Siegfrids *et al. Health Economics Review* (2025) 15:35
https://doi.org/10.1186/s13561-025-00628-5

Health Economics Review

RESEARCH Open Access

Cost-effectiveness of expanding the target population of biennial screening for breast cancer from ages 50–69 to 45 and/or 74: A cohort modelling study in the Finnish setting

Filip Siegfrids[1*], Sirpa Heinävaara[1], Tytti Sarkeala[1], Laura Niinikoski[1] and Juha Laine[2]

Abstract

Background Within Finland's breast cancer screening program, all women aged 50–69 are invited to biennial screening. Current European guidelines recommend screening in ages 45–49 and 70–74 conditional upon, inter alia, demonstrated context-specific cost-effectiveness. This study aims to determine the cost-effectiveness of expanding the target population of biennial screening to ages 45 and/or 74, compared to the current national breast cancer screening strategy, in the Finnish setting.

Methods Screening strategies' costs and quality-adjusted life years (QALY), aggregated over a lifetime horizon for the population simulated through a decision-analytic model, allow for comparison through incremental cost-effectiveness ratios. The model, using a Markov cohort simulation approach, was adapted to the cancer stage classification system used by the Finnish Cancer Registry (FCR) and calibrated to observed metrics in the Finnish female population. The analysis was conducted from a limited societal perspective, using a discount rate of 3% for costs and outcomes. Sensitivity analyses were performed to assess decision uncertainty, using an implicit willingness-to-pay (WTP) threshold range of €25 000–50 000 per incremental QALY.

Results Compared to the current national screening strategy, both strategies with a starting age of 45 were cost-effective at the WTP-threshold of €50 000 per incremental QALY. Biennial screening in ages 45–69 was also cost-effective at €25 000 per QALY and demonstrated the highest probability of cost-effectiveness of all screening strategies over the whole WTP-threshold range of €25 000–50 000 per QALY. Biennial screening in ages 50–74 was dominated by all strategies over the threshold range.

Conclusions Expanding the national screening strategy target population age is likely to produce net health benefits to acceptable costs, insofar as women aged 45–49 are covered by the expansion. Only expanding the target population to age 74 is unlikely to be cost-effective, given a WTP-threshold range of €25 000–50 000 per incremental QALY.

Keywords Cost-effectiveness, Breast cancer, Screening, Finland

*Correspondence:
Filip Siegfrids
filip.siegfrids@cancer.fi
[1]Finnish Cancer Registry, Mäkelänkatu 2, Helsinki 00500, Finland
[2]InFLAMES, University of Turku, Turku FI-20014, Finland

Introduction

For the female population of Europe, breast cancer is the leading cause of cancer incidence and mortality [1, 2]. Today, most European countries offer population-based biennial screening for the age group of 50–69, while some also offer it to younger and older women by different intervals. Countries also differ with respect to invitational coverage, screening participation and the role of opportunistic screening which, in most of Europe, coexists with the national screening program [3].

Finland implemented screening for breast cancer on a national level in 1992, initially inviting all women aged 50–59 on a biennial basis [4]. During the gradual implementation period up until its latest expansion to women aged 60–69, initiated in 2007, the national screening program is estimated to have decreased breast cancer mortality in Finland by a third [5]. However, the benefit of screening in terms of reduced breast cancer mortality is counterbalanced by the adverse effects on participants' Health-Related Quality of Life (HRQoL) it introduces, mainly due to false-positive tests and overdiagnosis [6, 7]. Furthermore, the relative benefit of early detection diminishes as breast cancer treatment improves over time [8].

As decisions on screening strategies of publicly funded screening programs are essentially taken on behalf of individuals who bear some or all its cost but realize only some or none of its benefits, strategies also need to prove sustainability and affordability, often expressed in terms of cost-effectiveness [9]. A screening strategy is considered cost-effective when expected to produce an incremental unit of health benefits in terms of length and quality of life, either to lower, equal or acceptably higher costs compared to another strategy [10]. Despite its associated adverse effects and recent improvements in treatment, screening can still offset some disutility associated with late-stage breast cancer treatment while improving life expectancy, as suggested by multiple studies demonstrating positive incremental cost-effectiveness ratios (ICER) of screening [11].

European Commission guidelines on breast cancer screening and diagnosis, having strongly advocated for biennial screening in ages 50–69 since 2016, currently feature conditional recommendations on screening for breast cancer in ages 45–49 and 70–74 [12]. The conditional recommendations prioritize research into context-specific cost-effectiveness of screening in these age groups [12]. To this background, this study aims to assess the cost-effectiveness of biennial screening in ages 45–49 and/or 70–74, as an expansion of the target population of the national breast cancer screening strategy, in the Finnish context.

Materials and methods

Screening pathway of the National screening program for breast cancer

In Finland, all women aged 50–69 are personally invited to attend the organized, nationwide breast cancer screening program free of charge every two years, using mammography as the primary method of screening. In case of abnormal results, the patient is called in for follow-up examinations and any possible treatments through the program [13].

Model structure and assumptions

The cost-effectiveness of the screening strategies is estimated through a decision-analytic model, adapting a Markov cohort simulation process, in which screening strategies are superimposed onto a natural history model. This stage-shift approach operates through interruption of the natural progression of breast cancer through early detection of tumors, offsetting costs and morbidity associated with more advanced breast cancer, as well as improving survival prospects of the diagnosed population. Each strategy's costs and utilities are recorded and aggregated over a lifetime horizon (up to 100 years) for the population cohort simulated through the model, allowing for comparison of the strategies' ICERs.

The model structure is illustrated in Fig. 1. Otherwise similar to the model in Rojnik et al. [14], the model structure is adapted to the cancer stage classification system used by the Finnish Cancer Registry (FCR), including invasive localized and non-localized breast cancer, as well as non-invasive ductal carcinoma in situ (DCIS). The latter is separated into a progressive and a non-progressive health state, allowing DCIS to progress and not to progress into invasive breast cancer. Both non-invasive health states are assumed to be limited to detection through screening only. Invasive breast cancer, on the other hand, can be detected either through screening in the preclinical phase or clinically upon turning symptomatic. The simulated cohort starts at 40 years of age in the disease-free health state, defined as either absence of breast cancer or presence of screening-detectable non-progressive localized breast cancer. The latter is only related to modelling overdiagnosis of screening. A false positive screening result is only possible in the disease-free health state, as all screening detected tumors in the preclinical phase are considered true-positive. State transitions occur according to the model structure within the cycle length of a calendar year, with the possibility to pass through one or more health states within a single cycle, unless identified through screening. Death from other causes than breast cancer can occur in the disease-free and preclinical phases, as well as in the health state of non-progressive DCIS recovery. Upon breast cancer diagnosis,

