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Modeling the Cost-Effectiveness of Alternative Upper Age Limits for Breast Cancer Screening in England and Wales

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ABSTRACT

Background: Currently in the United Kingdom, the National Health Service (NHS) Breast Screening Programme invites all women for triennial mammography between the ages of 47 and 73 years (the extension to 47–50 and 70–73 years is currently examined as part of a randomized controlled trial). The benefits and harms of screening in women 70 years and older, however, are less well documented. **Objectives:** The aim of this study was to examine whether extending screening to women older than 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:** A mathematical model that allows the impact of screening policies on cancer diagnosis and subsequent management to be assessed was built. The model has two parts: a natural history model of the progression of breast cancer up to discovery and a postdiagnosis 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 overdiagnosis 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 United Kingdom, our study suggests that an extension to screening up to the age of 78 years represents a cost-effective strategy. **Conclusions:** This study provides encouraging findings to support the extension of the screening program to older ages and suggests that further extension of the UK NHS Breast Screening Programme up to age 78 years beyond the current upper age limit of 73 years could be potentially cost-effective according to current NHS willingness-to-pay thresholds.

Keywords: cost-effectiveness, elderly, mammography, screening.

Introduction

Breast cancer is the most common malignancy in women, with most of the cancers diagnosed in women 65 years and older [1,2]. Although younger women have seen dramatic improvements in breast cancer survival 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 with younger women, women 70 years and older 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 favor 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 older than 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

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overdiagnosis [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 70 years and older. Only two trials recruited women up to the age of 74 years (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 years [12].

The cost-effectiveness of screening older women in the United Kingdom is not well documented. Economic evaluation conducted in other countries such as Korea, Slovenia, China, Japan, and the United States 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 ages beyond 73 years [20].

The aim of this study was to examine whether extending screening to women aged older than 70 years would represent a cost-effective use of National Health Service (NHS) resources and to identify the upper age limit at which screening mammography should be extended in England and Wales.

Methods

Model Structure

A patient-level simulation model was built in R Development Core Team (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 postdiagnosis model of treatment, recurrence, and survival. At present, the NHS Breast Screening Programme (NHSBSP) involves screening every woman aged between 50 and 70 years every 3 years with a program of extension ongoing up to age 73 years 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):

1. Strategy S_0: The current NHSBSP, which is defined as a final invitation at age 69 years. (In practice the age at which the final invitation is received varies from 68 to 70 years. For simplicity, the model assumes the same age for all women.)
2. Strategy S_1: One additional screening round for women aged 72 years.
3. Strategy S_2: Two additional screening rounds for women aged 72 and 75 years and so on up to Strategy S_7.
4. Strategy S_7: Seven additional screening rounds for women aged 72, 75, 78, 81, 84, 87, and 90 years.

Other screening intervals (i.e., annual, biennial, etc.) were not assessed because they were considered irrelevant for the UK context and for our research question, that is, the extension of the current screening program to elderly women aged 70 years and older.

The model compares the incremental costs and benefits of each strategy (S_{j+1}) with 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 (1 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 in which she does have detectable asymptomatic disease, whether screen detection actually occurs or fails because of either nonattendance or a false-negative test result. We also consider women who would be detected in the current NHSBSP (i.e., before the age of 69 years 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 modeled lifetime can occur randomly, but overall the events conform to a pattern that is specified by the evidence available. All simulated women are assumed to incur invitation costs. Invitation costs consist of costs associated with the letter of invitation to attend screening (postage, administration time, printing, etc.). 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 previously), 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

A natural history model describing the progression of breast cancer has been developed and is described here briefly (more detail is given in Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.06.006). 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 tumor size, nodal involvement, grade, and estrogen-receptor (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 the natural history of breast cancer, notably in the United States using the Surveillance, Epidemiology, and End Results (SEER) data set [22,23], parameters for this UK analysis were estimated using a calibration exercise that used an iterative approach. Such an approach was used for the model to fit to the following observed data: prognostic profile (tumor size, grade, ER, nodal status, and number of positive nodes) at diagnosis in women older than 70 years from the West Midlands Cancer Intelligence Unit 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 tumor size at detection in women older than 60 years (because data were limited in women older than 70 years).

