Appl Health Econ Health Policy
DOI 10.1007/s40258-017-0312-3

SYSTEMATIC REVIEW

Cost-Effectiveness Models in Breast Cancer Screening in the General Population: A Systematic Review

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Abstract

Background Many Western countries have long-established population-based mammography screening programs. Prior to implementing these programs, decision-analytic modeling was widely used to inform decisions.

Objective The aim of this study was to perform a systematic review of cost-effectiveness models in breast cancer screening in the general population to analyze their structural and methodological approaches.

Methods A systematic literature search for health economic models was performed in the electronic databases MEDLINE (Ovid), EMBASE, CRD Databases, Cochrane Library, and EconLit in August 2011 with updates in June 2013, April 2015, and November 2016. To assess studies systematically, a standardized form was applied to extract relevant information that was then summarized in evidence tables.

Results Thirty-five studies were included; 27 state-transition models were analyzed using cohort ($n = 12$) and individual-level simulation ($n = 15$). Twenty-one studies modeled the natural history of breast cancer and predicted mortality as a function of the early detection modality. The models employed different assumptions regarding ductal carcinoma in situ. Thirteen studies performed cost-utility analyses with different sources for utility values, but assumptions were often made about utility weights. Twenty-two models did not report any validation.

Conclusion State-transition modeling was the most frequently applied analytic approach. Different methods in modeling the progression of ductal carcinoma in situ to invasive cancer were identified because there is currently no agreement on the biological behavior of noninvasive breast cancer. Main weaknesses were the lack of precise utility estimates and insufficient reporting of validation. Sensitivity analyses of assumptions regarding ductal carcinoma in situ and in particular adequate validation are critical to minimize the risk of biased model outcomes.

Electronic supplementary material The online version of this article (doi:10.1007/s40258-017-0312-3) contains supplementary material, which is available to authorized users.

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Published online: 10 February 2017

Key Points for Decision Makers

State-transition modeling was the most common analytic approach in modeling breast cancer screening using individual-level microsimulation as statistical analysis.

Stage-shift modeling was the most used method of determining the effect of breast cancer screening but models made a variety of assumptions in the absence of a valid theory of the natural history of breast cancer.

Sensitivity analyses are critical to address uncertainties regarding modeling the natural history in breast cancer screening as well as validation steps to improve the confidence in outcomes of cost-effectiveness models.

1 Introduction

The high incidence and cost of breast cancer impose a considerable burden on healthcare systems [1–3]. Mammography screening is commonly used for early detection of breast cancer. Many countries have established population-based screening programs [4]. The introduction of such programs was the result of randomized controlled mammography screening trials that demonstrated a reduction in mortality from breast cancer [5, 6]. The implementation of screening with mammography has been based on the expectation of lower breast cancer mortality as well as cost effectiveness. The past assumption that breast cancer screening contributes to cost savings in the healthcare system has not been supported by evidence, though breast cancer screening may well be cost effective in that it may provide good value for the resources invested [7–11].

Cost-effectiveness analysis in breast cancer screening aims to compare different screening strategies to assess the most efficient intervention and serve as a tool to aid decision making. Owing to the context dependence of cost-effectiveness analyses in breast cancer screening given differences in health system structure, financing, population characteristics, and epidemiology, results are not transferable between different healthcare systems [12]. Limited healthcare resources and concerns about equity underlie the importance of making decisions about healthcare interventions based on cost-effectiveness evidence [13, 14].

Decision-analytic modeling is widely used in healthcare economic evaluations in general and in screening in particular [15–17]. Simulation models serve as a conceptual tool for translating complex real-world subject matter into a simplified form, when conducting randomized clinical trials are too time consuming, expensive, unethical, or not feasible for other reasons [18–20].

Various decision-analytic models and approaches have been used in breast cancer screening. These approaches require information synthesized from a wide range of sources including primary epidemiological data, the results of secondary data analyses, and expert opinion. Two relevant systematic reviews of health economic studies in breast cancer screening have been published in 2003 and 2013 [12, 21]. However, these reviews focus merely on cost-effectiveness issues rather than on methodological concerns. To fill this gap, we performed a systematic review of cost-effectiveness modeling studies in breast cancer screening focusing on the structural and analytic methods of these models. Another systematic review, quite recently published, focused on the critical evaluation of simulation models with more than one application [22].

2 Methods

The review objective, the research question (in PICO format: Population, Intervention, Comparison, Outcome in Table 1), as well as the inclusion and exclusion criteria were determined a priori and a review protocol was formulated.

2.1 Inclusion and Exclusion Criteria

We included only those studies that used a decision-analytic model to evaluate breast cancer screening strategies. The definition of the term ‘model’ was based on the report of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices—Modeling Studies, which “includes both resource consequences and health outcomes in a health economic evaluation framework” [23]. Published cost-effectiveness studies that fulfilled the criteria as listed in Table 2 were included.

2.2 Search Strategy

A systematic literature search of electronic databases was performed in MEDLINE (Ovid), EMBASE (WebSPIRS), CRD Databases (NHS Economic Evaluation Database), DARE, HTA Databases, The Cochrane Library, and EconLit. Additional sources were searched by hand including the Tufts Medical Center Cost-Effectiveness Analysis Registry [24] and Scopus, reference lists, and the Internet. The search strategies for MEDLINE and

Table 1 PICO question

P	Defined target group of healthy women of the general population at average risk for breast cancer
I	Organized screening strategy
C	Opportunistic screening or no screening
O	Incremental cost-effectiveness ratio (cost per life-year gained) and incremental cost-utility ratio (cost per quality-adjusted life-year gained)

PICO population, intervention, comparison, outcome

Table 2 Inclusion and exclusion criteria

Inclusion criteria
Defined target group of healthy women of the general population at average risk for breast cancer
(Organized) screening strategies with mammography vs. no screening or opportunistic screening
Decision-analytic model (mathematical model) evaluating both costs and health consequences
Outcome expressed as cost per life-years gained or cost per quality-adjusted life-years gained
Original cost-effectiveness or cost-utility studies published in English or German
Published studies in full text
Exclusion criteria
Economic evaluation alongside a clinical trial
Purely descriptive studies
Studies using models only as a means of illustration or tutorial
Screening for breast cancer with mammography in selected populations with certain diseases or high-risk populations
Screening with technologies other than mammography, e.g., clinical breast examination or a combination of mammography with clinical breast examination, magnetic resonance imaging
Study focuses on the cost effectiveness of specific aspects associated with breast cancer screening, e.g., attendance, interventions to increase participation, two- vs. one-view mammography
Studies on screening technologies (e.g., image recognition)
Reviews of cost-effectiveness analyses

EMBASE are provided in the Online Appendix. Search terms including 'mammography', 'breast cancer screening', 'Markov model', 'mathematical model', 'computer model', 'computer simulation', 'decision analytic model', 'microsimulation', and 'MISCAN model' were combined in the search code. There were no language restrictions. The first search was conducted in August 2011 with updates in June 2013, April 2015, and the latest search was done on 9 November, 2016. The systematic literature searches through database searching yielded a total of 2147 hits. The search algorithm is shown in Fig. 1.

