Option appraisal: Modelling the effectiveness and cost-effectiveness of screening policies for Breast Cancer in elderly women in England and Wales.

Report for the National Institute for Health Research.

10 January 2011

Final version

Rachid Rafia, researcher, lead modeller, University of Sheffield

Jason Madan, researcher, modeller, University of Bristol

Alan Brennan, Professor of Health economic and Decision modelling, Supervision of modelling team

Karen Collins, Principal Research Fellow, Centre for Health and Social Care Research

Malcolm Reed, Professor, Department of Oncology, University of Sheffield

Thomson Robinson, Professor of stroke medicine, University of Leicester

Gill Lawrence, Dr, Regional Director of Breast Screening Quality Assurance, WMCIU

Lynda Wyld, Senior Lecturer in Surgical Oncology and Honorary Consultant Surgeon, project leader

Executive Summary

Aims and Objectives

At present, the National Health Service Breast Screening Programme (NHS BSP) routinely invites all women aged between 50 and 70 years of age for breast screening every three years. Plans are in place to extend the upper age limit for routine invitation to 73 years between 2010 and 2013. Screening has been shown to be effective in reducing breast cancer mortality and halving the mastectomy rate in younger women. The benefits and harms of screening in women aged 70 years and over are less well documented. Whilst the incidence of breast cancer increases with age, the potential for over-diagnosis (detection of cancers that would have not presented from clinical symptoms in the absence of screening) from screening is higher in older women, given decreasing life expectancy and the presence of co-morbidities. There is also some doubt that the improvement in prognosis profile at diagnosis from screening would translate into an overall survival benefit.

A mathematical model of the natural history of breast cancer, using retrospective cancer registry data and data from the literature, was constructed to evaluate the optimal upper age for a screening policy; i.e the upper age at which screening represents a cost-effective use of NHS resources.

Evidence on the effectiveness of screening 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). 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. Cohort studies have been performed to overcome the absence of direct RCT evidence and have shown that screening was associated with a survival advantage in older women.

Modelling the impact of breast cancer screening

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. The natural history model was calibrated to available UK registry data and compared against published literature. Survival analysis was performed on registry data to evaluate the impact of prognostic profile at diagnosis on survival. Death from breast cancer causes was ascertained comparing survival in the general population and in breast cancer patients. Cost and benefits post-diagnosis were then calculated to identify the optimal screening age among elderly women regardless of health status and discounted at 3.5% annually. The management of breast cancer at diagnosis was estimated using registry

data and valued using official tariffs. Finally, utility weights from the published literature were used to adjust life years for the quality of life.

Policies analysed

We evaluated the following strategies for extending the current NHSBSP:

- Strategy S_0: The current NHSBSP, which we define as a final invitation at age 69 (in practice the age at which the final invitation is received varies between 68-70, but for simplicity we assume the same age for all women).
- Strategy S_1: One additional screening round for women aged 72.
- Strategy S_2: Two additional screening round 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

Results

Results of the calibration showed a reasonably good fit of the natural history model to observed data in the UK. For every 100,000 women invited for screening at the age of 72 years, the model estimated that 752 breast cancers would be detected by screening (this includes the number of breast cancer cases that would not have presented clinically or screen-detected before the age of 72 years). Of these, 6.2% would not present during the woman's life-time (over-diagnosis). Adding a further screening round at the age of 75 years would detect an additional 795 cases of breast cancer per 100,000 women invited, of which 9.4% would not present during the woman's lifetime. As expected, screening was estimated to lead to an improvement in the stage distribution at diagnosis. For instance, amongst cancers that would be detected by screening at the age of 72 years, 17.5%, 62.0%, 14.03%, 5.9% and 0.3% are estimated to be stage 0, I, II, III and IV respectively. The distribution in the absence of screening for those cancers was 0.0%, 36.7%, 24.2%, 30.2% and 8.9% respectively. Screening was also associated with a reduction in the number of deaths attributable to breast cancer, with benefits decreasing as age increases. We also found that screening would be associated with higher management costs for the treatment of the primary tumour given the earlier age at screen-detection. However, fewer costs would be incurred for the treatment of recurrence and management of palliative care for those with metastatic disease. Screening was found to lead to an improvement in life years, and life years adjusted for the quality of life (QALY).

Under commonly-quoted willingness to pay thresholds in the UK (£20,000 per QALY gained), our study suggests that screening represents a cost-effective strategy up to the age of 78 years. Univariate and multivariate sensitivity analyses were conducted and showed that results were mainly sensitive to the assumptions about the discount rate, recall rate for further investigation (i.e the proportion of women

undergoing further investigation after screening), impact of breast cancer diagnosis on quality of life and cost of the screening programme. No probabilistic sensitivity analysis was conducted in the absence of estimates about uncertainty in the natural history.

Conclusions

This study suggests that, under the assumptions made under our base case, an extension of the current NHSBSP upper age limit for invitations from 69 to 78 would represent a cost-effective use of NHS resources under commonly-used willingness to pay threshold in the UK (£20,000 per QALY gained).

Estimates in other countries indicated similar conclusions. Our model goes beyond previous published cost-effectiveness models in terms of biological plausibility (growth rate and inclusion of in-situ disease) and was calibrated to observed registry data in the UK. However, despite these strengths, there were some limitations due to the lack of data to calibrate the model, the assignment of costs and quality of life and the approach used to model survival.

This study indicates that further research is required about the impact of screening on survival and the impact of breast cancer diagnosis and treatment on quality of life.

Table of Contents

Contents

Table of figures

Table of tables

Acknowledgements

David Greenberg[1] kindly permitted us to use the ECRIC dataset and performed analysis on the ECRIC dataset on our behalf.

Gill Lawrence and her staff at the West Midlands Cancer Intelligence Unit (University of Birmingham) kindly prepared a dataset for analysis by the study team and provided advice on its interpretation. The British Association for Surgical Oncology (BASO) Breast Cancer Clinical Outcomes Monitoring (BCCOM) group and Professor Julietta Patnick and the screening QA for data returns.

A panel of experts and consumer representatives provided advice for the development of the economic model (include Karen Collins, Michelle Winslow, Tom Robinson, Malcolm Reed, Hazel Cocker and Tracy Green).

Marianne Lewis for helping with the report formatting.

[1] Senior Analyst, Eastern Cancer Registration and Information Centre (ECRIC), cambridge

Definition of terms and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

- **Definition of terms**

Axillary Lymph Node Dissection; complete surgical removal of all axillary lymph nodes from the ipsilateral axilla.

Carcinoma in-situ; early or pre-invasive form of breast cancer

Clinically significant cancer; women that would have presented from clinical symptoms before death;

Incremental-cost-effectiveness ratios; ratio of the change in costs and effectiveness

Lead time; time interval between screen-detection and the presence of clinical symptoms

Mastectomy; complete surgical excision of the breast

Over-Diagnosis; detection of cancers in women who would otherwise have died of other causes without a clinical diagnosis of breast cancer in the absence of screening

Palliative care; management care at the end of life

Recurrence; re-occurence of the cancer after primary treatment

Screening mammography; x-ray examination of the breast

Sensitivity; proportion of subjects correctly diagnosed with breast cancer

Sentinel Lymph Nodes Biopsy; radio-isotope and blue dye targeted surgical removal of one or more axillary lymph nodes most likely to contain tumour metastases

Sojourn time; time interval when the cancer is screen detectable but shows no clinical symptoms

Tumour Nodes Metastasis stage (TNM); stage classification based on tumour size, nodal involvement and presence of distant metastasis

Uptake rate; adherence to the screening programme

Utility weight; measure of quality of life

Wide Local Excision; removal of a malignant breast lump with a margin of normal tissue

- **List of abbreviations**

ALND	Axillary Lymph Node Dissection
BC	Breast Cancer
BSP	Breast Screening Programme
CBE	Clinical Breast Examination
CIS	Carcinoma In-Situ
DES	Discrete Event Simulation
DCIS	Ductal Carcinoma In-Situ
DPCP	Detectable Pre-Clinical Phase
ECRIC	Eastern Cancer Registration and Information Centre
EQ-5D	EuroQol 5 Dimension
ER	Oestrogen Receptor
HCSC	Hospital and Community Health Services
ICER	Incremental Cost Effectiveness Ratio
KM	Kaplan-Meier
LYG	Life Years Gained
NICE	National Institute of Clinical Excellence
NHS	National Health Service
NHSBSP	NHS Breast Cancer Screening Programme
NPI	Nottingham Prognostic Index
PSSRU	Personal Social Services Research Unit
ONS	Office of National Statistics
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Years
SA	Sensitivity analysis
SCHARR	School of Health and Related Research
SG	Standard Gamble
SLNB	Sentinel Lymph Node Biopsy
SMG	Screening Mammography
TNM	Tumour Nodes Metastasis
UK	United Kingdom
VAS	Visual Analogue Scale
WLE	Wide Local Excision
WMCIU	West Midlands Cancer Intelligence Unit

I. INTRODUCTION & BACKGROUND

1. EPIDEMIOLOGY OF BREAST CANCER IN ELDERLY WOMEN

Breast cancer is the most common malignancy in women, with the majority of cancers diagnosed in women aged 65 years and over. [1;2] Studies indicate that the probability of developing or dying from breast cancer increases with age, [2-4] with the most commonly cited risk factors being age, family history, geographical variation, late age at menopause, age at first pregnancy and lifestyle. [2]

The general increase in life expectancy leads older women to be the most rapidly increasing population group, with breast cancer being a public health issue due to the higher incidence and mortality rate in this age group. In the UK, it is estimated that breast cancer affects 13,000 women aged over 70 annually. [5] Evidence also suggests that older women present at a more advanced stage compared to younger women despite more favourable disease biology. [6;7]

Similarly, most of the deaths attributable to breast cancers are observed in the older population, despite the greater likelihood of dying from competing causes. It has been estimated that 56% of all breast cancer deaths (about 6,733 annually) occur in women aged over 70 years, with the main reason being the higher incidence in this age group, the reduced levels of screening and breast awareness and lack of improvement in the treatment for elderly women. [8;9] Whilst younger women have seen dramatic breast cancer survival improvements in the past few years with the introduction of screening and improvement in the management of breast cancer, the survival improvements have been much smaller in older women. Official UK statistics for breast cancer reported that since 1989, breast cancer mortality fell by 44% in women aged 40-49 years; by 44% in women aged 50-64; by 37% in women aged 65-69; but by only 19% in women aged over 70. [5] Compared to younger women, women aged 70 years and over are not routinely offered screening. Chemotherapy, Herceptin, surgery and radiotherapy are also withheld in some cases. [10;11]

2. CURRENT SCREENING STRATEGY IN THE UK

At present, the National Health Service Breast Screening Programme (NHSBSP) routinely invites all women aged between 50 to 70 years old for breast screening every three years, with a progressive extension to women in their late 40s and women up to the age of 73 years planned over the next 3 years.

In the UK, the screening consists of a mammogram, i.e. an x-ray examination of the breast, which involves a small dose of radiation. The aim of screening is the early detection of breast cancer before the appearance of clinical symptoms. However, screening by mammography may not identify all breast cancers.

3. SCREENING MAMMOGRAPHY IN OLDER WOMEN; ISSUES & LIMITATIONS

In younger women, screening is effective in reducing breast cancer mortality (between 25-39% [12]) and halving the mastectomy rate. [13] On the other hand, screening may also be harmful, leading to over-diagnosis and unnecessary treatments. [12;14;15] Indeed, screening may detect cancers that would not have presented within a woman's lifetime and therefore lead to unnecessary treatments and a reduction in quality of life. Other potential harms include psychological distress, unnecessary biopsies (both percutaneous and surgical) and the slight risk posed by the radiation exposure itself.

Whilst the benefits and harms of screening in women aged 70 years and over are less well documented, (partly due to the lack of data and the high incidence of co-morbidity in this age group), there is little doubt that screening older women would lead to an improvement in prognostic profile at the point of diagnosis (due to earlier detection), but there are some doubts that this would translate into a survival benefit.

Data from the NHSBSP indicates that the detection rate for cancer is much higher in older women compared to younger age cohorts. This is attributable to the fact that the sensitivity of mammograms is higher in older women and that older women have an increased probability of developing breast cancer. However, confounding factors are more likely to be present in older women, reducing the translation of improvement in surrogate markers to a survival benefit. The main confounding factor being the higher risk of co-morbidities in women aged 70 years old and over, i.e. the reduced life expectancy from causes other than breast cancer. Screening mammography may therefore cause more harms in the older age group. Indeed, while screening will detect more cancers in older women, many of these cancers would never have presented during the woman's life-time and may therefore be clinically-insignificant. [14] This is an important issue in older women who are more likely to die from causes other than breast cancer and therefore less likely to benefit from early detection of breast cancer. Evidence suggests that for a woman to benefit from earlier detection of breast cancer she must survive for long enough to see this benefit. Studies have reported that the percentage chance of dying from breast cancer in affected women is reduced as age increases. Diab et al (2000) indicated that 73% of deaths in breast cancer patients in the 50-54 year age group are due to their breast cancer, compared to only 29% of deaths in women aged over 85 years old. [6] Similar studies reported [16;17] that older women with 3 or more co-morbid diseases had a 20 times higher rate of non-breast cancer death, independent of the stage of their disease.

The increased probability of competing causes of death in women aged 70 years and over has some important clinical and economic implications in a screening setting, as screening would no longer confer a survival advantage in women with severe co-morbid disease. [18]. Finally, evidence suggests that interventions targeted to the frail population are also more likely to be harmful. [19]

II. AIMS & OBJECTIVES

The aim of this study was to explore the costs and benefits of extending the upper limit for the current NHSBSP. To do this, a decision-analytic model was developed that represented the natural history of breast cancer in older women and survival in this age group. Using this model, we explored the incremental benefit of each three-year extension to the current upper age-limit i.e. the incremental impact of each additional screening round, up to a maximum age of 90 years.

For each additional screening round, we used our model to estimate the number of life-years gained through screening, the extent to which screen-detection leads to over-treatment and the resource implications of the screening round. This allowed us to estimate the effectiveness and cost-effectiveness of each additional round, and determine the age at which the harms and costs outweigh the benefits.

III. EFFECTIVENESS OF SCREENING MAMMOGRAPHY IN WOMEN AGED 70 YEARS AND OVER

To date, there is a lack of direct RCT trial evidence on the effect of screening mammography in women aged 70 years and over. Most trials conducted in the last few decades included women up to the age of 69 years with only two trials recruiting women up to the age of 74 years (Swedish 2 Counties Trial and the Swedish Malmo Trial). However, the number of recruited women aged over 69 years was very low. A joint analysis of the Swedish studies indicated that there was insufficient power to determine whether there was a survival advantage for the cohort of screened women between ages 70 and 74 (Nystrom et al, 2002).

The lack of direct RCT trial data in older women has highlighted the need for alternative sources of evidence and retrospective cohort studies have been used to evaluate the impact of screening mammography in older women. McCarthy et al (2000) [20] examined the risk of death from breast cancer and the incidence of stage 1 or 2 disease in regular users or non-users of mammography in 3 age cohorts: 67-74, 75-85 and over 85. The authors found that the risk of breast cancer death was significantly lower in regular users in women aged 65 – 74 years old (RR 3.69, CI 2.58-5.27) and women aged 75 – 85 years old (RR 3.18, CI 2.27-4.46 67-74). Results were more uncertain for women aged over 85 years old. The authors also indicated that the survival benefit in women aged 67 to 85 years persisted after allowing for a 1.25 year lead time bias or after correction for co-morbidities.

Similarly, Van Dijck et al (1997) demonstrated a survival advantage for screened versus non-screened women in an age cohort from 68-83 years. [3] However the estimated relative survival rate in favour of screening was not significant (0.8; CI 0.53-1.22).

Finally, a further retrospective cohort study found a direct survival benefit for older screened women compared to non-screened women. [18] The authors reported that there was a significant relative survival difference in all age sub-groups over 70. Relative risk of death for women aged 70-74, 75-79 and 80 years old and over were estimated to be 0.45 (95% CI = 0.22–0.91), 0.47 (95% CI = 0.25–0.88) and 0.52 (95% CI = 0.33–0.80) respectively. The authors also indicated that women with severe or multiple co-morbidities experienced no improvement in survival. The interpretation of results from this study are however limited due to potential biases. The authors reported that selection bias may have occurred in the 75-79 year age group. Finally, compared to the study conducted by McCarthy et al (2000), [20] the data were not corrected for lead time bias.

In addition to cohort studies, data from existing screening programmes indicate potential survival benefits from screening older women. Data from the Netherland Screening Programme [21] reported a reduction in breast cancer mortality by 29.5% comparing a cohort of screened women at the age of 70-75 years to a similar cohort prior the introduction of screening. However, findings need to be considered with considerable caution given the improvements in management of breast cancer from 1986-1997 to 1997-2003.

Finally, modelling approaches have been used to estimate the effect of introducing screening to older age groups. These studies indicate that the relative benefit of screening older women compared to younger women decreases as age increases. [22] Published cost-effectiveness analyses of extending screening to the older age group are presented in section IV.

IV. RAPID REVIEW OF EXISTING COST-EFFECTIVENESS ANALYSES FOR THE EXTENSION OF SCREENING TO OLDER AGE GROUPS

1. INTRODUCTION

A rapid review of the literature of existing cost-effectiveness analysis of extending screening to women aged 70 years and over was undertaken, with the aim of identifying health economic models that could be used to inform the development of our model and/or provide some indication of the benefits of extending screening to the older age group. We focussed in particular on the modelling approach used and any assumptions made about the potential benefit of screening on survival. The critical appraisal of each of the identified studies is not presented in this report due to time constraints. We only report the main modelling approaches and conclusions as to whether extending screening to the older age group represent a cost-effective option.

2. PUBLISHED EXISTING REVIEW OF EVIDENCE OF EXTENDING SCREENING TO THE OLDER AGE GROUP

Mandelblatt et al (2003) reviewed published analyses of the cost-effectiveness of screening mammography in women older than 65 years old. The review was conducted between January 1994 and March 2002 and included studies that looked at the costs and benefits of extending screening mammography to the older age group. The authors identified ten relevant studies, [22] but indicated that there were some variations between the studies:

- discount rates varied from 3% to 6%,
- two studies included the effect of co-morbid conditions (dementia and congestive heart failure and hypertension respectively),
- no study addressed the impact of screening on carcinoma in situ (CIS),
- furthermore, no studies addressed the issue of over-diagnosis from screening; i.e. the detection of cancer or CIS that would not have become clinically evident,
- two studies attempted to incorporate the loss in quality of life from screening,
- most included studies examining a biennial screening interval, i.e. screening every two years,
- most models used Markov processes

- in most studies, a shift in stage distribution from screening was modelled, and survival evaluated using stage-specific survival,
- two studies explicitly modelled age-specific disease biology (i.e. an age dependent time for a pre-clinical detectable phase),
- all studies assumed the same sensitivity for screening mammography, regardless of age,
- most studies assumed a 100% uptake rate, with the exception of one study
- uncertainty was captured though univariate sensitivity analysis in most studies.

Overall, the authors suggested that over a range of assumptions, screening older women every two years according to current medical guidelines in the US remains a cost-effective option, with an incremental cost ranging from $34,000 to $88,000 per life years gained for screening beyond the age of 65 years. Univariate sensitivity analysis showed that parameters that affected the ICER most significantly were the breast cancer incidence rate, assumptions about mortality reduction, utility weights and discount rates.

Similarly, Barratt et al (2002) conducted a MEDLINE search from 1966 to July 2000 to identify decision analytic models reporting the life years gained of extending screening to women aged over 69 years. [22] The aim of the review was to evaluate the benefits, harms and cost of screening mammography in Australia using results from previous published economic models. Five studies met the inclusion criteria; three of which were not included in the review conducted by Mandelblatt. [23] Outcomes from the five economic models were used to estimate the relative benefit of the effectiveness of screening elderly women compared to women aged 50 – 69 years. Harms were then calculated using data from BreastScreen Queensland. The MISCAN model was then used to calculate the cost per QALY gained assuming a biennial screening programme among women aged 70 to 79 years old, with costs and benefits discounted at 5%. The authors found that the benefit of screening women aged 70-79 years ranged from 40-72% of that achieved in women aged 50-69 years and represented a cost-effective option, leading to a cost per QALY gained ranging from $8,119 to $27,751.

3. RAPID REVIEW OF COST-EFFECTIVENESS ANALYSIS PUBLISHED AFTER 2002

A rapid review of cost-effectiveness analyses of extending screening to older women conducted after 2002 was undertaken to identify potential cost-effectiveness analyses that were not picked up in the existing published systematic review of the literature. [22;24]

3.1. Search strategy

A rapid systematic search was conducted in MEDLINE from January 2002 to January 2010. The following search terms were used: "*mass screening*" or exploded Medical Subject Headings (MeSH) term "*Mass Screening*"; "*breast cancer*" or exploded MeSH term "*Breast Neoplasms*"; "*cost effectiveness*" or exploded MeSH term "*Cost-Benefit Analysis*". The additional MeSH term; "*Aged*" was included to limit searches to studies relevant to screening in the older population. This was chosen to replicate the search strategy undertaken by Mandelblatt et al (2003). [24;24]

3.2. Inclusion and Exclusion criteria

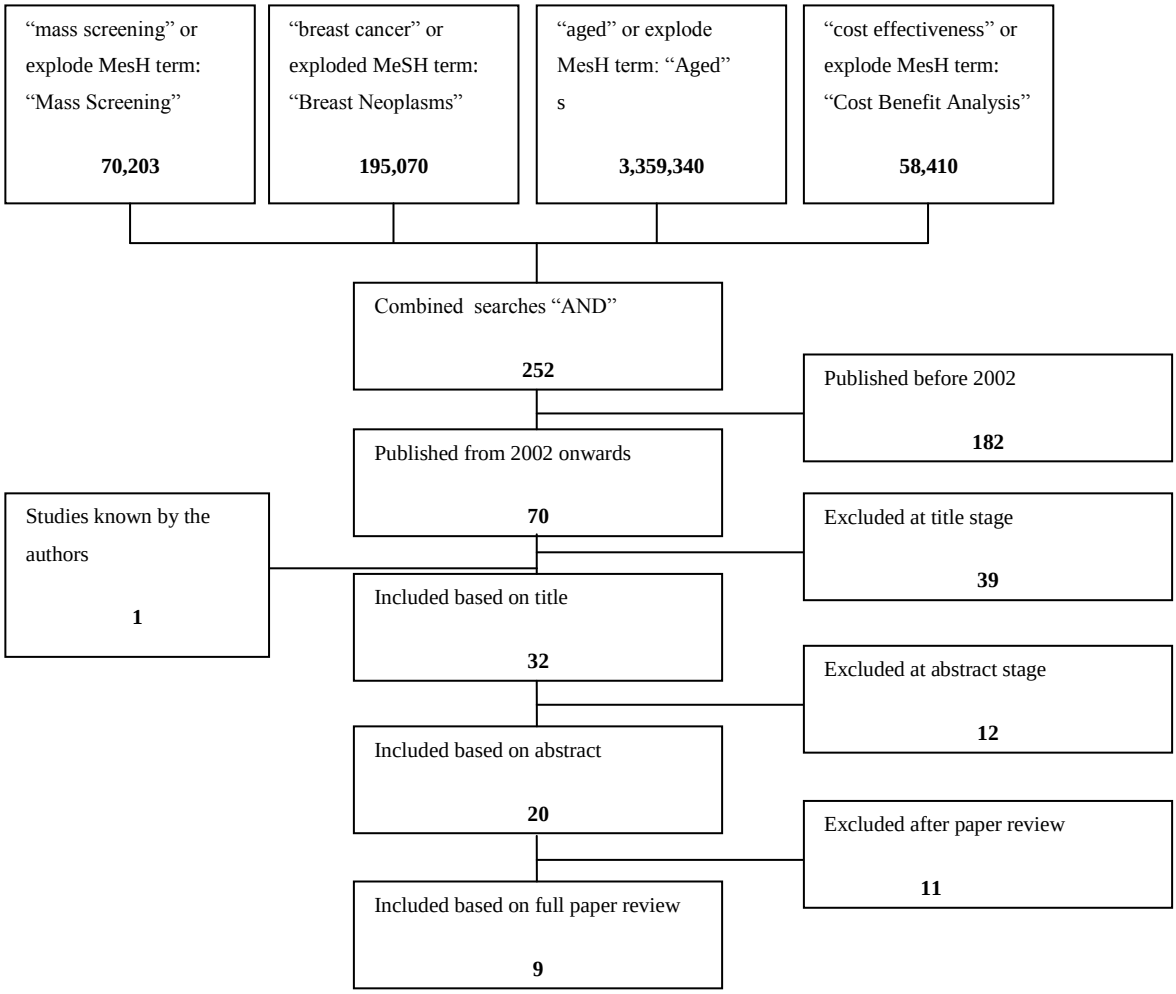
Titles, abstracts and eligible articles were examined by one reviewer. Inclusion criteria consisted of decision analytic models that evaluated the extension of screening to women aged 70 years and over. Cost-effectiveness analyses conducted in a specific population sub-group (for instance dialysis patients or high risk patients such as BRCA gene mutation carriers were excluded). Similarly, studies comparing screening mammography to MRI, or digital versus film mammography were also excluded. Finally, non-English studies and reviews were excluded.

The number of studies retrieved at each stage is presented in Figure 1. Of the 70 papers identified as potentially relevant, 9 studies met our inclusion criteria.

3.1. Description of studies identified though the rapid review of the literature

Lee et al (2009) investigated the most cost-effective strategy in terms of screening interval and target age range for Korean women. [25] Analysis was conducted from the perspective of the National Healthcare System (NHS) and modelled three health states; "disease-free"; "preclinical state" (in which the disease has no symptoms but can be diagnosed) and a "clinical state". The effectiveness of screening was evaluated in terms of the probability of detecting the breast cancer while in the "pre-clinical" health state. The sensitivity of the mammogram was assumed to be age-dependent. Similarly, the mean sojourn time was assumed to increase exponentially as age increased (2, 3 and 4 years among women aged less than 50 years, 50-59 and older than 60 years old respectively). The study included the cost associated with false-positives but did not included the potential reduction in quality of life associated with the pain and discomfort from screening mammography or recall for further investigation. The time horizon was 30 – 85 years of age.

Figure 1: Number of study retrieved and excluded at each stage



Costs and benefits were discounted at 3% and the authors evaluated forty possible screening strategies varying both the screening intervals (annual, biennial, triennial), starting age of screening (30, 35, 40, 45 years old) and ending age of screening (65, 70, 75 years old). One-way sensitivity analyses were conducted varying key model parameters. Results for each strategy examined are available in the full paper. [25] Only results assuming a triennial screening option starting from the age of 45 years old and ending at either 70 or 75 years old are presented in this section. This was selected to reproduce as closely as possible the screening programme in England and Wales. The authors found that screening every 3 years from the age of 45 years old to 70 years old would allow detection of 80.4 breast cancer cases per 100,000 screens for a total cost of $8,506,677. Extending screening to the age of 75 years old would allow detecting 85.5 cases per 100,000 screens for a total cost of $9,556,833. Based on these figures, the ICER of extending screening up to the age of 75 years old would be $205,913 per case found compared to screening up to 70 years old. Sensitivity analyses indicated that the model was mostly sensitive to the cost of screening mammography and discount rates.

Madan and colleagues (2008) performed a preliminary assessment of the cost-effectiveness of adding an extra-round to the NHSBSP at the age of 71-73. [26] Their model simulates a hypothetical cohort of 10,000 screened women between the ages of 71 and 73 years. The model starts by estimating the number of women who are referred for further investigation. From this group, a proportion of women are diagnosed with breast cancer and classified by NPI group (DCIS, excellent, moderate and poor). The model estimates the NPI distribution in the absence and presence of screening. Costs and survival are applied from the NPI group at the point of diagnosis. Data on the recall rate and positive predictive value was extracted from the NHSBSP. The impact of early detection on survival was derived from the BCCOM dataset in women aged 65- 79 years. The authors indicated that screening 10,000 women aged 71 -73 would lead to an ICER of £11,402 per QALY gained. Finally the authors examined the impact of including anxiety. This was shown to influence the cost-effectiveness of screening.

Rojnik and colleagues (2008a; 2008b) investigated the most cost-effective screening option for mass breast cancer screening in Slovenia. [27;28] The authors constructed a time-dependent Markov model and used a simplified TNM cancer stage classification. The natural history of the disease was described using four clinical stages (DCIS, local, regional, distant) when the cancer may be detected by screening but shows no clinical symptoms. Furthermore, the authors assumed that 60% of invasive breast cancers are not preceded by DCIS. The model used a 1 week cycle length and was conducted from the perspective of the health care payer. Costs and benefits were discounted at 3% annually. Several assumptions were used when modelling the impact of screening on survival. The authors notably assumed that the survival of women with pre-clinical stages of breast cancer, women screen-detected with DCIS and women with false-positive results had similar survival rates to that of women with no breast cancer. The mean sojourn time for DCIS, local, regional and distant pre-clinical state was assumed to be 5 yrs, 2.5 yrs, between 0.36 to 1.08 yrs and between 0.35 to 1.04 yrs respectively. The sensitivity of the mammogram was assumed to be age-dependent. The uptake rate and recall rate for further investigation were assumed to be 75% and 7% respectively. This study included quality of life, and was evaluated according to treatments received at the point of diagnosis. The authors also incorporated the reduction in quality of life after a false-positive result. The authors examined different screening options in regard to the starting age (40, 45, 50 years old), ending age (65, 70, 75, 80 years old) and screening intervals (annual, biannual, triennial). Sensitivity analysis and probabilistic sensitivity analysis were also conducted to ascertain the uncertainty in results. Results for the 36 scenarios examined are available in the full paper. [27] This section only presents the results for the screening option starting at the age of 50 years old assuming screening every 3 years. The authors estimated that screening from the age of 50 years old up to 70 years old would provide 0.0477 additional Life Years Gained (LYG) or 0.0415 QALYs compared to no screening for an additional cost of €294.20. Extending screening up to the age of 75 years would provide 0.0501 additional LYG and 0.0435 QALYs for an additional cost of €322.90 compared to no screening. Finally, extending screening up to the age of 80 years old was estimated to provide 0.0518 additional LYG and 0.0447 additional QALYs compared to no screening for an additional

cost of €354.30. Based on these figures, the ICER of extending screening up the age of 75 years compared to 70 years is estimated to be €11,958 per life years gained and €14,350 per QALY gained. The ICER of extending screening up to the age of 80 years old compared to screening up to 75 years old lead to an ICER of €18,471 per life year gained and €26,167 per QALY gained. The authors reported that results were most sensitive to discounting, percent of DCIS progression to invasive cancer, recall rate, relative mortality in the regional stage, percent of invasive diagnoses, cost of mammography examination and percent of invasive cancer preceded by DCIS.

Wong and colleagues (2007) investigated the cost-effectiveness of biennial mammography in Hong Kong Chinese women. [29] A state-transition Markov model was constructed and followed a hypothetical cohort of women from 40 years over a lifetime using a yearly cycle length. Five breast cancer states were defined; DCIS, stage I, stage II, stage III and stage IV invasive cancer. Women with DCIS were assumed to have an increased risk of developing breast cancer for the first 10 years. Women with invasive breast cancer were assigned a one year breast cancer specific mortality. Women diagnosed with stage I, II and III could then subsequently develop metastatic recurrence and transition to the stage IV health state. The sensitivity of screening was assumed to be the same, regardless of age. The authors assumed that all women diagnosed with invasive cancer would undergo annual mammography as a diagnostic tool. Costs and health effects were discounted at 3% annually and public and private sector costs were included. The authors included quality of life through QALYs. The utility weights for full health (disease free), stage I, stage II, stage III and stage IV was assumed to be 1, 0.95, 0.9, 0.8, 0.7 and 0.3 respectively for the time spent in each health state. Univariate and probabilistic sensitivity analyses were conducted. The authors compared biennial screening from the age of 40 or 50 years up to the age of 69 or 79 years compared to no screening. Results were also presented for a set of scenarios for Hong Kong or the US using a single or multiple cohort models. Only results for Hong Kong for the single cohort model are presented in this section. The authors found that the discounted life year for screening from the age of 50-69 years old was 2,375,330 for a total discounted cost of US $170.75 million. Extending screening to the age of 79 years lead to 2,375,450 life years for a total cost of US $201.99 million. Based on these figure, the ICER of extending screening up to the age of 79 years old compared to 69 years old is estimated to be US $260,333 per life year gained.

Stout and colleagues (2006) performed a retrospective cost-effectiveness analysis comparing actual and alternative screening mammography scenarios. [30] A discrete-event simulation (DES) model of breast cancer epidemiology was constructed to estimate the costs and the number of QALYs associated with different screening options. Unobservable model parameters for natural history were calibrated to fit age-adjusted, stage-specific breast cancer incidence from the SEER programme and breast cancer mortality data. The life history was generated through four separate models: the natural history of breast cancer, breast cancer detection, breast cancer treatment and breast cancer mortality. Breast cancer was assumed to progress

between disease states using a Gompertz growth model for tumour size. A stage (in situ, localized, regional and distant) was then assigned based on the tumour size and the spread of lymph nodes at the time of diagnosis. The sensitivity of screening was assumed to be a function of age and tumour size. The model assumed that all women received treatment at the time of breast cancer detection and the effectiveness of treatment was assumed to be dependent on age and prognostic profile at diagnosis. Age-specific utility weights were applied for each state and loss in quality of life from screening results was included. Costs were considered from a payer perspective and costs and health effects were discounted at 3% annually. The authors examined 65 scenarios in regard of the starting age (40, 45, 50, 55), ending age (65, 70, 75, 80) and screening interval (annual, biennial, triennial or every 5 years). Only results for triennial screening from the age of 55 years old up to 70 or 75 years old are presented in this section. The authors estimated that screening from the age of 55 years old up to 70 years old is associated with a mean cost of $130 billion for a mean number of QALYs of 946.4 million. Extending screening up to the age of 75 years would cost $136 billion for a mean number of QALYs of 946.5. This equates to an ICER of about $60,000 per QALY gained. The authors reported that results were mainly sensitive to the participation rate and assumptions about the quality of life.

