EEPRU

Policy Research Unit in Economic Evaluation of Health and Social Care Interventions

Research Report

Title: The likely impact of earlier diagnosis of cancer on costs and benefits to the NHS.

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The Department of Health's Policy Research Unit in Economic Evaluation of Health and Care Interventions is a 5 year programme of work that started in January 2011. The unit is led by Professor John Brazier (Director, University of Sheffield) and Professor Mark Sculpher (Deputy Director, University of York) with the aim of assisting policy makers in the Department of Health to improve the allocation of resources in health and social care.

Overview

This report presents a critical review of the five early awareness policy intervention models developed by Frontier Economics. For each issue highlighted within the review, the likely direction of the bias is discussed together with a suggestion of the extent to which these concerns could be rectified within the existing model structure.

Frontier Economics modelling approach

The model sets out to address two specific questions:

1. How would the costs to the NHS change if certain cancers (specifically, breast, colorectal, lung, prostate and melanoma) were detected and diagnosed appreciably earlier than is currently the norm (i.e. according to current survival rates)?

2. How would the benefits to individuals change if these cancers were detected and diagnosed appreciably earlier than is currently the norm?

   The model seeks to examine the impact that earlier detection and diagnosis would have on survival rates and on downstream costs and benefits. Benefits are limited to patient health benefits in terms of improved survival, i.e. change in life years. Costs include those that fall on the NHS, including diagnostics, screening, treatment, follow-up and end of life care.

   The general approach is to produce projections under a set of assumptions relating to current incidence and screening rates, referred to as the 'Business As Usual' (BAU) model. Also, to re-run this model making alternative assumptions about awareness and screening rates, referred to as the 'Policy Intervention' scenario. The impact of earlier diagnosis is measured by comparing the two scenarios (BAU and Policy Intervention), where the key difference between the scenarios relates to the assumptions about the effectiveness of the awareness programme and the efficiency of the screening programme in the given cancer area (when there is screening prgramme in place - colorectal and breast).

The goal of the awareness programme is to inform the population about the risks of developing cancer and the signs that alert a patient to symptoms suspicious of underlying malignant disease. It is expected that individuals would present earlier to their GP, with the result that diagnosis will occur at an earlier stage of cancer, leading to higher survival rates. The early awareness programme seeks to achieve Europe's best practice survival rates, i.e. the group of comparable countries in Europe with the highest survival rates. The key assumptions in the model relating to the effectiveness of the awareness campaign and the efficiency of the screening programme, in terms of recruiting more individuals, are altered to achieve the target 1-year survival rates of EUROCARE-4 good practice.

General logic of the model

Patients enter the model each year through either symptomatic presentation to their GP or detection via screening. For the current arrangements, life years gained are modelled on the basis of a fixed mean survival duration for each cancer stage applied to a "Business As Usual" stage distribution. Different stage distributions are applied to the screen-detected patients (for colorectal and breast) and to those presenting electively with symptoms.

Total costs are modelled as a function of the number of patients attending screening (where applicable), follow-up diagnostic tests for those testing positive at screening, costs of symptomatic presentation and diagnostic tests and stage-specific lifetime treatment costs.

The impact of the early awareness policy is applied within the model by [i] increasing the number of people attending screening and applying a more favourable stage distribution to those detected with an underling preclinical cancer (as compared against usual symptomatic presentation); and [ii] distinguishing a subgroup of symptomatic patients who become "high awareness patients" (those affected by the policy) who are given a new stage distribution which is the same as that of the screen-detected population under the policy. The logic of the model is illustrated in Figures 1a and 1b for colorectal cancer. A similar logic is applied to the other cancers.