2.3 Study Selection and Data Extraction

Three reviewers (ISF, BJ, MA) initially screened for titles and abstracts based on the defined inclusion criteria. Reviewers included all potentially relevant papers and screened these papers in full. A fourth reviewer (US) determined the outcomes of any disagreements regarding study eligibility. The first author (ISF) extracted the data, another author (BJ) checked the completeness and correctness of the data, and disagreements were resolved by discussion.

2.4 Information Extraction Process

We systematically assessed studies regarding model type, analytic methods, implementation of screening effects, costs, discounting, utility values, uncertainty analyses, validation, and approach to opportunistic screening. A standardized extraction form was used based on guidance for undertaking systematic reviews in healthcare [25] and the findings of each study were extracted and summarized in evidence tables.

We categorized the included studies according to the screening location (country) and strategies (Table I in the Online Appendix). Five categories of modeling approaches were used: (1) decision trees, (2) state-transition models, (3) discrete event simulation models, (4) stochastic models; and (5) models with an indeterminate analytic approach are outlined as other models.

Regarding the implementation of screening effects, two categories were used: (1) studies modeling stage shift and

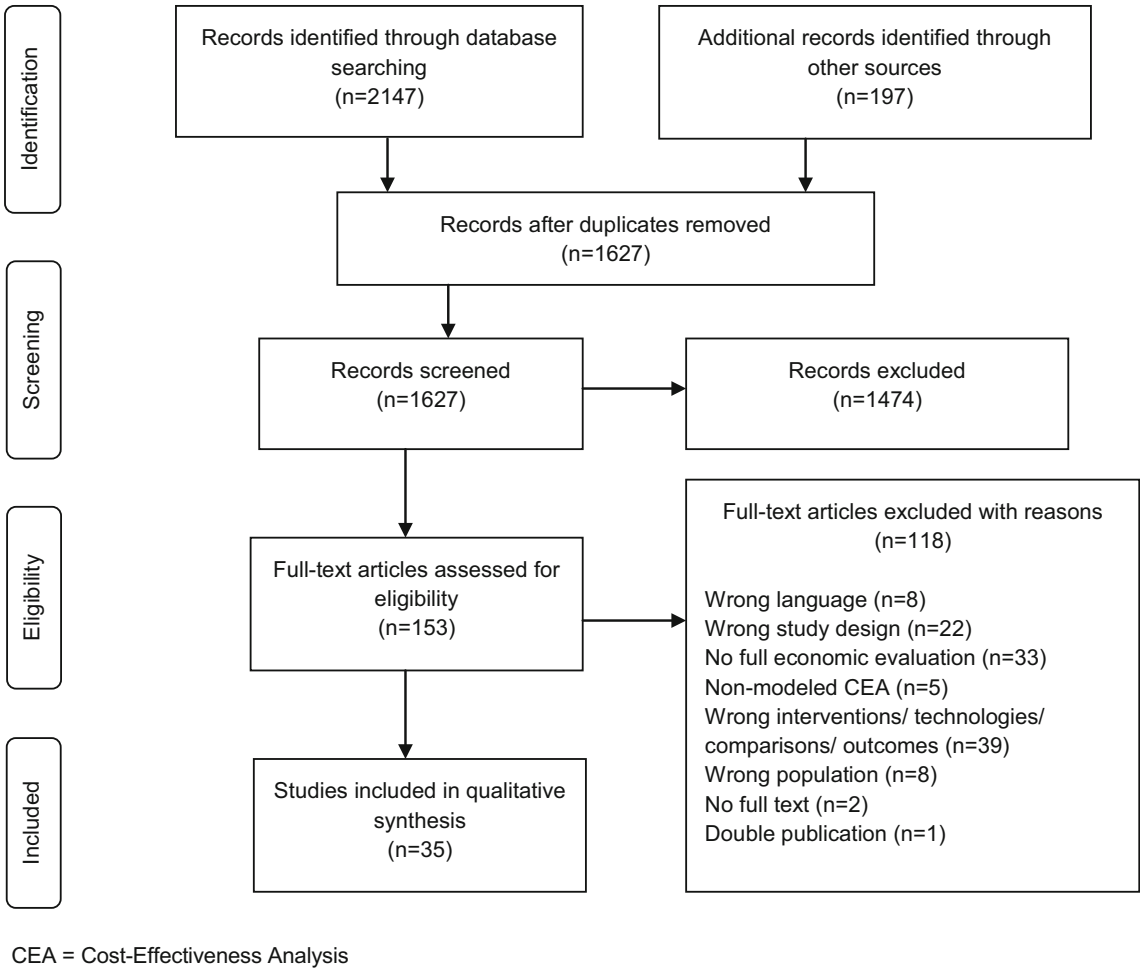

Fig. 1 Process of the systematic literature search (2011, 2013, 2015, and 2016) depicted in PRISMA 2009 flow. *CEA* cost-effectiveness analysis, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(2) studies using screen-related mortality reduction based on published literature data.

Models forecasting the impact of screening on the disease course are described as natural history models. The natural history of breast cancer is defined as the progression of the disease in an individual over time, in the absence of treatment [26]. Either stage-shift or cure models have been used to determine how diagnosis and treatment at earlier stages affect cancer-specific mortality. Cure models are based on the assumption that early identification will either lead to a therapy that will successfully prevent cancer-specific death or not alter the time and cause of death [27]. In stage-shift models, the effect of early detection by screening is entirely determined by stage shift and the improved cancer-specific survival associated with earlier cancer stages. In modeling stage distribution, either tumor size or a simplified version of the American Joint Committee of Cancer classification or the Surveillance, Epidemiology, and End Results (SEER) historical stage classification [28] are used.

In studies using screen-related mortality reduction based on published literature, an estimate of the reduction in cancer-specific mortality is applied to all cancers detected in the screening arm to estimate overall health gains compared with the no screening scenario. Various health states are designed to include the breast cancer screening pathway in these studies but tumor stages more specifically are not distinguished.

ISPOR-Society for Medical Decision Making Modeling Good Research Practices Task Force recommendations served as guidance in assessing the types of validation and sensitivity analyses carried out in the models [29, 30]. Internal validation is defined as a comparison of the model's results to the data used for deriving and calibrating the input parameters. Cross-validation involves comparing a model with others and determining the extent to which they calculate similar results. External validation is defined as a comparison of the predicted outcomes of a model to independent real-world data [30].

