Cost effectiveness of shortening screening interval or extending age range of NHS breast screening programme: computer simulation study

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Abstract

Objective: To compare the cost effectiveness of two possible modifications to the current UK screening programme: shortening the screening interval from three to two years and extending the age of invitation to a final screen from 64 to 69.

Design: Computer simulation model which first simulates life histories for women in the absence of a screening programme for breast cancer and then assesses how these life histories would be changed by introducing different screening policies. The model was informed by screening and cost data from the NHS breast screening programme.

Setting: North West region of England.

Main outcome measures: Numbers of deaths prevented, life years gained, and costs.

Results: Compared with the current breast screening programme both modifications would increase the number of deaths prevented and the number of life years saved. The current screening policy costs £2522 per life year gained; extending the age range of the programme would cost £2612 and shortening the interval £2709 per life year gained. The marginal cost per life year gained of extending the age range of the screening programme is £2990 and of shortening the screening interval is £3545.

Conclusions: If the budget for the NHS breast screening programme were to allow for two more invitations per woman, substantial mortality reductions would follow from extending the age range screened or reducing the screening interval. The difference between the two policies is so small that either could be chosen.

Introduction

In 1988 the NHS breast screening programme, on the recommendation of an expert committee, began screening women aged 50-64 years every three years. However, the committee also concluded that the optimum frequency of screening and the age range likely to benefit from breast screening were still undetermined.[1] We used the computer simulation package Microsimulation Screening Analysis (MISCAN) to compare the cost effectiveness of two possible modifications to the current UK screening programme: shortening the screening interval from three to two years and extending the age of invitation to a final screen from 64 to 69.

Methods

A full description of the Microsimulation Screening Analysis model has been published.[2] In brief, the model first simulates life histories for women in the absence of a screening programme for breast cancer and then assesses how these life histories would change as a consequence of introducing different screening policies.

The natural course of breast cancer is modelled as a progression from no breast cancer through preclinical cancer to clinical disease. Women reside in the first state (no breast cancer) before entering one of five preclinical states. There is an in situ state and four invasive states according to the tumour size (T state): $\leq$5 mm (T1a), $>$5-10 mm (T1b), $>$10-20 mm (T1c), and $>$20 mm (T2+). A cancer may be detected at screening, become clinically apparent in any one of these states, or if undiagnosed progress to the next preclinical state. The two end states of the model are death from breast cancer and death from other causes.

The model was set up using data from the Dutch screening trials at Utrecht and Nijmegen to provide estimates of the mean duration of the preclinical phase for women in different age groups and the mean duration of cancer in each of the five preclinical states. The dwelling time of a cancer in each preclinical state is assumed to follow an exponential distribution, and the rate at which cancers progress from the preclinical to the clinical state is inferred from the observed incidence and distribution of stages of clinically diagnosed cancers in the population being studied.

When modelling the performance of a screening programme, key indicators include the mean duration of the screen detectable phase, the sensitivity of the test, and the improvement in prognosis for screen detected cancers. The mean preclinical screen detectable period assumed in the model was based on data from the Dutch screening projects at Nijmegen and Utrecht and varied from 1.8 years at age 35 to 6.2 years at age 70.

The sensitivity of the screening test is assumed in the model to be the probability of detecting a cancer in the preclinical screen detectable state. For women aged over 50 it is fixed as 0.4, 0.65, 0.8, 0.9, and 0.95 for in situ disease, T1a, T1b, T1c, and T2+ tumours respectively. The improvement in prognosis for screen detected cancers was derived from the results of the Swedish breast screening trials.[3]

Applying model to UK population

The North West health region has a population of 4.1 million and is covered by five NHS breast screening programmes. The largest of these, the Manchester breast screening programme, has screened over 120 000 women and reported cancer detection rates similar to those elsewhere in the United Kingdom.[4] The number and size of cancers detected at a first and second screen and the occurrence and size of interval cancers in this programme have been used to inform the model. Estimates of screening and diagnostic costs are based on this programme assuming that two view

mammography is used at the first screen and single view mammography at subsequent screens. Treatment costs are derived from various sources, but primarily the Christie Hospital NHS Trust in Manchester. Full details of the costing, including sensitivity analysis, have been published.[5] Both costs and effects are discounted at 6%.

