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Modelling the likely effect of the increase of the upper age limit from 70 to 73 for breast screening in the UK National Programme

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The UK National Breast Screening Programme is planned to have the age range for invitation to screening expanded from 50–70 to 47–73. At the upper limit, this represents one additional screen taking place in the early 70s. We aimed to estimate the likely effect of this on breast cancer mortality and on overdiagnosis of breast cancer. We used estimates of breast cancer incidence and survival by detection mode (screening or symptomatic), screening lead time and mortality from competing causes to estimate the likely numbers of breast cancer deaths prevented per 1000 women screened, using both a stochastic continuous time model and a semi-deterministic discrete time model. In the continuous model, we estimated that per 1000 women screened 1.2 deaths would be prevented and in the discrete model 0.91 deaths. In the latter model, we also estimated that there would be around 6.8 years of life saved per 1000 women screened and an additional two diagnoses of breast cancer. These results suggest that the expansion of the upper age limit will be cost-effective. They remain to be confirmed by evaluation of the age extension. They provide prior estimates that may inform the evaluation of the age extension.

1 Introduction

In the UK, the National Breast Screening Programme offers 3-yearly mammography to women aged 50–70, the upper age limit having recently been extended from 64 years. The issue of whether to extend the upper age limit further is currently under evaluation. While in principle, mammography should be very effective at diagnosing cancers in women aged over 70 due to the low breast density in old age, it is not clear how many lives or years of life would be saved, due to the high death rate from competing causes during the potential lead time period.

In this article, we develop methods of prediction of the likely effect of extending the upper age limit. We use estimates of progression of breast cancer from asymptomatic

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screen-detectable to symptomatic disease, fatality rates from screen-detected and symptomatic cancers and deaths from all other causes. We first develop a stochastic model in continuous time to estimate the likely number of lives saved to age 88 by an additional screen at age 73. We also develop a semi-deterministic model in discrete time to estimate the corresponding number of life years saved to age 85.

2 Methods

We planned to estimate effects on the risk of dying of breast cancer up to immediately before a woman's 88th birthday, from tumours diagnosed between ages 70 and 87 inclusive. For simplicity, we consider the situation when a final screen takes place on the 70th birthday and compare this with the situation when one further screen takes place on the 73rd birthday. Tumours diagnosed at the 70th birthday screen are not included for the mortality comparison.

2.1 A stochastic Markov model in continuous time

We first assume that times to 'birth' of asymptomatic screen-detectable disease, to transition from asymptomatic to symptomatic disease, to death of screen-detected and symptomatic tumours, and to death from all causes other than breast cancer have exponential distributions.[1–3] Let λ_1 be the rate of incidence of asymptomatic screen-detectable disease; λ_2 be the rate of transition from asymptomatic screen detectable to symptomatic disease; λ_3 be the rate of death from breast cancer for symptomatic disease; λ_4 be the rate of death from all causes except breast cancer (assumed equal in non-diseased women, asymptomatic cases and symptomatic patients) and λ_5 be the rate of death from breast cancer for screen-detected (i.e., asymptomatic) disease, including any effect of lead time.

In the situation where one last screen takes place at the 70th birthday, the probability of dying of breast cancer by the 88th birthday, from tumours diagnosed after this last screen, is:

$$\begin{aligned} P_1 &= \int_0^{18} \lambda_1 e^{-\lambda_1 t} e^{-\lambda_4 t} \int_0^{18-t} \lambda_2 e^{-\lambda_2 s} e^{-\lambda_4 s} \int_0^{18-t-s} \lambda_3 e^{-\lambda_3 r} e^{-\lambda_4 r} \mathrm{d}r\mathrm{d}s\mathrm{d}t \\ &= \frac{\lambda_1\lambda_2\lambda_3}{(\lambda_3+\lambda_4)} \times \left\{ \frac{(1-e^{-18(\lambda_1+\lambda_4)})}{(\lambda_2+\lambda_4)(\lambda_1+\lambda_4)} - \frac{(e^{-18(\lambda_1+\lambda_4)}-e^{-18(\lambda_2+\lambda_4)})}{(\lambda_2-\lambda_1)} \left(\frac{1}{\lambda_2+\lambda_4} + \frac{1}{\lambda_3-\lambda_2} \right) \right. \\ &\quad \left. + \frac{(e^{-18(\lambda_1+\lambda_4)}-e^{-18(\lambda_3+\lambda_4)})}{(\lambda_3-\lambda_2)(\lambda_3-\lambda_1)} \right\}. \end{aligned}$$

