Modelling the cost-effectiveness of alternative upper age limits for breast cancer screening in England and Wales

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TITLE: MODELLING THE COST-EFFECTIVENESS OF ALTERNATIVE UPPER AGE LIMITS FOR BREAST CANCER SCREENING IN ENGLAND AND WALES

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ABSTRACT [First-level Header]

Objectives: Currently in the UK the NHS Breast Screening Programme (NHSBSP) invites all women for triennial mammography between the ages of 47 to 73 years (the extension to 47 - 50 and 70 - 73 years is currently examined as part of a RCT). The benefits and harms of screening in women aged 70 years and over, however, are less well documented.

Methods: A mathematical model was built that allows the impact of screening policies on cancer diagnosis and subsequent management to be assessed. The model has two parts - a natural history model of the progression of breast cancer up to discovery, and a post-diagnosis model of treatment, recurrence and survival. The natural history model was calibrated to available data and compared against published literature. The management of breast cancer at diagnosis was taken from registry data and valued using official UK tariffs.

Results: The model estimated that screening would lead to over-diagnosis in 6.2% of screen-detected women at the age of 72 years, increasing up to 37.9% at the age of 90 years. Under commonly-quoted willingness to pay thresholds in the UK, our study suggests that an extension to screening up to the age of 78 years represents a cost-effective strategy.

Conclusion: This study provides encouraging findings to support the extension of the screening programme to older ages and suggest that further extension of the UK NHSBSP beyond the current upper age limit of 73 could be potentially cost effective according to current NHS willingness to pay thresholds, up to age 78.

INTRODUCTION [First-level Header]

Breast cancer is the most common malignancy in women, with the majority of cancers diagnosed in women aged 65 years and over [1;2]. Whilst younger women have seen dramatic breast cancer survival improvements in the past few years with the introduction of screening and improvement in the treatment of breast cancer, the survival improvements have been much smaller in older women[3;4]. Compared to younger women, women aged 70 years and over are not routinely offered chemotherapy or trastuzumab, and frailer older women may not be offered surgery or radiotherapy[5;6].

The question of whether the upper age limit of screening should be increased, and to what level, is therefore of great importance in the drive to improve cancer outcomes in older women. One of the key arguments in favour of extending the upper age limit of screening is the increasing life expectancy of western populations. The fitness of cohorts of the same age decile has also increased over the same time period[7].

In deciding on the upper age limit, the benefits, harms and cost effectiveness of screening women aged over 70 years must be taken into account but these are less well documented compared with those in younger women. The potential benefits of screening in older women may include a higher cancer detection rate, a reduction in the mastectomy rate[8] and an improvement in the cancer stage at presentation[9]. The potential harms of screening include anxiety, harms from investigation and biopsies for those recalled for false positives and the potential for over-diagnosis[10]. In an older age group of women, the screening benefit will be diluted by competing causes of death.

There is a lack of trial evidence on the effectiveness of screening strategies for breast cancer in women aged 70 years and over. Only two trials recruited women up to the age of 74 years old (Swedish 2 Counties Trial and the Swedish Malmo Trial)[11] and a joint analysis of the Swedish

studies indicated that there was insufficient power to determine whether there was an overall survival advantage for the cohort of screened women between age 70 and 74[12].

The cost-effectiveness of screening older women in the UK is not well documented. Economic evaluation conducted in other countries such as in Korea, Slovenia, China, Japan and USA suggest that extending screening up to 80 years has the potential to be cost-effective[13-19]. One UK study investigated the costs and benefits of extending screening up to the age of 73 years but did not consider extending screening to older ages[20].

The aim of this study is to examine whether extending screening to women aged over 70 years would represent a cost-effective use of NHS resources and to identify the upper age limit at which screening mammography should be extended in England and Wales.