Table 3 Summary of the analytic framework

Author, year, country [reference]	Analytic approach	Statistical analysis	Uncertainty/ sensitivity analysis	Model validation
Arveux et al., 2003, France [38]	State-transition model (original colorectal cancer model)	Cohort simulation	Several deterministic 1-way	Internal validation
Beemsterboer et al., 1994 (MISCAN model)[a], Germany [52]	State-transition model (MISCAN model)	Microsimulation	Several deterministic 1-way	Internal validation
Beemsterboer et al., 1998, Spain [53]	State-transition model (MISCAN model)	Microsimulation	Several deterministic 1-way	Not stated
Boer et al., 1995, the Netherlands [54]	State-transition model (MISCAN model)	Microsimulation	1 deterministic 1-way	Not stated
Boer et al., 1998, UK [56]	State-transition model (MISCAN model)	Microsimulation	Reported in Street et al., 1996 [93]	Internal validation
Boer et al., 1999, the Netherlands [55]	State-transition model (MISCAN model)	Microsimulation	Not stated	Not stated
Carles et al., 2011, Spain [36]	Differential equations (original model Dana-Farber Cancer Institute)[b]	Cohort simulation	Several deterministic 1-way	Not stated
Carter et al., 1993, Australia [57]	State-transition model (MISCAN model), KNOX model	Microsimulation, statistical approach of KNOX model not stated	3 deterministic 1-way	Not stated
de Gelder et al., 2009, Switzerland [58]	State-transition model (MISCAN model)	Microsimulation	Several deterministic 1-way	Internal validation
de Koning et al., 1991, the Netherlands [59]	State-transition model (MISCAN model)	Microsimulation	Several deterministic 1-way	Not stated
Garuz et al., 1997, Spain [44]	Decision tree	Cohort simulation	Several deterministic 1-way	Not stated
Haghighat et al., 2016, Iran [60]	Decision tree combined with Markov model	Cohort simulation	Several deterministic 1-way, probabilistic	Not stated
IMS Health Pty Ltd., 2009, Australia [61]	State-transition model	Microsimulation	Several deterministic 1-way	Internal validation
Kerlikowske et al., 1999, USA [62]	State-transition model	Cohort simulation	Several deterministic 1-way	Not stated
Knox, 1988, UK [46]	Computer model	Statistical approach not stated	Several deterministic 1-way	Not stated
Lindfors et al., 1995, USA [40]	State-transition model	Cohort simulation	3 deterministic 1-way	Not stated[c]
Madan et al., 2010, UK [63]	State-transition model	Cohort simulation	Several deterministic 1-way, probabilistic	Not stated
Malcom, 1993, New Zealand [45]	Decision tree	Cohort simulation	Several deterministic 1-way	Not stated

Table 3 continued

Author, year, country [reference]	Analytic approach	Statistical analysis	Uncertainty/ sensitivity analysis	Model validation
Mandelblatt et al., 2004, USA [64]	State-transition model	Microsimulation	Several deterministic 1-way, multivariate	Internal validation
Mittmann et al., 2015, Canada [34]	Discrete-event simulation model (Original Wisconsin Breast Cancer Epidemiology Simulation Model)[e]	Microsimulation	Several deterministic 1-way	Internal validation[d]
Neeser et al., 2007, Switzerland [65]	State-transition model	Cohort simulation	Several deterministic 1-way, probabilistic	Internal validation
Okubo et al., 1991, Japan [47]	Mathematical model	Cohort simulation	Several deterministic 1-way	Not stated
Pataky et al., 2014, Canada [66]	State-transition model, not explicitly stated	Microsimulation	Several deterministic 1-way, probabilistic	External validation with data from UK Age trial [100], cross-validation with CISNET models [105]
Pharoah et al., 2013, UK [48]	Not specified, life-table approach	Cohort simulation	Probabilistic	Not stated
Rennert et al., 1991, Israel [67]	State-transition model, not explicitly stated (CAN*TROL)	Cohort simulation, not explicitly stated	Not stated	Not stated
Rojnik et al., 2008, Slovenia [68]	State-transition model	Cohort simulation	82 deterministic 1-way, probabilistic	External validation with published results of screening programs of other countries
Rosenquist et al., 1994 Not stated[c], USA [41]	State-transition model	Cohort simulation	Several deterministic 1-way	Not stated
Rosenquist et al., 1998 Not stated[c], USA [42]	State-transition model	Cohort simulation	Several deterministic 1-way	Not stated
Salzmann et al., 1997, USA [69]	State-transition model	Cohort simulation	Several deterministic 1-way, probabilistic	Not stated
Sankatsing et al., 2015, the Netherlands [70]	State-transition model (updated MISCAN model)	Microsimulation	Several deterministic 1-way	Internal validation
Stout et al., 2006, USA [33]	Discrete-event simulation model (Original Wisconsin Breast Cancer Epidemiology Simulation Model)[e]	Microsimulation	Several deterministic 1-way	Cross-validation with data from the Wisconsin Cancer Reporting System
Szeto et al., 1996, New Zealand [71]	State-transition model (Microlife)	Microsimulation	2 deterministic 1-way	Not stated
Van der Maas et al., 1989, the Netherlands [72]	State-transition model (MISCAN model)	Microsimulation	Not stated	Not stated
van Ineveld et al., 1993, UK, France, Spain, the Netherlands [73]	State-transition model (MISCAN model)	Microsimulation	Not stated	Not stated

Table 3 continued

Author, year, country [reference]	Analytic approach	Statistical analysis	Uncertainty/ sensitivity analysis	Model validation
Wong et al., 2007, Hong Kong [74]	State-transition model	Cohort simulation	1 deterministic 1-way, probabilistic	External validation using data from 8 randomized controlled breast cancer screening trials [101–104]

CISNET Cancer Intervention and Surveillance Monitoring Network, *MISCAN* Microsimulation Screening Analysis

[a] Original model Van Oortmarssen et al. [32]: internal validation with data from screening projects in the Netherlands [94, 95], model assumption about screen-related mortality reduction tested against results of Swedish breast cancer screening trial Kopparberg and Ostergötland [96]

[b] Original model Lee and Zelen [37]: internal validation

[c] Original model Lindfors and Rosenquist [43]: verified for accuracy

[d] Model prediction of breast cancer incidence compared with observed Canadian data described in Yaffe et al. [75]

[e] Original model Fryback et al. [35]: internal validation

3 Results

3.1 Systematic Literature Search

We assessed a total of 153 full-text articles for eligibility; reasons for exclusion are displayed in Fig. 1. For one study that was published twice, only the first publication was included because the subsequent version referred to the original publication for the structure and details of the model [31]. Thirty-five studies were ultimately included in the systematic review. The detailed list of excluded studies ($n = 118$) is shown in the Online Appendix in Table II.

The results of the systematic information extraction and synthesis are presented in the following sections. Table 3 shows a summary of the analytic framework and Table 4 gives an overview of model features of the included studies. We identified 18 cost-effectiveness studies that were applications of original models. Eleven studies used the Microsimulation Screening Analysis (MISCAN) model [32], two studies [33, 34] used the University of Wisconsin Breast Cancer Simulation model [35], one [36] the Cancer Intervention and Surveillance Modeling Network, Dana-Farber Cancer Institute model [37], one model [38] was based on a model originally designed to study the impact of colorectal cancer screening [39], and three studies [40–42] applied a former developed Markov model [43], other studies were single-use models.

3.2 Modeling Approaches

Modeling approaches are displayed in Fig. 2. Two studies used decision trees [44, 45], one study used a stochastic model [36]. Two studies employed a discrete event simulation model [33, 34]. State-transition modeling was the most common approach ($n = 27$). Three studies did not specify the model type [46–48]. As statistical analytic approach, cohort simulation and individual-level simulation was applied in 17 models each, one model did not report the statistical approach used [46].

3.2.1 Decision Tree Models

Only two studies were based on decision trees, one from Spain published in 1997 and a second from New Zealand that was published in 1993 [44, 45]. Neither New Zealand nor Spain had mass screening at that time. Both models derived the data for screening effects from the published literature [49–51] and included women aged 50 years, but one study analyzed women aged 45–49 years in addition [44]. Both studies performed cost-effectiveness analyses.