The corresponding probability when a further screen takes place on the 73rd birthday is:

$$\begin{aligned} P_2 &= \int_0^{3} \lambda_1 e^{-\lambda_1 t} e^{-\lambda_4 t} e^{-\lambda_2 (3-t)} e^{-\lambda_4 (3-t)} \mathrm{d}t \times \int_0^{15} \lambda_5 e^{-\lambda_5 s} e^{-\lambda_4 s} \mathrm{d}s \\ &\quad + \int_0^{3} \lambda_1 e^{-\lambda_1 t} e^{-\lambda_4 t} \int_0^{3-t} \lambda_2 e^{-\lambda_2 s} e^{-\lambda_4 s} \int_0^{18-t-s} \lambda_3 e^{-\lambda_3 r} e^{-\lambda_4 r} \mathrm{d}r\mathrm{d}s\mathrm{d}t \\ &\quad + e^{-3(\lambda_1+\lambda_4)} \times \{\mathrm{P}_1 \text{ above with 18 replaced by 15}\} \end{aligned}$$

$$= \frac{\lambda_1\lambda_5\left(e^{-3(\lambda_1+\lambda_4)} - e^{-3(\lambda_2+\lambda_4)}\right)\left(1 - e^{-15(\lambda_4+\lambda_5)}\right)}{(\lambda_2-\lambda_1)(\lambda_4+\lambda_5)} + \frac{\lambda_1\lambda_2\lambda_3}{(\lambda_3+\lambda_4)}$$
$$\times\left\{\left(\frac{(1-e^{-3(\lambda_1+\lambda_4)})}{(\lambda_1+\lambda_4)} - \frac{(e^{-3(\lambda_1+\lambda_4)} - e^{-3(\lambda_2+\lambda_4)})}{(\lambda_2-\lambda_1)}\right)\left(\frac{1}{\lambda_2+\lambda_4}\right)\right.$$
$$\left. - \frac{e^{-18(\lambda_3+\lambda_4)}}{(\lambda_3-\lambda_2)}\left(\frac{(e^{3(\lambda_3-\lambda_1)} - e^{3(\lambda_3-\lambda_2)})}{(\lambda_2-\lambda_1)} - \frac{(e^{3(\lambda_3-\lambda_1)}-1)}{(\lambda_3-\lambda_1)}\right)\right\}$$
$$+ e^{-3(\lambda_1+\lambda_4)} \times \left\{\mathrm{P}_1 \text{ above with 18 replaced by 15}\right\}.$$

By substitution of empirical estimates of the λ's, we can obtain the predicted probability of death from breast cancer under the two regimes, and from this estimate the number of breast cancer deaths prevented per additional 1000 screens.

2.2 A partly deterministic model for death at individual years of age

Suppose now that within each year i ($i = 1, 2, \ldots, 18$ denoting ages 70, 71, ..., 87), there is a uniform incidence of breast cancer b_i in the absence of screening. If there is a screen, which we assume to be 100% sensitive, on the 70th birthday, the incidence rate for year i, uncorrected for deaths from other causes, will be approximately:

$$b_i^* = b_i \frac{(\lambda_2 - e^{-\lambda_2(i-1)} + e^{-\lambda_2 i})}{\lambda_2}.$$

Since with uniform incidence I, the incidence in the year $(t-1, t]$ after a screen will be:

$$\int_0^{t-1} I \int_{t-s-1}^{t-s} \lambda_2 e^{-\lambda_2 r} dr ds + \int_{t-1}^{t} I \int_0^{t-s} \lambda_2 e^{-\lambda_2 r} dr ds = \frac{I}{\lambda_2}\left\{\lambda_2 - e^{-\lambda_2(t-1)} + e^{-\lambda_2 t}\right\},$$

where λ_2 is as above. If d_i is the death rate from all other causes for year i, we assume that the average time of an event, which occurs during a year is the midpoint of that year, then the breast cancer incidence, corrected for deaths from other causes, will be:

