VALUE IN HEALTH ▮ (2017) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Evaluation of a Stratified National Breast Screening Program in the United Kingdom: An Early Model-Based Cost-Effectiveness Analysis

Ewan Gray, PhD[1,2], Anna Donten, MSc[1], Nico Karssemeijer, PhD[1,3], Carla van Gils, PhD[1,4], D. Gareth Evans, MD, FRCP[1,5], Sue Astley, PhD[1,6], Katherine Payne, PhD[1,]*

[1]*Manchester Centre for Health Economics, University of Manchester, Manchester, UK;* [2]*Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK;* [3]*Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands;* [4]*University Medical Centre Utrecht, Utrecht, Netherlands;* [5]*Genesis Breast Cancer Prevention Centre and Nightingale Breast Screening Centre, University Hospital of South Manchester, Manchester, UK;* [6]*Department of Imaging Science and Biomedical Engineering, University of Manchester, Manchester, UK*

ABSTRACT

Objectives: To identify the incremental costs and consequences of stratified national breast screening programs (stratified NBSPs) and drivers of relative cost-effectiveness. **Methods:** A decision-analytic model (discrete event simulation) was conceptualized to represent four stratified NBSPs (risk 1, risk 2, masking [supplemental screening for women with higher breast density], and masking and risk 1) compared with the current UK NBSP and no screening. The model assumed a lifetime horizon, the health service perspective to identify costs (£, 2015), and measured consequences in quality-adjusted life-years (QALYs). Multiple data sources were used: systematic reviews of effectiveness and utility, published studies reporting costs, and cohort studies embedded in existing NBSPs. Model parameter uncertainty was assessed using probabilistic sensitivity analysis and one-way sensitivity analysis. **Results:** The base-case analysis, supported by probabilistic sensitivity analysis, suggested that the risk stratified NBSPs (risk 1 and risk-2) were relatively cost-effective when compared with the current UK NBSP, with incremental cost-effectiveness ratios of £16,689 per QALY and £23,924 per QALY, respectively. Stratified NBSP including masking approaches (supplemental screening for women with higher breast density) was not a cost-effective alternative, with incremental cost-effectiveness ratios of £212,947 per QALY (masking) and £75,254 per QALY (risk 1 and masking). When compared with no screening, all stratified NBSPs could be considered cost-effective. Key drivers of cost-effectiveness were discount rate, natural history model parameters, mammographic sensitivity, and biopsy rates for recalled cases. A key assumption was that the risk model used in the stratification process was perfectly calibrated to the population. **Conclusions:** This early model-based cost-effectiveness analysis provides indicative evidence for decision makers to understand the key drivers of costs and QALYs for exemplar stratified NBSP.

Keywords: breast cancer, cost-effectiveness analysis, discrete event simulation, screening.

Introduction

National breast screening programs (NBSPs) have emerged as important public health interventions that aim to reduce deaths from breast cancer through early detection [1]. NBSPs in different jurisdictions differ in terms of the age at which screening is first offered to women in the population (start of NBSP), the interval between screens (screening interval), and the age at which screening is stopped. In the United Kingdom, the current NBSP is targeted at women within the first 3 years of their 50th birthday until the age of 70 years with a 3-yearly screening interval [2]. In some areas of the United Kingdom, the age range has been extended to women aged 47 to 49 years and 71 to 73 years as part of an age extension trial [3]. The current UK NBSP is a standard program with the same screening modality (mammography) offered at the same screening interval to all women regardless of their risk of developing breast cancer.

A new concept called "stratified screening," also known as personalized screening, is being considered to replace the existing standard, or "one-size-fits-all" UK NBSP, with the aim of improving the predictive value of cancer detection and, therefore, the relative cost-effectiveness of the program [4]. Risks of breast cancer may vary across a wide range because of familial risk, mammographic density, and modifiable risk factors. The potential for improved clinical and relative cost-effectiveness is achieved by modifying the screening protocol depending on an

* *Address correspondence to:* Katherine Payne, Manchester Centre for Health Economics, University of Manchester, Oxford Road, Manchester M139PL, UK.

E-mail: Katherine.Payne@manchester.ac.uk.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2017.04.012

individual's characteristics such as breast cancer risk factors or the performance of the screening modality for that individual. The introduction of, or any modification to, an NBSP has an opportunity cost. It is therefore important for decision makers deciding how to allocate finite budgets for screening programs to understand the added value of any additions or changes to an NBSP.

A substantial, but heterogeneous, economic evidence base has been developed to quantify the potential added value of an NBSP. A systematic review, conducted in 2014, identified 71 economic evaluations of relevance to breast screening in a general population of women. Of these, 52 were model-based evaluations [5]. There were three studies identified that conducted model-based analyses of a stratified screening strategy. Two of these studies were based in the United States [6,7] with no relevance to health care systems outside that setting. One study was UK-based [8] but provided no detail on the study perspective, time horizon, nature, and source of model inputs or method of analysis, which meant it is not possible to critique the relevance and quality of the results. Given the lack of an existing evidence base, it was timely to design an early model-based cost-effectiveness analysis (CEA) to identify the potential impact of introducing stratified NBSP in the UK setting and key drivers of the relative cost-effectiveness of different types of stratified NBSPs.

Methods

An early model-based CEA was developed to address the key criteria as presented in Table 1 and reported in line with published criteria [9]. The concept of an early model-based economic evaluation is used in keeping with the definition offered by Annemans et al. [10]. Using an early model-based economic evaluation is in keeping with the recommendation by Sculpher et al. [11] to use an iterative approach to developing economic evidence to inform the introduction of new health care interventions.

Interventions

Four potential approaches (hereafter called risk 1, risk 2, masking, and masking and risk 1) to stratified NBSP (see Table 1) were developed as part of a European collaborative project called Adapting Breast Cancer Screening Strategy Using Personalised Risk Estimation (ASSURE) [4].

Comparators

The identified relevant comparator was the current UK NBSP (see Table 1). "No screening" was also identified as a comparator of interest. A pragmatic approach was taken to define no screening (see Table 1).