3.2.2 State-Transition Models

The most frequently used model approach was state-transition modeling. We identified 27 state-transition models [38, 40–42, 52–74], of these 12 models were analyzed using cohort simulation and 15 using an individual-level microsimulation. Twenty-two of 27 state-transition modeling studies included a cost-effectiveness analysis, four of these studies conducted also a cost-utility analysis [52, 58, 59, 74]. Five studies conducted only a cost-utility analysis [54, 60, 63, 66, 68], and five conducted a cost-utility analysis in sensitivity analyses [61, 62, 64, 69, 70]. Screening strategies differed according to the target populations, screening intervals, and participation rates. Fifteen studies included women under the age of 50 years [40–42, 57, 60, 61, 63–66, 68–71, 74], all other studies screened women aged 50 years and older. Two studies from Switzerland [58, 65] compared an organized screening program with opportunistic screening, whereas all other studies compared screening with a no-screening scenario.

Table 4 Summary of Model Features

Author, year, country [reference]	Research question/objectives	Target population	Study type	Perspective	Time horizon	Outcome measures
Arveux et al., 2003, France [38]	Cost effectiveness of screening vs. no screening in France	Women aged 50–65 years	CEA	Healthcare system	35 years	LY, ICER, cancer detected, recall for further assessment, bc deaths prevented, cumulative mortality reduction, cost
Beemsterboer et al., 1994, Germany [52]	Prediction of the effects and cost of bc screening in Germany	Women aged 50–69 years	CEA, CUA	Healthcare system	32 years	LY, QALY, ICER, ICUR, diagnosed bc, bc death prevented, bc mortality reduction, stage distribution, use of healthcare services, cost
Beemsterboer et al., 1998, Spain [53]	Cost effectiveness of different screening strategies in Catalonia	Women aged 50–64 years	CEA	Healthcare system	Beyond 27 years	LY, ICER, bc death prevented, bc mortality reduction, cost
Boer et al., 1995, the Netherlands [54]	Cost effectiveness of different upper age limits for bc screening	Women aged 50–69 years and >70 years	CUA	Healthcare system, not explicitly stated	27 years	LY, QALY, ICUR, extra incidence of bc cases, LY in lead time, cost
Boer et al., 1998, UK [56]	Cost effectiveness of shortening screening interval or extending age range	Women aged 50–64 (69) years	CEA	Healthcare system	27 years	LY, ICER, bc deaths prevented, total deaths prevented, mortality reduction, cost per death prevented, cost
Boer et al., 1999, the Netherlands [55]	Cost effectiveness of longer screening intervals for women aged over 65 years	Women aged 50–64 years and 65–82 years	CEA	Healthcare system	Life-time, not explicitly stated	LY, ICER, bc deaths prevented, extra incidence of bc cases, extra LY with the disease, cost
Carles et al., 2011, Spain [36]	Cost effectiveness of bc screening strategies in the Catalonia region of Spain	Women aged 40–79 years	CEA, CUA	Healthcare system	Life-time, not explicitly stated	LY, QALY, ICER, ICUR, lives extended, cost
Carter et al., 1993, Australia [57]	Cost effectiveness of mammographic screening in Australia	Women aged 40–49 years, 50–69 years	CEA	Healthcare system	30 years	LY, ICER, number of screens, true positives, cost
de Gelder et al., 2009, Switzerland [58]	Cost effectiveness of organized mammography screening program compared with opportunistic screening in Switzerland	Women aged 50–69 years	CEA, CUA	Healthcare system, not explicitly stated	Life-time	LY, QALY, ICER, ICUR, bc diagnosed, bc deaths prevented, cost
de Koning et al., 1991, the Netherlands [59]	Cost effectiveness of 5 screening variants, differing in age or screening intervals	Women aged 50–70 years	CEA, CUA	Payer	Life-time	LY, QALY, ICER, ICUR, bc death prevented, bc mortality reduction, cost
Garuz et al., 1997, Spain [44]	Cost effectiveness of screening compared with no screening	Women aged 50–65 years	CEA	Healthcare system	25 years	LY, ICER, bc cases, avoided deaths, cost
Haghighat et al., 2016, Iran [60]	Cost effectiveness of organized screening program (3 rounds of mammography) in Iran	Women aged 40–70 years	CUA	Healthcare system	50 years	QALY, life-time cost, ICUR
IMS Health Pty Ltd., Australia, 2009, Australia [61]	Cost effectiveness of the current BreastScreen Australia program compared with a hypothetical no screening scenario	Women aged 40–79 years	CEA, CUA in SA	Healthcare system	Life-time	LY, ICER, bc detected, bc deaths avoided, cost/bc deaths avoided, cost

Table 4 continued

Author, year, country [reference]	Research question/objectives	Target population	Study type	Perspective	Time horizon	Outcome measures
Kerlikowske et al., 1999, USA [62]	Cost effectiveness of mammography screening for specified time intervals and combinations with measurement of bone mineral densities (women aged 70–79 years)	Women aged 65 years or older	CEA, CUA in SA	Healthcare system (societal perspective stated)	Life-time	LY, ICER, DCIS, bc death prevented, cost
Knox, 1988, UK [46]	Estimation of cost of each life saved and reduction in mortality from bc	Women aged 50–65 years	CEA	Healthcare system, not explicitly stated	n.r.	Cost/LYG, cost/deaths saved
Lindfors et al., 1995, USA [40]	Cost effectiveness of different mammographic screening strategies	Women aged 40–79 years	CEA	Payer, not explicitly stated	Life-time, not explicitly stated	LY, ICER, cost
Madan et al., 2010, UK [63]	Cost effectiveness of a bc screening program for women aged 47–49 years	Women aged 47–49 years	CUA	Healthcare system, not explicitly stated	n. r.	LY, QALY, ICUR, bc diagnosed, survival rate, cost
Malcom, 1993, New Zealand [45]	Economic effectiveness of introducing a mass mammography screening program for bc	Women aged 50–71 years	CEA	Society	25 years	LY, ICER, cost
Mandelblatt et al., 2004, USA [64]	Cost effectiveness of biennial screening vs. intensified screening vs. optimal treatment in African American women	Women (African American) aged 40 years and older	CEA, CUA in SA	Healthcare system, not explicitly stated	Life-time	LY, ICER, abnormal mammograms, false-positives, bc cases, stage distribution, cost
Mittmann et al., 2015, Canada [34]	Cost effectiveness of various bc screening strategies in Canada	Women aged 40 (50) to 69 (74) years	CUA	Society	Life-time	QALY, ICUR, cost
Neeser et al., 2007, Switzerland [65]	Cost effectiveness of screening program in comparison with opportunistic screening in Switzerland	Women aged 40–70 years	CEA	Healthcare system	Life-time	LY, ICER, avoided deaths, NNS to prevent one death, all-cause mortality reduction, cost
Okubo et al., 1991, Japan [47]	Cost effectiveness of mass screening of bc in Japan	Women aged 30 years	CEA	Payer	Life-time	LY, ICER, cost per woman screened, cost
Pataky et al., 2014, Canada, [66]	Cost effectiveness of population-based mammography screening strategies by age range and frequency	Women aged 40–74 years	CUA	Healthcare system, not explicitly stated	Life-time	LY, QALY, ICUR, bc incidence, mode of detection, bc mortality, false-positives, biopsies, cost
Pharoah et al., 2013, UK [48]	Cost effectiveness of the NHS breast screening programme	Women aged 50–70 years	CUA	UK National Health Service	35 years	LY, QALY, ICUR, bc diagnoses, deaths from bc, deaths from other causes, person years of survival with bc, overdiagnosed bc, cost
Rennert et al., 1991, Israel [67]	Cost effectiveness of mammographic screening in different ethnic groups in Israel	Women aged 50–70 years	CEA	Healthcare system	40 years	LY, cost/LYG, mortality reduction, cost
Rojnik et al., 2008, Slovenia [68]	Cost effectiveness of alternative strategies of population-level screening for bc in Slovenia	Women aged 40–80 years	CUA	Healthcare system	Life-time	LY, QALY, ICER, ICUR, mortality reduction, cost

