Cost Effectiveness of Breast Cancer Screening and Prevention – A Systematic Review with a Focus on Risk-Adapted Strategies

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Conflicts of Interest/Competing interests

All authors have completed a unified conflict of Interest declaration form and declare that no company had supported the submitted work. There were no other relationships or activities than those disclosed.

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Ethics approval was not required for this literature review, as no patient-related individual data were used.

Consent to participate

Not applicable

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Not applicable

Authors' contributions

Nikolai Mühlberger: Systematic literature search and data extraction. Qualitative and quantitative analyses and interpr

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Abstract

Objectives Benefit and cost effectiveness of breast cancer screening are still matters of controversy. Risk-adapted strategies are proposed to improve its benefit-harm and cost-benefit relations. Our objective was to perform a systematic review on economic breast cancer models evaluating primary and secondary prevention strategies in the European health care setting, with specific focus on model results, model characteristics, and risk-adapted strategies.

Methods Literature databases were systematically searched for economic breast cancer models evaluating the cost effectiveness of breast cancer screening and prevention strategies in the European health care context. Characteristics, methodological details and results of the identified studies are reported in evidence tables. Economic model outputs are standardized to achieve comparable cost-effectiveness ratios.

Results Thirty-two economic evaluations of breast cancer screening and seven evaluations of primary breast cancer prevention were included. Five screening studies and none of the prevention studies considered risk-adapted strategies. Studies differed in methodologic features. Only about half of the screening studies modeled overdiagnosis-related harms, most often indirectly and without reporting their magnitude. All models predict gains in life expectancy and/or quality-adjusted life expectancy at acceptable costs. However, risk-adapted screening was shown to be more effective and efficient than conventional screening.

Conclusions Economic models suggest that breast cancer screening and prevention are cost effective in the European setting. All screening models predict gains in life expectancy, which has not yet been confirmed by trials. European models evaluating

risk-adapted screening strategies are rare, but suggest that risk-adapted screening is more effective and efficient than conventional screening.

Keywords

breast cancer screening; breast cancer prevention; cost effectiveness; decision analysis; risk stratification; overdiagnosis

Introduction

Breast cancer (BCa) is the most frequently diagnosed cancer and the third most frequent cause of cancer death overall (most frequent cause of cancer death in women) in Europe [1]. Breast cancer mortality has declined over the last decades in most European countries, which can be attributed to improved treatment and early detection [2-4]. Many European countries are currently running a mammography-based screening program with biennial or triennial screening rounds within the age range of 45 or 50 to 70 or 75 years. However, there is an increasing debate about the overall mortality benefit, the benefit-harm balance and the cost effectiveness of screening, in particular, because of its still unproven effect on overall mortality and potential harms due to false positive results, overdiagnosis and overtreatment [5-12], which are usually assessed by decision-analytic modeling [13-15]. Overdiagnosis is difficult to assess in empirical studies and estimates show wide variation. Estimates derived from trials suggest that 11-22% of the breast cancer cases detected by screening might be overdiagnosed [7].

Risk factors for breast cancer include hereditary and non-hereditary factors. Best known hereditary factors are mutations in the *BRCA* genes, which are involved in the production of not strictly tumor specific tumor suppressor proteins. *BRCA* mutations have been shown to be associated with multifold risk increases in both, breast and ovarian cancer, accounting for 5-10% of the breast and 15% of the ovarian cancer cases overall [16,17]. Women with detected *BRCA* mutation have preventive options to reduce their cancer risk, including prophylactic salpingo-oophorectomy and mastectomy, or chemoprevention. Therefore, genetic and non-genetic risk profiles can be used to develop risk-adapted screening and management strategies, which have the potential to provide more favorable benefit-harm and cost-benefit relations,

by reducing interventional harms in individuals with unfavorable benefit expectation. This can be achieved either by excluding individuals at low risk from screening or by assigning them to a less aggressive screening protocol (e.g., screening with a longer screening interval). To decide on the implementation of new health technologies, including risk-adapted strategies, scientific evidence on incremental benefit and cost effectiveness is needed from health-economic models comparing their long-term benefits, harms and costs against alternative strategies, including the current standard of care [18-20].

Up to date numerous health-economic models evaluating breast cancer screening and prevention have been published and there are a number of reviews on economic breast cancer models. However, each review has unique inclusion criteria, different methodological approaches, and specific focusses [21-30], mostly on either primary or secondary prevention, leaving comparative knowledge gaps.

Therefore, our objective was to perform a comprehensive and systematic semi-quantitative review on economic breast cancer models evaluating both primary and secondary prevention strategies in the European health care setting, with specific interest on model results, model characteristics, and risk adapted strategies. Specifically, this review was performed to provide answers to the following research questions:

1. Are breast cancer screening and prevention predicted to be cost effective in the European setting?
2. What are the methodological features of the applied models, particularly, are overdiagnosis-related harms accounted for?
3. What risk-adapted strategies are modeled, and how do they perform compared to conventional screening?

Results are discussed in the context of the ongoing debate about the benefits and harms of breast cancer screening.

Methods

Literature search and study selection

We performed a systematic literature search for economic breast cancer models evaluating the cost effectiveness of breast cancer screening and prevention strategies in the European health care context published in English language. Medical, economic and health technology assessment databases (i.e., PubMed, Ovid Medline, Embase, EconLit, Cochrane Library, CRD database) were searched up to April 2018 using MESH and search term combinations for breast cancer, detection or prevention, effectiveness, costs, and modeling. Records identified through database searches were screened for eligibility by abstract and full-text assessment. Publications meeting the inclusion criteria were selected for data extraction and qualitative synthesis. Publications were excluded, if they did not present a complete economic evaluation [31], did not consider the European health care context, were published in other languages than English, or did not represent a full research article. Reasons for exclusions were documented for each excluded study. Screening of titles and abstracts, study selection, and data extraction were performed independently by two reviewers. Disagreements were resolved by discussion. If necessary, a third party opinion was consulted.

Extraction of study and model characteristics

Characteristics and methodological details of the included studies were extracted using a standardized assessment form distinguishing between screening and primary prevention studies. Extracted data comprise the following items: a) First author, year, and country, b) Study objectives and target population, c) Compared strategies and assumed adherence rates, d) Type, analysis, and analytic time horizon of the model, e) Type of economic evaluation, perspective, included cost categories, discounting, and consideration of overdiagnosis-related harms, f) Reported outcome measures, g) Applied sensitivity analyses, h) Model validation.

Models were considered to account for overdiagnosis-related harms, if (1) overdiagnosis was modeled explicitly via model inputs or indirectly by simulating cancer genesis and frequency of cancer detection up to death in presence and absence of screening, and if (2) effects of diagnostic and therapeutic procedures on quality of life were considered.

Results are reported in evidence tables. To summarize the extracted data, frequencies of study characteristics and methodological model details were assessed. Studies modeling risk-adapted strategies were presented in more detail.

Extraction and processing of study results

The data extraction and processing of the results of the economic studies included several steps to make results comparable [32]. First, we extracted expected values for costs, life years and/or quality-adjusted life years (QALY) of the included strategies. Second, expected values were expressed as increments (i.e., differences), for example life-years gained (LYG), QALYs gained or incremental costs in comparison to no intervention. This harmonization step was performed, because

some studies reported costs and health outcomes incremental to no intervention but did not present outcome predictions for the no intervention strategy itself. Third, we followed the economic standard for the calculation of incremental cost-effectiveness ratios (ICER) or cost-utility ratios (ICUR) by comparing cost and health effects of each strategy to the next less expensive and economically rational strategy. Economically irrational strategies, that are either more costly and less effective than others (dominance), or yield additional health at higher costs than more effective strategies (extended dominance) were identified and excluded from the calculation of ICERs or ICURs. In addition, we converted costs based on different years or different currencies into current euros. Currency transformation was performed using gross domestic product purchasing power parities (GDP-PPP for the countries of the European Union) [33]. Inflation adjustment to current euros (2017) was based on national consumer price indices (CPI) [34]. Results of the incremental analyses performed on processed data were presented as a synopsis in comprehensive and standardized comparative evidence tables.

Results

Literature search and selection

Fig. 1 displays the PRISMA flow diagram depicting the steps and results of the literature search and selection process. Our search yielded 1988 non-duplicate records. Of those, 1810 were excluded by abstract screening. The remaining 178 publications were assessed for eligibility by full-text screening. Of those, 139 did not meet the inclusion criteria and were excluded for reasons specified in Fig. **1**. The remaining 39 publications, which comprised 32 economic evaluations of breast cancer screening strategies and seven economic evaluations of primary breast

cancer prevention strategies, met the inclusion criteria and were selected for the comparative synthesis in the evidence tables.

Study and model characteristics

Table 1 presents characteristics and methodological details of the 39 studies. The upper part of the table presents details of the 32 breast cancer screening studies sorted by year of publication.

Of these 32 screening studies, eight evaluated screening in the UK setting [35-42], six focused on the Netherlands [43-48], seven on Spain [49-55], three on Switzerland [56-58], and two on Germany [59,60]. Screening in Austria [61], Denmark [62], France [63], Norway [64] and Slovenia [65] was each evaluated by single country-specific studies. One single study evaluated screening in several country settings, including Spain, France, UK and the Netherlands [66].

Ten screening studies evaluated hypothetical screening programs or strategies. Six studies evaluated existing screening programs. Sixteen evaluated modifications or extensions of already established screening programs.

Twenty-nine studies evaluated screening in women with average breast cancer risk (either exclusively or additionally), of which 21 included strategies comparable to currently established breast cancer screening programs, like biennial or triennial mammography screening within the age range of 45-75 years. Three studies focused on screening in high risk populations only, either in women with *BRCA* mutations (two studies) or with a family history of breast cancer (one study).

Regarding the methodological modeling approach, discrete event simulation (DES) models were the predominant model type used in 15 studies [49,59,50,43,36,52,44,56,37,47,42,60,48,66,64]. Of those, ten were based on the

Dutch MISCAN model. State-transition models were used by six studies [63,46,57,39,65,61] and mathematical models (e.g., equation- or regression-based models) were used in five studies [35,51,62,58,55]. The remaining studies used other types of models, including two decision trees [53,54], two life-table models [40,41], and two mixed models combining different model types [45,38].

