However, if one does introduce production value in the evaluation along with other future effects such as future unrelated non-medical and medical costs, the effect on prioritization between programmes is major. Inclusion of production value will increase the incremental cost of screening the 50–54 year olds annually from 42 500 to 46 000 DKK while the incremental cost of screening the 65–74 year olds biennially increases to 86 000 DKK. The highest incremental cost (100 000 DKK) would be incurred when decreasing the screening interval from 1.5 years to 1 year for the 65–74 year olds. Hence the recommendation would in this case be to invite the younger age groups frequently before expanding the programme to include the older age groups.

Validation

In the following the results of the presented model are compared with results of other models developed by Eddy,[21] Office of Technology Assessment, USA[20] and Wagner *et al.*[28] All studies were based on Markov mathematic modelling, assuming different values on parameters such as sojourn time, sensitivity, specificity and costs of resource inputs.[29]

The results of Eddy's simulation of the cost and effect of yearly screening of 50–74 year olds for colorectal cancer gave an average cost of 165 DKK per life day gained (assuming an exchange rate conversion at 6.50 DKK, purchasing power parities have not been used). The model presented here produces an estimate of 102 DKK per life day. In Eddy's model the sensitivity is set to 60%, the average sojourn time is set to 4 years and the specificity is set at 98%. The cost of colonoscopy is 3000 DKK and the cost of the H-II test (including cost of mailing and analysis) is 30 DKK. The estimated increase in individual survival is estimated at 0.0059 whereas the estimated risk reduction in our model is 0.0083. Moreover, Eddy discounts extended life-expectancy rather than gained life-years, which exaggerates the discounting effect markedly. For a discussion of the impact of using different discounting methods, see Søgaard and Gyrd-Hansen.[30] Incorporating Eddy's mortality reduction, colonoscopy cost and method of discounting into our model produces an estimate in the region of 250 DKK. That our estimate is higher under this scenario may be explained by the fact that the present analysis assumes that no savings in treatment costs are incurred due to earlier detection of cancers.

The OTA model simulates the effect of screening above 65 year olds every year and assumes a sensitivity of 40%, an average sojourn time of 1 year and a specificity of 98%. The result is a cost-effectiveness estimate of 305.50 DKK per life-day. Our model gives an estimate of between 198 and 280 DKK depending on the survival rate (20–30%), using the same parameter assumptions but simulating the effect of screening up to the age of 74 only. Using our parameter values we obtain a much lower estimate of between 54 and 79 DKK. Some 76% of the discrepancy is caused by the different assumptions on sensitivity, specificity and sojourn time, whereas cost differences account for only 24% of the discrepancy. A combination of a very low sensitivity and a short sojourn time in the OTA model significantly reduces the effects of the screening programme and increases average costs.

In a recent analysis Wagner *et al.*[28] estimated the cost-effectiveness of annual FOB testing and estimated a cost of $9900 per life-year gained. This cost is significantly higher than that of the analysis presented here. However, Wagner *et al.* assumed a very low specificity of 90%, which largely explains the discrepancy.

The overall conclusion of the above comparisons are that given similar input values our model will produce estimates of the same order of magnitude as those estimated by Wagner *et al.*[28] and OTA.[20] Our model does, however, produce more conservative estimates when taking account of assumptions and methods used by Eddy.[21]

The cost-effectiveness ratios produced in this paper are lower than the ratios produced by the other authors. In each case an explanation can be found: Eddy uses a controversial method of discounting, Wagner *et al.* use a low level of specificity which is far from the true value for the unhydrated H-II test and OTA assumes an overall sensitivity that is lower than what has been observed in a recent randomized trial.[11]

DISCUSSION

The costs and effects are estimated for 60 mutually exclusive colorectal cancer screening programmes. These alternative programmes accrue from combinations of different target populations (i.e. inviting different age groups) and screening intervals; 54 of these 60 programmes were found to be inefficient.

From the characteristics of the six efficient programmes that were identified, the following can be concluded; First, in order to minimize average costs the screening programme should at the minimum invite the 65–74 year olds every 2 years. Second, the older age groups should have first priority when setting the target group, since the increasing risk by age clearly offsets the decreasing life-expectancy. Third, it is optimal to reduce the screening interval to 1 year before inviting the 50–54 year olds.