Table 4 continued

Author, year, country [reference]	Research question/objectives	Target population	Study type	Perspective	Time horizon	Outcome measures
Rosenquist et al., 1994, USA [41]	Cost effectiveness of mammographic screening in women 40–49 years	Women aged 40–49 years	CEA	Society (only direct cost included)	45 years	LY, ICER, cost
Rosenquist et al., 1998, USA [42]	Cost effectiveness of 4 age-related screening strategies, in the 40- to 49-year-old age group	Women aged 40–79 years	CEA	Society (only direct cost included)	n. r.	LY, ICER, cost
Salzmann et al., 1997, USA [69]	Cost effectiveness of screening mammography in women of different age groups	Women aged 40– 49 years and 50–69 years	CEA, CUA in SA	Payer, not explicitly stated	n. r.	LY, QALY, ICER, ICUR, prevented bc deaths, cost
Sankatsing et al., 2015, the Netherlands [70]	Cost effectiveness of digital mammography screening before the age of 50 years	Women aged 40–74 years	CEA, CUA in SA	Healthcare system	Life-time	LY, QALY, ICER, ICUR, screen and clinically detected bc, bc deaths, false-positives, cost
Stout et al., 2006, USA [33]	Retrospective cost-effectiveness analysis comparing actual with alternative screening mammography scenarios	Women aged 40–80 years	CUA	Payer	Life-time	QALY, ICUR, cost
Szeto et al., 1996, New Zealand [71]	Costeffectiveness of mammography screening in New Zealand relative to no screening	Women aged 45–69 years	CEA	Healthcare system	Life-time	LY, ICER, detected bc, number of screens, cost
van der Maas et al., 1989, the Netherlands [72]	Cost-effectiveness analysis before deciding on the implementation of mass screening in the Netherlands	Women aged 50–70 years	CEA	Society	Life-time	LY, ICER, deaths prevented, cost/deaths prevented, cost
van Ineveld et al., 1993, UK, France, Spain, the Netherlands [73]	Cost effectiveness in different EC countries (Spain, France, UK) compared with Dutch screening policy	Women aged 50–70 years	CEA	Healthcare system	Life-time	LY, cost/LYG, bc deaths prevented, cost
Wong et al., 2007, Hong Kong [74]	Cost effectiveness of biennial mammography in Hong Kong Chinese women	Women (Chinese) aged 40 years	CEA, CUA	Society	50 years	LY, QALY, ICER, ICUR, averted deaths, cost

bc breast cancer, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *DCIS* ductal carcinoma in situ, *EC* European Community, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *LY* life-years, *LYG* life-year gained, *NHS* National Health Service, *NNS* Number needed to screen, *n.r.* not reported, *QALY* quality-adjusted life-years, *SA* sensitivity analysis

3.2.3 Discrete Event Simulation Models

Stout and Rosenberg [33] conducted a study for the US context using a discrete event simulation model of breast cancer epidemiology in a population over time. The method had been developed at the University of Wisconsin as part of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network. The model assessed the impact of screening practices over the past decade in USA for women aged 40–80 years. The study performed a cost-utility analysis from a payer's perspective. To model the natural history, tumors were assigned stages, namely carcinoma in situ, localized stage, regional stage, distant-stage, and estrogen receptor status, but were assumed to progress according to a stochastic Gompertz-type growth model that controls the size and the extent of the tumors. A second study, published in 2015, customized this simulation model and used country-specific modified inputs [34], which are provided in a separate publication [75]. In addition, HER2/neu status was considered. The model studied women aged from 40 to 74 years and conducted a cost-utility analysis including the

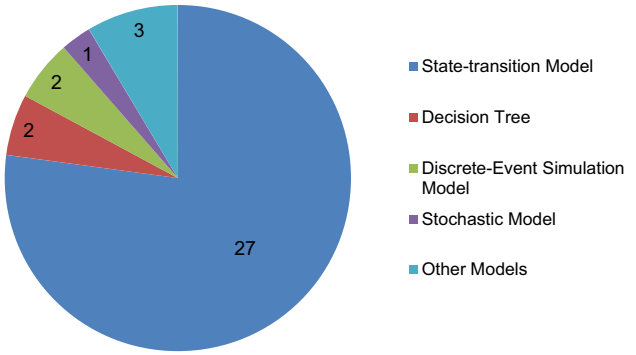

Fig. 2 Model types

costs of productivity loss and premature death to account for the societal perspective.

3.2.4 Stochastic Models

Carles et al. [36] used a published stochastic model of the Dana–Farber Cancer Institute [37] to assess the cost and outcomes of 20 possible screening strategies in Spain that varied in terms of both screening intervals and participant age, including women aged 40–79 years [36]. Previously published papers describe the inputs needed to model the Catalan data [76–78]. Disease progression was based on an idealized history of chronic disease. The study performed cost-effectiveness and cost-utility analyses.

3.2.5 Other Models

Knox and Okubo et al. published models that did not adhere to the categories above. A Japanese study [47] used a mathematical model and a UK study used the 'KNOX Model' [46]. Another study published in 2013 used a life-table approach [48]. These studies provided little information about the model structure, two performed a cost-effectiveness analysis [46, 47], and one carried out a cost-utility analysis from the perspective of the healthcare system. Two studies included women aged 50 years [46, 48], the Japanese study analyzed screening in women beginning at age 30 years [47].

3.3 Implementation of Screening Effects

3.3.1 Modeling of Stage Shift

Twenty-one studies modeled the natural history of breast cancer and implemented the screening effect of earlier detection by employing stage shift, but no cure models were identified. Thirteen studies modeled disease progression based on stages according to tumor size, of these 11 applied the MISCAN model [52–59, 70, 72, 73]. In assessing screening policies, tumor diameter played a central role because it determined the probability of detection and affected prognosis. The underlying concept is that early detection of cancer, even within a particular tumor size, leads to improved mortality compared with late detection of that same tumor size [32]. Six studies applied three invasive stages [52, 54, 57, 59, 72, 73], all other MISCAN applications used four stages. Szeto et al. [71] using a model called Microlife and the BreastScreen Australia study [61] applied diameter-based tumor stages with three invasive cancer stages similar to the MISCAN model.

In contrast to models that used tumor diameter, four studies [36, 38, 47, 74] used simplified tumor stages based on the classification of the American Joint Committee on Cancer [79]. Four studies [33, 34, 64, 68] used the SEER historical stage classification—ductal carcinoma in situ (DCIS), local, regional, distant—for depicting the natural history. The two discrete event simulation models [33, 34] assigned stages and considered also tumor size.