Thirteen models can be classified as population models considering the actual age structure of the local target population. All but five models considered a lifetime-time horizon, appropriate to account for the long-term consequences of screening.

More than half of the screening studies (18/32) and two thirds (14/21) of the screening studies, including strategies comparable to currently established breast cancer screening programs, performed a cost-utility analysis, which is the type of analysis required to account for all kinds of non-fatal health consequences, including most harms caused by overdiagnosis- and overtreatment. Sixteen studies, including 12 with strategies resembling currently established breast cancer screening programs, accounted for overdiagnosis-related harms at least partly and most often in an indirect way. However, model predictions on overdiagnosis and overtreatment are often not reported, particularly not in older studies. In addition, consecutive harms are rarely specified explicitly but modeled indirectly via relative utility reductions applied in the post-diagnosis phase. The economic evaluations adopted different perspectives including different cost categories. Twenty studies where performed from the payer's perspective including only direct medical costs. One study was performed from the perspective of insurance members including direct medical and non-medical costs and costs of other diseases in gained lifetime. Seven studies were performed from the perspective of the health care system including direct medical costs and program costs. The remaining studies were unclear about the perspective

or did not include all costs relevant for the specified perspective. Only one of the studies applied a societal perspective including indirect costs in a scenario analysis. Discounting was applied in 25 of the 32 economic evaluations. Among those, 22 applied equal discount rates for costs and effects, two used different discount rates for costs and effect, and one applied discounting only for costs. The remaining seven studies did not use any discounting.

Reported outcome measures for effectiveness and efficiency depended on the type of economic evaluation. Some studies did not present ICERs or ICURs but more condensed outcomes based on cost-effectiveness ratios and willingness-to-pay (e.g., cost effective screening intervals or upper age bounds).

Thirty studies reported systematic uncertainty analyses. Most frequently performed types of analysis were (series of) univariate deterministic sensitivity analyses and scenario analyses. Ten studies performed multivariate probabilistic sensitivity analyses.

Twenty-one of the 32 screening studies addressed model validation. Of those, eight validated their model against observed data, eleven against observed data and other models, and two against other models only.

Although several studies evaluated a variety of screening algorithms differing in screening ages, screening intervals and screening tests, adaptation of screening algorithms to breast cancer risk was only considered by five studies [37,45,58,40,55]. Jacobi et al. [45] assessed optimal starting ages of screening for women with familial predisposition without *BRCA* mutation depending on the number, relationship degree and age at diagnosis of the affected relatives. O'Mahony et al. [58] derived optimal screening intervals depending on hypothetical breast cancer risk. Gray et al. [37] evaluated mammography screening with intervals based on personalized risk

estimations and/or breast density dependent added ultrasound. Vilaprinyo et al. [55] evaluated mammography screening with risk-group specific intervals and age ranges accounting for breast density, family history and history of prior breast biopsy. Finally, Pashayan et al. [40] evaluated screening targeted only at women beyond certain thresholds of a risk score integrating genetic and non-genetic risk factors. All five studies considering risk-adaptated screening applied different modeling approaches.

Jacobi et al. [45] used a mixed-methods approach combining two models and external calculations. First, a prediction model was used to estimate breast cancer risks for different family history constellations. Second, these risk estimates were applied in a DES like screening model to simulate tumor onset and growth in different familial risk groups up to the point of tumor detection. Finally, outputs of the simulation model were further processed outside the models to derive long-term clinical and economic outcomes compared among strategies. Whether the complex multi-model approach used by Jacobi et al. accounts for overdiagnosis is unclear.

O'Mahony et al. [58] apply a simplified mathematical equation model applicable for rapid assessment of optimal risk-adapted screening intervals, when estimates from more complex economic models are not yet available. Overdiagnosis might be partially accounted for in this model.

Gray et al. [37] developed a DES model simulating the lifetime history of 100 million women depending on individual breast cancer risk, breast density and different screening options, including no screening, current screening without risk-stratification, and screening with risk-dependent intervals and/or additional ultrasound for women with high breast density. Individual breast cancer risk was assigned via microsimulation. As this model simulates cancer onset and progression and the

frequency of cancer detection with and without screening up to the time of death, overdiagnosis is indirectly accounted for.

Vilaprinyo et al. [55] applied a mathematical equation model to simulate the lifetime history of 100,000 women divided into four risk groups (low, moderate-low, moderate-high, high) defined by breast density, family history and prior breast biopsy and differing in BCa incidence. Risk group distribution and relative risks used to model risk-group specific incidences were derived from the Risk Estimation Dataset of the Breast Cancer Surveillance Consortium and published studies. Risk-stratified screening strategies were compared to currently established screening strategies and no screening. Overdiagnosis was explicitly modeled assuming that 15% of mammography-detected cancers are overdiagnosed.

Pashayan et al. [40] extended a life-table model previously developed for the economic evaluation of the UK national breast cancer screening program. To evaluate risk-stratified screening, relative risks associated with specific risk-scores were used to derive breast cancer incidence and mortality in different risk groups. Predicted outcomes for risk-based screening strategies were compared to outcome predictions for no screening and current standard screening. As in the original life-table model overdiagnosis was explicitly modeled assuming that 19% of the cancers detected during the active screening period are overdiagnosed.

The lower part of Table 1 summarizes characteristics and methodological details of the seven primary prevention studies sorted by year of publication.

Five studies evaluated primary prevention in the UK setting [67-71], one study focused on Norway [72] and one on Germany [73]. Different from the preceding screening models, all prevention models considered not only breast cancer, but also ovarian cancer.

While the Norwegian and German studies evaluated prophylactic salpingo-oophorectomy and/or mastectomy in *BRCA* mutation carriers, the five British studies evaluated *BRCA* or polygenic screening followed by prophylactic surgery.

Specifically, three studies evaluated population-based *BRCA* mutation screening in Jewish populations with elevated mutation prevalence against currently recommended family history based *BRCA* screening [68,69,71]. One study evaluated *BRCA* screening in ovarian cancer patients and their relatives against no screening [67], and one study evaluated polygenetic screening against family history based *BRCA* screening in the general population [70]. Risk adaptation was not considered in any of the prevention studies.

Three of the British studies by Manchanda et al. used a decision tree model [68-70], whereas the remaining studies applied state-transition models [67,73,72,71]. Six models applied cohort simulation and a lifelong time horizon. One model used microsimulation over a 50 year time horizon.

One study performed only cost-effectiveness analysis based on life-years, four studies performed only cost-utility analysis based on QALYs, and two studies performed both. All studies were performed from a payer's perspective including direct medical costs, with one exception, that is, the Norwegian study also applied a societal perspective, including also non-medical and indirect costs (costs due to productivity losses). All studies of primary interventions used equal discount rates for costs and effects.

Uncertainty was analyzed via one-way deterministic sensitivity and scenario analyses in the Norwegian study. All other studies additionally applied multivariate probabilistic sensitivity analysis.

One model was validated against observed data and other models, five models were validated against other models only, and one study did not address validation.

Study results

Table 2 presents the results of incremental cost-effectiveness and/or cost-utility analyses performed on processed data of the original studies. The first part of Table 2 shows analyses of screening studies sorted by country and publication year. Incremental analyses are only presented for 25 of the 32 screening studies, since seven studies did not report appropriate data to derive ICERs and/or ICURs.

Fig. 2 summarizes ICERs and ICURs of screening strategies reflecting currently established breast cancer screening programs in comparison to no screening, sorted by year of publication. Almost all estimates fall far below 30,000 Euros per life-year or QALY gained. The only exception is the ICUR of 64,433 Euros per QALY gained calculated from the study of Vilaprinyo et al. [55]. Higher ratios beyond 100,000 Euro per QALY or life year gained are only found for screening up to much higher ages in some studies, or when risk-adapted screening strategies with different risk thresholds are compared against each other in incremental analysis (see Table 2). Fig. 2 also indicates that all models published before 2003 predict ICERs or ICURs considerably below 20.000 Euros per life-year or QALY gained, while thereafter at least some of the models yield estimates above this threshold.

Of the five studies evaluating risk-adapted screening strategies, the studies by Jacobi et al. and O'Mahony et al. presented only highly processed results, which did not allow for incremental cost-utility or cost-effectiveness analyses. However, the study by Jacobi et al. [45] suggested that screening for women with familial predisposition below the age of 50 is only cost effective, if at least two relatives are affected of whom one is a first degree relative diagnosed below the age of 50. The study by

O'Mahony et al. [58] showed how the length of the economically optimal screening interval decreases with increasing breast cancer risk. The studies by Gray et al., Vilaprinyo et al. and Pashayan et al. provided data for incremental analysis. Data from Gray et al. [37] indicate that screening with risk-adapted intervals would be more expensive than current non-stratified screening, but provide additional QALYs at lower incremental costs, which indicates extended dominance. Data from Vilaprinyo et al. [55] indicate that screening with risk-group specific intervals and age ranges would provide more QALYs and be less costly than current non-risk adapted screening, which indicates dominance in the strong sense. A similar result was shown by Pashayan et al. [40] for risk-adapted screening restricted to women with a median or higher risk-score.

The second part of Table 2 presents incremental cost-effectiveness and/or cost-utility analyses performed on processed result data of the seven prevention studies considering breast and ovarian cancer.

Data from the two studies evaluating prophylactic salpingo-oophorectomy and/or mastectomy in *BRCA* mutation carriers suggest that prophylactic surgery is a cost effective option for mutation carriers. The Norwegian study [72] comparing prophylactic surgery to no intervention yielded an ICER below 3000 EUR/LYG for the payer's perspective and below 1000 EUR/LYG for the societal perspective, respectively. The German study [73] indicated that prophylactic surgery is cost-saving (dominant), that is yielding more life-years and QALYs at lower costs than standard care with intensified surveillance.

