

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

Nikolai Mühlberger¹, Gaby Sroczynski¹, Artemisa Gogollari¹, Beate Jahn¹, Nora Pashayan², Ewout Steyerberg^{3,4}, Martin Widschwendter⁵, Uwe Siebert^{1,6,7,8}

- 1) Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health, Health Services Research and Health Technology Assessment, UMIT – University for Health Sciences, Medical Informatics and Technology, Eduard-Wallnoefer-Zentrum I, A-6060 Hall i.T., Austria;
- 2) Institute of Epidemiology and Healthcare, Department of Applied Health Research, UCL - University College London, 1-19 Torrington Place, London WC1E 7HB, UK;
- 3) Department of Public Health, Erasmus MC, PO Box 9600, 3000 CA Rotterdam, The Netherlands;
- 4) Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands;
- 5) EGA Institute for Women's Health, Department of Women's Cancer, UCL - University College London, 74 Huntley St, Rm 340, London WC1E 6AU, UK;
- 6) ONCOTYROL - Center for Personalized Cancer Medicine, Division of Health Technology Assessment and Bioinformatics, Innsbruck, Austria;
- 7) Harvard T.H. Chan School of Public Health, Center for Health Decision Science, Department of Health Policy and Management, Boston, MA, USA;
- 8) Harvard Medical School, Institute for Technology Assessment and Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

Corresponding Author:

Uwe Siebert, MD, MPH, MSc, ScD

Institute of Public Health, Medical Decision Making and Health Technology Assessment, Department of Public Health, Health Services Research and Health Technology Assessment, UMIT – University for Health Sciences, Medical Informatics and Technology

Eduard-Wallnoefer-Zentrum 1, A-6060 Hall i.T., Austria Phone.: +43-50-8648-3930, Fax: +43-50-8648-6739310,

Email: public-health@umit.at

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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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Ethical Approval

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

Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

Nikolai Mühlberger: Systematic literature search and data extraction. Qualitative and quantitative analyses and interpretation of results. Results visualization and documentation. First draft manuscript writing.

Gaby Sroczynski: Project coordinator. Development of study design and research questions. Qualitative analysis and interpretation of results. Results visualization and

documentation. Manuscript writing and discussion.

Artemisa Gogollari: Systematic literature search and data extraction. Qualitative analyses and interpretation of results. Manuscript writing and discussion.

Beate Jahn: Qualitative analyses and interpretation of results. Manuscript review and discussion.

Nora Pashayan: Discussion and interpretation of results. Manuscript review and discussion.

Martin Widschwendter: FORECEE project lead. Discussion and interpretation of results. Manuscript review and discussion.

Ewout Steyerberg: Discussion and interpretation of results. Manuscript review and discussion.

Uwe Siebert: guarantor of this study. Responsible key researcher of the project. Qualitative analyses and interpretation of results. Manuscript writing and discussion.

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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

1 risk-adapted screening strategies are rare, but suggest that risk-adapted screening is
2 more effective and efficient than conventional screening.
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8 **Keywords**

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

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3 Breast cancer (BCa) is the most frequently diagnosed cancer and the third most
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5 frequent cause of cancer death overall (most frequent cause of cancer death in
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7 women) in Europe [1]. Breast cancer mortality has declined over the last decades in
8
9 most European countries, which can be attributed to improved treatment and early
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11 detection [2-4]. Many European countries are currently running a mammography-
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13 based screening program with biennial or triennial screening rounds within the age
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15 range of 45 or 50 to 70 or 75 years. However, there is an increasing debate about the
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17 overall mortality benefit, the benefit-harm balance and the cost effectiveness of
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19 screening, in particular, because of its still unproven effect on overall mortality and
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21 potential harms due to false positive results, overdiagnosis and overtreatment [5-12],
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23 which are usually assessed by decision-analytic modeling [13-15]. Overdiagnosis is
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25 difficult to assess in empirical studies and estimates show wide variation. Estimates
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27 derived from trials suggest that 11-22% of the breast cancer cases detected by
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29 screening might be overdiagnosed [7].
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36 Risk factors for breast cancer include hereditary and non-hereditary factors. Best
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38 known hereditary factors are mutations in the *BRCA* genes, which are involved in the
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40 production of not strictly tumor specific tumor suppressor proteins. *BRCA* mutations
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42 have been shown to be associated with multifold risk increases in both, breast and
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44 ovarian cancer, accounting for 5-10% of the breast and 15% of the ovarian cancer
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46 cases overall [16,17]. Women with detected *BRCA* mutation have preventive options
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48 to reduce their cancer risk, including prophylactic salpingo-oophorectomy and
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50 mastectomy, or chemoprevention. Therefore, genetic and non-genetic risk profiles
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52 can be used to develop risk-adapted screening and management strategies, which
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54 have the potential to provide more favorable benefit-harm and cost-benefit relations,
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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?

1 Results are discussed in the context of the ongoing debate about the benefits and
2 harms of breast cancer screening.
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8 **Methods**

11 Literature search and study selection

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13 We performed a systematic literature search for economic breast cancer models
14 evaluating the cost effectiveness of breast cancer screening and prevention
15 strategies in the European health care context published in English language.
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17 Medical, economic and health technology assessment databases (i.e., PubMed, Ovid
18 Medline, Embase, EconLit, Cochrane Library, CRD database) were searched up to
19 April 2018 using MESH and search term combinations for breast cancer, detection or
20 prevention, effectiveness, costs, and modeling. Records identified through database
21 searches were screened for eligibility by abstract and full-text assessment.
22
23 Publications meeting the inclusion criteria were selected for data extraction and
24 qualitative synthesis. Publications were excluded, if they did not present a complete
25 economic evaluation [31], did not consider the European health care context, were
26 published in other languages than English, or did not represent a full research article.
27
28 Reasons for exclusions were documented for each excluded study. Screening of
29 titles and abstracts, study selection, and data extraction were performed
30 independently by two reviewers. Disagreements were resolved by discussion. If
31 necessary, a third party opinion was consulted.
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52 Extraction of study and model characteristics

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

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

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

36 37 38 39 40 41 42 43 Extraction and processing of study results

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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

1 some studies reported costs and health outcomes incremental to no intervention but
2 did not present outcome predictions for the no intervention strategy itself. Third, we
3
4 followed the economic standard for the calculation of incremental cost-effectiveness
5 ratios (ICER) or cost-utility ratios (ICUR) by comparing cost and health effects of
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7 each strategy to the next less expensive and economically rational strategy.
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10 Economically irrational strategies, that are either more costly and less effective than
11 others (dominance), or yield additional health at higher costs than more effective
12 strategies (extended dominance) were identified and excluded from the calculation of
13 ICERs or ICURs. In addition, we converted costs based on different years or different
14 currencies into current euros. Currency transformation was performed using gross
15 domestic product purchasing power parities (GDP-PPP for the countries of the
16 European Union) [33]. Inflation adjustment to current euros (2017) was based on
17 national consumer price indices (CPI) [34]. Results of the incremental analyses
18 performed on processed data were presented as a synopsis in comprehensive and
19 standardized comparative evidence tables.
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40 **Results**

41 Literature search and selection

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43 Fig. 1 displays the PRISMA flow diagram depicting the steps and results of the
44 literature search and selection process. Our search yielded 1988 non-duplicate
45 records. Of those, 1810 were excluded by abstract screening. The remaining 178
46 publications were assessed for eligibility by full-text screening. Of those, 139 did not
47 meet the inclusion criteria and were excluded for reasons specified in Fig. 1. The
48 remaining 39 publications, which comprised 32 economic evaluations of breast
49 cancer screening strategies and seven economic evaluations of primary breast
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1 cancer prevention strategies, met the inclusion criteria and were selected for the
2 comparative synthesis in the evidence tables.
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4 Study and model characteristics 5

