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Cost-effectiveness of risk-based breast cancer screening: A systematic review

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Abstract

To analyse published evidence on the economic evaluation of risk-based screening (RBS), a full systematic literature review was conducted. After a quality appraisal, we compared the cost-effectiveness of risk-based strategies (low-risk, medium-risk and high-risk) with no screening and age-based screening. Studies were also analysed for modelling, risk stratification methods, input parameters, data sources and harms and benefits. The 10 modelling papers analysed were based on screening performance of film-based mammography (FBM) (three); digital mammography (DM) and FBM (two); DM alone (three); DM, ultrasound (US) and magnetic resonance imaging (one) and DM and US (one). Seven studies did not include the cost of risk-stratification, and one did not consider the cost of diagnosis. Disutility was incorporated in only six studies (one for screening and five for diagnosis). None of the studies reported disutility of risk-stratification (being considered as high-risk). Risk-stratification methods varied from only breast density (BD) to the combination of familial risk, genetic susceptibility, lifestyle, previous biopsies, Jewish ancestry and reproductive history. Less or no screening in low-risk women and more frequent mammography screening in high-risk women was more cost-effective compared to no screening and age-based screening. High-risk women screened annually yielded a higher mortality rate reduction and more quality-adjusted life years at the expense of higher cost and false positives. RBS can be cost effective compared to the alternatives. However, heterogeneity among risk-stratification methods, input parameters, and weaknesses in the methodologies hinder the derivation of robust conclusions. Therefore, further studies are warranted to assess newer technologies and innovative risk-stratification methods.

KEYWORDS
breast cancer, decision making, economic evaluation, risk-adapted screening, risk-based screening, risk-stratified screening, simulation models

Abbreviations: ABS, age-based screening; BC, breast cancer; BIRADS, breast imaging-reporting and data system; CE, cost-effective; CEA, cost-effective analysis; DCIS, ductal carcinoma in situ; DM, digital mammography; FBM, film-based mammography; FP, false positive; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; MRI, magnetic resonance imaging; MRISC, MRI screening study; NMB, net monetary benefit; NOS, no screening; OOPs, out of pocket expenditures; PROCAS, predicting the risk of cancer at screening; QALY, quality-adjusted life years; QoL, quality of life; RBS, risk-based screening; UK, United Kingdom; US, ultrasound; USA, United States of America; WTP, willingness to pay.

1 | INTRODUCTION

Unequivocally, early detection is a widely advocated tenet in cancer care. Regarding breast cancer (BC), proponents of mammography screening programs cite its capacity to reduce mortality.[1] Current evidence suggests that age-based screening (ABS) can effectively reduce (15%-40%) BC related mortality,[1-4] reduces the risk of stage III+ cancers detection (RR, 0.62).[4] Most countries have well established population-based mammography screening programs based on women's age.[5-7] The general assumption is that BC risk increases with age. Thus, the starting and ending age and frequency of screening are defined with a primary goal of increasing the benefits of the screening program while minimising the harms. However, uncertainty still exits[8] with regards to psychosocial harms,[9] over-diagnosis, false-positive (FP)[4,9] and financial implications due to recall.[10]

The increased understanding of individual risk factors potentially associated with BC has caused researchers to reassess current screening guidelines and analyse alternative paradigms in screening.[11] Several risk factors that can potentially improve the performance of BC screening have been identified.[12-14] A growing body of evidence seems to suggest that high-risk women, who tend to develop BC earlier than average-risk women, may benefit from an earlier starting age and more frequent screening.[7,11] On the contrary, a considerable proportion of women diagnosed with BC have no elevated background risk,[15] and the application of conventional risk factors for women age 50 and above failed to demonstrate benefits.[16] These contradictory findings call for accurate risk prediction methods and risk thresholds of declaring women being at low-risk or high-risk.

The overall hypothesis regarding risk-based BC screening is that adjusting the age and frequency of screening by factoring in the individual risk may improve the benefit-to-harm ratio. The overall cost of screening can potentially be reduced by reducing the total number of screens, FP and overdiagnosis.[17] Simultaneously, a possible decrease in FPs and overdiagnosis associated with ABS can potentially lead to less psychological harms. Both effects can result in an improved harm to benefits ratio.

Several cost-effectiveness analyses have been done on RBS.[13,17-19] Nevertheless, there is not a consensus on the subject. Studies reported that increasing the screening frequency for high-risk, dense breast women yield higher quality-adjusted life years (QALYs), avert more deaths, at the cost of increased FPs, benign biopsies and over-diagnosis.[18,20,21] Therefore, it is unclear what ratio of harms and benefits should be accepted.

The contradiction observed is mainly attributable to the complexity in evaluating and comparing the costs and benefits derived from RBS programs. First, the estimation of cost, benefits and harms depend on the assumed process of risk stratification and the screening technology. The risk stratification requires a comprehensive tool that incorporates all risk factors to precisely predict individual risk.[22] Secondly, other factors such as assumptions on quality of life (QoL), screening participation, risk stratification thresholds and costing elements are also equally important. For that, economic evaluations that effectively inform a decision to move from one-size-fits-all ABS to a risk-based approach require a solid evidence base.

What's New

Most countries have set up population-based mammography screening programmes based on women's age. However, the potential psychosocial harms, over-diagnosis, and increased costs together with the growing understanding of breast cancer risk factors have led researchers to seek alternative screening paradigms. This full systematic literature review compares the cost effectiveness of risk-based screening with no screening and age-based screening in the general population. The findings suggest that risk-based screening can be an economically efficient alternative and could potentially substitute current breast cancer screening programmes. Moreover, the review identifies several limitations that negatively impact the studies' methodological robustness and proposes possible solutions.

There is a lack of evidence on the factors that determine the value for money of RBS programs. To our knowledge, two systematic reviews have been published. Arnold[23] conducted a literature review focussing on the analysis of modelling techniques. Roman et al[24] reviewed previous studies on the effectiveness of RBS and the risk of bias. However, there is a lack of evidence to compare the superiority of BC screening interventions (risk-based vs routine) in the general population in terms of cost-effectiveness, optimal screening strategies at different willingness to pay (WTP) thresholds, clinical harms and benefits. We aim to analyse current evidence and include the above-mentioned aspects, and additionally review the modelling approaches, methods of risk estimation and stratification, input parameters, data sources used and technology under evaluation.

2 | METHODOLOGY

The review adopted published guidelines of systematic reviews[25-27] with slight modifications (see Supporting Information Material S1, Table S1).

2.1 | Search strategy, selection criteria and quality appraisal

We combined search terms for 'breast cancer', 'risk-based screening' and 'economic evaluation'. We searched the literature in PubMed, Web of Science and Econ Lit from January 1st, 1990 to June 4th 2020 (see Supporting Information Material S2).

The methodological quality of all the studies was assessed using a quality appraisal checklist,[28] and the quality of the articles was considered as one of the criteria for exclusion. Articles having a quality score under 60% were excluded (see Supporting Information Material S3).

2.2 | Data extraction

For each selected study, data related to screening strategy (the starting, stopping and frequency of screening), screening technology evaluated, methodology, input parameters, risk stratification methods, cost, benefit and harms were extracted for RBS compared to no screening and ABS.

2.3 | Analysis

We converted cost values reported in the individual studies to 2019 international dollars using purchasing power parity estimates from World Bank index[29] and United States of America (USA) consumer price index.[29] Then we characterised RBS strategies into three risk categories: low-risk, medium-risk and high-risk. For those studies that did not explicitly define the risk groups, we assigned our own risk groups based on the frequency of screening with a low frequency corresponding to a lower risk group. This characterisation of studies allowed for a homogeneous assessment of the results and to perform a direct comparison.