Impact of Breast Cancer Diagnosis on Survival

The impact of early detection of breast cancer on mortality was modeled 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 with allowing the disease to present symptomatically was estimated. Death from breast cancer causes was ascertained by comparing survival in the general population and in patients with breast cancer. Statistical survival analysis modeling 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 (tumor size, grade, and

nodal and ER status). A log-logistic parametric model was selected for the base case, but different parametric statistical models were also examined such as exponential, gompertz, and Weibull regression models (see Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.06.006).

In the scenario in which screening occurs, a similar approach is used. There are no directly reliable available data on the survival of screen-detected women older than 70 years (some data exist for opportunistic screening, but the sample size is low, and these women are also not representative of the general population at that age because, for example, 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. Because of random variability within the simulation runs, however, some women can be sampled as dying earlier from breast cancer in the screening arm than in the nonextended 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 lessening this assumption. These are described in Appendix 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.06.006.

The Management of Breast Cancer

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 presents the costs used within the model.

Resource use data for invasive disease were 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 (see Appendix 4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.06.006). 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. [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. [27] after inflation. Finally, on the basis of National Institute of Health and Care Excellence guidelines, we assumed that the follow-up after early breast cancer consists of one mammogram and one outpatient consultation every year for 5 years after breast cancer diagnosis [28].

Unit Costs for Breast Cancer Management

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

Table 1 – Unit costs of various aspects of breast cancer treatment, follow-up, and disease outcomes as used in the health economic model.

Activity	Cost used in the economic model (£)*	Source
Primary treatment of breast cancer		
Mastectomy alone	2,937	NHS reference cost 2006–2007 [28,43]
WLE alone	2,519	NHS reference cost 2006–2007 [28,43]
SLNB in combination with surgery	3,355—WLE 3,910— mastectomy	Derived from Pandharipande et al. [44]
ALND in combination with surgery and no SLND	3,914—WLE 4,562— mastectomy	Derived from Pandharipande et al. [44]
ALND in combination with surgery and SLND	5,345—WLE 6,231— mastectomy	Derived from Pandharipande et al. [44]
Radiotherapy	2,288	The PRIME trial [45]
Hormonal therapy per annum (maximum 4.5 y)	1,002	Cooper et al. [46]
Chemotherapy (6 mo)	8,788	Cooper et al. [46]
Follow-up after breast cancer diagnosis		
Follow-up attendance nonadmitted face to face (clinical oncology)—800	99	NHS reference cost 2008–2009 [47]
Band B1—Mammography (RBB1)	44.60	NHS reference cost 2005–2006 [48] uplifted to 2008–2009 [47]
Treatment for recurrence and palliative care		
Recurrence	18,018	Derived from Thomas et al. [26] and assumptions
Palliative care	3,228	Based on Guest et al. [27] and uplifted to 2008–2009 [47]
Costs associated with the screening program		
Screening	14.90	Legood and Gray [49] and uplifted to 2008–2009 [47]
Invitation for screening	11.90	Johnston et al. (1996) and uplifted to 2008–2009 [50]
Recall for further investigation	183.5	Derived from NHS reference cost (2006–2007) [43] uplifted to 2008–2009 [47] and NHSBSP [29]
Fine-needle biopsy of the breast—OPFNB1	271	NHS reference cost 2006 [50] and uplifted to 2008–2009 [47]
Ultrasound scan (diagnostic imaging: Other RA23Z)	71	NHS reference costs 2008–2009 [47]

ALND, axillary lymph node dissection; NHS, National Health Service; NHSBSP, National Health Service Breast Screening Programme; SLNB, sentinel lymph node biopsy; WLE, wide local excision.

* Inflated to 2008–2009.

because 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 of 388,866) of the women aged 65 to 70 years 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 of 15,457) of the women who are referred undergo cytology/core biopsy (NHSBSP) [29].