The remaining five British studies evaluated genetic screening followed by prophylactic surgery. Three of those suggest that population-based *BRCA* screening in Jewish populations with elevated *BRCA* prevalence might be a dominant or highly

cost effective option with costs per QALY gained below 1000 Euro, when compared to currently recommended family-history based BRCA screening [68,69,71]. The fourth study evaluating *BRCA* screening in ovarian cancer patients and their relatives against no screening yielded an ICUR below 5000 Euro/QALY [67]. The fifth study yielded an ICUR below 25,000 Euro/QALY for polygenetic screening in the general population, when compared to current family history based *BRCA* screening [70].

Discussion

We performed a comprehensive and systematic semi-quantitative review on European economic breast cancer models on both screening studies and primary prevention studies to integrate and compare results. This review included 32 screening and 7 primary prevention studies.

All models predict gains in life expectancy and/or quality-adjusted life expectancy. at acceptable costs. Almost all comparisons with no intervention strategies yielded incremental cost-effectiveness ratios lower than 30,000 EUR per LYG or QALY gained, which is a commonly accepted willingness-to-pay threshold in Europe [74].

In view of the ongoing controversy about the benefits and harms of breast cancer screening an almost uniform result like that, even in more recent studies, merits attention. Main arguments of screening critics are (1) that screening-related reductions in advanced breast cancer incidence and breast cancer mortality shown in trials seem to be not in line with observational data from screened and unscreened populations, and thus might be only marginal in real world settings [11], (2) that so far none of the trials has shown a statistically significant effect of screening on overall survival [7], and (3) that potential gains in lifetime are opposed by harms and

potential losses in quality of life due to overdiagnosis and overtreatment, which could strongly hamper the benefit-harm relation and reduce the cost effectiveness of screening [12,8,7,9]. About half of the included studies accounted for overdiagnosis-related harms, at least indirectly. However, the magnitude of overdiagnosis and the spectrum of considered harms most often remained unclear. Therefore, it is difficult to judge whether all relevant harms and costs due to overdiagnosis and overtreatment have been accounted for. In particular, economic evaluations with indirect consideration of overdiagnosis tend to lack transparency, because cancer detection rates in the absence and presence of screening are rarely reported in economic studies. Thus, it is often impossible for the reader to quantify the underlying magnitude of overdiagnosis, unless it is calculated and reported by the authors. It is also difficult to tell how strongly the inclusion of overdiagnosis-related harms affected specific model results. However, compared to earlier studies accounting for overdiagnosis, more recent studies indicate considerably larger discrepancy between cost per life-year and cost per QALY gained, which largely might be due to more complete consideration of overdiagnosis. In view of lacking convincing evidence for a beneficial effect of screening on overall mortality, it seems quite optimistic that all screening models predict gains in life years and thus reductions in overall mortality. The underlying model assumption that avoidance of breast cancer death automatically translates into increased life expectancy seems to be questionable, given that biological lifetime is finite and there is a multitude of competing causes of death, which could at least partly fill the gap, when a specific cause of death is eliminated. In this case, breast cancer screening might rather be seen as an option to avoid particularly undesired causes of death than as an option to prolong life [10,75]. This view is also supported by recent benefit-harm analyses by Zahl et al. [76], which

predict overall QALY losses by BCa screening, if reductions in BCa mortality are assumed to translated only in part into reductions of overall mortality. A recent modeling study by Heijnsdijk et al. [77] simulating the power of breast cancer screening trials suggests that a sample size of 300,000 women in each study arm and a 16-26 year follow-up would be needed to detect a significant difference in overall mortality, which by far exceeds the magnitude of existing trials. However, the simulation also indicates that reductions in BCa mortality do not fully translate into reductions in overall mortality, as some women will die from other causes in the same period of time, if they are prevented from breast cancer death. As revealed by the above discussion of our findings, existing health economic breast cancer screening models, like most models, at least partly rely on yet unconfirmed assumptions. Therefore, benefit-harm and cost-effectiveness ratios predicted by these models should rather be understood as a best guess, based on the evidence and knowledge available at a time, rather than the truth.

Risk-adapted strategies are suited to optimize the overall benefit-harm-cost balance of clinical interventions by assigning each risk group the most beneficial and cost effective intervention strategy and thus avoid unnecessary harms and costs. As the benefit-harm ratio of preventive measures, including screening, is likely to increase with risk, low-risk groups could be excluded from screening or be managed less intensely than high-risk groups. To identify and evaluate optimal intervention strategies for different risk groups is a domain of decision-analytic modeling. Therefore, another objective of our review was to investigate which risk-adapted strategies have been considered by European health-economic studies and how these strategies perform compared to currently established conventional screening.

Only five of the included studies evaluated risk-adapted breast cancer screening strategies, one focusing on screening in a high-risk population [45] and four on screening in the general population [37,58,40,55]. Among the latter, the studies by O'Mahony et al. [58], Gray et al. [37] and Vilaprinyo et al. [55] evaluated risk-adapted screening intervals, or risk-adapted intervals and age ranges, whereas Pashayan et al. [40] evaluated risk-based restrictions of the target population. Data provided by Gray et al., Vilaprinyo et al. and Pashayan et al. accounted for overdiagnosis-related harms and were suited to evaluate risk-adapted screening against the currently established screening strategy in incremental analyses. Results indicate that all three risk-adapted screening approaches might be more effective and more efficient (dominant in the strong or extended sense) than current screening.

Risk adaptation was not an issue in any of the reviewed prevention models, most likely since all studies, except one, a priori focused exclusively on high-risk populations and non-risk adapted strategies were predicted to be highly beneficial and cost effective even without risk adaptation.

Health-economic breast cancer screening models have been assessed in several previous reviews with different focusses [21-30]. In contrast to previous reviews, the particular strength of our systematic review is that (1) it includes both primary prevention and screening studies, which provides an broad overview on how breast cancer is modeled by European health economic models, without regard of the evaluated intervention (2) it also focuses on risk-adapted strategies, and (3) it focuses strongly on the results of comprehensive modeling studies and aspects relevant to the ongoing debate on the benefit-harm ratio of breast cancer screening such as overdiagnosis-related harms, the unclear effect of screening on overall mortality, and potential improvements by risk-adapted strategies. A further and

extremely important feature of our work is that we used extracted model outputs to perform truly (stepwise) incremental cost-effectiveness analyses comparing strategies to the next less costly non-dominated strategy, which provides cost-effectiveness ratios relevant to decision makers [18,19,14,78]. To improve comparability of study results all cost data were converted to 2017 Euros based on PPP and CPI. In addition, we used data from studies including strategies similar to established screening programs to derive comparable ICERs and/or ICURs for currently established screening compared to no screening. A 2017 review by Arnold et al. [21] already has reviewed economic models evaluating risk-adapted breast cancer screening without geographic restriction. However, this review focused primarily on cost and utility parameters of the models and all included studies, except one, were from countries outside Europe. A more recent review on personalized breast cancer screening, besides experimental and observational studies, also included mathematical models [79]. However, the focus of this review was neither on influential methodological details and assumptions of the models, nor on cost effectiveness.

Our review has several limitations. Firstly, the review is restricted to economic studies conducted in Europe. Therefore, the review does not include all existing models. However, the restriction seems justified from a European perspective, given that cost effectiveness depends on local epidemiology, treatment patterns and costs, which is also relevant for European BCa screening guidelines [80,81]. Secondly, our search focused on studies listed in electronic databases. Thus, it cannot be ruled out that further studies exist in the gray literature. However, as our search was performed in a variety of databases, this risk is low. Thirdly, our review includes economic evaluations published over a time period of almost three decades. Within that period

breast cancer treatment has significantly improved [82]. Since more effective treatment reduces the potential for health gains by early detection and treatment, cost per life year or QALY gained derived from older models are likely to be lower than ICERs in the modern setting. However, as shown by our review, also more recent economic models suggest that breast cancer screening provides additional health at acceptable cost. Nevertheless, it should be noted that this finding is inconsistent with screening-related QALY losses found in the recent benefit-harm analyses by Zahl et al. [76], who in their model explicitly tried to factor in the effectiveness of modern breast cancer treatment. A considerable decline of screening benefits over time has also been shown by Birnbaum et al. [83], who simulated and compared the expected outcomes of a virtual screening trial performed in 1975, 1999 and 2015, given the standard of care available at that times. According to the simulation, the trial performed in 1975 would have shown an absolute 10-year risk reduction of 5 deaths per 10,000 women, while the same trial in 2015 would have shown only a reduction of 3 death per 10,000. Fourthly, our synthesis is based only on the information given in the publications, which is not always comprehensive due to the limited word count allowed in scientific journals. Particularly, the judgement of benefit-harm predictions and ICURs is often hampered by scarce information on overdiagnosis, overtreatment and considered disutilities, which makes it difficult to judge whether all relevant harms due to overdiagnosis and overtreatment have been accounted for. Fifthly, a weakness lies in the methodological heterogeneity of the included studies themselves. For example, apart from differing model types, model assumptions, time horizons and perspectives, several studies did not perform discounting, or used different rates for discounting health outcomes and costs, which is not in line with current guidelines for economic evaluations such as the EUnetHTA

Guideline [84] and may strongly impair the comparability of ICERs and ICURs.

Finally, it may be regarded as a limitation of our study that no risk of bias (RoB) assessment of the included studies was performed. RoB assessment was omitted for two reasons. First of all, our objective was not to judge, which of the included models are least biased, and to come up with a most valid estimate of an (unbiased) “pooled” ICER, which would have required a much more focused review. Instead, we intended to provide a comprehensive overview of the CEA models used to evaluate the cost effectiveness of breast cancer screening and prevention strategies in Europe, including their findings and methodological approaches and features, which are relevant for the ongoing controversy about the benefit of breast cancer screening.

The second reason for not performing a RoB assessment was that currently there is no commonly accepted RoB checklist for model based economic evaluations [85]. The most comprehensive and appropriate tool might be the ECOBIAS checklist for bias in economic evaluation [86]. However, even this checklist needs further evaluation and is likely to provide very subjective results, as it is up to the reviewer to decide whether certain types of biases assessed by the checklist are relevant in the study context or not.