Model Conceptualization and Structure

A systematic review of economic evaluations of breast screening programs identified no relevant existing models that could be used without extensive modification [5]. A de novo model structure was conceptualized, in line with published recommendations [12], and developed with input from key clinical members in the ASSURE team (n = 5) and external experts (n = 15). The conceptualization process identified that the model required three components to represent: the stratification approach, breast cancer natural history with screening, and the diagnosis and treatment process after a cancer detected by screening. A discrete event simulation (DES) model was used to represent these three components. Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012 shows the model structures and descriptions in detail. The model codes, created in R statistical package (R Foundation for Statistical Computing, Vienna, Austria), are available on request.

Table 1 – Key design criteria.

Decision problem	What are the key drivers of the incremental costs and benefits of example stratified breast screening program compared with the current NBSP?
Interventions	Risk 1: a risk-based stratification defined by the risk algorithm used in a published study [5] enhanced with density and texture measures following the method of Brentnall et al. [44]. Three strata (with associated screening intervals) were defined by 10-y risks of breast cancer of 1) <3.5% (3-yearly), 2) 3.5%–8% (2-yearly), and 3) >8% (annually) Risk 2: a risk-based stratification defined by the same algorithm as risk 1 but with strata defined by dividing the population into thirds on the basis of 10-y risk (tertiles): 1) the lowest risk tertile (3-yearly), 2) the middle tertile (2-yearly), and 3) the highest risk tertile (annually) Masking (covering up of tumors in mammograms by dense breast tissue): current screening approach with supplemental ultrasound offered to women with high breast density, defined using VDG3 and VDG4 [45]. High risk was defined as greater than an 8% 10-y risk of breast cancer [46]. Women with both high breast density and high risk of breast cancer were offered supplemental magnetic resonance imaging instead of ultrasound Risk 1 with masking: the risk 1 stratification approach together with the strategy described in the masking approach
Comparators	Current UK NBSP: women between 50 and 70 y with screening every 3 y using mammography No screening: no use of mammography in the population for screening purposes; all cancers would present with clinical signs or symptoms
Model type	Discrete event simulation programmed in R
Population	Women eligible for an NBSP
Setting and perspective	National health care service Costs to individual women were excluded from the analysis
Time horizon	Lifetime
Costs	National currency (£) at 2014 prices
Benefits	Life-years and QALYs
Discounting	3.5% for both costs and benefits (base case) 3.5% for costs and 1.5% for benefits (sensitivity analysis)
Cost-effectiveness threshold	NICE UK-recommended threshold of £20,000 per QALY gained

NBSP, national breast screening program; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; VDG, Volpara Density Group.

Table 2 – List of parameters and definitions for equations.

Equation	Parameter	Definition
Equation 1	S(X),	Sensitivity of mammography to detect a tumor of size X (maximum diameter in millimeters)
	β_1	Sensitivity of mammography; β_1 determined how rapidly sensitivity changes with tumor size to approach the asymptotes of 0 and 1
	β_2	Sensitivity of mammography; β_2 places the location of the sensitivity curve in relation to tumor size, where $X-\beta_2=0$ and sensitivity is equal to 0.5
Equation 2	$Sen_{average}$	Sensitivity of mammography without density information
	Sen_X	Sensitivity of mammography given a tumor size X
	$Sen_{X,VDG}$	Size and VDG-specific sensitivity of mammography
Equation 3	$Sen_{average}$	Sensitivity of mammography without density information
	Sen_X	Sensitivity of mammography given a tumor size X
	$Sen_{X,VDG}$	Size and VDG-specific sensitivity of mammography
Equation 4	OR_{MRI}	The odds ratio for detecting cancer with MRI and mammography compared with mammography alone
	$c.d.r._{\cdot mammo,MRI}$	The cancer detection rate for the combined methods
	$c.d.r._{\cdot mammo}$	The cancer detection rate for mammography alone
Equation 5	$Sen_{X,VDG,MRI}$	The sensitivity of screening with mammography and MRI for a tumor of size X in women classified as in a given VDG
	$Sen_{X,VDG}$	The sensitivity for the same tumor for mammography alone
Equation 6	V_{max}	The assumed maximum tumor volume, equal to a sphere of 128-mm diameter
	V_{cell}	The assumed initial volume of an incident cancer, equal to a sphere of 0.025-mm diameter
Equation 7	V_{max}	The assumed maximum tumor volume, equal to a sphere of 128-mm diameter
	V_{cell}	The assumed initial volume of an incident cancer, equal to a sphere of 0.025-mm diameter
Equation 8	k_i	The individual growth rate parameter following a lognormal distribution $\ln N(\alpha_1,\alpha_2)$; individual growth rates are drawn from a lognormal distribution with mean α_1 and SD α_2
	V_{max}	The assumed maximum tumor volume, equal to a sphere of 128-mm diameter
	V_{cell}	The assumed initial volume of an incident cancer, equal to a sphere of 0.025-mm diameter
Equation 10	T_m	Survival time (age)
	λ	Scale parameter (=0.897)
	υ	Shape parameter (=86.74)
	U	Uniform(0,1) random draw
Equation 11	T_c	The survival time in years
	γ	The exponential survival function parameter, estimated in the parametric survival analysis, for a specific NPI group
Equation 12	T_d	The time to simulated clinical detection
	T_m	The previously calculated all-cause survival time
	T_c	The post–cancer diagnosis all-cause survival time

MRI, magnetic resonance imaging; NPI, Nottingham Prognostic Indicator; VDG, Volpara Density Group.

Model Input Parameters

The input parameters, with key assumptions, are now described for each of the three model components together with the values used for resource use costs and outcomes, quantified using survival and quality-adjusted life-years (QALYs).

The Stratification Process

Performance input parameters were required for each screening modality: mammography, mammography adjusted for masking, and ultrasonography (US) and magnetic resonance imaging (MRI).

Mammography. The sensitivity of mammography was defined as the conditional probability of a tumor being detected at a mammography event given the size of the tumor. This model took account of latent cancers that exist at a screening round, which were not detected, and subsequently do not present in the following interval. To obtain an estimate of screening sensitivity consistent with the presence of latent cancers in the model, the screening sensitivity as defined in Weedon-Fekjaer et al. [13] was used. Screening sensitivity was estimated jointly with the natural history parameters to be consistent with the presence of latent cancers that were simulated in this model. Sensitivity of mammography conditional on tumor size was parameterized as shown in Equation 1:

$$S(X)=\frac{\exp\left(\frac{X-\beta_2}{\beta_1}\right)}{1+\exp\left(\frac{X-\beta_2}{\beta_1}\right)}. \quad (1)$$

Table 2 presents the definitions for the parameters used in Equations 1 to 12.