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8 Table 1 presents characteristics and methodological details of the 39 studies. The
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10 upper part of the table presents details of the 32 breast cancer screening studies
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12 sorted by year of publication.
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16 Of these 32 screening studies, eight evaluated screening in the UK setting [35-42],
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18 six focused on the Netherlands [43-48], seven on Spain [49-55], three on Switzerland
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20 [56-58], and two on Germany [59,60]. Screening in Austria [61], Denmark [62],
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22 France [63], Norway [64] and Slovenia [65] was each evaluated by single country-
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24 specific studies. One single study evaluated screening in several country settings,
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26 including Spain, France, UK and the Netherlands [66].
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31 Ten screening studies evaluated hypothetical screening programs or strategies. Six
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33 studies evaluated existing screening programs. Sixteen evaluated modifications or
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35 extensions of already established screening programs.
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39 Twenty-nine studies evaluated screening in women with average breast cancer risk
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41 (either exclusively or additionally), of which 21 included strategies comparable to
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43 currently established breast cancer screening programs, like biennial or triennial
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45 mammography screening within the age range of 45-75 years. Three studies focused
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47 on screening in high risk populations only, either in women with *BRCA* mutations (two
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49 studies) or with a family history of breast cancer (one study).
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54 Regarding the methodological modeling approach, discrete event simulation (DES)
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56 models were the predominant model type used in 15 studies
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58 [49,59,50,43,36,52,44,56,37,47,42,60,48,66,64]. Of those, ten were based on the
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1 Dutch MISCAN model. State-transition models were used by six studies
2 [63,46,57,39,65,61] and mathematical models (e.g., equation- or regression-based
3 models) were used in five studies [35,51,62,58,55]. The remaining studies used other
4 types of models, including two decision trees [53,54], two life-table models [40,41],
5 and two mixed models combining different model types [45,38].
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11 Thirteen models can be classified as population models considering the actual age
12 structure of the local target population. All but five models considered a lifetime-time
13 horizon, appropriate to account for the long-term consequences of screening.
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18 More than half of the screening studies (18/32) and two thirds (14/21) of the
19 screening studies, including strategies comparable to currently established breast
20 cancer screening programs, performed a cost-utility analysis, which is the type of
21 analysis required to account for all kinds of non-fatal health consequences, including
22 most harms caused by overdiagnosis- and overtreatment. Sixteen studies, including
23 12 with strategies resembling currently established breast cancer screening
24 programs, accounted for overdiagnosis-related harms at least partly and most often
25 in an indirect way. However, model predictions on overdiagnosis and overtreatment
26 are often not reported, particularly not in older studies. In addition, consecutive harms
27 are rarely specified explicitly but modeled indirectly via relative utility reductions
28 applied in the post-diagnosis phase. The economic evaluations adopted different
29 perspectives including different cost categories. Twenty studies were performed
30 from the payer's perspective including only direct medical costs. One study was
31 performed from the perspective of insurance members including direct medical and
32 non-medical costs and costs of other diseases in gained lifetime. Seven studies were
33 performed from the perspective of the health care system including direct medical
34 costs and program costs. The remaining studies were unclear about the perspective
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1 or did not include all costs relevant for the specified perspective. Only one of the
2 studies applied a societal perspective including indirect costs in a scenario analysis.
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4 Discounting was applied in 25 of the 32 economic evaluations. Among those, 22
5 applied equal discount rates for costs and effects, two used different discount rates
6 for costs and effect, and one applied discounting only for costs. The remaining seven
7 studies did not use any discounting.
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15 Reported outcome measures for effectiveness and efficiency depended on the type
16 of economic evaluation. Some studies did not present ICERs or ICURs but more
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18 condensed outcomes based on cost-effectiveness ratios and willingness-to-pay (e.g.,
19 cost effective screening intervals or upper age bounds).
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25 Thirty studies reported systematic uncertainty analyses. Most frequently performed
26 types of analysis were (series of) univariate deterministic sensitivity analyses and
27 scenario analyses. Ten studies performed multivariate probabilistic sensitivity
28 analyses.
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35 Twenty-one of the 32 screening studies addressed model validation. Of those, eight
36 validated their model against observed data, eleven against observed data and other
37 models, and two against other models only.
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43 Although several studies evaluated a variety of screening algorithms differing in
44 screening ages, screening intervals and screening tests, adaptation of screening
45 algorithms to breast cancer risk was only considered by five studies [37,45,58,40,55].
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50 Jacobi et al. [45] assessed optimal starting ages of screening for women with familial
51 predisposition without *BRCA* mutation depending on the number, relationship degree
52 and age at diagnosis of the affected relatives. O'Mahony et al. [58] derived optimal
53 screening intervals depending on hypothetical breast cancer risk. Gray et al. [37]
54 evaluated mammography screening with intervals based on personalized risk
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1 estimations and/or breast density dependent added ultrasound. Vilapriyo et al. [55]
2 evaluated mammography screening with risk-group specific intervals and age ranges
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4 accounting for breast density, family history and history of prior breast biopsy. Finally,
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7 Pashayan et al. [40] evaluated screening targeted only at women beyond certain
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10 thresholds of a risk score integrating genetic and non-genetic risk factors. All five
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12 studies considering risk-adaptated screening applied different modeling approaches.

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

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

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45 Gray et al. [37] developed a DES model simulating the lifetime history of 100 million
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48 women depending on individual breast cancer risk, breast density and different
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50 screening options, including no screening, current screening without risk-
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52 stratification, and screening with risk-dependent intervals and/or additional ultrasound
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55 for women with high breast density. Individual breast cancer risk was assigned via
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1 frequency of cancer detection with and without screening up to the time of death,
2 overdiagnosis is indirectly accounted for.
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5 VilaprinYO et al. [55] applied a mathematical equation model to simulate the lifetime
7 history of 100,000 women divided into four risk groups (low, moderate-low, moderate-
8 high, high) defined by breast density, family history and prior breast biopsy and
10 differing in BCa incidence. Risk group distribution and relative risks used to model
12 risk-group specific incidences were derived from the Risk Estimation Dataset of the
13 Breast Cancer Surveillance Consortium and published studies. Risk-stratified
15 screening strategies were compared to currently established screening strategies
17 and no screening. Overdiagnosis was explicitly modeled assuming that 15% of
18 mammography-detected cancers are overdiagnosed.
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22 Pashayan et al. [40] extended a life-table model previously developed for the
23 economic evaluation of the UK national breast cancer screening program. To
24 evaluate risk-stratified screening, relative risks associated with specific risk-scores
25 were used to derive breast cancer incidence and mortality in different risk groups.
26 Predicted outcomes for risk-based screening strategies were compared to outcome
27 predictions for no screening and current standard screening. As in the original life-
28 table model overdiagnosis was explicitly modeled assuming that 19% of the cancers
29 detected during the active screening period are overdiagnosed.
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47 The lower part of Table 1 summarizes characteristics and methodological details of
48 the seven primary prevention studies sorted by year of publication.
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51 Five studies evaluated primary prevention in the UK setting [67-71], one study
52 focused on Norway [72] and one on Germany [73]. Different from the preceding
53 screening models, all prevention models considered not only breast cancer, but also
54 ovarian cancer.
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1 While the Norwegian and German studies evaluated prophylactic salpingo-
2 oophorectomy and/or mastectomy in *BRCA* mutation carriers, the five British studies
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4 evaluated *BRCA* or polygenic screening followed by prophylactic surgery.
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7 Specifically, three studies evaluated population-based *BRCA* mutation screening in
9 Jewish populations with elevated mutation prevalence against currently
10 recommended family history based *BRCA* screening [68,69,71]. One study evaluated
12 *BRCA* screening in ovarian cancer patients and their relatives against no screening
14 [67], and one study evaluated polygenetic screening against family history based
15 *BRCA* screening in the general population [70]. Risk adaptation was not considered
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17 in any of the prevention studies.
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23 Three of the British studies by Manchanda et al. used a decision tree model [68-70],
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25 whereas the remaining studies applied state-transition models [67,73,72,71]. Six
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27 models applied cohort simulation and a lifelong time horizon. One model used
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29 microsimulation over a 50 year time horizon.
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33 One study performed only cost-effectiveness analysis based on life-years, four
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35 studies performed only cost-utility analysis based on QALYs, and two studies
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37 performed both. All studies were performed from a payer's perspective including
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39 direct medical costs, with one exception, that is, the Norwegian study also applied a
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41 societal perspective, including also non-medical and indirect costs (costs due to
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43 productivity losses). All studies of primary interventions used equal discount rates for
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45 costs and effects.
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52 Uncertainty was analyzed via one-way deterministic sensitivity and scenario analyses
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54 in the Norwegian study. All other studies additionally applied multivariate probabilistic
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56 sensitivity analysis.
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1 One model was validated against observed data and other models, five models were
2 validated against other models only, and one study did not address validation.
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4 Study results 5