Key assumptions of the modelling approach

The key assumptions applied in the model include:

(i) Current survival rates are conditional on the stage of cancer
(ii) Survival rates by stage remain unchanged by the awareness programme
(iii) Baseline distribution of incidence by stage differs according to whether individuals are screened or symptomatic
(iv) Distribution of incidence by stage for the awareness programme is the same as the screened-detected programme
(v) Costs of diagnosis and treatment by stage remain unchanged over time

Figure 1a: Model under Business as Usual (BAU)

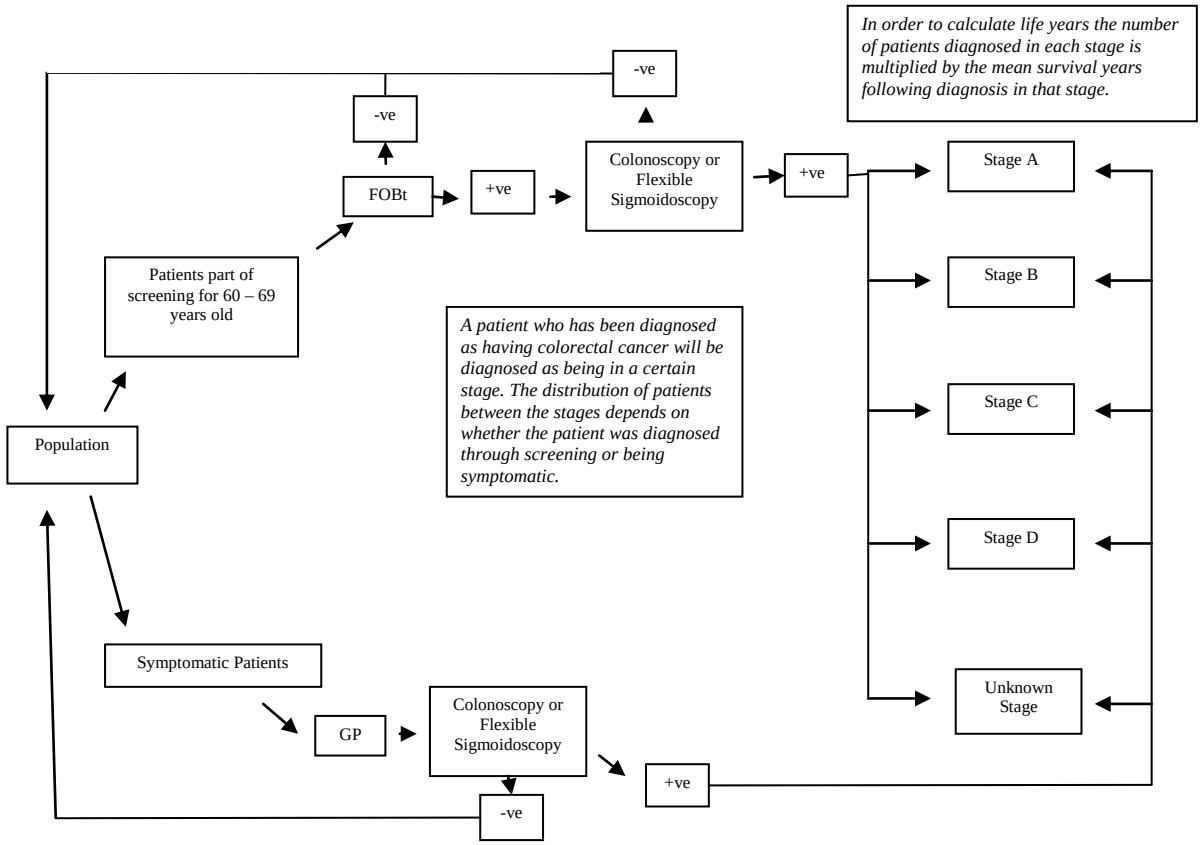
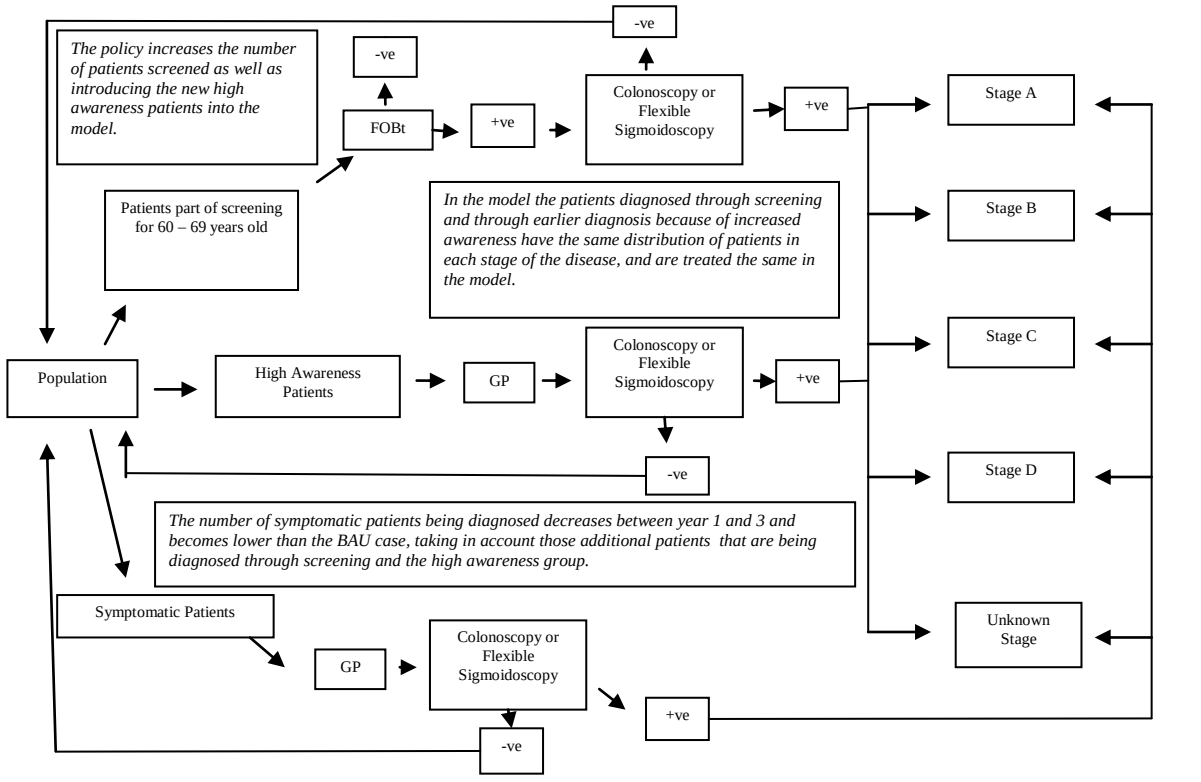