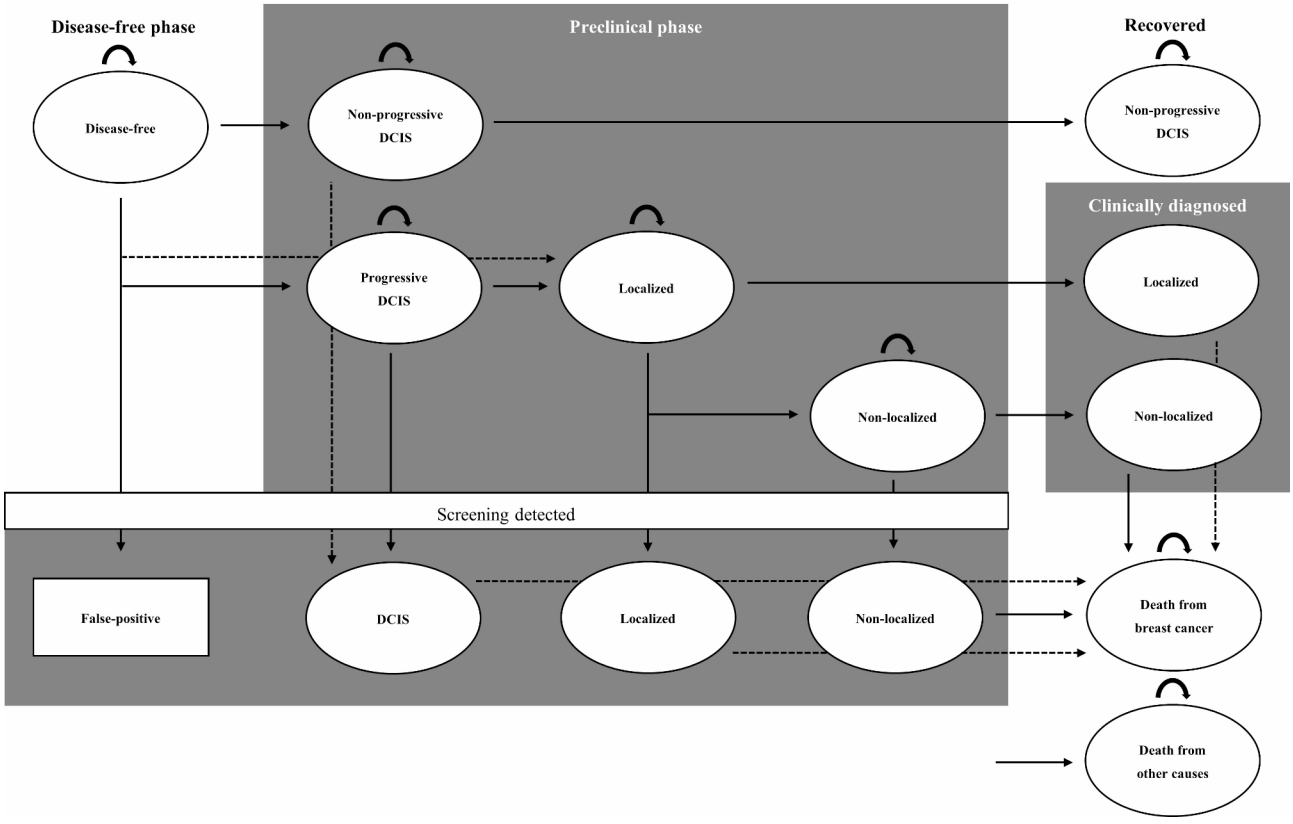

Fig. 1 Markov cohort-based model structure. Health states are represented by elliptical shapes. Straight arrows represent transition possibilities through model health states, while curved arrows represent the possibility to stay in a health state. Dashed arrows are used when the arrow is interrupted by an elliptical shape representing another health state

one is assigned to treatment followed by surveillance and, eventually, death.

Input parameters

Natural history parameters

Natural history parameters are based on published estimates and calibrated, in a stepwise manner according to age, to observed incidence rates, accounting for biennial screening in ages 50–69. Due to different assumptions used in the studies informing the underlying incidence parameters for localized invasive breast cancer and progressive DCIS, they were adjusted downwards according to the proportion of invasive cancers preceded by progressive DCIS. See Additional file 1 for further details on the synthetization of parameter inputs.

In lack of suitable estimates, the natural history parameters for ages 70 and over relied entirely on calibrated estimates for younger ages, which set the boundaries for calibration input parameters for this age group. Input parameters guiding the underlying incidence rate were assigned lower bound measures of variation equal to the calibrated point estimates of the corresponding parameters for ages 60–69. Due to its inconsistent variation with age in other age groups, the lower bound for the transition rate from progressive DCIS to preclinical invasive breast cancer was derived the same way. To sufficiently allow for the underlying incidence to increase with age, the parameters were assigned upper bound measures of variation equal to the corresponding parameters' calibrated point estimates multiplied by a factor of 2. Other transition probabilities for ages ≥ 70 were assigned upper bounds equal to the calibrated point estimates of corresponding parameter for ages 60–69 and lower bounds equal to the same value multiplied by a factor of 0.5, reflecting the observed decreasing rate of tumor progression with age. Please see Table 1, Additional file 1 for natural history parameter calibration inputs.

Screening accuracy parameters

Screening accuracy parameters, following the same age stratification as the natural history parameters, are based on published estimates insofar as appropriate estimates were found. For ages 50–69, screening sensitivity parameters for in situ and invasive breast cancer, respectively, were calibrated alongside the natural history parameters against observed detection rates and stage distributions [15]. Invasive breast cancer screening specificity parameters for the same age group, were calibrated separately

Table 1 Calibrated screening parameter validation against observed detection rates, positive predictive values (PPV) and stage distributions

AGE:	**50–59**			**60–69**		
Detection rate	DCIS	BC		DCIS	BC	
Target [a] (CI 95%) [b]	0.59 (0.47–0.72)	3.96 (3.65–4.29)		0.86 (0.72–1.02)	6.79 (6.38–7.22)	
Model [a]	0.63	3.98		0.95	6.55	
PPV	DCIS + BC			DCIS + BC		
Target (%) (CI 95%) [b]	14.3 (13.3–15.4)			31.3 (29.5–33.2)		
Model (%)	14.5			32.4		
Stage distribution	DCIS	BC local	BC non-local	DCIS	BC local	BC non-local
Target (%) (CI 95%) [b]	9.6 (7.8–11.6)	57.4 (52.9–62.1)	33.1 (29.7–36.7)	11.3 (9.5–13.3)	60.5 (56.3–65.0)	28.2 (25.3–31.3)
Model (%)	9.1	59.0	31.9	10.1	63.7	26.2

CI confidence interval, *DCIS* ductal carcinoma in situ, *BC* breast cancer, *BC local* localized breast cancer, *BC non-local* non-localized breast cancer

[a] Per 1 000 screens

[b] Target 95% CI's were approximated by Poisson rate confidence intervals [19]

Table 2 Discounted individual outcomes and ICERs of expanded strategies compared to current strategy

Target pop. age	**50–69**		**45–69**		**50–74**		**45–74**	
Perspective	Lim.Soc.	HC	Lim.Soc.	HC	Lim.Soc.	HC	Lim.Soc.	HC
Costs (€)	4 301	3 347	4 387	3 416	4 382	3 413	4 467	3 481
QALYs	21.855		21.860		21.857		21.861	
LYG	24.027		24.032		24.029		24.034	
ICER (€ per incremental QALY)			**20 509**	**16 460**	**58 191**	**47 108**	**29 893**	**24 093**

pop. population, *Lim.Soc.* limited societal, *HC* healthcare, *LYG* life years gained, *QALYs* quality-adjusted life years, *ICER* incremental cost-effectiveness ratio

against positive predictive values (PPV) observed within the national screening program [15]. Based on observed participation within the national screening program in 2019 [16], screening participation was set at 81% for ages 45–59 and 82% for ages 60–74.

Where invasive breast cancer screening parameters' measures of variation were not available, upper and lower bounds were set equal to the deterministic values or calibrated point estimates of corresponding parameters for older and younger age groups, respectively, reflecting the pattern of increasing sensitivity and specificity with age. More specifically, unknown parameter upper bounds for ages 45–49 were set equal to deterministic parameter values for ages 50–59, whereas unknown parameter lower bounds were based on best assumptions. For ages over 59, unknown parameter lower bounds were set equal to the calibrated parameter point estimates of the closest younger age group, whereas unknown parameter upper bounds were assumed to be 1. The deterministic value of DCIS sensitivity parameters were assumed to be 15% higher than that of invasive breast cancer for the same age group, following [17]. In lack of better evidence, DCIS specificity was assumed equal to that of invasive breast cancer. Please see Table 2, Additional file 1 for screening parameter calibration inputs.

The best fit set of calibrated parameters was identified through random search, as the one minimizing the deviation between model predictions and calibration targets, from 10 000 iterations per age group. Figure 2 shows the 10 best fit calibrated natural history and screening sensitivity parameters sets, plotted against the 95% confidence interval (CI) of the observed breast cancer incidence rate in 2021 [18]. Calibrated screening parameter point estimates, validated against observed metrics, are presented in Table 1.