6 Table 2 presents the results of incremental cost-effectiveness and/or cost-utility
7 analyses performed on processed data of the original studies. The first part of Table 2
8 shows analyses of screening studies sorted by country and publication year.
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10 Incremental analyses are only presented for 25 of the 32 screening studies, since
11 seven studies did not report appropriate data to derive ICERs and/or ICURs.
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13 Fig. 2 summarizes ICERs and ICURs of screening strategies reflecting currently
14 established breast cancer screening programs in comparison to no screening, sorted
15 by year of publication. Almost all estimates fall far below 30,000 Euros per life-year or
16 QALY gained. The only exception is the ICUR of 64,433 Euros per QALY gained
17 calculated from the study of VilaprinYO et al. [55]. Higher ratios beyond 100,000 Euro
18 per QALY or life year gained are only found for screening up to much higher ages in
19 some studies, or when risk-adapted screening strategies with different risk thresholds
20 are compared against each other in incremental analysis (see Table 2). Fig. 2 also
21 indicates that all models published before 2003 predict ICERs or ICURs considerably
22 below 20.000 Euros per life-year or QALY gained, while thereafter at least some of
23 the models yield estimates above this threshold.
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26 Of the five studies evaluating risk-adapted screening strategies, the studies by Jacobi
27 et al. and O'Mahony et al. presented only highly processed results, which did not
28 allow for incremental cost-utility or cost-effectiveness analyses. However, the study
29 by Jacobi et al. [45] suggested that screening for women with familial predisposition
30 below the age of 50 is only cost effective, if at least two relatives are affected of
31 whom one is a first degree relative diagnosed below the age of 50. The study by
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1 O'Mahony et al. [58] showed how the length of the economically optimal screening
2 interval decreases with increasing breast cancer risk. The studies by Gray et al.,
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4 Vilaprinayo et al. and Pashayan et al. provided data for incremental analysis. Data
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6 from Gray et al. [37] indicate that screening with risk-adapted intervals would be more
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8 expensive than current non-stratified screening, but provide additional QALYs at
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10 lower incremental costs, which indicates extended dominance. Data from Vilaprinayo
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12 et al. [55] indicate that screening with risk-group specific intervals and age ranges
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14 would provide more QALYs and be less costly than current non-risk adapted
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16 screening, which indicates dominance in the strong sense. A similar result was
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18 shown by Pashayan et al. [40] for risk-adapted screening restricted to women with a
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20 median or higher risk-score.
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22 The second part of Table 2 presents incremental cost-effectiveness and/or cost-utility
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24 analyses performed on processed result data of the seven prevention studies
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26 considering breast and ovarian cancer.
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28 Data from the two studies evaluating prophylactic salpingo-oophorectomy and/or
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30 mastectomy in *BRCA* mutation carriers suggest that prophylactic surgery is a cost
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32 effective option for mutation carriers. The Norwegian study [72] comparing
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34 prophylactic surgery to no intervention yielded an ICER below 3000 EUR/LYG for the
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36 payer's perspective and below 1000 EUR/LYG for the societal perspective,
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38 respectively. The German study [73] indicated that prophylactic surgery is cost-
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40 saving (dominant), that is yielding more life-years and QALYs at lower costs than
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42 standard care with intensified surveillance.
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45 The remaining five British studies evaluated genetic screening followed by
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47 prophylactic surgery. Three of those suggest that population-based *BRCA* screening
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49 in Jewish populations with elevated *BRCA* prevalence might be a dominant or highly
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1 cost effective option with costs per QALY gained below 1000 Euro, when compared
2 to currently recommended family-history based BRCA screening [68,69,71]. The
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4 fourth study evaluating *BRCA* screening in ovarian cancer patients and their relatives
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6 against no screening yielded an ICUR below 5000 Euro/QALY [67]. The fifth study
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8 yielded an ICUR below 25,000 Euro/QALY for polygenetic screening in the general
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10 population, when compared to current family history based *BRCA* screening [70].
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18 **Discussion**

19 We performed a comprehensive and systematic semi-quantitative review on
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21 European economic breast cancer models on both screening studies and primary
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23 prevention studies to integrate and compare results. This review included 32
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25 screening and 7 primary prevention studies.
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29 All models predict gains in life expectancy and/or quality-adjusted life expectancy. at
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31 acceptable costs. Almost all comparisons with no intervention strategies yielded
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33 incremental cost-effectiveness ratios lower than 30,000 EUR per LYG or QALY
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35 gained, which is a commonly accepted willingness-to-pay threshold in Europe [74].
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40 In view of the ongoing controversy about the benefits and harms of breast cancer
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42 screening an almost uniform result like that, even in more recent studies, merits
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44 attention. Main arguments of screening critics are (1) that screening-related
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46 reductions in advanced breast cancer incidence and breast cancer mortality shown in
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48 trials seem to be not in line with observational data from screened and unscreened
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50 populations, and thus might be only marginal in real world settings [11], (2) that so far
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52 none of the trials has shown a statistically significant effect of screening on overall
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54 survival [7], and (3) that potential gains in lifetime are opposed by harms and
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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

1 predict overall QALY losses by BCa screening, if reductions in BCa mortality are
2 assumed to translated only in part into reductions of overall mortality. A recent
3 modeling study by Heijnsdijk et al. [77] simulating the power of breast cancer
4 screening trials suggests that a sample size of 300,000 women in each study arm
5 and a 16-26 year follow-up would be needed to detect a significant difference in
6 overall mortality, which by far exceeds the magnitude of existing trials. However, the
7 simulation also indicates that reductions in BCa mortality do not fully translate into
8 reductions in overall mortality, as some women will die from other causes in the same
9 period of time, if they are prevented from breast cancer death. As revealed by the
10 above discussion of our findings, existing health economic breast cancer screening
11 models, like most models, at least partly rely on yet unconfirmed assumptions.

12 Therefore, benefit-harm and cost-effectiveness ratios predicted by these models
13 should rather be understood as a best guess, based on the evidence and knowledge
14 available at a time, rather than the truth.

15 Risk-adapted strategies are suited to optimize the overall benefit-harm-cost balance
16 of clinical interventions by assigning each risk group the most beneficial and cost
17 effective intervention strategy and thus avoid unnecessary harms and costs. As the
18 benefit-harm ratio of preventive measures, including screening, is likely to increase
19 with risk, low-risk groups could be excluded from screening or be managed less
20 intensely than high-risk groups. To identify and evaluate optimal intervention
21 strategies for different risk groups is a domain of decision-analytic modeling.

22 Therefore, another objective of our review was to investigate which risk-adapted
23 strategies have been considered by European health-economic studies and how
24 these strategies perform compared to currently established conventional screening.

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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

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

17 Our review has several limitations. Firstly, the review is restricted to economic studies
18 conducted in Europe. Therefore, the review does not include all existing models.