Health-Related Quality of Life

Utility weights are applied to six predefined 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 (QOL); therefore, expert opinion was necessary. The model assumes that women diagnosed with stage 0, stage I/II, stage III, and stage IV breast cancer have a decrease in QOL for 1 year, 2 years, 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; inter-quartile (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 et al. [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 the utility weight for women with stage I breast cancer. The model also includes the negative impact associated with the pain of undertaking a mammogram (reduction of 20% in QOL for 2 hours) and the anxiety after recall for further investigation (reduction of 35% in QOL for 3 weeks) using published data [32,33] supported by expert opinion.

Analysis

Costs and health effects are discounted at 3.5% according to National Institute for Health and Care Excellence (NICE) recommendations for health economic evaluation in the United Kingdom [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 (ICERs). Notably, the model examines different parametric distributions for survival in patients with breast cancer (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 state, variation in the recall rate for further investigation, different sensitivity associated with screening, and tumor growth rate. Parameters are varied over a feasible range of plausible values.

Results

Number of Cases Detected through Screening per 100,000 Women Invited to Screening

The model predicts (Fig. 1) that the addition of one screening round at the age of 72 years 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 overdiagnosis (i.e., the patient would have died of other causes before presenting with breast cancer in the absence of screening).

Although the number of breast cancer cases per 100,000 women invited to screening remains relatively stable with the addition of screening up to age 90 years, the model predicts that the proportion of breast cancer cases detected that are overdiagnosed increases substantially as age increases, up to 37.9% for screening women at the age of 90 years.

Incremental Discounted Life-Years and QOL Years per 100,000 Women Invited to Screening

Figure 2 shows that the extension of screening up to the age of 72 years (addition of one screening round) is associated with an incremental 653 life-years and 512 quality-adjusted life-years (QALYs) per 100,000 women invited to screening, respectively, compared with screening up to 69 years, the current screening strategy in the United Kingdom. The addition of an additional screening round (second round) at the age of 75 years was associated with an incremental 462 life-years and 354 QALYs per 100,000 invitations compared with screening up to the age of 72 years. 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) compared with the

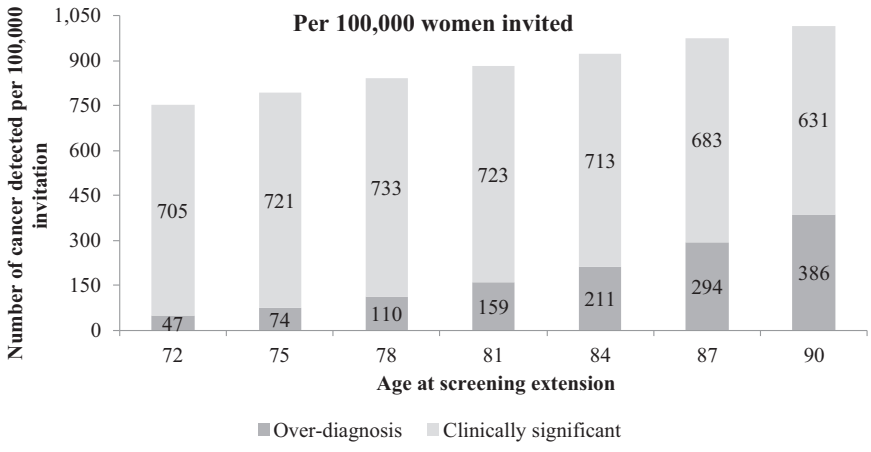

Fig. 1 – Predicted number of breast cancer cases detected and overdiagnosis per 100,000 women invited in each age group to screening (compared with the previous screening strategy).