Conclusions

From our comprehensive and systematic review, it can be concluded that European economic models almost unanimously suggest that breast cancer screening and primary prevention are cost effective in the European setting, even in more recent studies when overdiagnosis-related harms are accounted for more explicitly. However, it also is shown that all models assume that reductions in breast cancer mortality translate into gains in life-expectancy, which has not been convincingly

shown in trials yet. European models evaluating risk-adapted screening strategies are still rare. However, existing evaluations suggest that risk-adapted screening should be more effective and efficient than conventional screening. Therefore, future evaluations of breast cancer screening should more strongly focus on risk-adapted strategies. What is needed are strong and reliable predictors of breast cancer risk that can be translated into optimized and individualized screening algorithms with risk-adapted intervals or target selection in order to maximize benefits and minimize harms for screened women.

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Table 1 Characteristics of economic studies modeling breast cancer screening (upper part) and breast cancer primary prevention strategies (lower part). Studies in both parts of the table are presented by year of publication.

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Screening models							
de Koning 1991 NL [44]	Evaluation of different mammography screening strategies P: Women age 40+	5 mammography screening strategies at different ages and intervals vs no screening A: 65-75% (age dependent)	DES closed population model (MISCAN) A: Microsimulation H: 27 years (lifetime)	CEA, CUA P: Payer, (insurance members in scenario analysis) C: Direct medical costs (scenario analysis incl. direct non-medical costs and costs of other diseases in gained lifetime) D: 5% (costs and effects) O: Considered	Mortality reduction, LYG, QALYs gained, costs, ICER, ICUR	Deterministic SA, scenario analyses	Against observed data
van Ineveld 1993 ES, FR, UK, NL [66]	Evaluation of hypothetical mammography screening programs in different EC countries P: Women age 50+	Biennial mammography screening at age 50-70 vs no screening A: 65-75% (age dependent)	DES closed population model (MISCAN) A: Microsimulation H: 27 years (lifetime)	CEA P: Health care system C: Program costs and direct medical costs D: 5% (costs and effects) O: n.a.	Mortality reduction, LYG, costs, ICER	Scenario analyses	Partly, but not reported (Dutch model against observed data)

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Beemsterboer 1994 DE [59]	Evaluation of hypothetical mammography screening in Germany P: Women age 40+	Biennial mammography screening at age 50-70 vs no screening A: 47%	DES closed population model (MISCAN) A: Microsimulation H: 27 years (lifetime)	CEA, CUA P: Payer C: Direct medical costs D: 5% (costs and effects) O: Considered	Mortality reduction, LYG, QALYs gained, costs, ICER, ICUR	Deterministic SA, scenario analyses	Not reported
Boer 1995 NL [43]	Evaluation of different upper age limits of mammography screening P: Women age 50+	Mammography screening with different upper age bounds and intervals vs no screening A: 21-75% (age dependent), 100% in benefit-harm analysis	DES closed population model (MISCAN) A: Microsimulation H: 27 years (lifetime)	CUA P: Insurance members (society?) C: Direct medical and non-medical costs (costs of other diseases in gained lifetime?) D: 5% (costs and effects) O: Partly considered	Mortality reduction, LYG, QALYs gained, costs, ICUR	Scenario analyses (best- and worst-case analyses)	Against observed data
Garuz 1997 ES [53]	Evaluation of hypothetical mammography screening programs P: Women age 45+	Biennial mammography screening with starting age 50 and 45 and no screening A: 70%	Cycled decision tree to model effects and CE (open population model), Markov model to calculate cost parameters A: Staggered cohort simulation (decision tree), Microsimulation (Markov model) H: 25 years (program duration)	CEA P: Health care system C: Program costs and direct medical costs D: 6% (costs and effects) O: n.a.	Mortality reduction, LYG, costs, ICER	Deterministic SA, scenario analyses	Not reported

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Baker 1998 UK [35]	Evaluation of different mammography screening strategies P: Women age 48+	Mammography screening at different ages and intervals and no screening A: 100%	Maximum-likelihood model A: Analytical solution H: Lifetime	Quasi CBA (costs expressed in month of life lost, where 8 screens equal one month of life lost) P: Health care system C: Costs of screening and cost of life lost (one month of life equals the costs of 8 screens =£200) D: Not applied O: n.a.	Mortality reduction, YLL, costs of cancer (i.e., cost of screening + cost of YLL due to cancer)	Scenario analysis (doubling the cost of month of life lost)	Against observed data and other models
Beemsterboer 1998 ES (Catalonia) [50]	Evaluation of hypothetical mammography screening programs P: Women age 40+	Mammography screening at different ages and intervals vs no screening A: 69-75% (age dependent)	DES closed population model (MISCAN) A: Microsimulation H: 27 years (lifetime)	CEA P: Payer C: Direct medical costs D: 5% (costs and effects) O: n.a.	Mortality reduction, LYG, costs, ICER	Deterministic SA, scenario analyses	Partly, but not reported (dutch model against observed data)
Boer 1998 UK [36]	Evaluation of hypothetical changes to the NHS mammography screening program P: Women age 50+	2 mammography screening strategies with extended upper age bound and shorter interval vs no screening and established NHS program A: 68-74% (age	DES closed population model (MISCAN) A: Microsimulation H: 27 years (lifetime)	CEA P: Payer C: Direct medical costs	Mortality reduction, LYG, costs, ICER	Not reported dependent)	Against observed data

D: 6% (costs and effects) O: n.a.

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Gyrd-Hansen 2000 DK [62]	Evaluation of hypothetical mammography screening programs P: Women age 50+	12 mammography screening strategies at different ages and intervals and no screening A: 71-92% (depending on education and strategy)	Regression model (ordered logit model) A: Numeric solution (discrete ranking modeling) H: 30 years, according to mortality risk presented on interview cards (lifetime)	CBA P: unclear (Screening candidate?) C: Out-of-pocket costs for screening, intangible costs, cost of statistical life D: Not applied O: n.a.	Reduction in BCa mortality, Utility, Marginal WTP per extra test	Not reported	Not applied (primarily method-logical work)
Arveux 2003 FR [63]	Evaluation of a decentralized mammography screening program P: Women age 50+	Biennial decentralized mammography screening at age 50-65 vs no screening A: 54%	State-transition closed population model A: Cohort simulation H: 20 years	CEA P: Health care system C: Program costs and direct medical costs D: 5% (costs only) O: n.a.	Mortality reduction, LYG, costs, ICER	Deterministic SA (costs and attendance)	Against observed data and other models
Jacobi 2006 NL [45]	Identification of risk-dependent optimal early starting ages of screening (below age 50) in women with a family history of breast cancer without *BRCA* mutation P: Women age 30+ without *BRCA*1/2 mutation differing in familial breast cancer risk	Mammography screening with different intervals and starting ages below age 50 vs biennial screening at age 50-75 (current standard) A: Not reported (100%)	Jonker genetic model (to derive the lifetime risks of BCa in familiy risk strata), DES-like screening model modeling cancer detection among specified risk groups, (calculation of LYG and costs performed outside the model) A: Microsimulation H: Not reported (lifetime)	CEA, CUA P: Not specified (cannot be derived from included cost components) C: Costs of screening and diagnosis D: Not reported (none) O: Unclear	Lower age bounds for cost effective screening based on ICUR (underlying LYG and QALYs gained, costs, ICER, ICUR are not presented in detail),	Scenario analyses	Not applied

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Neeser 2007 CH [57]	Evaluation of a quality-controlled mammography screening program vs established opportunistic screening P: Women age 40+	Quality-controlled mammography screening program vs opportunistic screening A: 70% (quality-controlled program, 20% (opportunistic screening)	State-transition model (Markov model) A: Cohort simulation (different age cohorts) H: Lifetime and 10 years	CEA P: Statutory health insurances C: Direct medical costs covered by insurance D: 0-3% for costs and 0-1.5% for effects O: n.a.	10 year mortality and NNS, LE, lifetime costs, ICER	Deterministic and probabilistic SA	Against observed data
Norman 2007 UK [39]	Evaluation of breast cancer screening with and without MRI in *BRCA*1 mutation carriers below age 50 P: Women age 30-49 with *BRCA*1 mutation	Annual mammography, annual MRI, mammography and MRI in parallel, and no screening A: Not reported (100%)	State-transition model (Markov model) A: Cohort simulation (different age cohorts) H: Lifetime	CUA P: Payer C: Direct medical costs D: 3.5% (costs and effects) O: Unclear	QALYs gained, lifetime costs, ICUR	Deterministic and probabilistic SA	Not reported
Rojnik 2008 SL [65]	Evaluation of hypothetical mammography screening policies P: Women age 40+	36 mammography screening strategies at different ages and intervals, and no screening A: 75%	State-transition model (Markov model) H: Lifetime A: Cohort simulation	CEA, CUA P: Payer D: 3% (costs and effects) O: C: Direct medical costs Considered	QALYs, lifetime costs, ICUR, (LYG text) and ICER presented in	Deterministic and probabilistic SA	Against observed data and other models

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Gelder 2009 CH [56]	Evaluation of existing organized and opportunistic mammography screening P: Women age 50+	No screening and 5 scenarios of organized and opportunistic biennial mammography screening (differing in attendance and OP/MSP mix) A: 40-80% (depending on scenario)	DES closed population model (MISCAN) A: Microsimulation H: Lifetime (20 years for mortality predictions)	CEA, CUA P: Payer C: Direct medical costs D: 3% (costs and effects) O: Considered	Mortality reduction, LYG, QALYs, gained costs, ICER, ICUR	Deterministic SA, scenario analyses	Against observed data
Madan 2010 UK [38]	Evaluation of a hypothetical additional round below age 50 (rapid-response analysis)	One-time mammography screening at ages 47-49 vs no screening A: 100%	Decision tree (?) A: Cohort simulation H: Lifetime	CUA P: Payer C: Direct medical costs D: 3.5% (costs and effects) O: Partly considered (?) CEA, CUA	QALYs gained, costs, ICUR, Mortality reduction, Lives extended, LYG. QALYs gained, costs, ICUR	Deterministic probabilistic SA and ("plausible bounds" method) Deterministic SA, scenario analyses	Not applied Against other mode
Carles 2011 ES [51]	Evaluation of different hypothetical mammography screening strategies P: Women age 40+	20 mammography screening strategies at different ages and intervals, and no screening A: 75% (100% in scenario analysis)	Mathematical equation model (Lee and Zelen stochastic model) A: Analytical solution H: Until age 79 (lifetime)	P: Payer C: Direct medical costs D: 3% (costs and effects) O: Considered			