$$c_1 = b_1^*(1 - 0.5d_1)$$

For $i > 1$,

$$c_i = b_i^*(1 - 0.5d_i)\prod_{j=1}^{i-1}(1-d_j)(1-b_j^*).$$

The probability of dying from breast cancer in year $i+h$, given diagnosis in year i, uncorrected for deaths from other causes, is:

$$r_h = \int_{h-0.5}^{h+0.5} \lambda_3 e^{-\lambda_3 t} dt = (e^{-\lambda_3(h-0.5)} - e^{-\lambda_3(h+0.5)}),$$

where $h > 0$ and λ_3 is as before. For death in the same year as diagnosis, $h = 0$, we have:

$$r_0 = \int_0^{0.5} \lambda_3 e^{-\lambda_3 t} \mathrm{d}t = (1 - e^{-0.5\lambda_3}).$$

Thus, the overall probability of dying from breast cancer in year i is:

$$s_i = \sum_{j=1}^{i-1} c_j(1 - 0.5d_j) \left(\prod_{k=j+1}^{i-1} (1 - d_k) \right) r_{i-j}(1 - 0.5d_i) + c_i r_0 (1 - 0.5d_i).$$

For $i > 1$, the probability of dying from breast cancer within 1 year of the 70th birthday ($i = 1$) is:

$$s_1 = c_1 r_0 (1 - 0.5d_1).$$

Now suppose a screen at the end of year 3, that is, on the 73rd birthday, and for this situation denote the probability of diagnosis of breast cancer in year i by c_i^1 and the probability of dying of breast cancer in year i by s_i^1. Now,

$$c_i^1 = c_i \quad \text{and} \quad s_i^1 = s_i \quad \text{for } i = 1, 2, 3.$$

The probability of having a cancer detected at the extra screen is:

$$v_4 = \frac{b_4(1 - e^{-3\lambda_2})}{\lambda_2} \prod_{i=1}^{3} (1 - d_i).$$

Since with uniform incidence I, the probability of a presymptomatic cancer occurring within 3 years and remaining presymptomatic to the end of the 3-year period is:

$$\int_0^3 I e^{-\lambda_2(3-s)} ds = \frac{I(1 - e^{-3\lambda_2})}{\lambda_2}.$$

Incidence of symptomatic cancer in year 4 is:

$$c_4{}^* = \frac{b_4(\lambda_2 - 1 + e^{-\lambda_2})(1 - 0.5d_4)}{\lambda_2}$$

and for $i = 4, 5, \ldots, 15$:

$$c_i{}^* = \frac{b_i(\lambda_2 - e^{-\lambda_2(i-4)} + e^{-\lambda_2(i-3)})(1 - 0.5d_i)}{\lambda_2} \prod_{j=4}^{i-1} (1 - d_j)(1 - b_j).$$

Thus,

$$c_i^* = b_i^1(1 - 0.5d_i)\prod_{j=4}^{i-1}(1 - d_j)(1 - b_j),$$

where

$$b_i^1 = b_i\frac{(\lambda_2 - e^{-\lambda_2(i-4)} + e^{-\lambda_2(i-3)})}{\lambda_2}.$$

Overall incidence of breast cancer in these years is therefore $c_4^1 = c_4^* + v_4$ and $c_i^1 = c_i^*$ for $i = 5, 6, \ldots, 18$.

The probability of dying in year i ($i > 3$) from a cancer detected by screening at the end of year 3, uncorrected for deaths from other causes, is:

$$t_i = \int_{i-4}^{i-3} \lambda_5 e^{-\lambda_5 s} ds = e^{-\lambda_5(i-4)} - e^{-\lambda_5(i-3)}.$$

As noted above, the probability of death from breast cancer in years 1–3 remains unchanged. For year 4, the probability of death from breast cancer is:

$$s_4^1 = (c_4{}^* r_0 + v_4 t_4)(1 - 0.5d_4) + \sum_{j=1}^{3} c_j(1 - 0.5d_j)\left(\prod_{k=j+1}^{3}(1 - d_k)\right) r_{4-j}(1 - 0.5d_4),$$

where λ_5 is as before. For year 5 and above, the probability is:

$$\begin{aligned} s_i^1 = {} & v_4 t_i(1 - 0.5d_i)\prod_{j=4}^{i-1}(1 - d_j) + \sum_{j=1}^{3} c_j(1 - 0.5d_j)\left(\prod_{k=j+1}^{i-1}(1 - d_k)\right) r_{i-j}(1 - 0.5d_i) \\ & + \sum_{j=4}^{i-1} c_j{}^* r_{i-j}(1 - 0.5d_j)\left(\prod_{k=j+1}^{i-1}(1 - d_k)\right)(1 - 0.5d_i) + c_i{}^* r_0(1 - 0.5d_i). \end{aligned}$$