19 However, the restriction seems justified from a European perspective, given that cost
20 effectiveness depends on local epidemiology, treatment patterns and costs, which is
21 also relevant for European BCa screening guidelines [80,81]. Secondly, our search
22 focused on studies listed in electronic databases. Thus, it cannot be ruled out that
23 further studies exist in the gray literature. However, as our search was performed in a
24 variety of databases, this risk is low. Thirdly, our review includes economic
25 evaluations published over a time period of almost three decades. Within that period

1 breast cancer treatment has significantly improved [82]. Since more effective
2 treatment reduces the potential for health gains by early detection and treatment,
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4 cost per life year or QALY gained derived from older models are likely to be lower
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6 than ICERs in the modern setting. However, as shown by our review, also more
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8 recent economic models suggest that breast cancer screening provides additional
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10 health at acceptable cost. Nevertheless, it should be noted that this finding is
11
12 inconsistent with screening-related QALY losses found in the recent benefit-harm
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14 analyses by Zahl et al. [76], who in their model explicitly tried to factor in the
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16 effectiveness of modern breast cancer treatment. A considerable decline of screening
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18 benefits over time has also been shown by Birnbaum et al. [83], who simulated and
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20 compared the expected outcomes of a virtual screening trial performed in 1975, 1999
21
22 and 2015, given the standard of care available at that times. According to the
23
24 simulation, the trial performed in 1975 would have shown an absolute 10-year risk
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26 reduction of 5 deaths per 10,000 women, while the same trial in 2015 would have
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28 shown only a reduction of 3 death per 10,000. Fourthly, our synthesis is based only
29
30 on the information given in the publications, which is not always comprehensive due
31
32 to the limited word count allowed in scientific journals. Particularly, the judgement of
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34 benefit-harm predictions and ICURs is often hampered by scarce information on
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36 overdiagnosis, overtreatment and considered disutilities, which makes it difficult to
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38 judge whether all relevant harms due to overdiagnosis and overtreatment have been
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40 accounted for. Fifthly, a weakness lies in the methodological heterogeneity of the
41
42 included studies themselves. For example, apart from differing model types, model
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44 assumptions, time horizons and perspectives, several studies did not perform
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46 discounting, or used different rates for discounting health outcomes and costs, which
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48 is not in line with current guidelines for economic evaluations such as the EUnetHTA
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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

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

- 24 1. Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J.W., Comber, H., Forman,
25 D., Bray, F.: Cancer incidence and mortality patterns in Europe: estimates for 40 countries in
26 2012. *European journal of cancer (Oxford, England : 1990)* **49**(6), 1374-1403 (2013).
27 doi:10.1016/j.ejca.2012.12.027
- 28 2. Amaro, J., Severo, M., Vilela, S., Fonseca, S., Fontes, F., La Vecchia, C., Lunet, N.: Patterns of breast
29 cancer mortality trends in Europe. *Breast* **22**(3), 244-253 (2013).
30 doi:10.1016/j.breast.2013.02.007
- 31 3. Autier, P., Boniol, M., La Vecchia, C., Vatten, L., Gavin, A., Hery, C., Heanue, M.: Disparities in breast
32 cancer mortality trends between 30 European countries: retrospective trend analysis of WHO
33 mortality database. *BMJ (Clinical research ed.)* **341**, c3620 (2010). doi:10.1136/bmj.c3620
- 34 4. De Angelis, R., Sant, M., Coleman, M.P., Francisci, S., Baili, P., Pierannunzio, D., Trama, A., Visser,
35 O., Brenner, H., Ardanaz, E., Bielska-Lasota, M., Engholm, G., Nennecke, A., Siesling, S.,
36 Berrino, F., Capocaccia, R., Group, E.-W.: Cancer survival in Europe 1999-2007 by country and
37 age: results of EURO CARE--5-a population-based study. *Lancet Oncol* **15**(1), 23-34 (2014).
38 doi:10.1016/S1470-2045(13)70546-1
- 39 5. Chetlen, A., Mack, J., Chan, T.: Breast cancer screening controversies: who, when, why, and how?
40 *Clin Imaging* **40**(2), 279-282 (2016). doi:10.1016/j.clinimag.2015.05.017
- 41 6. Jorgensen, K.J., Kalager, M., Barratt, A., Baines, C., Zahl, P.H., Brodersen, J., Harris, R.P.: Overview
42 of guidelines on breast screening: Why recommendations differ and what to do about it.
43 *Breast* **31**, 261-269 (2017). doi:10.1016/j.breast.2016.08.002
- 44 7. Nelson, H.D., Cantor, A., Humphrey, L., Fu, R., Pappas, M., Daeges, M., Griffin, J.: Screening for
45 Breast Cancer: A Systematic Review to Update the 2009 U.S. Preventive Services Task Force
46 Recommendation. In: *Screening for Breast Cancer: A Systematic Review to Update the 2009*
47 *U.S. Preventive Services Task Force Recommendation. U.S. Preventive Services Task Force*
48 *Evidence Syntheses, formerly Systematic Evidence Reviews. Rockville (MD) (2016)*
- 49 8. Marmot, M.G., Altman, D.G., Cameron, D.A., Dewar, J.A., Thompson, S.G., Wilcox, M.: The benefits
50 and harms of breast cancer screening: an independent review. *Br J Cancer* **108**(11), 2205-
51 2240 (2013). doi:10.1038/bjc.2013.177
52
53
54
55
56
57
58
59