Figure 1b: Model under Policy



Critique of the modelling approach
The following sections outline the authors' main concerns with the model.

(1) Absence of a natural history model
The models do not include full natural history components involving transitions between preclinical states (before diagnosis) and "clinically diagnosed" states. Instead, outcomes for patients are included only for the incident true-positive detected cohort. This gives rise to a number of potential concerns with respect to the credibility of the model results. These issues are interrelated but can be considered in terms of two main problems: (i) the absence of competing risks and no consideration of variability; and (ii) issues relating to modelling only the positive benefits of the true-positive incident cohort.

(i) Absence of competing risks and no consideration of variability
The model does not capture any competing risks of other events on either the costs or outcomes for the patient population. Once diagnosed, a patient is given credit for a fixed survival duration from the point of disease detection. For example, in the colorectal cancer model, patients with Dukes' stage A/B are given 11 years of fixed survival, Dukes' stage C are given 8.7 years, and stage D are given 1.4 years. A fifth group with "unknown stage" (which most likely relates to gaps in data collection) is given 2.5 years.

This general modelling approach appears to run the risk of both lead-time bias and length bias. Lead-time bias occurs when an intervention results in the earlier diagnosis of an underlying cancer, but the time of death remains otherwise unaffected, hence survival following diagnosis appears more favourable due to the intervention. Length bias refers to the situation whereby slower-progressing tumours have a longer preclinical phase, and hence an increased chance of being detected by early intervention before they would otherwise be detected through symptomatic presentation. This leads to the disproportionate identification of slowly progressing tumours compared with faster more aggressive tumours.

Whilst these issues are relevant to the evaluation of any intervention for the early detection of cancer, their potential effects could have been ameliorated by incorporating competing risks within the model and by reflecting disease progression rates through the preclinical states. These competing risks may influence a patient's prognosis and costs. For example, if a patient is diagnosed at age 93, they are likely to be at a considerably increased risk of other-cause mortality and their treatment options are likely to be much more restrictive than those for a younger patient.