Ohnuki and colleagues (2006) investigated the cost-effectiveness of different screening strategies (annual Clinical Breast Examination (CBE), annual CBE and screening mammography and biennal CBE and mammography and screening intervals. [31] The model simulated a cohort of 100,000 women participating in screening. Those who did not develop breast cancer since the previous screening are then included, i.e. that those women who have developed breast cancer are excluded thereafter. The number of subjects recalled for further investigation and the number of cancers detected was calculated from the sensitivity and specificity of the appropriate screening strategy. Costs were evaluated from a payer's perspective and costs and life years were discounted at an annual rate of 3%. Sensitivity analysis was also carried out to identify key parameters that influenced the ICER. Assuming biennial screening CBE and mammography, the ICER for screening women at the age of 70-79 was estimated to be YEN 4,009,740 / year (≈ £31,000 / year). Sensitivity analyses indicated that results were sensitive to the sensitivity, specificity and cost of screening mammography.

Finally, Mandelblatt and collaegues (2005) evaluated several screening policies based on age and quartile of life expectancy. [32] The authors constructed a discrete-event simulation (DES) of the natural history of breast cancer using Monte Carlo Simulation. Biennial screening was started at the age of 50 years and extended up to 70 or 79 years or a lifetime. The life history of the "same" woman was simulated under all 3 screening strategies. For each simulated woman, the model assigned a date of death, a date of preclinical disease and an age at presentation due to clinical symptoms. The stage distribution at diagnosis in asymptomatic women was then sampled from the age specific distribution in unscreened women. If a tumour

was detected before the age at presentation from clinical symptoms, a new stage was calculated using Bayes' theorem. Women who developed breast cancer were randomly assigned an ER status and treatment was sampled from the current pattern of care given the age, stage at presentation and ER status. Survival was sampled from the age, stage, ER status and treatment. The authors also included age-specific test characteristics. The study included the impact on quality of life in sensitivity analysis assuming a utility weight of 0.95 in the absence of treatment, 0.87 in the presence of DCIS, 0.84 for local and regional disease, 0.55 for distant disease, 0.93 for surviving cancer and 0.55 for living with metastasis. Utilities were applied for 1 year post diagnosis. This study was conducted from a payer perspective and cost and health effects are discounted at 3% annually. The uncertainty was considered through univariate sensitivity analysis. The authors reported that extending screening up to the age of 79 years old compared to screening up to 70 years led to an ICER of $82,063 per life years gained. The ICER increase to $151,434 per life year gained when extending screening over lifetime. The cost per QALY gained was $155,865 and $368,801 respectively. The authors also reported that the ICER for screening women with a life expectancy in the first and second quartiles was $57,934 and $126,629 per life years gained respectively. Finally, univariate sensitivity analysis indicated that results were mainly sensitive to the quality of life, discount rate, screening interval, incidence rate and dwell time.

4. CONCLUSION OF THE REVIEW

Since the last published review [24], several cost-effectiveness analyses have been conducted investigating the costs and benefits of extending screening to older women. Similar to the finding from the previous review of the literature, the methodology and assumptions used between most cost-effectiveness analyses varied. However, recent models use more complex modelling approaches and tried to match as closely as possible the natural history of breast cancer. Compared to previous published cost-effectiveness analysis, more models identified after 2002 included the impact of early detection on CIS and potential over-diagnosis.

Overall, despite differences in methodology and assumptions, studies indicates that extending screening up to 80 years old has the potential to represent a cost-effective option.

V. SCHARR COST-EFFECTIVENESS MODEL

1. MODEL OVERVIEW

A patient-level simulation model of breast cancer screening among older women has been built in R software (version 2.11.1) that allows the impact of different screening policies on cancer diagnosis and subsequent survival 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 model is calibrated to routine data from the NHSBSP, registry data from the West Midlands Cancer Intelligence Unit (WMCIU) and data from the Eastern Cancer Registration and Information Centre (ECRIC). [33;34] The impact of breast cancer diagnosis on survival is evaluated using registry data derived from the impact of prognostic profile at diagnosis. Cost and benefits post-diagnosis are then calculated to determine the upper age limit at which screening mammography represents a cost-effectiveness use of NHS resources among elderly women regardless of health status.

2. PART ONE: MODELLING THE NATURAL HISTORY OF BREAST CANCER IN ELDERLY WOMEN

2.1. Model structure

The natural history model has two aspects – metastatic progression and growth of the primary tumour. Figure 2 illustrates how the model represents the spread of the disease. There are four stages of progression – in situ, local, regional and distant. In addition, regional metastasis is divided into two states according to the number of nodes involved – few nodes (1-3) and many nodes (4+).

The model simulates progression through these stages for individual women. Each woman develops a carcinoma in situ at age "*tstart*", which becomes invasive at age "*tstart+tcis*". Nodal involvement occurs at age "*tstart+tcis+treg*", and distant metastasis at age "*tstart+tcis+treg+tdist*". If "*treg*" is less than "*tdist*", then the woman will go through a state of regional metastasis with 4+ nodes involved, lasting from age "*tstart+tcis+treg+treg*" to age "*t0+tcis+treg+tdist*".

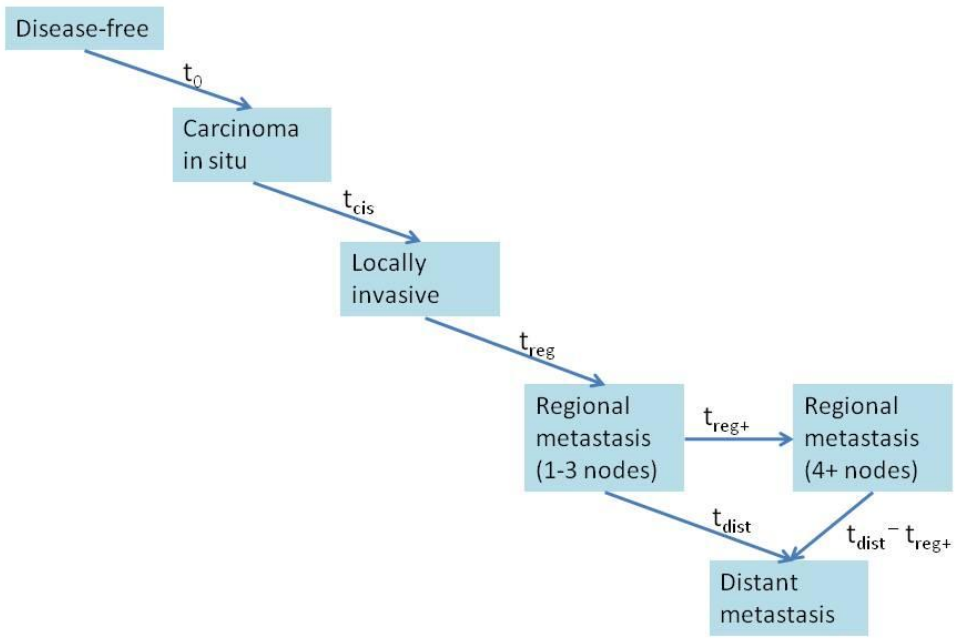
We define each state in terms of clinically detectable disease. One consequence is that by the time a tumour is detectable, it may have already become invasive. We use the index "*ICIS*" for this case, so that "*ICIS*" = 1 if the disease passes through a detectable in situ stage, and "*ICIS*" = 0 if it is already invasive at the earliest point at which it is detectable. Then, "*tcis*" is defined as 0 if "*ICIS*" = 0, and "*tinv*" if "*ICIS*" = 1, where "*tinv*" is the time for a detectable carcinoma in situ to become invasive.

The second component of our natural history model is a growth model for the primary tumour. We assume that the tumour follows a Gompertz growth curve, in which the size at time S_t depends on the time from invasion ($t - t_0$), the time at which the tumour would present in the absence of screening (tsymp),the size at t_0 (S_0) and the size at presentation (S_P), and a growth rate parameter τ, according to the formula:

Formula 1:Gompertz growth curve

$$S_t = \left(\frac{(t - t_0)}{t_{symp}} \right)^{\tau} (S_P - S_0)$$

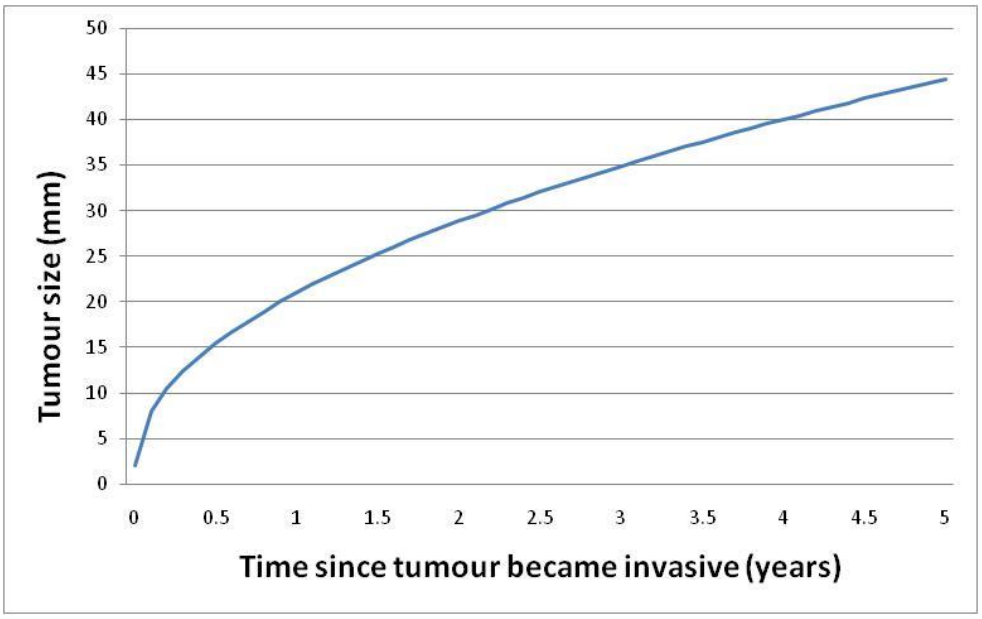
Figure 2: Health states for progression component of breast cancer natural history mode[2]l.



[2] Each arrow indicates the direction in which the disease progresses over time, and is labelled with the time until the transition occurs.

An example Gompertz growth curve where τ=0.5, Sp=40mm and tsymp = 4 is illustrated in Figure 3. We assume that presentation in the absence of screening is linked to the size of the tumour, and that this occurs when the tumour reaches a size S_P. The growth model can then be used to determine the time t_{symp} taken for the tumour to reach this size. This gives the age at presentation in the absence of screening ("*t0+tcis+tsymp*"). This can be compared with "*treg, treg+*" and "*tdist*" to determine the stage at presentation.

Figure 3: Illustration of a Gompertz tumour growth model.



To allow for variability in the course of the disease between women, we define probability distributions from which the times given above are sampled for each individual. Table 1 gives a list of the variables (transition times and other variables) used by the model. Transition times are assumed to have a Weibull distribution with shape α (referred to in table one as parameter 1) and scale λ (referred to in table one as parameter 2). The size of the primary tumour at presentation is assumed to have a lognormal distribution with mean μ_P and standard deviation σ_P. Each woman is assigned a grade g=1,2 or 3 which remains fixed during the course of the disease. To allow for disease heterogeneity, "*tsymp*" and "*treg*" are assumed to depend on tumour grade. For these times, the scale of its Weibull distribution is assumed to follow the equation $\log(\lambda) = \beta^0 + \beta^1(g-2)$. We also allowed the mean and standard error of Sp to depend on grade in a similar way.

Table 1: List of variables used in the natural history model.

Variable	Description	Distribution	Parameter1	Parameter2
t_{start}	Age at which detectable disease first appears	Weibull	α_0	λ_0
t_{inv}	Time for disease which is CIS at t0 to become invasive.	Weibull	α_{inv}	λ_{inv}
t_{CIS}	Time from t0 to local invasion	function of t_{inv} and I_{CIS}		
t_{reg}	Time from local invasion to nodal involvement	Weibull	α_{reg}	$\lambda_{reg\pm}$ λ_{reg_grade}
t_{reg+}	Time from initial nodal involvement to involvement of 4+ nodes.	Weibull	α_{reg+}	λ_{reg+}
t_{dist}	Time from nodal involvement to distant metastasis	Weibull	α_{dista} α_{distb}	λ_{dista} λ_{distb}
t_{symp}	Time from local invasion to symptomatic presentation in the absence of screening	Weibull	α_{symp}	$\lambda_{symp\pm}$ λ_{symp_grade}
S_p	Size of primary tumour at presentation	lognormal	$\mu_{P\pm}\mu_{P\_grade}$	$\sigma_{P\pm}$ σ_{P_grade}
I_{CIS}	Equals 1 if the disease is CIS at t_0, 0 otherwise	Bernouilli	p_{CIS}	
τ	rate	Bernouilli	p_r	
δ_{inv}	probability of detection for invasive cancer	Bernouilli	$pSens_{inv}$	
δ_{cis}	probability of detection for CIS	Bernouilli	$pSens_{CIS}$	

The model as described allows for the impact of any screening programme to be assessed in terms of its potential to change the prognostic profile (size and metastatic status) at detection. From the growth curve, it is possible to determine the size of the tumour (if one is present) for any woman in any given screening round. If an invasive tumour is present, the test sensitivity ρ_{inv} is assumed to depend on tumour size at screen

(S_m) according to the formula $\rho_{inv} = 1 - \exp(\delta_{inv} * S_m)$. For CIS, the sensitivity ρ_{CIS} is assumed to be constant. Sensitivity was defined as the probability of detecting the cancer in case of screening.

For the transition times that are grade dependent (t_{symp} & t_{reg}), determining the scale requires two parameters (β^0, β^1) rather than one, which adds two additional parameters. Two further parameters are needed to represent the link between grade and size at presentation (S_p). We also need values for the growth rate τ in the Gompertz growth formula, and the two sensitivity parameters (δ_{cis} & δ_{inv}).For the model to be used to simulate individual life histories and analyse alternative screening strategies, values must be found for the 24 parameters listed in Table 1.

2.2. Description of suitable data to calibrate the model

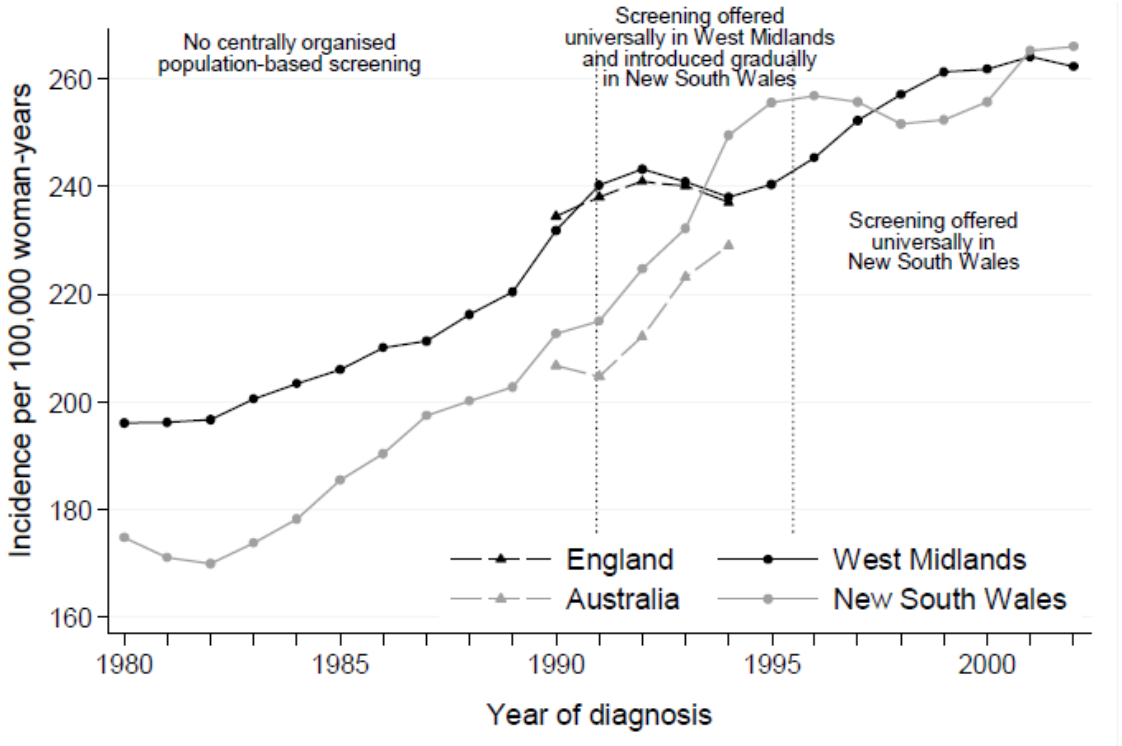
2.2.1. Published literature on the age-specific incidence of breast cancer in the absence of screening

Data about the incidence of breast cancer in England and Wales in the absence of screening is necessary to calibrate the model. However, most studies conducted only report the incidence of breast cancer after the implementation of the screening programme. This led to overestimation of the "true" incidence of breast cancer in the absence of screening as screening is expected to lead to earlier and over-diagnosis.

The literature was searched to identify potential data sources about the incidence of breast cancer in England and Wales before the implementation of the screening programme. A recent published study by Woods et al (2010) was identified comparing breast cancer incidence in England and Australia by age, extent of disease and deprivation at different time period before and after the implementation of screening. [35] Data from 68,725 women aged 15-99 years diagnosed with breast cancer were analysed in the West Midlands between 1980 to 2002 and were compared to data from England from a previous published study conducted among 143,560 women with breast cancer after the implementation of screening.

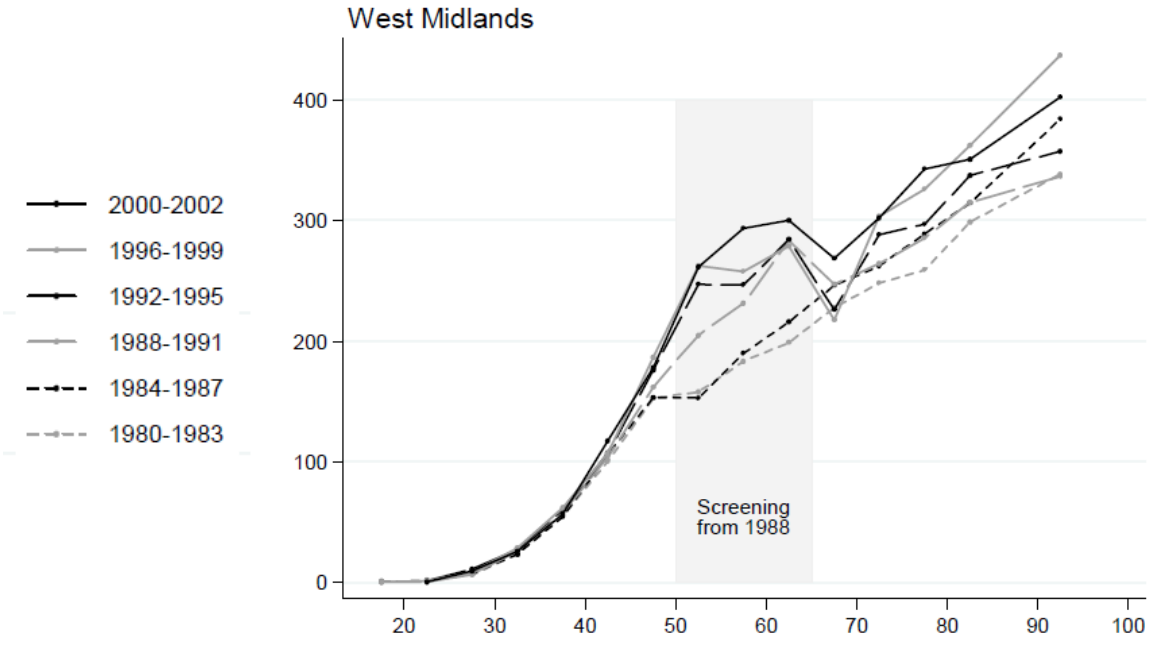
Incidence by age was not reported by Woods et al for England as a whole, but was available for the West Midlands. [35] Analysis showed that the age-standardised incidence rates for primary invasive breast cancer in the West Midlands and England were very similar (Figure 4) during the period 1988-1994 (period for which data were available for England). The incidence before screening from the West Midlands was therefore used to represent the incidence of breast cancer in England and Wales before the implementation of the screening programme.

Figure 4: Comparison of the age-standardised incidence rate in England and in the West Midlands (reproduction of Figure 1 [35])



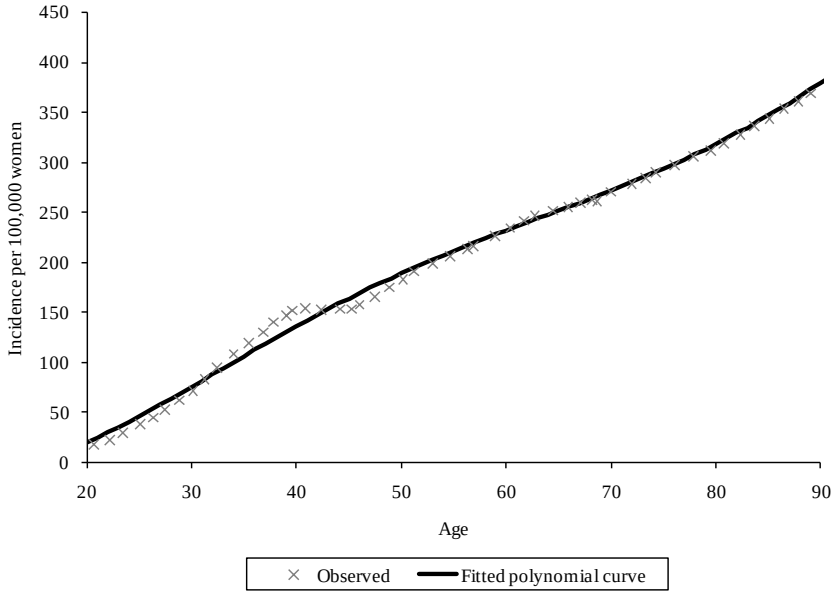
Age-specific incidence was available in the West Midlands for different time periods (Figure 5). We used data for the year 1984-1987 as this was the closest period before the implementation of the screening programme in England and Wales.

Figure 5: Age-specific incidence of breast cancer per 100,000 women-years in the West Midlands (reproduction of Figure 2 [35])



Unfortunately, it was not possible to have direct access to the data from this study. Therefore, a polynomial curve was fitted to the observed age-specific incidence in the West midlands estimated using TechDig (Figure 5) in order to approximate the age-specific incidence from the age of 20 to 89 years old. The fitting of the estimated curve is presented in Figure 6.

Figure 6: Fitted curve to the observed age-specific incidence in the West Midlands for the period 1984-1987



2.2.2. Data on the impact of screening on the detection of carcinoma in situ and invasive cancer

We used data collected from the NHS Breast Cancer Screening Programme (NHSBSP) to evaluate the impact of screening on the detection rate (sensitivity) for carcinoma in situ and invasive cancers. Routine screening is not yet available among women aged over 70 years old. Consequently, data for women aged 60 – 70 years was used to approximate the effect among older women. While some data were available for women aged over 70 years old, it was believed that these women would not be representative of the "true" impact of screening as some of them are believed to have self-referred after suspicion of breast cancer symptoms. Data for the year 2006 were used and included data on the number of women screened; the number of women detected and the tumour size at detection (Table 2 & Table 3).

Table 2: Screening data among women invited for the first time (NHSBSP)

AGE	No. (SN) Screened	Cancers Detected No. (% of Screened)	Status known	CIS No. (% of Status known)	0-10mm No. (% of Status known)	10-15mm No. (% of Status known)	15-20mm No. (% of Status known)	20-50mm No. (% of Status known)	>50mm No. (% of Status known)
60-64	7028 (100%)	90 (1.28%)	89 (100%)	12 (13.5%)	17 (19.1%)	20 (22.5%)	10 (11.2%)	29 (32.6%)	1 (1.1%)
65-69	4869 (100%)	87 (1.79%)	81 (100%)	17 (21.0%)	17 (21.0%)	18 (22.2%)	14 (17.3%)	15 (18.5%)	0 (0.0%)
70	581 (100%)	11 (1.89%)	11 (100%)	3 (27.3%)	2 (18.2%)	1 (9.1%)	1 (9.1%)	3 (27.3%)	1 (9.1%)

Table 3: Screening data among women that previously attended screening (NHSBSP)

Category two – repeat attendees

AGE	No. (SN) Screened Screened	Cancers detected	Status known Known	CIS No. (% of Status known)	0-10mm No. (% of Status known)	10-15mm No. (% of Status known)	15-20mm No. (% of Status known)	20-50mm No. (% of Status known)	>50mm No. (% of Status known)
60-64	338794 (100%)	2727 (0.80%)	2649 (100%)	520 (19.6%)	571 (21.6%)	595 (22.5%)	436 (16.5%)	489 (18.5%)	38 (1.4%)
65-69	227803 (100%)	2019 (0.89%)	1972 (100%)	371 (18.8%)	409 (20.7%)	493 (25.0%)	303 (15.4%)	379 (19.2%)	17 (0.9%)
70	14777 (100%)	145 (0.98%)	144 (100%)	24 (16.7%)	37 (25.7%)	40 (27.8%)	18 (12.5%)	24 (16.7%)	1 (0.7%)

2.2.3. Registry data from the West Midlands Cancer Intelligence Unit

Anonymised patient level data on the prognostic profile at diagnosis of older women (over 70) with breast cancer in the West Midlands was made available (Jan 03 – Dec 07). The dataset included 6,859 women with breast cancer aged 70 years and over. The mean age was 79.77±6.4 years old and 98.24% (n=6,738) of women presented due to symptoms. Data was available for 3,564, 5,327, 5,683 and 3,641 women on their tumour size, grade, ER status and number of positive nodes. [33]

The mean tumour size at diagnosis was 25.17±16.24 mm and the mean NPI score was 4.26±1.25. Eighty-five percent of women were ER+ (n=4,855). Furthermore, 15.17% (n=808), 53.61% (n=2,856) and 31.22%

(n=1,663) of women were grade 1, 2 and 3 respectively. Finally, information was available for distant metastasis among 6,836 women with only 0.34% (n=23) women diagnosed with distant metastases. About 3.7% (n=257) of women had carcinoma in-situ (CIS).

Data from the WMCIU (2003-2007) were used to calibrate the natural history of breast cancer in older women in the absence of screening. [33] This provided information on the tumour size distribution at diagnosis, ER status, nodes and grade. Table 4 presents the distribution of older women that presented due to symptoms by grade, nodes, ER status and tumour size group. The model was calibrated against this table.

Table 4: Distribution of older women (70+) diagnosed with breast cancer by grade, nodes, ER status and tumour size (n = 2,940)

	ER- Grade			ER+ Grade		
	1	2	3	1	2	3
No positive nodes						
0 to 10 mm	2	9	12	49	67	10
10 to 15 mm	0	14	19	77	157	35
15 to 20 mm	4	13	37	67	202	72
20 to 25 mm	0	9	40	50	181	73
25 to 30 mm	0	4	34	20	123	51
30 to 40 mm	0	8	35	20	88	39
40 mm+	0	7	30	11	51	30
1 to 3 positive nodes						
0 to 10 mm	0	0	3	5	2	1
10 to 15 mm	1	3	3	15	29	8
15 to 20 mm	0	5	10	19	68	31
20 to 25 mm	2	9	11	13	78	36
25 to 30 mm	0	0	14	10	42	44
30 to 40 mm	0	4	20	12	69	35
40 mm+	0	6	24	1	54	42
4 positive nodes or +						
0 to 10 mm	0	0	1	1	2	0
10 to 15 mm	0	0	2	1	5	5
15 to 20 mm	1	5	9	2	22	13
20 to 25 mm	0	0	10	2	33	19
25 to 30 mm	0	3	10	4	33	18
30 to 40 mm	0	4	16	3	46	44
40 mm+	0	6	32	4	54	66

2.2.4. Eastern Cancer Registration and Information Centre

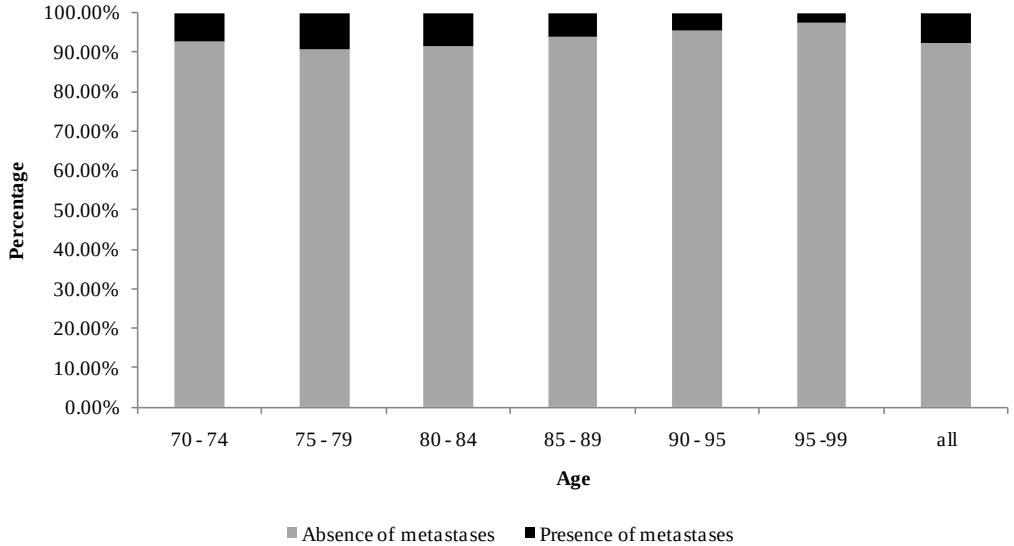
Data from the WMCIU were complemented with registry data from ECRIC. [33;34] It was not possible to have direct access to an anonymised patient level dataset. However, we were able to make some requests to run specific analyses. The dataset included 3,757 women aged over 70 years and diagnosed with breast cancer. The mean age was 78.9±6.3 years and 95.7% (n =3,596) of women presented due to clinical symptoms. Data was available for 2,653, 2,902, 2,081 and 1,842 women on their tumour size, grade, ER status and number of positive nodes.

The mean tumour size at diagnosis was 27.7±18.7 mm and the mean NPI score was 4.2±1.2. Eighty-six percent of women were ER+ (n=1,788). Furthermore, 17.3% (n=502), 54.79% (n=1,590) and 27.91% (n=810) of women were grade 1, 2 and 3 respectively. Finally, information was available for distant metastasis among 3,578 elderly women with 7.7% (n=276) women diagnosed with distant metastases.

We used data from the ECRIC for two purposes: [34]

- to calibrate the proportion of women presenting from distant metastasis (Figure 7), as we felt this was more likely to be accurate (compared to WMCIU[3]) based on other published estimates,
- validate the results of the calibration of the natural history model. The natural history was calibrated against the WMCIU data. [33] ECRIC data was used to ensure that the calibrated natural history would be representative of other regions in England and Wales. [34]

Figure 7: Proportion of women presenting with distant metastasis by age group (ECRIC)



[3] data from the WMCIU could not be used for that purpose given the very small number of women diagnosed with distant metastasis and consequent uncertainty about data quality in this respect..

2.3. Calibration approach

Of the 24 model parameters, only 6 are directly observable (those relating to grade and size at presentation). These were fitted directly to the WMCIU dataset. [33] Fitting the remaining 16 parameters is not straightforward, since they are not directly observable. We used Monte Carlo simulation to estimate the value of the likelihood. This involves simulation of a cohort of women given a set of model parameter values. Once the life history of the cohort is simulated, this information can be used to generate estimated values for the observed data to which the model is being fitted. These estimated values can be used to calculate proportions, which are estimates of the true probabilities for the multinomial data. If the cohort is sufficiently large, the resulting estimates of the likelihood at the given input parameter values will be reasonably accurate.

The Monte Carlo estimation procedure begins with selecting a trial vector of parameter values. These are used to sample transition times for a cohort of N women (N was set at 1 million for fitting each model, based on PC memory limits). The simulated life histories are used to generate predicted values for the available data. This data consists of tables, and the likelihood function for the data is therefore multinomial, and dependent on the probability that any given individual would be in any given cell of the relevant table. We estimate the values for these probabilities for the chosen trial vector by converting the predicted values into proportions in each cell. This gives an estimated value for the likelihood function of the data. We sought values for the parameters that maximised the likelihood of the available data, estimating using Monte Carlo simulation as described above. That process estimates the likelihood with an error due to the finite size of the simulated cohort, which makes use of common numerical methods for finding maxima problematic. We chose to use a simple but robust search algorithm to identify parameter values that maximised the likelihood:

This involved a 5 step approach:

- Step zero: Choose a starting vector of model parameters,
- Step one: Generate a random sample (we used a sample size of 50) of parameter values with a mean equal to the starting vector,
- Step two: For each vector, estimate the likelihood using the Monte Carlo simulation process,
- Step three: Fit a regression model to the results from step two, with the likelihood as the dependent variable and the parameter values as the explanatory variable,
- Step four: Identify the parameter value which gives the highest likelihood under the regression model,
- Step five: return to step one, setting the starting value to equal to the vector identified in step four.

This process is repeated until the likelihood achieved is stable for 100 iterations.