The number of breast cancer deaths prevented by age 88 can be calculated as the difference between the cumulative sums of s_i and s_i^1. At each age from 70 to 87, the expected years of life remaining, excluding breast cancer as a cause of death, is calculated as:

$$E_i = \sum_{j=i}^{18}(j - i + 0.5)d_j\prod_{k=i}^{j-1}(1 - d_k).$$

The term in the product is defined as 1 if $i > j - 1$. The total years of life saved as a result of the screen at age 73 is calculated as:

$$T = \sum_{i=1}^{18} E_i(s_i - s_i^1).$$

2.3 Rate estimates used in the calculations

For purposes of the continuous time model, we used estimates of the preclinical incidence rate from rates of breast cancer incidence in women aged 70 or over in the UK[4] and of mortality from other causes calculated from published mortality rates in the UK.[5] These gave $\lambda_1 = 0.0035$ and $\lambda_4 = 0.0488$. The rate of progression from preclinical to symptomatic clinical disease and the fatality rates for preclinical and clinical breast cancers were derived from the Swedish Two-County Trial of Breast Cancer Screening.[6] This gave $\lambda_2 = 0.2500$, $\lambda_3 = 0.0565$ and $\lambda_5 = 0.0130$.

For the discrete time model, we used the same estimates of λ_2, λ_3 and λ_5. We used the same sources for the incidence of and mortality from breast cancer, but interpolated the incidence and mortality figures, published in 5-year age groups to give individual rates of incidence (b_i) and death from other causes (d_i) for each year of age between the 70th and 88th birthday. The estimates are shown in Table 1.

Table 1 England and Wales incidence rates of breast cancer and mortality rates from causes other than breast cancer by individual year of age, 70–88

Age	Breast cancer incidence rate per 1000 (b_i)	Mortality rate per 1000 from other causes (d_i)
70–71	3.23	16.43
71–72	3.21	19.74
72–73	3.19	23.04
73–74	3.25	26.35
74–75	3.30	29.66
75–76	3.36	32.97
76–77	3.42	36.27
77–78	3.47	39.58
78–79	3.51	42.89
79–80	3.55	46.20
80–81	3.58	49.50
81–82	3.62	60.31
82–83	3.66	71.11
83–84	3.76	81.92
84–85	3.87	92.72
85–86	3.97	103.52
86–87	4.08	114.33
87–88	4.19	125.13

3 Results

For the continuous time model, we obtain cumulative probabilities of death from breast cancer between age 70 and 88 of $P_1 = 0.0087$ and $P_2 = 0.0075$. That is per 1000 women alive at age 70, the effect of a screen (with 100% attendance of those still alive) at age 73 would be to prevent 1.2 deaths from breast cancer by age 88. Sensitivity analyses in which the rates of transition from preclinical to clinical disease and breast cancer death rates were 50% greater or 50% smaller than those listed above gave a range of deaths prevented from 0.5 to 1.5. Mixtures of populations with different rates of transition to clinical disease and correspondingly different rates of death from breast cancer (to model possible length bias) yielded an estimate of 1.1 breast cancer deaths prevented.

Table 2 shows the cumulative incidence and mortality from breast cancer for the two screening policies, from the discrete time model. For every 1000 women, 0.91 deaths would be prevented as a result of the additional screen at age 73, 6.8 years of life would be saved and an additional 2.2 breast cancer diagnoses would result. An additional 13.1 years of life would be spent with a diagnosis of breast cancer. Thus, for each death prevented, there would be two additional diagnoses of breast cancer, and for each year of life saved, there would be two additional years spent with breast cancer.