- 1 9. Welch, H.G., Prorok, P.C., O'Malley, A.J., Kramer, B.S.: Breast-Cancer Tumor Size, Overdiagnosis,
2 and Mammography Screening Effectiveness. *The New England journal of medicine* **375**(15),
3 1438-1447 (2016). doi:10.1056/NEJMoa1600249
- 4 10. Adami, H.O., Kalager, M., Valdimarsdottir, U., Bretthauer, M., Ioannidis, J.P.A.: Time to abandon
5 early detection cancer screening. *Eur J Clin Invest*, e13062 (2018). doi:10.1111/eci.13062
- 6 11. Autier, P., Boniol, M.: Mammography screening: A major issue in medicine. *European journal of*
7 *cancer (Oxford, England : 1990)* **90**, 34-62 (2018). doi:10.1016/j.ejca.2017.11.002
- 8 12. Autier, P., Boniol, M., Koechlin, A., Pizot, C., Boniol, M.: Effectiveness of and overdiagnosis from
9 mammography screening in the Netherlands: population based study. *BMJ (Clinical research*
10 *ed.)* **359**, j5224 (2017). doi:10.1136/bmj.j5224
- 11 13. Caro, J.J., Briggs, A.H., Siebert, U., Kuntz, K.M., Force, I.-S.M.G.R.P.T.: Modeling good research
12 practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task
13 Force-1. *Medical decision making : an international journal of the Society for Medical*
14 *Decision Making* **32**(5), 667-677 (2012). doi:10.1177/0272989X12454577
- 15 14. Siebert, U.: When should decision-analytic modeling be used in the economic evaluation of health
16 care? [Editorial]. *The European Journal of Health Economics* **4**(3), 143–150 (2003).
- 17 15. Siebert, U., Alagoz, O., Bayoumi, A.M., Jahn, B., Owens, D.K., Cohen, D.J., Kuntz, K.M.: State-
18 transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task
19 Force-3. *Medical decision making : an international journal of the Society for Medical*
20 *Decision Making* **32**(5), 690-700 (2012). doi:10.1177/0272989X12455463
- 21 16. National Cancer Institute: BRCA Mutations: Cancer Risk and Genetic Testing (Fact Sheet).
22 Available at: [https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-](https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#r4)
23 [sheet#r4](https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#r4), Accessed: November 2019. (2015).
- 24 17. Levy-Lahad, E., Friedman, E.: Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br J Cancer*
25 **96**(1), 11-15 (2007). doi:10.1038/sj.bjc.6603535
- 26 18. Gold, M.R., Siegel, J.E., Russell, L.B., Weinstein, M.C.: *Cost-Effectiveness in Health and Medicine*.
27 Oxford University Press Inc., New York (1996)
- 28 19. Hunink, M., Glasziou, P., Siegel, J., Weeks, S., Pliskin, J., Elstein, A., Weinstein, M.: *Decision making*
29 *in health and medicine. Integrating evidence and values*. Cambridge University Press,
30 Cambridge (2001)
- 31 20. Weinstein, M.C.: High-priced technology can be good value for money. *Annals of internal*
32 *medicine* **130**(10), 857-858 (1999).
- 33 21. Arnold, M.: Simulation modeling for stratified breast cancer screening - a systematic review of
34 cost and quality of life assumptions. *BMC health services research* **17**(1), 802 (2017).
35 doi:10.1186/s12913-017-2766-2
- 36 22. Barratt, A.L., Les Irwig, M., Glasziou, P.P., Salkeld, G.P., Houssami, N.: Benefits, harms and costs of
37 screening mammography in women 70 years and over: a systematic review. *The Medical*
38 *journal of Australia* **176**(6), 266-271 (2002).
- 39 23. Brown, D.W., French, M.T., Schweitzer, M.E., McGeary, K.A., McCoy, C.B., Ullmann, S.G.:
40 Economic evaluation of breast cancer screening: A review. *Cancer practice* **7**(1), 28-33 (1999).
- 41 24. De Koning, H.J.: Breast cancer screening; cost-effective in practice? *European journal of radiology*
42 **33**(1), 32-37 (2000).
- 43 25. Koleva-Kolarova, R.G., Zhan, Z., Greuter, M.J., Feenstra, T.L., De Bock, G.H.: To screen or not to
44 screen for breast cancer? How do modelling studies answer the question? *Current oncology*
45 (Toronto, Ont.) **22**(5), e380-382 (2015). doi:10.3747/co.22.2889
- 46 26. Koleva-Kolarova, R.G., Zhan, Z., Greuter, M.J., Feenstra, T.L., De Bock, G.H.: Simulation models in
47 population breast cancer screening: A systematic review. *Breast* **24**(4), 354-363 (2015).
48 doi:10.1016/j.breast.2015.03.013
- 49 27. Mandelblatt, J., Saha, S., Teutsch, S., Hoerger, T., Siu, A.L., Atkins, D., Klein, J., Helfand, M.: The
50 cost-effectiveness of screening mammography beyond age 65 years: a systematic review for
51 the U.S. Preventive Services Task Force. *Annals of internal medicine* **139**(10), 835-842 (2003).
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54
55
56
57
58
59
28. Petelin, L., Trainer, A.H., Mitchell, G., Liew, D., James, P.A.: Cost-effectiveness and comparative effectiveness of cancer risk management strategies in BRCA1/2 mutation carriers: a systematic review. *Genetics in medicine : official journal of the American College of Medical Genetics* (2018). doi:10.1038/gim.2017.255
29. Rashidian, A., Barfar, E., Hosseini, H., Nosratnejad, S., Barooti, E.: Cost effectiveness of breast cancer screening using mammography; a systematic review. *Iranian journal of public health* **42**(4), 347-357 (2013).
30. Schiller-Fruhwrth, I.C., Jahn, B., Arvandi, M., Siebert, U.: Cost-Effectiveness Models in Breast Cancer Screening in the General Population: A Systematic Review. *Applied health economics and health policy* (2017). doi:10.1007/s40258-017-0312-3
31. Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L., Torrance, G.W.: *Methods for the Economic Evaluation of Health Care Programmes*, 4th ed. Oxford University Press, (2015)
32. Siebert, U.: *Using Decision-Analytic Modelling to Transfer International Evidence from Health Technology Assessment to the Context of the German Health Care System*. Health Technology Assessment Vol 15. (Series of the German Institute for Medical Documentation and Information commissioned by the Federal Ministry of Health and Social Security). DIMDI, Cologne (2005)
33. OECD statistics. Purchasing Power Parities for GDP and related indicators. Available at: <https://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP> Accessed: April 2018.
<https://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP>. Accessed April 2018
34. OECD statistics. National CPI weights. Available at:
https://stats.oecd.org/Index.aspx?DataSetCode=MEI_CPI_WEIGHTS Accessed: April 2018.
https://stats.oecd.org/Index.aspx?DataSetCode=MEI_CPI_WEIGHTS. Accessed April 2018
35. Baker, R.D.: Use of a mathematical model to evaluate breast cancer screening policy. *Health care management science* **1**(2), 103-113 (1998).
36. Boer, R., Koning, H., Threlfall, A., Warmderdam, P., Street, A., Friedman, E., Woodman, C.: Cost effectiveness of shortening screening interval or extending age range of NHS breast screening programme: computer simulation study. *BMJ (Clinical research ed.)* (1998).
37. Gray, E., Donten, A., Karssemeijer, N., van Gils, C., Evans, D.G., Astley, S., Payne, K.: Evaluation of a Stratified National Breast Screening Program in the United Kingdom: An Early Model-Based Cost-Effectiveness Analysis. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* **20**(8), 1100-1109 (2017). doi:10.1016/j.jval.2017.04.012
38. Madan, J., Rawdin, A., Stevenson, M., Tappenden, P.: A rapid-response economic evaluation of the UK NHS Cancer Reform Strategy breast cancer screening program extension via a plausible bounds approach. *Value in Health* (2010).
39. Norman, R.P., Evans, D.G., Easton, D.F., Young, K.C.: The cost-utility of magnetic resonance imaging for breast cancer in BRCA1 mutation carriers aged 30-49. *The European journal of health economics : HEPAC : health economics in prevention and care* **8**(2), 137-144 (2007). doi:10.1007/s10198-007-0042-9
40. Pashayan, N., Morris, S., Gilbert, F.J., Pharoah, P.D.P.: Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. *JAMA Oncol* (2018). doi:10.1001/jamaoncol.2018.1901
41. Pharoah, P.D., Sewell, B., Fitzsimmons, D., Bennett, H.S., Pashayan, N.: Cost effectiveness of the NHS breast screening programme: life table model. *BMJ (Clinical research ed.)* **346**, f2618 (2013). doi:10.1136/bmj.f2618
42. Rafia, R., Brennan, A., Madan, J., Collins, K., Reed, M.W., Lawrence, G., Robinson, T., Greenberg, D., Wyld, L.: Modeling the Cost-Effectiveness of Alternative Upper Age Limits for Breast Cancer Screening in England and Wales. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* **19**(4), 404-412 (2016). doi:10.1016/j.jval.2015.06.006