METHODS [First-level Header]

Model structure [Second-level Header]

A patient level simulation model was built in R software (version 2.11.1) that allows the impact of screening policies on cancer diagnosis and subsequent management to be assessed. The model has two parts - a natural history model of the progression of breast cancer up to discovery, and a post-diagnosis model of treatment, recurrence and survival. At present, the NHSBSP involves screening every woman aged between 50-70 years every three years with a programme of extension ongoing up to age 73 in process at the moment and being evaluated in detail as part of the current screening extension trial.

The model evaluates the following strategies for extending the current NHSBSP (assuming triennial screening):

- Strategy S_0: The current NHSBSP, which is defined as a final invitation at age 69 (In practice the age at which the final invitation is received varies from 68-70. For simplicity the model assumes the same age for all women).
- Strategy S_1: One additional screening round for women aged 72.
- Strategy S_2: Two additional screening rounds for women aged 72 and 75

  and so on up to....
- Strategy S_7: Seven additional screening rounds for women aged 72, 75, 78, 81, 84, 87 and 90

Other screening intervals (i.e. annual, biennial...) were not assessed as they were considered irrelevant for the UK context and for our research question, i.e. extension of the current screening programme to the elderly woman aged 70 years old and over.

The model compares the incremental costs and benefits of each strategy (S_{j+1}) to the previous strategy (S_j) and therefore, the costs and benefits relate to the incremental effect of each additional screening round.

The model simulates the life histories of a sufficiently large sample of women (one million) who may or may not develop breast cancer. For each simulated woman, we determine her stage of disease and in particular whether she has detectable asymptomatic disease at any of the screening rounds included in strategy S_7. We then determine, for each screening round where she does have detectable asymptomatic disease, whether screen-detection actually occurs or fails due to either non-attendance or a false negative test. We also consider women that would be detected in the current NHSBSP (i.e. before the age of 69 in the model).

The simulation of the individual women event histories uses what is known as the Monte Carlo sampling approach. This means that each uncertain event within the woman's modelled lifetime can occur randomly, but overall the events conform to a pattern which is specified by the evidence available.

All simulated women are assumed to incur invitation costs. Invitation costs consist of the costs associated with the letter of invitation to attend screening (postage, administration time, printing…). The women who actually attend incur screening costs in addition to invitation costs. Those who receive a positive result incur diagnostic costs. For those who are diagnosed (identified as described above), we calculate the net costs and benefits of screening by determining the costs and survival of these women, then subtracting the costs and benefits that would accrue if they had not been detected through screening.

Further details of the methodology, assumptions and inputs are available in a full report available through the Web[21].

The natural history of breast cancer [Second-level Header]

A natural history model describing the progression of breast cancer has been developed and is described here briefly (Further details of the methodology, assumptions and inputs are available in a full report available through the Web[21]). For each woman entering the simulation, the natural history model enables us to simulate the time at which breast cancer presents and the characteristics of the cancer (in terms of tumour size, nodal involvement, grade, and ER status) at the time of detection in the absence of screening and the characteristics of the cancer if detected earlier through screening.

We represented the disease progression of breast cancer in a mathematical form and we used published and unpublished data to inform the model structure and input parameters. Although there are some published data on natural history of breast cancer, notably in the US using the SEER dataset,[22;23] parameters for this UK analysis were estimated using a calibration exercise which used an iterative approach. Such approach was used in order for the model to fit to the following observed data; prognostic profile (tumour size, grade, ER, nodal status and number of positive nodes) at diagnosis in women aged over 70 from the West Midlands Cancer Intelligence Unit (WMCIU) and the Eastern Cancer Registry Information Centre (ECRIC), age-related breast cancer incidence in the West Midlands before the implementation of screening, and routine data from the NHSBSP on screening tumour size at detection in women aged over 60 years (as data were limited in women aged over 70 years).