Overdiagnosis is defined, for the purpose of this analysis, as screening detected DCIS on one hand and invasive breast cancer on the other, that in the absence of screening never naturally would progress into invasive breast cancer or turn symptomatic over the course of one's lifetime, respectively. Hence, non-progressive DCIS detected by screening is, by definition, a case of overdiagnosis. Overdiagnosis of invasive breast cancer is modelled as a proportion of all screening detected localized tumors within the target population age group, adjusted to produce an overdiagnosis rate of 10% from a population perspective, following Zackrisson et al. [20]. The overdiagnosis rate was calculated as a proportion of all screening detected invasive tumors. This approach was further validated by comparing the difference in modelled cumulative incidence rates when removing the screening effect, against published cumulative incidence differences of 7% between screened and estimated unscreened cohorts of women aged 50–59 in Finland

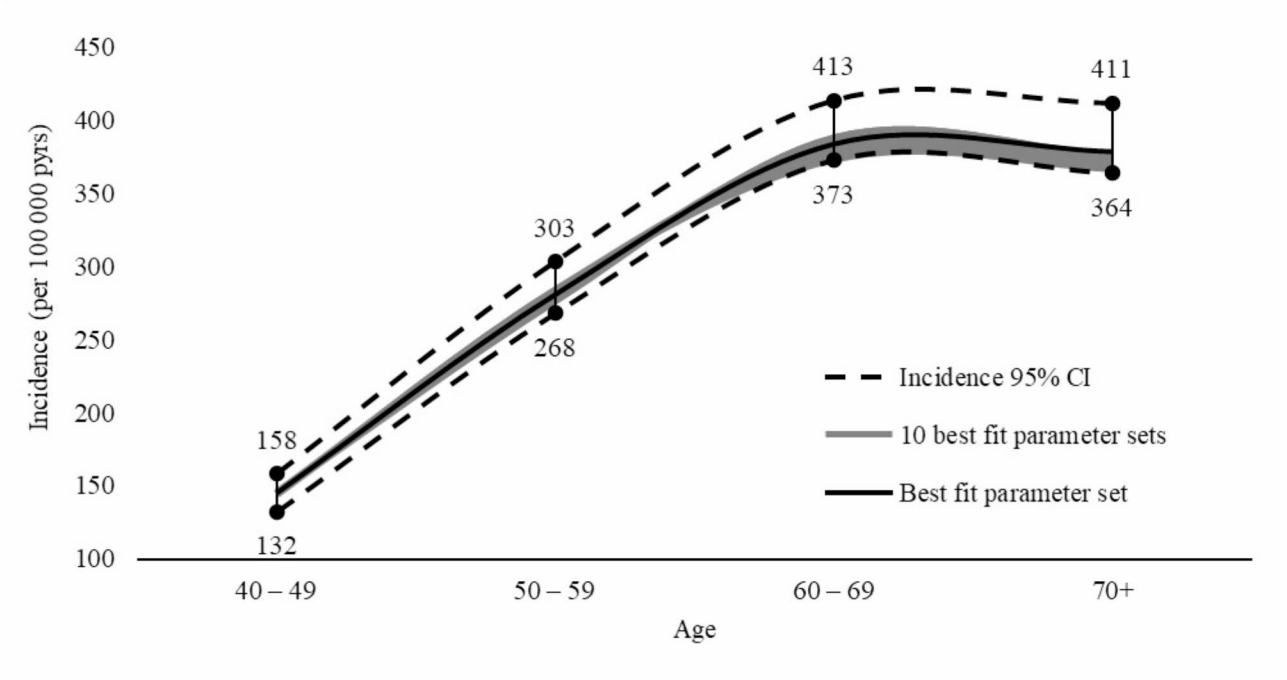

Fig. 2 Natural history and screening sensitivity parameter goodness of fit of the 10 best fit calibrated parameter sets, plotted against the 2021 observed breast cancer incidence rate 95% CI. The age-specific confidence intervals were approximated by Poisson rate confidence intervals [19]

[21]. In lack of better evidence, the model assumed overdiagnosis to be constant across age groups.

Survival parameters

Every cycle, the disease-free and undiagnosed simulated population runs an age-specific risk of baseline death, based on FCR estimated all-cause survival rates. The population diagnosed with DCIS follows baseline survival, while the invasive breast cancer population follows survival specifications according to cancer stage and age at diagnosis. The non-localized breast cancer diagnosed population is separated into lymph node positive (LN+) and metastasized breast cancer according to observed age-specific stage distributions [22].

Invasive breast cancer survival functions were estimated by fitting parametric models to observed breast cancer survival. The empirical survival data is based on FCR estimated age- and stage specific relative risks for Finnish women with a maximum follow-up of 25 years [15]. Based on best fit to observed survival, according to Akaike's Information Criteria and Bayesian Information Criterion as well as visual fit, Weibull and log-logistic distributions were parameterized to annual survival probabilities up until 25 years since diagnosis, followed by baseline survival. Please see Fig. 1, Additional file 2 for estimated age- and stage specific survival functions plotted against empirical survival.

Cost and utility parameters

Cost parameters follow a limited societal perspective including direct healthcare and non-healthcare costs, informal care costs and productivity loss. Direct healthcare costs include age- and stage specific treatment costs, as well as screening costs related to primary screening and diagnostic follow-up examination. Direct non-healthcare costs consist of transportation costs, indirect healthcare costs of informal care costs and indirect non-healthcare costs of productivity loss, associated with screening and different phases of surveillance following diagnosis. Direct healthcare treatment costs used in the model, estimated as annual costs for the first year after diagnosis, the last year before death and the time in between [22], are applied as such. All direct screening related costs were applied as a one-off cost per screening round for participants. Treatment related costs of transportation, informal care and productivity loss were estimated for periods of six months for primary treatment (< 6 months from diagnosis), rehabilitation (6–18 months from diagnosis), remission (> 18 months from diagnosis) and metastatic breast cancer [23]. Furthermore, palliative care (i.e., end-of-life care after termination of metastatic breast cancer treatment) related costs of informal care and productivity loss were estimated for an approx. two-month period [24]. All costs except for direct healthcare treatment costs were converted to annual costs, after which all costs were converted to 2024 price levels using official consumer price indices [25]. Please see Tables 1,

2, 3, 4 and 5, Additional file 3 for more details on all cost parameters.

Utility parameters include baseline population HRQoL, utility associated with breast cancer treatment and different phases of surveillance following diagnosis, as well as disutility experienced from screening follow-up examinations. Treatment related utility was estimated for six month periods for primary treatment (< 6 months from diagnosis), recovery (6–18 months from diagnosis), remission (> 18 months from diagnosis), metastatic breast cancer and palliative care [26], and were converted to annual utilities. Because treatment and screening related utility parameters are not specific to age, baseline HRQoL is also modelled as constant across age groups. Disutility from diagnostic follow-up applies only when confirmatory biopsy is required which, on average within the Finnish breast cancer screening program in 2019, was approximately a third of the time [16]. This proportion applies to the whole screening detected modelled population regardless of age. Please see Table 6, Additional file 3 for more details on utility parameters.

Costs and utilities are both discounted at 3%, following the national Pharmaceutical Pricing Board instructions for reimbursement status applications [27]. To account for the asymmetrical distribution of the timing of events within a model cycle [27, 28], all discounted outcomes were half-cycle corrected.

Sensitivity analysis

In order to assess decision uncertainty due to imperfect information on model parameters, deterministic and probabilistic sensitivity analyses were performed. The impact of adjusting the overdiagnosis rate on the ICER of expanded screening strategies, compared to the current national strategy, was explored through deterministic sensitivity analysis.

For the purpose of probabilistic sensitivity analysis (PSA), all calibrated parameters, including stage distributions for non-localized breast cancer between LN + and metastatic tumors, were assigned beta and Dirichlet distributions based on the nature of the data informing them, for which alpha and beta parameters were estimated with a standard error of 0.05. Cost and utility estimates, for which no measures of variation were reported, were assigned gamma and beta distributions, respectively, with a standard error of 0.2 to allow for sufficient parameter variation in assessing decision uncertainty. The proportions of over diagnosed screening detected localized cancers and confirmatory biopsy needed in diagnostic follow-up examination were assigned beta distributions with a standard error of 0.2. The uncertainty of invasive breast cancer survival parameters was reflected in the PSA by Cholesky decomposition of the variance-covariance matrix for fitted parametric distributions.