The incorporation of evidence from screening models and other sources (e.g. life tables), particularly with respect to probabilities of progression and presentation, calibrated against available evidence from screening trials, would add considerable information to inform this part of the model and would, to some degree, protect against these types of bias.

DIRECTION OF POTENTIAL BIAS: LIKELY TO BE OVERLY FAVOURABLE TO EARLY AWARENESS PROGRAMMES
EFFORT REQUIRED TO RESOLVE ISSUES: DIFFERENT MODEL REQUIRED

(ii) Issues relating to modelling only the positive benefits of the true positive incident cohort

The model only considers the outcomes associated with the incident true-positive diagnosed cancer cohort each year. Costs associated with false-negative and false-positive test results are incorporated, but outcomes for individuals who test negative are not included in the cost-effectiveness analysis. The model does not consider the sensitivity and specificity of diagnostic testing and essentially assumes a fixed positivity rate for the probability of having cancer given attendance at follow-up. There are a number of consequences of this approach:

(1) In certain cancer areas, early detection of premalignant lesions may enable excision and avoid the malignancy altogether (e.g. removal of adenomatous colorectal polyps may provide protection of cancer [see Atkin et al, Lancet 2010]). Whilst few of these would be symptomatic, these patients, and the potential benefits of the early awareness policy, are not considered in the model whatsoever.
(2) By considering only the incident cohort each year, the model fails to account for the change in the underlying distribution of patients who have relevant preclinical potentially detectable disease. As more cases are detected, the ability of any intervention to detect further cases will decrease. This is a particular issue with the colorectal cancer model as the prevalence round screening results are applied in every year (Steele et al, BMJ); in reality one would expect the effectiveness of screening to be lower in incident screening rounds.
(3) By assuming a fixed positivity rate for the likelihood of cancer diagnosis, the model does not consider changes over time. Related to the point above, as more cases are detected, the positivity rate would be reduced because the underlying risk of preclinical disease would be reduced.
(4) A potential increase in true-negative “worried well” individuals, resulting from implementation of the policy intervention, is not accounted for in the model. It might be expected that the programme would attract a large number of individuals presenting to their GP, who do or do not have cancer. It is unclear whether the primary care costs associated with the ‘worried well’ individuals are fully reflected in the model. The model estimates the number of people going through testing who are or are not diagnosed with cancer by dividing the number of people diagnosed with cancer by the percentage of people who have the test and are diagnosed with cancer. However, this probability, which is based on current practice, is likely to change as a result of the policy intervention programme. As public awareness is generated, the probability of patients testing negative will increase. It may have been appropriate to incorporate a rate of true-negatives into the model and to vary this rate to explore how sensitive the total costs of the programme are to the rate assumed. A threshold analysis could be used to determine the critical

proportion of worried wells, which, if exceeded, would cease to make the policy intervention cost-effective.

DIRECTION OF POTENTIAL BIAS: OVERALL, THIS STRUCTURAL APPROACH IS LIKELY TO BIAS IN FAVOUR OF THE POLICY
EFFORT REQUIRED TO RESOLVE ISSUES: FOR THE MOST PART, A DIFFERENT MODEL IS REQUIRED. THRESHOLD ANALYSIS TO EXAMINE THE POTENTIAL IMPACT OF THE "WORRIED WELL" COULD BE INCORPORATED INTO THE EXISTING MODEL

(2) No consideration of uncertainty

The model does not include any consideration of parameter uncertainty in any of the model parameters. This uncertainty is ubiquitous and its omission implies an unfounded level of confidence in the model results. From a structural perspective, adopting a model structure which does not include a full natural history component does not mean that the uncertainty is no longer relevant. The model is highly uncertain because of the nature of the evidence and the nature of the assumptions applied throughout. Very little justification is provided for the choice of data used. In addition, the model does not explore the assumptions in the evidence through sensitivity analyses. Given the high level of uncertainty in the parameter values, sensitivity analysis would be expected at minimum.