Impact of breast cancer diagnosis on survival [Second-level Header]

The impact of early detection of breast cancer on mortality was modelled by a shift in prognosis profile at diagnosis which in turn translates into a shift in survival. Having identified the women within the simulation who would be detected at each screening round, the impact of that detection compared to allowing the disease to present symptomatically was estimated. Death from breast cancer causes was ascertained by comparing survival in the general population and in breast cancer patients. Statistical survival analysis modelling was performed on registry data[24] to evaluate the impact of prognostic profile at diagnosis on survival and applied at the age at which the cancer presents

symptomatically, according to the biology of the cancer (tumour size, grade, nodal and ER status). A log-logistic parametric model was selected for the basecase, but different parametric statistical models were also examined such as exponential, gompertz, and Weibull regression models (Further details of the methodology, assumptions and inputs are available in a full report available through the Web[21]

In the scenario where screening occurs, a similar approach is used. There are no directly reliable available data on the survival of screen detected women over the age of 70 (some data exists for opportunistic screening; but the sample size is low, these women are also not representative of the general population at that age, since e.g. they may have had a recent ambiguous screen result). Instead, we assumed that the relationship between the prognostic profile covariates and survival is the same for the screen-detected as it is for the symptomatically-detected women. Due to random variability within the simulation runs, however, some women can be sampled as dying earlier from breast cancer in the screening arm compared with the non-extended screening arm, especially if the time between screen-detection and the age at which the cancer would present symptomatically is long enough.

Two alternative scenarios are presented relaxing this assumption.

The management of breast cancer [Second-level Header]

The economic model includes resources used and costs associated with the primary treatment of breast cancer, treatment for recurrence, follow-up after breast cancer diagnosis and management for palliative care. Table 1 show the costs used within the model. Resource use for invasive disease was taken from the ECRIC[24]. Logistic regression models were constructed from registry data to calculate the probability of incurring each type of resource use adjusted for a set of covariates (Further details of the methodology, assumptions and inputs are available in a full report available through the Web[21]).

Resource use associated with the management of in-situ disease was derived from an analysis conducted in elderly women diagnosed in the West Midlands[25].

For resource use associated with recurrent disease, the model calculates the probability of having and being treated for recurrence, using data from the West Midlands cancer registry[25]. The costs associated with the management of recurrences were derived from a study by Thomas et al (2009)[26] adjusting for the fact that older women receive less chemotherapy compared with younger women and other factors. Palliative care costs are applied to the last year of life for women dying from breast cancer and were taken from Guest et al. (2002) after inflation [27]. Finally, based on NICE guidelines, we assumed that the follow-up after early breast cancer consists of one mammogram and one outpatient consultation every year for 5 years post-breast cancer diagnosis[28].

Unit costs for breast cancer management[Second-level Header]

Costs are estimated from the NHS perspective and are derived from official tariffs, published literature and assumptions when appropriate. Costs are expressed in 2008/2009 UK pounds as this was the price year used at the time the analysis was conducted to inform decision making. Unit costs and sources used in the model are presented in Table 1.

Data from the NHSBSP showed that about 4.0% (n = 15,457 / 388,866) of women aged 65-70 are referred for assessment (incident screen data).[29] The mean cost for management of further investigation was estimated to be about £183.5 for the central case. Among women recalled for assessment, the model assumes that all referrals will undergo either further mammography or an ultrasound and uses the average cost of the two procedures (£57.80). It is also assumed that 46.4% (n = 7,176 / 15,457) of women who are referred undergo cytology/core biopsy (NHS BSP).[29]

[INSERT TABLE 1 HERE]

Health-related Quality of Life [Second-level Header]

Utility weights are applied to 6 pre-defined health states; disease free, in-situ disease, stage I (no nodal involvement), stage II (1-3 nodes), stage III (4+ nodes, but no metastases) and stage IV(4+ nodes and metastases). There is a lack of data on the duration of the diagnostic process for breast cancer on quality of life; therefore expert opinion was necessary. The model assumes that women diagnosed with stage 0, stage I/II, stage III and stage IV have a decrease in quality of life for 1, 2, 3 years and their lifetime respectively.