Mammography and Adjustment for Masking. Masking was defined as the case in which a cancer was present but not detected at screening because of the view of the cancer being obscured in the images by other tissues [14]. In mammography, masking was expected to occur more frequently when there was high breast density or if particular textural patterns of the breast tissue were present. To quantify masking due to breast density it was necessary to rely on a comparison of screen-detected and interval breast cancer rates within different density groups. From such a comparison it was possible to estimate the sensitivity of screening mammography for each group by the method of counting the screen-detected cancers as true positives and the interval cancers as false negatives.

Table 3 – Input parameters for base-case analysis.

Parameter	Value	Source
Breast cancer risk factors	Varied	[5,45] (random sample from individual patient data)
Summary statistics risk factors, mean ± SD		
Age (y)	48.93 ± 1.09	[45]
10-y risk (%)	3.04 ± 1.43	[45]
Lifetime risk (%)	13.21 ± 1.43	[45]
Density (Volpara) (%)	8.02 ± 5.26	[45]
Cancer incidence parameters		
Conditional on breast cancer in lifetime, probability that it originates at age t	See Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012	[19]
Cancer growth parameters		
Tumor starting size (diameter)	0.25 mm	[13]
Maximum tumor size	128 mm	[13]
Growth rate mean (lognormal) α_1	1.07	[13]
Growth rate SD α_2	1.31	[13]
All-cause mortality		
Weibull shape	8.97	Fit to life table for UK population [30]
Weibull scale	86.74	Fit to life table for UK population [30]
Mammography		
Sensitivity by tumor size modeled as logistic-type function		[13]
β_1: sets increase with size	1.47	
β_2: sets sensitivity relative to size	6.51	
Maximum sensitivity	0.95%	[13]
Sensitivity by VDG, used to calculate relative sensitivity given tumor size		
Sensitivity VDG1	85.0%	[48]
Sensitivity VDG2	77.6%	[48]
Sensitivity VDG3	69.0%	[48]
Sensitivity VDG4	58.6%	[48]
Recall rate	4.0 per 100 examinations	[16]
False-positive biopsy proportion	2.4%	[16]
Proportion of screen-detected cancers that are DCIS	20.3%	[26]
Clinically detected (interval cancers)		
Cancer size at clinical detection, mean	6.5 doublings (22.62 mm)	[20]
Cancer size at clinical detection, SD	0.535 doublings	[20]
Survival after breast cancer diagnosis		
γ NPI 1	−5.413	[31]
γ NPI 2	−4.023	[31]
γ NPI 3	−2.465	[31]
γ Advanced cancer, age <50 y	−0.527	[29]
γ Advanced cancer, age 50–69 y	−0.537	[29]
γ Advanced cancer, age ≥70 y	−0.849	[29]
US cancer detection		
VDG3/4 incremental cancers detected with supplemental US	3 per 1000 examinations	[17]
False-positive (recall) rate, US	98 per 1000 examinations	[17]
Biopsy rate, US	2.4%	Assumed same as mammography
Proportion cancers detected by supplemental US that are DCIS	21%	Assumed same as mammography
MRI cancer detection		
VDG3/4 incremental cancers detected with supplemental US	5 per 1000 examinations	Vreemann et al. (personal communication, 2015)
False-positive (recall) rate, MRI	41.15 per 1000 examinations	Vreemann et al. (personal communication, 2015)
Biopsy rate, MRI	3.03%	Vreemann et al. (personal communication, 2015)
Proportion of cancers detected by supplemental MRI that are DCIS	14.3%	Vreemann et al. (personal communication, 2015)

continued on next page

Table 3 – *continued*

Parameter	Value	Source
Costs		
Mammography	£54	[15]
Follow-up, mean	£95	[15]
Biopsy, mean	£160	[49]
NPI 1 treatment, mean	£11,630	[15]
NPI 2 treatment, mean	£12,978	[15]
NPI 3 treatment, mean	£15,405	[15]
Advanced cancer, mean	£23,449	[13]
Screening ABUS	£80	Expert opinion
Screening HHUS	£80	Expert opinion
Screening MRI	£220	[49]
Stratification process	£10.57	[5]; expert opinion
Utility		
Early breast cancer, first year	0.696	[36]
Early breast cancer, subsequent years	0.779	[36]
Advanced breast cancer, first year	0.685	[36]
Advanced breast cancer, subsequent years	0.685	[36]

ABUS, automated equipment; DCIS, ductal carcinoma in situ; HHUS, hand-hand equipment; MRI, magnetic resonance imaging; NPI, Nottingham Prognostic Index; US, ultrasonography; VDG, Volpara Density Group.

To calculate the Volpara Density Group (VDG)–specific sensitivity (Sen_{VDG};see Equation 2 and Table 2) of mammography for a tumor of a given size, the ratio of the odds of a true positive result for that VDG compared with the population average odds (OR_{VDG}; see Equation 3 and Table 2) was combined with the odds of a true positive result given the tumor size alone. The resultant value for odds was then converted back to a probability to give VDG-specific and tumor size–specific sensitivity. For simplicity, it was assumed that the relative sensitivities (i.e., odds ratios) between VDGs were equal across all tumor sizes.

$$OR_{VDG} = \frac{Sen_{VDG}/(1-Sen_{VDG})}{Sen_{average}/(1-Sen_{average})}, \quad (2)$$

$$Sen_{X,VDG} = \frac{Sen_X/(1-Sen_x) \times OR_{VDG}}{1+(Sen_X/(1-Sen_x) \times OR_{VDG})}. \quad (3)$$

Mammography Recall Rate (True Positives and False Positives). The rate of recalls that result in biopsy (true positives) was taken from a previous economic evaluation [15]. The recall rate, for women in whom no cancer is present (false positives), was calculated by identifying the overall recall rate for the UK NBSP from published program statistics 2011 to 2012 [16]. About 20% of recalls were cited to be true positives, which indicated that the estimated recall rate, excluding true positives, was 3.2%.