Based on the extracted data on cost and utility measure, we computed the Net Monetary Benefit (NMB) as follow[28]:

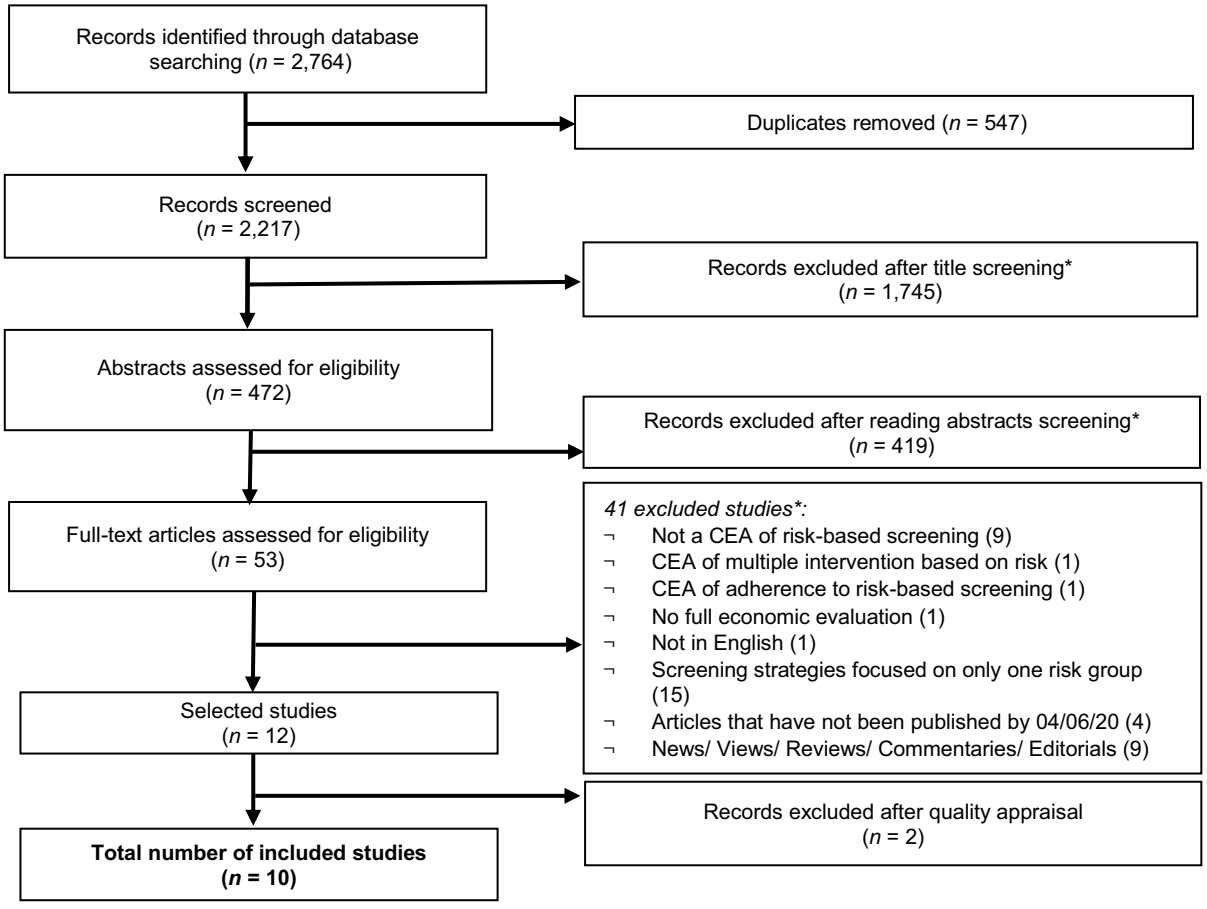
$$\mathrm{NMB} = (\mathrm{QALY} \times \mathrm{WTP\ threshold}) - \mathrm{Costs}$$

Where QALY is quality adjusted life years and WTP is willingness to pay threshold. The NMB was calculated for each strategy and directly compared to other strategies. The strategy with the highest positive value was considered optimal. This standardised metric allowed us to estimate the optimal screening strategy at different WTP thresholds.

3 | RESULTS

The initial electronic search retrieved 2764 records. After the stepwise screening process (Figure 1), 12 articles were selected and critically appraised for quality. Two articles[19,30] were excluded based on quality (Van-Dyck et al[19] 35.9%; Evans et al[30] 58.1%).

The main characteristics of the 10 studies included are shown in Table 1. All studies are either from upper-middle-income (China and



*List of excluded studies with reason for exclusion will be provided by the authors upon request.

FIGURE 1 PRISMA flow diagram—study selection

TABLE 1 Main characteristics of the selected studies

Study	Country	Perspective	Time horizon	Discount rate	Outcomes	Screening age in years	Screening technology	Quality appraisal[a]
Tosteson et al[35]	USA	Societal and Payer	Lifetime	0.030	QALYs	40-69	DM & FBM	85.9%
Schousboe et al[13]	USA	Payer	Lifetime	0.030	QALYs	40-79	FBM	93.5%
Vilaprinyo et al[17]	Spain	NHS	40-79 years	0.030	QALYs and LE	40-74	FBM	96.7%
Stout et al[21]	USA	Payer	Lifetime	0.030	QALYs	40–74	DM and FBM	90.0%
Trentham-Dietz et al[18]	USA	Payer[b]	Lifetime	0.030	QALYs	50-74	DM	85.4%
Gray et al[33]	UK	NHS	Lifetime	0.035	QALYs	50-70	DM, US and MRI	98.3%
Sun, Legood et al[36]	China	Societal	Lifetime	0.030	QALYs	40-69	DM and US	87.1%
Pashayan et al[32]	UK	NHS	50-85 years	0.035	QALYs	50-69	DM	93.3%
Arnold et al[31]	Germany	Payer	Lifetime	0.030	QALYs and MRR	50–69	FBM	94.8%
Sankatsing et al[34]	Netherlands	Payer[b]	Lifetime	3.500	LYG	40-84	DM	75.8%

Abbreviations: USA, United States of America; QALY, Quality adjusted life years; DM, Digital Mammography; FBM, Film-based Mammography; NHS, National Health System; LE, Life extended; UK, United Kingdom; US, Ultrasound; MRI, Magnetic resonance imaging; MRR, Mortality rate reduction; LYG, Life years gained.

[a]Quality Appraisal estimated based on the Drummond et al[28] checklist.

[b]Not mentioned in the study, inferred from the given data.

Source: Authors elaboration, based on the extracted data.

Spain) or high-income countries (World Bank classification). Most of the studies adopted the payer perspective (government taxation and/or health insurance financing).[13,17,18,21,31-34] The societal perspective, which in addition to direct medical costs, also considers the cost of care that do not fall on the payer's perspective (OOPs, caregiver effects and patient time) and the indirect costs (productivity losses related to morbidity and mortality) are broadly neglected. Two articles[35,36] reported only costs for waiting time[35] and days lost due to treatment,[36] which can be considered only as a partial societal perspective. The predominantly adopted outcome measure was the cost per QALY metric, while digital mammography (DM) and film-based mammography (FBM) screening were the most common technologies assessed.

Methods of risk estimations and stratifications are summarised in Table 2. Two studies[33,36] used risk prediction models. Similarly, two studies[21,35] stratified women based only on the individual's breast density and age. Four studies[13,17,18,31] estimated relative risk using a combination of breast density, family history and other risk factors. Pashayan et al[32] used genetic susceptibility loci and epidemiological risk factors, and Sankatsing et al[34] did not report the included risk factors.