The list of efficient programmes turned out to be very robust and was only altered when effects were left undiscounted or future unrelated health care costs were included. Choosing life-years as an effect unit prioritizes young people over older people, all other things being equal. Discounting reduces this advantage since life-years gained in the distant future are of less value than life-years saved today. In this case, omitting to discount life-years means that it becomes more cost efficient to screen the 50–54 year olds. The new efficiency curve suggests that if one wishes to expand the screening programme beyond screening the 55–74 year olds every 2 years, one should initially encompass the 50–54 year olds and thereafter consider decreasing the screening interval. This conclusion holds when future health care costs are included.

If the scope of the analysis is that of society rather than the national health care sector, the list of efficient programmes will remain unaffected but overall cost-effectiveness will rise by approximately 79 000 DKK per life-year gained for all programmes. This conclusion holds as long as production value is not included on the cost side of the evaluation. If earnings are included the list of efficient programmes will change, but the incremental cost per life-year of screening the 50–74 year olds annually does not exceed 100 000 DKK.

It can be seen in Fig. 1 that the efficiency curve is relatively flat over the first programmes on the curve, illustrated by relatively low incremental costs per life-year, whereafter the incremental cost per life-year rises at an increasing rate as one moves up along the efficiency curve. The incremental costs are listed in Table 1 and lie in the range 17 000–42 500 DKK when only direct health care costs are included. Screening the 55–74 years olds will cost between 23 000 and 35 500 DKK per

life year, depending on choice of screening interval. Even the most intensive of the six efficient screening programmes, which entails screening the 50–74 year olds every year, is cost-effective with an incremental cost per life-year of 42 500 DKK.

In a report published in 1994 by the Danish Ministry of Health[31] on the cost-effectiveness of mammography screening, screening the 50–59 years olds every second year for breast cancer was estimated to cost 416 400 DKK per life gained (in 1993 prices) corresponding to approximately 40 000 DKK per discounted life-year. Screening the 60–69 year olds every 2 years costs 217 650 DKK per life, corresponding to around 29 500 DKK per discounted life-year. The analysis included only direct health care costs. Comparing these estimates with those of this analysis suggests that it is more cost-effective to introduce an annual colorectal cancer screening programmes for the 55–74 year olds than to offer biennial mammography to the 50–59 year olds. Moreover, screening the 55–74 year olds every 1.5 years for colorectal cancer is approximately as cost-effective as screening the 60–69 year olds biennially for breast cancer.

Gyrd-Hansen *et al.*[32] analysed the economics of cervical cancer screening in Denmark using the pap-smear test, including only direct health care costs. The incremental cost per life-year of the programme that is currently being recommended by the Danish Ministry of Health was estimated at 113 500 DKK per life-year (in 1992 prices), which is clearly a less cost-effective programme than those presented here. In the sensitivity analysis a pessimistic scenario was simulated which resulted in the same set of efficient colorectal cancer screening programmes with incremental costs ranging from 43 470 to 118 220 DKK. Even under these extreme assumptions, the incremental cost per life-year for most of the efficient programmes is still below the cost of the most expensive life-years gained in the screening programme for cervical cancer that is currently running in many Danish counties.

CONCLUSION

Using a mathematical model, the costs and effects of a range of mutually exclusive screening programmes were simulated. The model was constructed on the basis of new knowledge gathered from the randomized screening programme in Funen County. The aim of this analysis was to build upon the knowledge acquired from this screening programme, in order to give a basis on which to evaluate the cost-effectiveness of alternative colorectal cancer screening programmes using the unhydrated H-II test.

The analysis identified a range of efficient programmes with incremental cost-effectiveness ratios lying in the range 17 000–42 500 DKK. All efficient screening programmes are cost-effective health care interventions.

By identifying efficient colorectal cancer screening programmes and emphasizing the cost-effectiveness of such programmes compared with other health care interventions, this paper's model projections should be helpful in planning future resource allocations.

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