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Pharoah 2013 UK [41]	Evaluation of the NHS breast screening program P: Women age 50+	Triennial mammography screening at ages 50-70 vs no screening A: 75% (100% in scenario analysis)	Life table model A: Life table calculations (based on 35 year follow-up data) H: Until age 85 (lifetime)	CUA P: Health care system C: Program costs and direct medical costs D: 3.5% (costs and effects) O: Considered	Incidence and mortality reduction, LYG, QALYs gained, costs, ICUR	Probabilistic SA scenario analyses	Against observed data and other models
Comas 35 2014 36 ES [52]	Evaluation of the budgetary impact of switching to digital mammography screening P: Women age 50+	Biennial digital mammography screening vs biennial film-mammography at ages 50-69 A: 79% (initial screening, 83% (consecutive screenings)	DES dynamic population model D: Microsimulation H: 20 years (2010-2029)	BIA (plus screening effect on incidence and mortality) P: Health care system C: Program costs and direct medical costs D: Not applied O: n.a.	Incidence and mortality reduction, costs	Probabilistic SA scenario analyses	Against observed data
Vilaprinyo 2014 ES [55]	Evaluation of risk-based screening strategies (risk based on breast density, family history and history of breast biopsy) P: Women age 40+ divided in four risk groups (differing in cancer incidence)	Mammography screening with risk depending intervals and age ranges (2601 risk adapted screening strategies) vs uniform screening and no screening A: Not reported	Mathematical equation model (Lee and Zelen stochastic model) A: Analytical solution H: Until age 79 (lifetime)	Benefit-harm analyses, CEA, CUA P: Health care system C: Direct medical costs D: 3% (costs and effects) O: Considered (15% of mammograms)	Lives extended, QALYs gained, false positive and false negative cases, overdiag- nosed cases, interval cancers costs, ICER, ICUR	Deterministic SA, scenario analyses	Against observed data and other models

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Sankatsing 2015 NL [48]	Evaluation of digital mammography screening below age 50 P: Women age 40+	Digital mammography screening differing in starting age below 50 and intervals A: 80%	DES model simulating the history of 50 year old women (MISCAN) A: Microsimulation H: Lifetime	CEA, CUA (in Appendix) P: Payer C: Direct medical costs D: 3.5% (costs and effects), scenario analysis with 4% for costs and 1.5% for effects O: Considered CUA	Mortality reduction, LYG, QALYs gained, costs, ICER, ICUR	Deterministic SA, scenario analyses	Against observed data
O'Mahony 2015 CH [58]	Identification of risk- dependent optimal screening intervals (using a simplified model) P: Women age 50+with different risk of cancer onset (preclinical incidence)	Mammography screening with risk-adapted intervals (risk adapted screening) A: Not applicable (100%)	Mathematical equation model (Rapid first estimation tool) A: Analytical solution H: Not reported (lifetime)	P: Health care system C: Program costs and direct medical costs for screening and diagnosis (treatment costs not incl.) D: Not applied O: Partly considered	Optimal screening interval given BCa risk and WTP per QALY gained	Deterministic SA, scenario analyses	Against MISCAN model
Ruile 2015 DE [60]	Evaluation of switching from digital mammography to breast CT (prospective HTA analysis) P: Women age 50+	Biennial CT screening vs digital mammography screening at ages 50-69 A: 54% (mammography), 54-72% (CT)	DES dynamic population model combined with systems dynamic model A: Microsimulation H: 12 years (2016-2027)	BIA (plus screening effect on incidence) P: Payer C: Direct medical costs D: Not applied O: n.a.	Stage-shift (stage specific incidence), costs	Deterministic SA, scenario analyses	Not applied

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Arrospide 2016 ES [49]	Evaluation of the established mammography screening program in terms of cost effectiveness and budget impact P: Women age 50+	Biennial mammography screening at ages 50-69 vs no screening A: 80% (50% and 30% in scenario analyses)	DES dynamic population model A: Microsimulation (multi-cohort and single cohort simulation) H: Lifetime, (BIA 15 years 1996-2011)	CUA, BIA P: Payer C: Direct medical costs D: CUA (3% costs and effects), BIA (no discounting) O: Partly considered	QALYs gained, lifetime costs, annual costs (BIA), ICUR	Probabilistic SA scenario analyses	Against observed data and other models
Obdeijn 2016 NL [47]	Evaluation of postponed mammography screening in *BRCA*1 mutation carriers P: Women age 25+ with *BRCA*1 mutation	Annual MRI from age 25-60, annual digital mammography from age 30-60, and biennial digital mammography from age 60-74 (Dutch guideline) vs modified strategy with annual mammography postponed to age 40 A: Not reported (might be in appendix)	DES model simulating the history of women with BRACA1 mutation born in 1980 (MISCAN) A: Microsimulation H: Lifetime	CEA P: Payer C: Direct medical costs D: 3% (costs and effects) O: n.a.	BCa incidence and mortality incl. radiation induced cases, LYG, costs, ICER	Deterministic SA, scenario analyses	Against observed data
Rafia 2016 UK [42]	Evaluation of extending the NHS mammography screening program beyond age 70 P: Women age 50+	Triennial mammography screening with additional screening rounds after age 70 (up to age 90) vs screening ending at age 69 A: Not reported (might be in appendix)	DES model A: Microsimulation H: Lifetime	CEA, CUA P: Health care system C: Invitation costs and direct medical costs D: 3.5% (costs and effects) O:Partly considered	Mortality reduction, LYG, QALYs gained, costs, ICER, ICUR	Deterministic SA, scenario analyses	Against observed data and other models

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Posso 2016 ES [54]	Evaluation of double reading vs. single reading of digital mammograms in a population screening program P: Women age 50+	Double reading (current standard), single reading, prevalence screening with double reading and incidence screening with single reading A: 58.7%	Decision tree A: Cohort simulation H: 4 years (one screening round plus 2 years follow-up)	CEA P: Payer C: Direct medical costs of screening and diagnosis D: Not applied O: n.a.	Detection rates, costs, ICER (costs per additionally detected cancer)	Deterministic SA	Not reported
Gray 2017 UK [37]	Evaluation of potential stratified national breast screening programs and identification of model drivers P: Women age 50+ differing in breast cancer risk and breast density (masking)	Mammography screening with risk dependent intervals and/or breast density dependent added ultrasound vs current triennial screening and no screening A: Not reported	DES model A: Microsimulation H: Lifetime	CUA P: Payer C: Direct medical costs D: 3.5% (costs and effects), scenario analysis with 3.5% for costs and 1.5% for effects, and scenario without discounting O: Considered	QALYs, gained costs, ICUR	Deterministic SA, probabilistic SA, scenario analyses	Not applied
van Luijt 2017 NO [64]	Evaluation of the Norwegian national breast cancer screening program P: Women age 50+	National biennial screening program vs no screening A: observed data (not reported)	MISCAN (newborn cohort model (base case) and closed population model considering actual age structure (scenario) calibrated to national epidemiologic data) A: Microsimulation H: Lifetime	CUA, (CEA not reported) P: Payer and societal C: Base case: direct medical costs of screening, diagnosis and treatment; Scenario: Direct medical cost, direct non-medical costs, indirect costs D: 3.5% (costs and effects) O: Considered	Various events rates, QALYs gained, costs, ICURs (LYG not reported)	Scenario analyses	Against observed data and other models

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Schiller-Fruehwirth 2017 AT [61]	Evaluation of the Austrian national breast cancer screening program P: Women age 45+	Organized biennial screening vs opportunistic screening and no screening A: organized screening 60%, opportunistic screening 45-55% (age dependent)	State-transition model A: Microsimulation H: Lifetime	CEA P: Payer C:Direct medical costs D: 3% (costs and effects) O: n.a.	Mortality reduction, LYG, costs, ICER	Deterministic SA, probabilistic SA, scenario analyses	Against observed data and other models
Koleva-Kolarova 2018 NL [46]	Evaluation of additional mammography screening rounds below age 50 P: Women age 46+	Biennial mammography screening from age 46-74 or 48-74 vs current biennial screening from age 50-74 A: Not reported	State-transition model A: Microsimulation H: Lifetime	CEA P: Payer C:Direct medical costs D: Base-case 4% costs and 1.5% effects, scenario analysis 3% costs and effects O: n.a.	Various events rates, LYG, costs, ICER	Deterministic SA, scenario analyses	Against observed data and other models
Pashayan 2018 UK [40]	Evaluation of potential risk-stratified screening accounting for genetic and non-genetic risk factors (combined risk score) P: Women age 50 differing in breast cancer risk score	Triennial digital mammography screening from age 50-69 depending on risk thresholds vs triennial risk-independent screening (current standard) and no screening A: 75% (100% and 90% in scenario analyses)	Life table model A: Life table simulation H: Until age 85 (lifetime)	CEA, CUA P: Health care system C: Program costs and direct medical costs of treatment and risk assessment D: 3.5% (costs and effects) O: Considered (19% of cancers detected during screening period)	Various events rates incl. over-diagnosis, LYG, QALYs gained, costs, ICER, ICUR	Deterministic SA, probabilistic SA, scenario analyses	Against observed data and other models
Prevention models							