2.4. Results of the calibration exercise

2.4.1. Calibrated distribution

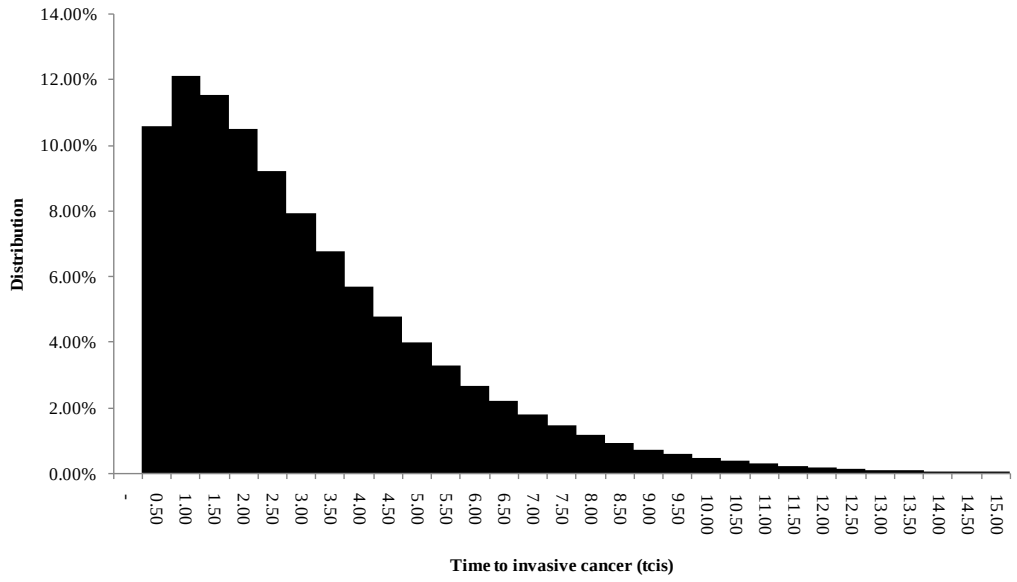
- Proportion of invasive cancer preceded by CIS ("*Icis*")

We estimated that about 46% of invasive cancers are preceded with CIS

- Time to invasive cancer among women with invasive breast cancer preceded by CIS ("*tcis*")

We estimated that the mean time from CIS development to invasive cancer was 2.92 ±2.44 years (median; 2.28; IQ: 1.10 – 4.07). The time distribution is presented in Figure 8.

Figure 8: Time distribution from appearence of the disease to the presence of invasive cancer (among women who have invasive cancer preceded by CIS)



- Time at which the disease is present due to clinical symptoms from the point at which the disease become invasive ("*tsymp*")

We assumed that time at which the disease presents with clinical symptoms was correlated with the grade status. The mean time was estimated to be 3.89±1.60 (median: 3.80; IQ: 2.73 – 4.97 years), 3.83±1.57 (median: 3.75; IQ: 2.68 – 4.89 years) and 3.77±1.55 (median: 3.70; IQ: 2.64 – 3.78 years) for women diagnosed with grade I, II and III respectively.

Figure 9: Time to symptoms (grade 1)

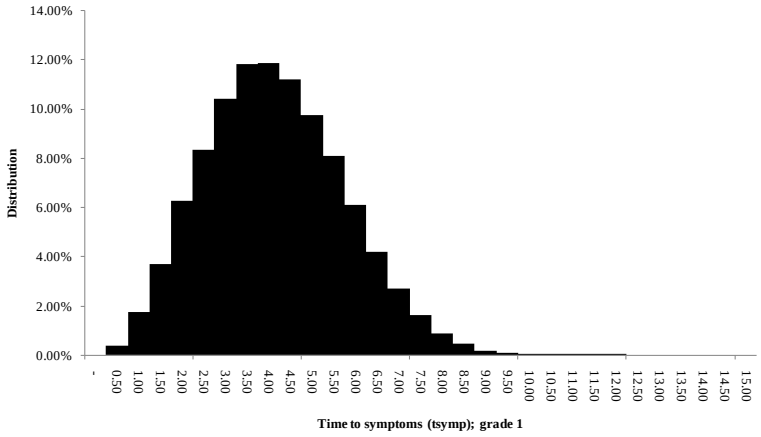


Figure 10: Time to symptoms (grade 2)

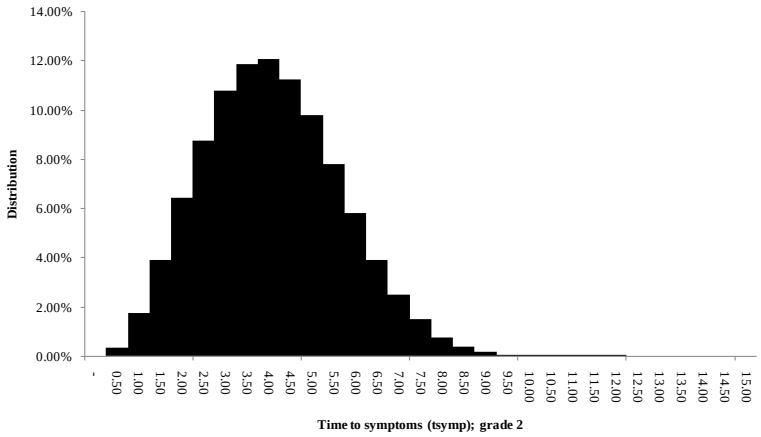
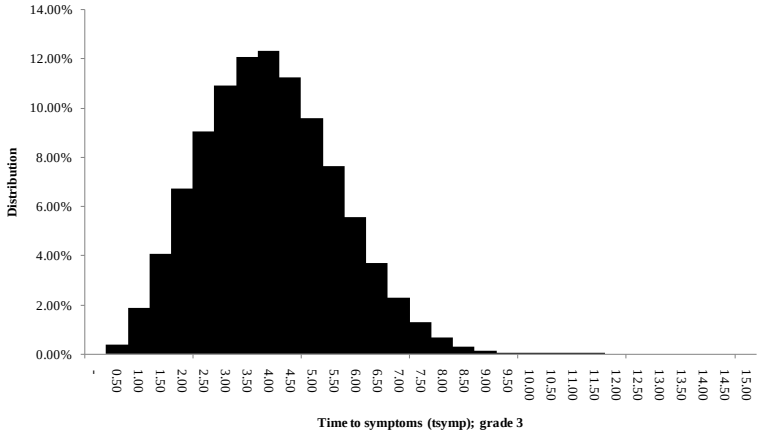


Figure 11: Time to symptoms (grade 3)



- Time to nodal invasion ("t*reg*")

We assumed that time to nodal invasion was correlated with the grade status. The mean time was estimated to be 4.87±2.67 (median: 4.51; IQ: 2.84 – 6.52 years), 3.59±1.97 (median: 3.33; IQ: 2.10 – 4.80 years) and 2.64±1.45 (median: 2.45; IQ: 1.54 – 3.53 years) for women diagnosed with grade I, II and III respectively.

Figure 12: Time to nodal invasion; Grade 1

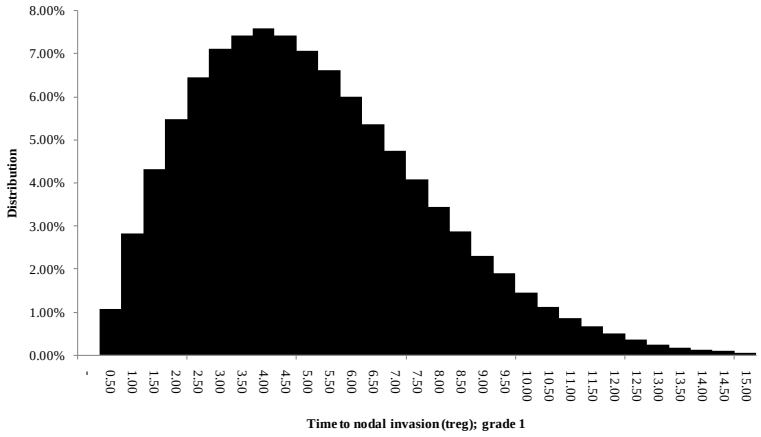


Figure 13: Time to nodal invasion; Grade 2

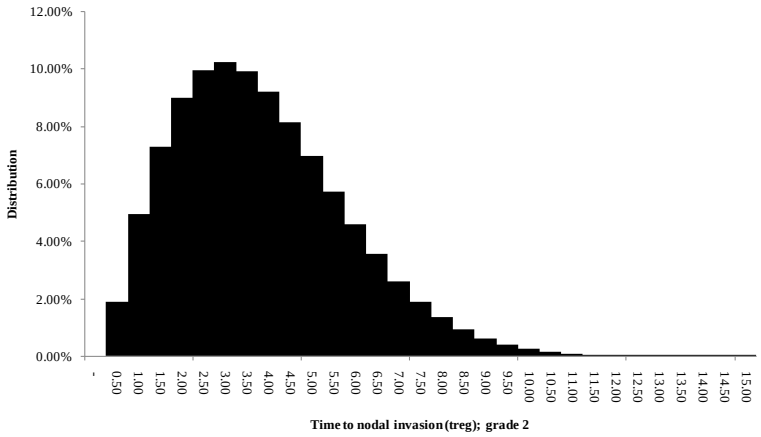
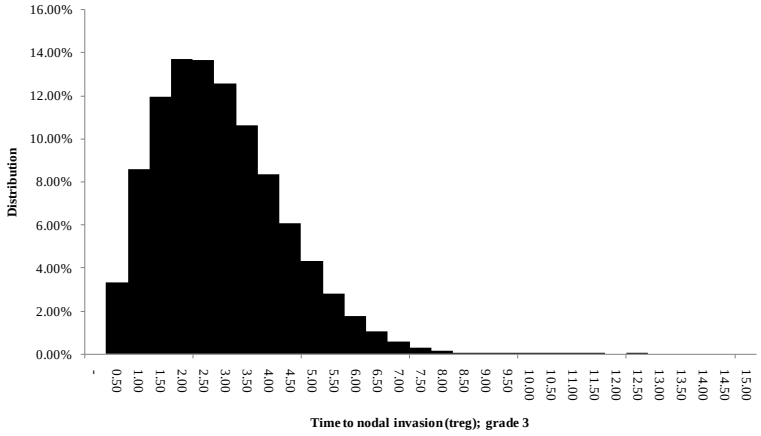


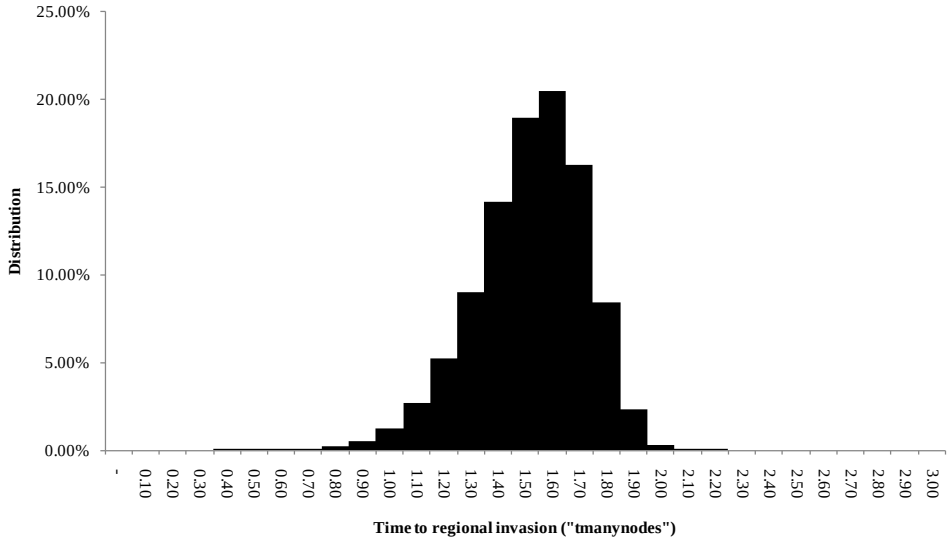
Figure 14: Time to nodal invasion; Grade 3



- Time to regional invasion ("*tmanynodes*")

We estimated that the mean time to regional invasion was 1.47 ±0.20 years (median; 1.49; IQ: 1.35 – 1.61). The time distribution is presented in Figure 15.

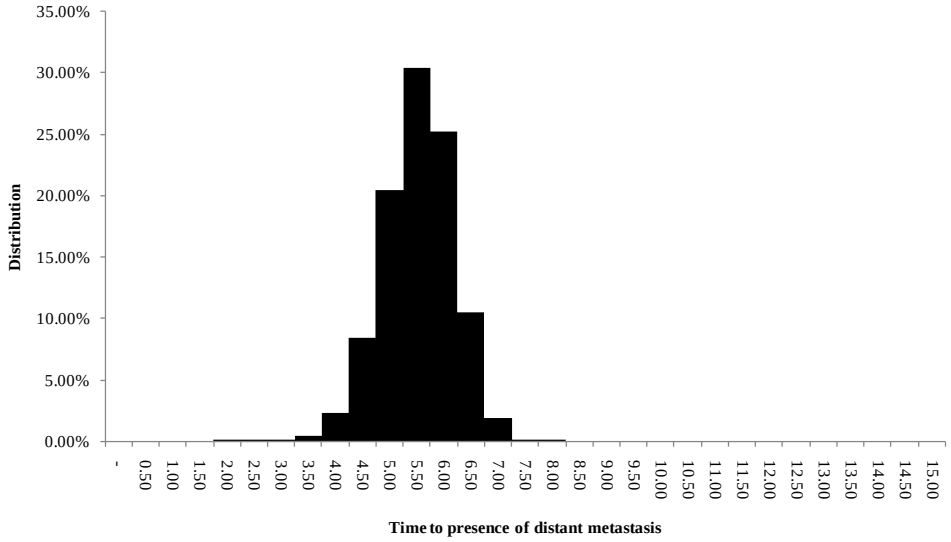
Figure 15: Time to regional invasion



- Time to presence of distant metastasis due to clinical symptoms

This was a function of "*tdist*" and "*tmetspres*". We estimated that the mean time to presence due to distant metastasis was 5.28 ±0.64 years (median; 5.304; IQ: 4.87 – 5.72). The time distribution is presented in Figure 16.

Figure 16: Time from presentation to distant metastasis



- Tumour size distribution at presentation, in the absence of screening

We assumed that tumour size was correlated with the grade status. The mean tumour size was estimated to be 23.93±10.68 (median: 21.87; IQ: 16.42 – 29.11 mm), 24.83±13.37 (median: 21.86; IQ: 15.56 – 30.73 mm) and 25.88±16.30 (median: 21.88; IQ: 14.81 – 32.37 mm) for women diagnosed with grade I, II and III respectively.

Figure 17: Tumour size (grade1)

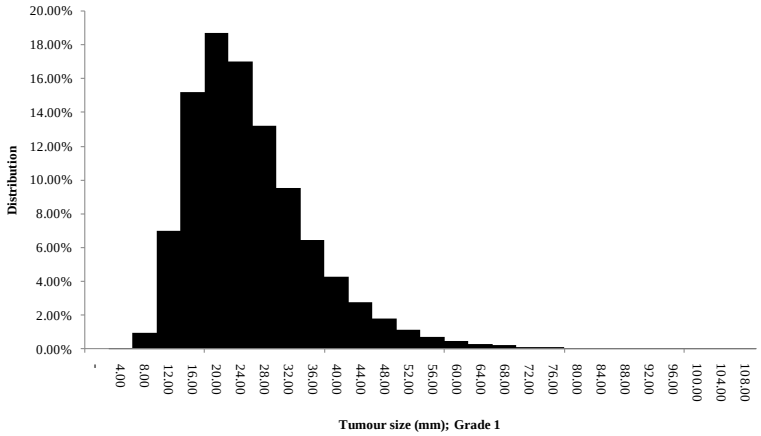


Figure 18: Tumour size (grade 2)

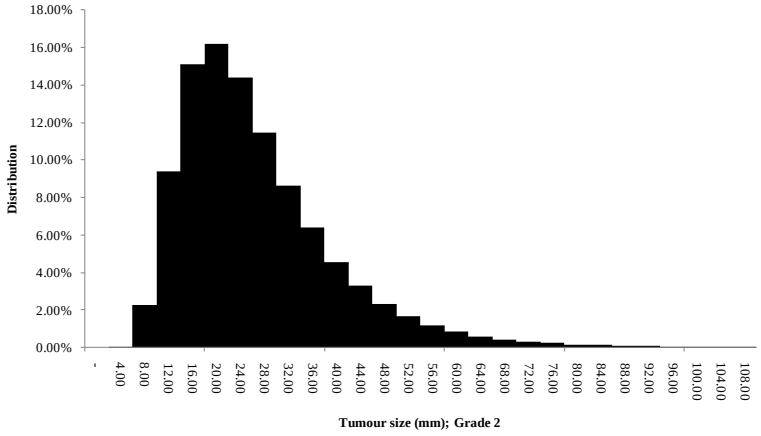
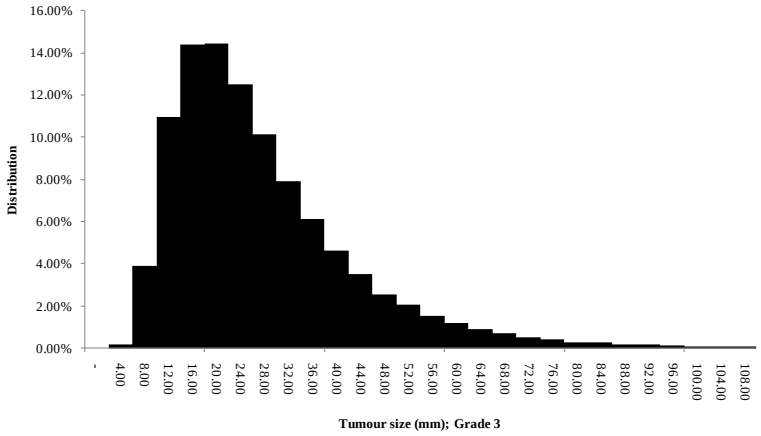


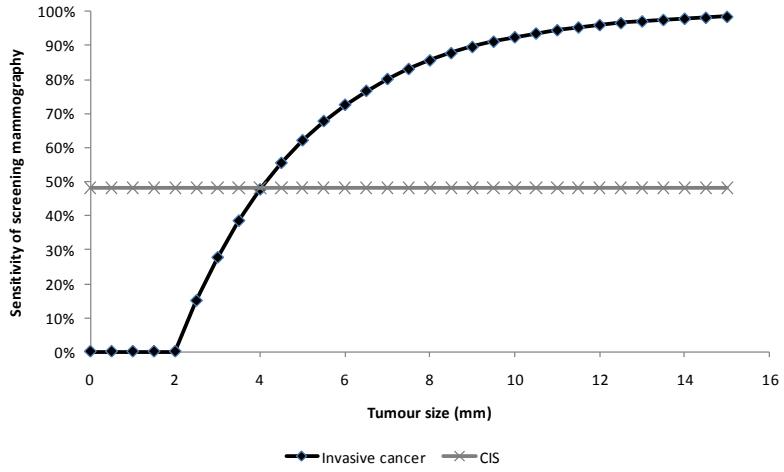
Figure 19: Tumour size (grade 3)



- Calibrated probability of detection by screening

The probability of detection for invasive cancer was assumed to be size-dependent and to increase exponentially as the tumour size increased (Figure 20). We also modelled separately the probability of detection for CIS, this was estimated to be around 49.24%. Note that the probability of detecting CIS was modelled to be constant given the structure of the model (we assumed that CIS is a categorical variable, i.e that that women would either present with or without a CIS)

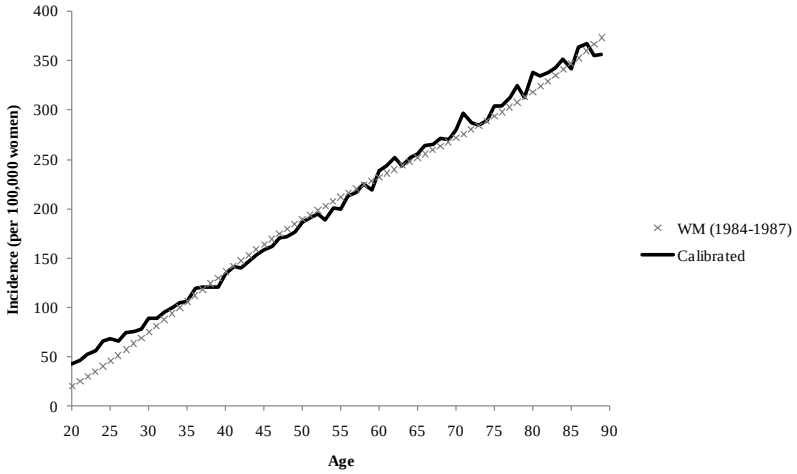
Figure 20: sensitivity for cis and sensitivity for invasive cancer for screening mammography



2.4.2. Comparison of observed versus predicted

Overall, the calibration algorithm provides a good fit of the model to the whole of the calibrated data. The predicted age specific breast cancer incidence closely matches the incidence data observed in the West Midlands (Figure 21). As sligtly poorer fit in breast cancer incidence was observed in younger women aged less than 40 years old. The fit also diverged after the age of 85 years old. This may arise from the structural assumptions and the use of a Weibull distribution to model the time of the start of the disease.

Figure 21: Calibrated incidence versus Observed incidence before screening (Figure 6: 1984-1987 in WM)



Similarly, a reasonably good fit was observed for the screening data overall (NHSBSP 2006). The poorest fit was observed for data in women aged 70 years (Figure 24) given the small sample size. Indeed, the calibration algorithm put more weight in the younger age group where more data were available (345,822 in women aged 60-64, 232,672 in women aged 65-69 and only 15,358 in women aged 70 years old). The model provided a reasonably good fit in women aged between 60-64 and 65- 69 years in terms of numbers of cancers detected, type of cancer detected (carcinoma in situ or invasive) and tumour size distribution at detection (Figure 22 & Figure 23). Furthermore, a better fit was observed for women that previously attended screening compared to women screened for the first time. This is likely to arise from the greater number of women that previously attended screening compared to women that have been screened for the first time.

Figure 22: Calibrated tumour size at detection vs observed distribution from the NHSBSP (2006) in women aged 60-64 years old (previous attenders Table 3)

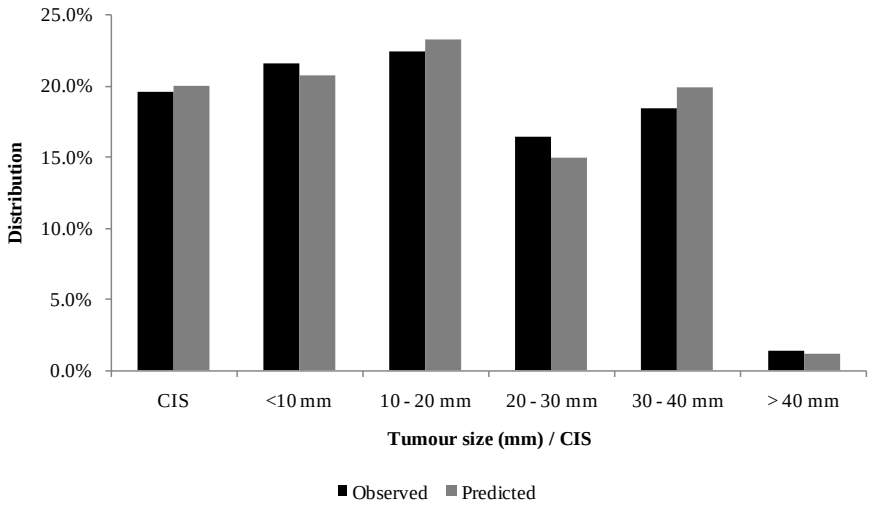


Figure 23: Calibrated tumour size at detection vs observed distribution from the NHSBSP (2006) in women aged 65-69 years old (previous attenders Table 3)

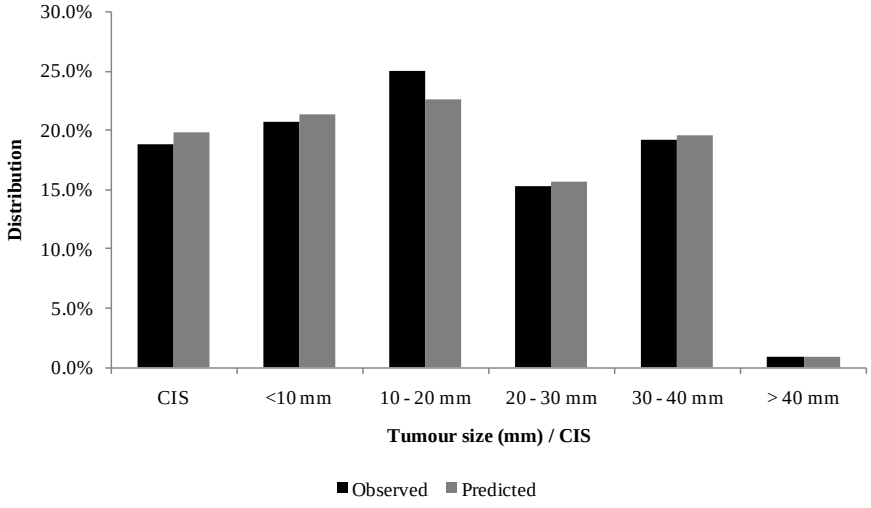
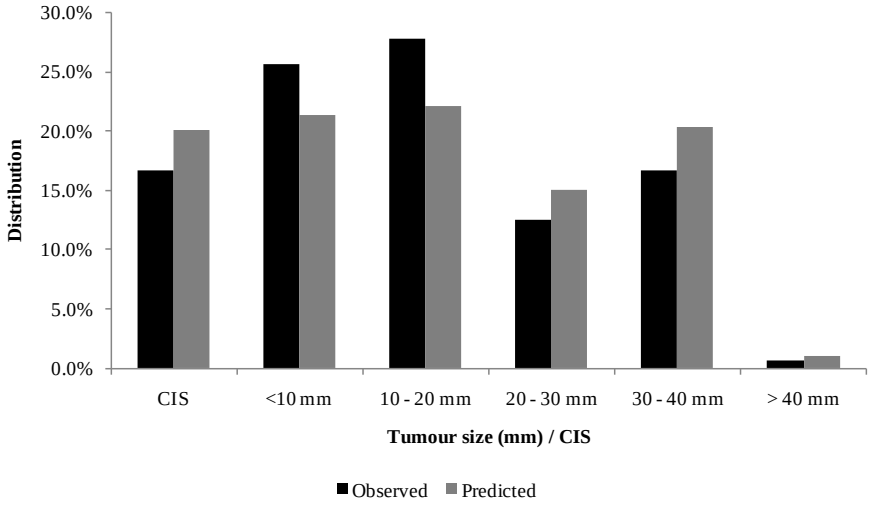


Figure 24: Calibrated tumour size at detection vs observed distribution from the NHS BSP (2006) in women aged 70 years old (previous attenders Table 3)



Finally, the model was also calibrated against natural history data from the West Midlands and East Anglia for older women presenting due to clinical symptoms of breast cancer. The fit was found to be reasonably good when comparing the proportion of elderly women by grade, nodal status, ER status and tumour size (Figure 25 & Figure 26). A good fit was also observed for the proportion of women presenting with distant metastasis compared to data from the ECRIC (Figure 27). [34]

Figure 25: Calibrated distribution of patient by grade, nodes and ER in symptomatic women vs observed distribution from the WMCIU in women aged 70+ (Table 4)

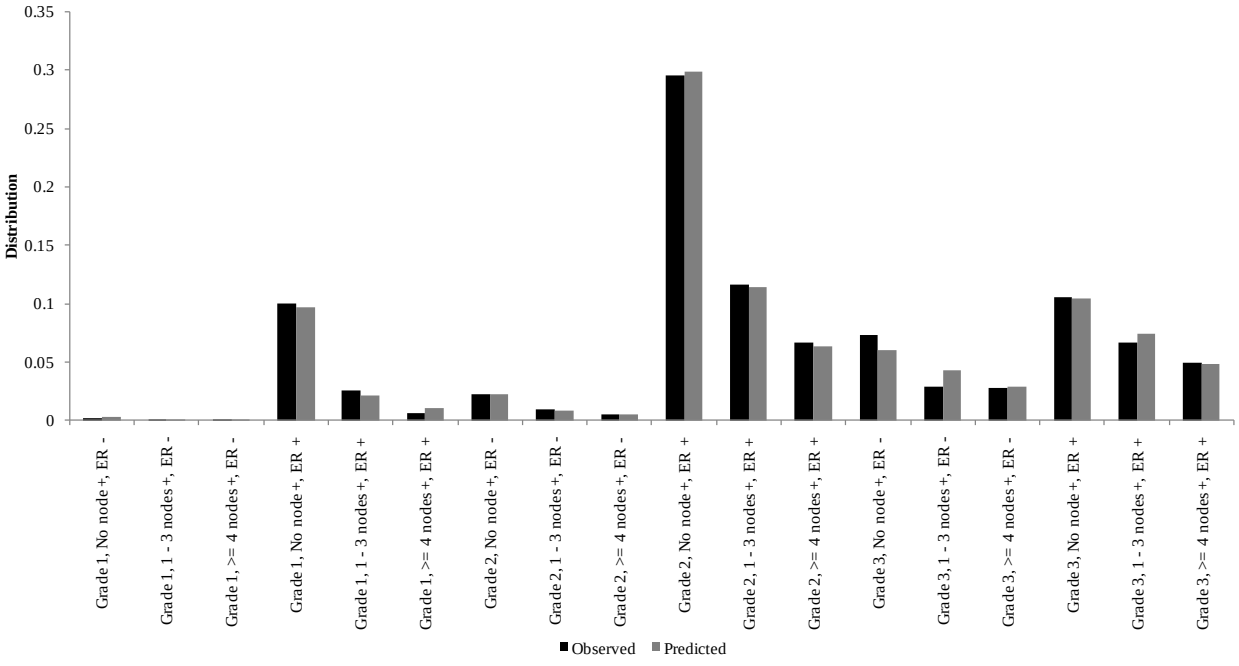


Figure 26: Calibrated tumour size distribution among women presenting symptomatically vs observed distribution from the WMCIU in women aged 70+ (Table 4)

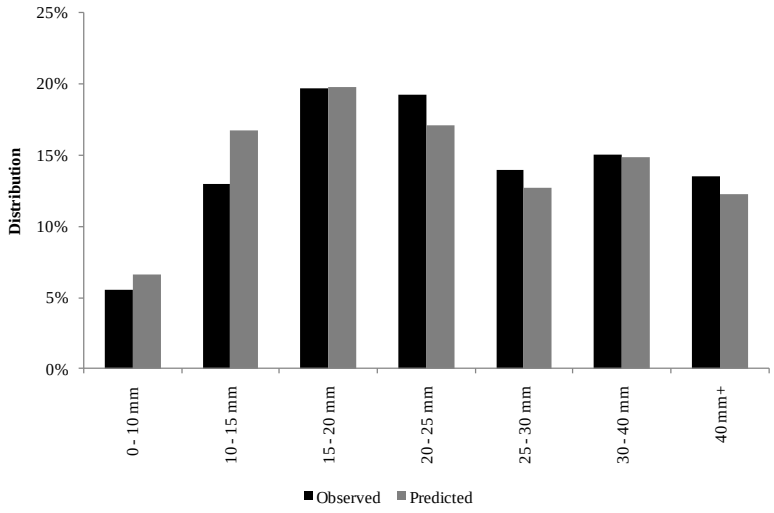
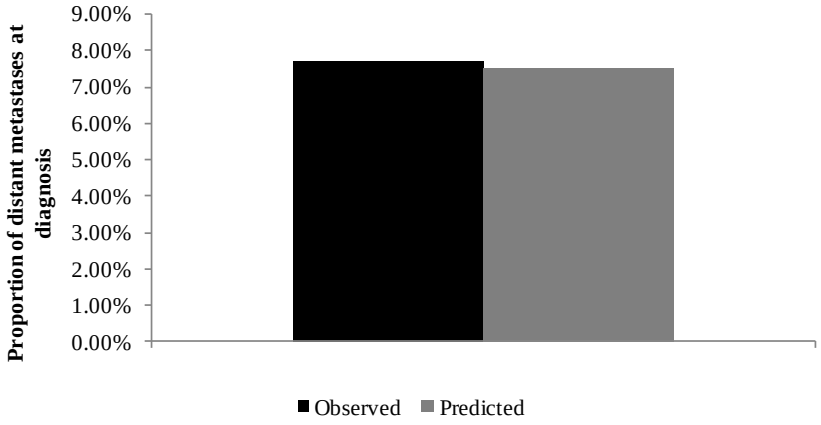


Figure 27: Calibrated proportion of patients presenting from distant metastasis vs observed proportion from the ECRIC in women aged 70+ (Figure 7)



2.5. Model validation

2.5.1. Natural history

The calibrated natural history was validated against a separate dataset; the ECRIC dataset and was found to be similar in terms of the proportion of women aged 70 years old and over by grade, nodal status, ER status and tumour size groups (Figure 28 & Figure 29). [34]

Figure 28: Calibrated distribution of patient by grade, nodes and ER in symptomatic women vs observed distribution from the ECRIC in women aged 70+

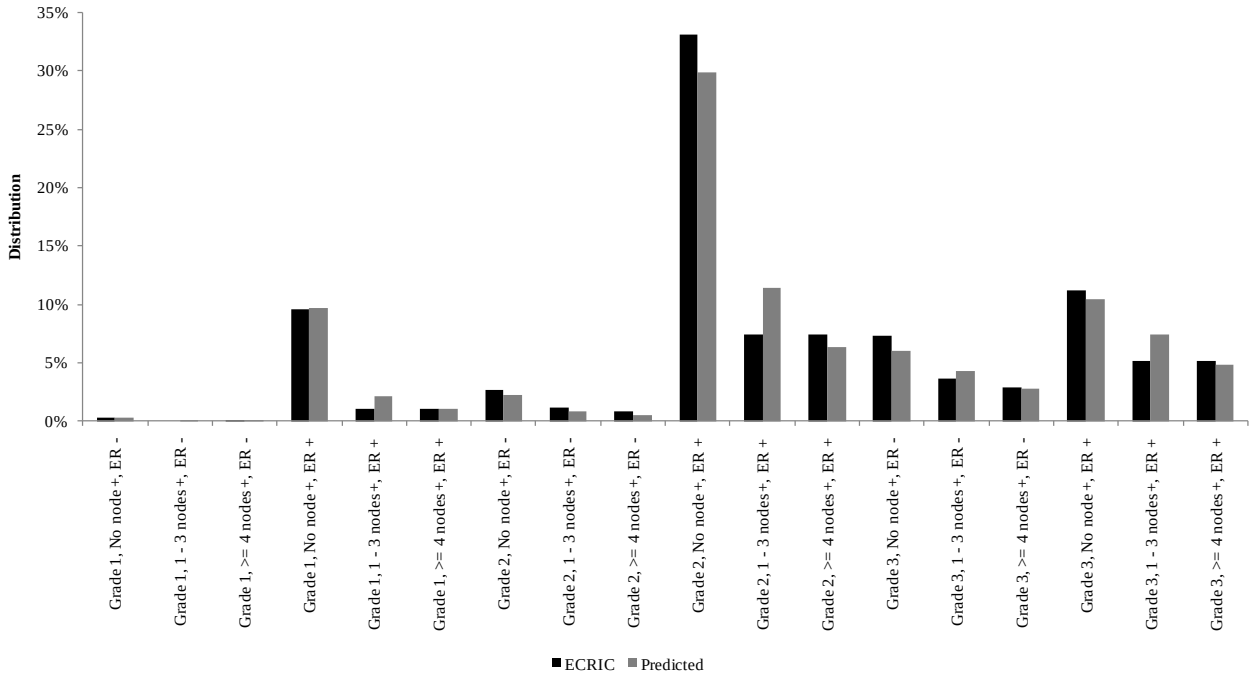
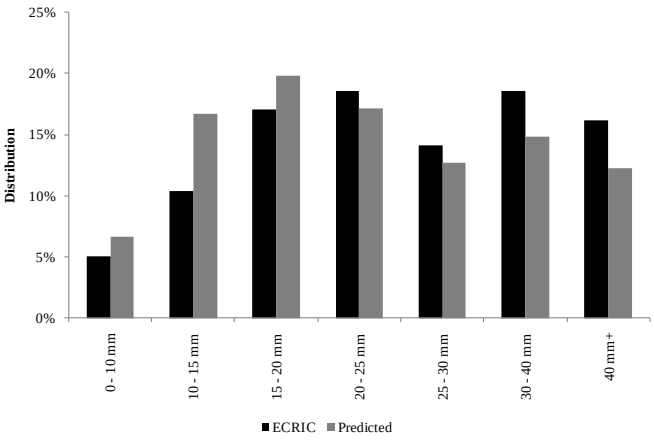
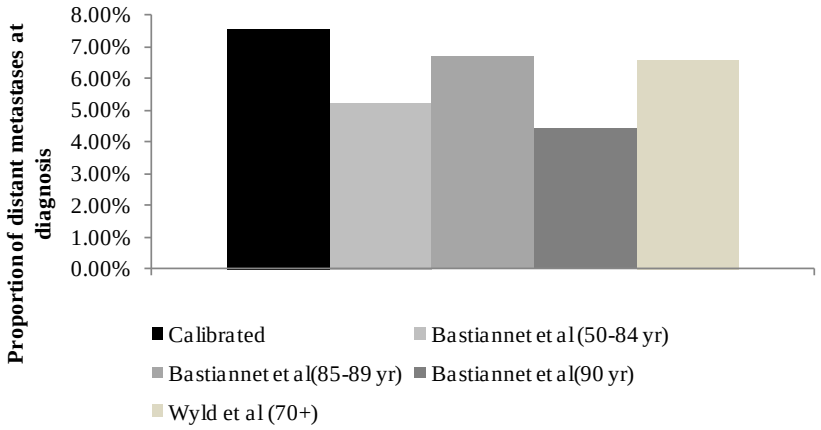


Figure 29: Calibrated tumour size distribution versus observed distribution from the ECRIC in women aged 70+



Furthermore, we estimated that about 7.5% of women would present from distant metastasis derived from data from the ECRIC. [34] This was similar to the proportion reported in other studies conducted in older women. In a Dutch cohort, Bastiannet et al (2010) indicated that 3.7% of women aged 15 – 64 presented from distant metastasis, compared to 5.2% for 50-84 years old, 6.7% for 85-89 and 4.4% for women aged over 90 years old. [36] Similarly, a UK study conducted reported that 6.6% of women aged 70 years and over presented from distant metastasis (Figure 30). [10]

Figure 30: Proportion of patients diagnosed with distant metastasis.