US and MRI. Two supplemental screening modalities were relevant. US supplemental screening, delivered using either hand-hand equipment or automated equipment, was proposed for women with high breast density (VDG3 and VDG4). For women at high risk who also have high breast density, MRI was used as a supplemental screening technology.

It was necessary to assume that the only available published estimates of supplemental US and MRI screening sensitivity and specificity in this group were approximately equal to those for the relevant population (mammogram-negative women of screening age). The estimate of US screening performance was taken from a published systematic review and meta-analysis [17]. This review included studies only in the high-risk population but was the only available source that provided a quantitative synthesis of sensitivity and specificity for US. For MRI, data from an ongoing trial in a high-risk population of women in this area (Vreemann et al., personal communication, 2015) were used to inform the MRI screening performance parameters in the model.

The same approach was taken to calculate the screening performance for US and MRI. Reported cancer detection rates from each source were used to calculate the odds ratio for detecting cancer with US, MRI, and mammography compared with mammography alone. The estimated odds ratio was assumed to be constant across tumor size. Equation 4 (see Table 2) shows the case for MRI:

$$OR_{MRI} = \frac{c.d.r._{mammo,MRI}/(1000-c.d.r._{mammo,MRI})}{c.d.r._{mammo}/(1000-c.d.r._{mammo})}. \quad (4)$$

The cancer detection rate with mammography and MRI reported by Vreemann et al. (personal communication, 2015) was 12.14 per 1000 examinations, whereas the cancer detection rate for mammography alone in this group was 4.2 per 1000 examinations [17]. The estimated odds ratio was 2.91, which was then applied to the tumor size and breast density– specific odds of a cancer being detected with mammography alone. These odds can then be converted back to probabilities for use in the simulation of individual screening events using the formula in Equation 5 (see Table 2):

$$Sen_{X,VDG,MRI} = \frac{Sen_{X,VDG}/(1-Sen_{X,VDG}) \times OR_{MRI}}{1+(Sen_{X,VDG}/(1-Sen_{X,VDG}) \times OR_{MRI})}. \quad (5)$$

US and MRI Recall Rate. The recall rate for US was 98 per 1000 examinations and for MRI it was 41 per 1000 examinations [17]. It was assumed that the biopsy rate for recalls is the same as the current NBSP, which was informed by the opinion of three experts (radiologists) in the ASSURE project [4].

Breast Cancer Natural History with Screening

Breast cancer natural history was represented using a continuous time and tumor size growth model to allow variation in growth rates. The natural history of breast cancer was defined by estimating the incidence of breast cancer with screening and the growth of tumors once detected.

Breast cancer incidence. The occurrence of breast cancer for an individual was assumed equal to the lifetime risk score of that individual, estimated using the Tyrer-Cuzick algorithm [18]. This assumption implies that the risk model used in the stratification process is perfectly calibrated to the population. The age of breast cancer incidence (malignant neoplasm of breast [*International Classification of Diseases, Ninth Revision*, C50] and carcinoma in situ of breast [*International Classification of Diseases, Ninth Revision*, D05]), conditional on lifetime occurrence, was then estimated for each individual on the basis of the Office of National Statistics cancer registry data [19] (see Appendix 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012).

Breast Cancer Growth. A continuous time model was used to estimate the growth of tumors of the breast (see Appendix 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012). Four candidate growth models [13,20–22] were identified from a systematic review of economic evaluations of NBSPs [5]. Each identified growth model used a unique combination of parameters, which meant a formal quantitative synthesis was not appropriate, and the natural history model published by Weedon-Fekjaer et al. [13] was judged to be the best available because of the use of a continuous growth model, the high quality of the reporting, and the relatively close match in location (Europe) and time period to the current UK setting. The natural history model parameterization was described by two steps. The parameter estimates are presented in Table 3.

Step 1. Equations 6 and 7 (see Table 2) show the logistic tumor growth function (using tumor volume V mm^3, diameter s mm, time in years t, and growth rate k, and assuming a spherical shape as is in Weedon-Fekjaer et al. [13]):

$$V(t)=\frac{V_{max}}{\left[1+\left(\left(\frac{V_{max}}{V_{cell}}\right)^{0.25}-1\right)e^{-0.25kt}\right]}, \quad (6)$$

$$s(t)=2\left(V(t)/\left(\frac{4}{3}\pi\right)\right)^{1/3}. \quad (7)$$

Step 2. Equations 8 and 9 (see Table 2) show the extension to individual growth rates (mixed model):

$$V_i(t)=\frac{V_{max}}{\left[1+\left(\left(\frac{V_{max}}{V_{cell}}\right)^{0.25}-1\right)e^{-0.25k_it}\right]}, \quad (8)$$

$$s_i(t)=2\left(V_i(t)/\left(\frac{4}{3}\pi\right)\right)^{1/3}. \quad (9)$$

Diagnosis and Treatment Process

After a screen-detected cancer, the model captured the diagnostic and subsequent treatment process. Three types of tumors for breast cancer were reflected in the model: invasive, non- or micro-invasive, and advanced.

Invasive Tumors. For invasive cancers, the Nottingham Prognostic Index (NPI), a commonly used and validated classification system, was used to group the diagnosed tumors into three prognostic groups [23,24]. A systematic review was used to identify reported survival for NPI-defined subgroups (see Appendix 4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012). A meta-regression analysis showed that there was substantial heterogeneity between the studies that was driven by the date on which the data were collected and a trend for improved survival over time, which implied that it was more appropriate to select the most recent data to inform the probability of NPI group membership conditional on invasive tumor size category and survival for women diagnosed with breast cancer (see Table 2). Allocation of invasive cancer cases to NPI categories used the probability of NPI group membership conditional on tumor size category, as reported in Kollias et al. [25], which was the only study identified reporting the required cross tabulation of size and NPI category. The required probabilities of NPI subgroup membership were calculated using the reported cross tabulation of size category by NPI category (see Appendix 3 in Supplemental Materials).