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Norum 2008 NO [72]	Evaluation of prophylactic bilateral salpingo-oophorectomy with and without prophylactic bilateral mastectomy P: Women age 30 with *BRCA*1 mutation	Prophylactic bilateral salpingo-oophorectomy with or without prophylactic bilateral mastectomy vs no intervention A: 100% (Salpingo-oophorectomy plus mastectomy), 70-100%, (Salpingo-oophorectomy alone)	State-transition model (Markov model) A: Cohort simulation H: Until age 100 (lifetime)	CEA P: Payer, insurance members, society C: Direct medical and non-medical costs, indirect costs (depending on perspective) D: 3% (costs and effects) O: n.a.	LYG, lifetime costs, ICER	Deterministic SA, scenario analyses	Against observed data (cancer incidence) and other models
Manchanda 2015 UK [68]	Evaluation of population-based genetic screening for *BRCA*1/2 gene mutations P: Ashkenazi Jewish women age 30+	Population-based genetic screening for *BRCA*1/2 mutation followed by prophylactic salpingo-oophorectomy and annual MRI-mammography or prophylactic mastectomy vs screening in women with strong family history only (family history based screening) A: 71%	Decision tree A: Cohort simulation H: Lifetime	CEA, CUA P: Payer C: Direct medical costs D: 3.5% (costs and effects) O: n.a.	LYG, QALYs gained, costs, ICUR	Deterministic and probabilistic SA, scenario analyses	Against other models
Müller 2017 DE [73]	Evaluation of different strategies to prevent breast and ovarian cancer in *BRCA*1/2 mutation carriers P: Women age 30 with *BRCA*1/2 mutation	Prophylactic bilateral mastectomy (PBM), prophylactic bilateral salpingo-oophorectomy (PBSO), PBM plus PBSO, PBM plus delayed PBSO at age 40 vs intensified surveillance A: not reported	State-transition model A: Cohort simulation H: Lifetime (until age 105)	CEA, CUA P: Payer C: Direct medical costs D: 3% (costs and effects) O: n.a.	LYG, QALYs gained, costs, ICER ICUR	Deterministic and probabilistic SA, scenario analyses	Against other models

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Manchanda 2017 UK [69]	Evaluation of population-based genetic screening for *BRCA*1/2 gene mutations for women with different degrees of Ashkenazi Jewish ancestry P: Ashkenazi Jewish women age 30+	Population-based genetic screening for *BRCA*1/2 mutation followed by prophylactic salpingo-oophorectomy and/or prophylactic mastectomy vs family history based screening A: n.r. for screening	Decision tree A: Cohort simulation H: Until age 83 (lifetime)	CUA P: Payer C: Direct medical costs D: 3.5% (costs and effects) O: n.a.	LYG (only not discounted), QALYs gained, costs, ICUR	Deterministic and probabilistic SA, scenario analyses	Against other models
Eccleston 2017 UK [67]	Evaluation of genetic screening for *BRCA*1/2 gene mutations in women with ovarian cancer and relatives of detected mutation carriers P: British ovarian cancer patients and fist- and second degree relatives	*BRCA*1/2 mutation screening in ovarian cancer patients and their relatives with the option of prophylactic salpingo-oophorectomy and/or mastectomy in affected relatives vs no *BRCA* testing A: 100%	State-transition closed population model simulating British cancer patients and their relatives A: Microsimulation H: 50 years	CUA P: Payer C: Direct medical costs D: 3.5% (costs and effects) O: n.a. C: Direct medical costs	Various events, QALYs gained, costs, ICUR	Deterministic and probabilistic SA, scenario analyses	Against other models
Patel 2018 UK [71]	Evaluation of population-based genetic screening for *BRCA*1 gene mutations P: Sephardi Jewish women age 30+	Population-based genetic screening for *BRCA*1 mutation followed by prophylactic salpingo-oophorectomy and MRI/mammography screening or prophylactic mastectomy vs family history based screening A: n.r. for screening	State-transition model H: Until age 83 (lifetime) A: Cohort simulation	CUA D: 3.5% (costs and effects) O: n.a. P: Payer	LYG (only not discounted), QALYs gained, costs, ICUR	Deterministic and probabilistic SA, scenario analyses	Not reported

Author Year Setting	Objectives Target population (P)	Compared strategies Adherence (A)	Model type Analysis approach (A) Time horizon (H)	Economic evaluation Perspective (P) Incl. cost categories (C) Discounting (D) OverDx-related harms (O)*	Outcomes	Sensitivity and scenario analyses	Validation
Manchanda 2018 UK [70]	Evaluation of population- based genetic panel screening for high/moderate- penetrance ovarian and breast cancer gene mutations (Panel: *BRCA*1, *BRCA*2, *RAD51C, RAD51D*, *BRIP*1, and *PALB2*) P: Non-Jewish women of the general population age 30+	Population-based and family history based panel screening followed by prophylactic salpingo- oophorectomy and MRI/mammography screening or prophylactic mastectomy or chemoprevention vs current family history based BRACA1/2 screening A: 71%	Decision tree A: Cohort simulation H: Lifetime	CUA P: Payer C: Direct medical costs D: 3.5% (costs and effects) O: n.a.	Various event rates, LYG, QALYs gained, costs, ICER, ICUR	Deterministic and probabilistic SA, scenario analyses	Against other model

* only relevant for screening evaluations applying cost-utility analyses

BCa: breast cancer, BIA: budget impact analysis, CEA: cost-effectiveness analysis, CUA: cost-utility analysis, CBA: cost-benefit analysis, DES: discrete event simulation, ICER: incremental cost-effectiveness ratio, ICUR: incremental cost-utility ratio, LE: life expectancy, LYG: life year gained, n.a.: not applicable, NNS: number needed to screen, OverDx: overdiagnosis, QALY: quality-adjusted life year, SA: sensitivity analysis, WTP: willingness-to-pay, YLL: year of life lost, n.a.: not applicable

Table 2 Incremental cost-effectiveness and/or cost-utility analyses performed on discounted data from economic breast cancer screening (upper part) and prevention studies (lower part) with all cost data converted to 2017 Euros. Depending on the underlying modeling approach displayed costs and effects either represent population totals or average individual values. Analyses in the upper and lower part of the table are presented by country and year of publication.

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
Screening for breast cancer (Mammography, MRI)									
Schiller-Fruehwirth, 2017, AT [61]	No screening	0	0						
	MG 45-69, 2y (organized)	701	0.0320		701	0.0320		21,901	
	MG 45-69, 2y (opportunist.)	713	0.0230		12	-0.0090		D	
Neeser 2007, CH [57]	No screening (opportunistic)	0	0						
	MG 70-death, 2y	602	0.008		602	0.008		ED	
	MG 60-death, 2y	781	0.014		179	0.006		ED	
	MG 50-death, 2y	918	0.020		137	0.006		ED	
	MG 40-death, 2y	975	0.022		57	0.002		44,304	
Gelder 2009, CH [56] (80% adher.)	No screening	0	0	0					
	Organized MG 50-69, 2y	394,349,489	34,000	31,506	394,349,489	34,000	31,506	11,599	12,517
	Opportunistic MG 50-69, 2y	802,818,909	33,700	31,161	408,469,420	-300	-345	D	D
O'Mahony 2015, CH [58]	No screening								
	MG strategies	n.r.		n.r.					CUA n.a
Beemsterboer 1994, DE [59]	No screening	0	0	0					
	MG 50-70, 2y	3,096,008,904	206,500	197,000	3,096,008,904	206,500	197,000	14,993	15,716
Ruile 2015, DE [60]	DMG 50-69, 2	n.r.	n.a.	n.a.				CEA n.a	CUA n.a
	Breast CT 50-69, 2	n.r.	n.a.	n.a.				CEA n.a	CUA n.a
Gyrd-Hansen 2000, DK [62]	No screening								
	MG strategies	n.r.		n.r.					CUA n.a
van Ineveld 1993, ES, FR, NL, UK [66]	**Model Spain**								
	No screening	0	0						
	MG 50-70, 2y	876,423,693	79,000		876,423,693	79,000		11,094	
Garuz	No screening	0	0						

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
1997, ES [53]	MG 50-65, 2y	disc. data n.r.	disc. data n.r.					3,739	
Beemsterboer	No screening	0	0						
1998, ES	MG 50-64, 3y	102,254,455	11,991		102,254,455	11,991		8,528	
(Catalonia)	MG 50-69, 3y	129,504,136	15,734		27,249,680	3,743		7,280	
[50]	MG 50-64, 2y	147,579,717	17,049		18,075,582	1,315		ED	
	MG 50-69, 2y	171,593,572	19,447		24,013,855	2,398		11,336	
	MG 45-64, 2y	180,637,290	17,559		9,043,717	-1,888		D	
	MG 40-64, 2y	231,272,624	18,566		50,635,335	1,007		D	
	MG 50-64, 1y	250,343,845	22,864		19,071,220	4,298		23,047	
Carles	No screening	0	0	0					
2011, ES [51]	MG 50-69, 2y	19,612,974	4,691	3,614	19,612,974	4,691	3,614	4,181	5,427
	MG 50-70, 2y	21,074,810	4,812	3,722	1,461,837	121	108	ED	ED
	MG 50-74, 2y	23,998,484	4,990	3,891	2,923,673	178	169	ED	ED
	MG 45-69, 2y	29,480,371	5,842	4,447	5,481,887	852	556	8,573	11,846
	MG 50-79, 2y	29,480,371	5,008	3,881	0	-834	-566	D	D
	MG 45-74, 2y	32,404,044	6,038	4,633	2,923,673	1,030	752	ED	15,719
	MG 45-79, 2y	40,565,965	6,075	4,625	8,161,921	37	-8	ED	D
	MG 50-69, 1y	40,809,604	6,528	5,003	243,639	453	378	ED	ED
	MG 40-69, 2y	41,662,342	6,630	4,943	852,738	102	-60	ED	D
	MG 40-70, 2y	43,002,359	6,751	5,051	1,340,017	121	108	ED	ED
	MG 40-74, 2y	46,047,852	6,929	5,220	3,045,493	178	169	ED	ED
	MG 50-74, 1y	48,362,426	6,781	5,234	2,314,575	-148	14	D	ED
	MG 40-79, 2y	51,529,739	6,947	5,210	3,167,313	166	-24	ED	D
	MG 50-79, 1y	59,204,381	6,800	5,199	7,674,642	-147	-11	D	D
	MG 45-69, 1y	59,326,200	7,917	5,979	121,820	1,117	780	14,384	20,002
	MG 45-74, 1y	66,757,203	8,170	6,210	7,431,003	253	231	ED	ED
	MG 45-79, 1y	77,599,157	8,190	6,175	10,841,954	20	-35	ED	D
	MG 40-69, 1y	82,959,225	9,117	6,756	5,360,067	927	581	19,694	30,416
	MG 40-74, 1y	90,390,227	9,370	6,987	7,431,003	253	231	29,372	32,169
	MG 40-79, 1y	101,232,182	9,390	6,952	10,841,954	20	-35	542,098	D
Comas	MG 50-69, 2y	disc. data n.r.	n.r.	n.r.					
2014, ES [52]	DMG 50-69, 2y	disc. data n.r.	n.r.	n.r.				CEA n.a	CUA n.a
Vilaprinyo	No screening	0		0					