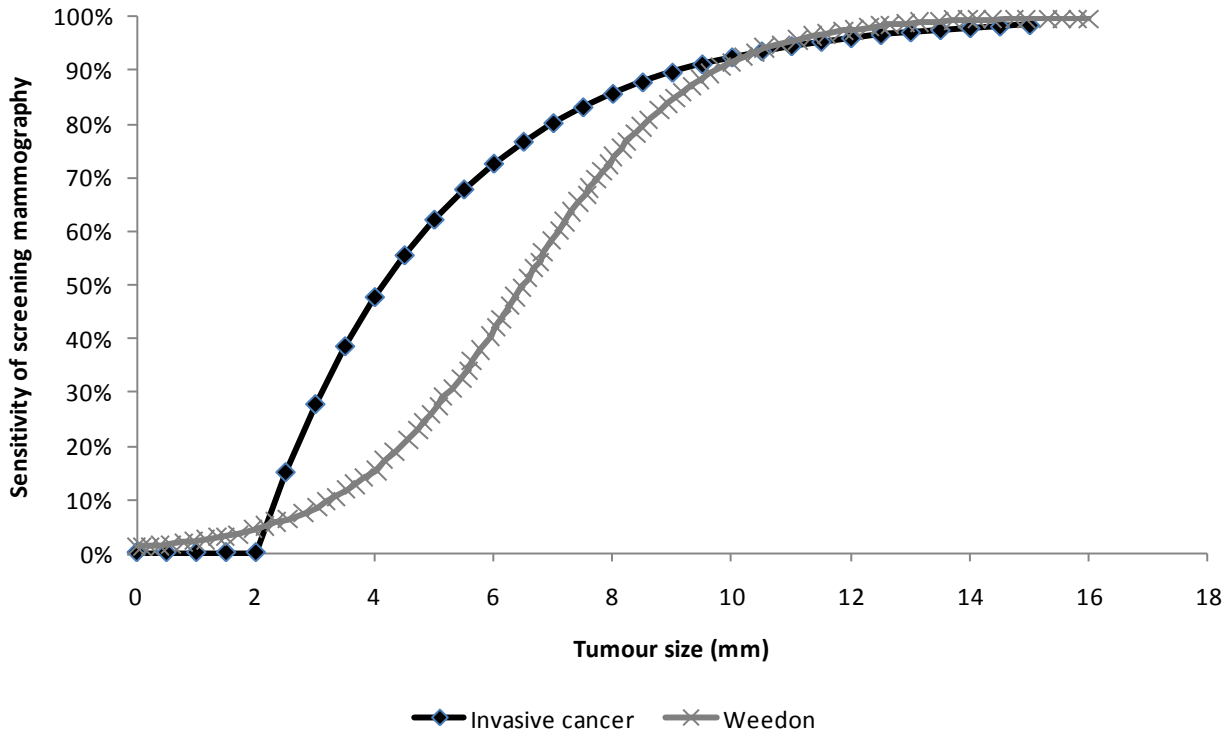
Finally, we also compared the mean sojourn time estimated from our model to estimates from the literature. Our model predicted a mean sojourn time of about 5.15 years (median: 4.67; IQ: 3.28 – 6.42) including CIS. The mean sojourn time without CIS was estimated to be 3.82 years (median: 3.74; IQ: 2.67 – 4.87). Evidence from the literature suggests that the mean sojourn time lies between two to four years in women aged 50-69 years old and that the better biology in older women would lead to a longer mean sojourn time. [37-40]

Weedon Fekjaer and colleagues (2005) estimated the mean sojourn time to be 4.6 years in women aged 50-59 years and 4.9 for women aged 60-69 years old (increasing up to 7.0 years when excluding data from women reporting earlier mammography prior to the screening programme). [40] A recent study conducted by the same authors estimated the mean sojourn time to be 2.3 years for women aged 50-59 years old and 3.5 years for women aged 60-69 years old. [41] While it is difficult to compare our estimate with previous studies, the estimated mean sojourn time is in line with findings from the literature.

2.5.2. Impact of screening

As women aged 70 years and over are not currently part of the NHSBSP, it is difficult to validate the estimated impact of screening from our model. Data from the literature around the sensitivity of screening mammography in elderly women was however available and indicated that the sensitivity for invasive cancer ranged from 85-95%, with the sensitivity increasing with age. Our study assumed the probability of detection to be size-dependent. To our knowledge there is no direct evidence on the sensitivity of screening mammography by tumour size. A previous modelling study found that the screen test sensitivity increased sharply with tumour size (Figure 31). [42] We also found the sensitivity to increase rapidly with size. Finally, while it is difficult to estimate the probability of detection for CIS in the absence of a gold standard, studies indicated that the sensitivity for screening mammography for detecting DCIS was variable and ranged from 22% to 86%. [43-46] Our estimate for the probability for detecting CIS was well within this range, at around 49.2%.

Figure 31: Calibrated sensitivity of screening mammography for invasive cancer vs estimated sensitivity reported by Weedon et al (2007)



3. PART TWO: MODELLING THE IMPACT OF SCREENING ON RESOURCE USE, COSTS AND BENEFITS

3.1. Decision problem and method of analysis

We evaluated the following strategies for extending the current NHSBSP:

- Strategy S_0: The current NHSBSP, which we define as a final invitation at age 69 (in practice the age at which the final invitation is received varies between 68-70, but for simplicity we assume the same age for all women).
- Strategy S_1: One additional screening round for women aged 72.
- Strategy S_2: Two additional screening round 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

We compared the incremental costs and benefits of each strategy S_{j+1} to the previous strategy S_j. In each case, these costs and benefits relate to the additional screening round. Therefore, we estimate the costs and benefits of each screening round in turn. We identify the costs and benefits for each screening round as follows:

1) We use the natural history model described in section V.2 to simulate life histories for a large sample (1 million, determined by PC memory limits) of women.
2) For each simulated woman, we determine whether she has detectable asymptomatic disease at any of the screening rounds included in strategy S_7
3) We then determine, for each screening round where this is the case, whether screen-detection occurs or fails due to either non-attendance or a false negative test. Where screen detection would occur in more than one round, we assume that it actually occurs at the earliest instance. Where the Detectable Pre-Clinical Phase begins before age 69, we also consider whether the disease would actually be detected in the current NHSBSP. If so, no costs or benefits accrue for any of the strategies given above. All simulated women who have not been diagnosed with breast cancer (either symptomatically or in a previous screen) are assumed to incur invitation costs. The women who actually attend incur screening 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 treatment and costs of recurrence and survival of these women, then subtracting the costs and benefits that would accrue if they had not been detected through screening.
4) The final step is to calculate the incremental costs and benefits of S_{j+1} compared to the previous strategy S_j

3.2. Overview of the model structure

This section describes a model to evaluate the impact of the implementation of screening mammography in older women upon resource use, costs, mortality and morbidity (quality of life) compared to current practice in the UK, i.e. no routine screening.

A Discrete Event Simulation (DES) type model was developed in R Version 2.11.1 Software. The model is separated into five components:

- modelling the life history of breast cancer in older women in the absence screening (i.e. current strategy),
- evaluate the impact of introducing screening mammography on the stage at diagnosis of breast cancer,
- estimate the survival after diagnosis of breast cancer among women presenting due to clinical symptoms and screen-detected women,
- evaluate resource use, costs and impact of breast cancer diagnosis on quality of life
- calculation of the ICER

3.2.1. Modelling the life history of breast cancer in older women in the absence of screening

We simulated the life history of one million of women using the natural history model and calibrated the parameter set described in section V.2. We sampled a million women who would potentially develop breast cancer after the age of 60 years.

For each individual woman, the model simulates the age at which the disease appears ("tstart"), the age at which the cancer become invasive ("tcis) and the age at which the cancer become symptomatic ("tsymp") in the absence of screening. The model also simulates the spread of the disease (in-situ, local, regional, distant) and tumour growth at the point of diagnosis.

The life history can be described using the following equation: "*tstart"*→ "*tcis"* → "*tsymp*".

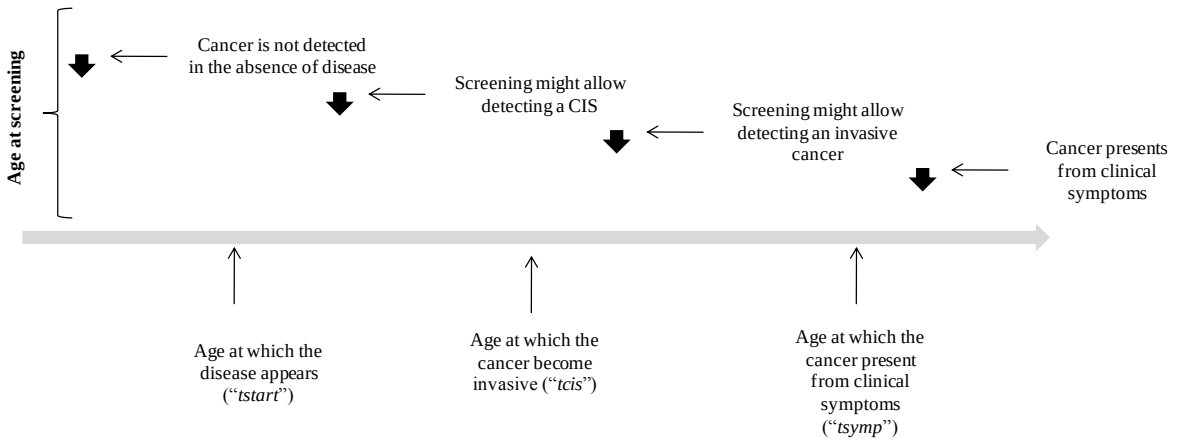
3.2.2. Evaluation of the impact of implementing screening upon the natural history of breast cancer

The life history of the "same" women was then simulated under 8 possible screening strategies (no screening and up to 7 screening rounds).

The interest of screening (early detection) lies in the time between the ages at which the disease appears ("*tstart*") and the ages at which the disease presents due to clinical symptoms "*tsymp*". The terms "window of opportunity" or "Detectable Pre-Clinical Phase" (DPCP) will be used throughout the report to describe this time interval.

For each woman entering the model, we evaluate the impact of screening comparing the age at screening and the DPCP. If the screening age comes before the age at which the disease appears ("*tstart*"), there will be no benefits for screening as the disease is not yet present. Similarly, if the age at screening is greater than the age at presentation due to clinical symptoms ("*tsymp*"), there will be no benefits for screening as the cancer have already been detected through clinical symptoms. However, if the age at screening lies within the DPCP, early detection from screening is possible; either in terms of in-situ disease (age at screening lies between "*tstart*" and "*tcis*") or invasive cancer (age at screening lies between "*tcis*" and "*tsymp*"). The concept of "window of opportunity" is summarised in Figure 32

Figure 32: Concept of "windows of opportunity"



We evaluate the impact of screening assuming triennial screening (every 3 years) from the age of 66 years up to 90 years (i.e. adding up to seven rounds to the current screening programme – 72 – 90 yrs old). 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. At present, the NHSBSP involves screening every woman aged between 50-69 years every three years.

As previously mentioned, the life history of breast cancer in a million of women was simulated. For the "**same**" women, the model evaluates the impact of screening assuming seven screening rounds; i.e. extension of screening up to the age of 72, 75, 78, 81, 84, 87 and 90 years old. Two additional screening-ages were added at 66 and 69 years old to account for the fact not all cancers would have been detected at the previous screen. At each screening round, we determine whether each simulated woman has screen-detectable disease i.e. whether the screening takes place during her DPCP. If so, screen-detection occurs with a probability equal to the size-dependent sensitivity estimated during model calibration (Figure 20). Where screen-detection occurs in more than one round, we assume the identification is made at the earliest round. For each screening round, we identify the set of women detected at that round and record their prognostic profile (tumour size, grade, nodal involvment) with and without screening. Finally, the model also assumes that a proportion of women invited do not attend screening. However, this is likely to not impact the ICER if the benefits are proportional to the costs associated with screening mammography. A simplified schematic of the model structure is presented in Figure 34.

3.2.3. Estimate of survival among older women presenting due to clinical symptoms or early detection through screening

Having identified the women within our simulation who would be detected at each screening round, we wanted to estimate the impact of that detection compared to allowing the disease to present symptomatically. We consider firstly the impact on her life expectancy. This was done using the following approach:

-step one: simulate her age of death from causes other than breast cancer.

-step two: estimate her age of death if the disease is allowed to present clinically.

-step three: estimate her age of death if the disease is detected through screening.

The implicit assumption being that the life expectancy of patients with breast cancer dying from other causes is similar to the life expectancy in women without breast cancer. This assumption is supported by evidence. [47] We did not used data on breast cancer mortality directly given the possible misclassification of the cause of death.

a. Step one: Estimate the age at death from causes other than breast cancer

We gathered data on UK mortality from all causes, and breast cancer mortality in particular, from the ONS (2006). [48] This was used to fit a Gompertz distribution representing UK mortality from all causes except breast cancer. We used this distribution to sample the age at which each screen-detected woman would die from some cause other than her breast cancer, conditional on being alive at the age of screening. An example is presented in Figure 33.

Figure 33: Illustration of the method used to calculate survival time

b. Step two: Estimate over-diagnosis and the age of death if the disease is allowed to present symptomatically

For each eligible woman, the sampled age at death from causes other than breast cancer from the general population was compared to the age at which the disease would present due to clinical symptoms in order to identify over-diagnosis from screening, i.e. screen-detected women who would not have presented from clinical symptoms in the absence of screening.

If the sampled age at death was less than the age at which the disease would present due to clinical symptoms, screening is associated with over-diagnosis and considered as harmful as this would lead to unnecessary costs but also a reduction in the quality of life from treatment for breast cancer. In the absence of screening, this woman would have had a "normal" life and died from other causes with no knowledge of the presence of breast cancer.

Where the cancer would present before death occurs due to other causes, we used registry data for older women aged over 70 years and diagnosed with breast cancer to calculate a survival model that predicted the age at death using the prognostic profile at the point of diagnosis. This model is described in more detail below (section 3.3.2). We then took whichever came first, the age of death due to causes other than breast cancer sampled in step one, or the age of death due to breast cancer sampled in step two, to be the age of death in the absence of screening.

c. Step three: estimate the age of death if the disease was screen-detected.

As with symptomatic disease, the natural history model gave us the prognostic profile of the disease at the point of screen detection. However, the transferability of the survival model (section 3.3.2) to screen detected women is uncertain. In the absence of data about survival in screen-detected women or robust data about the impact of screening on survival in elderly women, we assumed as our base case that relationships between prognostic profile and mortality were the same whether the disease was screen-detected or symptomatic.

The impact of screen detection in our base case model is that life expectancy from the point of detection will increase to the extent that the prognostic profile of the disease is improved. However, screening also brings forward that point of detection, and the net result in some individual cases was that screen-detection led to an earlier death. This may seem implausible, although it has been argued that treatment can in some cases lead to metastatic progression that might not otherwise have occurred or that earlier death may arise as a result of complications from breast cancer therapies such as chemotherapy, radiotherapy and surgery. At the same time, it has been argued that screen-detection leads to better survival even where the prognostic profile is the same. One important issue is the fact that we combine data from two different sources, i.e the natural history model outputs and survival model from asymptomatic women. By doing so, a proportion of women would do better without screening if the time interval between age at detection from screening and symptomatic is long enough despite the improvement in prognostic profile at diagnosis. Therefore, inconsistencies may be observed at the individual level, but to a lesser extent at the population level. In the model, about 10% of women die earlier in case of screening. To reflect different possible assumptions in using survival data from symptomatic patients to estimate screen-detected survival, we consider three scenarios: (Figure 35);

- *Scenario 1 (most conservative scenario):* Screening leads to earlier detection, but can also lead to earlier death compared to no screening at individual level. The survival is applied from the age at screen detection using the prognostic profile at the point of diagnosis. Therefore if time at death in case of screening (ex 89) is greater than the time at death without screening (ex 92), no adjustment (death at 89 years old if screened)

- *Scenario 2 (neutral scenario):* Screening leads to earlier detection, but cannot lead to premature death compared to no screening at the individual level. The survival is applied from the age at screen detection using the prognostic profile at diagnosis. If the sampled age at death due to breast cancer assuming screening (ex 89) is lower than the sampled age at death for the "same" woman in the absence of screening (ex 92), the woman is assumed to die at the same age she would have died in the absence of screening (here 92 years old).
- *Scenario 3 (Optimistic scenario):* Screening leads to earlier detection and is necessarily associated with a survival advantage due to the shift in prognostic profile at the individual level. In this scenario, the survival in case of screen-detection is applied from the age at which the women would present due to clinical symptoms using the prognostic profile from the point at screen detection. Therefore, as screening leads to earlier detection, screening would ultimately lead to an improvement in the prognostic profile and therefore improved survival compared to the absence of screening.

Figure 34: Simplified schematic of the model structure

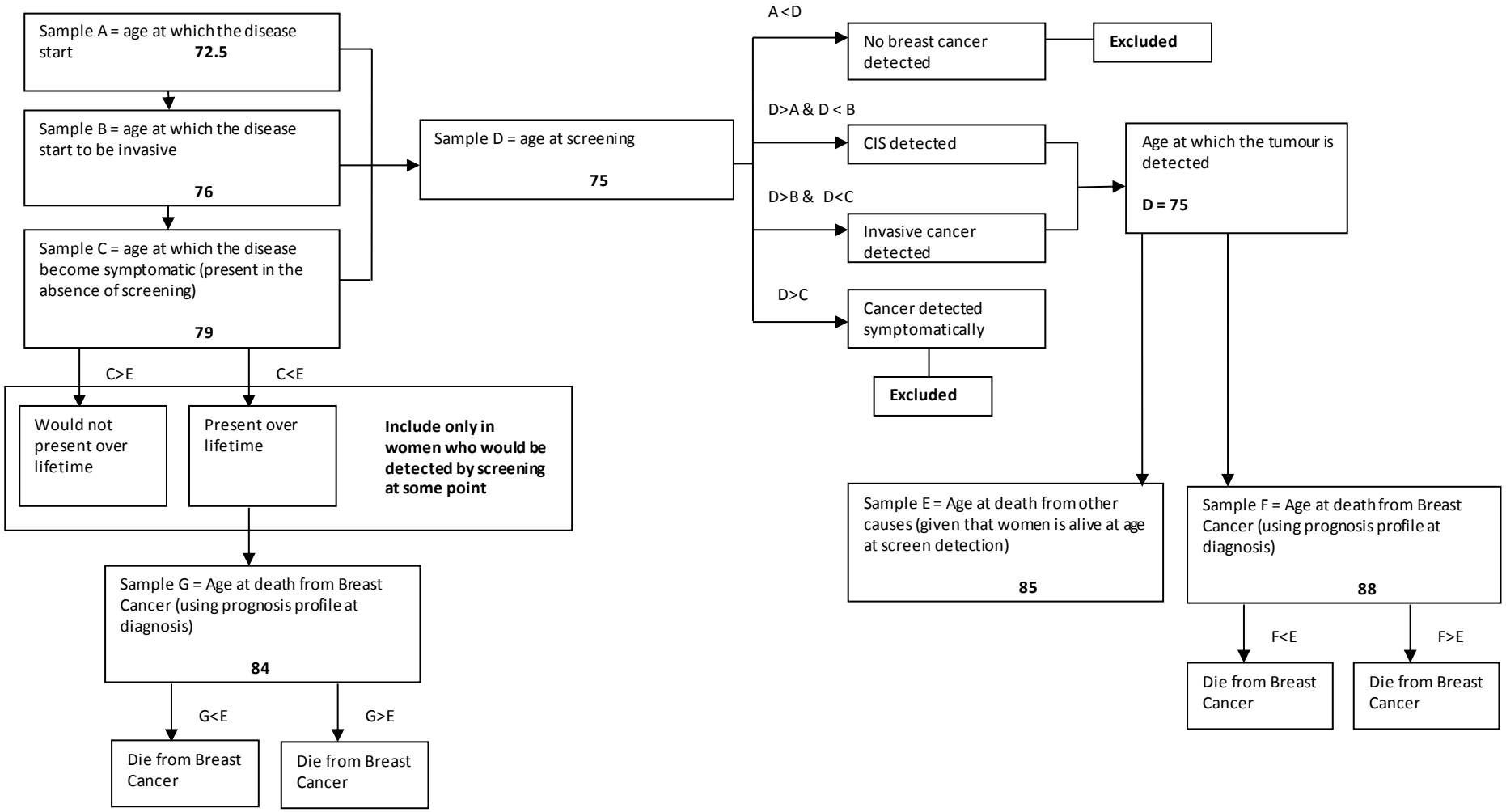
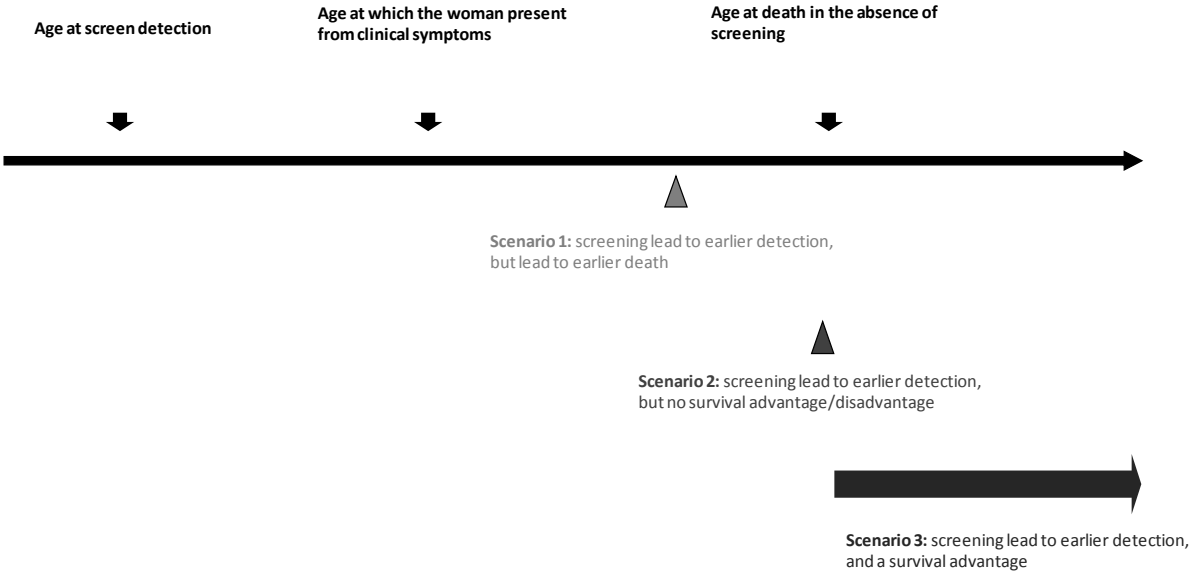


Figure 35: Simplified schematic of the survival scenarios for screen detected women

Let's assume that the sample age at death for women A undergoing screening is below the age at death in the absence of screening.

- Under scenario 1, screening lead to earlier detection, but lead to earlier death
- Under scenario 2, screening lead to earlier detection, but would not change the survival for that women
- Under scenario 3, screening lead to earlier detection and would lead to a survival advantage due to the shift in prognostic profile at diagnosis



3.2.4. Impact of diagnosis on resources used, costs and quality of life

The model included 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. Resource use associated with the primary treatment for breast cancer at diagnosis were estimated from registry data. Treatment for recurrence was modelled as a proportion of patients treated for recurrence from registry data. We did not directly model time from diagnosis to recurrence or recurrence to death. Follow-up consultation after diagnosis of breast cancer was derived from NICE recommendation for the management of breast cancer follow-up. [49] Finally, palliative care costs were applied to the last year of life for women dying from breast cancer causes. Costs related to the screening programme were also included and

comprised costs of the mammogram and the cost for the management for women recalled for further investigation. Costs were estimated from the NHS perspective and were derived from official tariffs, published literature and assumptions when appropriate.

The reduction in quality of life associated with the diagnosis of breast cancer was also considered in order to calculate the cost per QALY gained. Utility weights were applied to 6 health states (disease free, in-situ, stage I, stage II, stage III and stage IV) for a pre-defined duration. Utility weights were derived from published literature and assumptions when appropriate. The negative impact associated with the pain of undertaking a mammogram and the anxiety after recall for further investigation was also considered based on data from published sources and assumptions.

Costs and health effects were discounted at 3.5% according NICE recommendations for health economic evaluation. [50]

3.2.5. Model outcomes

Results are presented per 100,000 women invited for screening. The model calculates the costs and benefits associated with the addition of a screening round among women who did not contract breast cancer to the previous screening round, i.e. that results are presented incrementally.

Results are presented in terms of:

- number of cancers detected and shift in stage distribution,
- mortality change from breast cancer,
- life years gained
- QALY gained
- management and costs of breast cancer diagnosis
- cost per life years gained and cost per QALY gained

Univariate sensitivity analysis was also conducted to estimate the effect of varying key model parameters and assumptions on the ICER.

3.3. Key model parameters and main assumptions

3.3.1. Survival from causes others than breast cancer in the general population

Data about the life expectancy by age was available in England and Wales from ONS life tables. [48] However, this included deaths from breast cancers. Consequently, we adjusted the life expectancy to exclude deaths from breast cancer by using separate data about the cause of death in the general population by age group (Office for National Statistics 2008). [51]

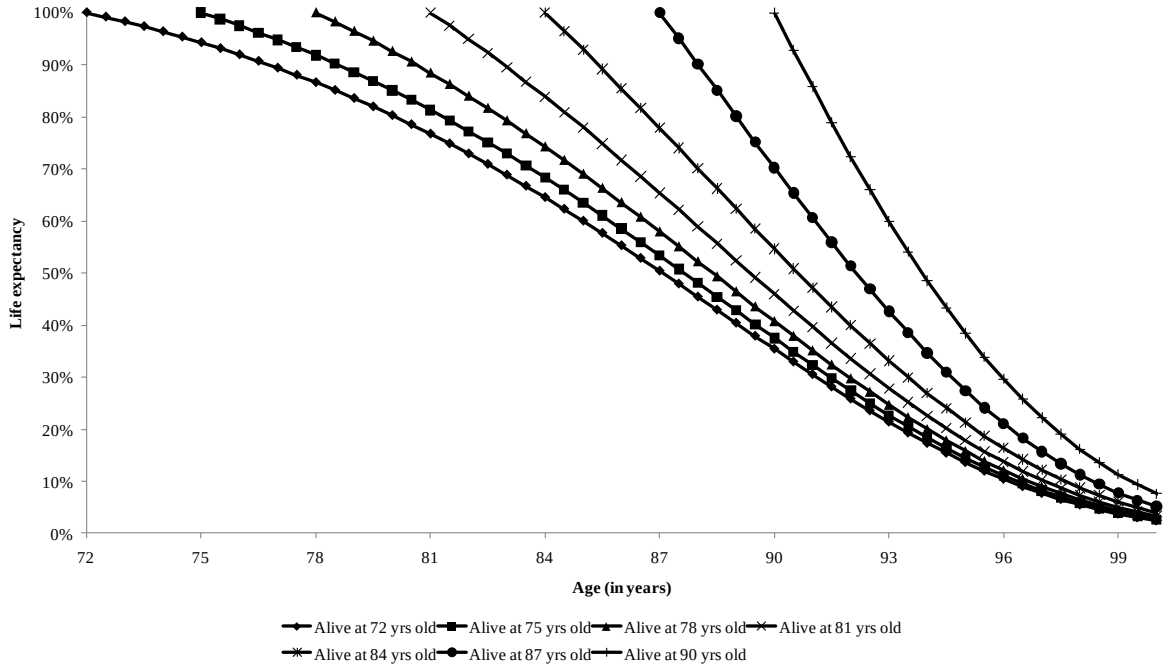
We compared the probability of death by age group for all cause mortality and causes other than breast cancer (Table 5). The ratio of the two probabilities was then calculated and applied to data on life expectancy to approximate life expectancy from death other than from breast cancer.

Table 5: probability of death by age in women only

Age group	Probability of dying from causes other than breast cancer	All causes probability of dying	Adjustment
70-74	1.71%	1.81%	94.57%
75-79	3.09%	3.21%	96.14%
80-84	5.77%	5.94%	97.12%
85-89	10.22%	10.46%	97.74%
90+	22.16%	22.54%	98.34%

The adjusted life expectancy was then used to estimate seven survival curves assuming the woman being alive at the age of 72, 75, 78, 81, 84, 87 and 90 years old, corresponding to the possible modelled age at screen-detection. This was done to adjust for the fact that the probability of death was dependent on being alive at the age of screen-detection. Gompertz parametric models were fitted to the calculated survival curves, with parameters estimated using Solver in order to indentify the set of parameters that would minimise the difference between the observed and expected life expectancy. The calculated survival models for the different age at screen-detection are presented in Figure 36.

Figure 36: Estimated life expectancy from death other than breast cancer in the general population by age



3.3.2. All cause survival in women diagnosed with breast cancer

All-cause survival in women diagnosed with breast cancer was derived from registry data from the WMCIU. [33] A description of the data is presented in section V.2.2.3.

We divided elderly women into three distinct groups according to their prognostic profile at the point of diagnosis:

- In-situ cancer (n = 257),
- Invasive cancer but no metastasis (n = 6,579)
- Distant metastasis (n = 23)

The reported cause of death is presented in Table 6.