The utility weight in the absence of disease (disease-free) is assumed to be that of the general population. Utility weights for stage I (0.91; IQ: 0.5 – 1), stage II (0.75; IQ: 0.26 – 0.99), stage III (0.51; IQ: 0.25 – 0.94) and stage IV (0.36; IQ: 0 – 0.75) breast cancer are taken from Schleinitz and colleagues (2006)[30] and are age-adjusted in the model using the trend observed in the general population[31]. Finally, the model assumes that the utility weight for women with in-situ disease is between the utility weight for women with no breast cancer and women with stage I breast cancer.

The model also includes the negative impact associated with the pain of undertaking a mammogram (reduction in QoL of 20% for 2 hours) and the anxiety after recall for further investigation (reduction in QoL of 35% for 3 weeks) using published data [32;33]supported by expert opinion.

Analysis [Second-level Header]

Costs and health effects are discounted at 3.5% according to NICE recommendations for health economic evaluation in the UK[34].

Univariate and multivariate sensitivity analyses are performed to assess the impact of varying key model parameters and assumptions on the incremental cost effectiveness ratios (ICER). Notably, the model examines different parametric distributions for survival in breast cancer patients (exponential, weibull, gompertz, log-logistic), variation in costs (screening cost, recall for further investigation, primary treatment, follow-up, recurrence), different utility weight and duration in each health states, variation in the recall rate for further investigation, different sensitivity associated with screening and tumour growth rate. Parameters are varied over a feasible range of plausible values.

RESULTS [First-level Header]

Number of cases detected through screening per 100,000 women invited to screening [Second-level Header]

The model predicts (Fig. 1) that the addition of one screening round at the age of 72 years old would allow the detection of 752 breast cancer cases per 100,000 women invited to screening, of which 6.2% (n = 47 cases per 100,000 invitation) would result in over-diagnosis, i.e. would have died of other causes before presenting with breast cancer in the absence of screening. Whilst the number of breast cancer cases per 100,000 women invited to screening remains relatively stable with the addition of screening up to 90 years of age, the model predicts that the proportion of breast cancer cases detected which are over-diagnosed increases substantially as age increases up to 37.9% for screening women at the age of 90 years.

[INSERT Figure 1]

Incremental discounted life years and quality of life years per 100,000 women invited to screening [Second-level Header]

Figure 2 shows that the extension of screening up to the age of 72 years old (addition of one screening round) is associated with an incremental 653 life years and 512 QALYs per 100,000 women invited to screening respectively compared with screening up to 69 years old, the current screening strategy in the UK. The addition of an additional screening round (2^{nd} round) at the age of 75 years old was associated with an incremental 462 life years and 354 QALYs per 100,000 invitations compared with screening up to 72 years old. The estimated incremental life years gained decreases as the number of screening rounds increases, but the addition of a further screening round (up to 90 years old) compared with the previous screening strategy is always estimated to be associated with an increase in

life years. In contrast, the incremental QALY gained for the addition of a screening round beyond 84 years old was small (due to the small gain in life years driven by competing risks for women at older ages) and was outweighed by the reduction in health related quality of life associated with the mammogram and recall for further investigation.

Incremental discounted costs per 100,000 women invited to screening [Second-level Header]

Table 2 details a breakdown of the costs for the addition of each screening round including additional screening costs (the invitation, the mammogram itself, and recalls for further investigation), as well as the additional costs for the primary treatment of breast cancer, and follow-up . In all scenarios, these additional costs of screening were not outweighed by the reduction in costs of treatment, recurrence and palliative care due to early detection. The addition of one screening round at the age of 72 years old was associated with an incremental discounted total cost of £2,995,000 per 100,000 women invited to screening (Fig. 2) compared with screening up to 69 years old (current screening strategy). The incremental cost of extending screening up to 90 years old compared with screening up to 87 years was £2,941,000 per 100,000 women invited to screening.