A higher number of risk factors were incorporated in the recent studies,[18,32,33,36] such as Jewish ancestry, reproductive and lifestyle factors, genetic susceptibility loci and exposure to ionising radiations. The risk group categories varied among the studies: two risk groups (high-risk and low-risk),[21,32,34-36] three risk groups (high-risk, medium-risk and low-risk),[31,33] four risk groups (low-risk, medium-low-risk, medium-high-risk and high-risk),[17] and 16 population subgroups.[18] One study did not categorise the study population in risk clusters[13]

3.1 | Cost-effectiveness of risk-based screening

All studies, except for Arnold et al,[31] reported significant QALY/LYG for RBS strategies. Among the articles[32,33,36] that incorporated risk-stratification cost, Gray et al[33] and Sun et al[36] reported no cost-savings. At the same time, Pashayan et al[32] concluded that RBS has higher cost if women above the 25th risk percentile are screened but when screening is exclusively offered to women above the risk threshold of the 32nd, 62nd and 70th percentile, cost is reduced by 0.36%, 7.90% and 9.55%, with 0.349%, 0.346% and 0.344% gain in QALYs, respectively.

Also, change in screening adherence rate, from full adherence to country-specific participation rate (54% for Germany and 80% for the Netherlands), seems to have a homogeneous effect on cost and QALYs/LYG. Thus, ICERs almost remain the same.[31,34]

Table 2 shows the result on cost-effectiveness ratios of RBS for all the studies included. Studies were divided into two groups depending on the risk factors considered for stratification: (a) only age and breast density and (b) multiple risk factors.

TABLE 2 Risk stratification factors, risk levels, proposed RBS strategies and their cost-effectiveness

Study	Risk factors	Relative risk (baseline) and risk distribution	Risk level (based on the included risk factors)			Screening strategies evaluated for risk groups	Proposed RBS strategies compared to no or ABS (ICER and WTP threshold)
			Low-risk	Medium-risk	High-risk		
RBS based on age and breast density							
Tosteson et al[35]	Age Breast density	Lifetime risk in dense breast women= 1.5	1. BIRADS I-II	–	1. BIRADS III-IV	1. Annual age-density targeted DM screening • DM for dense breasted women 40 + years • Not dense breasted women, DM for 40-50 years women, and FBM for 50+ aged women2. Annual FBM for women aged 40+	Annual age-density targeted DM screening is considered cost-effective compared to annual FBM screening. ICER = $84 500/QALY gained. Comparisons with NoS are not given in the article.
Schousboe et al[13a]	Age Breast density	*Relative risk:* *Age 65:* Heterogeneously dense breast= 1.55; extremely dense breast= 2.01 *Age ≥ 65:* Heterogeneously dense breast= 1.388; extremely dense breast= 1.450	1. Age 40-49: BIRADS I-II 2. Age 50-79: BIRADS I	–	1. Age 40-49: BIRADS III-IV 2. Age 50-79: BIRADS II-III-IV	All given strategies were applied to each risk-group. 1. NoS 2. Annual screening 3. Biennial screening 4. 3-4 yearly screening	The following strategies are considered CE at WTP threshold of < $100 000/QALY gain in comparison to NoS: 1. Age 40-49 BIRADS I-II: NoS 2. Age 50-79 BIRADS I: 3-4 yearly screening 3. Age 40-49 BIRADS III-IV Biennial screening 4. Age 50-79 BIRADS II-III-IV Biennial screening
Stout et al[21]	Age Breast density	*Relative risk:* Heterogeneously dense breast= 3.64 extremely dense breast= 4.35	1. BIRADS I-II	–	1. BIRADS III-IV	1. Biennial DM for BIRADS-I and II women, and annual DM age 40-74 years for BIRADS-III and IV women. 2. Biennial DM age 50-74 years for all women	1. RBS strategies are compared to NoS[b] (Cost/QALY gained): Model E—$39 474; Model W–$36 086; Model D—$50 000; Model G-E—$46 957; Model M—$99 231

(Continues)

TABLE 2 (Continued)

Study	Risk factors	Relative risk (baseline) and risk distribution	Risk level (based on the included risk factors)			Screening strategies evaluated for risk groups	Proposed RBS strategies compared to no or ABS (ICER and WTP threshold)
			Low-risk	Medium-risk	High-risk		
						3. NoS	2. RBS strategy are compared to ABS[b] (Cost/QALY gained): Model E—$73 000; Model W—$59 300; Model D—$168 000; Model G-E–$181 700; Model M—$264 700
RBS based on multiple risk factors criteria							
Schousboe et al[13a]	Age Breast density Familial risk Previous biopsy	*Risk factors and relative risk*: Family history= 1.454 Previous biopsy= 1.495 Age <65: Heterogeneously dense breast= 1.55 and extremely dense breast= 2.012 Age ≥65: Heterogeneously dense breast= 1.388 and extremely dense breast= 1.450	1. Age 40-49: BIRADS I or II, and BIRADS I and 1 RF +ve	1. Age 50-59: BIRADS I, BIRADS I and 1 or 2 RF +ve 2. Age 60-79: BIRADS I, BIRADS I and 1 RF +ve 3. Age 70-79: BIRADS I, BIRADS I and 1 RF +ve	1. Age 40-49 years: BIRADS III-IV, BIRADS II-III or IV and 1 or 2 RF +ve 2. Age 50-79 years: BIRADS II-III-IV, BIRADS I and 2 RF +ve, BIRADS II and 1 or 2 RF +ve	All given strategies were applied to each risk-group. 1. NoS 2. Annual screening 3. Biennial screening 4. 3-4 yearly screening	The following strategies are considered CE at WTP threshold of < $100 000/ QALY gained in comparison to NoS: *3-4 yearly screening* • Age 50-59: BIRADS I, BIRADS I and 1 or 2 RF positive • Age 60-79: BIRADS I, BIRADS I and 1 RF positive • Age 70-79: BIRADS I, BIRADS I and 1 RF positive*Biennial screening* • Age 40-49: BIRADS III and IV, BIRADS II-III or IV and 1 or 2 RF positive • Age 50-79: BIRADS II, III and IV, BIRADS I and 2 RF positive, BIRADS II and 1 or 2 RF positive

TABLE 2 (Continued)