Non- or Micro-Invasive Tumors. Three simplifying assumptions were made to capture the impact of detecting non- or micro-invasive tumors, defined as "ductal carcinoma in situ (DCIS)." A vanishingly small proportion of DCIS tumors will not be screen-detected and, therefore, it was assumed that only screen-detected cancers may be assigned to the DCIS category. The proportion of screen-detected DCIS cancers was assumed to be constant regardless of the screening interval. This assumption was supported by the proportions of DCIS in screen-detected cancers in the UK NBSP (3-year interval; 20.3%) [26] compared with the Netherlands NBSP (2-year interval; 20.9%) [27] being similar. Survival for DCIS diagnosed and treated patients was assumed to be the same as for the general population, in line with an audit of UK screen-detected breast cancers [26]. On this basis, any screen-detected cancer was given a probability of 0.203 of being assigned to the DCIS category. DCIS cancer cases have the same all-cause survival as the general population.

Advanced Tumors. A small proportion of all breast cancers will present at the advanced stage with distant metastases defined as being stage IV in the Tumor, Node, Metastasis classification system [28]. The probability of a breast cancer of a given size presenting at an advanced stage was assumed not to be related to the type of screening modality or interval. The source for the probabilities of advanced breast cancer at diagnosis conditional on tumor size was taken from the National Health Service audit of screen-detected breast cancers (2013) (see Appendix 3 in Supplemental Materials). Estimates of 10-year survival for patients with advanced breast cancer were obtained from a meta-analysis of registries in six countries [29].

Survival, Invasive (Nonadvanced) Breast Cancer

For women without a diagnosis of breast cancer, survival was taken from published population life tables [30], and the parameters of a Weibull survival distribution were estimated. Simulation of individual age of mortality was achieved by inverting the Weibull cumulative distribution function and taking a random draw from the uniform (0,1) distribution using Equation 10 (see Table 2):

$$T_m=\left(\frac{\log(U)}{\lambda}\right)^{1/\nu}. \quad (10)$$

The observed effect of data collection date on survival from the meta-regression (manuscript under review) meant that the most appropriate estimate of survival for women with a diagnosis of breast cancer was the most up-to-date estimate (see Fong et al. [31]). The parameters of four functional forms for the baseline hazard function were estimated in a regression-based survival analysis: exponential, Weibull, lognormal, and log-logistic. The exponential model was selected on the basis of the Akaike information criterion (a measure of model fit) and visual inspection of Cox-Snell residuals (see Appendix 4 in Supplemental Materials). Estimated coefficients (Table 3) from the parametric survival model were used to simulate a survival

Table 4 – Base-case deterministic analyses of example stratified NBSP.

Screening program	QALYs (3.5% discount rate)	Cost (£, 2015; 3.5% discount rate)	ICER vs.			
			No screening (3.5% discount rate)	UK NBSP (3.5% discount rate)	No screening (1.5% health, 3.5% costs)	UK NBSP (1.5% health, 3.5% costs)
No screening*	17.6919	246	NA	NA	NA	NA
Current UK NBSP	17.7095	654	£23,197	NA	£11,343	NA
Risk 1†	17.7119	694	£22,413	£16,689	£11,363	£11,565
Risk 2‡	17.7181	858	£23,435	£23,924	£11,425	£11,592
Masking§	17.7102	809	£30,772	£212,947	£15,065	£105,412
Risk 1 and masking‖	17.7124	870	£30,532	£75,254	£14,707	£33,199

ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; NA, not applicable; NBSP, national breast screening program; NICE, National Institute for Health and Care Excellence; VDG, Volpara Density Group.

* No mammography used in the population for screening purposes and all cancers would present with clinical signs or symptoms.

† Risk-based stratification with three strata as defined by a published risk algorithm [16] for 10-y risks of breast cancer and associated screening intervals: <3.5% with 3-yearly screening interval; 3.5%–8% with 2-yearly screening interval; >8% with annual screening interval.

‡ Risk-based stratification with three strata defined by dividing the population into thirds on the basis of risk (tertiles): lowest risk tertile with 3-yearly screening interval; middle tertile with 2-yearly screening interval; highest risk tertile with annual screening interval.

§ Current UK NBSP with supplemental ultrasound offered to women with high breast density. Women with both high breast density and high risk of breast cancer were offered supplemental MRI instead of ultrasound. High breast density was defined using VDG3 and VDG4 and high risk was defined as >8% 10-y risk of breast cancer on the basis of the NICE definition of high risk (30% lifetime risk ≈ 8% 10-y risk) [46].

‖ Risk-based stratification (with three strata as defined by a published risk algorithm [16] for 10-y risk of breast cancer and associated screening intervals: <3.5% with 3-yearly screening interval; 3.5%–8% with 2-yearly screening interval; >8% with annual screening interval) and current UK NBSP with supplemental ultrasound offered to women with high breast density. Women with both high breast density and high risk of breast cancer were offered supplemental MRI instead of ultrasound. High breast density was defined using VDG3 and VDG4 and high risk was defined as >8% 10-y risk of breast cancer.

time by inverting the survival function and use of a random number generator using Equation 11 (see Table 2):

$$T_c = \frac{-\log(U(0,1))}{\gamma}. \quad (11)$$

Fong et al. [31] presented data for women aged 50 to 65 years, including both screen-detected and interval cancers, and it was necessary to age-adjust these data for women older than 65 years. A further adjustment was made to account for lead time in screen-detected cancers by reversing the process of lead time bias correction as described in Duffy et al. [32] to introduce lead time for screen-detected cancers. Mortality from breast cancer for screen-detected cancers was, therefore, calculated from the simulated time the cancer would have presented clinically rather than the time of screen detection. Standard all-cause mortality was applied in the period between screen detection and clinical presentation. This adjustment implied that an assumption was made that there was no important short-term negative effect on mortality from treatment. It was further assumed that breast cancer did not affect survival beyond 10 years after clinical presentation (hazard rate returns to the population rate). Overall survival time post–breast cancer diagnosis (T_o) was calculated using Equation 12 (see Table 2):

$$\text{If } (T_m \le T_d),\ T_o = T_m,\quad \text{else } T_o = T_c + T_d. \quad (12)$$

Quality-Adjusted Life-Years

QALYs were used to capture the consequence of each screening program. In accordance with standard practice, life-years were adjusted for average health-related quality of life at a given age [33]. Estimates for these age-specific average utility weights were taken from the study by Ara and Brazier [34]. The multiplicative method was used to combine health state utility weights and age-specific average utility weights [33]. Utility weights were identified by updating a published systematic review for breast cancer health states [35]. An identical search strategy limited to the period January 2010 to October 2015 yielded 11 additional studies. Consistent with the suggestions made by Peasgood et al. [35], heterogeneity in the studies meant that meta-analysis of utility weights was inappropriate. Therefore, relevant utility weights were identified from studies that most closely represented the health states in the model structure. No studies were identified that defined breast cancer health states for specific NPI categories. Therefore, the selected utility weights (see Table 2) were taken from Lidgren et al. [36] and were used for early disease and advanced (distant metastases) disease, for the first year after diagnosis and subsequent years. These selected utility weights were assumed to also account for the impact of disutility from treatment, which is in keeping with the original source for these data.