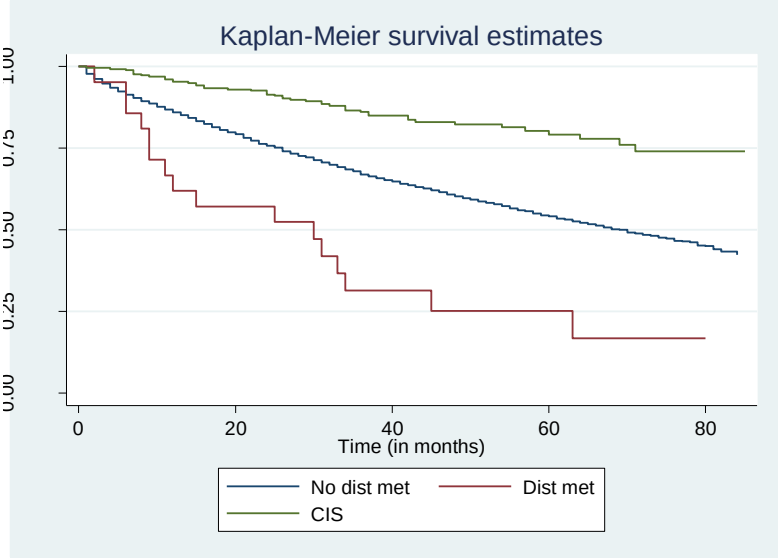
Table 6: Cause of death in WMCIU dataset

	No. of women	No of death	% of death (no women/no of deaths)	No of deaths due to BC	No of deaths due to other causes	% of deaths due to BC (no of deaths due to BC/no of deaths)	% of deaths due to other causes (no of deaths due to other causes/no of deaths)
CIS	257	47	18.29%	5	42	10.64%	89.36%
<10 mm	257	32	12.45%	12	20	37.50%	62.50%
>=10 & <15 mm	468	78	16.67%	20	58	25.64%	74.36%
>=15 & <20 mm	688	147	21.37%	51	96	34.69%	65.31%
>=20 & <25 mm	664	164	24.70%	64	100	39.02%	60.98%
>=25 & <30 mm	473	141	29.81%	65	76	46.10%	53.90%
>=30 & <35 mm	346	121	34.97%	58	63	47.93%	52.07%
>=35 & <40 mm	182	70	38.46%	35	35	50.00%	50.00%
>=40 mm	3501	2155	61.55%	1054	1101	48.91%	51.09%
Dist met	23	18	78.26%	14	4	77.78%	22.22%
All women	6859	2973	43.35%	1378	1595	46.35%	53.65%

We calculated the Kaplan-Meier survival curve for all cause mortality for women with in-situ disease, invasive cancer without metastasis and women diagnosed with distant metastasis.

Women diagnosed with distant metastasis had a median survival of 30 months (95% CI: 9 – 45). This was significantly lower compared to other women with invasive cancer; 70 months (95% CI: 66 – 73). It was not possible to estimate the median survival for women diagnosed with CIS given that 75% of women were still alive at the end of the follow-up duration.

Figure 37: Kaplan meier survival estimate



a. Survival in women diagnosed with in-situ disease (CIS)

Inconsistencies were found after analysis of the data for women diagnosed with in-situ disease. We found that about 10.6% of women who died during the follow-up period were reported to have died from breast cancer causes. After discussion with clinical experts and review of the literature, the proportion was believed to be high and questionable. Indeed, many in-situ cancers will not progress to invasive cancer, and those that do are likely to be managed successfully at the time of progression. The literature suggests that the life expectancy for women diagnosed with in-situ is similar to the life expectancy in the general population.

Inconsistencies in the data are likely to have arisen from the small sample size of women diagnosed with in-situ disease. There is also the possibility of misclassification in the dataset.

Consequently, we assumed that women diagnosed with in-situ disease would follow the same survival as the general population (Figure 36). This assumption was that made by most of the economic models reviewed in section IV.

b. Survival in women diagnosed with invasive cancer, but no metastasis

A parametric survival regression model was constructed among women diagnosed with invasive breast cancer but no metastasis. Included covariates were pre-specified and consisted of prognostic profiles that were believed to affect treatment choice and therefore survival in older women. This was governed by the fact that there is a direct relationship between prognostic profile and treatment and treatment and survival.

The estimated survival model uses ages (in months), tumour size (in mm), number of positive nodes (0, 1-3, 4+) and ER status as covariates. We also included the interaction between age at diagnosis and tumour size to account for the fact that tumour size is greater as the age at diagnosis increased. Note that we didn't include grade as a covariate for two reasons; first, our model did not include the direct shift in grade associated to screening; and finally there is a relationship between tumour size, nodal status and grade.

The model was constructed among 3,057 women. The coefficients for age, tumour size and nodal involvement were negative. This indicates that women would have a worse survival as the age or the tumour size or the nodal involvement increase. The coefficient for ER status was however positive, indicating that women with ER^{+ve} tumours had a better survival compared to women with ER^{-ve} tumours.

A Log-Logistic parametric survival model was fitted to the data for the central case. This was selected as this was shown to fit best the data using the AIC and BIC criteria calculated in Stata (Table 7) and behaviour of the plotted curve to KM data.

Equation 1: Log Logistic regression model to predict the age at death among women diagnosed with invasive cancers but no metastasis

No. of subjects =	3057	Number of obs. =	3057
No. of failures =	775		
Time at risk =	142389	LR chi2(6) =	440.74
Log likelihood =	-2132.1589	Prob > chi2 =	0.0000

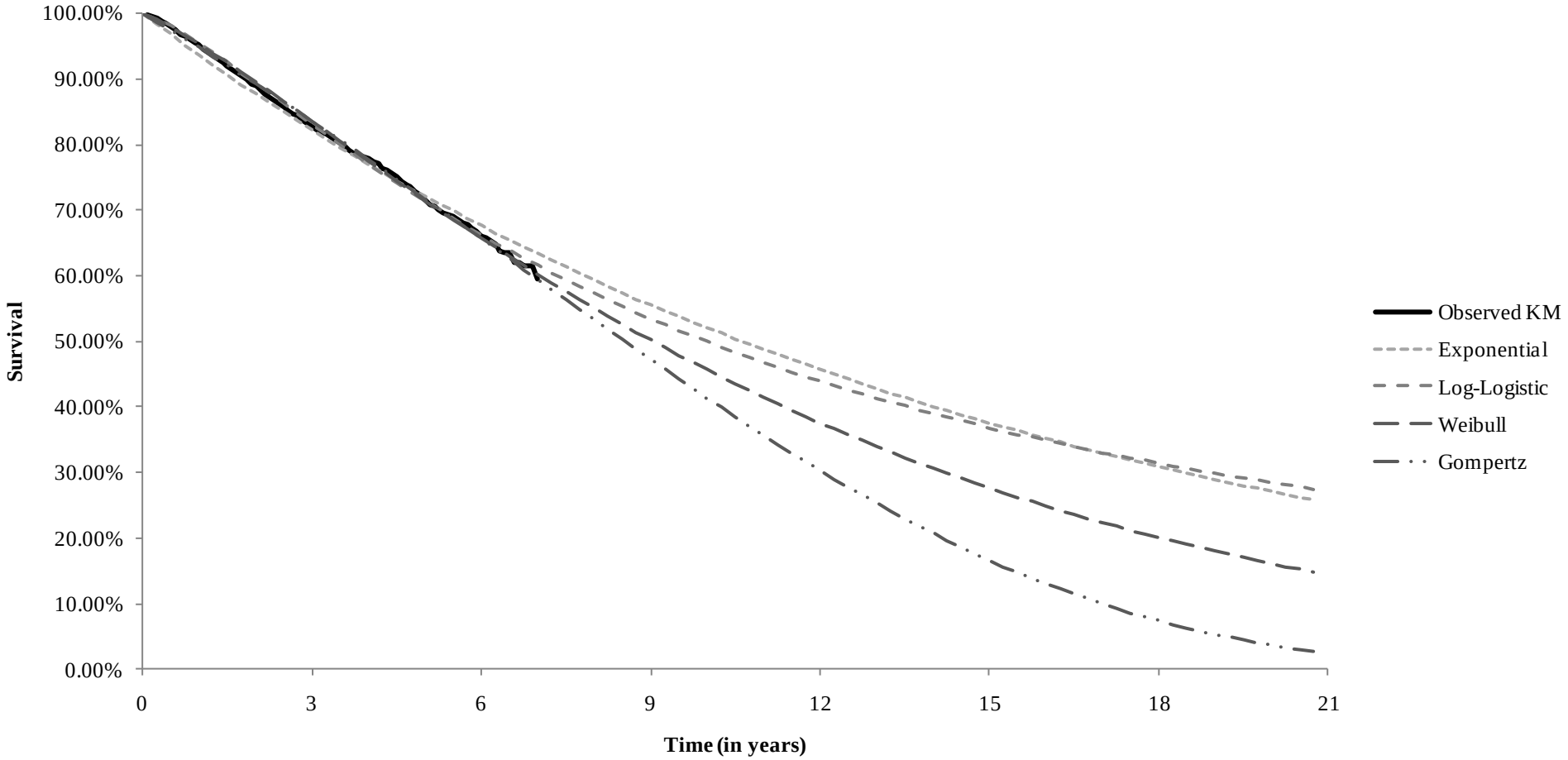
_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
ageatdiagn~s	-.0056413	.0009211	-6.12	0.000	-.0074467	-.0038359
invsize	-.0308522	.0248117	-1.24	0.214	-.0794823	.0177779
agesize	.0000193	.0000263	0.73	0.464	-.0000323	.0000708
_Inodes_2	-.2889889	.0717084	-4.03	0.000	-.4295347	-.1484431
_Inodes_3	-.9108843	.0786228	-11.59	0.000	-1.064982	-.7567866
ER	.5415645	.0708132	7.65	0.000	.4027732	.6803558
_cons	10.09477	.8689685	11.62	0.000	8.391622	11.79792
/ln_gam	-.3962368	.0315016	-12.58	0.000	-.4579789	-.3344947
gamma	.6728474	.0211958			.6325608	.7156996

Table 7: AIC and BIC (invasive cancer) by distribution type

	AIC	BIC
Exp	4,345.51	4,387.68
Weib	4,284.06	4,332.26
Gomp	4,301.68	4,349.88
Log-Log	4,280.32	4,328.52

We plotted the observed KM and the estimated parametric survival curve in Figure 38 (before adjustment for covariates). While all survival curves were found to fit relatively well to the observed data, the behaviour of the curve at the end of the evidence was shown to be different. Indeed, 27.07% of women were still alive at 20 years using the exponential model The figure for the weibull, gompertz and log logistic models were 16.03%, 3.64% and 28.41% respectively. Consequently, survival models using alternative parametric distributions (Exponential, Weibull, Gompertz) were examined in sensitivity analysis.

Figure 38: Plot of observed and predicted all cause survival in women with breast cancer diagnosed with invasive cancer (n = 3,057)



c. Survival in women diagnosed with distant metastasis

Finally, we constructed a survival regression model to estimate the age at death among women diagnosed with distant metastasis. The statistical model included only age as a covariate and was constructed based on a small sample size of 21 women. The small sample size is likely to bias results. However, the median survival for these patients was found close to the survival expected for this group of women; i.e. 30 months (95% CI: 9 – 45).

Equation 2: Exponential regression model to predict the age at death among women diagnosed with distant metastasis

No. of subjects =	21	Number of obs =	21
No. of failures =	16		
Time at risk =	599	LR chi2(1) =	0.93
Log likelihood =	-30.128859	Prob > chi2 =	0.3345

_t	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
ageatdiagn~s	.0044218	.0045493	0.97	0.331	-.0044947	.0133383
_cons	-7.866117	4.402877	-1.79	0.074	-16.4956	.7633635

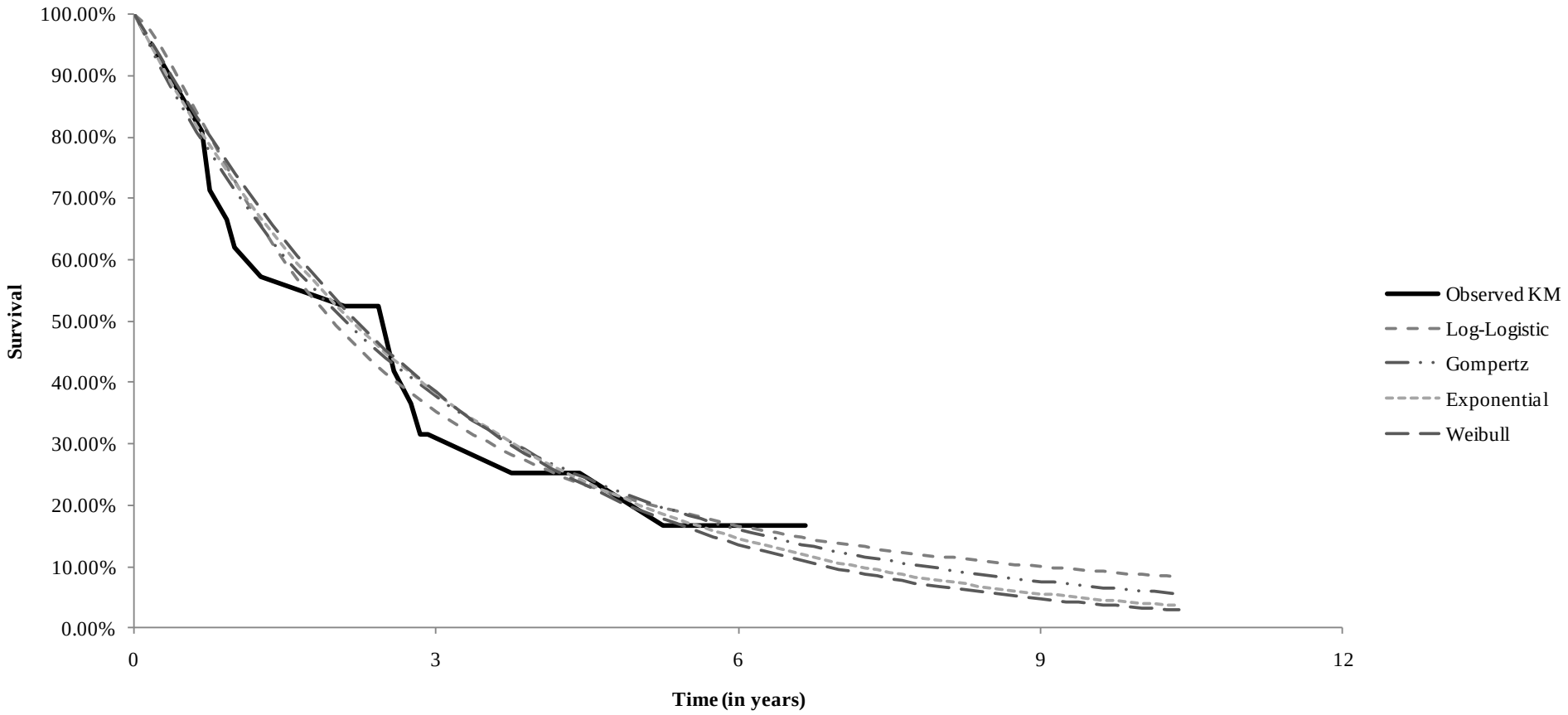
The coefficient for age was negative indicating that survival was expected to decrease as age increased. Using the AIC and BIC (Table 8), an exponential distribution was fitted to the survival in women diagnosed with disease metastasis for the central case. Other distributions were also tested in sensitivity analysis.

Table 8: AIC and BIC (metastasis) by distribution type

	AIC	BIC
Exp	64.26	66.35
Weib	66.16	69.29
Gomp	66.23	69.36
Log-Log	65.90	69.04

The observed KM was plotted to the predicted survival time using different parametric distributions in Figure 39 (before adjustment for covariates).

Figure 39: Plot of observed and predicted all cause survival in women with breast cancer diagnosed with distant metastasis (n = 21)



3.3.3. Management post-diagnosis of breast cancer in elderly women

The management of breast cancer post-diagnosis comprises:

- primary treatment directly after diagnosis,
- management of recurrence,
- follow-up management after diagnosis of breast cancer,
- management of palliative care before death from breast cancer

a. Rapid search on evidence about costs in breast cancer patients

A rapid general search was conducted in MEDLINE from January 2000 to January 2010 with the aim to identify publications that provided information of costs associated with the management/diagnosis of breast cancer. The following search terms were used: "*cost.mp*". or exploded MeSH term "*Costs and Cost Analysis*"; "*breast cancer*" or exploded MeSH term "*Breast Neoplasms*"; "*united kingdom.mp*". or exploded MeSH term "*Great Britain*". Primary studies, clinical trials or cost-effectiveness analysis were included. Studies conducted outside the UK were excluded. Of the 30 relevant papers identified at the abstract stage, 22 papers included an economic evaluation. Due to time constraints, we have not extracted data from each individual study as the population included was not specific to elderly women, and therefore not relevant for the purpose of our analysis. However, potentially relevant papers were examined when appropriate.

b. Primary treatment in elderly women diagnosed with invasive cancer

While the rapid review identified studies reporting the cost for the primary treatment of breast cancer, there is a lack of UK data on the management of breast cancer post-diagnosis in older women. The population of concern in most studies was constrained to women with early breast cancer aged below 65 years or represented a mix of different ages. Furthermore, the population included in most studies was specific in terms of prognostic profile (ER +, distant metastasis).

We expect that older women with early breast cancer would be treated less aggressively, i.e. receive less invasive procedures such as surgery, little chemotherapy, no Herceptin and slightly less radiotherapy. This is justified by the increase risk of complications and a trade-off with the lower expected benefit in this population given the older age.

Registry data were therefore analysed to provide some indication about the management associated with a diagnosis of breast cancer among older women. Data from the ECRIC dataset were analysed and found to contain information about the primary treatment in breast cancer patients in the Eastern region of England. [34] A description of the dataset is available in section V.2.2.4. Resource use was limited to surgery (Wide Local Excision (WLE) and/or Mastectomy), the use of radiotherapy, the use of hormonal therapy, the use of chemotherapy, axiliary node sampling and axiliary block dissection. The dataset did not included data on neo-adjuvant therapies. Nevertheless, this was shown to be very rare in older women after an exploratory analysis conducted in a separate dataset provided by the WMCIU. [33] Indeed, less than 0.2% of women received neo-adjuvant chemotherapy. The proportion of women treated with neo-adjuvant radiotherapy and hormonal therapy was 0.3% and 3.1% respectively.

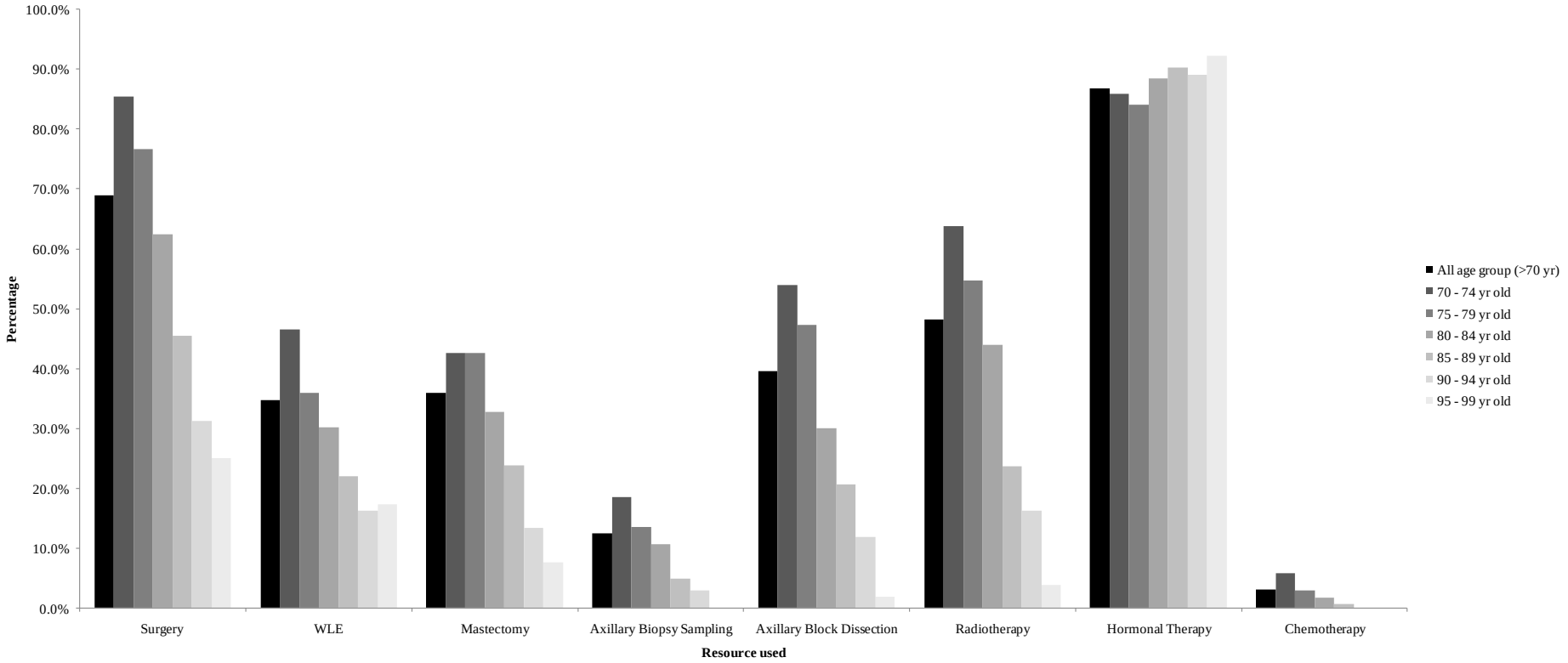
Using the ECRIC data, 48.23% (n = 1,812) of older women aged 70 years and over were treated with radiotherapy. [34] Eighty-seven percent (n = 3,260) of women were also treated with hormonal therapies while only 3.03% (n = 114) of women received chemotherapy. Sixty-nine percent (n = 2,589) of older women aged 70 years and over received surgery, with 50.41% (n = 1,305) treated with WLE and 52.14% (n = 1,350) treated with mastectomy. Finally, 18.12% (n = 469) and 57.36% (n = 1,485) of women treated with surgery (n = 2,589) had axiliary node sampling or axiliary block dissection respectively.

The distribution of resource-use by 5 year age-bands is presented in Figure 40 and indicates that the probability for older women to be treated with surgery, radiotherapy and chemotherapy decreased as age increased. This was not the case for hormonal therapies, where the probability of being treated with hormonal therapy was shown to increase as age increased. This confirms previous research that age is a major determinant in treatment for older women diagnosed with breast cancer.

This has important economic implications when modelling the impact of screening in older women as screening leads to earlier detection, and may therefore lead to a higher probability of treatment despite the differences in prognostic profile at diagnosis. However, age is not the sole determinant of resource use in older women, and it is expected that tumour size and nodal involvement are also used to inform treatment choice.

Logistic regression models were constructed to calculate the likelihood of resource used from the ECRIC dataset adjusted for a set of covariates (tumour size, grade, ER status, nodal involvment, age, distant metastasis). [34] Given the impossibility to have direct access to the data, covariates were pre-specified and validated by clinical opinion. The estimated models allowed calculation of the probability of resource use for each woman. A random number was then generated and the women was assumed to be treated if the probability was greater than the generated random number.

Figure 40: Distribution of resource use by age



- Probability of surgery

We constructed a statistical model to predict the probability of receiving surgery post-diagnosis in elderly women only. The model uses age (in years), tumour size (in mm) and the presence of distant metastasis as the main determinants (Equation 3). The coefficient for age, tumour size and presence of distant metastasis was negative. This indicated that the probability of surgery decreases as the patient's age or tumour size increase or in the presence of distant metastasis.

Equation 3: logistic regression model to predict the likelihood of surgery

Logistic regression — Number of obs = 2621
LR chi2(3) = 561.99
Prob > chi2 = 0.0000
Log likelihood = -1050.8181 — Pseudo R2 = 0.2110

surgery	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Age	-.1491155	.0091827	-16.24	0.000	-.1671132	-.1311178
tum_size	-.0300775	.002898	-10.38	0.000	-.0357575	-.0243976
distant_mets	-2.102293	.2222609	-9.46	0.000	-2.537916	-1.666669
_cons	14.30809	.7609744	18.80	0.000	12.81661	15.79957

- Probability of surgery being WLE

We assumed that women receiving surgery could either be treated with WLE or mastectomy. Consequently, a regression model was constructed to estimate the likelihood of WLE given that the woman received surgery. The regression model was constructed only among women known to have been treated with surgery and included age (in years), tumour size (in mm) and the presence of distant metastasis as covariates. The coefficient of the regression model was negative for age and tumour size indicating that the probability of surgery being WLE decreases as age and tumour size increase. Nevertheless, the regression's coefficient for distant metastasis was positive, indicating WLE was more likely to be perform compared to other type of surgery in the presence of distant metastasis.

The probability of mastectomy was calculated from the above.

Equation 4: logistic regression model to predict the probability of surgery being wide local excision

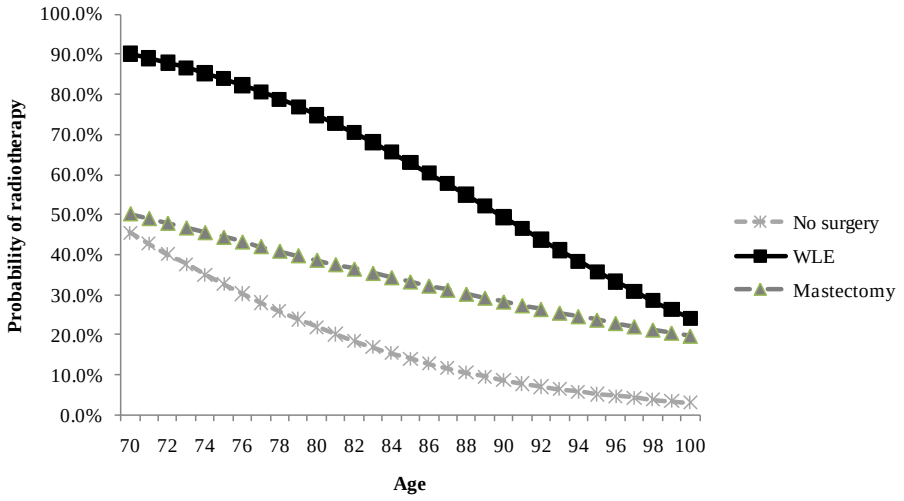
Logistic regression — Number of obs = 2082
LR chi2(3) = 231.74
Prob > chi2 = 0.0000
Log likelihood = -1327.0468 — Pseudo R2 = 0.0803

wle	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0023957	.0084935	-0.28	0.778	-.0190427	.0142512
tum_size	-.0573701	.0044387	-12.93	0.000	-.0660697	-.0486704
distant_mets	.1334907	.3339516	0.40	0.689	-.5210424	.7880238
_cons	1.581254	.6581936	2.40	0.016	.2912182	2.87129

- Probability of radiotherapy

After obtaining clinical opinion and performing an exploratory analysis on the ECRIC dataset, [34] the likelihood of radiotherapy was found to be different among women who have not been treated with surgery, women who have treated with WLE, and women receiving mastectomy. Therefore, three separate logistic regression models were constructed for each of the identified sub-groups. The estimated model only uses age as a covariate as this was believed to be the most relevant determinant for the decision to perform radiotherapy in addition to the type of surgery. In all the sub-groups, the regression coefficient for age was negative, indicating that age is inversely correlated with the probability of radiotherapy. Figure 41 presents the probability of radiotherapy by age for the different subgroups.

Figure 41: Probability of radiotherapy by age



Equation 5: logistic regression model to predict the probability of radiotherapy among women who did not receive surgery

Logistic regression — Number of obs = 1168
LR chi2(1) = 83.41
Prob > chi2 = 0.0000
Log likelihood = -544.69934 — Pseudo R2 = 0.0711

radiotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.1087436	.0126583	-8.59	0.000	-.1335535	-.0839338
_cons	7.429745	1.012724	7.34	0.000	5.444844	9.414647

Equation 6: logistic regression model to predict the probability of radiotherapy among women who received wide local excision

Logistic regression — Number of obs = 1305
LR chi2(1) = 91.06
Prob > chi2 = 0.0000
Log likelihood = -631.68679 — Pseudo R2 = 0.0672

radiotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.1117668	.011994	-9.32	0.000	-.1352746	-.088259
_cons	10.03281	.9491101	10.57	0.000	8.172587	11.89303

Equation 7: logistic regression model to predict the probability of radiotherapy among women who received mastectomy

Logistic regression — Number of obs = 1350
LR chi2(1) = 19.71
Prob > chi2 = 0.0000
Log likelihood = -907.55672 — Pseudo R2 = 0.0107

radiotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0469548	.0107403	-4.37	0.000	-.0680055	-.0259042
_cons	3.294294	.8298219	3.97	0.000	1.667873	4.920715

- Probability of chemotherapy

Only a small proportion of elderly women in the ECRIC dataset were treated with chemotherapy. [34] A logistic regression model was constructed to estimate the likelihood of receiving chemotherapy using age only as covariate. This was believed to be the main determinant in the treatment decision in older women. Age was found to be inversely correlated with the likelihood of receiving chemotherapy among elderly women (Equation 8).

Equation 8: logistic regression model to predict the probability of chemotherapy

Logistic regression	Number of obs	=	3757
	LR chi2(1)	=	60.52
	Prob > chi2	=	0.0000
Log likelihood = -480.4425	Pseudo R2	=	0.0593

chemotherapy	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.1466639	.0216693	-6.77	0.000	-.1891348	-.1041929
_cons	7.779509	1.625621	4.79	0.000	4.593352	10.96567

- Probability of hormonal therapy

While only a small fraction of women were treated with chemotherapy, a large majority of women received hormonal therapy. As shown in Figure 40, while the proportion of women receiving hormonal therapy tends to increase by age, age doesn't seem to be the most relevant determinant for receiving hormonal treatment. After discussion with clinical opinion, a logistic regression model was constructed to estimate the likelihood of hormonal therapy using age and ER status as covariates (Equation 9). Age and tumour ER positivity were positively correlated with the probability of hormonal therapy, meaning that the probability increases as age increases and in women having ER^{+ive} tumours.

Equation 9: logistic regression model to predict the probability of hormonal therapy

Logistic regression	Number of obs	=	2080
	LR chi2(2)	=	392.10
	Prob > chi2	=	0.0000
Log likelihood = -700.34358	Pseudo R2	=	0.2187

hormone	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	.0202352	.011841	1.71	0.087	-.0029727	.0434432
_Ier_statu~3	2.843215	.1479378	19.22	0.000	2.553262	3.133168
_cons	-1.99883	.9342194	-2.14	0.032	-3.829866	-.1677932

- Probability of axillary sentinel node biopsy or sampling

Pre-analysis of the data showed a very different likelihood between women treated with WLE and women treated with mastectomy, with a very low probability among women treated with mastectomy. Clinical opinion indicated that the probability of SLNB or sampling would be similar whatever the type of surgery in clinical practice. There may be a tendency for more complete axillary dissection (ALND) in women undergoing mastectomy as this may have been mandated by a larger tumour size which correlates with node positivity. Consequently, a regression model was constructed only in women treated with WLE and applied to both women treated with WLE and mastectomy (Equation 10). The regression model included only age as a covariate. The regression's coefficient for age was negative, indicating that the probability of SLNB decreases as age increases.

Equation 10: logistic regression model to predict the probability of axxillary biopsy sampling among women receiving wide local excision

Logistic regression	Number of obs	=	1305
	LR chi2(1)	=	23.77
	Prob > chi2	=	0.0000
Log likelihood = -828.77775	Pseudo R2	=	0.0141

auxiliary_b~g	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0528274	.011137	-4.74	0.000	-.0746555	-.0309993
_cons	3.421105	.8553669	4.00	0.000	1.744616	5.097593

- Probability of axillary block dissection

Finally, we evaluated the probability associated with axillary block dissection (or ALND) in older women. Clinical opinion and pre-analysis of the data indicated that that the likelihood of ALND was different between women who have been treated with WLE and women who have been treated with mastectomy probably due to women with larger primary cancers having a greater likely hood of requiring mastectomy and also of having nodal disease (both are correlated with tumour size). Consequently, two separate regression models were constructed. Both models included age, the number of nodes positive (0, 1 – 3, >= 4) and having received SLNB. Age and SLNB were inversely correlated with the likelihood of ALND while a greater nodal involvement was associated with a greater probability of ALND as would be expected.

Equation 11: logistic regression model to predict the probability of auxiliary block dissection among women receiving wide local excision

Logistic regression — Number of obs = 849
LR chi2(4) = 775.47
Prob > chi2 = 0.0000
Log likelihood = -195.64064 — Pseudo R2 = 0.6646

auxiliary_b~n	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0622697	.0287548	-2.17	0.030	-.1186282	-.0059113
_InodesG_1	.8188293	.3661105	2.24	0.025	.1012658	1.536393
_InodesG_2	.9852105	.5963994	1.65	0.099	-.1837108	2.154132
auxiliary_b~g	-5.646704	.3250771	-17.37	0.000	-6.283843	-5.009565
_cons	6.9675	2.216077	3.14	0.002	2.62407	11.31093

Equation 12: logistic regression model to predict the probability of axxillary block dissection among women mastectomy

Logistic regression — Number of obs = 1037
LR chi2(4) = 84.37
Prob > chi2 = 0.0000
Log likelihood = -518.83806 — Pseudo R2 = 0.0752

auxilliry_b~n	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	-.0263396	.0145816	-1.81	0.071	-.0549189	.0022397
_InodesG_1	.3845568	.1764802	2.18	0.029	.0386619	.7304517
_InodesG_2	1.073512	.2406881	4.46	0.000	.6017717	1.545252
auxiliary_b~g	-2.670834	.4112446	-6.49	0.000	-3.476859	-1.864809
_cons	3.078369	1.130585	2.72	0.006	.8624626	5.294276

c. *Primary treatment for breast cancer in elderly women diagnosed with carcinoma in situ*

Unfortunately, it was not possible to identify women with in-situ disease in the ECRIC dataset and therefore estimate their management after diagnosis of breast cancer. [34] Therefore, data from the WMCIU was analysed and included 257 elderly women aged over 70 years old diagnosed with in-situ disease (ICD-10 codes: D050, D051, D057, D059). [33] The mean age of these patients was 76.5±5.7.