All strategies' net monetary benefits (NMB) and expanded strategies' ICERs compared to the current national screening strategy, associated with each iteration of a total of 1 000, were estimated through Monte-Carlo simulation. Simulated ICERs are plotted on a cost-effectiveness plane (CE-plane) to display the uncertainty surrounding its true value, against fixed WTP-thresholds. The expanded strategies' respective probability to be cost-effective, at a given threshold, can be calculated as the proportion of times over all iterations they record the highest NMB of all strategies. The probability of cost-effectiveness over a range of WTP-thresholds are presented with cost-effectiveness acceptability curves (CEAC). Furthermore, to identify drivers of decision uncertainty, value of information analysis was conducted for all intervention strategies. Expected Value of Partially Perfect Information (EVPPI) was estimated for groups of model parameters based on uploaded PSA outputs to the University of Sheffield Accelerated Value of Information (SAVI) online application, using nonparametric methods according to Strong, Oakley and Brennan [29].

Results

Deterministic analysis

Table 2 shows all strategies' accumulated discounted individual (i.e., per capita) costs, life years and quality-adjusted life years (QALY) over the lifetime of a simulated population of 100 000, using model parameters' deterministic values. All expanded strategies produced more life years and QALYs to higher costs, compared to the current national screening strategy. In other words, none of the strategies strictly dominated the current national screening strategy (i.e., produced more QALYs to lower or the same cost). Neither were any of the intervention strategies strongly dominated by another (i.e., produced less QALYs to higher or the same cost). From a healthcare perspective, all expanded strategies have ICERs below or within the WTP-threshold range of €25 000–50 000 per incremental QALY, however, only screening strategies with a starting age of 45 produced ICERs within or below the threshold range also from the limited societal perspective. The ICER of the strategy covering ages 45–69 falls below the lower limit WTP-threshold of €25 000 per QALY by a margin of €4 491, while that of the strategy covering ages 45–74 exceeds it by €4 893. The discounted ICER of the strategy covering ages 50–74 is notably higher than that of the strategies with a starting age of 45, exceeding the upper limit WTP-threshold of €50 000 per QALY by €8 191.

To assess the impact of the uncertainty surrounding overdiagnosis on strategies' discounted ICERs, deterministic overdiagnosis rates of invasive cancers were adjusted according to Fig. 3. The greatest impact was observed for the strategy covering ages 50–74, especially when

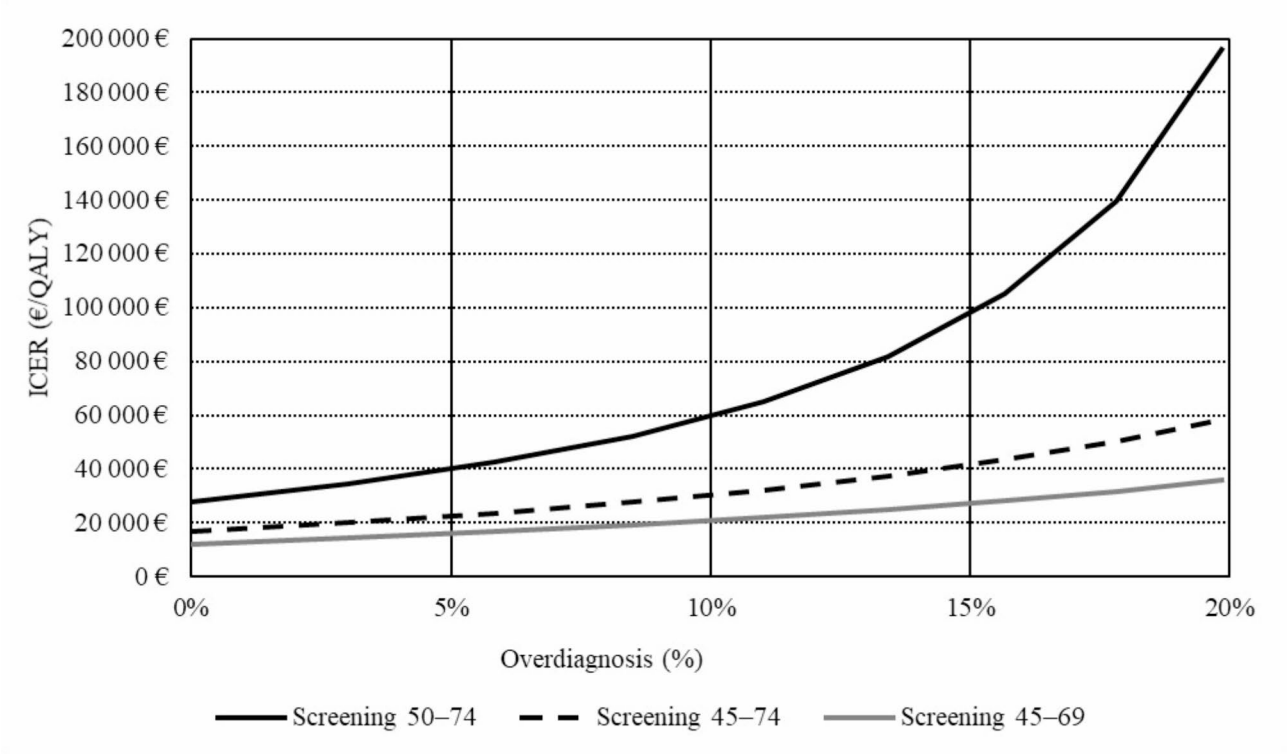

Fig. 3 Deterministic sensitivity analysis on the impact of overdiagnosis on expanded strategies' incremental cost-effectiveness ratio (ICER) compared to the current national screening strategy

increasing it from baseline at around 10% which raised the ICER to €200 000 per QALY at 20%. The impact of adjusting the overdiagnosis rate on the ICERs of the strategies expanding screening to age 45 was moderate in comparison.

Probabilistic analysis

The dispersion of data points on the CE-plane displayed in Fig. 4, representing simulated ICERs of expanded strategies compared to the current national screening strategy, reflects the impact of parameter uncertainty on accumulated discounted outcomes. Most iterations are in the north-east quadrant of the CE-plane, representing positive incremental QALYs to higher costs, while some iterations are in the north-west quadrant representing negative incremental QALYs to higher costs. The dispersion of ICERs for the most extensive strategy covering ages 45–74 is clearly more north-east oriented than the others, suggesting relatively higher incremental QALYs to higher costs. Most of the ICERs in the north-west quadrant are produced by the strategy covering ages 50–74, suggesting low return to resources of screening in ages 70–74 in terms of health-related quality of life.

The CEACs illustrated in Fig. 5 are drawn against a range of WTP-thresholds between €0 and €75 000, to sufficiently demonstrate their respective probability of cost-effectiveness at specific thresholds. Up until the WTP-threshold of around €20 000 per QALY, the current national screening strategy has a higher probability of cost-effectiveness (i.e., a higher average NMB over simulated iterations) than all expanded strategies, after which it is exceeded by the strategy covering ages 45–69. The latter, in turn, peaks between a WTP-threshold of €30 000–€35 000 per QALY, after which it decreases and is exceeded by the strategy covering ages 45–74 around a WTP-threshold of €58 000 per QALY. The probability of cost-effectiveness of the strategy covering ages 50–74 peaks around the lower limit WTP-threshold of €25 000 per QALY but remains below 10% over all thresholds considered.

Figure 6 shows the EVPPI of model parameters, estimated with the lower limit WTP-threshold of €25 000 per QALY, grouped into parameter sets of natural history, screening accuracy, utility and direct healthcare-, transportation-, informal- and productivity costs. Parameters on direct healthcare costs, natural history and productivity loss are associated with the highest rate of return to research, meaning that collecting more evidence informing these parameters would have a greater impact on reducing decision uncertainty compared to other model parameters.