It could be argued that these are underestimates of the absolute benefit in screened women since women who are already seriously ill and likely to die in the near future will

Table 2 Projected cumulative incidence of and mortality from breast cancer up to age 88 per 1000 women screened for the last time at either age 70 or 73

	Last screen at age 70		Last screen at age 73	
Age	Cumulative breast cancer incidence per 1000	Cumulative breast cancer mortality per 1000	Cumulative breast cancer incidence per 1000	Cumulative breast cancer mortality per 1000
70–71	0.37	0.01	0.37	0.01
71–72	1.34	0.06	1.34	0.06
72–73	2.75	0.16	2.75	0.16
73–74	4.50	0.35	9.58	0.39
74–75	6.50	0.62	10.56	0.64
75–76	8.68	0.98	12.00	0.93
76–77	10.98	1.43	13.76	1.30
77–78	13.34	1.97	15.76	1.73
78–79	15.71	2.58	17.89	2.23
79–80	18.06	3.26	20.10	2.81
80–81	20.37	3.99	22.32	3.45
81–82	22.60	4.77	24.53	4.14
82–83	24.73	5.58	26.67	4.87
83–84	26.77	6.39	28.74	5.62
84–85	28.69	7.19	30.71	6.37
85–86	30.47	7.97	32.55	7.11
86–87	32.10	8.72	34.24	7.83
87–88	33.58	9.42	35.78	8.51

be unlikely to self-select for screening. In women who do not die of other causes than breast cancer before age 88, 2.6 breast cancer deaths would be avoided, 6.3 additional diagnoses of breast cancer would result, and the gain in years of life due to the additional screen was estimated as 20.3 per 1000 screened. An additional 50.8 years of life would be spent with a diagnosis of breast cancer per 1000 screened, around 2.5 extra years spent with breast cancer per year of life saved from the disease.

4 Discussion

We used estimates of survival of screen-detected and symptomatic tumours, screening lead time and rates of death from competing causes to estimate the likely effect of adding an extra screen at age 73 in the UK Breast Screening Programme on breast cancer incidence and mortality. We estimated that around one breast cancer death would be avoided per 1000 women attending for an extra screen. For each death prevented, around 7 years of life are estimated as saved, and around two additional diagnoses of breast cancer would occur. In the National Programme at the moment, a similar number of breast cancer deaths prevented are estimated per 1000 screening episodes, but for each life saved, 18 years of life is estimated to be saved and only one additional breast cancer diagnosis is estimated to occur.[7] The smaller number of years of life saved and the larger number of 'overdiagnosed' cases per life saved is due to the shorter life expectancy at age 73 than in ages 50–70.

If we apply the same screening costs as in the National Programme, this would amount to a cost of between £7000 and £8000 per year of life saved. Although this is more than twice the £3000 estimated for the National Programme, it could still be argued to be well within the criteria of cost-effectiveness.[8]

As one would expect, the effects are estimated to be greater in those women not destined to die of other causes in the 15 years of life between age 73 and 88, with around 2.6 breast cancer deaths avoided and 20.3 years of life saved (albeit at a greater cost of extra years of life spent with a diagnosis of breast cancer). This is relevant as comorbidity is often associated with not attending for screening. In the UK Breast Screening Frequency Trial, all-cause mortality in the following 3 years was around 2.6 times higher in those not attending than in those attending the first screen (data available from the authors). Thus, the benefit of the screening activity might be expected to lie between our figures of 6.8 and 20.3 years of life saved, for the population as a whole and the subgroup who do not die of other causes in the intervening 15 years.

Our figures are predicted from data from a number of separate sources. They cannot be regarded as definitive. The expansion of the age range for screening from 50–70 to 47–73 will be designed in such a way as to allow a randomised comparison of outcomes at each end of the age range. The results here should assist with scenario planning in the meantime.

In analysis of data from the previous extension of the age range for screening to include the 65–70 age group, Bennett *et al.*[9] found that the performance characteristics (detection rates, positive predictive values, etc.) of screening in this age group were good and that uptake rates were high. Although one might expect uptake rates to decline with age, the performance characteristics in women aged 71–73 can be expected to equal those of the 65–70 age group.

In conclusion, our results suggest a slightly more modest benefit of screening at age 73 than in ages 50–70 and at a higher price in terms of overdiagnosis. It is difficult to judge the value of the years of life saved against the overdiagnosis, but the financial cost per year of life saved is well within cost-effectiveness criteria in the developed world. The estimates remain to be confirmed or refuted by the results of the increase of the upper age limit for screening. It is hoped that they will contribute to the planning of the evaluation of the age extension.

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