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
2014, ES [55]	L risk: MG 50-69, 5y	1,379		0.023403	1,379		0.023403		ED
	ML risk: MG 45-74, 5y								
	MH risk: MG 45-74, 5y								
	H risk: MG 45-74, 1y	1,383		0.023683	5		0.000280		ED
	L risk: MG 50-69, 5y								
	ML risk: MG 45-74, 5y								
	MH risk: MG 45-74, 5y								
	H risk: MG 40-74, 1y								
	MG 50-69, 2y	1,503		0.023333	120		-0.000350		D
	L risk: MG 50-74, 5y	1,511		0.028602	7		0.005269		D
	ML risk: MG 50-74, 5y								
	MH risk: MG 40-74, 1y	1,511		0.029628	0		0.001026		50,994
	H risk: MG 40-74, 1y								
	L risk: MG 45-74, 5y								
	ML risk: MG 45-74, 5y								
	MH risk: MG 45-74, 1y								
	H risk: MG 40-74, 1y								
	MG 45-74, 2y	1,664		0.028488	153		-0.001140		D
Arrospide 2016, ES [49]	No screening	0		0					
	MG 50-69, 2y	37,036,774		8,666	37,036,774		8,666		4,274
Posso 2016, ES [54]	No screening	n.a.	n.a.	n.a.					
	DMG reading strategies	n.a.	n.a.	n.a.				CEA n.a.	
van Ineveld 1993, ES, FR, NL, UK [66]	**Model France**								
	No screening	0	0						
	MG 50-70, 2y	1,387,973,925	155,000		1,387,973,925	155,000		8,955	
Arveux 2003, FR [63]	No screening	0	0						
	MG 50-65, 2y	40,874,326	1,522		40,874,326	1,522		26,856	
de Koning 1991, NL [44]	No screening	0	0	0					
	MG 50-65, 3y	208,028,844	41,000	39,300	208,028,844	41,000	39,300	5,074	5,293
	MG 50-70, 2y	364,441,509	61,000	57,500	156,412,665	20,000	18,200	7,821	8,594
	MG 50-75, 2y	414,493,562	64,500	59,500	50,052,053	3,500	2,000	14,301	ED
	MG 50-70, 1.3y	513,033,541	70,000	66,000	98,539,979	5,500	6,500	17,916	17,481
	MG 40-70, 2y	541,187,821	64,000	59,500	28,154,280	-6,000	-6,500	D	D

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
van Ineveld 1993, ES, FR, NL, UK [66]	**Model Netherlands**								
	No screening	0	0						
	MG 50-70, 2y	364,441,683	61,000		364,441,683	61,000		5,974	
Boer 1995, NL [43]	**Optimistic Model**								
	No screening	0		0					
	MG 50-66, 2y	104		0.018577	104		0.018577		5,592
	MG 50-68, 2y	113		0.020029	9		0.001452		6,208
	MG 50-70, 2y	122		0.021292	9		0.001263		7,000
	MG 50-72, 2y	130		0.022365	8		0.001073		7,806
	MG 50-74, 2y	138		0.023218	8		0.000853		9,617
	MG 50-76, 2y	146		0.023993	8		0.000775		10,007
	MG 50-78, 2y	154		0.024645	8		0.000652		11,525
	MG 50-80, 2y	161		0.025109	8		0.000464		16,343
	MG 50-82, 2y	168		0.025427	7		0.000318		22,058
	MG 50-84, 2y	175		0.025620	6		0.000193		33,308
	MG 50-86, 2y	180		0.025727	6		0.000107		53,797
	MG 50-88, 2y	185		0.025772	5		0.000045		109,917
	Pessimistic Model								
	No screening	0		0					
	MG 50-66, 2y	225		0.018473	225		0.018473		12,188
	MG 50-68, 2y	247		0.019923	21		0.001450		14,798
	MG 50-70, 2y	269		0.021128	22		0.001205		18,436
	MG 50-72, 2y	291		0.022170	23		0.001042		21,700
	MG 50-74, 2y	315		0.022967	24		0.000797		29,820
	MG 50-76, 2y	341		0.023607	26		0.000640		40,447
	MG 50-78, 2y	370		0.024024	29		0.000417		69,764
	MG 50-80, 2y	403		0.024159	33		0.000135		241,154
	MG 50-82, 2y	438		0.024083	36		-0.000076		D
	MG 50-84, 2y	473		0.023864	35		-0.000219		D
	MG 50-86, 2y	511		0.023529	37		-0.000335		D
	MG 50-88, 2y	548		0.023124	37		-0.000405		D
Jacobi 2006, NL [45]	No screening								
	MG strategies	n.r.		n.r.					CUA n.a
Sankatsing 2015, NL [48]	No screening	0	0	0					
	DMG 50-74, 2y	139	0.041	0.054	139	0.041	0.054	3,400	2,581

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
	DMG 49+50-74, 2y	161	0.044	0.058	22	0.003	0.004	ED	ED
	DMG 48-74, 2y	166	0.046	0.061	5	0.002	0.003	5,420	3,872
	DMG 45-74, 2y	214	0.052	0.069	47	0.006	0.008	7,887	5,915
	DMG 45-49, 1y + 50-74, 2y	286	0.056	0.075	73	0.004	0.006	ED	ED
	DMG 40-74, 2y	312	0.061	0.08	25	0.005	0.005	10,889	8,909
	DMG 40-49, 1y + 50-74, 2y	484	0.07	0.092	172	0.009	0.012	19,078	14,309
Obdeijn 2016, NL [47]	MRI 25-60, 1y + DMG 40-60, 1y + 60-74, 2y	10,812	23						
	MRI 25-60, 1y + DMG 30-60, 1y + 60-74, 2y	11,365	23		546	0		276,670	
Koleva-Kolarova, 2018, NL [46]	No screening	0	0						
	MG 50-74, 2y	29,702	1.3151		29,702	1.3151		ED	
	MG 48-74, 2y	31,128	1.4282		1,426	0.1131		21795	
	MG 46-74, 2y	32,622	1.4925		1,494	0.0643		23248	
van Luijt, 2017, NO [64]	**Payer's perspective**								
	No screening	0		0					
	MG 50-69, 2y	211		0.0254	211		0.0254		8,327
	Societal perspective								
	No screening	0		0					
	MG 50-69, 2y	357		0.0254	357		0.0254		14,072
Rojnik 2008, SL [65] (only undominated strategies presented)	No screening	0	0	0					
	MG 50-65, 3y	191	0.0403	0.0359	191	0.0403	0.0359	4,730	5,310
	MG 45-65, 3y	254	0.0518	0.0465	64	0.0115	0.0106	5,545	6,015
	MG 45-70, 3y	296	0.0583	0.0521	41	0.0065	0.0056	6,381	7,407
	MG 40-70, 3y	395	0.0701	0.0626	100	0.0118	0.0105	8,442	9,487
	MG 40-75, 3y	411	0.0718	0.064	16	0.0017	0.0014	9,215	11,189
	MG 40-80, 3y	435	0.0737	0.0654	24	0.0019	0.0014	12,541	17,020
	MG 40-80, 2y	645	0.0797	0.0697	210	0.0060	0.0043	35,062	48,924
van Ineveld 1993, ES, FR, NL, UK [66]	**Model UK**								
	No screening	0	0						
	MG 50-70, 2y	968,238,121	252,000		968,238,121	252,000		3,842	
Baker 1998, UK [35]	No screening								
	MG strategies	n.r.	n.r.					CEA n.a.	

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
Boer 1998, UK [36]	No screening	0	0						
	MG 50-64, 3y	61,175,956	12,251		61,175,956	12,251		4,994	
	MG 50-69, 3y	78,400,255	15,161		17,224,298	2,910		5,919	
	MG 50-64, 2y	80,380,059	14,987		1,979,804	-174		D	
Norman 2007, UK [39]	**Age 40-49 years**								
	No screening	0		0					
	MG 40-49, 1y	2,813		0.575	2,813		0.575		4,892
	MRI 40-49, 1y	5,792		0.792	2,979		0.217		ED
	MG +MRI 40-49, 1y	6,591		0.864	799		0.072		13,074
	Age 30-39 years								
	No screening	0		0					
	MG 30-39, 1y	2,331		0.265	2,331		0.265		8,796
	MRI 30-39, 1y	5,340		0.402	3,009		0.137		21,966
	MG +MRI 30-39, 1y	6,103		0.432	762		0.030		25,413
Madan 2010, UK [38]	No screening	0		0					
	MG 47-49, 3y	75		0.00175	75		0.00175		42,947
Pharoah 2013, UK [41]	No screening	0	0	0					
	MG 50-70, 3y	47,576,392	6,907	2,040	47,576,392	6,907	2,040	6,888	23,322
Rafia 2016, UK [42]	No screening	n.r.	n.r.	n.r.					
	MG 50-69, 3y	0	0	0					
	MG 50-72, 3y	49	0.00653	0.00512	49	0.00653	0.00512	7,430	9,470
	MG 50-75, 3y	97	0.01116	0.00866	49	0.00462	0.00354	10,562	13,806
	MG 50-78, 3y	145	0.01430	0.01097	48	0.00314	0.00231	15,163	20,633
	MG 50-81, 3y	193	0.01616	0.01225	48	0.00186	0.00127	25,643	37,382
	MG 50-84, 3y	240	0.01703	0.01270	47	0.00088	0.00045	53,997	104,036
	MG 50-87, 3y	286	0.01735	0.01265	47	0.00032	-0.00005	145,870	D
	MG 50-90, 3y	331	0.01747	0.01234	44	0.00012	-0.00031	361,677	D
Gray 2017, UK [37]	A: No screening	0		0					
	B: MG 50-70, 3y (current standard)	464		0.0176	464		0.0176		ED