Resource Use and Costs

In accordance with the assumed health care system perspective, resource use and associated costs accruing to the health services were used as model input parameters (see Table 2). Initial treatment and follow-up health care costs were included. Costs associated with treatment for breast cancer cases of DCIS, NPI categories 1 to 3, and advanced cancer were taken from published studies [15,24,37]. These estimates from 1992 were inflated to 2015 prices using the retail price index produced by the Office of National Statistics [38]. Supplementary imaging (US and MRI) costs were taken from the National Health Service schedule of reference costs (2013/2014) from the categories diagnostic whole breast ultrasound (no complications) and diagnostic breast MRI (no complications). Mammography costs were sourced from Madan et al. [15] and reflected estimates from a screening program. An estimate of the cost of administering risk and breast density–based stratification

was made on the basis of experience from the Predicting Risk of Cancer at Screening (PROCAS) study [5]. The average cost per woman was estimated as £10.57 (see Appendix 1 in Supplemental Materials for further details).

Data Analysis

The base-case analysis calculated the total costs and QALYs for a sample of 100 million women over a lifetime from the relevant age (in years) reflecting the start of each of the four specified stratified breast screening programs, current UK NBSP, and no screening. Appendix 5 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012 shows how using a sample of 100 million women should be sufficient to be confident that the model had sufficiently converged.

Incremental analysis was performed by comparing each stratified NBSP with 1) current NBSP and 2) no screening. In addition, a full incremental analysis was performed. All costs and QALYs were discounted at a rate of 3.5%.

One-way sensitivity analyses were used to explore the impact of selected input parameters (see Appendix 6 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012). In addition, the National Institute for Health and Care Excellence recommends that a relevant sensitivity analysis for interventions such as screening with long-term outcomes is to apply a 1.5% discount rate for health outcomes and a 3.5% discount rate for costs [39]. In common with previously published economic evaluations in screening, a no discounting scenario was also estimated. Probabilistic sensitivity analysis (PSA) [40] was performed to quantify the effect of the joint uncertainty (see Appendix 7 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.04.012) using a generalized additive model [41].

Results

Table 4 presents the results of the base-case analysis for a risk-based stratified NBSP (using risk 1 or risk 2), a masking-based stratified NBSP (masking), and a risk and masking–based stratified NBSP (risk 1 and masking). The risk 1 and risk 2 stratified NBSPs were relatively cost-effective when compared with the current UK NBSP. The masking stratified NBSP does not appear to be a cost-effective alternative when compared with the current UK NBSP. Using an alternative discounting rate of 3.5% for costs and 1.5% for benefits resulted in relatively lower estimated incremental cost-effectiveness ratios (ICERs) for all stratified NBSPs compared with the UK NBSP. When compared with no screening, all screening programs may be considered cost-effective. A full incremental analysis is available in Appendix 7 in Supplemental Materials. This shows that masking and risk 1 and masking were dominated by the next alternative (current NBSP and risk 1 stratified NBSP, respectively). The ICERs for the remaining comparisons were £23,197 per QALY for the current NBSP compared with no screening, £16,689 per QALY for risk 1 stratified NBSP compared with masking, and £26,749 for risk 2 stratified NBSP compared with masking and risk 1 stratified NBSP.

Sensitivity Analyses

To examine the decision between using the suggested stratified NBSP and the current UK NBSP, a cost-effectiveness acceptability curve is presented in Figure 1 using the results of the PSA. Figure 2 shows the associated cost-effectiveness acceptability frontier, which suggests that the current UK NBSP would be selected as the preferred program with a threshold of cost per QALY gained of less than £20,000 per QALY gained, whereas the risk 2 stratified NBSP would be chosen at higher thresholds of cost per QALY gained.

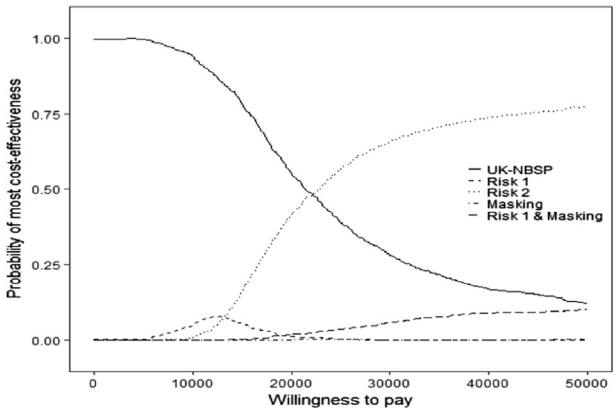

Fig. 1 – Cost-effectiveness acceptability curve for all stratified NBSPs and comparators. NBSP, national breast screening program.

One-way sensitivity analysis (see Appendix 6 in Supplemental Materials) showed that the reported total costs, total QALYs, and ICERs were sensitive to natural history parameter values (α_2 and mean tumor size at clinical detection) and screening performance of mammography (β_2). ICERs for stratified programs were moderately sensitive to the cost of stratification although costs would need to be several times the base-case value for ICERs to increase beyond a threshold of £30,000 per QALY. In all alternative programs, total costs were sensitive to the treatment cost parameters; varying these parameters, however, did not greatly change the ICERs compared with the base case. Estimates of total QALYs were sensitive to the utility weights for cancer states; varying utility weights moderately altered the ICERs of stratified programs compared with the NBSP. The results were relatively insensitive (within the ranges tested) to the probability of recall, costs of MRI, the relative sensitivity of mammography by VDG group, and US/MRI additional cancer detection rate.