To simulate the life histories of women with breast cancer before a screening programme is introduced the model requires information on the age, distribution of stage, and survival of women with breast cancer. Neither the prescreening distribution of stage nor stage specific survival rates before screening was introduced were available for the North West's population. However, the prescreening stage distribution in Scotland[6] and in East Anglia (J McCann, East Anglian Cancer Registry, personal communication) was similar to that of the control population in the Utrecht screening trial. We therefore assumed that the prescreening stage distribution in the North West was similar to that used in setting up the computer model. The stage distribution in women aged 50-69 at diagnosis in the Utrecht control population was: 4.6% in situ, 1.5% T1a, 6.3% T1b, 32.6% T1c, and 55% T2+. Having assumed this stage distribution, we derived stage and age specific survival rates by fitting the North West's observed mortality for 1987 to the observed incidence for 1987. This produced an overall five year survival for women aged 50-59 and women aged 60-69 of 67% and 68% respectively. A life table describing the probability of dying from causes other than breast cancer in the North West was used to derive the number of life years gained per breast cancer death prevented.

The model was unable to simulate the detection rate and distribution of stages observed at first screening in the North West. More small cancers were observed in the North West than were predicted by the model. This discrepancy was resolved by assuming a longer screen detectable preclinical phase for small tumours. When it was assumed that small tumours (less than 10 mm) dwelt in a screen detectable phase for twice as long as that used in the initial set up, the model adequately fitted the detection rate and stage distribution observed at first screening in the North West.

This model was used to simulate the effects and costs of three screening programmes for the North West: firstly, the current UK screening policy, in which women aged between 50 and 64 are invited for screening every three years; secondly, screening every three years but extending the age of women screened from 64 to 69 years; and, finally, reducing the screening interval from three to two years while maintaining the current age range. Attendance for screening was assumed to fall by 0.5% for each year of age, from 74.2% at age 50 to 67.9% at age 70; attendance at repeat invitations was assumed to be 78% higher than among those who attended the previous invitation. Each screening programme was assumed to run for 27 years.

Results

The final model adequately predicted the rates of screen detected cancers observed at the first and second screening round, the distribution of stages observed at the first screen but not the distribution observed at the second screen, and the interval cancer rates observed after a first screen (tables 1-3).

Table 1 Observed and computer modelled rates of detection of breast cancer per 1000 women screened

	First screening		Second screening	
Age	**Observed**	**Modelled**	**Observed**	**Modelled**
50-54	5.5	4.6	NA	3.7
55-59	5.6	5.6	NA	4.0
60-64	7.1	7.6	NA	5.5
All ages	6.0	5.9	4.7	4.6

NA=not available.

Table 2 Observed and computer modelled distribution of tumour stage (T state). Values are percentages of women

	First screening		Second screening	
Stage	**Observed**	**Modelled**	**Observed**	**Modelled**
In situ	14.2	14.9	17.0	15.1
T1a	8.6	9.1	3.8	13.0
T1b	31.5	31.0	29.6	38.8
T1c	31.0	30.2	33.9	25.6
T2+	14.7	14.8	15.7	7.5

Table 3 Observed and computer modelled rates of interval cancer after first screening per 10 000 women screened

Months after screen	Observed	Modelled
0-11	5.5	5.4
12-23	9.2	9.8
24-35	14.9	13.0
Total	29.5	28.2

Table 4 Effects and costs of three screening policies for breast cancer

	Current programme	Extension to age 69	Two year interval
Effectiveness (no discounting)			
Reduction in mortality (%)*	12.8	16.4	15.3
Deaths prevented/year*	147	188	175
Total deaths prevented	4 079	5 311	4 880
Life years gained	66 187	78 221	81 322
Costs (£m) (6% discounted)			
Screening	26.8	34.7	36.9
Diagnosis (screening)	17.4	21.1	19.7
Diagnosis (outside screening)	–11.1	–14.1	–12.9
Primary treatment	6.2	9.1	7.1
Adjuvant therapy	–1.5	–2.1	–1.8
Follow up	2.9	4.0	3.5
Advanced disease	–9.8	–13.1	–11.8
Total	30.9	39.6	40.6
Effectiveness (6% discounted)			
Deaths prevented	1 229	1 636	1 457
Life years gained	12 251	15 161	14 987
Cost effectiveness (6% discounted)			
Cost per death prevented (£)	25 142	24 205	27 865
Cost per life year gained (£)	2 522	2 611	2 709
Marginal cost effectiveness/life year gained (£)		2 990	3 545

*In a steady state.