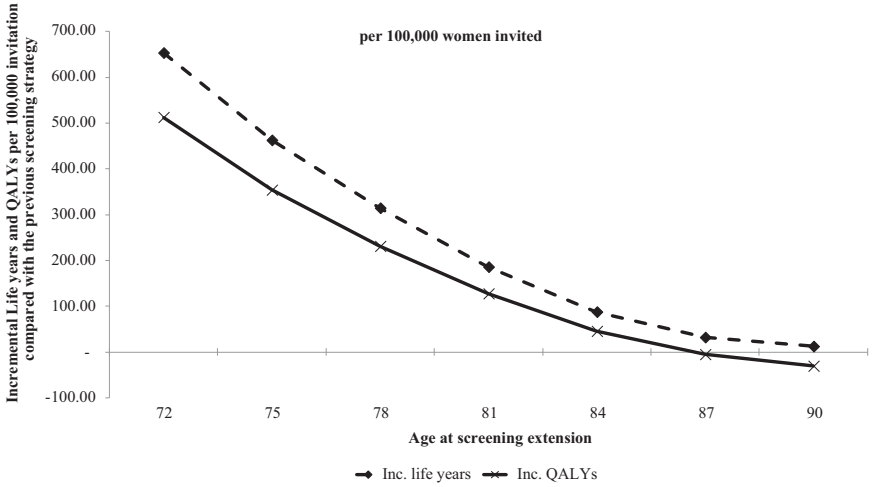

Fig. 2 – Incremental life-years, QALYs, and costs per 100,000 women invited to screening (compared with the previous screening strategy). QALY, quality-adjusted life-year.

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 age 84 years was small (as a result of the small gain in life-years driven by competing risks for women at older ages) and was outweighed by the reduction in health-related QOL associated with the mammogram and recall for further investigation.

Incremental Discounted Costs per 100,000 Women Invited to Screening

Table 2 details a breakdown of costs for the addition of each screening round, including additional screening costs (the invitation, the mammogram itself, and recalls for further investigation) and 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 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 age 69 years (current screening strategy). The incremental cost of extending screening up to age 90 years compared with screening up to age 87 years was £2,941,000 per 100,000 women invited to screening.

Discounted Costs per Life-Years Gained and QALY Gained

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 United Kingdom (£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

Table 2 – Incremental cost per life-years and QALY gained (compared with the previous screening strategy).

Outcome	Strategy 1 (up to 72 y)	Strategy 2 (up to 75 y)	Strategy 3 (up to 78 y)	Strategy 4 (up to 81 y)	Strategy 5 (up to 84 y)	Strategy 6 (up to 87 y)	Strategy 6 (up to 87 y)
Primary treatment (£)	1,442,274	1,546,467	1,639,677	1,726,968	1,734,939	1,743,803	1,682,331
Recurrence (£)	–457,125	–326,562	–339,639	–275,051	–186,559	–139,789	–109,518
Follow-up cost (£)	92,071	98,554	104,931	114,897	117,823	122,740	126,338
Palliative care (£)	–389,359	–328,405	–248,314	–182,399	–99,243	–27,885	–549
Screening mammography (£)	1,116,888	1,007,829	908,935	819,434	738,811	666,562	601,403
Invitation cost (£)	1,190,000	1,073,312	968,066	873,140	787,522	710,300	640,650
Recall for investigation (£)	550,364	496,530	447,704	401,650	358,452	324,444	295,776
Total incremental costs (£)	3,545,114	3,567,725	3,481,361	3,478,639	3,451,744	3,400,175	3,236,430
Incremental life-years	653.16	462.44	314.31	185.71	87.51	31.91	12.25
Incremental QALYs associated with breast cancer	561.07	396.73	268.88	160.63	74.38	20.26	–7.99
Disutility associated with screening	–48.61	–42.96	–37.91	–33.24	–28.96	–25.54	–22.64
Total incremental QALYs	512.47	353.77	230.98	127.39	45.42	–5.27	–30.63
Cost per life- year gained (£)	5,428	7,715	11,076	18,731	39,445	106,554	264,289
Cost per QALY gained (£)	6,918	10,085	15,072	27,306	75,997	Dominated	Dominated

QALY, quality-adjusted life-year.

cost per QALY gained of £15,072 compared with screening up to age 75 years), that is, the addition of three 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 (i.e., screening beyond the age of 84 years is estimated to cause net health harms).