Discussion

This study used an early model-based CEA to generate estimates of the relative costs and consequences of four exemplar stratified NBSPs compared with no screening and current practice in the UK NBSP. The risk 1 and risk 2 stratified NBSPs compared with the current UK NBSP were deemed to be cost-effective uses of health care resources relative to a threshold range of £20,000 to 30,000

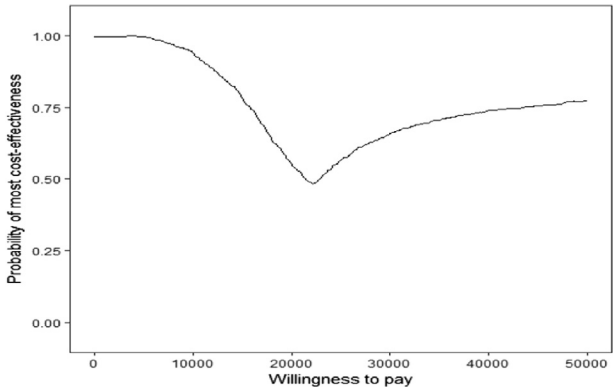

Fig. 2 – Cost-effectiveness acceptability frontier for all stratified NBSPs and comparators. NBSP, national breast screening program.

per QALY gained. The ICERs for the current UK NBSP compared with no screening were somewhat higher than previous analyses [15,42] but were very similar to the most recently published study [43]. Results were not directly comparable with previous model-based analyses of stratified screening [6,7] because of differences in modeling strategy and also in comparators.

The masking stratified NBSP was relatively the less cost-effective strategy. Combining the two stratification approaches using risk 1 and masking simultaneously resulted in modest QALY gain when compared with either risk 1 or masking stratified NBSP. The modest gains from masking-based strategies could be due to increased overdiagnosis overwhelming the potential QALY gains from early detection of a tumor. Overdiagnosis is a commonly cited problem with NBSP [1]. Overdiagnosis suggests that NBSPs are too effective at detecting small, and slow growing, tumors that would not affect a woman's health within her lifetime if left undetected. Follow-up procedures such as biopsies and treatment for such overdiagnosed cases are expensive and may cause harm [44].

The interpretation of the cost-effectiveness results for stratified breast screening was strongly influenced by the choice of discount rate. The choice of discount rate is not a simple technical question and the preferred discounting procedure for producing cost-effectiveness results for economic evaluations in health is a contested issue [39]. Decision makers should consider which discounting scenario best reflects the values and preferences of those for whom they are making a decision.

This early economic analysis was based on the best available data sourced from a combination of rapid reviews, systematic reviews, and analysis of data from two key published prospective studies [31,45]. Key data gaps were the relative sensitivity of mammography by density given the tumor size, the detection rate of supplemental ultrasound, and the recall rate and biopsy rate. Most importantly, the lack of randomized trials, or sufficiently long robust observational studies, meant that there were no direct estimates of the effect of supplemental screening modalities on mortality or other long-term outcomes. Robust, up-to-date data on the cost of treating women with breast cancer were not available. This meant that it was necessary to rely on estimates from a now-dated study for the cost of treatment stratified by a prognostic indicator [37]. In addition, on the advice of clinical experts, the implications of screening on use of different targeted treatment options for human epidermal receptor 2 or estrogen receptor status were not included in this model. These important uncertainties, because of the lack of robust data for several key parameters, suggest that the results of this model-based CEA should be treated as indicative. The focus should be on the model structure itself and on the identified key drivers of relative cost-effectiveness. The most important drivers of cost-effectiveness after the discount rate were the natural history parameters, cost of stratification, and mammographic sensitivity parameters. Future research should be directed at improving the robustness of these data. Some one-way sensitivity analysis results may appear inconsistent (US and MRI cancer detection rates) and this may be due to the Monte-Carlo error for alternatives in which the differences between strategies were small or the result of nonlinearity in the model.

Decision makers using the results of this DES model-based CEA must recognize the inherent limitations of mathematical models of disease natural history and screening that may introduce structural uncertainty. Using a DES was in line with published models in cancer screening [46]. DES allowed the influence of individual patient characteristics to be captured, the flexibility for cancer growth to be modeled as a continuous process, and the use of prognostic categories to group treatment options. It may be that modeling choices, such as how cancer growth rates can vary between individuals, were influential in driving the relative cost-effectiveness of a particular NBSP. No formal external validation or calibration of this early decision-analytic model was conducted. External validation against more extensive clinical trial or observational data should be a goal of any future investigation of the cost-effectiveness of stratified NBSP.

A key important assumption, in the absence of data to prove otherwise, was that the risk model used in the stratification process was perfectly calibrated to the population. This "structural" uncertainty is not reflected in the results of the PSA and therefore users must exercise judgment when interpreting the results. A further limitation to be aware of is that the use of regression models within a PSA is a new and developing methodology and therefore these results should perhaps be treated with some caution. Structural uncertainty may be best addressed by planning external validation studies in future research relating to all aspects of the economic model, including the risk models used in stratification and the natural history models of breast cancer. External validation studies of the risk model to be used in a stratified NBSP are essential if there is reason to believe calibration may be poor, which also requires consensus to be reached on the appropriate risk categories to use in practice. Previous experience in a research context suggests that embedding stratification in the existing NBSP is feasible [5], but no data exist on the effects of stratification on screening uptake and this is an important topic for further research.

Conclusions

This early model-based CEA presents indicative results that suggest that a risk stratified NBSP is potentially a cost-effective use of health care resources when compared with the current UK NBSP. The proposed model structure will be a key resource as more data become available to support the introduction of stratified NBSP such as the sensitivity and effectiveness of the new screening modalities, the effect of risk communication strategies on NBSP uptake, and the cost of newer treatments for breast cancer. The choice of discount rate will be crucial in interpreting the results. A prespecified external validation analysis should be conducted alongside any more definitive economic evaluation.

Acknowledgments

We thank the members of the ASSURE research team who contributed to the development of this analysis during useful discussions in project meetings.

Source of Financial Support: The ASSURE project was funded from a collaborative project grant within the FP7-HEALTH-2012-INNOVATION-1 call (project number: 306088).

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2017.04.012 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Marmot M, Altman D, Cameron D, et al. The Benefits and Harms of Breast Cancer Screening: An Independent Review. London: Cancer Research UK and the Department of Health (England), 2012.