Discounted costs per life years gained and QALY gained[Second-level Header]

Table 2 also presents the estimated discounted incremental cost per life year and QALY gained of extending screening triennially up to the age of 90 years. Extending screening to an older age becomes less and less cost-effective as the screening-age is extended. Under a commonly accepted cost-effectiveness threshold in the UK (£20,000 per QALY gained), screening older women is estimated to be a cost-effective use of NHS resource up to the age of 78 years (with an estimated incremental cost per QALY gained of £15,072 compared with screening up to 75 years) i.e. the addition of 3 further screening rounds beyond recent practice in England and Wales. The model also predicts that the estimated harms would begin to outweigh the potential benefits if screening is

extended beyond the age of 84 years old (i.e. screening beyond the age of 84 is estimated to cause net health harms).

Examining different assumptions on the impact of screening on survival [Second-level Header]

Two alternative scenarios were conducted. Under *Scenario 1*, (i.e. where the model assumes that screen-detected women die at the same time as if not detected through screening), the results are broadly similar to the base case. Screening older women is still estimated to be a cost-effective use of NHS resource up to the age of 78 years, with an estimated incremental cost per QALY gained of £13,338 compared with screening up to 75 years (a slightly lower incremental cost per quality gained than the £15,072 estimated in the base case).

Under *Scenario 2*, (i.e. where the model assumes that screening necessarily translates into an improvement in survival), the results suggest that a fourth additional screening round could potentially be cost effective. Under this scenario, screening older women would be estimated as cost-effective up to the age of 81 years (with an estimated incremental cost per QALY gained of £19,204 compared with screening up to 78 years). The incremental cost per QALY of screening up to age 78 years compared with screening up to 75 years would then be estimated at £11,437.

Sensitivity analyses [Second-level Header]

The base case model estimated screening up to 78 years old to be the most cost effective strategy. We have examined the robustness of this conclusion using sensitivity analysis in which parameters in the model are varied to find a threshold level which would change our conclusions. Figure 3 shows that this strategy would no longer be cost-effective assuming a recall rate for further investigation of 10% (£23,499), lower utility weights for the diagnosis of breast cancer, assuming duration of 3 years for each health state excluding metastasis (£22,124), or assuming a cost of screening equal to £40.40 (£21,807).

[INSERT FIGURE 3 HERE]

DISCUSSION [First-level Header]

This study is the first to attempt to use cost-effectiveness modelling to identify the upper age limit at which screening mammography should be extended in England and Wales. The analysis is derived from a mathematical model comprising two parts – a natural history model of the progression of breast cancer up to discovery, and a post-diagnosis model of treatment, recurrence and survival. Routine data from cancer registries (WMCIU and ECRIC) alongside data from the NHSBSP were used to calibrate the natural history and screening model parameters for women both detected through screening and presenting with clinical symptoms in the absence of screening[24;25;29]. Our study suggests that an extension of the screening program to 78 years old may represent a cost-effective use of NHS resources under a commonly-accepted 'willingness to pay thresholds' in the UK of £20,000 per QALY gained. Of note, a pilot of extension (examined within a RCT) to 73 years of age is already in place but results will not be available for many years.

This modelling study is based on a number of data sources specific to England and Wales, and as such we would not suggest that the specific findings are directly generalizable to other settings / countries. Nevertheless, the general structure of the model, its use of published evidence and relatively common types of data sources (e.g. cancer registry data), means that wider adaptations to other countries is very likely to be possible where research data sources exist.