43. Boer, R., de Koning, H.J., van Oortmarsen, G.J., van der Maas, P.J.: In search of the best age limit for breast cancer screening. *European journal of cancer (Oxford, England)* **31a**(12), 2040-2043 (1995).
44. de Koning, H.J., van Ineveld, B.M., van Oortmarsen, G.J., de Haes, J.C., Collette, H.J., Hendriks, J.H., van der Maas, P.J.: Breast cancer screening and cost-effectiveness; policy alternatives, quality of life considerations and the possible impact of uncertain factors. *Int J Cancer* **49**(4), 531-537 (1991).
45. Jacobi, C.E., Nagelkerke, N.J., van Houwelingen, J.H., de Bock, G.H.: Breast cancer screening, outside the population-screening program, of women from breast cancer families without proven BRCA1/BRCA2 mutations: a simulation study. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **15**(3), 429-436 (2006). doi:10.1158/1055-9965.epi-05-0223
46. Koleva-Kolarova, R.G., Daszczuck, A.M., de Jonge, C., Abu Hantash, M.K., Zhan, Z.Z., Postema, E.J., Feenstra, T.L., Pijnappel, R.M., Greuter, M.J.W., de Bock, G.H.: A modelling study to evaluate the costs and effects of lowering the starting age of population breast cancer screening. *Maturitas* **109**, 81-88 (2018). doi:10.1016/j.maturitas.2017.12.009
47. Obdeijn, I.M., Heijnsdijk, E.A., Hunink, M.G., Tilanus-Linthorst, M.M., de Koning, H.J.: Mammographic screening in BRCA1 mutation carriers postponed until age 40: Evaluation of benefits, costs and radiation risks using models. *European journal of cancer (Oxford, England)* **63**, 135-142 (2016). doi:10.1016/j.ejca.2016.05.012
48. Sankatsing, V.D., Heijnsdijk, E.A., van Luijt, P.A., van Ravesteyn, N.T., Fracheboud, J., de Koning, H.J.: Cost-effectiveness of digital mammography screening before the age of 50 in The Netherlands. *International Journal of Cancer* **137**(8), 1990-1999 (2015).
49. Arrospeide, A., Rue, M., van Ravesteyn, N.T., Comas, M., Soto-Gordoa, M., Sarriugarte, G., Mar, J.: Economic evaluation of the breast cancer screening programme in the Basque Country: retrospective cost-effectiveness and budget impact analysis. *BMC Cancer* **16**(1), 344 (2016). doi:10.1186/s12885-016-2386-y
50. BEEMSTERBOER, P.M.M., WARMERDAM, P.G., BOER, R., BORRAS, J.M., MORENO, V., VILADIU, P., DE KONING, H.J.: Screening for breast cancer in Catalonia. Which policy is to be preferred? *European journal of cancer (Oxford, England)* **8**(3), 241-246 (1998). doi:10.1093/eurpub/8.3.241
51. Carles, M., Vilapriño, E., Cots, F., Gregori, A., Pla, R., Roman, R., Sala, M., Macia, F., Castells, X., Rue, M.: Cost-effectiveness of early detection of breast cancer in Catalonia (Spain). *BMC Cancer* (2011).
52. Comas, M., Arrospeide, A., Mar, J., Sala, M., Vilapriño, E., Hernandez, C., Cots, F., Martinez, J., Castells, X.: Budget impact analysis of switching to digital mammography in a population-based breast cancer screening program: a discrete event simulation model. *PloS one* **9**(5), e97459 (2014).
53. Garuz, R., Forcen, T., Cabases, J., Antonanzas, F., Trinxet, C., Rovira, J., Anton, F.: Economic evaluation of a mammography-based breast cancer screening programme in Spain. *European Journal of Public Health* (1997).
54. Posso, M., Carles, M., Rue, M., Puig, T., Bonfill, X.: Cost-Effectiveness of Double Reading versus Single Reading of Mammograms in a Breast Cancer Screening Programme. *PloS one* **11**(7), e0159806 (2016). doi:10.1371/journal.pone.0159806
55. Vilapriño, E., Forne, C., Carles, M., Sala, M., Pla, R., Castells, X., Domingo, L., Rue, M.: Cost-effectiveness and harm-benefit analyses of risk-based screening strategies for breast cancer. *PloS one* **9**(2), e86858 (2014). doi:10.1371/journal.pone.0086858
56. Gelder, R., Bulliard, J.L., Wolf, C., Fracheboud, J., Draisma, G., Schopper, D., Koning, H.J.: Cost-effectiveness of opportunistic versus organised mammography screening in Switzerland. *European Journal of Cancer* (2009).
57. Neeser, K., Szucs, T., Bulliard, J.L., Bachmann, G., Schramm, W.: Cost-effectiveness analysis of a quality-controlled mammography screening program from the Swiss statutory health-care

perspective: quantitative assessment of the most influential factors (Structured abstract).
Value in Health (2007).

58. O'Mahony, J.F., van Rosmalen, J., Mushkudiani, N.A., Goudsmit, F.W., Eijkemans, M.J., Heijnsdijk, E.A., Steyerberg, E.W., Habbema, J.D.: The influence of disease risk on the optimal time interval between screens for the early detection of cancer: a mathematical approach. *Medical decision making : an international journal of the Society for Medical Decision Making* **35**(2), 183-195 (2015). doi:10.1177/0272989x14528380
59. Beemsterboer, P.M., de Koning, H.J., Warmerdam, P.G., Boer, R., Swart, E., Dierks, M.L., Robra, B.P.: Prediction of the effects and costs of breast-cancer screening in Germany. *Int J Cancer* **58**(5), 623-628 (1994).
60. Ruile, G., Djanatljev, A., Kriza, C., Meier, F., Leb, I., Kalender, W.A., Kolominsky-Rabas, P.L.: Screening for breast cancer with Breast-CT in a ProHTA simulation. *Journal of comparative effectiveness research* **4**(6), 553-567 (2015). doi:10.2217/cer.15.42
61. Schiller-Fruehwirth, I., Jahn, B., Einzinger, P., Zauner, G., Urach, C., Siebert, U.: The Long-Term Effectiveness and Cost Effectiveness of Organized versus Opportunistic Screening for Breast Cancer in Austria. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* **20**(8), 1048-1057 (2017). doi:10.1016/j.jval.2017.04.009
62. Gyrd-Hansen, D.: Cost-benefit analysis of mammography screening in Denmark based on discrete ranking data. *International journal of technology assessment in health care* **16**(3), 811-821 (2000).
63. Arveux, P., Wait, S., Schaffer, P.: Building a model to determine the cost-effectiveness of breast cancer screening in France. *European journal of cancer care* **12**(2), 143-153 (2003).
64. van Luijt, P.A., Heijnsdijk, E.A., de Koning, H.J.: Cost-effectiveness of the Norwegian breast cancer screening program. *Int J Cancer* **140**(4), 833-840 (2017). doi:10.1002/ijc.30513
65. Rojnik, K., Naversnik, K., Mateovic-Rojnik, T., PrimicZakelj, M.: Probabilistic cost-effectiveness modeling of different breast cancer screening policies in Slovenia. *Value in Health* (2008).
66. van Ineveld, B.M., van Oortmarsen, G.J., de Koning, H.J., Boer, R., van der Maas, P.J.: How cost-effective is breast cancer screening in different EC countries? *European journal of cancer* (Oxford, England : 1990) **29a**(12), 1663-1668 (1993).
67. Eccleston, A., Bentley, A., Dyer, M., Strydom, A., Vereecken, W., George, A., Rahman, N.: A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* **20**(4), 567-576 (2017). doi:10.1016/j.jval.2017.01.004
68. Manchanda, R., Legood, R., Burnell, M., McGuire, A., Raikou, M., Loggenberg, K., Wardle, J., Sanderson, S., Gessler, S., Side, L., Balogun, N., Desai, R., Kumar, A., Dorkins, H., Wallis, Y., Chapman, C., Taylor, R., Jacobs, C., Tomlinson, I., Beller, U., Menon, U., Jacobs, I.: Cost-effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared with family history-based testing. *Journal of the National Cancer Institute* **107**(1), 380 (2015). doi:10.1093/jnci/dju380
69. Manchanda, R., Patel, S., Antoniou, A.C., Levy-Lahad, E., Turnbull, C., Evans, D.G., Hopper, J.L., Macinnis, R.J., Menon, U., Jacobs, I., Legood, R.: Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. *American journal of obstetrics and gynecology* **217**(5), 578.e571-578.e512 (2017). doi:10.1016/j.ajog.2017.06.038
70. Manchanda, R., Patel, S., Gordeev, V.S., Antoniou, A.C., Smith, S., Lee, A., Hopper, J.L., MacInnis, R.J., Turnbull, C., Ramus, S.J., Gayther, S.A., Pharoah, P.D.P., Menon, U., Jacobs, I., Legood, R.: Cost-effectiveness of Population-Based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 Mutation Testing in Unselected General Population Women. *Journal of the National Cancer Institute* (2018). doi:10.1093/jnci/djx265
71. Patel, S., Legood, R., Evans, D.G., Turnbull, C., Antoniou, A.C., Menon, U., Jacobs, I., Manchanda, R.: Cost effectiveness of population based BRCA1 founder mutation testing in Sephardi