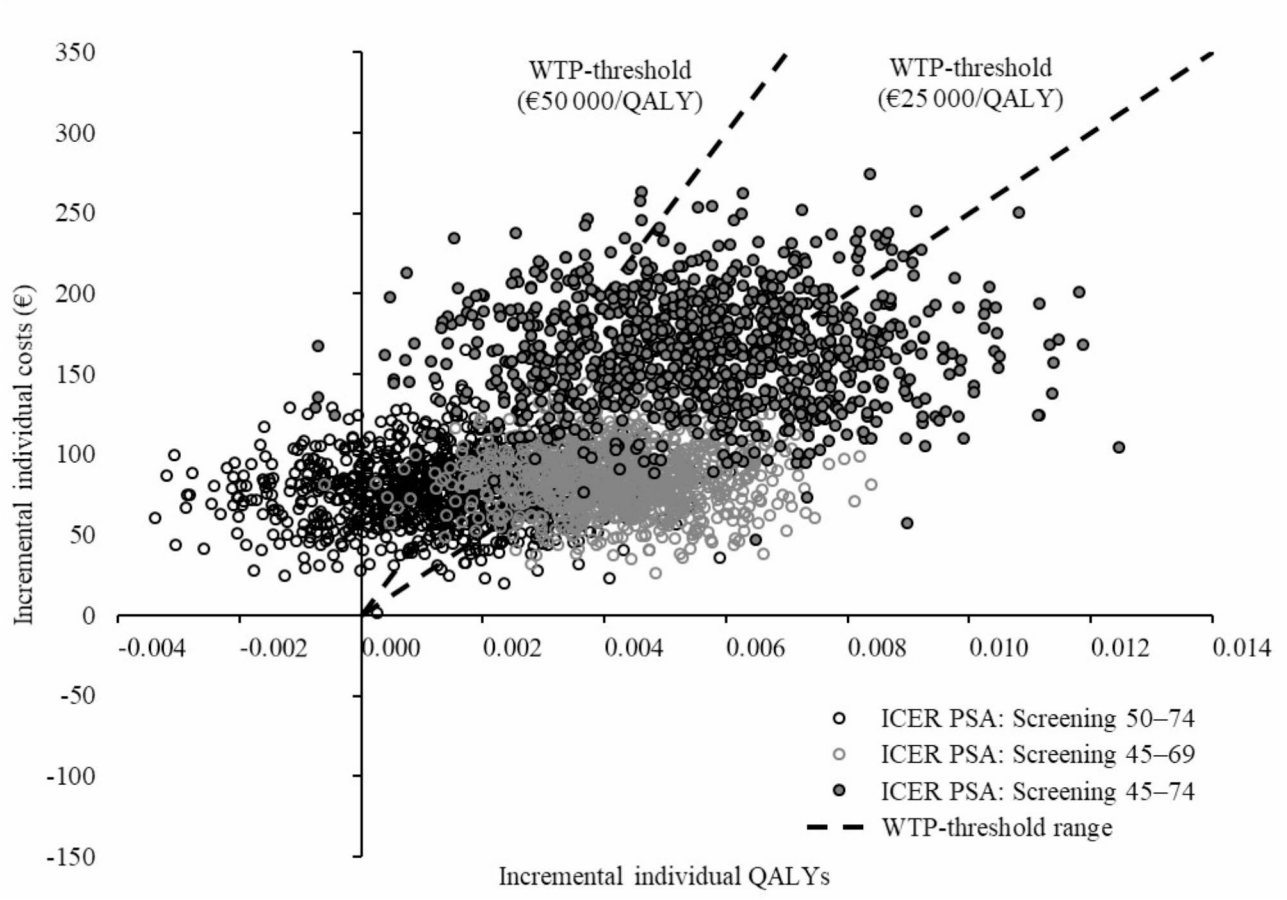

Fig. 4 Cost-effectiveness plane for expanded strategies compared to the current national screening strategy. Incremental cost-effectiveness ratios (ICER) in the north-east quadrant below or between the diagonal lines representing the willingness-to-pay (WTP) threshold range of €25 000–€50 000 per quality-adjusted life year (QALY) are considered cost-effective

Discussion

According to the results, from a healthcare perspective, all expanded screening strategies are cost-effective at the WTP-threshold of €50 000 per incremental QALY, whereas only strategies expanding screening to age 45 show cost-effectiveness also from the limited societal perspective. An expansion of the national breast cancer screening program target population only to age 45 is also cost-effective at the WTP-threshold of €25 000 per QALY and has a higher probability of cost-effectiveness than other strategies over the WTP-thresholds range of €25 000–50 000 per QALY. At a WTP-threshold of around €58 000 per QALY, the decision on the optimal screening strategy changes in favor of the strategy covering ages 50–74. The strategy covering ages 50–74 is dominated by both screening strategies expanding screening to ages 45 over all thresholds considered, as well as by the current national screening strategy up until a WTP-threshold of approximately €55 000 per QALY, where the probability of cost-effectiveness is below 1% for both strategies. In other words, at a threshold range of €25 000–50 000 per QALY, expanding the national breast cancer screening program target population only to age 45 is very likely to be cost-effective, compared to the current national screening strategy. Expanding the target population only to age 74 is unlikely to be cost-effective, while simultaneously expanding to age 45 remarkably increases the probability of cost-effectiveness.

The choice on perspectives adapted for this analysis are based on Finnish health technology assessment (HTA) guidelines [27], stating that "The calculation of costs must include, irrespective of the payer, all direct health care and comparable social welfare costs related to the therapies that are being compared", including direct healthcare and non-healthcare costs on one hand, and losses of productivity due to patient's premature death or reduced work ability as well as losses of time and/or productivity for informal caregivers on the other. A cost-effectiveness analysis accounting for these cost components is best comparable to one adapting a limited societal perspective as defined by Kim et al. [30]. In addition to a limited societal perspective, the Finnish HTA guidelines also recommend presenting results based on healthcare costs only.

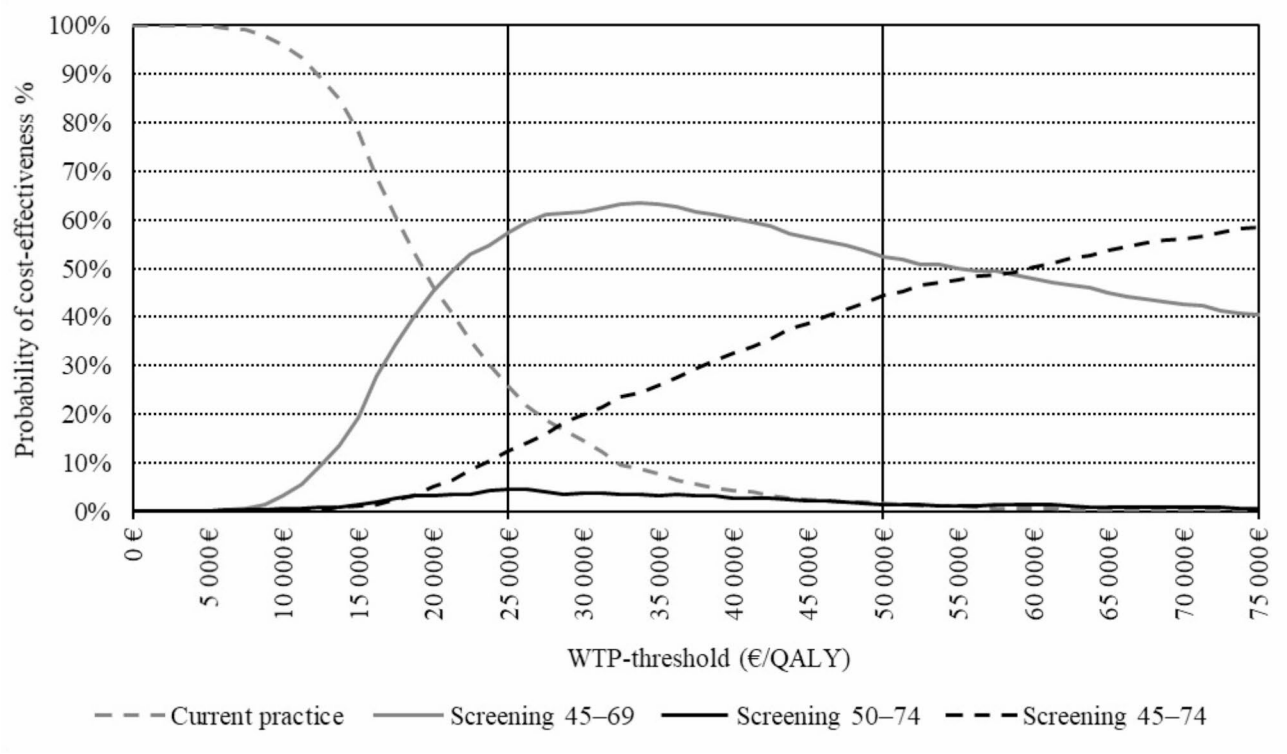

Fig. 5 Cost-effectiveness acceptability curves (CEAC) for all strategies based on highest net monetary benefits at each willingness-to-pay (WTP) threshold. CEACs appearing to the left of or in between the vertical lines representing the WTP-threshold range of €25 000–€50 000 per quality-adjusted life year (QALY) are considered cost-effective with a probability corresponding to the relevant WTP-threshold