Study	Risk factors	Relative risk (baseline) and risk distribution	Risk level (based on the included risk factors)			Screening strategies evaluated for risk groups	Proposed RBS strategies compared to no or ABS (ICER and WTP threshold)
			Low-risk	Medium-risk	High-risk		
Vilaprinyo et al[17]	Age Breast density, Familial risk, Previous biopsy	*Risk factors and relative risk*: Family history= 1.5 Previous biopsy= 1.5 Age <65: Heterogeneously dense breast=1.55 and extremely dense breast= 2.012 Age ≥65: Heterogeneously dense breast= 1.388 and extremely dense breast= 1.450	1. BIRADS I and 1 RF +ve or BIRADS II and no RF +ve	1. *Medium-low*: BIRADS I and 2RF +ve or BIRADS II and 1 RF +ve or BIRADS III or IV 2. *Medium-High*: BIRADS II and 2 RF +ve or BIRADS III or IV and 1 RF +ve	1. BIRADS III or IV and 2 RF +ve	2624 screening strategies were obtained by combining age of start (40, 45 and 50 years), stop age (69 and 74 years) and frequency of screening (no, annual, biennial, triennial and quinquennial)	The following strategies are considered CE at ICER of €54 216/ QALY gained in comparison to biennial screening ABS, women age 50-69 years: • Low risk: Quinquennial screening for women age 50-69 years • Medium low-risk and medium-high risk: Quinquennial screening for women age 45-74 years • High-risk: Annual screening for women age 40-74 years
Trentham-Dietz et al[18c]	Breast density, familial risk, history of previous benign/ proliferative disease, reproductive factors, lifestyle factors, polygenic risk score/ SNPs	*Risk factors and risk categories*: 1. Relative risk= 1 to 1.3: Reproductive history, postmenopausal hormone use, alcohol use, BMI, one FDR with BC 2. Relative Risk= 2: History of benign and proliferative disease and ≥2 FDR with BC 3. Relative Risk= 4: History of lobular carcinoma, 1% polygenic risk score, history of atypical hyperplasia	1. Relative risk 1.0 or 1.3 and BIRADS I-II	1. Relative Risk 1.3 to 2.0 and most density subgroups I-II-III-IV	1. Relative risk 4.0 regardless of breast density	16 risk subgroups (based on the combination of four breast density and four risk categories) were offered annual, biennial and triennial screening.	The following strategies are considered CE at WTP threshold of < $100 000/ QALY gained in comparison to NoS: • Low-risk[c] (Relative risk 1.0 or 1.3 and BIRADS I and II): Triennial screening age 50-74 years. • Medium-risk (Relative Risk 1.3-2.0 and most density subgroups I-II-III-IV): Biennial Screening age 59-74 years. • High-risk (Relative Risk 4.0 regardless of breast density): Annual screening age 50-74 years.

(Continues)

TABLE 2 (Continued)

Study	Risk factors	Relative risk (baseline) and risk distribution	Risk level (based on the included risk factors)			Screening strategies evaluated for risk groups	Proposed RBS strategies compared to no or ABS (ICER and WTP threshold)
			Low-risk	Medium-risk	High-risk		
Gray et al[33]	Age, race, breast density, familial risk, history of previous disease, reproductive factors, lifestyle factors	10 years relative risk= 3.5%, 8.0% and ≥8.0%. Risk groups stratification: Risk 1: 10 years relative risk of each Individual Risk 2: Dividing the whole population in three risk quantiles	1. Strategy one (Risk 1): Individual risk <3.5% 2. Strategy two (Risk 2): Population risk quantile <3.5%	1. Strategy one (Risk 1): Individual risk 3.5%–8% risk 2. Strategy two (Risk 2): Population risk quantile 3.5% to 8%	1. Strategy one (Risk 1): individual risk: >8% risk 2. Strategy two (Risk 2): Population risk quantile >8%	1. RBS • Low-risk: Triennial DM age 50-70 • Medium-risk: Biennial DM age 50-70 • High-risk: Annual DM age 50-70 2. High-risk and dense breast women: Annual DM age 50-70 and MRI. 3. Triennial ABS: All women age 50-70 years 4. Dense breast women: Triennial DM and supplemental ultrasound 5. NoS: All women age 50-74 y	The following strategies are considered CE at WTP threshold of < £30 000/ QALY gained in comparison to NoS (cost/QALY gained): • RBS compared to NoS: Risk 1—£22 413; Risk 2—£23 435. • RBS compared to ABS: Risk 1—£16 689; Risk 2—£23 924.Addition of MRI to screen high-risk dense breast women is not CE compared to NoS and ABS at WTP threshold of £30 000/QALY gained: • High risk and dense breast strategy compared to NoS: £30 532. • High-risk and dense breast risk strategy compared to ABS strategy: £75 254.
Sun, Legood et al[36]	Age, familial risk, reproductive factors, oral contraceptive, exposure to ionising radiations, Jewish inheritance[d]	20 years relative risk = 2.0	1. Relative risk of ≤2.0	–	1. Relative risk of >2.0	RBS strategies offering US and DM (age 45-69 years) 1. Low-risk: NoS. High-risk: Annual US age 40-44; annual US and DM age 45-69.	The following strategies are considered CE at WTP threshold of US $23050/QALY gained (Three times the Chinese GDP per Capita in 2014.) in comparison to NoS:

TABLE 2 (Continued)

Study	Risk factors	Relative risk (baseline) and risk distribution	Risk level (based on the included risk factors)			Screening strategies evaluated for risk groups	Proposed RBS strategies compared to no or ABS (ICER and WTP threshold)
			Low-risk	Medium-risk	High-risk		
						2. Low-risk: NoS. High-risk: Triennial US age 40-44; triennial US and DM age 45-69. 3. Low-risk: NoS. High-risk: Five yearly US age 40-44; 5 yearly US and DM age 45-69.RBS strategies offering only DM (age 45-69 years) 1. Low-risk: NoS. High-risk: Annual US age 40-44; annual DM age 45-69. 2. Low-risk: NoS. High-risk: Annual US age 40-44; triennial DM age 45-69. 3. Low-risk: NoS. High-risk: Annual US age 40-44; five yearly DM age 45-69.	• Strategy 1: $8253/QALY gained • Strategy 2: $6671/QALY gained • Strategy 3: $6971/QALY gainedRisk strategies offering DM only yield less QALYs compared to the strategies offering both DM and US.
Pashayan et al[32]	Age, breast density, familial risk, history of previous benign disease, reproductive factors, lifestyle factors, oral contraceptive, polygenic risk score/SNPs	Risk distribution= 0.99%, 1.48%, 1.69%, 2.81% and 3.24%.	Percentile[e] 1. <10th 2. <25th 3. <32nd 4. <62nd 5. <70th	–	Percentile[e] 1. >10th 2. >25th 3. >32nd 4. >62nd 5. >70th	1. NoS for <10th percentile risk, and triennial screening for >10th percentile risk 2. NoS for <25th percentile risk, and triennial screening for >25th percentile risk 3. NoS for <32nd percentile risk, and triennial screening for >32nd percentile risk	All strategies are considered CE in comparison to age-based, and NoS at WTP threshold of £30 000/QALY gained.

(Continues)

TABLE 2 (Continued)

Study	Risk factors	Relative risk (baseline) and risk distribution	Risk level (based on the included risk factors)			Screening strategies evaluated for risk groups	Proposed RBS strategies compared to no or ABS (ICER and WTP threshold)
			Low-risk	Medium-risk	High-risk		
						4. NoS for <62nd percentile risk, and triennial screening for >62nd percentile risk 5. NoS for <70th percentile risk, and triennial screening for >70th percentile risk	
Arnold et al[31]	Age, breast density, familial risk, previous biopsy	*Relative risk:* Family history +ve= 1.454 Previous +ve biopsy = 1.495 Age 50-70+ breast density I-IV= 0.338 to 1.675 Five risk groups were made based on the risk thresholds	1. RR < 1.0 2. RR < 0.5 3. RR < 1.0 4. RR < 0.5 5. RR < 0.5	1. RR = 1.0 to 2.0 2. RR = 0.5 to 1.0 3. RR = 1.0 to 1.5 4. RR = 0.5 to 1.5 5. RR = 0.5 to 2.0	1. RR >2.0 2. RR >1.0 3. RR >1.5 4. RR >1.5 5. RR >2.0	Five risk groups were made based on risk thresholds assigned to low-risk, medium-risk, high-risk women (given in risk level columns). Each risk group was screened as: • Low-risk: Triennial screening • Medium-risk: Biennial screening • High-risk: Annual screening	RBS strategies are considered CE compared to NoS[f], given below are the ICERs for each strategy (cost/QALY gained): (1) €9180; (2) €14 498; (3) €9998.7; (4) €10 356; (5) €11 147Germany has no established WTP threshold. However, authors reported that RBS strategy 1 is economically efficient alternative at WTP threshold of €36 000/QALY gained in comparison to ABS.
Sankatsing et al[34]	Common factors[g]	Lifetime relative risk = 0.75, 1.0 and 1.8.	1. RR = 0.75	1. RR = 1[h]	1. RR = 1.8	• Low-risk: 101 strategies combining starting age (50 and 60 years), stop age (64–74), and biennial and triennial screening intervals. • High-risk: 182 strategies combining starting age (40 and 50 years), stop age	The following strategies are considered CE (also have high benefit-harms ratio) compared to NoS: • Low-risk: Triennial screening for women age 50-71 years. ICER = €7840/LYG