- Jewish women. American journal of obstetrics and gynecology **218**(4), 431.e431-431.e412 (2018). doi:10.1016/j.ajog.2017.12.221
72. Norum, J., Hagen, A.I., Maehle, L., Apold, J., Burn, J., Moller, P.: Prophylactic bilateral salpingo-oophorectomy (PBSO) with or without prophylactic bilateral mastectomy (PBM) or no intervention in BRCA1 mutation carriers: a cost-effectiveness analysis. European Journal of Cancer (2008).
73. Muller, D., Danner, M., Rhiem, K., Stollenwerk, B., Engel, C., Rasche, L., Borsi, L., Schmutzler, R., Stock, S.: Cost-effectiveness of different strategies to prevent breast and ovarian cancer in German women with a BRCA 1 or 2 mutation. The European journal of health economics : HEPAC : health economics in prevention and care (2017). doi:10.1007/s10198-017-0887-5
74. Schwarzer, R., Rochau, U., Saverno, K., Jahn, B., Bornschein, B., Muehlberger, N., Flatscher-Thoeni, M., Schnell-Inderst, P., Sroczynski, G., Lackner, M., Schall, I., Hebborn, A., Pugnner, K., Fehervary, A., Brixner, D., Siebert, U.: Systematic overview of cost-effectiveness thresholds in ten countries across four continents. Journal of comparative effectiveness research **4**(5), 485-504 (2015). doi:10.2217/ce.15.38
75. Prasad, V., Lenzer, J., Newman, D.H.: Why cancer screening has never been shown to "save lives"-and what we can do about it. BMJ (Clinical research ed.) **352**, h6080 (2016). doi:10.1136/bmj.h6080
76. Zahl, P.H., Kalager, M., Suhrke, P., Nord, E.: Quality-of-life effects of screening mammography in Norway. Int J Cancer (2019). doi:10.1002/ijc.32539
77. Heijnsdijk, E.A.M., Csanadi, M., Gini, A., Ten Haaf, K., Bendes, R., Anttila, A., Senore, C., de Koning, H.J.: All-cause mortality versus cancer-specific mortality as outcome in cancer screening trials: A review and modeling study. Cancer Med **8**(13), 6127-6138 (2019). doi:10.1002/cam4.2476
78. Weinstein, M.C., Stason, W.B.: Foundations of cost-effectiveness analysis for health and medical practices. The New England journal of medicine **296**(13), 716-721 (1977). doi:10.1056/NEJM197703312961304
79. Roman, M., Sala, M., Domingo, L., Posso, M., Louro, J., Castells, X.: Personalized breast cancer screening strategies: A systematic review and quality assessment. PloS one **14**(12), e0226352 (2019). doi:10.1371/journal.pone.0226352
80. Cardoso, F., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rubio, I.T., Zackrisson, S., Senkus, E.: Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2019). doi:10.1093/annonc/mdz173
81. European Commission Initiative on Breast Cancer (ECIBC): European guidelines on breast cancer screening and diagnosis. Available at: <https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines>, Accessed: November 2019. (2019).
82. Zurrida, S., Veronesi, U.: Milestones in breast cancer treatment. Breast J **21**(1), 3-12 (2015). doi:10.1111/tbj.12361
83. Birnbaum, J., Gadi, V.K., Markowitz, E., Etzioni, R.: The Effect of Treatment Advances on the Mortality Results of Breast Cancer Screening Trials: A Microsimulation Model. Annals of internal medicine **164**(4), 236-243 (2016). doi:10.7326/M15-0754
84. European Network for Health Technology Assessment (EUnetHTA): Guideline Methods for health economic evaluations -A guideline based on current practices in Europe. Available at: https://www.eunetha.eu/wp-content/uploads/2018/03/Methods_for_health_economic_evaluations.pdf. https://www.eunetha.eu/wp-content/uploads/2018/03/Methods_for_health_economic_evaluations.pdf (2015) November 2019
85. Philips, Z., Bojke, L., Sculpher, M., Claxton, K., Golder, S.: Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics **24**(4), 355-371 (2006). doi:10.2165/00019053-200624040-00006

86. Adarkwah, C.C., van Gils, P.F., Hiligsmann, M., Evers, S.M.: Risk of bias in model-based economic
1 evaluations: the ECOBIAS checklist. *Expert Rev Pharmacoecon Outcomes Res* **16**(4), 5
(2016). doi:10.1586/14737167.2015.1103185

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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 CEA	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)	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)

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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) <u>OverDx-related harms (O)*</u>	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

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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) <u>OverDx-related harms (O)*</u>	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 57	Mortality reduction, LYG, costs, ICER	Not reported dependent)	Against observed data

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

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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) <u>OverDx-related harms (O)*</u>	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)	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 <i>BRCA</i> mutation P: Women age 30+ without <i>BRCA1/2</i> 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 family 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)	O: n.a. 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

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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) <u>OverDx-related harms (O)*</u>	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 <i>BRCA1</i> mutation carriers below age 50 P: Women age 30-49 with <i>BRCA1</i> 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)	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	O: Unclear CEA, CUA P: Payer D: 3% (costs and effects) O: C: Direct medical costs Considered	QALYs, lifetime costs, ICUR, (LYG and ICER presented in text)	Deterministic and probabilistic SA	Against observed data and other models

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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) <u>OverDx-related harms (O)*</u>	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 screening (differing in attendance and OP/MSP mix)	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, costs, ICER, ICUR	Deterministic SA, scenario analyses	Against observed data
Madan 2010 UK [38]	Evaluation of a hypothetical policy on round below age 50 (rapid-response analysis)	One-time mammography screening at ages 47-49 A: 40-80% (depending on scenario) vs no screening A: 100%	Decision tree (?) A: Cohort simulation H: Lifetime	GUA P: Payer C: Direct medical costs D: 3.5% (costs and effects) O: Partly considered (?) CEA, CUA	Mortality reduction, QALYs gained, costs, ICUR	Deterministic and probabilistic SA ("plausible bounds" method)	Not applied
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	Lives extended, LYG, QALYs gained, costs, ICUR	Deterministic SA, scenario analyses	Against other models

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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) <u>OverDx-related harms (O)*</u>	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)	Incidence and mortality reduction, LYG, QALYs gained, costs, ICUR	Probabilistic SA scenario analyses	Against observed data and other models
Comas 2014 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 A: Microsimulation H: 20 years (2010-2029)	BA (plus screening effect on incidence and mortality) O: Considered P: Health care system C: Program costs and direct medical costs	Incidence and mortality reduction costs	Probabilistic SA scenario analyses	Against observed data
Vilapriyo 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)	D: Not applied O: n.a. Benefit-harm analyses, CEA, CUA P: Health care system C: Direct medical costs D: 3% (costs and effects) O: Considered (15% of mammograms)	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

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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	Digital mammography screening differing in starting age below and intervals	DES model simulating the history of 50 year old women (MISCAN) A: Microsimulation H: Lifetime	CUA (in Appendix) 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)	Mammography screening with 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	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)	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

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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) <u>OverDx-related harms (O)*</u>	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 BRCA1 mutation carriers P: Women age 25+ with BRCA1 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 no screening 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 D: Direct medical costs O: n.a.	BCa incidence and mortality incl. radiation cases, LYG, 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

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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) <u>OverDx-related harms (O)*</u>	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	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	O: Considered 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

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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) <u>OverDx-related harms (O)*</u>	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**