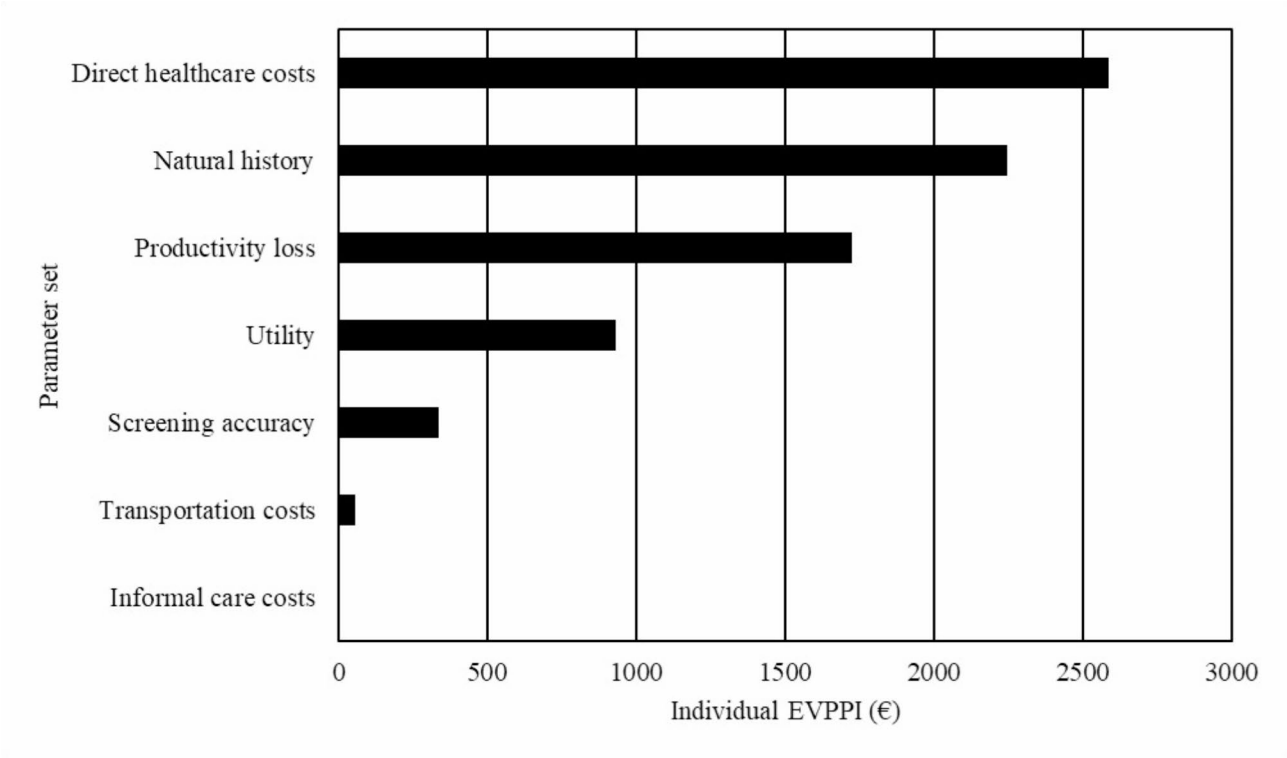

Fig. 6 Expected Value of Partially Perfect Information (EVPPI) for selected parameter groups using a WTP-threshold of €25 000 per QALY

The WTP-threshold range chosen for this analysis was far from straightforward, as no official guidelines on thresholds to be used for health economic evaluations in the Finnish context exist [31]. The World Health Organization recommends a WTP-threshold of between one and three times the GDP per capita per QALY [32]. In 2020, twice the GDP per capita in Finland was around €80 000 [33]. Compared to this, the often-cited National Institute of Health Excellence (NICE) WTP-threshold recommendations, currently set at GBP 20 000–30 000 per QALY [34], which corresponds to roughly €24 000–36 000 using 2020–2022 Finnish and UK purchasing power parities [35], is rather conservative [36]. A threshold of €50 000/QALY is recurringly cited [31], however, the literature does not support its position as common practice in Finland. To the background of the ambiguity surrounding the WTP-threshold in the Finnish context, a threshold range of €25 000–50 000 was deemed adequate to reflect the Finnish population's willingness to pay for an incremental QALY.

Strengths

The structure of the model, in which a population is simulated through the natural history of breast cancer, reflecting the stage classification of the FCR, allows for assessment of costs and outcomes associated with alternative screening strategies in the Finnish setting. Furthermore, the survival parameters of the model were based on survival data on Finnish women with a stage stratification matching the model structure, with a follow-up of up to 25 years, providing a solid basis for survival analysis. Calibration of natural history and screening accuracy parameters improves the credibility of uncertain and unknown parameters, generating estimates in line with age-specific observed incidence and stage distributions relevant to the modelled population. Including screening sensitivity parameters in the calibration process also prevents over- and underestimation of screening detected tumors, while calibrating screening specificity parameters ensures consistency between modelled and observed false-positive rates.

The state values (i.e., costs and utilities) associated with each modelled health state were highly relevant for the population setting for which the screening strategies were evaluated, considering all major components associated with the limited societal perspective as recommended in national guidelines. This enabled expected costs and outcomes of breast cancer screening in the Finnish setting, over an appropriate time horizon, to be evaluated within the framework of a cost-utility analysis. This study is the first of its kind conducted for the Finnish setting, in a time when population-based health interventions, in general, are increasingly being scrutinized to their cost-effectiveness and budget impact. Assessing the optimal strategy in terms of cost-effectiveness for the national breast cancer screening program, specifically, is also highly relevant in light of current EU guidelines on screening ages and frequencies.

Limitations

The limitations of the analysis are mainly attributed to the model choice, the nature of the evidence informing the model parameters, assumptions made in synthetization of the evidence and modelling the natural disease progression.

The state-transition Markov model, which is widely used for evaluating the cost-effectiveness of breast cancer screening was chosen for its simplicity and, while suffering the limitation of assuming a homogenous population with regard to risk factors of breast cancer (e.g., breast density), it was considered adequate for modelling risk-indiscriminate strategies for a population-based screening program. Another limitation of the model approach, attributable to the "Markovian property" (i.e., the inability to track previous health states in which the simulated population has resided), is that it cannot separate between screening rounds and therefore cannot adjust for differences in sensitivity and specificity typically observed between first and subsequent screens [37].

The estimates used as inputs for calibrating the natural disease progression parameters were derived from multiple sources using different stage classifications. Duffy et al. [38] separated between lymph node positive and negative invasive breast cancer, while Wu et al. [39] followed the FCR stage classification of localized and non-localized tumors. Despite the similarity between the studies' estimated transition probabilities for ages 50–59, the potential inconsistency between the stage classifications may contest their compatibility with the model structure, even after calibration. These parameter estimates were, however, considered the best available evidence given the limited published literature natural history parameters, suitable for the model structure. Integrating the DCIS natural history parameters estimated by Yen et al. [40] with invasive breast cancer transition parameters required adjustment to the underlying incidence rates, as the study assumed all invasive tumors to be preceded by DCIS.