TABLE 2 (Continued)

Study	Risk factors	Relative risk (baseline) and risk distribution	Risk level (based on the included risk factors)			Screening strategies evaluated for risk groups	Proposed RBS strategies compared to no or ABS (ICER and WTP threshold)
			Low-risk	Medium-risk	High-risk		
						(74 and 84 years), and annual and biennial screening intervals.	• Average-risk: Biennial screening for women age 48-72 years (current ABS program) ICER = €8883/LYG[g] • High-risk: Biennial screening for women age 40-74 years. ICER = €6062/LYG

Abbreviations: ABS, age-based screening; BIRADS, breast imaging reporting and data system; CE, cost-effective; DM, digital mammography; FBM, film based mammography; FDR, first-degree relative; GDP, gross domestic product.; ICER, incremental cost effectiveness ratio; MRI, magnetic resonance imaging; NoS, no screening; QALY, quality adjusted life years; RBS, risk-based screening; RF, risk factor; SNPs, single nucleotide polymorphisms; US, ultrasound; WTP, willingness to pay; Y, years.

[a]Schousboe et al[13] did not mention risk groups, rather the authors mentioned positive risk factors. Risk groups are authors' elaboration.

[b]Model W (University of Wisconsin and Harvard Medical School), Model E (Erasmus University Medical Center) Model G-E (Georgetown University Medical Center and Albert Einstein College of Medicine), Model D (Dana-Farber Cancer Institute) Model M (MD Anderson Cancer Center).

[c]Trentham-Dietz et al[18] did not mention low-risk population, rather it is an average risk population.

[d]higher prevalence of BRAC1/2 gene mutations.

[e]The 10-year absolute risk equivalent for the 10th, 25th, 32nd, 68th and 70th percentiles of risk distribution are 0.99%, 1.48%, 1.69%, 2.81% and 3.24%, respectively.

[f]German health system determines optimal strategies based on effectiveness only (not cost-effectiveness), and biennial age-based screening has higher mortality rate reduction in comparison to risk-based screening. However, based on cost/QALY, risk-based screening is cost efficient compared to age-based screening at 54% adherence rate.

[g]The authors did not mention risk factors used to stratify women. Instead, they illustrated that breast density and BRCA mutations were not included in the risk factors.

[h]Average risk group is not a stratified subgroup rather than it includes whole population eligible for screening based on age 48-72 year.

TABLE 3 Model characteristics and input parameters

			Sources of input parameters				
Study	**Country**	**Model**	**Natural history model**	**Incidence, mortality/ survival data**	**Risk factors**	**Cost**	**Utility**
Tosteson et al[35]	USA	Discrete Event Simulation Model W[a]	CISNET model developed, validated, and calibrated using USA specific data.	The USA SEER data from 1975 through 2000 and RCT (DIMST) data.	RCT (DIMST) data[54]	Screening and diagnostic work up cost were estimated using the data from DIMST RCT[54] and unit cost from USA Medicare reimbursement rates. Treatment cost were derived from a cost study published in 1995.[55] Cost of waiting time from USA Department of Labour statistics data.	EQ-5D, USA female health status survey data used to estimate utilities for BC stages.[56]
Schousboe et al[13]	USA	Markov Microsimulation Model	Model developed and validated using the SEER 1975-2005 data and BCSC data base from 1996 through 2006. No state transition was modelled from local to regional and distant stages. Assumed that the distribution of stages at diagnosis would capture the stage transition.	Incidence and mortality data from the SEER data from 1975 to 2005 and BCSC data from 1996 through 2006.	Published USA literature[57]	Cost of screening was taken from Medicare reimbursement rates. Diagnostic cost were from the published USA literature,[35] and the treatment cost from cost study[55] published in 1995.	EQ-5D, Utilities were obtained from Swedish estimates from the general population, and BC stages.[37,58]
Vilaprinyo et al[17]	Spain	Markov Microsimulation Model	Lee and Zalen model developed, calibrated, and validated, under CISNET initiative using SEER data and BCSC data for USA population.	BC incidence, mortality, and survival data from the cancer registries of Girona and Tarragona provinces of Catalonia.	Published USA literature[13,57]	The cost of screening and diagnostic work were derived from screening program (PSMAR) Barcelona. Treatment cost taken from the published literature.[59]	EQ-5D, Utilities were obtained from Swedish estimates for BC stages,[58] and utility estimates for FP screening was taken from USA study.[13]
Stout et al[21]	USA	Microsimulation—D, E, GE, M, W[a]	Published CISNET models D, E, GE, M, W[a] based on USA data.[60]	BCSC data published between 2001 and 2008.	Published literature[61]	Cost of screening and diagnosis were taken from Health Care Common Procedure Coding System and DRGs. Cost of treatment was referenced from USA previous published estimates.[62]	EQ-5D, Utility assumptions based on USA adult population for healthy women, and BC patients.[56,81] Utility effect of screening and diagnostic effect based on Netherland's study.[64]

TABLE 3 (Continued)

Study	Country	Model	Sources of input parameters				
			Natural history model	Incidence, mortality/ survival data	Risk factors	Cost	Utility
Trentham-Dietz et al[18]	USA	Microsimulation—E, GE, W[a]	Published CISNET models E, GE, W[a] based on USA data.	SEER and BCSC data from 1994 to 2013. Previous published literature.[63,65-67]	Published literature.[68-80]	Cost of screening and diagnosis were taken from Health Care Common Procedure Coding System and DRGs. Cost of treatment was derived from USA previous published estimates.[21,62]	EQ-5D, Utility estimates were based on published USA literature for healthy women, and BC stages.[56,81] Utility effect of screening and diagnostic effect were based on Netherland's study.[64]
Gray et al[33]	UK	Discrete Event Simulation	The continuous tumour growth model and growth parameters were based on Norwegian BC model.[82]	Office of National Statistics UK, 2008–10. UK, National Life Tables, 1980-82 to 2011-13. NHS BC Screening Programme Annual Review 2012.[83] NHS Audit of Screen Detected BCs for the Year of Screening April 2013 to March 2014, and published literature[84,85]	Population based risk factor study (PROCAS)[86]	Cost of risk-stratification was estimated by expert opinion. Cost of screening, diagnosis and treatment were derived from UK published studies.[6,82,87] Cost of treatment was derived from a study[88] published in 1992.	EQ-5D, Utilities were obtained from Swedish estimates for BC stages[58]
Sun, Legood et al[36]	China	Markov Microsimulation Model	Relative risk of DCIS progression to invasive cancer was modelled using online available SEER data. Transition within the stages (Stage I to Stage IV) was modelled using the data from a published USA literature.[89]	Incidence of invasive BC from the Chinese cancer registry report 2012.[90,91]	Harvard Cancer Index online tool called "Your Disease Risk"[92,93]	Cost of risk-stratification, screening and diagnosis was obtained from the Chinese screening program, and cost of treatment was derived from the published Chinese cost studies.[94,95]	EQ-5D, Utility estimates were based on the Chinese published literature for FP,[39] and BC stages.[96]
Pashayan et al[32]	UK	Life Table Model	The Life table approach was used to model incidence and mortality in screened and in nonscreened women population between the ages 50-69 years.	Population-based data for BC for England and Wales, 2009 and 1988.	Combination of polygenic risk scores and epidemiological risk factors taken from published literature[97]	Cost of risk-stratification was measured through empirical estimates (no reference available). Screening cost was extracted from NHS BC screening program.[98] Cost of treatment was refrred from NHS reference costs and published literature[98,99]	EQ-5D, Utility values for healthy women and age-related decline in utility from the published UK literature,[100] and utility values of BC patients taken from the published review of 49 studies.[39]