Examining Different Assumptions on the Impact of Screening on Survival

Two alternative scenarios were conducted. Under scenario 1 (i.e., in which 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 resources up to the age of 78 years, with an estimated incremental cost per QALY gained of £13,338 compared with screening up to age 75 years (a slightly lower incremental cost per QALY gained than the £15,072 estimated in the base case).

Under scenario 2 (i.e., in which 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 age 78 years). The incremental cost per QALY of screening up to age 78 years compared with screening up to age 75 years would then be estimated at £11,437.

Sensitivity Analyses

The base-case model estimated screening up to age 78 years 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 that would change our conclusions. Figure 3 shows that this strategy would no longer be cost-effective assuming a recall rate of 10% (£23,499) for further investigation, lower utility weights for the diagnosis of breast cancer, assuming a duration of 3 years for each health state excluding metastasis (£22,124), or assuming a cost of screening equal to £40.40 (£21,807).

Discussion

This study is the first to attempt to use cost-effectiveness modeling 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 postdiagnosis model of treatment, recurrence, and survival. Routine data from cancer registries (West Midlands Cancer Intelligence Unit 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 age 78 years may represent a cost-effective use of NHS resources under a commonly accepted "willingness-to-pay threshold" of £20,000 per QALY gained in the United Kingdom. Of note, a pilot of extension (examined within a randomized controlled trial) to age 73 years is already in place, but results will not be available for many years.

This modeling 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. [35] reported that extending the upper age limit for screening in Slovenia from 70 to 75 years would lead to an ICER of €14,350 per QALY gained. The ICER for extending screening up to age 80 years compared with age 75 years was estimated to be €18,471. In the United States, Mandelblatt et al. [18] estimated that the cost per QALY gained of extending screening up to age 79 years compared with age 70 years was $155,865 per QALY gained. Furthermore, Barratt et al. [36] estimated the cost per QALY gained to range from $8,119 to $27,751 for extending screening up to age 79 years in Australia. This variation in results is partly explained by different assumptions about the impact of breast cancer diagnosis on the QOL, higher management costs observed in the United States, 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 has an effect 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 [37]. 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 QOL 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 overdiagnosis may be defined differently in the literature [38], 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 overdiagnosis is about 19% [39]. The true figure is likely to be sensitive to the age of the population [40] under study. In the present analysis, the term overdiagnosis 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 overdiagnosis 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 overdiagnosis used in this study does not make any difference to our results because we are modeling the costs and benefits for everyone irrespective of whether they are considered to fall into a definition of overdiagnosis. Finally, neither probabilistic sensitivity analysis nor value of information was undertaken to establish which parameters are the most uncertain.

There are also several further developments to the modeling and analysis that could be of benefit to decision makers. The use of a more complex calibration approach such as Bayesian Markov Chain Monte-Carlo [41] 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