One model omitted DCIS as the screen-detectable stage including only invasive cancer stages [36]. Two models did not consider DCIS as a precursor of invasive cancer and therefore did now allow for a transition from DCIS to invasive breast cancer [38, 74]. One model [38] regarded in situ cancer as a prognostic category of its own while the other model [74] estimated an increased risk of invasive cancer for women with a history of DCIS. One study included stage 0, likely DCIS, but did not report any assumptions about this stage [47]. One study reported the transition probability of progressing from DCIS to invasive cancer as being exactly the same as the probability of progressing from no cancer to invasive cancer. They used this approach because of a lack of consensus in the research community regarding the proportion of DCIS that progresses to invasive cancer and the timing of this progression [61].

The original MISCAN model [32] stated that 5% of invasive breast cancers are preceded by screen-detectable DCIS and that all screen-detectable DCIS cases are progressive and develop into invasive cancer. Nine application models [52–57, 59, 72, 73] were based on these model assumptions but other parameters of the model have been adjusted such as mean duration of screen-detectable preclinical phase [58, 70], number of stages, and corresponding tumor size. In 2015, a further MISCAN application model [70] assumed that 18% of invasive breast cancers are preceded by screen-detectable DCIS and 2% of DCIS regress in the absence of screening based on an updated MISCAN model [80]. One study [68] assumed 60% of invasive breast cancers are not preceded by DCIS and 65% of DCIS progress to invasive cancer. Likewise,

Stout assumed that not all in situ or small localized invasive cancers progress to a fatal disease [33].

3.3.2 *Modeling of Mortality Reduction Estimates from Literature*

Fourteen studies [40–42, 44–46, 48, 60, 62, 63, 65–67, 69] determined an overall reduction in breast cancer mortality attributable to screening from the published literature or original data from screening programs. This was used as the model's input. The applied mortality reduction from published literature differed depending on age and screening frequency and ranged from 4% [40] for biennial screening to 36% [42] for annual screening in women aged 40–49 years, from 15% [65] in a setting with established opportunistic screening to 27% [69] for biennial screening in women 50–69 years, and 27% for invasive breast cancer and 44% for DCIS in biennial screening in women aged 65–79 years [62]. One study [60] derived the data of screen-related mortality reduction from three unpublished mammography screening programs conducted on small populations in Iran. One study [66] used country-specific population data of screened and non-screened populations to determine the overall reduction in mortality attributable to screening [81, 82] and another study [48] applied a 20% screen-related mortality reduction in triennial screening in women aged 50–70 years based on a review [83]. Details are shown in the Online Appendix in Table III.

3.4 Cost and Discounting

Four studies [42, 46, 63, 69] did not report the time horizon for costs and health effects. Thirty studies adopted the perspective of the payer or healthcare system and included direct medical cost; three of these studies claimed to take a societal perspective but only included direct costs [41, 42, 62]. Four studies [45, 64, 72, 74] included indirect costs such as travel time, waiting time, and testing time of women screened and one study [34] included the cost of productivity loss and premature death. Eight studies [40, 46, 54, 58, 63, 64, 66, 69] did not clearly state the perspective of the evaluation. Discounting of health outcomes and cost was applied in two studies at a rate of 6%, in 12 studies at a rate of 5%, in 11 studies at a rate of 3%, and in four studies at a rate of 3.5%. In three studies, costs were discounted but health outcomes were discounted at a different rate than costs [38, 47, 65] and three studies did not apply discounting at all [40, 41, 67]. Currency, price-year, and discount rates of each study are listed in Table IV in the Online Appendix. All but two models derived long-term costs based on resource utilization, data from national administrative databases, expert opinions, screening programs, or screening trials. The KNOX model did not report categories of cost and their sources [46], another study reviewed the short-term costs of screening but assumed that cost incurred and saved by screening including additional diagnostics, therapy, and palliative care would have a zero net balance, but full details of the costing were published elsewhere [56].

3.5 Utility Values

Thirteen studies reported cost-utility ratios [33, 34, 36, 48, 52, 54, 58–60, 63, 66, 68, 74]. In addition, five studies performed a limited cost-utility analysis in their sensitivity analyses [61, 62, 64, 69, 70]. Different sources of utility values were reported from the literature, but often assumptions were made about utility weights. Five studies, two conducted in the Netherlands [54, 59], one in Slovenia [68], one in Switzerland [58], and one in the German healthcare context [52] based their estimates for utilities on a study conducted in the Netherlands in 1991 [84]. Breast cancer and public health experts assigned quality-of-life values to the disease and treatment phases using the rating scale method. One study conducted in Slovenia [68] applied in addition utilities for chemotherapy in metastatic breast cancer patients derived from a study based in the UK in 1996 [85]. Utilities for the various health states were established "by use of standard gamble and visual analogue methods assessed by 30 oncology nurses in the UK who were acting as proxy patients" [85]. Three studies, conducted in USA [33], Spain [36], and Canada [34] used percentages of the age-specific utility weights for healthy women derived from the US Medical Expenditure Panel Survey in 2000 to estimate the negative effects in different breast cancer stages. The Canadian study [34] did not report the exact quality-of-life decrements used, the two other studies applied the same percentages for a given breast cancer stage and period of time. One Canadian study [66] obtained utilities for diagnostic mammography, biopsy, breast cancer treatment by stage at diagnosis, and metastatic disease from three different studies conducted in USA, two studies used standard gamble estimates [86, 87]. Utilities for two health states were obtained from a study using visual analog scales [88], which were scaled up to be comparable to standard gamble estimates.

One study conducted for the UK derived utility data from a study published in 1999 [89]. The nationally representative interview survey collected information on health status using the EuroQol (EQ-5D) descriptive system in the UK, but only limited information on the data was provided. Another study from the UK [48] reported the weight for health-related quality of life for a 50-year-old healthy women, the annual decline and the relative reduction in quality of life associated with living after a

diagnosis of breast cancer, referring to a comprehensive review of studies evaluating health-related quality-of-life in breast cancer [90]. A study conducted in Hong Kong [74] used slightly different utilities as reported in the limited cost-utility analysis performed in a US model [64]. A study conducted in Iran [60] applied the same utilities as reported in Wong et al. [74] except for the value of quality of life of breast cancer-free women.

Five studies [61, 62, 64, 69, 70] performing limited cost-utility analyses derived utility values from different sources. One study conducted in the Australian context [61] used utility values for mastectomy from Sweden [91] and utility values for breast-conserving surgery from the Netherlands [59]. Two studies conducted in USA [62, 69] derived utility values for breast cancer treatment outcomes and for metastatic disease from an Australian study that had used the time trade-off technique to derive values from a survey of women with and without breast cancer [92]. A third study from USA [64] assigned utilities to stages except for DCIS but did not provide any information about the source of these values. One study conducted in 2015 in the Netherlands [70] used utilities associated with screening from a study conducted in the Netherlands in 1991 [84] and adjusted health utilities for breast cancer treatment reported by Stout et al. [33].