DIRECTION OF POTENTIAL BIAS: ASSUMES COMPLETE CERTAINTY
EFFORT REQUIRED TO RESOLVE ISSUES: INCORPORATING DISTRIBUTIONS FOR THE MODEL PARAMETERS WOULD NOT BE TECHNICALLY DIFFICULT, BUT A DIFFERENT MODEL WOULD BE REQUIRED TO ACCOUNT FOR UNCERTAINTY IN THE NATURAL HISTORY. SENSITIVITY ANALYSIS COULD EASILY BE USED TO VARY PARTICULAR PARAMETERS OF INTEREST.

(3) Impact of screening and/or awareness policy on stage distribution

The model appears to apply the impact of early detection programmes (both screening and public awareness) inconsistently between the policy intervention and "Business As Usual" groups. These are shown in Table 1 for colorectal cancer. The screen-detected stage distribution under BAU differs to the screen-detected distribution for the policy intervention. The model also assumes that the "High-awareness" group results in the same stage distribution as the screen-detected. However, patients who present earlier with symptoms in the high awareness group, who would not otherwise have presented in the absence of the policy intervention, may not necessarily match those identified through a screening programme in terms of stage distribution.

Table 1 Stage distribution by programme and subgroup (colorectal)

	Business As Usual			Policy Intervention		
Stage	Symptomatic	"High-awareness"	Screen-detected	Symptomatic	"High-awareness"	Screen-detected
Dukes' A	9%	N/a	48%	9%	31%	31%
Dukes' B	24%	N/a	25%	24%	32%	32%
Dukes' C	24%	N/a	26%	24%	27%	27%
Stage D	9%	N/a	1%	9%	10%	10%
Unknown	34%	N/a	0%	34%	0%	0%

EFFORT REQUIRED TO RESOLVE ISSUES: A DIFFERENT MODEL WOULD BE REQUIRED TO MORE APPROPRIATELY HANDLE THE IMPACT OF SCREENING/AWARENESS POLICIES ON STAGE DISTRIBUTION OVER TIME

(4) Cost of the early awareness policy

The models do not include a cost associated with the organisation or delivery of the programme.

DIRECTION OF POTENTIAL BIAS: THIS INEVITABLY FAVOURS THE POLICY
EFFORT REQUIRED TO RESOLVE ISSUES: MINOR AMENDMENTS REQUIRED TO INCORPORATE THE COSTS OF THE POLICY INTERVENTION

(5) Omission of negative effects of diagnosis

The model does not include any negative impacts associated with screening or diagnosis. Some diagnostic/follow-up tests such as flexible sigmoidoscopy and colonoscopy are invasive and carry a risk of perforation, bleeding and in a minority of cases, death. The omission of these effects in the context of early diagnosis interventions is a flaw, especially since the intervention is anticipated to increase the number of individuals undergoing this element of the cancer service.

DIRECTION OF POTENTIAL BIAS: THIS IS LIKELY TO BE OVERLY OPTIMISTIC TO THE EARLY AWARENESS PROGRAMME
EFFORT REQUIRED TO RESOLVE ISSUES: DEPENDS ON LEVEL OF DETAIL REQUIRED (E.G. INCLUSION OF SUBSEQUENT TESTS FOLLOWING HARMS) BUT POTENTIALLY MINOR AMENDMENTS REQUIRED TO REFLECT THIS CONCERN

(6) Contextual relevance of service pathways

The representation of cancer systems within the models is very simplistic and, in some instances, appears excessively "blunt." For example, a single fixed diagnostic pathway is assumed for colorectal cancer involving FOBT (for screening), subsequent follow-up tests and treatment. In reality, patients may enter the service through this type of elective route, but they may undergo alternative diagnostic tests (e.g. barium enema or CT colonography). The sensitivity/specificity profile of any of

these tests is not considered but will influence the probability of a positive diagnosis given the presence of underlying histology. Alternatively they may already be in secondary care, they may present with emergency symptoms and undergo very different tests, or they may be picked up through screening/surveillance due to some known increased risk factor (e.g. individual's history of adenomas, family history of colorectal cancer, inherited syndromes [familial adenomatous polyposis [FAP] or hereditary non-polyposis colorectal cancer [HNPCC]). These alternative entry routes are not considered.