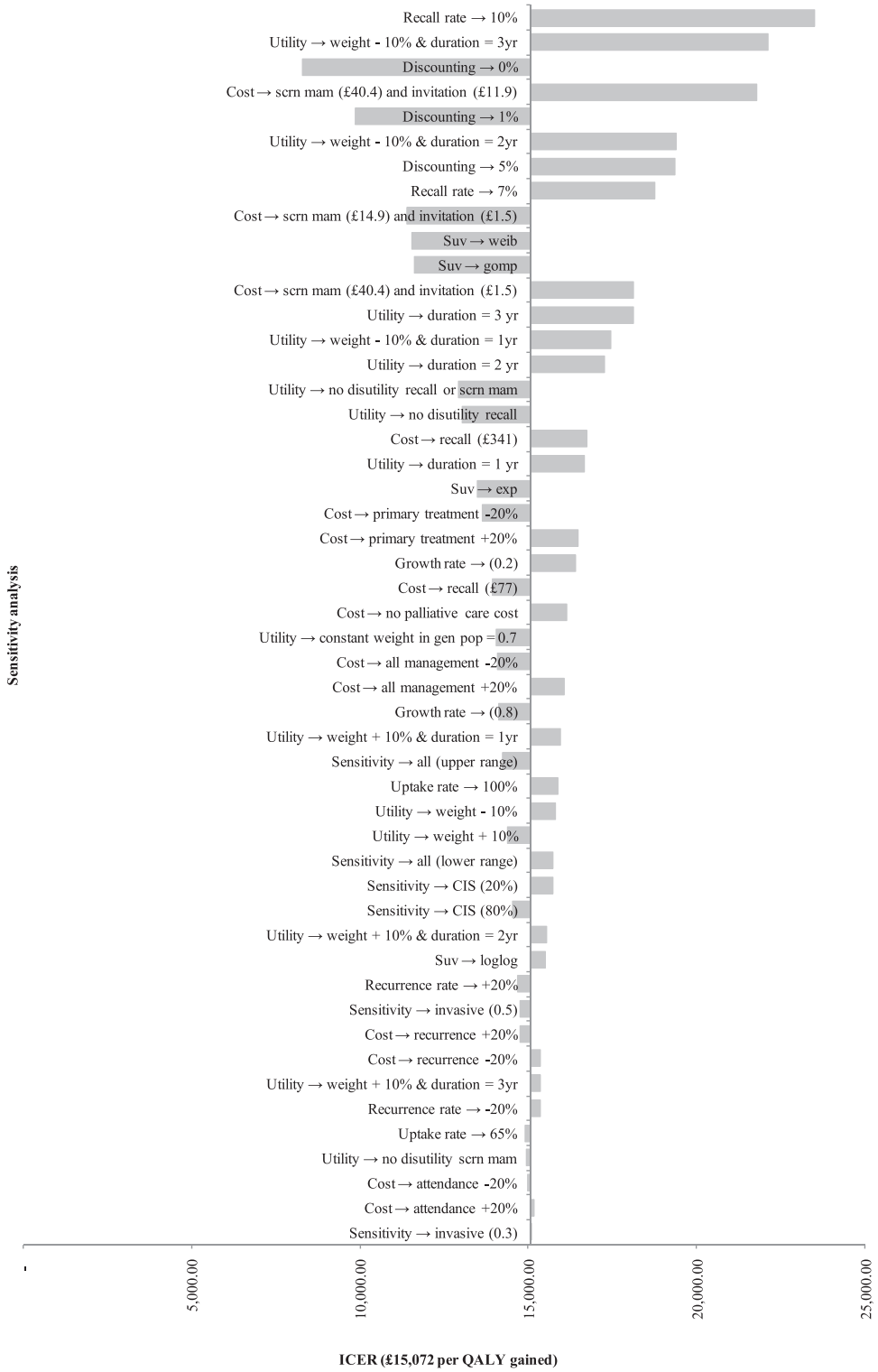

Fig. 3 – Univariate sensitivity analysis: testing the robustness of base-case conclusion that screening (scrn) up to age 78 years is the most cost-effective strategy. CIS, carcinoma in situ; Gomp, gompertz; ICER, incremental cost-effectiveness ratio; mam, mammography; QALY, quality-adjusted life-year; suv, survival curve; weib, weibull.

scenarios could potentially be modeled in which prognostic factors for individual women in terms of both their breast cancer risk and the competing risk of other-cause mortality might be taken into account in designing the screening program strategy.

Although our findings are encouraging for an extension of the NHSBSP to older ages, further research and modeling is needed before extending screening to older ages because some uncertainty remains both about some of the model parameters and how implementation in practice would occur. There are

also further developments to the modeling and analysis that could be useful. Previous considerations of extending the screening program, including the current extension to age 73 years (examined within a randomized controlled trial), 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 overdiagnosis because of the relatively reduced life expectancy of this older cohort of women.

Conclusions

The findings of our analysis suggest that extending the NHSBSP beyond the current upper age limit of 73 years (at the moment, the extension to 73 years is examined within a randomized controlled trial) to around 78 years 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 modeling. This study provides encouraging findings to support the extension of the screening program to older ages in England and Wales, and we hope that policymakers would consider the findings from this study as part of the decision-making process regarding future possible extension of the breast screening program. It is important that any further age extension makes women aware of the potential risks of screening as well as the potential benefit [42].

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2015.06.006 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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