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
	C: Screening with risk adapted intervals (risk stratification <3.5%; 3.5-8%; >8%)	509		0.0200	45		0.0024		25,469
	D: Strategy B with suppl. US or MRI for women with high breast density	640		0.0183	131		-0.0017		D
	E: Screening with risk adapted intervals (risk stratification tertiles)	696		0.0262	56		0.0079		30,076
	F: Strategy C with suppl. US or MRI for women with high breast density	709		0.0205	14		-0.0057		D
Pashayan 2018 UK [40]	No screening	0	0	0					
	DMG 50-69, 3y (for 75th risk percentile)	21,729,584 33,594,658	4,177 6,167	1,689 2,028	21,729,584 11,865,074	4,177 1,990	1,689 339	5,202 ED	12,866 35,035
	DMG 50-69, 3y (for 50th risk percentile)	45,088,946	8,198	1,916	11,494,288	2,030	-111	5,810	D
	DMG 50-69, 3y (independent of risk)	48,471,568	7,423	2,069	3,382,622	-774	152	D	361,634
	DMG 50-69, 3y (for 25th risk percentile)								
Prevention strategies in women at high risk for breast cancer									
Müller 2017, DE [73]	No intervention	n.r.	n.r.	n.r.					
	PBM + PBSO at age 30	29,434	19.86	17.66					
	PBM + delayed PBSO	30,810	19.53	17.28	1,376	-0.33	-0.38	D	D
	PBSO	34,802	19.32	16.71	3,992	-0.21	-0.57	D	D
	PBM	37,307	18.49	16.27	2,505	-0.83	-0.44	D	D
	Intensified surveillance	45,480	17.65	14.96	8,173	-0.84	-1.31	D	D
Norum 2008, NO [72]	**Payer's perspective**								
	No intervention	0	0						
	PBSO	6,742	3.1		6,742	3.1		2,175	
	PBSO + PBM	15,702	6.4		8,960	3.3		2,715	
	Societal perspective								
	No intervention	0	0						

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
	PBSO + PBM	3,947	6.4		3,947	6.4		617	
	PBSO	4,950	3.1		1,002	-3.3		D	
Manchanda 2015, UK [68]	No *BRCA* screening	n.r.	n.r.	n.r.					
	Pop. based *BRCA* screening with PBSO/PBM	2140	23.205	23.141					
	FH based *BRCA* screening with PBSO/PBM	2221	23.180	23.110	82	-0.025	-0.031	D	D
Manchanda 2017, UK [69]	**Women with 4 Ashkenazi Jewish grandparents**								
	No *BRCA* screening	n.r.	n.r.	n.r.					
	Pop-based *BRCA* screening with PBSO/PBM	2,032	only undisc.	23.15					
	FH-based *BRCA* screening with PBSO/PBM	2,134	only undisc.	23.12	103		-0.0300		D
	Women with 3 Ashkenazi Jewish grandparents								
	No *BRCA* screening	n.r.	n.r.	n.r.					
	Pop-based *BRCA* screening with PBSO/PBM	1,979	only undisc.	23.16					
	FH-based *BRCA* screening with PBSO/PBM	2,047	only undisc.	23.13	68		-0.0300		D
	Women with 2 Ashkenazi Jewish grandparents								
	No *BRCA* screening	n.r.	n.r.	n.r.					
	Pop-based *BRCA* screening with PBSO/PBM	1,928	only undisc.	23.16					
	FH-based *BRCA* screening with PBSO/PBM	1,956	only undisc.	23.14	28		-0.0200		D
	Women with 1 Ashkenazi Jewish grandparent								
	No *BRCA* screening	n.r.	n.r.	n.r.					
	FH-based *BRCA* screening with PBSO/PBM	1,862	only undisc.	23.15					
	Pop-based *BRCA* screening with PBSO/PBM	1,876	only undisc.	23.17	14		0.0151		942

Study	Compared Strategies	Costs over no intervention*	LY over no intervention*	QALYs over no intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (EUR/LY)	ICUR (EUR/QALY)
Eccleston 2017, UK [67]	No *BRCA* screening in ovarian cancer patients and relatives	0		0					
	*BRCA*1/2 screening in ovarian cancer patients and relatives with PBSO/PBM	3,427,258		706	3,427,258		706		4,854
Patel 2018, UK [71]	No *BRCA* screening	n.r.	n.r.	n.r.					
	FH-based *BRCA* screening	1,844	only undisc.	22.42					
	Pop-based *BRCA* screening	1,920	only undisc.	23.42	75		1.0006		75
Manchanda 2018, UK [70]	No genetic screening	n.r.	n.r.	n.r.					
	FH-based *BRCA*1/2 screening	1,732	23.76	23.69					
	FH-based Panel screening	1,73	23.76	23.69		0.000			
	Pop-based Panel screening	1,94	23.77	23.70		0.007			

* Values are standardized to be incremental to no intervention, unless estimates for no intervention were not modeled or reported, which is indicated by n.r. in the no intervention row. In this instance average expected values are reported (not incremental to no intervention).

CEA: cost-effectiveness analysis, CUA: cost-utility analysis, D: dominance, DMG: digital mammography, ED: extended dominance, FH: family history, ICER: incremental cost-effectiveness ratio, ICUR: incremental cost-utility ratio, LY: life year, MG: mammography, L risk: low risk group, ML risk: medium-low risk group, MH risk: medium-high risk group, H risk: high risk group, MRI: magnetic resonance imaging, n.a.: not applicable, n.r.: not reported, PBM: prophylactic bilateral mastectomy, PBSO: prophylactic bilateral salpingo-oophorectomy, Pop: population, QALY: quality-adjusted life year. Costs were converted to 2017 Euro using gross domestic product purchasing power parities for the countries of the European Union (GDP-PPP) and national consumer price indices (CPI).

Fig. 1 PRISMA flow diagram: steps and results of the literature search and the selection process. CEA: Cost-effectiveness analysis

Fig. 2 Cost effectiveness in costs per life-year and/or QALY gained over no screening by different screening strategies reflecting currently established screening programs for women at average risk. Studies are presented by year of publication.

Strategies are described by screening test, age range and interval of screening. DMG: digital mammography, MG: mammography, QALY: quality-adjusted life year, y: year. Costs were converted to 2017 Euros using gross domestic product purchasing power parities for the countries of the European Union (GDP-PPP) and national consumer price indices (CPI).

Figure 1

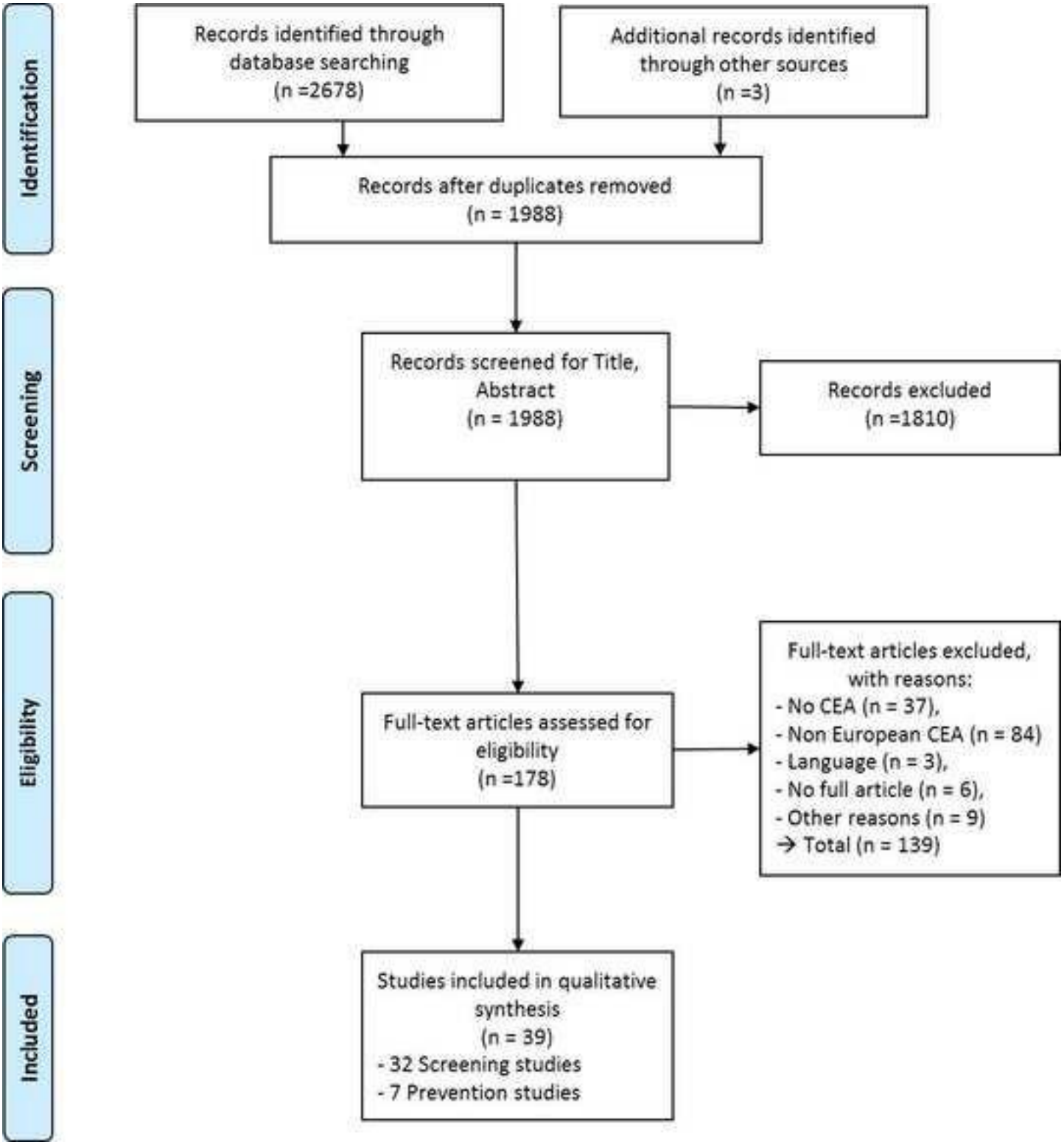

Figure 2

Click here to access/download;Figure;Figure2.jpg