3.6 Uncertainty Analysis and Model Validation

Twenty-five studies addressed the issue of uncertainty by means of several univariate or multivariate deterministic sensitivity analyses. Eight models performed multivariate probabilistic sensitivity analyses [48, 60, 63, 65, 66, 68, 69, 74]. All but two [48, 74] performed both comprehensive one-way and probabilistic sensitivity analyses. Four studies did not report any sensitivity analyses [55, 67, 72, 73]. One study [56] stated that full details of the sensitivity analysis were published elsewhere [93], other studies did limited deterministic one-way sensitivity analyses [40, 54, 57, 71, 74]. Assumptions regarding discount rates [34, 40, 42, 61, 62, 68, 71], screening efficacy [40, 41, 57, 59, 65, 66], participation rates [33, 36, 38, 44], and progression from DCIS to invasive cancer [61, 68] were found to have the largest effect on the model's cost effectiveness. The sensitivity of mammography [52, 58] and participation rates [38, 52] were reported to have the largest impact on the predicted mortality reduction.

The original MISCAN model [32] has been calibrated with data from the Dutch pilot screening projects [94, 95]. The model assumption about screen-related mortality reduction was tested against results of the Swedish breast cancer screening trial Kopparberg and Ostergötland [96]. Later, the model was refined and slightly adjusted [97], but an external validation process was not performed. The most recently published MISCAN application [70] applying digital instead of film mammography as a screening tool recalibrated the model using Dutch digital screening data [98, 99] and the latest available data on breast cancer incidence in the Netherlands, but did not perform an external validation. Three MISCAN applications [52, 56, 58] calibrated or adjusted the model for different country-specific situations, seven other MISCAN applications [53–55, 57, 59, 72, 73] did not report internal validation results.

Apart from the 11 applications of the MISCAN models mentioned above, five studies performed some form of internal validation [34, 38, 61, 64, 65]. Two studies [66, 74] conducted a partial external validation using independent screening data from randomized screening trials [100–104], one study [68] used published results of screening programs of other countries not otherwise specified. In addition, one study [66] performed cross-validation with outcomes from six of the US Cancer Intervention and Surveillance Monitoring Network models [105]. One study [33] employing the Wisconsin Breast Cancer Epidemiology Simulation Model [35] calibrated the model with data from the SEER program and reported a cross-validation against data from the Wisconsin Cancer Reporting System, a cancer registry independent of SEER. The recently published application of the Wisconsin Breast Cancer Epidemiology Simulation Model [34] performed an internal validation, described in another publication [75]. Fifteen studies [36, 40–42, 44–48, 60, 62, 63, 67, 69, 71] did not report any validation process.

3.7 Approach to Opportunistic Screening

Five cost-effectiveness studies were conducted in European countries where opportunistic screening was the prevailing screening modality, including two from Switzerland [58, 65] and one each from Germany [52], France [38], and Slovenia [68]. The German study applied the MISCAN model with special attention to the decentralized German healthcare system, but did not address the issue of opportunistic screening. The authors of the Slovenian study chose to compare their intervention with the no-screening option because the extent of opportunistic screening was unknown and therefore it was omitted from the analysis. In the French study, a no screening scenario was chosen despite the fact that opportunistic screening in France is quite common according to the authors.

Neeser compared an organized screening program with opportunistic screening in Switzerland [65]. One of the key model inputs was the reduction in breast cancer mortality assuming a 15% reduction through organized screening in

the presence of established opportunistic screening. Comprehensive sensitivity analyses were conducted to address the issue of uncertainty and identified breast cancer mortality as the most influential factor on cost effectiveness.

The second study conducted in Switzerland applied a MISCAN model to compare the cost effectiveness of alternative organized and opportunistic screening strategies with no screening. Both Neeser and de Gelder [58, 65] concluded that organized mammography screening is cost effective compared with opportunistic mammography screening, but de Gelder found that the cost per life-year gained for opportunistic screening was twice of those for organized screening.

4 Discussion

We systematically reviewed cost-effectiveness analyses in breast cancer screening in the general population by providing information about their structural and analytical approaches. This assessment included 35 studies published over 29 years, the first dating back to 1988. The studies included reflected the healthcare systems of 15 different countries. Thirty-three studies evaluated different screening strategies with mammography vs. no screening. Two studies compared organized screening with opportunistic screening in Switzerland.

The different model approaches and model types applied in the studies included state-transition models, decision trees, a stochastic model, and discrete event-simulation models. State-transition modeling was the most common approach built around a "set of mutually exclusive and collectively exhaustive health states" [106]. We identified 12 state-transition models that applied cohort simulation and 15 studies that used individual-based (first-order Monte Carlo) simulation. The cohort simulation approach is simpler than the individual-level simulation approach; models may be less complex, easier to generate and debug, and they require less computation time as they analyze cohorts rather than individuals proceeding through the health states. However, the most important disadvantage of cohort simulation can be the lack of memory known as the Markovian property; this implies that the transition probability from one state to another does not depend on past history [106]. This assumption can be very limiting because prior states and times in a given state tend to be strong determinants of future events in clinical practice. If, however, a valid representation of characteristics would lead to an large number of states, international guidelines recommend using an individual-level state-transition model approach, which simulates one individual at a time with its individual history [23] and then averages the outcomes of the individuals.

However, a disadvantage is that individual-based microsimulation requires large computational capacity and a great number of simulation runs to get robust estimates of the expected outcomes of interest [107]. In addition, joint distributions of multiple input parameters are often unknown. By using a system to simulate individuals, these models more closely resemble reality than cohort models, which do not distinguish between individual members of a pre-defined cohort [107]. If the intention is to simulate many different subgroups and individual patient histories, as in breast cancer screening, without danger of a state explosion, individual-based microsimulation represents a viable and worthwhile option.

By definition, models are simplified representations of the real world and therefore incomplete [108]. According to the recommendations of the Panel on Cost-Effectiveness in Health and Medicine and the Report of the ISPOR-Society for Medical Decision Making Modeling Good Research Practices Task Force, all modeling studies should include extensive sensitivity analyses of key parameters for judging the model's prediction accuracy [23, 29, 30, 109]. Either deterministic (one-way and multi-way) or multi-way probabilistic sensitivity analyses are appropriate and usually it is reasonable to report both types. Twenty-five studies addressed the issue of uncertainty by means of several univariate or multi-way deterministic sensitivity analyses. Eight studies performed a probabilistic sensitivity analysis but only six did so in addition to deterministic sensitivity analyses. However, a probabilistic sensitivity analysis should not replace deterministic one- or two-way sensitivity analyses because analyzing structural uncertainty may be at least as important as parameter uncertainty [29].

Current guidelines recommend validation for both multi- and single-application models [23, 30]. Despite these recommendations, validation of any type was not reported in 22 of 35 publications included in this review. Cross-validation and external validation can improve the confidence in the model's predictions, where external validation is critical as it most closely corresponds to the model's purpose to support decision makers in decision making [30]. However, external validation was often not performed, only three models reported to some extent validation with data from independent sources. This could be owing to known restrictions such as insufficient useful validation data. The lack of external validation, but even more importantly, the lack of any validation efforts can be considered a shortcoming in models increasing the risk for biased model outcomes [22, 110].

Twenty-one studies modeled the natural history of breast cancer in a scenario with and without mammography screening. Discrete tumor stages were categorized either by size or a simplified version of the American Joint

Committee of Cancer classification or the SEER historical stage classification.