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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) <u>OverDx-related harms (O)*</u>	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 <i>BRCA1</i> 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 <i>BRCA1/2</i> gene mutations P: Ashkenazi Jewish women age 30+	Population-based genetic screening for <i>BRCA1/2</i> 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 <i>BRCA1/2</i> mutation carriers P: Women age 30 with <i>BRCA1/2</i> 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

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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) <u>OverDx-related harms (O)*</u>	Outcomes	Sensitivity and scenario analyses	Validation
Manchanda 2017 UK [69]	Evaluation of population-based genetic screening for <i>BRCA1/2</i> gene mutations for women with different degrees of Ashkenazi Jewish ancestry P: Ashkenazi Jewish women age 30+	Population-based genetic screening for <i>BRCA1/2</i> 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 <i>BRCA1/2</i> gene mutations in women with ovarian cancer and relatives of detected mutation carriers P: British ovarian cancer patients and first- and second degree relatives	A: n.r. for screening screening in ovarian cancer patients and their relatives with the option of prophylactic salpingo-oophorectomy and/or mastectomy in affected relatives vs no <i>BRCA</i> 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.	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 <i>BRCA1</i> gene mutations P: Sephardi Jewish women age 30+	Population-based genetic screening for <i>BRCA1</i> mutation followed by prophylactic salpingo-oophorectomy and/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) P: Payer	LYG (only not discounted), QALYs gained, costs, ICUR	Deterministic and probabilistic SA, scenario analyses	Not reported

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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 mutations (Panel: <i>BRCA1</i> , <i>BRCA2</i> , <i>RAD51C</i> , <i>RAD51D</i> , <i>BRIP1</i> , and <i>PALB2</i>) P: Non-Jewish women of the general population age 30+	Population-based and family history based panel screening followed by prophylactic salpingo-oophorectomy and prophylactic mastectomy or chemoprevention vs current family history based BRCA1/2 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 models

* 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 MG 45-69, 2y (organized) MG 45-69, 2y (opportunistic.)	0 701 713	0 0.0320 0.0230						
					701 12	0.0320 -0.0090		21,901 D	
Neeser 2007, CH [57]	No screening (opportunistic) MG 70-death, 2y MG 60-death, 2y MG 50-death, 2y MG 40-death, 2y	0 602 781 918 975	0 0.008 0.014 0.020 0.022						
					602 179 137 57	0.008 0.006 0.006 0.002		ED ED ED 44,304	
Gelder 2009, CH [56] (80% adher.)	No screening Organized MG 50-69, 2y Opportunistic MG 50-69, 2y	0 394,349,489 802,818,909	0 34,000 33,700	0 31,506 31,161					
					394,349,489 408,469,420	34,000 -300	31,506 -345	11,599 D	12,517 D
O'Mahony 2015, CH [58]	No screening MG strategies	n.r.		n.r.					CUA n.a
Beemsterboer 1994, DE [59]	No screening MG 50-70, 2y	0 3,096,008,904	0 206,500	0 197,000					
					3,096,008,904	206,500	197,000	14,993	15,716
Ruile 2015, DE [60]	DMG 50-69, 2 Breast CT 50-69, 2	n.r. n.r.	n.a. n.a.	n.a. n.a.				CEA n.a CEA n.a	CUA 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 MG 50-70, 2y	0 876,423,693	0 79,000						
					876,423,693	79,000		11,094	
Garuz	No screening	0	0						

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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 1998, ES (Catalonia) [50]	No screening	0	0						
	MG 50-64, 3y	102,254,455	11,991		102,254,455	11,991		8,528	
	MG 50-69, 3y	129,504,136	15,734		27,249,680	3,743		7,280	
	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 2011, ES [51]	No screening	0	0	0					
	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 2014, ES [52]	MG 50-69, 2y	disc. data n.r.	n.r.	n.r.					
	DMG 50-69, 2y	disc. data n.r.	n.r.	n.r.				CEA n.a	CUA n.a
VilaprinYO	No screening	0		0					

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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								
	H risk: MG 40-74, 1y	1,511		0.029628	0		0.001026		50,994
	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	No screening	0		0					
2016, ES [49]	MG 50-69, 2y	37,036,774		8,666	37,036,774		8,666		4,274
Posso	No screening	n.a.	n.a.	n.a.					
2016, ES [54]	DMG reading strategies	n.a.	n.a.	n.a.				CEA n.a.	
van Ineveld	Model France								
1993, ES, FR, NL, UK [66]	No screening	0	0						
	MG 50-70, 2y	1,387,973,925	155,000		1,387,973,925	155,000		8,955	
Arveux	No screening	0	0						
2003, FR [63]	MG 50-65, 2y	40,874,326	1,522		40,874,326	1,522		26,856	
de Koning	No screening	0	0	0					
1991, NL [44]	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

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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)
Model Netherlands									
van Ineveld 1993, ES, FR, NL, UK [66]	No screening MG 50-70, 2y	0 364,441,683	0 61,000						
					364,441,683	61,000		5,974	
Optimistic Model									
Boer 1995, NL [43]	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]									
Jacobi 2006, NL [45]	No screening MG strategies	n.r.		n.r.					CUA n.a
Sankatsing 2015, NL [48]									
Sankatsing 2015, NL [48]	No screening DMG 50-74, 2y	0 139	0 0.041	0 0.054					
					139	0.041	0.054	3,400	2,581 47

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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.	

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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

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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						

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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 <i>BRCA</i> screening	n.r.	n.r.	n.r.					
	Pop. based <i>BRCA</i> screening with PBSO/PBM	2140	23.205	23.141					
	FH based <i>BRCA</i> 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 <i>BRCA</i> screening	n.r.	n.r.	n.r.					
	Pop-based <i>BRCA</i> screening with PBSO/PBM	2,032	only undisc.	23.15					
	FH-based <i>BRCA</i> screening with PBSO/PBM	2,134	only undisc.	23.12	103		-0.0300		D
	Women with 3 Ashkenazi Jewish grandparents								
	No <i>BRCA</i> screening	n.r.	n.r.	n.r.					
	Pop-based <i>BRCA</i> screening with PBSO/PBM	1,979	only undisc.	23.16					
	FH-based <i>BRCA</i> screening with PBSO/PBM	2,047	only undisc.	23.13	68		-0.0300		D
	Women with 2 Ashkenazi Jewish grandparents								
	No <i>BRCA</i> screening	n.r.	n.r.	n.r.					
	Pop-based <i>BRCA</i> screening with PBSO/PBM	1,928	only undisc.	23.16					
	FH-based <i>BRCA</i> screening with PBSO/PBM	1,956	only undisc.	23.14	28		-0.0200		D
	Women with 1 Ashkenazi Jewish grandparent								
	No <i>BRCA</i> screening	n.r.	n.r.	n.r.					
	FH-based <i>BRCA</i> screening with PBSO/PBM	1,862	only undisc.	23.15					
	Pop-based <i>BRCA</i> screening with PBSO/PBM	1,876	only undisc.	23.17	14		0.0151		942

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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 <i>BRCA</i> screening in ovarian cancer patients and relatives <i>BRCA</i> 1/2 screening in ovarian cancer patients and relatives with PBSO/PBM	0 3,427,258		0 706					
Patel 2018, UK [71]	No <i>BRCA</i> screening FH-based <i>BRCA</i> screening Pop-based <i>BRCA</i> screening	n.r. 1,844 1,920	n.r. only undisc. only undisc.	n.r. 22.42 23.42		75		1.0006	75
Manchanda 2018, UK [70]	No genetic screening FH-based <i>BRCA</i> 1/2 screening FH-based Panel screening Pop-based Panel screening	n.r. 1,732 1,73: 1,94:	n.r. 23.76 23.76 23.77	n.r. 23.69 23.69 23.70				0.000 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).