[2] UK Government. Breast screening: programme overview. 2015: Available from: https://www.gov.uk/guidance/breast-screening-programme-overview#screeningage. [Accessed May 30, 2016].

[3] UK Government. Breast screening: age extension trial 2015: Available from: https://www.gov.uk/government/publications/nhs-breast-screening-age-extension-trial. [Accessed May 30, 2016].
[4] ASSURE. Personalised breast screening 2014: Available from: http://www.assure-project.eu/. [Accessed May 30, 2016].
[5] Evans DG, Astley S, Stavrinos P, et al. Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study. Southampton, UK: NIHR Journals Library, August 2016. Programme Grants for Applied Research.
[6] Tosteson ANA, Stout NK, Fryback DG, et al. Cost-effectiveness of digital mammography breast cancer screening. Ann Intern Med 2008;148:1.
[7] Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Ann Intern Med 2011;155:10–21.
[8] Van Dyck W, Gassull D, Vértes G, et al. Unlocking the value of personalised healthcare in Europe—breast cancer stratification. Health Policy Technol 2012;1:63–8.
[9] Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMC Med 2013;11:80.
[10] Annemans L, Genesté B, Jolain B. Early modelling for assessing health and economic outcomes of drug therapy. Value Health 2000;3:427–34.
[11] Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. J Health Serv Res Policy 1997;2:26–30.
[12] Roberts M, Russell LB, Paltiel AD, et al. Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. Med Decis Making 2012;32:678–89.
[13] Weedon-Fekjaer H, Lindqvist BH, Vatten LJ, et al. Breast cancer tumor growth estimated through mammography screening data. Breast Cancer Res 2008;10:R41.
[14] Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. Radiology 2004;230:29–41.
[15] 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 Health 2010;13:215–21.
[16] Patnick J. NHS Breast Screening Programme Annual Review 2012. London: National Health Service, 2012.
[17] Tice J, Ollendorf D, Lee J, Pearson S. The Comparative Clinical Effectiveness and Value of Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue. San Francisco, CA: California Technology Assessment Forum, 2013.
[18] Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23:1111–30.
[19] Office of National Statistics. Cancer Incidence and Mortality in the United Kingdom—2008–10. London: Office of National Statistics, 2012.
[20] Baker RD. Use of a mathematical model to evaluate breast cancer screening policy. Health Care Manag Sci 1998;1:103–13.
[21] Van Oortmarssen GJ, Habbema JDF, Van Der Maas PJ. A model for breast cancer screening. Cancer 1990;66:1601–12.
[22] Tan KHX, Simonella L, Wee HL, et al. Quantifying the natural history of breast cancer. Br J Cancer 2013;109:2035–43.
[23] Haybittle JL, Blamey RW, Elston CW, et al. A prognostic index in primary breast cancer. Br J Cancer 1982;45:361–6.
[24] Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham prognostic index in primary breast cancer. Breast Cancer Res Treat 1992;22:207–19.
[25] Kollias J, Murphy CA, Ellis IO, et al. The prognosis of small primary breast cancers. Eur J Cancer 1999;35:908–12.
[26] UK NHSBSP and ABS Screening Audit Group. NHS Breast Screening Programme and Association of Breast Surgery; An Audit of Screen Detected Breast Cancers for the Year of Screening April 2013 to March 2014. London: Public Health England, 2015.
[27] Bluekens AMJ, Holland R, Karssemeijer N, et al. Comparison of digital screening mammography and screen-film mammography in the early detection of clinically relevant cancers: a multicenter study. Radiology 2012;265:707–14.
[28] Sobin LH, Gospodarowicz MK, Wittekind Ch, International Union against Cancer. TNM Classification of Malignant Tumours. New York, NY: Wiley-Blackwell, 2009.
[29] Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. Thorax 2013;68:551–64.
[30] Office of National Statistics. United Kingdom, National Life Tables, 1980–82 to 2011–13. London: Office of National Statistics, 2014.
[31] Fong Y, Evans J, Brook D, et al. The Nottingham Prognostic Index: five- and ten-year data for all-cause survival within a screened population. Ann R Coll Surg Engl 2015;97:137–9.
[32] Duffy SW, Nagtegaal ID, Wallis M, et al. Correcting for lead time and length bias in estimating the effect of screen detection on cancer survival. Am J Epidemiol 2008;168:98–104.
[33] Ara R, Wailoo A, NICE DSU. Technical Support Document 12: the use of health state utility values in decision models. 2011:1–30.
[34] Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health 2011;14:539–45.
[35] Peasgood T, Ward SE, Brazier J. Health-state utility values in breast cancer. Expert Rev Pharmacoecon Outcomes Res 2010;10:553–66.
[36] Lidgren M, Wilking N, Jönsson B, Rehnberg C. Health related quality of life in different states of breast cancer. Qual Life Res 2007;16:1073–81.
[37] Johnston K. Modelling the future costs of breast screening. Eur J Cancer 2001;37:1752–8.
[38] Office of National Statistics. Consumer Price Indices—RPI Indices: 1987 to 2015. London: Office of National Statistics, 2015.
[39] Jonsson P, Robertson J. Briefing paper for methods review working party on discounting. London: National Institute for Health and Care Excellence, 2013.
[40] Claxton K, Sculpher M, McCabe C, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ 2005;14:339–47.
[41] Strong M, Oakley JE, Brennan A. Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach. Med Decis Making 2014;34:311–26.
[42] Forrest P. Breast Cancer Screening: Report to Health Ministers of England, Wales, Scotland and Northern Ireland. London: HMSO, 1986.
[43] Pharoah PDP, Sewell B, Fitzsimmons D, Bennett HS. Cost effectiveness of the NHS breast screening programme: life table model. BMJ 2013;346: f2618.
[44] Brentnall AR, Harkness EF, Astley SM, Donnelly LS, Stavrinos P, Sampson S, Fox L, Sergeant JC, Harvie MN, Wilson M, Beetles U. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. Breast Cancer Research 2015 Dec 1;17(1):147.
[45] Evans DGR, Donnelly LS, Harkness EF, et al. Breast cancer risk feedback to women in the UK NHS breast screening population. Br J Cancer 2016;114:1045–52.
[46] Pilgrim H, Tappenden P, Chilcott J, et al. The costs and benefits of bowel cancer service developments using discrete event simulation. J Oper Res Soc 2008;60:1305–14.