Studies that have investigated the cost-effectiveness of mammography in other countries have reported results that differ widely.[18;35;36] For example, a recent study by Rojnik et al. (2008) reported that extending the upper age limit for screening in Slovenia from 70 to 75would lead to an ICER of €14,350 per QALY gained.[37] The ICER for extending screening up to the age of 80 years old compared to 75 years old was estimated to be €18,471. In the US, Mandelblatt et al. (2005) estimated that the cost per QALY gained of extending screening up to 79 years old compared to 70

years old was $155,865 per QALY gained.[38] Furthermore, Barratt et al. (2002) estimated the cost per QALY gained to range from $8,119 to $27,751 for extending screening up to 79 years old in Australia.[36] This variation in results is partly explained by different assumptions about the impact of breast cancer diagnosis on the quality of life, higher management costs observed in the US and differences in assumptions about the impact of earlier detection on survival.

As with any analysis, there are some potential limitations that need to be considered when interpreting our findings. A key driver of the benefit of screening is the extent to which early detection impacts on survival. We used registry data from women who had presented symptomatically. Costs were also estimated from an NHS perspective only, despite studies suggesting that women treated for breast cancer pay directly for complementary therapies[39]. There was also uncertainty around the cost for screening mammography with a cost ranging from £15 to about £41 in the literature which was shown to influence the ICER. We also assumed that the cost of screening mammography was similar by age group, which may not be true. Robust data on the impact of breast cancer diagnosis on the quality of life and the recall rate may also be useful and provide a more accurate estimate. The natural history of breast cancer could also be represented in different ways; which may influence results. We also acknowledge that over-diagnosis may be defined differently in the literature [40] which may have a marked impact on the percentage calculated. The Marmot review provided a very detailed overview of this issue and estimated that the most likely level of over diagnosis is about 19%.[41] The true figure is likely to be sensitive to the age of the population [42] under study. In the current analysis, the term of over-diagnosis was used to define cancers that would be detected in women who would otherwise have died of other causes without a clinical diagnosis of breast cancer in the absence of screening. The model estimated that screening would lead to over-diagnosis in 6.2% of screen-detected women at the age of 72 years, increasing up to 30.1% at the age of 90 years. The definition for ‘over-diagnosis’ used in this study does not make any difference to our results as we are modelling the costs and benefits for everyone irrespective of whether they are considered to fall into a definition

of over-diagnosis. Finally, neither probabilistic sensitivity analysis nor value of information were undertaken to establish which the most uncertain parameters are.

There are also several further developments to the modelling and analysis which could be of benefit to decision makers. The use of more complex calibration approach such as Bayesian Markov Chain Monte Carlo[43] would enable not only central estimates of model parameters to be obtained, but also an expression of the uncertainty around these estimates and would enable a fuller probabilistic sensitivity analysis to be undertaken. We have also assumed within the model that an additional screening round would have universal invitation, but more complex scenarios could potentially be modelled in which the prognostic factors for individual women both in terms of their breast cancer risk and competing risk of other-cause mortality might be taken into account in designing the screening programme strategy.

Whilst our findings are encouraging for an extension of the breast screening programme to older ages, further research and modelling is needed before extending screening to older ages, because there remains uncertainty about both some of the model parameters and how implementation in practice would occur. There are also further developments to the modelling and analysis which could be useful. Previous considerations of extending the screening programme, including the current extension to age 73 (examined within a RCT), involved substantial pilot work and use of clinical and management resources.

One of the key issues relating to the clinical benefit of screening is that of overdiagnosis. Extending screening by a further two rounds would undoubtedly be associated with a higher rate of over-diagnosis due to the relatively reduced life expectancy of this older cohort of women.

CONCLUSION [First-level Header]

The findings of our analysis suggest that extending the breast screening programme beyond the current upper age limit of73 (at the moment, the extension to 73 is examined within a RCT) to around 78 could be a potentially cost-effective use of NHS resources. Our sensitivity analyses demonstrate that this finding has a degree of robustness, and also suggest some priorities for research in terms of data collection and further detailed modelling. This study provides encouraging findings to support the extension of the screening programme to older ages in England and Wales, and we hope that policy makers would consider the findings from this study as part of the decision-making process regarding future possible extension of the breast screening programme. It is important that any further age extension makes women aware of the potential risks of screening as well as the potential benefit[44].

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