The models that included DCIS in their natural history made different assumptions about the progression of DCIS to invasive cancer. In general, when in situ carcinoma is included in any model, screening can detect lesions before they progress to invasive disease. If in situ breast cancer is not included in the model, tumors are only recognizable once they reach a small localized stage. Observed trends of in situ breast cancer show that screening detects many cases in this early stage [111–114]. Not modeling the opportunity for early detection would underestimate the benefit of screening. However, DCIS is a lesion in which a certain percentage of cases will never progress to invasive breast cancer. Because such cases will not lead to death, their detection by screening constitutes an overdiagnosis. Five studies reported that not all DCIS progress to invasive cancers [33, 34, 58, 68, 70]. The reported fractions range from 11% [70] to 65% [68]. The assumption about the progression from DCIS to invasive cancer was found to have the largest effect on cost effectiveness in two models [53, 61].

Different models also made different assumptions about the fraction of invasive cancers with a screen-detectable DCIS stage, ranging from 5% [32] to 18% [70] and to 40% [68]. A debate has ensued about whether breast cancer in situ is an obligate precursor to invasive breast cancer and what proportion of in situ breast lesions progresses to invasive cancer [112]. A review of breast cancer in situ strongly suggests that DCIS is an early stage of invasive cancer but notes a wide range in estimates (14–60%) of the proportion of DCIS that will progress to invasive stages in 10 years if left untreated [115]. Because the natural history of DCIS is not yet observable, no direct evidence exists on the 'true' progression and regression rate [116]. However, the option for DCIS not to progress or even regress should be considered in modeling.

The natural history of DCIS as well as the relationship between DCIS and invasive breast cancer remain unknown [117]. Therefore, the models that include DCIS in their natural history should conduct sensitivity analyses of these parameters. In addition, not all invasive breast cancers will progress to lethal disease. These indolent tumors spend a longer time in the asymptomatic phase than faster growing tumors, and are therefore, more likely to be detected by screening and contribute to higher incidence rates. Consequently, the benefits provided by screening are overestimated causing biased modeling results; therefore, the option for cancers not to progress should also be considered in modeling [118].

Health state utilities are an essential component of cost-utility analyses. In 2010, the University of Sheffield published a review and meta-analysis of health state utility values in breast cancer [90]. Numerous studies have examined the utility values associated with breast cancer. The review reported important differences regarding valuation methods and the type of subjects who weighted quality of life (e.g., patients, physicians, or general population). A systematic review of breast cancer utility weights presented at the ISPOR 13th Annual International Meeting in 2008 revealed a high level of uncertainty about the evidence base used in cost-utility analyses examining this topic [119]. The direct utility effects of breast cancer screening are largely unknown as well as long-term health-state utility values in breast cancer. Most of the studies failed to sufficiently report the sources of utility values and provided little to no information beyond the references for the utility data. The most frequently used utility values came from a 1991 study conducted in the Netherlands that derived values from clinicians and public health experts to assess health states [84]. Only a few studies have concentrated on obtaining quality-of-life values for use in cost-effectiveness analyses of mammography screening. Two of these studies are more than 20 years old and may not represent current screening and treatment practices [84, 92]. The validity and reliability of the applied utilities are unknown, but concerns remain about the quality of utility data used in the analyses. There is a need for high-quality and precise utility estimates to establish a standardized set of health state utilities in breast cancer screening and subsequent diagnosis and treatment of breast cancer.

We also compared the results of our review with similar published reviews [11, 12, 21, 22, 120]. Some of these reviews focused more on the results of modeling studies, that is, the cost-effectiveness ratio of screening strategies [11, 21, 120], which was not the focus of our review. One review focused on breast cancer modeling in the specific setting from low- and middle-income countries [12], whereas the other, quite recently published, provided a critical evaluation of simulation models with more than one application [22]. One of the strengths compared with other reviews is our particular focus on methodological characteristics and the issues of cost-effectiveness models in breast cancer screening.

This review has several limitations. First, the review is restricted to cost-effectiveness analyses, which are only one type of economic evaluation, although this form of economic evaluation is increasingly common [121]. Results may reveal different model types and other related key characteristics when taking all economic evaluations of breast cancer screening into consideration.

Although we defined a thorough a priori search strategy, some cost-effective analyses may have been missed because they were indexed in other databases or fell outside the study's inclusion criteria [122]. Furthermore, this

review did not include gray literature [123]. Another limitation is that this review is based solely on the information ascertained from the publications. The review author did not contact study authors. Some journals have limited model descriptions owing to publishing constraints. This lack of information may have led to a misinterpretation of the available data. No assessment of the performance and validity of the models was made in this analysis.

Furthermore, the use of one rather than two reviewers to extract data that was then checked by another could bias the results. The review focused primarily on the structure and analytic approaches of economic modeling in breast cancer screening. However, other aspects of these studies such as the reliability or comparability of the results were not addressed. Finally, this review did not intend to assess and compare the cost effectiveness of breast cancer screening strategies in different countries owing to considerable variations in healthcare systems, including the cost structure and epidemiology.

5 Conclusion

In this review, we examined various cost-effectiveness models in breast cancer screening in the general population. We identified stage-shift modeling based on the natural history of breast cancer as the most used method of determining the effect of breast cancer screening. In most cases, studies used state-transition models, usually individual-level microsimulation models that seemed adequate to capture the heterogeneity of age groups, screening pathways and test characteristics as they enabled the authors to keep the number of health states manageable. However, the review did not identify a best approach for modeling the progression of DCIS to invasive cancer in the absence of a valid theory of biological behavior. Conflicting views exist on whether or not DCIS constitutes a precursor of invasive breast cancer. Owing to inadequate information on the natural history of in situ disease, models made a variety of assumptions. Therefore, it seems important that models address these parameters in sensitivity analyses. Furthermore, almost all studies were insufficient in reporting information about the utility values they used, likely because precise utility estimates for breast cancer and the screening process are still lacking. There was also a large heterogeneity in the level of validation performed. Finally, sensitivity analyses are critical to minimize the risk of biased model outcomes in cost-effectiveness studies in breast cancer screening.

Acknowledgements We thank Jen Manne-Goehler, MD, DSc, Clinical Fellow in Medicine, Harvard Medical School, for reviewing and editing the manuscript for English language. In addition, we would like to thank Tarquin Mittermayr, BA, Information Specialist at Ludwig Boltzmann Institute for Health Technology Assessment, who conducted the literature searches.

Compliance with Ethical Standards

Funding This work was supported in part by the COMET Center ONCOTYROL, which is funded by the Austrian Federal Ministries BMVIT/BMWFJ (via FFG) and the Tiroler Zukunftsstiftung/Standortagentur Tirol (SAT). The funding source had no role in designing the study, interpreting the data, and writing or publishing the manuscript.

Conflict of interest Irmgard Schiller-Frühwirth is an employee of the Main Association of Austrian Social Security Institutions and declares no conflicts of interest. Both authors, Beate Jahn and Uwe Siebert were employed by the sponsor. Marjan Arvandi is an employee of UMIT and declares no conflicts of interest.

Author contributions IS-F conceptualized and performed the systematic review and wrote the report. BJ, MA, and US contributed to the study selection. IS-F, BJ, and MA screened for titles and abstracts but screened also the full papers. US determined the outcomes of any disagreements regarding study eligibility. IS-F extracted the data; BJ checked the completeness and accuracy of the extracted study information. The first author coordinated this work and made final decisions. BJ and US reviewed and recommended revisions to the final submitted manuscript.

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