According to EVPPI of selected parameter groups, even with calibration, natural history parameters were associated with a high return to research, suggesting high uncertainty surrounding their true value. Calibration inputs generated for ages over 69, for which no relevant estimates were found, followed the general pattern of decreasing rates of progression and increasing underlying incidence rates with age. However, as the estimation of parameters for this age group relies entirely on the calibration process, they are inherently more uncertain

than for other age groups, as multiple intercorrelated elements affect the natural disease progression of the model. Uncertainty is also expected to be higher for screening accuracy parameters for ages under and over 50–69 which, due to the lack of relevant evidence and calibration targets, followed the general pattern of increasing sensitivity and specificity with age.

Due to the utility estimates associated with treatment and surveillance following breast cancer diagnosis applied in the model being indiscriminate to age, baseline utility is assumed to be constant across age groups, in contradiction to estimates on general population HRQoL indicating a decreasing utility at higher ages [41]. This may over- or underestimate the cost-effectiveness of the screening strategies considered, however, given that the comparator strategy is biennial screening in ages 50–69 rather than no screening, the difference in HRQoL in the age groups of the expanded strategies is not expected to differ much from that of the comparator strategy.

The approach for modelling overdiagnosis associated with invasive breast cancer assumes that screening detected progressive tumors are never over diagnosed. Theoretically, overdiagnosis includes not only tumors that would never haveprogressed to the clinical phase in the absence of screening, but also tumors that never progress before the time of death from natural causes. However, as the proportion of nonprogressive tumors of all over diagnosed tumors is unknown, adjustment for tumors never progressing before the time of death cannot be made. Although the latter represents only a fraction of all over diagnosed cancers in young ages due to low associated baseline mortality, it may overestimate overdiagnosis in older ages with a higher baseline mortality.

Comparability and transferability of results

Published evidence on cost-effectiveness of screening strategies going beyond the age group of 50–69 is rather mixed. The intuitive answer to why this study suggests a more favorable ICER for screening women under 50, is that it offsets more costs and disutility of non-localized breast cancer than it inflicts through overdiagnosis and false-positives, compared to screening in ages 70–74. Although disutility associated with breast cancer treatment only differs between non-metastasized and metastasized cancer, the latter representing only a fraction of all non-localized tumors, the difference in treatment costs between localized and non-localized cancer is more apparent. The intuition is also supported by the difference in survival between localized and non-localized breast cancer and, crucially, how it changes with age. As seen in Fig. 1 of Additional file 2, the difference in the probability of survival between localized and non-localized cancer is greater for ages 20–49 than for ages 70–79, over the entire follow-up and extrapolated period of time since diagnosis. Consequently, as the preclinical phase of the model structure only separates between localized and non-localized cancer, there is more to gain from screening in ages under than ages over 50–69. This finding, however, is far from unanimously supported in published literature.

A study conducted by the Swedish National Board of Health and Welfare [42] estimated relative risk-reductions to model the effect of screening on breast cancer mortality and the cost-effectiveness of different scaled-down biennial strategies. Essentially, they found the ICER of screening only women aged 50–74 favorable to that of screening only women aged 40–69, compared to their current national screening strategy covering all women aged 40–74. In the study, it was noted that the results were particularly sensitive to the method for calculating costs associated with productivity loss. This suggests that productivity loss offset, which is contingent upon age as it does not apply to those retired from the workforce, can partly explain the difference between the study's estimated ICERs of screening in younger and older age groups.

A study by Kregting et al. [43] estimated the cost-effectiveness of 920 different screening strategies for the healthcare setting of the Netherlands compared to their current national screening strategy inviting all women aged 50–74 to biennial screening. The study found the comparator strategy dominated by, among others, a biennial strategy covering ages 43–73. This is in line with the findings of this analysis, when comparing the strategy covering ages 45–74 with the strategy covering 50–74.

The findings of this study are transferable in so far as they are applied to the context of a similar setting with a similar healthcare system, when comparing expected costs and consequences of the screening strategies used in this analysis, from a similar perspective. The model was designed to reflect costs and outcomes associated with breast cancer and screening, relevant for the Finnish setting. The cost parameters are estimated specifically for the healthcare system and the female population of Finland and, therefore, are unlikely to be relevant for other settings. Precaution is advised regarding the population to which the findings of this study are applied. While the applicability of the natural history parameters may not be exclusive to the Finnish female population, it might not be appropriate to reflect that of all ethnicities.

Conclusions

The findings of this analysis suggest that expanding the target population for the Finnish breast cancer screening program is cost-effective. Essentially, they indicate that expanding the target population to age 45 is more likely to be cost-effective than only expanding it to age 74. The potential expansion of the national screening program

to women outside of the current target population, in line with European guidelines, requires careful evaluation in other aspects as well. However, evidence on cost-effectiveness is a crucial element in making informed decisions on the desired target population for national screening programs for breast cancer.

Abbreviations

CEAC	Cost-Effectiveness Acceptability Curve
CE-plane	Cost-Effectiveness Plane
CI	Confidence Interval
DCIS	Ductal Carcinoma In Situ
EVPPI	Expected Value of Partially Perfect Information
FCR	Finnish Cancer Registry
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
LN +	Lymph Node Positive
NMB	Net Monetary Benefit
PPV	Positive Predictive Value
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
WTP	Willingness-To-Pay

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13561-025-00628-5.

Supplementary Material 1: Additional file 1. Microsoft Word Document. Natural history parameter calibration inputs. Description of synthetization of natural history parameters related to the underlying incidence of localized breast cancer and progressive DCIS. Table including point values and measures of variation for all inputs used in the natural history parameter calibration

Supplementary Material 2:Additional file 2. Microsoft Word Document. Invasive breast cancer survival probabilities. Figures on estimated age- and stage specific survival curves plotted against empirical survival curves

Supplementary Material 3: Additional file 3. Microsoft Word Document. Cost and utility parameters. Tables containing all cost and utility parameters applied in the analysis

Acknowledgements
Not applicable.

Author contributions
Filip Siegfrids was responsible for model development, literature review, analysis and interpretation of results, drafting and submission of the manuscript and the supplementary material. Sirpa Heinävaara and Tytti Sarkeala were responsible for conceptualization and have reviewed all versions of the manuscript. Juha Laine has reviewed and provided support in drafting the final version of the manuscript. Laura Niinikoski has reviewed and provided considerable support in the revision of the manuscript.

Funding
This work was supported by Cancer Foundation Finland Grant (grant number 200080). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files, except for natural history parameters generated through calibration and data used for survival parameter estimation. The former are not provided as they were deemed to provide little added value to the calibration inputs and their measures of variation available in Additional file 1, based on which all calibrated parameters were generated. Breast cancer specific survival data is not provided as it is based on internal Finnish Cancer Registry estimates. The datasets are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Tytti Sarkeala is a member of the National Screening Board. Sirpa Heinävaara and Laura Niinikoski are members of the National Advisory Group for Breast Cancer Screening.