(Continues)

TABLE 3 (Continued)

Study	Country	Model	Sources of input parameters				
			Natural history model	Incidence, mortality/ survival data	Risk factors	Cost	Utility
Arnold et al[31]	Germany	Markov Microsimulation Model	German cancer registry data, USA-BCSC data and published USA literature.[13,101]	Population-based data for BC from German Cancer Registry for incidence, and mortality estimates from Munich cancer registry reports.	Published USA literature[13,57]	Screening and diagnostic cost were valued according to the German national tariff data. For treatment cost, proportion of treatment for each stage was modelled from previous published studies,[102,103] and valued according to the German national tariffs.	EQ-5D, Utility impact of screening was based on USA estimates,[104] effect of vacuum-assisted breast biopsy from Greece estimates,[105] effect of imaging guided core needle biopsy from USA estimates (SF-36).[106] BC stages disutility based on Swedish estimates[13,58]
Sankatsing et al[34]	Netherlands	MISCAN Microsimulation model	The model simulated individual life histories of women. Model calibration and validation were conducted using Netherland's data.	Dutch screening program 2004-2013. Data from Netherlands comprehensive care organisation 1975-2013.[107]	Not mentioned	Cost of screening, diagnosis and treatment were modelled from previous published MRISC study for Dutch women.[108]	Utilities were not included

Abbreviations: BC, breast cancer; BCSC, breast cancer surveillance consortium; CISNET, cancer intervention and surveillance modelling network; DCIS, ductal carcinoma in situ; DIMST, digital mammographic imaging screening trial; DRGs, diagnosis-related groups; FP, false positive; MISCAN, microsimulation screening analysis; MRISC, MRI screening study; NHS, national health system; PROCAS, predicting the risk of cancer at screening; PSMAR, program of parc de salut mar; RCT, randomised control trial; SEER, surveillance, epidemiology, and end results; UK, United Kingdom; USA, United States of America.
[a]Model D (Dana-Farber Cancer Institute) model E (Erasmus University Medical Center) model G-E (Georgetown University Medical Center and Albert Einstein College of Medicine) model M (MD Anderson Cancer Center), model W (University of Wisconsin and Harvard Medical School).

Regarding RBS strategies based on age and breast density, the reviewed studies suggest that offering low-frequency screening to women with lower breast density and vice versa can be considered cost-effective compared to no screening and ABS. Nevertheless, results are inconsistent about starting ages and screening intervals. Schousboe et al[13] suggested no screening in BRADS-I women aged 40-49 years, 3-4 yearly screening in BIRADS-I women aged 50-79 years and biennial screening was considered cost-effective in dense breast (BIRADS-III and BIRADS-IV) women compared to no screening. Contrarily, Tosteson et al[35] suggested annual screening for women with dense breast. Besides, Tosteson et al,[35] and Stout et al,[21] who evaluated DM and FBM, reported that age and density targeted DM screening has far less favourable outcomes than age-targeted DM or FBM screening.

Concerning RBS based on multiple risk factors criteria, studies found RBS to be cost-effective compared to no screening or ABS. Notably, Arnold's et al[31] study did not identify any gains in QALYs, but they revealed cost savings from the RBS strategy. The German study[31] reported an incremental cost per QALY gain of €9180 (compared to no screening), the UK studies[32,33] and USA studies[13,18] considered