Table 4 provides a summary of the costs and effects of the three screening policies compared with no screening. This suggests that the current North West screening programme reduces mortality by 12.8%, preventing 4079 deaths over 27 years; this is equivalent to 66 187 life years gained or 12 251 life years discounted to present values.

Screening to age 69 reduced mortality by 16.4%, preventing 5311 deaths over 27 years (equivalent to

Key messages

- Computer modelling suggested that the current breast screening programme in North West England will reduce total female breast cancer mortality by 12.8%
- Extending the programme to age 69 would reduce mortality by 16.4% at a marginal cost per life year saved of £2990 while reducing the interval to two years would reduce mortality by 15.3% at a marginal cost per life year saved of £3545
- Extending the age range prevents more deaths from breast cancer but shortening the interval gains more life years
- If the budget for the NHS breast screening programme would allow for two more invitations per woman either of the two options could be chosen

78 221 life years gained or 15 161 life years discounted to present values). A screening interval of two years reduced mortality by 15.3%, preventing 4880 deaths (equivalent to 81 322 life years gained or 14 987 life years discounted to present values).

The cost of the current programme is £30.9 million. This increases to £39.6 million if the age range of the programme is extended and to £40.6 million if the screening interval is reduced. Most of the money is spent on screening and investigation of women recalled with a suspicious result, but some money is saved because of the reduced diagnostic and treatment costs in women who would otherwise have presented with symptoms.

These data suggest that the cost of a life year gained by screening when costs and benefits are discounted at 6% (derived by dividing discounted life years gained by the cost of the programme) is £2522 in the current programme, £2611 if the age range of the programme is extended, and £2709 if the screening interval is shortened. The impact of changing the current screening policy is best summarised by comparing the marginal cost effectiveness of the two modified policies, which is calculated by dividing the difference in total costs of the current and proposed policies by the difference in life years gained. The marginal cost per life year saved of extending the age range of the screening programme is £2990 and of shortening the screening interval £3545.

We also conducted the cost effectiveness analysis using the lower and upper unit cost estimates for screening, diagnosis, and treatment and different discount rates. Under all scenarios considered the current programme had a lower marginal cost per life year saved or death prevented than the two other policies.[5] Two other models using different assumptions about the length of the preclinical detectable phase and the size distribution of tumours at presentation were also explored, and the relative outcomes on cost effectiveness were the same. These models were rejected, however, because they did not fit all the available data as adequately as the model described.

Discussion

The computer model was developed and refined at the Erasmus University, Rotterdam. It has been validated with data from the Netherlands[2] and Sweden,[3] assumptions underpinning the model have been evaluated by others,[7] and the results from the model have been used to evaluate screening programmes in several European countries.[8–11] For the model to simulate the detection rates and distribution of stages observed at first screening in the North West we had to assume a longer preclinical detectable phase for smaller tumours than was estimated from the Dutch pilot projects and the Dutch national screening programme. A longer preclinical detectable phase is in accordance with a lower threshold of detection of breast cancer at screening.

The model adequately simulated the number of cancers occurring in the interval between screens and those detected at a second screen, but it predicted a better stage distribution at repeat screening than was observed. This discrepancy has been reported before[11] and is being investigated by the Erasmus team. It is unlikely, however, that the discrepancy substantially affected the conclusion since a better stage distribution at repeat screens is modelled in all policy options and the overall reduction in mortality predicted for each screening policy option is not greater than the reductions reported from the randomised trials of breast screening.

Which is the best policy?

In cost effectiveness analysis of programmes whose main effect is to extend life the usual measure of benefit is life years gained. Compared with the current breast screening programme both of the alternatives evaluated offer improved effectiveness; both are predicted to increase the number of life years gained and number of deaths prevented. Choice of policy will depend on which outcome measure is chosen, whether discounting is undertaken, and whether costs are considered. If health effects are not discounted and costs are ignored, extending the age range prevents more deaths but reducing the screening intervals results in more life years gained.