Received: 23 May 2024 / Accepted: 4 April 2025
Published online: 11 April 2025

References

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356–87.
2. European Commission. BREAST CANCER IN THE EU [Internet]. 2023 Oct [cited 2023 Nov 2]. Available from: ecis.jrc.ec.europa.eu/pdf/Breast_cancer_2022-Oct_2023.pdf
3. Zielonke N, Kregting LM, Heijnsdijk EAM, Veerus P, Heinävaara S, McKee M, et al. The potential of breast cancer screening in Europe. Int J Cancer. 2021;148(2):406–18.
4. Hakama M, Pukkala E, Heikkila M, Kallio M. Effectiveness of the public health policy for breast cancer screening in Finland: population based cohort study. BMJ. 1997;314(7084):864–864.
5. Heinävaara S, Sarkeala T, Anttila A. Impact of organised mammography screening on breast cancer mortality in a case–control and cohort study. Br J Cancer. 2016;114(9):1038–44.
6. Duffy SW, Nagtegaal ID, Wallis M, Cafferty FH, Houssami N, Warwick J, et al. Correcting for lead time and length bias in estimating the effect of screen detection on cancer survival. Am J Epidemiol. 2008;168(1):98–104.
7. Zielonke N, Geuzinge A, Heijnsdijk E, Heinävaara S, Senore C, Jarm K, et al. Extending age ranges in breast cancer screening in four European countries: model estimations of Harm-to-Benefit ratios. Cancers. 2021;13(13):3360.
8. Jatoi I. The impact of advances in treatment on the efficacy of mammography screening. Prev Med. 2011;53(3):103–4.
9. Goldie SJ. Chapter 15: public health policy and Cost-Effectiveness analysis. JNCI Monogr. 2003;2003(31):102–10.
10. Drummond MF, Schulpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Volume 25, 4th ed. Oxford University Press; 2015. pp. 5–7.
11. Jayasekera J, Mandelblatt JS. Systematic review of the cost effectiveness of breast cancer prevention, screening, and treatment interventions. J Clin Oncol. 2020;38(4):332–50.
12. Schünemann HJ, Lerda D, Quinn C, Follmann M, Alonso-Coello P, Rossi PG, et al. Breast cancer screening and diagnosis: A synopsis of the European breast guidelines. Ann Intern Med. 2020;172(1):46.
13. Johanna Alanko R, Aaltonen K, Aittomäki M, Bärlund Päivi, Heikkilä S, Heinävaara FICAN et al. 2024 Apr. Available from: https://syoparekisteri.fi/assets/files/2024/12/Quality-manual-for-breast-cancer-screening.pdf
14. Rojnik K, Naveršnik K, Mateović-Rojnik T, PrimicŽakelj M. Probabilistic Cost-Effectiveness modeling of different breast cancer screening policies in Slovenia. Value Health. 2008;11(2):139–48.
15. Finnish Cancer Registry. Cancer statistics. URL https://cancerregistry.fi/statistics/cancer-statistics/, analysed using the popEpi package in R (Miettinen J, Rantanen M, Seppä K. popEpi: Functions for Epidemiological Analysis using Population Data. R package version 0.4.13. [Internet]. Available from: http://CRAN.R-project.org/package=popEpi)
16. Anttila A, Lehtinen M, Mäki S, Leivonen A, Heinävaara S, Sarkeala T. RINTASYÖVÄN SEULONTAOHJELMA - VUOSIKATSAUS 2021 [Internet]. 2021. Available from: https://syoparekisteri.fi/assets/files/2021/09/Rintasyovan_seulontaohjelman_vuosikatsaus_2021.pdf
17. Ernster VL. Detection of ductal carcinoma in situ in women undergoing screening mammography. CancerSpectrum Knowl Environ. 2002;94(20):1546–54.

18. Finnish Cancer Registry. Cancer statistics. Available from: https://cancerregistry.fi/statistics/cancer-statistics/
19. Ulm K, A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol. 1990;131(2):373–5.
20. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. BMJ. 2006;332(7543):689–92.
21. Heinävaara S, Sarkeala T, Anttila A. Overdiagnosis due to breast cancer screening: updated estimates of the Helsinki service study in Finland. Br J Cancer. 2014;111(7):1463–8.
22. Lehtinen M, Heinävaara S, Sarkeala T, Karlsson A, Tukiainen M, Huovinen R, et al. Potilaan Ikä Ja Syövän Levinneisyys Vaikuttavat Rintasyövän Hoitokustannuksiin. LÄÄKETIETEELLINEN AIKAKAUSKIRJA DUODECIM. 2019;135(10):953–60.
23. Roine E, Färkkilä N, Sintonen H, Taari K, Roine RP, Saarto T. Costs in different States of breast cancer. Anticancer Res. 2019;39(1):353–9.
24. Haltia O, Färkkilä N, Roine RP, Sintonen H, Taari K, Hänninen J, et al. The indirect costs of palliative care in end-stage cancer: A real-life longitudinal register- and questionnaire-based study. Palliat Med. 2018;32(2):493–9.
25. Official Statistics of Finland. Consumer price index [Internet]. 2024 Apr [cited 2024 Apr 20]. Available from: https://stat.fi/en/statistics/khi#tables-cl2rgffkqbe980bumb1ls7oec
26. Rautalin M, Färkkilä N, Sintonen H, Saarto T, Taari K, Jahkola T, et al. Health-related quality of life in different States of breast cancer– comparing different instruments. Acta Oncol. 2018;57(5):622–8.
27. Pharmaceuticals Pricing Board, PREPARING A HEALTH ECONOMIC EVALUATION TO BE ATTACHED TO THE APPLICATION FOR REIMBURSEMENT STATUS, AND WHOLESALE PRICE FOR A MEDICINAL PRODUCT [Internet]. 2024 [cited 2025 Feb 20]. Available from: https://www.hila.fi/content/uploads/2024/06/Instructions_TTS_2024_190624.pdf
28. Edlin R, McCabe C, Hulme C, Hall P, Wright J. Cost Effectiveness Modelling for Health Technology Assessment: A Practical Course [Internet]. pp. 84–85: Springer International Publishing; 2015 [cited 2023 Nov 14]. Available from: https://link.springer.com/https://doi.org/10.1007/978-3-319-15744-3
29. 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 Mak. 2014;34(3):311–26.
30. Kim DD, Silver MC, Kunst N, Cohen JT, Ollendorf DA, Neumann PJ. Perspective and costing in Cost-Effectiveness analysis, 1974–2018. PharmacoEconomics. 2020;38(10):1135–45.
31. Soini J. Contingent valuation of eight new treatments: what is the clinician's and Politician's willingness to pay?? Open Complement Med J. 2012;4(1):1–11.
32. McDougall JA, Furnback WE, Wang BCM, Mahlich J. Understanding the global measurement of willingness to pay in health. J Mark Access Health Policy. 2020;8(1):1717030.
33. Official Statistics of Finland. Gross domestic product per capita [Internet]. 2023 Nov [cited 2023 Dec 4]. Available from: www2.stat.fi/tup/suoluk/suoluk_kansantalous_en.html
34. Minacori R, Geale K, Geale K. Is there evidence of a difference between willingness to pay and willingness to accept thresholds?? A review of nice technology appraisals. Value Health. 2016;19(7):A492–3.
35. OECD. Purchasing power parities (PPP). 2023; Available from: https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm
36. Soini E, Virtanen O, Väätäinen S, Briere JB, Bowrin K, Millier A. Cost-Effectiveness of coronary and peripheral artery disease antithrombotic treatments in Finland. Adv Ther. 2020;37(7):3348–69.
37. Schiller-Frühwirth IC, Jahn B, Arvandi M, Siebert U. Cost-Effectiveness models in breast cancer screening in the general population: A systematic review. Appl Health Econ Health Policy. 2017;15(3):333–51.
38. Duffy SW, Day NE, Tabár L, Chen HH, Smith TC. Markov models of breast tumor progression: some Age-Specific results. JNCI Monogr. 1997;1997(22):93–7.
39. Wu JCY, Hakama M, Anttila A, Yen AMF, Malila N, Sarkeala T, et al. Estimation of natural history parameters of breast cancer based on non-randomized organized screening data: subsidiary analysis of effects of inter-screening interval, sensitivity, and attendance rate on reduction of advanced cancer. Breast Cancer Res Treat. 2010;122(2):553–66.
40. Yen MF, Tabár L, Vitak B, Smith RA, Chen HH, Duffy SW. Quantifying the potential problem of overdiagnosis of ductal carcinoma in situ in breast cancer screening. Eur J Cancer. 2003;39(12):1746–54.
41. Janssen B, Szende A. Population Norms for the EQ-5D. In: Szende A, Janssen B, Cabases J, editors. Self-Reported Population Health: An International Perspective based on EQ-5D [Internet]. Dordrecht: Springer Netherlands; 2014 [cited 2025 Mar 20]. pp. 19–30. Available from: http://link.springer.com/https://doi.org/10.1007/978-94-007-7596-1_3
42. National Board of Health and Welfare. Värdet av populationsbaserad screening för bröstcancer– hälsoekonomisk analys. 2019; Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/nationella-screeningprogram/screening-brostcancer-halsoekonomi-analys.pdf
43. Kregting LM, Sankatsing VDV, Heijnsdijk EAM, de Koning HJ, van Ravesteyn NT. Finding the optimal mammography screening strategy: A cost-effectiveness analysis of 920 modelled strategies. Int J Cancer. 2022;151(2):287–96.

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