A rapid exploratory analysis showed that about 80.9% (n= 208) of older women have been treated surgically for their carcinoma in-situ. This was found to be greater compared to the proportion of women estimated to receive surgery in the ECRIC dataset among women with invasive cancer (Figure 40). [34] The data also showed that only 18.5% (n = 47/254), 1.2% (n = 3/254) and 6.2% (n = 16/257) of elderly women received radiotherapy, chemotherapy and hormonal therapy for the treatment of their carcinoma in-situ. It is likely that the 1.2% who had chemotherapy had been misclassified as DCIS in the dataset as this is not usual clinical practice. It may represent change of classification following surgery.

Based on the proportion of women treated with surgery, radiotherapy, chemotherapy and hormonal therapy, the mean cost of the management of carcinoma in situ in elderly women was estimated to be £3,015 (Table 9).

Table 9: cost for cis

	Proportion	Unit cost (Table 10)	Total cost
Surgery	80.9%	£2,728	£2,208
Radiotherapy	18.5%	£2,288	£423
Chemotherapy	1.2%	£8,788	£103
Hormonal therapy	6.2%	£4,509	£281
			£3,015

The mean cost was then applied to each woman detected with carcinoma in-situ in the economic model.

d. Treatment for recurrence

- Probability of being treated for recurrence

Our simulations include many cases of breast cancer leading to premature death. Consequently, this implicitly includes the impact of potential recurrence on survival. An alternative approach would be to model recurrence conditional on the prognostic profile, and then model the relationship between recurrence and death separately. This was not possible for this project in the absence of data about the relationship between recurrence rate and survival in older women and the impact of primary treatment on further progression.

However, while the probability of recurrence is implicitly taken into consideration in the calculated survival regression models, recurrence rates are also associated with high management costs. To our knowledge, there is a lack of data about the risk of recurrence among older women in the UK. Data from the WMCIU was analysed and indicated that 1.6% (n = 4/ 257) of women diagnosed with carcinoma in situ were treated for recurrence over a mean follow-up period of 45.64±19.73 months. [33] The recurrence rate among older women with invasive cancer was 8.6% (n = 566/6,579) over a mean follow-up period of 38.8±23.1 months. Finally, the recurrence rate among older women diagnosed with distant metastasis was 26.9% (n = 6/23) over a mean follow-up period of 26.04±22.52 months.

Based on this data, we were able to estimate the probability of recurrence and include the associated resource use associated with treatment of recurrence. Based on this data, we assumed the probability of having and being treated for recurrence was 1.6% for women diagnosed with carcinoma in situ and 26.9% for women diagnosed with distant metastasis. To estimate the probability of recurrence for women with invasive local or regional disease, a logistic regression model was constructed using tumour size, nodal involvement and ER status as covariates from WMCIU data (Equation 13). The model showed that tumour size and nodal involvement were positively correlated with the probability of being treated for recurrence. However, being ER^{+ve} was found to be negatively correlated with the probability of recurrence. This can be explained by the fact that ER^{+ve} women are more likely to receive hormonal therapies, and therefore less likely to develop further recurrence.

Equation 13: Probability of recurrence

Logistic regression — Number of obs = 3067

LR chi2(4) = 82.15

Prob > chi2 = 0.0000

Log likelihood = -674.09914 — Pseudo R2 = 0.0574

recurr	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
invsize	.010331	.0042367	2.44	0.015	.0020272	.0186347
_Inodes_2	.6088369	.1873561	3.25	0.001	.2416257	.976048
_Inodes_3	1.163717	.1919702	6.06	0.000	.7874619	1.539971
ER	-.8176205	.167554	-4.88	0.000	-1.14602	-.4892208
_cons	-2.790886	.2011193	-13.88	0.000	-3.185072	-2.396699

- Management cost of recurrence

Our main aim in estimating recurrence was to include the costs of treating it in the economic analysis. The rapid review of the literature indicated no data on the management of breast cancer after recurrence in the UK specific to older women was available. Two primary studies were however identified reporting the cost of managing recurrence in mixed young and older population.

Karnon et al (2007) estimated the 5-year cost of recurrence to be £16,640 for metastatic recurrence and about £24,000 for contralateral or locoregional recurrence. [52] This study included 199 women with early breast cancer who experienced a recurrence between 1991 and 2004. The median age was 59 years (40 – 82). The majority had ER^{+ve} tumours and around half were node negative at primary diagnosis. The median survival from loco-regional recurrence to distant metastasis was about 55 months. The survival from distant metastasis was lower at about 10 months.

Thomas et al (2009) presented the total hospital and community cost of managing patients with relapsed breast cancer. [53] This study included 77 women who had relapsed breast cancer between 2000-2005 from the Bedford Breast Cancer database. The mean age of the cohort was 62.3 years (32-95). Thirty nine percent were originally node positive, 20% ER^{-ve} and 21% had unknown ER status. The median survival was 40.1 months from time to relapse to death and the average time from diagnosis to relapse was 71.2 months. The authors reported that the lifetime total hospital and community cost of managing relapsed disease until death was £25,186 on average (median: £19,886).

While none of these studies reported the cost specific to older women, data from *Thomas et al* (2009) was used to approximate the lifetime cost of recurrence among older women. The author reported a mean lifetime cost of approximately £25,186 pounds. However, looking at the breakdown of costs, £6,097 was allocated for hospital outpatient drug costs which will probably represent chemotherapy costs. These may be applied to some older women but only a small minority. Consequently, we assumed that older women would incur only ¼ of the reported chemotherapy cost. Furthermore, this study included the cost associated with palliative care. We attempted to remove the cost associated with the management in palliative care to avoid double counting in the model. Therefore, costs for hospice nights (£1,146), hospice visits (£72), hospice drugs (£272), palliative community telephone (£63), and palliative community visits (£542) were removed. The lifetime cost for managing recurrence in the elderly (excluding palliative care) was assumed to be £18,018.

e. Follow-up consultation post-primary treatment for breast cancer

NICE recommends that women who have been diagnosed with early breast cancer or carcinoma in-situ undergo regular check-ups. Derived from NICE guidelines and assumptions, we assumed that the follow-up after early breast cancer consists of one mammogram (£44.6) and one outpatient consultation (£99) every year for 5 years post-breast cancer diagnosis. [49]

f. Management before death due to breast cancer; i.e. palliative care

The costs associated with the management of terminal illness from breast cancer were also included in the economic model. One study was identified and reported the cost of palliative management in women with advanced breast cancer in the UK. [54] This study included 122 women with breast cancer with 61% of the sample aged over 65 years old. Palliative care was determined from the start of strong opioid treatment for a mean duration of 372 days.

The author calculated the cost of palliative care to be £2,482 (2001 prices). In the economic model, the cost was uplifted to 2008/2009 prices (£3,228) using inflation indices from the PSSRU (+30%). [55]

Note that there are some issues when considering the cost associated with palliative care into screening models as while screening may save a death from breast cancer, the women may die from another cancer or causes associated with higher or similar management cost of palliative care.

3.3.4. Unit costs for breast cancer treatments

Unit costs were extracted from a range of sources. Official tariffs where used when appropriate.

The cost of surgery (either mastectomy or WLE) alone (i.e. without SLNB or ALND) was derived from a recent economic evaluation in early and locally advanced breast cancer conducted for NICE. [49] Costs were estimated to be £2,731 for mastectomy and £2,343 for WLE using data from NHS reference costs 2006-2007. [56] Costs from this study were uplifted to 2008/2009 (+7.5%) using cost indices from the PSSRU (HCSC indices). [55]

SLNB was assumed to be carried out at the same time as the breast surgery.
ALND was assumed to be carried out either:

- at the same time as the breast surgery if no sampling is performed due to a pre-operative diagnosis of axillary disease based on ultrasound and core biopsy results.
- after breast surgery as a second operation if axillary nodes are involved on the formal histology of the SLNB or (infrequently in the UK at present) at the same time as the SLNB if the unit has access to immediate frozen section or PCR analysis of the SLNB.

Unfortunately, the NHS reference cost do not provide separate costs data whether SLNB and ALND are carried out at the same time or at a different time of the initial surgery. One study from the United States was identified which reported the costs of breast surgery alone, SLNB together with breast surgery, ALND together with breast surgery, SLNB and ALND together with surgery. [57] The relative ratios between each of these procedures were used to adjust the UK costs of breast surgery to obtain the costs of SLNB and/or ALND together in combination with breast surgery. One assumption was made: that 50 % of women would receive SLNB and ALND at the same time as the surgery.

The cost associated with radiotherapy treatment was extracted from the PRIME trial (£2,128; 2007 cost), conducted in women aged 65 years or more with 'low-risk' axilliary node negative breast cancer (T0–2) treated by breast-conserving surgery and endocrine therapy. [58] This study included the cost associated with the session, NHS transport, accommodation and referral. The cost was uplifted to 2008/2009 (+7.5%) using cost indices from the PSSRU (HCSC indices). [55]

The annual cost associated with hormonal treatment was estimated to be £1002 per year for 4 and a half years based on a recent study. [59] The cost for chemotherapy was assumed to be £8,788 for 6 months. [59]

Finally, the annual cost associated with follow-up consultation after a diagnosis of breast cancer was assumed to be £143.60 based from the cost of follow-up, non-admitted attendance for clinical oncology from the NHS reference cost 2008/2009 and the cost of a mammogram. [60;61]

Table 10: unit costs

Activity	Cost	Inflated cost	
Mastectomy alone	£2,731	£2,937	NHS reference cost 2006/2007 [49;56]
WLE alone	£2,343	£2,519	NHS reference cost 2006/2007 [49;56]
SLNB in combination with surgery		£3,355 - WLE £3,910 - mastectomy	Derived from Pandharipande et al, 2008 [57]
ALND in combination with surgery and no SLND		£3,914 - WLE £4,562 - mastectomy	Derived from Pandharipande et al, 2008 [57]
ALND in combination with surgery and SLND		£5,345 - WLE £6,231 - mastectomy	Derived from Pandharipande et al, 2008 [57]
Radiotherapy	2,128	2,288	The PRIME trial (2007) [58]
Hormonal therapy		£1002 per year (max 4.5 years)	Cooper et al (2010) [59]
Chemotherapy (6 months)		£8,788	Cooper et al (2010) [59]
Follow up Attendance Non-Admitted Face to Face (clinical oncology) - 800		£99	NHS reference cost 2008/2009 [60]
Band B1 – Mammography [RBB1]	£40	£44.60	NHS reference cost 2005/2006 [61]

3.3.5. Screening performance and resource use associated with screening

a. Screening performance

The sensitivity of screening mammography was calibrated using data from the NHSBSP among women aged 60 years old and over. (see section V.2.4.1). The sensitivity for invasive cancer was assumed to be size-dependent. The sensitivity for CIS was also modelled separately.

b. Compliance rate

The uptake rate of screening was based on the uptake rate among women aged 65-69 years attending the NHS breast screening programme. This was assumed to be 75% in the central case but varied in sensitivity analysis from 65% to 100%. [62] The compliance rate was assumed to be independent between screening rounds.

c. Cost per screens/invitation

The screening cost is composed from two elements:

- the cost associated with the invitation,
- the cost of the screening mammogram.

A study was identified describing the cost associated with the extension of screening to women aged 65-69 years [63] registered with a GP in one of the following demonstration sites; East Sussex, Brighton and Hove, Nottingham, Leeds and Wakefield. Unit costs were extracted from Johnston et al (1996) [64] and the cost of an invitation was estimated to be £8.37. The cost of a screen on a mobile van and at a static unit was estimated to be £10.78 and £12.01 respectively. The study reported that all women in East Sussex and Brighton and Hove were screened on a mobile van. The proportion was 88% and 28% for Leeds,Wakefield and Nottingham respectively. Across the 3 sites, the average proportion of technical recalls (recall for screening when the imaging is not readable) was found to be 0.86% for women aged 50–64 years and 0.92% for women aged 65–69 years.

Similarly, Legood et al (2004) [65] compared the cost of full field digital mammography (FFDM) systems with conventional mammography for use in breast cancer screening. The study included direct costs associated the equipment system, consumables, storage and staff workload. The authors estimated that the cost for conventional mammography was £113,700 per 10,000 screens (£85,286 – £147,839). The cost of the FFDM system was calculated to be £231,578 per 10,000 screens (£182,230 – £288,571) with hard copies and £157,623 (£126,506 - £192,946) without hard copies (2002 prices).

A further analysis conducted by Brown et al (2006) [66] estimated the cost associated with screening and further investigation using information from five participating centres enrolled in the MARIBS study. The study included 649 women aged 35 – 49 years at high risk of breast cancer, either because of their strong family history or tested carriers for a mutation. This authors reported the cost of screening mammography to

be £33.50 (2003/2004 prices). [55] This was similar to the national average costs for mammography at the same time period (£31.67; IQR £26.44 - £39.65).

For the central case, we assumed that the cost per screen was £14.9 derived from Legood et al (2004) [65] assuming that 50% of screens would be carried out in a static unit and with 0.92% technical recalls. Sensitivity analysis was conducted assuming a cost of £40.4 derived from Brown et al (2006) [66].

Furthermore, the cost associated with the invitation was assumed to be £11.90 based on Johnston et al (1996). [64] Sensitivity was conducted assuming a cost of £1.50.

d. Recall rate for assessment among screened women

A proportion of women would eventually be contacted for further investigation. 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). [62]

e. Cost associated with the management of women recalled for assessment

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). The cost associated with ultrasound was extracted from the NHS reference costs 2008/2009 based on the cost of an ultrasound scan taking less than 20 minutes (Diagnostic Imaging: Other RA23Z) and was assumed to be £71. [60;67] It is also assumed that 46.4% (n = 7,176 / 15,457) of women who are referred undergo cytology/core biopsy (NHS BSP). The cost associated with fine needle biopsy of the breast was taken from NHS reference costs for 2006 (£243 - OPFNB1) and uplifted to 2008/2009 using the inflation indices from the PSSRU (£271). [55;56]

The mean cost for management of further investigation was estimated to be about £195.66 for the central case. Data from Johnston et al (1996) and Brown et al (2006) was used in sensitivity analysis reporting a cost ranging from £75.6 to £341.0 after adjustment to 2008/2009 prices respectively. [55;64;66] Table 11 summarise the costs associated with the screening program.

Table 11: Summary of costs associated with the screening program

	Cost	Source
Screening	£14.9	Legood et al (2004)
Invitation	£11.9	Johnston et al (1996)
Recall for further investigation	£195.66	NHS reference cost and NHSBSP

3.3.6. Health-Related Quality of life

An exploratory analysis was undertaken to explore the impact of screening and breast cancer diagnosis on morbidity and quality of life.

a. Review of the literature

Two recent systematic reviews of utility weights in breast cancer were identified and indicated that there was a considerable amount of published evidence on the impact, post-diagnosis, of breast cancer on quality of life. [68;69] Utility weights were reported by treatment, stage at diagnosis or general diagnosis for breast cancer. Studies were also available on the impact of screening mammography on morbidity.

However, the conclusions of the two reviews suggests that despite the large amount of literature in breast cancer, there is a wide variation in the definition of health states, populations included and valuation approaches. Furthermore, the samples were often found to be small and results were very uncertain. Finally, there are no studies that cover all disease pathways, from diagnosis to death. Consequently, findings from these studies need to be considered with considerable caution which therefore limits the interpretation of results from this analysis.

b. Calculation of QALYs in the economic model

QALYs were calculated using utility weights according to the stage at diagnosis. Treatment specific utility weights were not used given the uncertainty of combining data from separate studies using different approaches and valuation methods. There were also some uncertainties around assumptions for women receiving more than one therapy at once.

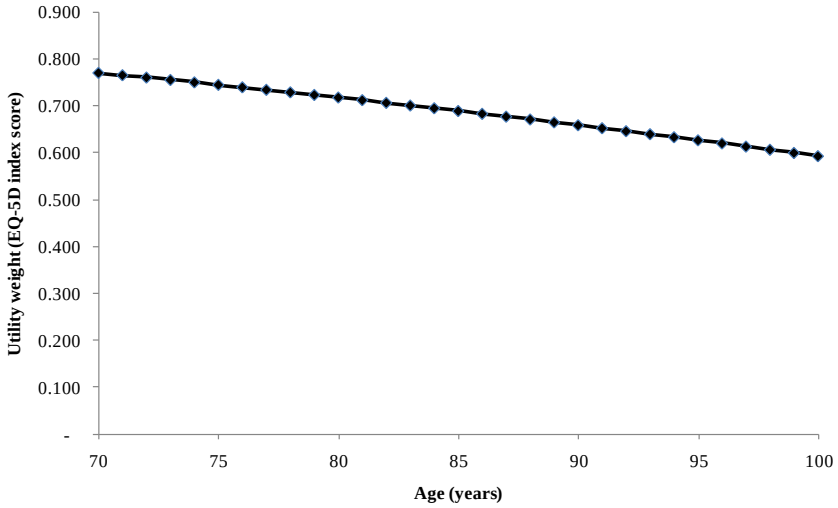
In the economic model, health state utilities were applied to six health states; disease free, stage 0 or CIS, stage I, stage II, stage III and stage IV breast cancer. Women enter the model "disease-free" until diagnosis of breast cancer. At the time of diagnosis, women are assumed to move to one of the five breast cancer health state depending on their prognostic profile at the point of diagnosis and remain in that health state for a pre-defined duration. There is a lack of data on the duration of the diagnostic process for breast cancer on quality of life and assumptions were therefore necessary. Women diagnosed with stage 0, stage I/II, stage III and stage IV were assumed to have a decrease in quality of life for 1, 2,or 3 years and their lifetime respectively and return to the disease free-state at the end of the health state duration. The duration of each health state was tested in sensitivity analysis.

c. Health state utilities used in the economic model

- Disease-free

Age-adjusted utility weights from the UK general population measured using the EQ-5D index were used to represent the quality of life in the "disease-free" health state. The utility weight was shown to vary by age (Figure 42) and was calculated from a published regression model. [70] Consequently, we assumed that the quality of life in the "disease-free" health state was not constant over time but was age-dependent.

Figure 42: Utility weight (EQ-5D index) adjusted for age (general population)



- Breast cancer diagnosis

Schleinitz and colleagues (2006) estimated the utility weights associated with stage I, stage II, stage III and stage IV breast cancer. [71] The study was conducted in the US and included 156 English-speaking women not currently undergoing breast cancer treatments. [71] Utilities were assessed using the standard gamble (SG) approach describing anticipated physical symptoms and risk of recurrence, which may affect psychological well-being. Median utilities for the 4 stages of breast cancers at diagnosis were: stage I disease, 0.91 (IQ: 0.5 – 1); stage II, 0.75(IQ: 0.26 – 0.99); stage III, 0.51 (IQ: 0.25 – 0.94), stage IV, 0.36 – 0.4 (IQ: 0 – 79).

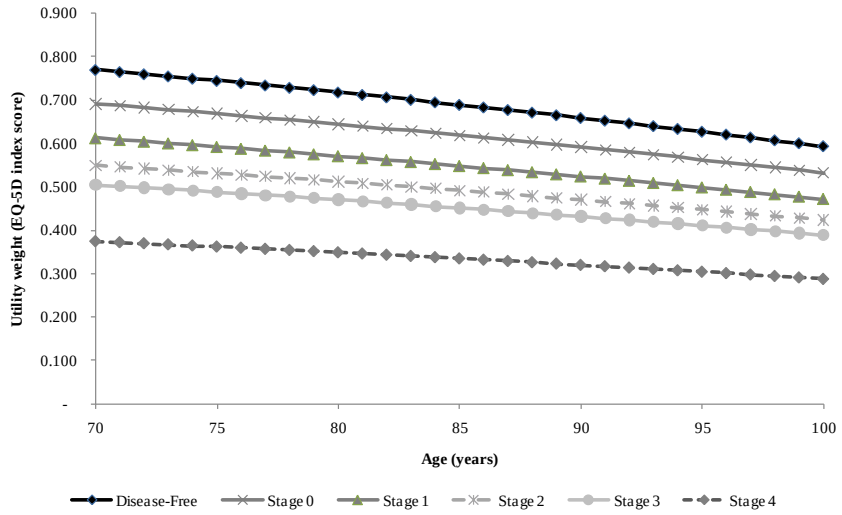
Data from Schleinitz and collaegues (2006) were then used to approximate the loss in utility (compared to full health) associated with different stages of breast cancer. [71] Given that this study included both women aged below 50 years and women aged 50 years and above, utility weights needed to be age-adjusted to account for the variation of utilities by age. Assumptions were however needed. Firstly, the study did not report EQ-5D data. We therefore had to assume that the utility calculated using EQ-5D and standard gamble approached was transferable. Secondly, the study did not report the mean age of included patients. We assumed a mean age of 50 years.

A three step process was employed to estimate the loss in utility associated with a breast cancer diagnosis:

- Step one: calculate the utility weight in the general population for a mean age of 50 years old (0.855)
- Step two: calculate the ratio between the utility weight in the general population and utility weight post-diagnosis by stage. For example, Schleinitz reported a mean utility score of 0.68 for stage I diagnosis using the SG method. The utility in the general population using EQ-5D was estimated to be 0.855. Consequently, the diagnosis of stage I breast cancer is assumed to lead to a reduction in utility by about 20%. The figure for stage II, III and IV were calculated to be 29%, 34% and 51% respectively.
- Step 3: estimate the age-adjusted utility by stage at diagnosis. This is done by applying the calculated ratio to the regression model used to estimate the utility weight in the general population.

Unfortunately Schleinitz et al (2006) did not report the loss in quality of life associated with the diagnosis of CIS. [71] Consequently, we assumed that the utility for CIS lie between the utility in the general population and the utility for stage I breast cancer.

Figure 43: Utility by health states



- Loss in quality of life from screening mammography

There is a general belief that screening may lead to a reduction in quality of life associated with the pain of undergoing a mammogram and the stress after recall for further investigation. Bonomi et al (2008) included 131 women aged 50-79 years old randomly selected from the breast cancer screening program and obtained quality of life valuation associated with mammography screening using a visual analogue scale anchored by death (0) to perfect health (100). [72] The mean age was 62 years old and the quality of life measured using the VAS was 0.804 for screening mammography and 0.553 for diagnostic mammography. After adjustment for age (assuming transferability of EQ-5D and VAS score), this led to a reduction in quality of life of 0.40% for screening mammography and 31.5% for diagnostic mammography. Other studies showed no reduction in quality of life using EQ-5D before and after screening mammography. [73]

A conservative approach was used assuming a reduction in utility of 20% for 2hrs associated with the pain of undertaking a mammogram. The dis-utility for diagnostic mammography (i.e. recall for further investigation) was assumed to be 35% for 3 weeks based on assumption.

3.4. Discounting

Cost and benefits were discounted at 3.5% as per NICE recommendations for economic evaluation. [50] We assumed all primary treatments occurred during the 1st year post diagnosis. Palliative care was discounted from the time at death. Follow-up consultations were assumed to occur for a period of up to five years starting from the time of diagnosis. Finally, since we did not have data on the time to recurrence, it was assumed that this time had a uniform distribution over the interval from initial diagnosis to death.

3.5. Assessment of uncertainty

Univariate sensitivity analysis was conducted to assess the impact of varying key model parameters and assumptions on the ICER. We examined four different parametric distributions for survival in breast cancer patients (exponential, weibull, gompertz, log-logistic). Costs (screening cost, recall for further investigation, primary treatment, follow-up, recurrence) were also varied within ±20%. Duration of health state utilities were also varied from 1 to 3 years. Similarly, we examined the impact assuming of different utility values for health states by ± 10%. The recall rate and recurrence rate were also varied within a range of ± 20%. Finally, the sensitivity and tumour growth rate were also varied by ± 20%.

4. RESULTS

This chapter presents results per 100,000 women invited up to the age of 90 years. Results are presented incrementally, i.e. the additional number of women that would be screen-detected given no detection at the previous screening round. Women who have contracted breast cancer or been diagnosed at the previous screening round are excluded.

We also present outcomes under three scenarios about the impact of screening on survival;

- *Scenario 1*: screening leads to earlier detection but can lead to premature death at the individual level,
- *Scenario 2*: screening leads to earlier detection but cannot lead to premature death at the individual level. Adding screening would not confer any advantage for a proportion of women,
- *Scenario 3*: screening leads to earlier detection. The shift in prognostic profile necessarily translates into survival benefit.

The following terminology is also used throughout the results section;

- Screen-detected women are separated into two categories depending on the age at detection and age at death;
    - "clinically significant cancer"; this refers to women that would have presented from clinical symptoms before death;
    - "over-diagnosis"; this refers to the detection of cancers in women who would otherwise have died or other causes without a clinical diagnosis of breast cancer in absence of screening.
- Women diagnosed with breast cancers are assigned a stage distribution (simplified), with;
    - "stage 0" → CIS,
    - "stage I" → no positive nodes (no nodal involvement),
    - "stage II" → 1 – 3 positives nodes,
    - "stage III" → 4 positive nodes or plus, but no presence of distant metastasis,
    - "stage IV" → 4 positive nodes or plus, but presence of distant metastasis

4.1. Clinical impact of extending screening to older age (per 100,000 women invited)

4.1.1. Rate and number of cancers-detected through screening mammography

Table 13 reports the additional number of cancers that would be detected through screening by extending screening mammography up to 90 years old. For 100,000 women invited to screening at the age of 72 years old, the model predicted that 752 breast cancer cases would be detected by the addition of one screening round at the age of 72 years of which 6.2% (n = 47) would result from over-diagnosis, i.e. would have never presented in the absence of screening. An additional screening round at the age of 75 years (100,000 invitation) would allow detection of 795 breast cancer cases, of which 9.4% (74) result in over-diagnosis. The number of breast cancer cases detected by screening age per 100,000 invitation increase as the age at screening increases. This is attributable to the fact that the probability of developing breast cancer increases with age. However, the proportion of breast cancer cases attributable to over-diagnosis tends also to increase as age increases. This is explained by the increased risk of non breast cancer mortality as women get older.

Applying these detection rates to the number of women in England and Wales by age give an indication of the potential number of women detected through screening (*Table 12*). For instance, the addition of a screening round at the age of 72 years old would enable detection of 752 cancers per 100,000 women invited (i.e 0.752% detection rate). Assuming that all women aged 72 years old in England and Wales are invited to screening, the implementation of screening is estimated to enable detection of 1,727 breast cancers (taking into account the compliance rate). An additional screening round at the age of 75 years old would enable detection of an additional 1,612 cases. Although the probability of detection increases as the age increases, the potential number of cases detected would not follow the same trend, as the number of women invited decreases as the age increases. Overall, if screening is extended up to the age of 78 years old, we estimated that about 5,000 breast cancer cases would be detected through screening in addition to cases that would have presented symptomatically otherwise.

Table 12: Expected number of breast cancer cases in England and Wales detected through screening (assuming that all women are invited).

Age	Nb of women invited	Detection rate	Number of women detected (addition of one screening round)	Cumulative number of breast cancer cases
72	229,700	0.752%	1,727	1,727
75	202,800	0.795%	1,612	3,340
78	194,200	0.843%	1,637	4,977
81	162,500	0.882%	1,433	6,410
84	137,700	0.924%	1,272	7,682
87	111,900	0.977%	1,093	8,776
89[4]	87000	1.017%	885	9,660

[4] Proxy for 90 years old.

4.1.2. Lead time

Table 14 presents the mean lead time for screen-detected cancers, i.e. the time interval between screen-detection and the presence of clinical symptoms. The mean lead time was found to decrease by age from 2.99 to 2.20 years among all women screen-detected. Similar findings were made when results were analysed for clinically significant (2.98 to 2.30 years) and over-diagnosis (3.04 to 2.03 years) sub-groups.

4.1.1. Shift in stage distribution

Table 15 presents the potential shift in stage distribution by screen-age compared to no screening. Overall, the implementation of screening leads to an improvement in the stage distribution at diagnosis among elderly women, with more CIS detected and less aggressive breast cancers at earlier stage.

Table 13: Number of detected-cancers for different screening strategies

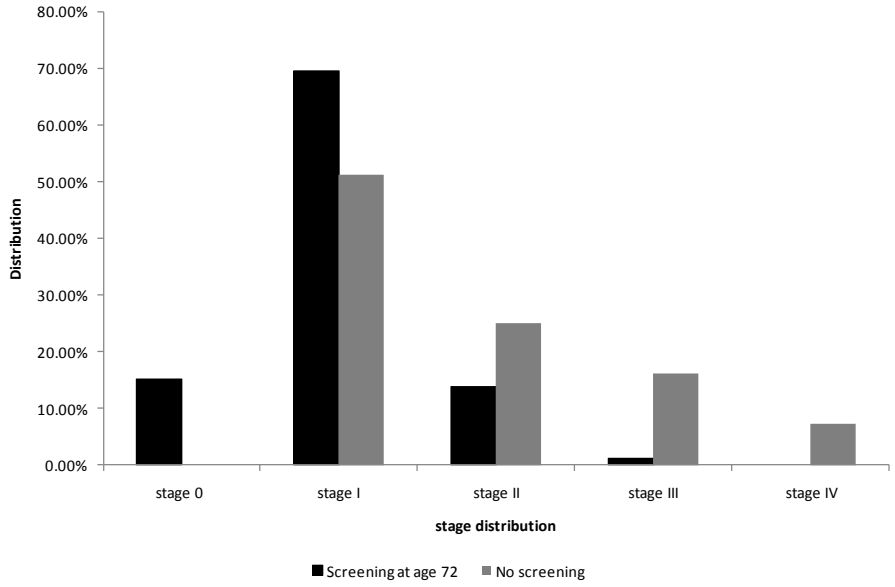
	Age at screening													
	72		75		78		81		84		87		90	
Number of cancers detected (per 100,000 women invited)	752		795		843		882		924		977		1,017	
Of which:														
• *clinically significant*	705	93.8%	721	90.6%	732	86.9%	723	82.0%	713	77.2%	682	69.9%	631	62.1%
• *over diagnosis*	47	6.2%	74	9.4%	110	13.1%	159	18.0%	211	22.8%	294	30.1%	386	37.9%

Table 14: Lead time from age at diagnosis from symptoms to age at screen detection

	Age at screening						
	72	75	78	81	84	87	90
Mean lead time among all cancer detected through screening	2.99	2.92	2.81	2.76	2.57	2.39	2.20
Of which:							
• *clinically significant*	2.98	2.92	2.82	2.77	2.63	2.43	2.30
• *over diagnosis*	3.04	2.97	2.74	2.72	2.39	2.29	2.03

Results by sub-groups; clinically significant cancers and over-diagnosis from screening are presented in Table 23 in appendix VII.1. Among the 705 breast cancer cases detected through screening by the addition of one screening round at the age of 72 years old and would have presented over a womans' lifetime (clinically significant cases), 17.5% (n = 124), 62.0% (n = 437), 14.03% (n = 101), 5.9% (n = 42) and 0.3% (n = 2) are estimated to be stage 0, I, II, III and IV respectively. In the absence of screening, 36.7% (n = 259), 24.2% (n = 170), 30.2% (n = 213) and 8.9% (n = 63) of those cancers would have been diagnosed as stage I, II, III and IV respectively (Figure 44). Similar finding was found for other policies, with a decrease in the proportion of detected stage 0 and increase in other breast cancer stages as the age increase (Table 23).

Figure 44: Shift in stage distribution of extending screening to the age of 72 years old (clinically significant)



4.1.1. Causes of death

Table 16 presents the cause of death in the absence of screening and after screening for each screen-age. Among the 752 women detected per 100,000 invitation at the age of 72 years old, 46.8% (n = 352) women would have died from breast cancer causes in the absence of screening. The introduction of screening is estimated to reduce the number of deaths attributable to breast cancer from 175 (conservative estimate) to 221 (optimistic estimate) cases. The benefit of screening is shown to decrease as women get older (* only women potentially identified throught screening

Figure 45)[5]. Results by sub-groups; clinically relevant and over-diagnosis are presented in Appendix 2

Table 24 in VII.2.