Whether either of the proposed changes to the programme is cost effective depends on the value the NHS is willing to place on improvements in the effectiveness of the programme. Compared with no screening and assuming a discount rate of 6% applied to all costs and outcomes the current programme costs £25 142 per death prevented and £2522 per life year saved. The cost per life year saved is higher with both proposed changes, but extending screening to women aged 69 reduces the cost per death prevented. If cost per death prevented is taken as the appropriate outcome measure then extending the age of screening is more cost effective than the current policy. This policy also has a smaller increase in cost per life gained than two year screening compared with the current programme.

In conclusion, if the budget for the NHS breast screening programme would allow for two more invitations per woman, the computer model predicts that the difference between extending the age range screened or reducing the screening interval from three to two years is so small that either could be chosen. This conclusion was not affected by using upper and lower estimates of the costs of screening, diagnosis, and treatment or by varying the discount rate of costs and benefits.

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Contributors: EF initiated the project. AT and CW collated screening and epidemiological data. RB, HK, and PW did the simulation analysis. AS collated and analysed economic data. All authors participated in consultations on study design and the interpretation of the findings. RB, AT, and CW wrote the paper with input from all members of the project team. RB is guarantor of the work.

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Safety and toxicity of amphotericin B in glucose 5% or intralipid 20% in neutropenic patients with pneumonia or fever of unknown origin: randomised study

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Abstract

Objective: To compare the feasibility of treatment, safety, and toxicity of intravenous amphotericin B deoxycholate prepared in either glucose or intralipid for empirical antimycotic treatment of neutropenic cancer patients.

Design: Single centre stratified, randomised non-blinded phase II study.

Setting: University hospital providing tertiary clinical care.

Subjects: 51 neutropenic patients (leukaemia (35), lymphoma (11), solid tumours (5)) with refractory fever of unknown origin (24) or pneumonia (27).

Interventions: Amphotericin B 0.75 mg/kg/day in 250 ml glucose 5% solution or mixed with 250 ml intralipid 20%, given on eight consecutive days then alternate days, as a 1-4 hour infusion.

Main outcome measures: Feasibility of treatment, subjective tolerance (questionnaire), and objective toxicity (common toxicity criteria of the National Cancer Institute).

Results: Study arms were balanced for age, sex, underlying malignancy, renal and liver function, and pre- and concomitant treatment with antibiotics and nephrotoxic agents. No statistically significant or clinically relevant differences were found between the treatment groups for: daily or cumulative dose and duration of treatment with amphotericin B; incidence and time of dose modifications or infusion duration changes related to toxicity; dose or duration of symptomatic support with opiates, antipyretics, or antihistamines; renal function; subjective tolerance; most common toxicity scores; course of infection; and incidence of treatment failures. Patients treated with amphotericin B in intralipid were given fewer diuretics ($P < 0.05$) and therefore had more peripheral oedema ($P < 0.01$) and needed less potassium supplementation ($P < 0.05$) than patients given amphotericin in glucose. Acute respiratory events were more common in the intralipid arm ($P < 0.05$).

Conclusions: Amphotericin B 0.75 mg/kg/day in intralipid given on eight consecutive days then alternate days provides no benefit and is associated with potential pulmonary side effects possibly because of fat overload or an incompatibility of the two drugs.

Introduction

Amphotericin B is regarded as the agent of choice for treatment of life threatening mycoses in neutropenic patients because of its broad antimycotic activity.[1] It is conventionally given intravenously in glucose 5%, as a colloidal suspension with the detergent sodium deoxycholate. Amphotericin B is associated with a high incidence of renal toxicity, potassium loss, fever, and chills. Attempts have been made to overcome its dose limiting renal toxicity.[2] Well tolerated, highly expensive liposomal formulations are commercially available, and can be used in patients developing renal toxicity after exposure to amphotericin B deoxycholate.

Non-liposomal lipid emulsions are also known to reduce toxic effects of amphotericin in vitro and in vivo and have been given to patients.[3–11] Intralipid, a

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