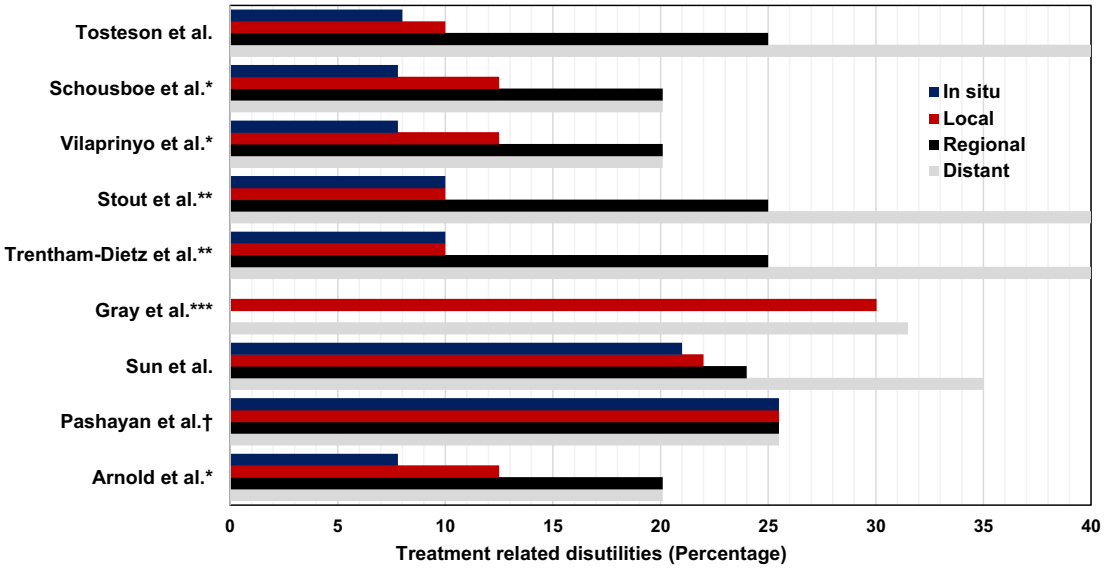


FIGURE 2 Health-related quality of life effect for breast cancer patients

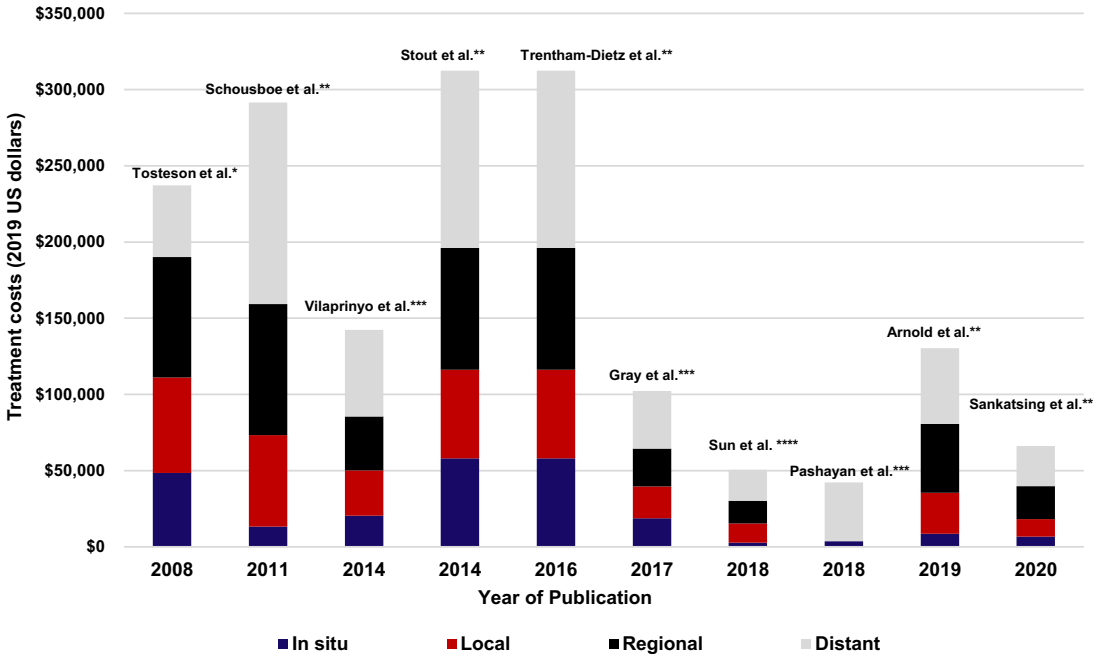


FIGURE 3 Treatment cost by year of publication

RBS cost-effective (CE) at WTP threshold of £30 000/QALY, and less than $100 000/QALY gained, respectively. Sankatsing et al[34] and Schousboe et al[13] suggested biennial screening in high-risk women in the US and the Netherlands (ICER = €6062/LYG). The Spanish study[17] found quinquennial screening CE for low-risk and medium-risk women and annual screening CE for high-risk women compared to ABS. Sun, Legood et al[36] (relative risk of two) and Pashayan et al[32] (70-percentile risk—10-years absolute risk of 3.24%) recommended not to screen women below certain risk thresholds. Gray et al[33] suggested that the addition of MRI to mammography for dense breast high-risk women can be considered a costly intervention, and it could increase the ICER up to £75 254/QALY gained.

3.2 | Model inputs

Model characteristics and sources of input parameters are shown in Table 3. All selected articles used simulation models. To quantify the model, a series of parameters that reflect the context where the strategy would be applied are required. These can be classified into four groups: (a) natural history of the disease, (b) risk stratification, (c) health outcomes adjusted by the quality of life and (d) costs. All studies informed their natural history models with context-specific sources of information. Similarly, most of the studies used country-specific information for risk stratification. Only two studies, Vilaprinyo et al[17] (Spain) and Arnold et al[31] (Germany) used data from the USA to define the risk stratification parameters.

The majority (90%) of the studies applied utility elicited using the generic EQ-5D instrument. Four studies[13,17,31,33] transferred utility values estimated from the Swedish general population. Only Schousboe et al[13] discussed the appropriateness of transferring utility values to the respective country of study. He compared the Swedish[37] and the American[38] studies' results and argued that mean age specific general population quality weights for healthy women are approximately the same. However, he did not mention the differences between BC stages. Three USA studies,[18,21,35] and one Chinese study[36] used utility values derived from their respective contexts. The remaining study[32] used patient utility values from a published review of Qol estimates.[39] The USA utility tariffs reported treatment dis-utilities in distant cancers in the order of 40%, which are considerably higher than the dis-utilities reported in the Swedish tariffs (around 25%) (Figure 2).

All studies, except Sankatsing et al[34] which used LYG as outcome measure, integrated disutility for BC treatment. Disutility due to screening was incorporated in only one study,[18] while five studies considered diagnostic dis-utilities.[17,18,21,31,36] None of the studies incorporated the QoL effects of informing a woman of her higher BC risk (see Supporting Information Material S4, Table S4).

All studies used recent country-specific cost data, only Gray et al[33] estimated costs from a 1992 costing study and inflated them. Total cost estimates that include all healthcare delivery phases (risk-stratification, screening, diagnosis and treatment) were not presented. Only Gray et al[33] ($73), Pashayan et al[32] ($17) and Sun Legood et al[36] ($2) included the cost of risk-assessment. All studies included the cost of screening, ranging from $52.2 to $361. Only Pashayan et al[32] did not include diagnostic cost (see Supporting Information Material S4, Table S4). Regarding treatment, Figure 3 shows that the most recent estimations of the total treatment cost are considerably lower.

3.3 | Clinical benefits and harms of risk-based screening

There is considerable heterogeneity in the benefits and harms of RBS. The benefits and harms mainly depend on the methods of risk-stratification, screening frequency, masking effect of breast density, screening participation rates and age. For instance, inconsistent results on mortality reduction were reported in six studies.

The results mainly indicate that increasing the frequency of screening saves more lives,[18] and vice versa.[31,32,35] Hence, age-based biennial screening saves more lives compared to risk-based screening.[31,32,35] Arnold et al[31] also indicated that adherence to screening has a significant role in saving lives where full adherence (100%) saves more lives than partial participation.

In addition to the mortality effects, the studies reported varying degrees of reduction in over-diagnosis and FP rates due to RBS strategies. Pashayan et al[32] reported a 27%-71% reduction in over-diagnosis. Vilaprinyo et al[17] mentioned a 25% reduction in overdiagnosis and 17.2% reduction in FP, while Arnold et al[31] reported a 6.67% reduction in benign biopsies compared to ABS. False negative rates increased by 26.2% compared to ABS.[17] Trentham-Dietz et al[18] and Sankatsing et al[34] suggested that more frequent (yearly or biennially screening, starting from a younger age) can potentially increase the harms such as FP and over-diagnosis compared to biannual ABS (see Supporting Information Material S5, Table S5).

Additionally, higher FP rates were reported in dense breast women compared to non-dense breast women.[13,21] Stout et al[21] reported a 2-fold increase in FP rates if dense breasted women are screened annually. Schousboe et al[13] reported a 15.9% incidence of FP in 10 years in BIRADS-I women compared to 35.9% in BIRADS-IV women of the same age.

3.4 | Optimal screening strategy at different willingness to pay thresholds

NMB was calculated at different WTP thresholds ranging from $5000/QALY to $150 000/QALY and three times GDP per capita for individual countries (details in Supporting Information Material S6, Table S6). Studies that stratified based on the breast density suggest age-based DM as the cost-effective strategy at the WTP threshold of $100 000/QALY gained. Stout et al[21] found biennial DM, breast density-based screening, and annual DM to be cost-effective at WTP threshold of $100 000/QALY. Among the studies[17,32,33,34,36] that stratified women based on multiple risk factors, most of the studies[17,32,33,36] indicate RBS to be cost-effective at WTP thresholds of

not less than $40 000. Arnold et al[31] reported that RBS as the cost-effective strategy at a WTP threshold of €36 000 per QALY gained.

3.5 | Sensitivity analysis

All articles, except for Trentham-Dietz et al[18] explored the uncertainty around the estimated ICERs. Four studies[17,21,34,35] limited uncertainty analysis to one-way deterministic sensitivity analysis. Five studies[13,31-33,36] conducted deterministic and probabilistic sensitivity analyses. Predominantly, studies[13,21,31,35,36] explored the sensitivity to variations on cost of screening and treatment.[13,17,31,33,36] A few studies investigated the sensitivity around risk stratification,[32,33] diagnostic work cost,[31] overdiagnosis[13,17] and mortality rates.[13,31] ICERs appear to be particularly sensitive to risk distribution,[17,21,32,34,35] cost of screening,[21,31,35] cost of risk stratification,[32,33] incidence of BC,[13,31,32] utility parameters,[13,21,31] FP and over-diagnosis[13,17] (see Supporting Information Material S7, Table S7).