[5] These figure relates solely to the impact on those whose disease is detected through screening The mortality reduction will be lower when women are included who would present with interval cancers between screening rounds

Table 15: Shift in the stage distribution at diagnosis (per 100,000 women invited)

screen-age		n	stage 0		stage I		stage II		stage III		stage IV	
72												
	screen-detected cases	752	144	19.15%	458	61.00%	104	13.89%	43	5.71%	2	0.25%
	absence of screening*	705	0	0.00%	259	36.72%	170	24.16%	213	30.24%	63	8.88%
75												
	screen-detected cases	795	155	19.55%	488	61.41%	110	13.83%	39	4.91%	2	0.30%
	absence of screening*	721	0	0.00%	270	37.52%	176	24.48%	213	29.51%	61	8.49%
78												
	screen-detected cases	843	154	18.28%	524	62.19%	112	13.33%	49	5.82%	3	0.37%
	absence of screening*	732	0	0.00%	272	37.21%	174	23.73%	225	30.75%	61	8.32%
81												
	screen-detected cases	882	171	19.40%	542	61.42%	115	13.07%	50	5.69%	4	0.42%
	absence of screening*	723	0	0.00%	267	36.97%	174	24.06%	224	30.92%	58	8.05%
84												
	screen-detected cases	924	174	18.80%	578	62.61%	122	13.26%	47	5.09%	2	0.23%
	absence of screening*	713	0	0.00%	276	38.72%	172	24.13%	212	29.75%	53	7.41%
87												
	screen-detected cases	977	185	18.94%	610	62.44%	125	12.78%	54	5.52%	3	0.32%
	absence of screening*	682	0	0.00%	262	38.40%	170	24.93%	203	29.77%	47	6.90%
90												
	screen-detected cases	1,017	194	19.09%	628	61.75%	135	13.28%	56	5.53%	4	0.35%
	absence of screening*	631	0	0.00%	255	40.36%	151	23.99%	179	28.38%	46	7.27%

* only women potentially identified throught screening

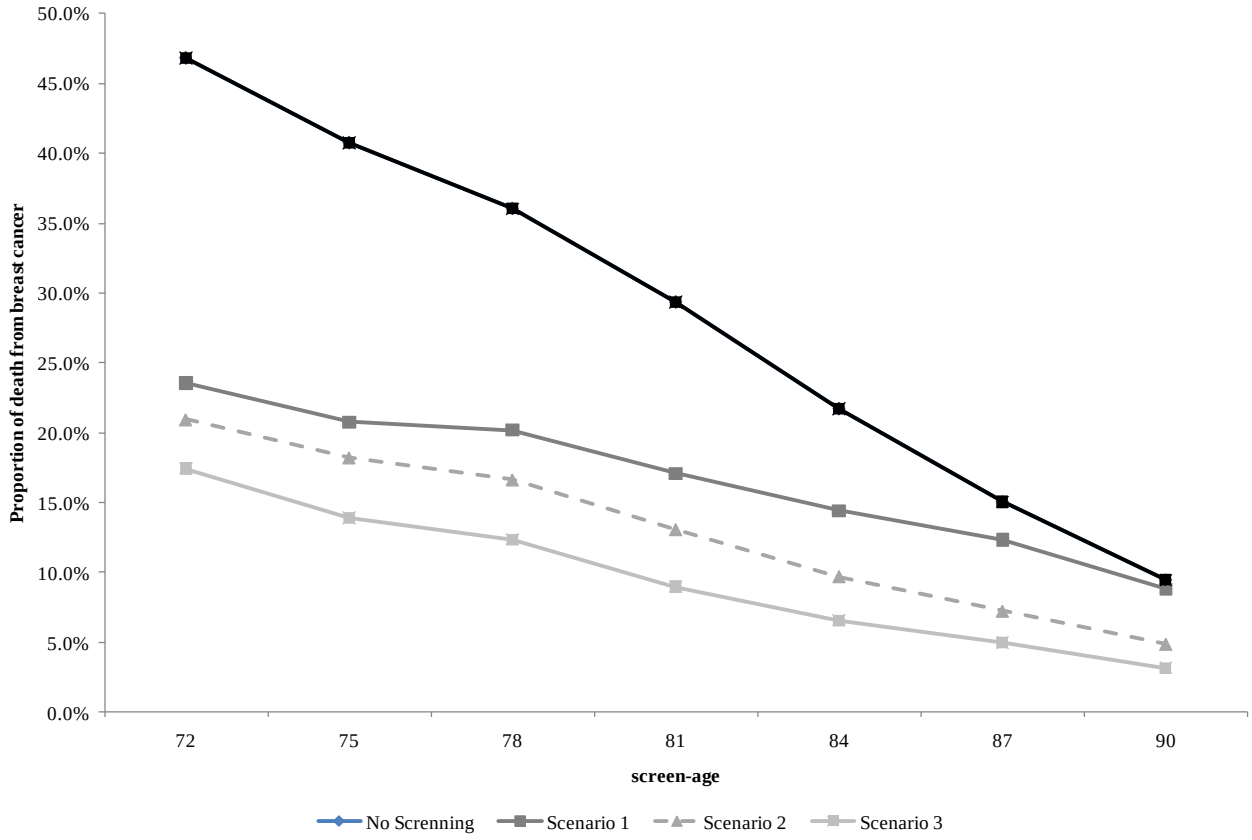
Table 16: Cause of deaths (per 100,000 invitation)

screen-age		Absence of screening		screening (scenario 1)		screening (scenario 2)		screening (scenario 3)	
72									
	Total number of deaths	752*							
	Of which:								
	Die from breast cancer	352	46.8%	177	23.6%	157	20.9%	131	17.4%
	Die from other causes	400	53.2%	575	76.4%	594	79.1%	621	82.6%
	absolute change			-175		-195		-221	
	relative change			-49.7%		-55.3%		-62.8%	
75									
	Total number of deaths	795 *							
	Of which:								
	Die from breast cancer	324	40.8%	165	20.8%	145	18.2%	111	13.9%
	Die from other causes	471	59.2%	630	79.2%	650	81.8%	684	86.1%
	absolute change			-159		-179		-213	
	relative change			-49.0%		-55.3%		-65.9%	
78									
	Total number of deaths	843*							
	Of which:								
	Die from breast cancer	304	36.0%	170	20.2%	140	16.6%	104	12.4%
	Die from other causes	539	64.0%	673	79.8%	702	83.4%	739	87.6%
	absolute change			-134		-164		-200	
	relative change			-44.0%		-53.8%		-65.7%	
81									
	Total number of deaths	882*							
	Of which:								
	Die from breast cancer	259	29.4%	151	17.1%	115	13.1%	79	9.0%
	Die from other causes	623	70.6%	731	82.9%	767	86.9%	803	91.0%
	absolute change			-108		-144		-180	
	relative change			-41.8%		-55.5%		-69.5%	
84									
	Total number of deaths	924*							
	Of which:								
	Die from breast cancer	201	21.7%	133	14.4%	90	9.7%	61	6.6%
	Die from other causes	723	78.3%	791	85.6%	834	90.3%	863	93.4%
	absolute change			-68		-111		-140	
	relative change			-33.7%		-55.3%		-69.8%	

87								
	Total number of deaths	977*						
	Of which:							
	Die from breast cancer	147	15.1%	120	12.3%	71	7.2%	48	5.0%
	Die from other causes	830	84.9%	856	87.7%	906	92.8%	928	95.0%
	absolute change			-27		-76		-99	
	relative change			-18.1%		-52.0%		-67.0%	
90								
	Total number of deaths	1,017 *						
	Of which:							
	Die from breast cancer	96	9.5%	90	8.8%	49	4.9%	32	3.2%
	Die from other causes	921	90.5%	927	91.2%	967	95.1%	985	96.8%
	absolute change			-7		-47		-64	
	relative change			-7.0%		-48.6%		-66.7%	

* only women potentially identified throught screening

Figure 45: Proportion of deaths attributable to breast cancers



4.1.2. Life-years gained

Table 17 shows the incremental life years gained for each policy option. Extending screening to the age of 72 years old is expected to lead to an increase in life years ranging from 0.87 years to 1.02 years per person dectected. The incremental life years decrease as the screen-age increase (Figure 46).

Table 17: Incremental life years gained (discounted) among potentially detected cases

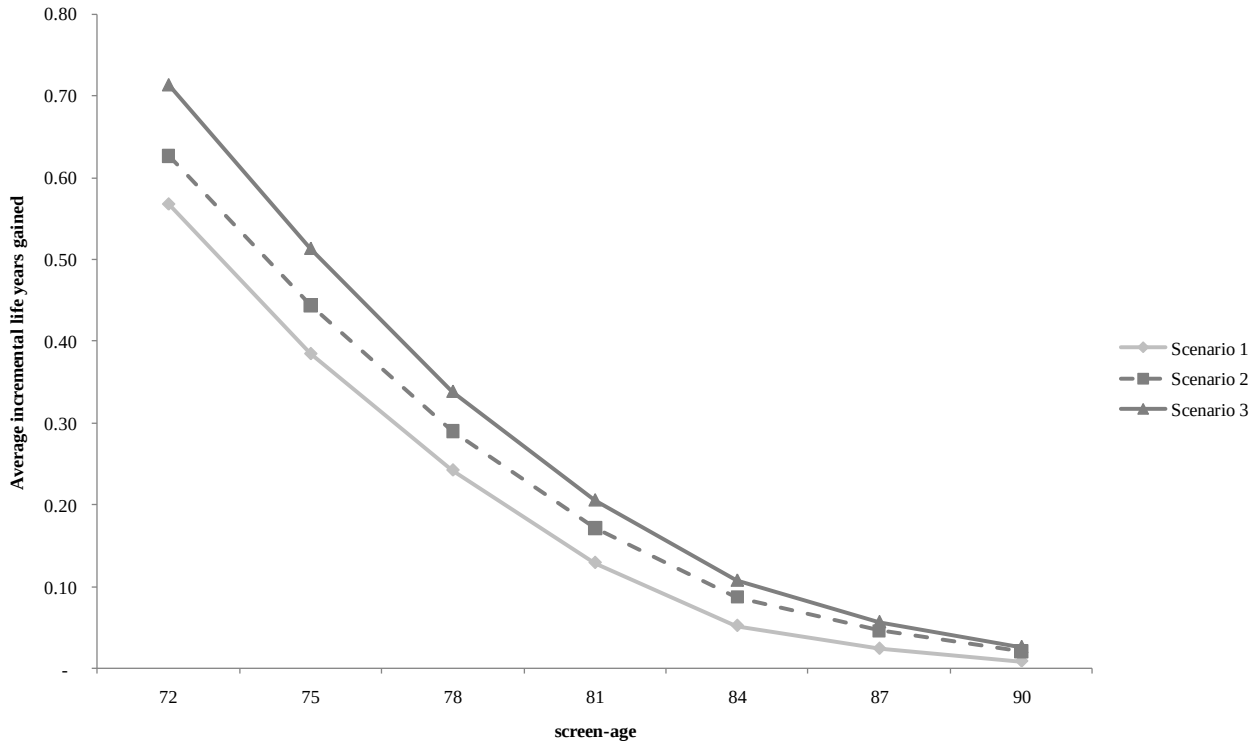
		No screening	Scenario 1	Scenario 2	Scenario 3
72	Total life years *	7,464	8,117	8,155	8,228
	Incremental life years gained*		653.16	690.36	763.78
	Average life years gained	9.93	10.80	10.85	10.95
	Incremental life years gained**		0.87	0.92	1.02
75	Total life years*	8,685	9,147	9,181	9,245
	Incremental life years gained*		462.44	496.51	560.59
	Average life years gained	10.93	11.51	11.55	11.63
	Incremental life years gained**		0.58	0.62	0.71
78	Total life years*	9,991	10,305	10,344	10,397
	Incremental life years gained*		314.31	352.85	406.49
	Average life years gained	11.86	12.23	12.28	12.34
	Incremental life years gained**		0.37	0.42	0.48
81	Total life years*	11,327	11,512	11,548	11,585
	Incremental life years gained*		185.71	221.57	258.07
	Average life years gained	12.84	13.05	13.09	13.13
	Incremental life years gained**		0.21	0.25	0.29
84	Total life years*	12,805	12,892	12,922	12,946
	Incremental life years gained*		87.51	117.36	141.81
	Average life years gained	13.86	13.96	13.99	14.02
	Incremental life years gained**		0.09	0.13	0.15

87	Total life years*	14,520	14,552	14,576	14,589
	Incremental life years gained*		31.91	56.27	68.78
	Average life years gained	14.87	14.90	14.93	14.94
	Incremental life years gained**		0.03	0.06	0.07
90	Total life years*	16,100	16,113	16,129	16,136
	Incremental life years gained*		12.25	28.94	35.68
	Average life years gained	15.83	15.85	15.86	15.87
	Incremental life years gained**		0.01	0.03	0.04

* per 100,000 women invited

** per person

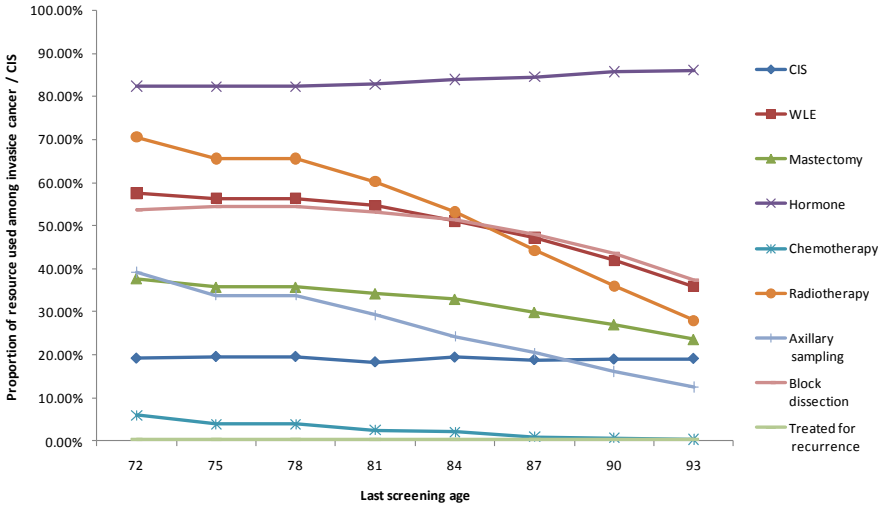
Figure 46: Incremental life years gained per person detected



4.2. Impact of screening on resource use and management of breast cancer

Table 18 shows the distribution of primary treatment post-diagnosis of breast cancer and the proportion of women treated for recurrence. The probability of resource use decreases as the age at screen-detection increases with one exception: for hormonal therapies[6] (Figure 47). This is due to the fact that older women are less likely to be treated heavily as age increase. Furthermore, we estimated that fewer women would develop a recurrence, and therefore receive treatment after the implementation of screening.

Figure 47: Proportion of resources used among screen-detected women treated for invasive cancer/CIS



[6] Note that results for WLE, mastectomy, hormonal therapy, radiotherapy, chemotherapy, axillary sampling and block dissection are presented for women with invasive cancer only.

Table 18: Impact of screening on resources used per 100,000 women invited

	Age at screen	Invasive cancer	CIS	WLE		Mastectomy		Hormone		Chemotherapy		Radiotherapy		Axillary sampling		Block dissection		Treated for recurrence	
72																			
	Screened	608	144	350	57.55%	229	37.74%	500	82.34%	36	5.97%	429	70.61%	238	39.17%	326	53.63%	2	0.32%
	Symptomatic	705	0	315	44.61%	303	42.91%	584	82.80%	28	3.92%	424	60.15%	232	32.97%	376	53.37%	65	9.19%
75																			
	Screened	640	155	360	56.36%	229	35.74%	526	82.26%	25	3.93%	419	65.52%	216	33.81%	348	54.40%	3	0.42%
	Symptomatic	721	0	305	42.26%	289	40.12%	597	82.85%	20	2.80%	390	54.19%	201	27.84%	368	51.11%	59	8.23%
78																			
	Screened	689	154	376	54.59%	236	34.23%	570	82.82%	18	2.55%	415	60.24%	201	29.23%	367	53.25%	2	0.29%
	Symptomatic	732	0	287	39.15%	273	37.23%	610	83.35%	14	1.86%	348	47.49%	169	23.10%	357	48.79%	66	9.02%
81																			
	Screened	711	171	363	51.10%	234	32.96%	597	83.90%	15	2.08%	378	53.12%	173	24.30%	365	51.31%	2	0.28%
	Symptomatic	723	0	257	35.50%	247	34.14%	611	84.51%	11	1.51%	294	40.68%	133	18.40%	330	45.60%	65	9.06%
84																			
	Screened	750	174	354	47.16%	224	29.93%	634	84.55%	7	1.00%	332	44.25%	154	20.49%	359	47.90%	3	0.34%
	Symptomatic	713	0	224	31.42%	210	29.52%	605	84.87%	4	0.60%	230	32.30%	107	15.07%	283	39.77%	64	9.03%
87																			
	Screened	792	185	332	41.93%	214	27.09%	679	85.74%	6	0.74%	285	36.00%	128	16.12%	345	43.54%	2	0.25%
	Symptomatic	682	0	187	27.41%	168	24.69%	589	86.30%	4	0.62%	175	25.58%	77	11.26%	234	34.30%	57	8.31%
90																			
	Screened	823	194	296	35.92%	195	23.67%	708	86.05%	3	0.39%	230	27.95%	103	12.55%	308	37.38%	2	0.28%
	Symptomatic	631	0	138	21.80%	130	20.67%	542	85.82%	2	0.31%	119	18.84%	51	8.05%	176	27.94%	55	8.73%

4.3. Impact of screening on quality of life

Table 19 shows the incremental QALY gained for each policy option. Extending screening to the age of 72 years old is expected to lead to an increase in QALY ranging from 0.75 years to 0.85 years per person detected. The incremental QALYs decrease as the screening-age increases. The reduction in quality of life associated with the mammogram and recall for further investigation is expected to outweigh the gain in QALY from screening after 87 years.

Table 19: impact of screening on QALY (discounted) among potentially dectected cases

		No screening	Scenario 1	Scenario 2	Scenario 3
72	QALY associated with diagnosis of breast cancer & full health*	5,062.39	5,623.47	5,648.79	5,701.56
	*Disutility associated with screening mammography**	0.00	-2.60	-2.60	-2.60
	*Disutility associated with recall for further assessment**	0.00	-46.01	-46.01	-46.01
	Total QALY*	5,062.39	5,574.86	5,600.19	5,652.96
	Incremental QALY*		512.47	537.80	590.57
	Average QALY** (detected cancer only)	6.73	7.48	7.51	7.59
	Average incremental QALY (detected cancers only)**		0.75	0.78	0.85
75	QALY associated with diagnosis of breast cancer & full health*	5,988.74	6,385.47	6,407.93	6,452.93
	*Disutility associated with screening mammography**	0.00	-2.30	-2.30	-2.30
	*Disutility associated with recall for further assessment**	0.00	-40.66	-40.66	-40.66
	Total QALY*	5,988.74	6,342.51	6,364.97	6,409.96
	Incremental QALY*		353.77	376.22	421.22
	Average QALY** (detected cancer only)	7.53	8.03	8.06	8.12
	Average incremental QALY (detected cancers only)**		0.50	0.53	0.58

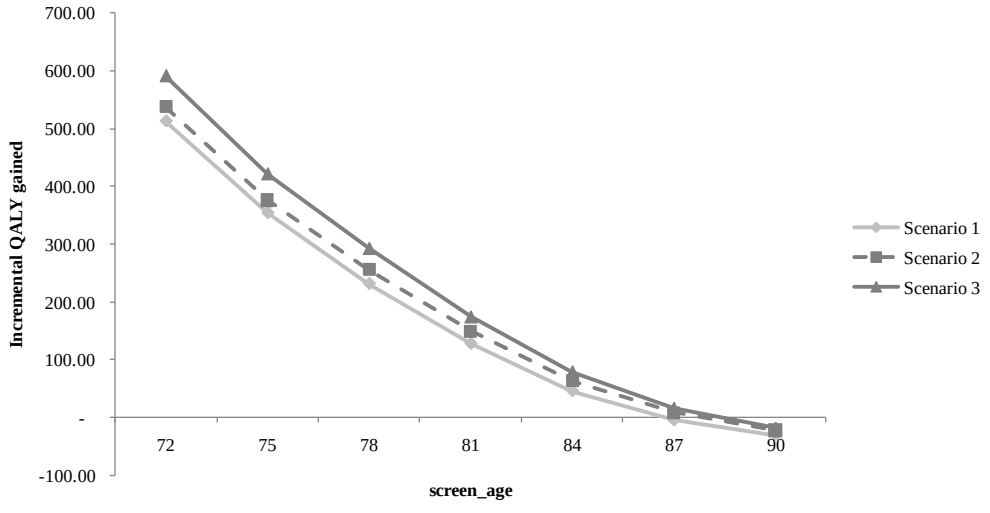
78	QALY associated with diagnosis of breast cancer & full health*	6,954.95	7,223.83	7,248.43	7,285.31
	*Disutility associated with screening mammography**	0.00	-2.03	-2.03	-2.03
	*Disutility associated with recall for further assessment**	0.00	-35.88	-35.88	-35.88
	Total QALY*	6,954.95	7,185.93	7,210.53	7,247.41
	Incremental QALY*		230.98	255.58	292.46
	Average QALY** (detected cancer only)	8.25	8.57	8.60	8.65
	Average incremental QALY (detected cancers only)**		0.32	0.35	0.39
81	QALY associated with diagnosis of breast cancer & full health*	7,933.47	8,094.10	8,116.33	8,140.82
	*Disutility associated with screening mammography**	0.00	-1.79	-1.79	-1.79
	*Disutility associated with recall for further assessment**	0.00	-31.45	-31.45	-31.45
	Total QALY*	7,933.47	8,060.86	8,083.09	8,107.58
	Incremental QALY*		127.39	149.62	174.11
	Average QALY** (detected cancer only)	8.99	9.18	9.20	9.23
	Average incremental QALY (detected cancers only)**		0.18	0.21	0.24
84	QALY associated with diagnosis of breast cancer & full health*	8,994.71	9,069.10	9,087.05	9,103.04
	*Disutility associated with screening mammography**	0.00	-1.57	-1.57	-1.57
	*Disutility associated with recall for further assessment**	0.00	-27.39	-27.39	-27.39
	Total QALY*	8,994.71	9,040.13	9,058.09	9,074.07
	Incremental QALY*		45.42	63.37	79.36
	Average QALY** (detected cancer only)	9.74	9.82	9.84	9.86
	Average incremental QALY (detected cancers only)**		0.08	0.10	0.12

87	QALY associated with diagnosis of breast cancer & full health*	10,202.76	10,223.03	10,236.64	10,244.57
	*Disutility associated with screening mammography**	0.00	-1.38	-1.38	-1.38
	*Disutility associated with recall for further assessment**	0.00	-24.16	-24.16	-24.16
	Total QALY*	10,202.76	10,197.49	10,211.10	10,219.04
	Incremental QALY*		-5.27	8.33	16.27
	Average QALY** (detected cancer only)	10.45	10.47	10.48	10.49
	Average incremental QALY (detected cancers only)**		0.02	0.03	0.04
90	QALY associated with diagnosis of breast cancer & full health*	11,299.84	11,291.85	11,300.46	11,304.59
	*Disutility associated with screening mammography**	0.00	-1.21	-1.21	-1.21
	*Disutility associated with recall for further assessment**	0.00	-21.42	-21.42	-21.42
	Total QALY*	11,299.84	11,269.21	11,277.82	11,281.96
	Incremental QALY*		-30.63	-22.01	-17.88
	Average QALY** (detected cancer only)	11.11	11.10	11.11	11.12
	Average incremental QALY (detected cancers only)**		-0.01	0.00	0.00

* per 100,000 invitation

* per person

Figure 48: Incremental QALYs gained among all potentially detected cases



4.4. Impact of screening on costs

The impact of screening on costs is presented in Table 20 for scenario 1 only. Costs under scenario 2 and 3 for the screening options are very similar, with the main differences attributable to discounting and extra life years.

The early detection from screening translates into higher costs of primary treatment for breast cancer and higher costs for follow-up after primary treatment. However, the costs associated with treatment for recurrence and palliative care, are considerably lower.

Finally, screening options lead also to considerable costs associated with the mammogram itself, the cost of the invitation and management for recall for further investigation.

Table 20: impact of screening on costs per 100,000 invitation (discounted)

	Age at screen	Total cost	Primary treatment	Recurrence	Cost follow-up	Palliative care	screening mammography	invitation cost	recall for assessment
72									
	Screened	11,197,298	6,935,243	471,652	479,154	453,997	1,116,888	1,190,000	550,364
	Symptomatic	7,652,185	5,492,969	928,777	387,083	843,356	0	0	0
	incremental	3,545,113	1,442,274	-457,125	92,071	-389,359	1,116,888	1,190,000	550,364
75									
	Screened	10,176,535	6,304,742	451,589	449,092	393,441	1,007,829	1,073,312	496,530
	Symptomatic	6,608,810	4,758,275	778,151	350,538	721,846	0	0	0
	incremental	3,567,725	1,546,467	-326,562	98,554	-328,405	1,007,829	1,073,312	496,530
78									
	Screened	9,296,681	5,716,855	460,552	416,507	378,062	908,935	968,066	447,704
	Symptomatic	5,815,320	4,077,177	800,191	311,576	626,376	0	0	0
	incremental	3,481,360	1,639,677	-339,639	104,931	-248,314	908,935	968,066	447,704
81									
	Screened	8,345,091	5,107,964	450,353	382,027	310,523	819,434	873,140	401,650
	Symptomatic	4,866,453	3,380,997	725,404	267,130	492,922	0	0	0
	incremental	3,478,639	1,726,968	-275,051	114,897	-182,399	819,434	873,140	401,650
84									
	Screened	7,370,213	4,419,448	466,678	345,084	254,218	738,811	787,522	358,452
	Symptomatic	3,918,468	2,684,509	653,237	227,261	353,461	0	0	0
	incremental	3,451,745	1,734,939	-186,559	117,823	-99,243	738,811	787,522	358,452
87									
	Screened	6,462,613	3,849,597	389,062	311,385	211,263	666,562	710,300	324,444
	Symptomatic	3,062,438	2,105,794	528,851	188,645	239,148	0	0	0
	incremental	3,400,175	1,743,803	-139,789	122,740	-27,885	666,562	710,300	324,444
90									
	Screened	5,499,238	3,186,659	359,725	270,824	144,201	601,403	640,650	295,776
	Symptomatic	2,262,808	1,504,328	469,243	144,486	144,751	0	0	0
	incremental	3,236,431	1,682,331	-109,518	126,338	-549	601,403	640,650	295,776

4.5. Incremental Cost-Effectiveness Ratios

4.5.1. Incremental cost per Life Years Gained

Table 21 presents the incremental cost per life years gained of extending screening up to the age of 90 years. The cost per life years gained ranged from £4,487 to £5,428 for the addition of one screening round at the age of 72 years old. The addition of an additional screening round at the age of 75 years in complement to screening at the age of 72 years old is associated with a cost of £6,141 - £7,715 per life years gained. Extending screening to an older age become less and less cost-effective as the screening-age increases.

Table 21: Incremental cost per life years gained

	72	75	78	81	84	87	90
Scenario 1	£5,428	£7,715	£11,076	£18,731	£39,445	£106,554	£264,289
Scenario 2	£5,067	£7,097	£9,697	£15,408	£28,789	£59,032	£109,909
Scenario 3	£4,487	£6,141	£8,228	£12,957	£23,465	£47,786	£88,444

4.5.2. Incremental cost per QALY Gained

Table 22 presents the incremental cost per QALY gained of extending screening up to the age of 90 years. Under commonly accepted cost-effectiveness threshold in the UK (£20,000 per QALY gained), screening older women was found to be a cost-effective use of NHS resource up to the age of 78 years. The harms outweigh potential benefit for a screening strategy after 87 years old.

Table 22: Incremental cost per QALY gained

	72	75	78	81	84	87	90
Scenario 1	£6,918	£10,085	£15,072	£27,306	£75,997	Dominated	Dominated
Scenario 2	£6,504	£9,366	£13,388	£22,817	£53,313	£398,564	Dominated
Scenario 3	£5,804	£8,173	£11,437	£19,204	£41,931	£201,965	Dominated

4.6. Sensitivity analysis

A set of univariate and multivariate sensitivity analysis were conducted to evaluate the impact of varying key model parameters and assumptions that affect the ICER (Figure 49).

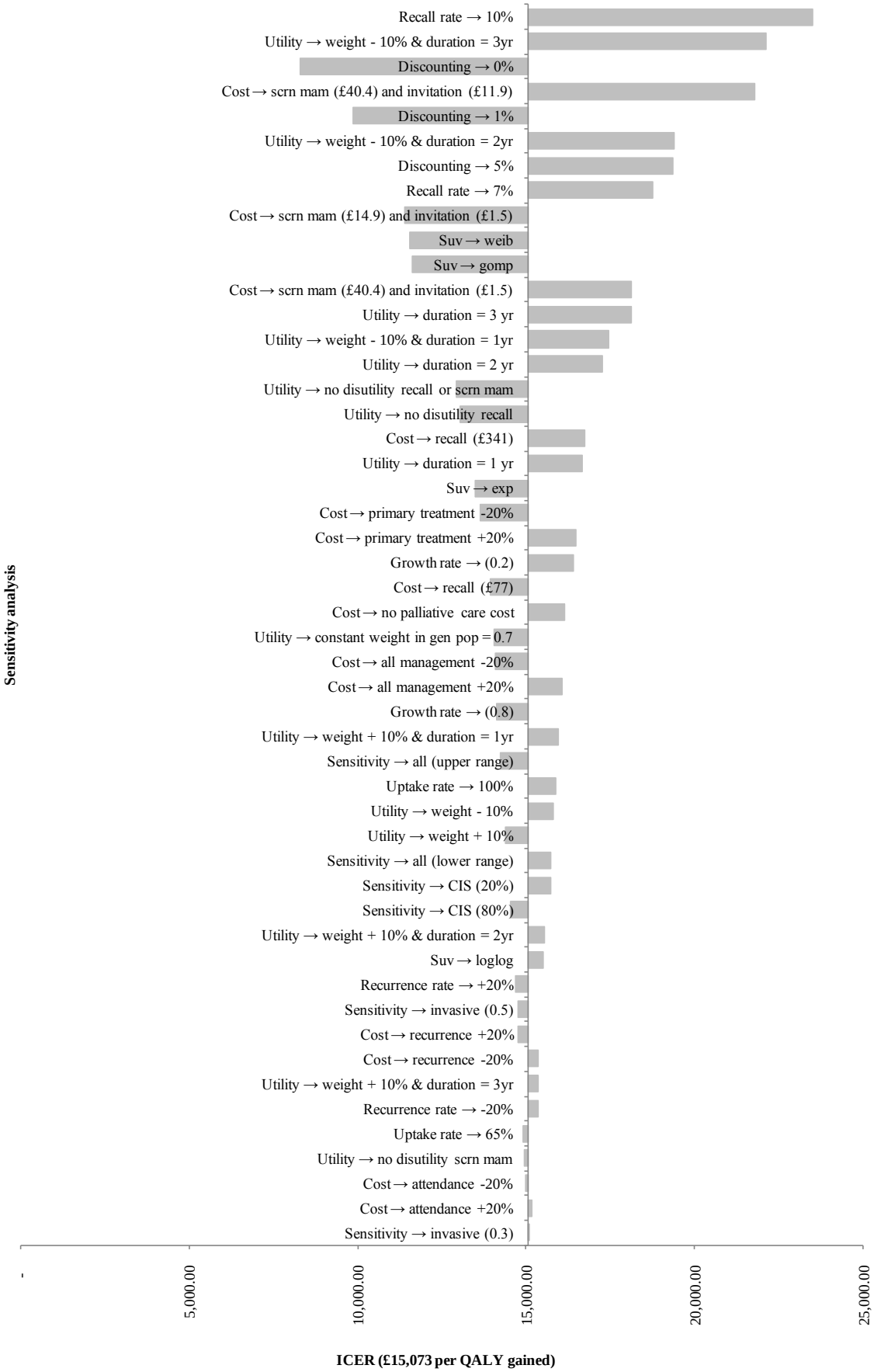
The ICER was mostly sensitive to the assumptions about the duration and quality of life spent in each state (from 1 to 3 years) after the diagnosis of breast cancer (reduction in quality of life), the recall rate for further investigation, discounting, the parametric survival regression model used to evaluate deaths in breast cancer patients, the assumptions about the reduction in quality of life associated with the pain and anxiety from the mammogram and the recall for further investigation.

Treatment costs, utility weights, sensitivity of screening mammography for invasive cancer or CIS and uptake rate had a lower impact on the ICER.

Assuming 78 years old to be the upper age limit for screening based on the cost per QALY gained (£15,072) below the commonly cited £20,000 per QALY gained, the strategy would no longer be cost-effective or close to the threshold assuming a discount rate of 5% (£19,342), a recall rate for further investigation of 10% (£23,499), lower utility weights for the diagnosis of breast cancer and assuming a duration of 3 years for each health states excluding metastasis (£22,124), a cost of screening equal to £40.4 (£21,807), lower utility weights for the diagnosis of breast cancer and assuming a duration of 2 years for each health state excluding metastasis (£19,386) and a recall rate equal to 7% (£18,748).

If the willingness to pay threshold is £30,000 per QALY gained our results suggest that screening can be extended up to 81 years old under our base case assumptions. However, the ICER was found to be very sensitive and the ICER was beyond £30,000 per QALY gained assuming the same duration of utility by stage, lower utility weight for breast cancer diagnosis, primary management costs, cost of screening mammography, cost for recall for further investigation, the recall rate, the tumour growth rate and discount rates.

Figure 49: sensitivity analysis



5. DISCUSSION AND MAIN LIMITATIONS

To our knowledge, this study is the first that has attempted to identify the upper age limit at which screening mammography should be extended in England and Wales. We perfomed a cost-effectiveness analysis which suggests that, under the assumptions made under our base case, an extension of the current NHSBSP upper age limit for invitations from 70 to 78 would represent a cost-effective use of NHS resources under commonly-used willingness to pay threshold in the UK (£20,000 per QALY gained). These results are 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) were used to calibrate the model and estimate the natural history of breast cancer among women presenting from clinical symptoms in the absence of screening. [33;34] Data were complemented with data from the NHSBSP to evaluate the impact of screening mammography.

Studies that have investigated the cost-effectiveness of mammography in other countries have reported results that differ widely. 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. [27] 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. [32] 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. 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. We explored the impact of varying a wide range of assumptions through sensitivity analysis, and found that the ICER was most sensitive to the rate for recall for further investigation, assumptions about the impact of breast cancer diagnosis on quality of life, discounting, the cost for screening mammography and the impact of screening on survival. Similar findings were made by previous authors. [27]

There are many examples of the use of decision-analytic modelling to analyse the impact of screening by mammography. We chose to develop a model *de novo* because we felt that no single model fully captured aspects of the natural history of the disease which would have a direct impact on the costs and benefits of screening. Indeed, most of the identified models used a simple stage approach (CIS, local , regional and distant). We would not argue that our model fully captures the complexities of this issue either, but it makes several steps in that direction. In particular, we represent both tumour growth and metastatic progression

(including CIS), include aspects of disease heterogeneity (grade and ER status), and explicitly link this heterogeneity to the aggression of the disease (in terms of growth rate and time to metastatic progression).

Given the complexity of our model, its calibration was a challenging exercise. We had UK data for this, both from cancer registries and the current NHSBSP. The challenges arose from the complex indirect relationship between the data and our model parameters. We developed a technique which we call Monte Carlo Likelihood simulation to estimate the optimum set of parameters that best fit the observed data. This process was found to be very effective and provided a reasonably good fit to the observed data.