DIRECTION OF POTENTIAL BIAS: THE DIRECTION OF THIS BIAS IS UNCLEAR – THIS IS AN ISSUE OF MODEL DEPTH
EFFORT REQUIRED TO RESOLVE ISSUES: THIS ISSUE COULD POTENTIALLY BE INCORPORATED INTO A SIMILAR SIMPLE MODEL STRUCTURE

(7) Inappropriate application of discounting

The implementation of discounting to account for the time at which benefits and costs are accrued is incomplete. A 3.5% discount rate is included (see Inputs and assumption sheet) and is used to calculate the net present value (NPV) of the total costs associated with the diagnosis and treatment of the cancer. These figures are used to calculate the gain from the policy in monetary terms in the NPV section of the Results sheet. However, discounting is not applied in the calculation of the incremental cost per life year gained. The model assumes that the total lifetime costs and outcomes occur instantaneously at the point at which the patient is diagnosed with cancer. The incomplete implementation of discounting is likely to favour the policy programme because the costs of the awareness policy will be incurred sooner than the potential benefits are accrued.

DIRECTION OF POTENTIAL BIAS: LIKELY TO BE OPTIMISTIC IN FAVOUR OF THE EARLY AWARENESS PROGRAMME
EFFORT REQUIRED TO RESOLVE ISSUES: MINOR AMENDMENT REQUIRED

(8) Calculation of model results

During the first two years following implementation of the early awareness policy the costs and number of life years gained differ from subsequent years. One of the sets of results quoted in the report relates to the population benefit of 41,000 life years gained and an incremental cost of £6,241 per life gained. For the previous 2 years, the incremental cost per life year gained is lower than this value. Beyond 2014, the long-term 'equilibrium' effectiveness is applied throughout. In the new equilibrium section in the Results sheet the new equilibrium is given as the year 2023 and the costs used are derived from the expected results for the year 2023. However, the total expected years of life gained from the policy included in the new equilibrium section is taken from the year 2031 (see Results sheet, rows 50-102). This is arbitrary, but does not alter the results beyond 2014.

DIRECTION OF POTENTIAL BIAS: THE RESULTS FOR THE FIRST 2 YEARS ARE MORE FAVOURABLE – THE MEAN OVER THE ENTIRE TIME HORIZON WOULD FALL SLIGHTLY
EFFORT REQUIRED TO RESOLVE ISSUES: MINOR

(9) Evidence used to populate the model

The evidence used to populate the model does not appear to have been systematically collected. There is no information on a systematic search of the literature to identify, select and retrieve relevant studies. In general, the report is not very transparent in terms of the approach taken or the evidence used to populate the model. Very little justification is given for the choice of modelling approach, the appropriateness of the approach and why particular assumptions were applied. Where effectiveness data were not available, arbitrary values were applied. For example, for colorectal cancer, the percentage of patients screened and subsequently diagnosed is assumed to be 0.25%, but no justification is provided for this choice. Key parameter values have not been explored in sensitivity analysis to assess how sensitive the cost-effective results are to the assumptions applied. More recent sources of evidence may be available for some parameters. For example, the costs associated with diagnosis and treatment of colorectal cancer are taken from the ScHARR options appraisal, 2004. However, a more recent comprehensive assessment of the economic burden of treating colorectal cancer has been completed by ScHARR and the York Health Economics Consortium, 2007 (see http://www.sheffield.ac.uk/scharr/sections/heds/modelling/colorectal-cancers.html for further details). Overall, the credibility of the model is highly uncertain because of the nature of the evidence and lack of justification for parameter values.

DIRECTION OF POTENTIAL BIAS: NOT CERTAIN BUT SHOULD BE ACKNOWLEDGED IN THE REPORT
EFFORT REQUIRED TO RESOLVE ISSUES: SYSTEMATIC REVIEW OF THE LITERAURE REQUIRED AND APPROPRIATE SOURCES IDENTIFIED. PROPER REFERENCING IS NEEDED THROUGHOUT THE REPORT.