4 | DISCUSSION

We compiled and analysed the published evidence regarding RBS strategies. Despite some discrepancies, results suggest that RBS strategies based on age and breast density can be considered cost-effective compared to no screening and ABS. Nevertheless, discrepancies exist regarding starting age and screening intervals. Similarly, RBS based on multiple risk factors is cost-effective in comparison to no screening or ABS. Moreover, results indicate that MRI, in addition to DM for dense breasted women, is not cost-effective.

Key weaknesses in the current models need to be highlighted. First, most of the studies were conducted in the context of FBM screening. FBM is currently obsolete in most parts of the world,[13,31,40,41] making findings irrelevant to inform policy decisions. Similarly, newer technologies that are showing promising results, such as DBT[42] and abbreviated breast MRI,[43] and the impact of interventions, such as training of radiologists and artificial intelligence (AI) aided detection,[44] have not been evaluated in terms of their effects on the cost-effectiveness of RBS in comparison to ABS. In addition to that, analysis from the societal perspective is highly overlooked. Thus, productivity changes due to BC screening, which account for a significant attributable economic cost, are mostly ignored.[45,46]

Cost and utility effects of risk-stratification are largely ignored. A full systematic review of simulation models for stratified BC screening conducted by Arnold[23] suggests that risk-stratification has no considerable cost implication but being declared high-risk could significantly reduce QoL. We identified two studies[32,33] where results suggest that an increase in the cost of risk stratification might cause the risk-based strategy not to be cost-effective compared to ABS (WTP threshold £30 000/QALY gained). None of the studies explicitly included the additional costs needed to implement risk-based care. Yet, implementation of risk-based interventions requires many resources such as human resource training and health system preparedness.[47] Utility loses related to screening and diagnostics are ignored in 90% and 50% of the identified articles. This may over-estimate the QALYs in high-risk subgroups screened more frequently and are usually associated with higher numbers of FPs.[13,18,21]

The transferability of utility values estimated based on the Swedish population to the USA,[13] Spain,[17] Germany[31] or the UK[33] populations is not clear. The assumption that the Swedish EQ-5D tariff can be transferable (which can be invalid) might introduce biases into the reported ICERs. Similarly, when incorporating risk factors data—studies conducted in Germany[31] and Spain[17] used USA data for risk stratification, potentially biasing the risk estimate.

The impact of RBS also depends on the accuracy of risk estimation and chosen risk threshold to declare women at high-risk, medium-risk, or low-risk.[17,31] For example, Arnold et al[31] defined relative risk thresholds as low (0 to <1), average (1 to <2) and high (>2) and considered triennial, biennial and annual screening, respectively. This strategy potentially reduced the mortality rate by 14.26% at €9180 cost per QALY gained. Also, Arnold et al[31] tested a different set of risk thresholds at low (<0.5), medium (0.5 to 1.0) and high (>1.0). Their results suggest that this would generate a higher reduction in mortality (16.46%) at a higher cost per QALY gained (€14 498/QALY), and almost a two folds increase in the number of biopsies after a FP screening. Interestingly, two studies[17,32] advocated for not offering or significantly reducing screening in women below a certain risk threshold (low-risk group). On the contrary, Trentham-Dietz et al[18] mentioned that offering low frequency screening could result in fewer gains (3.4 deaths averted and 50 LYG/1000 women aged 50-74 years screened triennially, compared to 4.1 deaths averted and 64 LYG/1000 same group of women screened biannually). Thus, this recommendation of no screening[32] or reducing screening frequency to 5-years[17] can easily be perceived as unethical by a significant proportion of the population. A survey-based Swedish study reported that 87% of the respondents agreed to more frequent screening if declared high-risk. On the contrary, 27% agreed to no screening if declared low-risk.[48] Therefore, particular attention should be given to the value of being sure that one (low-risk woman) is disease-free, and the trade-offs woman or society is willing to make between reduced screening intervals and risk of being detected with more advanced cancer.

The screening participation rate is generally considered one of the main indicators of a screening program's success. Arnold et al[31] argued that adherence rates had not been adequately considered in the economic evaluation of screening programs. His analysis suggests that for every 1.0% increase in adherence, there is a corresponding increase in QALYs gained of 0.85%. Therefore, a 100% adherence assumption for screening, diagnosis, and treatment is a potential limitation. Additionally, previous evidence suggests that a FP result can have a psychological impact that persists for years and negatively affects subsequent screening participation rates by almost 35%.[49,50] Likewise, dis-utilities from FP rates are also an essential element to consider. Identified articles indicate a higher number of FPs with annual screenings compared to biennial screenings.[18,21] Thus, going

forward, when including personalised approaches in the model, a focus is needed on disutility, and adherence rates in the high-risk group screened annually.

Weighing the harms and benefits balance is crucial to understanding age-based and risk-based approaches. Unfortunately, benefits and harms were not adequately reported across all studies because most of the studies' focus was not to communicate benefits and harms. For those studies that reported these, the benefits and harms were modelled based on assumptions and or published literature. Thus, except for breast density, there is a lack of empirical evidence on how personalised risk influences FP rates and over-diagnosis.

Overall, RBS continues to be controversial and under consistent criticism. RBS generally decreases harms, such as FP rates and over-diagnosis.[17,32] On the contrary, an increase in breast density can substantially increase FP rates due to a masking effect. Ninety percent high FP rates are reported in heterogeneously dense breast women compared to fatty breast women screened biennially.[18] Moreover, increasing screening frequency also increase FP rates.[21]

Nevertheless, a substantial decrease in FP rate could be achieved if breast density is combined with other risk factors. For instance, Trentham-Dietz et al[18] results suggest that offering annual screening to women of average-risk, aged 50-74 years and having heterogeneously dense breasts, will yield 2123 FPs per 1000 women screened lifetime, while at the same age and breast density, women having BC relative risk of 4.0 screened annually will yield 1778 FPs per 1000 women screened during lifetime. Additionally, the inclusion of breast density in risk calculation raises the challenge on how to obtain baseline mammogram before risk estimation. More importantly, the FP rate of first DM reported is 7.5%.[31]

There is a lack of empirical evidence that estimates the tumour growth rate separately for high-risk and low-risk women. In addition, there is an important knowledge gap regarding the accurate identification of BC risk. Successful implementation of personalised strategies requires a precise understanding of an individual's risk.[51,52] For instance, risk due to genetic susceptibility loci was included in only two articles. Similarly, the presence of second-degree relatives can potentially increase the risk of BC by 1.5-folds.[53] However, most of the studies in the review did not include familial risk due to second-degree relatives.

This systematic review's main limitation is that the information extracted is based on the few articles published until today. Even though the data search was extensive, with articles between the dates 1990 and 2019 sought, our analysis is based on only 10 articles. Unfortunately, evaluating the cost-effectiveness of risk-based BC screening remains in the early stage of investigation.

5 | CONCLUSION

Although RBS is considered cost-effective compared to ABS, results cannot be generalised, and the recommendations in these studies should be considered cautiously. First, besides the inherent differences between population characteristics, there is also a wide variation in screening protocols and screening outcomes, particularly the recall rate, which may vary substantially across countries. Therefore, data from the USA might not reflect population characteristics in other countries such as Germany or Spain. Furthermore, studies might have a potential bias due to not integrating cost and utility parameters for all phases of screening and diagnosis. Thus, more evidence is needed in terms of risk calculation, risk thresholds, screening outcomes (harms-benefits) in relation to risk categories (especially low-risk) and cost and utility parameters.

CONFLICT OF INTEREST

The authors declare no conflicts of interest..

DATA AVAILABILITY STATEMENT

Publicly available data were used in this review, and details are given in the methodology section. Further information is available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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