We also validated the calibrated natural history against estimates from the published literature. The results of our calibration exercise were within the range of estimates found in the published literature in terms of sensitivity. Similarly, the model estimated the mean sojourn time to be about 5.2 years (including the period when the woman has a screen-detectable CIS). Evidence from the published literature suggested that the mean sojourn time is between 1.3 to 4.2 years in younger women, and that sojourn time increases with age. [37] For instance, Van Oortmassen et al (1990) estimated that the mean sojourn time increased from 2 years at the age of 40 to 5 years at the age of 70. [74] Similarly, evidence from the published literature suggests that the mean lead time is approximately two years. Our estimate was around 3 years (excluding the time taken to become invasive), and this may reflect the more favorable biology that tumours tend to have in older women.

In our study, 36% - 47% of women were found to die from breast cancer causes in the absence of screening up to the age of 80 years old. Similar figures have been reported in the literature. Bastiannet et al (2010) reported that after the age of 75 years , more than 50% of deceased patients with breast cancer die of other causes than their breast cancer. The proportion after 90 years old was about 25% respectively. [75] Diab et al (2000) indicated that 73% of deaths in breast cancer patients in the 50-54 year age group are due to their breast cancer, compared to only 29% of deaths in women aged over 85 years old. [6]

A strength of the model is that it allows us to identify over-diagnosis from screening (i.e cancer that would never present 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. Previous estimates of this figure in the literature have varied considerably, in relation to estimates of the sojourn time. For instance, Paci et al (2005) estimated over-diagnosis to be 2% for invasive cancer and 5% including CIS assuming a mean lead time of 3.7 years in women aged 50 to 69 years. [76] Morrell et al

(2010) estimated the rate of over-diagnosis to be 15% in women aged 65-69 years old allowing for a 5-year lead time bias. [15] Similarly, Paci et al (2006) estimated the excess ratio due to over-diagnosis to be 4.6% (2 – 7%) after correction for lead time bias and 3.2% for invasive cancer (1 – 6%). [38] Finally, Duffy et al (2005) calculated the risk of over-diagnosis to be 5% after adjustment for lead time. [77] Our model illustrates the extent to which over-diagnosis becomes an increasing problem as the age at screening increases.

A considerable mortality reduction from screening was observed in our model up to 81-84 years old (33% - 46%). However this figure relates solely to the impact on those whose disease is detected through screening. The mortality reduction will be lower when women are included who would present with interval cancers between screening rounds. Evidence from the published literature suggests a mortality reduction of around 30% for women aged 40-74 years. [78] In the Swedish trials, a 10-13% mortality reduction was found in women aged 40-49 and 29-31% in women aged 50-69. Finally, Duffy et al (2006) estimated a significant 43% reduction in incidence based breast cancer mortality among screened women after adjusting for self-selection bias. [79]

Finally, the management of breast cancer after diagnosis was estimated from cancer registry data among older women to reflect potential differences in the management of breast cancer in the older population compared to younger women. We also used age-specific data to estimate the proportion of women treated for recurrence.

Despite the strengths, there were limitations to our analysis. Firstly, although our model captures a considerable amount of the underlying biology of breast cancer, there is potential for improvement. For instance, grade was assumed to be constant in the current study, and it is possible that grade will increase over time if tumours are not detected. There are also some limitations related to the data and to the calibration approach. Indeed, few data were available to fit the model. The inclusion of more data, by age group for example would have been more relevant. It was not possible to use data by age group in the current study due to the small sample size. The calibration approach showed also some difficultly to converge with the necessity to calibrate part of the model manually to ensure that results of the calibration were sensible and in line with evidence from the published literature. The calibration approach also did not allow us to ascertain the uncertainty in the natural history in the absence of acceptance criteria. Other forms of calibration methods could have been used to allow us to capture the uncertainty such as Metropolis Hasting. [80] This is particularly important given that an infinite set of parameter values could have been estimated and fitted equally the observed data. To a lesser extent, there are also potential limitations associated with the

use of registry data, with potential misclassification of patients. We also used incidence data before the introduction of screening in the late 80s despise the general tendency for an increase in the incidence over time without screening. This is likely to affect the sojourn time. Unfortunately, it was not possible to explore the impact of different incidence rates due to time constraints. Finally, we also assumed that women cannot present symptomatically due to CIS, even though this does occur occasionally (Paget's disease of the nipple, bleeding from the nipple and the occasional palpable mass).

One important limitation was the assumption around the impact of breast cancer diagnosis on survival. A key driver of the benefit of screening is the extent to which early detection impacts on survival. Not only were we restricted by the lack of RCT data to estimate this relationship, we also only had useful routine survival data in this cohort for women who had presented symptomatically. To overcome this, we explored a number of assumptions when extrapolating from this data to estimate the impact of earlier detection through screening on survival. These assumptions reflected different levels of optimism in the ability to delay death through early detection, and illustrate the extent to which these assumptions drive the cost-effectiveness.

Furthermore, primary treatments were limited and comprised only surgery, hormonal therapy, chemotherapy and radiotherapy. Simplified assumptions have also to be made in the assignment of costs given the model structure. Costs were also estimated from an NHS perspective only. Rees et al (2000) showed that women treated for breast cancer undergo a lot of complementary therapies. [81] There was also uncertainty around the cost for screening mammography with a cost ranging from £15 to about £41 in the literature. This was shown to influence the ICER. We also assumed that the cost of screening mammography was similar by age group. This may not be true as older women may require more time due to frailty. There were also some limitations around the cost of the invitation to screening, with estimates suggesting a cost around £12. It was also not possible to estimate the time to recurrence, or timing of each treatment in the model. This was due to the absence of data about the impact of primary treatment on further progression and therefore death. While this is less important for costing purposes this is likely to represent an issue when discounting. This is particularly important as discounting was found to be one of the assumption that influenced the ICER most strongly. Finally, treatment for CIS was also estimated among a small sample size of 257 patients and included a limited number of resource used. There is also the possibility of misclassification of these patients.

We tried to include compliance rates. While this is less an issue for the ICER, a simplified assumption was used assuming the compliance to be independent at each screening round. This may represent a limitation, as some women may never attend, some may attend sometimes, and some women may always be compliant.

Finally, despite the large amount of literature about the impact of breast cancer diagnosis on quality of life, [82] [69] there are considerable uncertainties around quality of life in breast cancer patients given the wide variation in estimates between studies. There are also uncertainties about the most appropriate approach to ascertain the quality of life, in terms of stage or treatment utility weights. Our study used data from a US study conducted in women without breast cancer. This may represent a potential weakness in our assumptions. The utilities were also calculated using SG and we assumed that results were transferable to EQ-5D. This may bias the estimate. We also made some assumptions about the duration of reduction in quality of life after diagnosis of breast cancer in the absence of evidence.

VI. CONCLUSION

This study suggests that, under the assumptions made under our base case, an extension of the current NHSBSP upper age limit for invitations from 69 to 78 would represent a cost-effective use of NHS resources under commonly-used willingness to pay threshold in the UK (£20,000 per QALY gained).

Estimates in other countries indicated similar conclusions. Our model goes beyond previously published cost-effectiveness models in terms of biological plausibility and was calibrated to observed registry data in the UK. However, despite these strengths, there were some limitations due to the lack of data to calibrate the model, the assignment of costs and quality of life and the approach used to model survival.

VII. APPENDICES

1. APPENDIX 1

Table 23: Shift in Stage Distribution per 100,000 invitation (results by subgroup)

screen-age		n		stage post-diagnosis: stage 0		stage I		stage II		stage III		stage IV	
72													
	Screen-detected cases	752		144	19.2%	458	61.0%	104	13.9%	43	5.7%	2	0.2%
	Of which												
	• *clinically significant*	705	93.8%	124	17.5%	437	62.0%	101	14.3%	42	5.9%	2	0.3%
	• *over-diagnosis*	47	6.2%	20	43.6%	22	46.3%	4	7.9%	1	2.2%	0	0.0%
	Absence of screening	705		0	0.0%	259	36.7%	170	24.2%	213	30.2%	63	8.9%
75													
	Screen-detected cases	795		155	19.5%	488	61.4%	110	13.8%	39	4.9%	2	0.3%
	Of which												
	• *clinically significant*	721	90.6%	123	17.1%	454	63.1%	104	14.4%	37	5.1%	2	0.3%
	• *over-diagnosis*	74	9.4%	33	43.7%	34	45.5%	6	8.1%	2	2.6%	0	0.0%
	Absence of screening	721		0	0.0%	270	37.5%	176	24.5%	213	29.5%	61	8.5%
78													
	Screen-detected cases	843		154	18.3%	524	62.2%	112	13.3%	49	5.8%	3	0.4%
	Of which												
	• *clinically significant*	732	86.9%	110	15.0%	471	64.3%	102	14.0%	46	6.2%	3	0.4%
	• *over-diagnosis*	110	13.1%	44	39.7%	53	48.1%	10	9.0%	4	3.2%	0	0.0%
	Absence of screening	732		0	0.0%	272	37.2%	174	23.7%	225	30.7%	61	8.3%

81												
	Screen-detected cases	882		171	19.4%	542	61.4%	115	13.1%	50	5.7%	4	0.4%
	Of which												
	• *clinically significant*	723	82.0%	107	14.8%	463	64.0%	104	14.3%	46	6.4%	3	0.5%
	• *over-diagnosis*	159	18.0%	64	40.2%	79	49.9%	12	7.3%	4	2.4%	0	0.2%
	Absence of screening	723		0	0.0%	267	37.0%	174	24.1%	224	30.9%	58	8.0%
84												
	Screen-detected cases	924		174	18.8%	578	62.6%	122	13.3%	47	5.1%	2	0.2%
	Of which												
	• *clinically significant*	713	77.2%	95	13.3%	469	65.8%	105	14.7%	42	5.9%	2	0.3%
	• *over-diagnosis*	211	22.8%	79	37.3%	110	52.0%	18	8.4%	5	2.3%	0	0.1%
	Absence of screening	713		0	0.0%	276	38.7%	172	24.1%	212	29.7%	53	7.4%
87												
	Screen-detected cases	977		185	18.9%	610	62.4%	125	12.8%	54	5.5%	3	0.3%
	Of which												
	• *clinically significant*	682	69.9%	76	11.1%	456	66.8%	101	14.9%	46	6.8%	3	0.5%
	• *over-diagnosis*	294	30.1%	109	37.1%	154	52.4%	23	8.0%	7	2.5%	0	0.0%
	Absence of screening	682		0	0.0%	262	38.4%	170	24.9%	203	29.8%	47	6.9%
90												
	Screen-detected cases	1,017		194	19.1%	628	61.7%	135	13.3%	56	5.5%	4	0.3%
	Of which												
	• *clinically significant*	631	62.1%	63	10.0%	418	66.2%	103	16.4%	44	6.9%	3	0.5%
	• *over-diagnosis*	386	37.9%	131	34.0%	210	54.5%	32	8.2%	13	3.2%	0	0.1%
	Absence of screening	631		0	0.0%	255	40.4%	151	24.0%	179	28.4%	46	7.3%

2. APPENDIX 2

Table 24: Distribution of death by cause of mortality per 100,000 invitation (extension of screening up to the age of 90 years old)

last screening round		Absence of screening		screening (scenario 1)		screening (scenario 2)		screening (scenario 3)	
72									
	Total number of deaths	752							
All screen detected cancers	**Of which:**								
	• *BC death*	352	46.8%	177	23.6%	157	20.9%	131	17.4%
	• *Non BC death*	400	53.2%	575	76.4%	594	79.1%	621	82.6%
	Abs reduction (BC death)			-175		-195		-221	
	Rel reduction (BC death)			-49.7%		-55.3%		-62.8%	
	All death causes			705		705		705	
	Of which:								
Clinically relevant	• *BC death*			171	24.2%	157	22.3%	131	18.6%
	• *Non BC death*			534	75.8%	548	77.7%	574	81.4%
	All death causes			47		47		47	
Over-diagnosis	**Of which:**								
	• *BC death*			6	13.8%	0	0.0%	0	0.0%
	• *Non BC death*			40	86.2%	47	100.0%	47	100.0%
75									
	Total number of deaths	795							
All screen detected cancers	**Of which:**								
	• *BC death*	324	40.8%	165	20.8%	145	18.2%	111	13.9%
	• *Non BC death*	471	59.2%	630	79.2%	650	81.8%	684	86.1%
	Abs reduction (BC death)			-159		-179		-213	
	Rel reduction (BC death)			-49.0%		-55.3%		-65.9%	
	All death causes			721		721		721	
	Of which:								
Clinically relevant	• *BC death*			156	21.6%	145	20.1%	111	15.3%
	• *Non BC death*			565	78.4%	576	79.9%	610	84.7%
	All death causes			74		74		74	
Over-diagnosis	**Of which:**								
	• *BC death*			9	12.5%	0	0.0%	0	0.0%
	• *Non BC death*			65	87.5%	74	100.0%	74	100.0%

78									
	Total number of deaths	843							
All screen detected cancers	**Of which:**								
	• *BC death*	304	36.0%	170	20.2%	140	16.6%	104	12.4%
	• *Non BC death*	539	64.0%	673	79.8%	702	83.4%	739	87.6%
	Abs reduction (BC death)			-134		-164		-200	
	Rel reduction (BC death)			-44.0%		-53.8%		-65.7%	
	All death causes			732		732		732	
	Of which:								
Clinically relevant	• *BC death*			155	21.2%	140	19.1%	104	14.2%
	• *Non BC death*			577	78.8%	592	80.9%	628	85.8%
	All death causes			110		110		110	
Over-diagnosis	**Of which:**								
	• *BC death*			15	13.6%	0	0.0%	0	0.0%
	• *Non BC death*			95	86.4%	110	100.0%	110	100.0%
81									
	Total number of deaths	882							
All screen detected cancers	**Of which:**								
	• *BC death*	259	29.4%	151	17.1%	115	13.1%	79	9.0%
	• *Non BC death*	623	70.6%	731	82.9%	767	86.9%	803	91.0%
	Abs reduction (BC death)			-108		-144		-180	
	Rel reduction (BC death)			-41.8%		-55.5%		-69.5%	
	All death causes			723		723		723	
	Of which:								
Clinically relevant	• *BC death*			134	18.5%	115	15.9%	79	10.9%
	• *Non BC death*			589	81.5%	608	84.1%	644	89.1%
	All death causes			159		159		159	
Over-diagnosis	**Of which:**								
	• *BC death*			17	10.6%	0	0.0%	0	0.0%
	• *Non BC death*			142	89.4%	159	100.0%	159	100.0%

84									
	Total number of deaths	924							
All screen detected cancers	**Of which:**								
	• *BC death*	201	21.7%	133	14.4%	90	9.7%	61	6.6%
	• *Non BC death*	723	78.3%	791	85.6%	834	90.3%	863	93.4%
	Abs reduction (BC death)			-68		-111		-140	
	Rel reduction (BC death)			-33.7%		-55.3%		-69.8%	
	All death causes			713		713		713	
	Of which:								
Clinically relevant	• *BC death*			114	15.9%	90	12.6%	61	8.5%
	• *Non BC death*			599	84.1%	623	87.4%	652	91.5%
	All death causes			211		211		211	
Over-diagnosis	**Of which:**								
	• *BC death*			19	9.2%	0	0.0%	0	0.0%
	• *Non BC death*			191	90.8%	211	100.0%	211	100.0%
87									
	Total number of deaths	977							
All screen detected cancers	**Of which:**								
	• *BC death*	147	15.1%	120	12.3%	71	7.2%	48	5.0%
	• *Non BC death*	830	84.9%	856	87.7%	906	92.8%	928	95.0%
	Abs reduction (BC death)			-27		-76		-99	
	Rel reduction (BC death)			-18.1%		-52.0%		-67.0%	
	All death causes			682		682		682	
	Of which:								
Clinically relevant	• *BC death*			97	14.2%	71	10.3%	48	7.1%
	• *Non BC death*			586	85.8%	612	89.7%	634	92.9%
	All death causes			294		294		294	
Over-diagnosis	**Of which:**								
	• *BC death*			24	8.1%	0	0.0%	0	0.0%
	• *Non BC death*			270	91.9%	294	100.0%	294	100.0%

90									
	Total number of deaths	1,017							
All screen detected cancers	**Of which:**								
	• *BC death*	96	9.5%	90	8.8%	49	4.9%	32	3.2%
	• *Non BC death*	921	90.5%	927	91.2%	967	95.1%	985	96.8%
	Abs reduction (BC death)			-7		-47		-64	
	Rel reduction (BC death)			-7.0%		-48.6%		-66.7%	
	All death causes			631		631		631	
	Of which:								
Clinically relevant	• *BC death*			71	11.3%	49	7.8%	32	5.1%
	• *Non BC death*			560	88.7%	582	92.2%	599	94.9%
	All death causes			386		386		386	
Over-diagnosis	**Of which:**								
	• *BC death*			18	4.7%	0	0.0%	0	0.0%
	• *Non BC death*			367	95.3%	386	100.0%	386	100.0%

Reference List

1 Raik BL, Miller FG, Fins JJ, Raik BL, Miller FG, Fins JJ: Screening and cognitive impairment: ethics of forgoing mammography in older women. Journal of the American Geriatrics Society 2004;52:440-444.

2 McPherson K, Steel CM, Dixon JM: ABC of breast disease: Breast cancer-epidemiology, risk factors, and genetics. British Medical Journal 2000;321:624-628.

3 Van Dijck J, Verbeek A, Beex L, Hendriks J, Holland R, Mravnac M, Straatman H, Were J: Breast cancer mortality in a non randomised trial on mammographic screening in women over age 65. Int J Cancer 1997;70:164-168.

4 Kaplan RM, Saltzstein SL, Kaplan RM, Saltzstein SL: Reduced mammographic screening may explain declines in breast carcinoma in older women. Journal of the American Geriatrics Society 2005;53:862-866.

5 CRUK: Breast cancer: Key facts; 2010.

6 Diab SG, Elledge RM, Clark GM: Tumor characteristics and clinical outcome of elderly women with breast cancer. Journal of the National Cancer Institute 2000;92:550-556.

7 Mccarty KS, Silva JS, Cox EB, Leight GS, Wells SA, Mccarty KS: Relationship of Age and Menopausal Status to Estrogen-Receptor Content in Primary-Carcinoma of the Breast. Annals of Surgery 1983;197:123-127.

8 Collins K, Winslow M, Reed MW, Walters SJ, Robinson T, Madan J, Green T, Cocker H, Wyld L: The views of older women towards mammographic screening: a qualitative and quantitative study. British Journal of Cancer 2010;102:1461-1467.

9 SMaS G: Sociodemographic variations in breast cancer screening behaviour among Australian women: results from the 1995 national health survey. Preventative Medicine 2002;35:174-180.

10 Wyld L, Kumar ID, Brown H, Reed MWR: Stage and treatment variation with age in postmenopausal women with breast cancer. British Journal of Surgery 2004;91:1230.

11 Lavelle K, Todd C, Moran A, Howell A, Bundred N, Campbell M: Non-standard management of breast cancer increases with age in the UK: a population based cohort of women >= 65 years. British Journal of Cancer 2007;96:1197-1203.

12 Tabar L, Yen MF, Vitak B, Chen HHT, Smith RA, Duffy SW: Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet 2003;361:1405-1410.

13 Cheung S, Lagord N, Williams C, Kearins L, O.Lawrence: All breast cancer report: A UK analysis of all symptomatic and screen detected breast cancers diagnosed in 2006; NHS Cancer Screening Programmes 2009, 2009.

14 Smith-Bindman R, Kerlikowske K, Gebretsadik T, Newman J: Is screening mammography effective elderly women? American Journal of Medicine 2000;108:112-119.

15 Morrell S, Barratt A, Irwig L, Howard K, Biesheuvel C, Armstrong B: Estimates of overdiagnosis of invasive breast cancer associated with screening mammography. Cancer Causes & Control 2010;21:275-282.

16 Satariano WA, Ragland DR: The Effect of Comorbidity on 3-Year Survival of Women with Primary Breast-Cancer. Annals of Internal Medicine 1994;120:104-110.

17 Siegelmann-Danielli N, Khandelwal V, Wood GC: Breast cancer in elderly women: Combined effect of tumour feature, age, co-morbidities and treatment approach. Poster at the San Antonio Breast Cancer Conference, 2004 2004.

18 McPherson CP, Swenson KK, Lee MW: The effects of mammographic detection and comorbidity on the survival of older women with breast cancer. Journal of the American Geriatrics Society 2002;50:1061-1068.

19 Walter LC, Eng C, Covinsky KE: Screening mammography for frail older women: What are the burdens? Journal of the American Geriatrics Society 2001;49:S122-S123.

20 McCarthy EP, Burns RB, Freund KM, Ash AS, Shwartz M, Marwill SL, Moskowitz MA: Mammography use, breast cancer stage at diagnosis, and survival among older women. Journal of the American Geriatrics Society 2000;48:1226-1233.

21 Fracheboud J, Groenewoud JH, Boer R, Draisma G, de Bruijn AE, Verbeek AL, de Koning HJ: Seventy-five years is an appropriate upper age limit for population-based mammography screening. International Journal of Cancer 2006;118:2020-2025.

22 Barratt AL, Les IM, Glasziou PP, Salkeld GP, Houssami N: Benefits, harms and costs of screening mammography in women 70 years and over: a systematic review. [Review] [24 refs]. Medical Journal of Australia 2002;176:266-271.

23 Mandelblatt J, Saha S, Teutsch S, Hoerger T, Siu AL, Atkins D, Klein J, Helfand M, Cost Work Group of the U.S.Preventive Services Task Force: The cost-effectiveness of screening mammography beyond age 65 years: a systematic review for the U.S. Preventive Services Task Force. [Review] [45 refs][Summary for patients in Ann Intern Med. 2003 Nov 18;139(10):I34; PMID: 14623641]. Annals of Internal Medicine 2003;139:835-842.

24 Mandelblatt J, Saha S, Teutsch S, Hoerger T, Siu AL, Atkins D, Klein J, Helfand M, Cost Work Group of the U.S.Preventive Services Task Force: The cost-effectiveness of screening mammography beyond age 65 years: a systematic review for the U.S. Preventive Services Task Force. [Review] [45 refs][Summary for patients in Ann Intern Med. 2003 Nov 18;139(10):I34; PMID: 14623641]. Annals of Internal Medicine 2003;139:835-842.

25 Lee SY, Jeong SH, Kim YN, Kim J, Kang DR, Kim HC, Nam CM: Cost-effective mammography screening in Korea: high incidence of breast cancer in young women. Cancer Science 2009;100:1105-1111.

26 Madan J, Rawdin A: An initial assessment of the merits of extending routine breast cancer screening to women aged 47-49 years to assist the appraisal of options for extending the NHSBSP with appendix considering women aged 71-73; School of Health of Related Research, 2008.

27 Rojnik K, Naversnik K, Mateovic-Rojnik T, Primiczakelj M: Probabilistic cost-effectiveness modeling of different breast cancer screening policies in Slovenia. Value in Health 2008;11:139-148.

28 Rojnik K, Naversnik K: Gaussian process metamodeling in Bayesian value of information analysis: a case of the complex health economic model for breast cancer screening. Value in Health 2008;11:240-250.

29 Wong IO, Kuntz KM, Cowling BJ, Lam CL, Leung GM: Cost effectiveness of mammography screening for Chinese women. Cancer 2007;110:885-895.

30 Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG: Retrospective cost-effectiveness analysis of screening mammography. Journal of the National Cancer Institute 2006;98:774-782.

31 Ohnuki K, Kuriyama S, Shoji N, Nishino Y, Tsuji I, Ohuchi N: Cost-effectiveness analysis of screening modalities for breast cancer in Japan with special reference to women aged 40-49 years. Cancer Science 2006;97:1242-1247.

32 Mandelblatt JS, Schechter CB, Yabroff KR, Lawrence W, Dignam J, Extermann M, Fox S, Orosz G, Silliman R, Cullen J, Balducci L, Breast Cancer in Older Women Research Consortium: Toward optimal screening strategies for older women. Costs, benefits, and harms of breast cancer screening by age, biology, and health status. Journal of General Internal Medicine 2005;20:487-496.

33 WMCIU registry data: Data on file 2010.

34 ECRIC registry data: Data on file 2010.

35 Woods LM, Rachet B, O'Connell DL, Lawrence G, Tracey E, Willmore A, Coleman MP: Differences in breast cancer incidence in Australia and England by age, extent of disease and deprivation status: women diagnosed 1980-2002. Australian and New Zealand Journal of Public Health 2010;34:206-213.

36 Bastiaannet E, Kiefers G, de Craen A, Kuppen P, van de Water W, Portielje J, van der Geest L, Janssen-Heijnen M, Dekkers O, van de Velde C, Westendorp R: Breast cancer in elderly compared to younger patients in the Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat 2010.

37 Michaelson J, Satija S, Moore R, Weber G, Halpern E, Garland A, Kopans D: Estimates of breast cancer growth rates and sojourn time from screening database information. Journal of Women's Imaging 2003;5:11-19.

38 Paci E, Miccinesi G, Puliti D, Baldazzi P, De Lisi V, Falcini F, Cirilli C, Ferretti S, Mangone L, Finarelli AC, Rosso S, Segnan N, Stracci F, Traina A, Tumino R, Zorzi M: Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. Breast Cancer Research 2006;8.

39 Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, Aalen O, Tretli S: Estimating mean sojourn time and screening sensitivity using questionnaire data on time since previous screening. Journal of Medical Screening 2008;15:83-90.

40 Weedon-Fekjaer H, Vatten LJ, Aalen OO, Lindqvist B, Tretli S: Estimating mean sojourn time and screening test sensitivity in breast cancer mammography screening: new results. Journal of Medical Screening 2005;12:172-178.

41 Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, Aalen O, Tretli S: Estimating mean sojourn time and screening sensitivity using questionnaire data on time since previous screening. Journal of Medical Screening 2008;15:83-90.

42 Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, Aalen OO, Tretli S: Breast cancer tumor growth estimated through mammography screening data. Breast Cancer Research 2008;10.

43 Burstein HJ, Polyak K, Wong JS, Lester SC, Kaelin CM: Medical progress - Ductal carcinoma in situ of the breast. New England Journal of Medicine 2004;350:1430-1441.

44 Bluemke DA, Gatsonis CA, Chen MH, DeAngelis GA, DeBruhl N, Harms S, Heywang-Kobrunner SH, Hylton N, Kuhl CK, Lehman C, Pisano ED, Causer P, Schnitt SJ, Smazal SF, Stelling CB, Weatherall PT, Schnall MD: Magnetic resonance imaging of the breast prior to biopsy. Jama-Journal of the American Medical Association 2004;292:2735-2742.

45 Hwang EW, Kinkel K, Esserman LJ, Lu Y, Weidner N, Hylton NM: Magnetic resonance imaging in patients diagnosed with ductal carcinoma-in-situ: Value in the diagnosis of residual disease, occult invasion, and multicentricity. Annals of Surgical Oncology 2003;10:381-388.

46 Orel SG, Mendonca MH, Reynolds C, Schnall MD, Solin LJ, Sullivan DC: MR imaging of ductal carcinoma in situ. Radiology 1997;202:413-420.

47 Koch M, Hanson J, Gaedke H, Wilson D: Competing causes of death in breast cancer patients. In Paterson AHG, Lees AW, eds Proceedings of the Second International Symposium on FundamentalProblems in Breast Cancer, Alberta, Canada Banff, Alberta:Nijhoff, 1986; pp 265-272 2010.

48 National statistics: Interim life table 2006. http://www gad gov uk/Demography%20Data/Life%20Tables/index html 2006.

49 Yarnold J: Early and Locally Advanced Breast Cancer: Diagnosis and Treatment National Institute for Health and Clinical Excellence Guideline 2009. Clinical Oncology 2009;21:159-160.

50 NICE: Guide to the methods of technology appraisals. National Institute for Clinical Excellence. NICE 2008.

51 Office for national statistics: **Mortality statistics.** Deaths registered in 2008. http://www statistics gov uk/downloads/theme_health/DR2008/DR_08 pdf 2008.

52 Karnon J, Kerr GR, Jack W, Papo NL, Cameron DA: Health care costs for the treatment of breast cancer recurrent events: estimates from a UK-based patient-level analysis. British Journal of Cancer 2007;97:479-485.

53 Thomas RJ, Williams M, Glen J, Callam M: Comparing the cost of adjuvant anastrozole with the benefits of managing less patients with relapsed breast cancer. Breast Cancer Research & Treatment 2009;117:289-295.

54 Guest JF, Ruiz FJ, Greener MJ, Trotman IF: Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. European Journal of Cancer Care 2006;15:65-73.

55 Curtis L: Unit costs of health and social care 2009; Personal Social Services Research Unit, 2009.

56 Department of Health: NHS reference costs 2006-07. Department of Health 2008.

57 Pandharipande PV, Harisinghani MG, Ozanne EM, Specht MC, Hur C, Lee JM, Gazelle GS: Staging MR Lymphangiography of the Axilla for Early Breast Cancer: Cost-Effectiveness Analysis. American Journal of Roentgenology 2008;191:1308-1319.

58 Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, Goh TT, Lindley R, Cairns J: A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technology Assessment (Winchester, England) /20;11:1-149.

59 Cooper K, Meng Y, Hanan S, Ward S, Fitzgerald P, Papaioannou D: Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in breast cancer: systematic review and economic evaluation. Health Technol Assess. In press.

60 Department of Health: NHS reference costs 2008-09. Department of Health 2010.

61 Department of Health: NHS reference costs 2005-06. Department of Health 2006.

62 NHS BSP: Breast Screening results from the NHSBSP 2007/2008. Cancer screening evaluation unit 2009.

63 Moss SM, Brown J, Garvican L, Coleman DA, Johns LE, Blanks RG, Rubin G, Oswald J, Page A, Evans A, Gamble P, Wilson R, Lee L, Liston J, Sturdy L, Sutton G, Wardman G, Patnick J, Winder R: Routine breast screening for women aged 65-69: results from evaluation of the demonstration sites. British Journal of Cancer 2001;85:1289-1294.

64 Johnston K, Gerard K, Morton A, Brown J: *NHS Costs for the Breast Screening Frequency and Age Trials*. Health Economics Research Group Discussion paper number 16 Brunel University, 1996 1996.

65 Legood R, Gray A: A cost comparison of full field digital mammography (FFDM) with film-screen mammography in breast cancer screening;NHSBSP Equipment Report 0403. Health Economics Research Centre, University of Oxford, 2004.

66 Brown J, Welton NJ, Bankhead C, Richards SH, Roberts L, Tydeman C, Peters TJ: A Bayesian approach to analysing the cost-effectiveness of two primary care interventions aimed at improving attendance for breast screening. Health Economics 2006;15:435-445.

67 Madan J, Rawdin A, Stevenson M, Tappenden P: A rapid-response economic evaluation of the UK NHS Cancer Reform Strategy breast cancer screening program extension via a plausible bounds approach. Value in Health 2010;13:215-221.

68 Peasgood T, Ward S, Brazier J: Health-state utility values in breast cancer. Expert Rev Pharmacoeconomics Outcomes Res. In press.

69 Brennan V, Wolowacz S: A systematic review of breast cancer utility weights. systematic review of breast cancer utility weights Abstract #PCN77 ISPOR 13th Annual International Meeting 2008, May 3-7, 2009, Toronto, Ontario, Canada 2007.

70 Kind P, Dolan P, Gudex C, Williams A: Variations in population health status: results from a United Kingdom national questionnaire survey. British Medical Journal 1998;316:736-741.

71 Schleinitz MD, DePalo D, Blume J, Stein M: Can differences in breast cancer utilities explain disparities in breast cancer care? Journal of General Internal Medicine 2006;21:1253-1260.

72 Bonomi AE, Boudreau DM, Fishman PA, Ludman E, Mohelnitzky A, Cannon EA, Seger D: Quality of life valuations of mammography screening. Quality of Life Research 2008;17:801-814.

73 Rijnsburger AJ, Essink-Bot ML, van Dooren S, Borsboom GJJM, Seynaeve C, Bartels CCM, Klijn JGM, Tibben A, de Koning HJ: Impact of screening for breast cancer in high-risk women on health-related quality of life. British Journal of Cancer 2004;91:69-76.

74 Vanoortmarssen GJ, Habbema JDF, Vandermaas PJ, Dekoning HJ, Collette HJA, Verbeek ALM, Geerts AT, Lubbe KTN: A Model for Breast-Cancer Screening. Cancer 1990;66:1601-1612.

75 Singletary SE, Shallenberger R, Guinee VF: Breast-Cancer in the Elderly. Annals of Surgery 1993;218:667-671.

76 Paci E, Miccinesi G, Puliti D, Baldazzi P, De Lisi V, Falcini F, Cirilli C, Ferretti S, Mangone L, Finarelli AC, Rosso S, Segnan N, Stracci F, Traina A, Tumino R, Zorzi M: Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. Breast Cancer Research 2006;8.

77 Duffy SW, Agbaje O, Tabar L, Vitak B, Bjurstam N, Bjorneld L, Myles JP, Warwick J: Overdiagnosis and overtreatment of breast cancer - Estimates of overdiagnosis from two trials of mammographic screening for breast cancer. Breast Cancer Research 2005;7:258-265.

78 Tabar L, Gad A, Holmberg LH, Ljungquist U, Eklund G, Fagerberg CJG, Baldetorp L, Grontoft O, Lundstrom B, Manson JC, Day NE, Pettersson F: Reduction in Mortality from Breast-Cancer After Mass-Screening with Mammography. Lancet 1985;1:829-832.

79 Duffy SW, Tabar L, Chen THH, Smith RA, Holmberg L, Jonsson H, Lenner P, Nystrom L, Tornberg S: Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. Cancer Epidemiology Biomarkers & Prevention 2006;15:45-51.

80 Whyte S, Walsh C, Chilcott J: Bayesian calibration of a natural history model with application to a population model for colorectal cancer. Medical decision making 2010;In press.

81 Rees RW, Feigel I, Vickers A, Zollman C, McGurk R, Smith C: Prevalence of complementary therapy use by women with breast cancer. A population-based survey. European Journal of Cancer 2000;36:1359-1364.

82 Peasgood T, Ward S, Brazier J: Health-state utility values in breast cancer. Expert Rev Pharmacoeconomics Outcomes Res. In press.