A systematic review of personalized breast cancer screening strategies

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BACKGROUND

Mammography screening has been associated with a reduction in breast cancer mortality. However, there is an ongoing discussion about the balance between the benefits and harms of this practice. A "one-size fits all" recommendation is followed in the US and Europe, with most screening-programs in Europe biennially screening women aged 50 to 70 years. Personalised risk-based screening strategies have been suggested to improve the effectiveness and benefit-harm ratio of breast cancer screening. Our aim was to systematically review studies assessing personalized breast cancer screening strategies and conduct a risk of bias assessment.

METHODS

The standard methods of the Cochrane Collaboration and the PRISMA declaration were used, searching in the *Medline*, *EMBASE* and *Clinical Trials* databases. We included studies published in English whose main objective was to assess personalized breast cancer screening strategies. The ISPOR-AMCP-NPC Questionnaire and The Cochrane Risk of Bias Tool were used to evaluate the quality of studies. Two independent reviewers screened full texts and evaluated the risk of bias.

RESULTS

We included 13 studies out of the 1119 initially retrieved citations (Figure 1). Three studies were randomized controlled trials, whereas nine were mathematical modeling studies, and one was an observational pilot study targeted to women aged 40-49 years (1). Among the trials, 2 are in the recruitment phase, and another begins in 2018 (Table 1). Among the mathematical modeling studies, the main risk factor used to define risk groups were breast density, age, family history, and previous biopsies were (Table 2). Six studies used also genetic information. The most common outcome measures were the gain in quality adjusted life years and costs, whereas the detection rate was the main outcome in the observational study.

The quality of the studies was good in the randomized trials. The modeling studies had a moderate to low risk of bias, but there was a wide variability across studies, whereas the observational study had a low risk of bias but its utility was moderate because the results are insufficient to properly assess personalized strategies.

Figure 1: Flowchart of studies selection

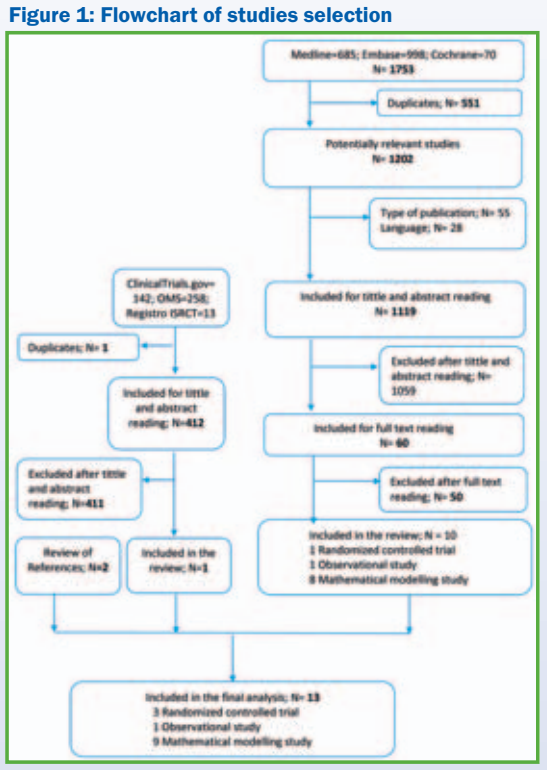

Table 1: Characteristics of randomized trial assessing risk-based personalized screening strategies

Name	Country	Period	Design	Study population	Risk factors	Comparison groups	Intervention/ Strategy	Primary result
WISDOM Study	USA	2016-2020 (recruitment phase)	Pragmatic adaptative randomized trial	Women 40-74 years N? 100.000	Previous biopsies, family history, genetic markers	Comparison group: Cribado anual mammography screening (standard Athena strategy). Intervention group: Screening based on breast cancer risk, measured using a model including previous biopsies, family history, and genetic markers.	Annual mammography vs.MRI/annual/ biennial/no screeninguntil age 50 years.	- Advanced breast cancer: proportion of tumors diagnosed at stage IIB or higher. - Reduction in recall rate and number of biopsies.
TBST Study	Italy	2013-2022 (recruitment phase)	Randomized trial, non-inferiority	Women 44-50 years N? 33.200	Age, breast density	Comparison group: annual screening from age 44-45 years. Biennial mammography from age 50 years. Intervention group: Women 44-45 years with dense breast (BIRADS 3, 4) at baseline mammography invited for annual screening. Women 44-45 years with fatty breast (BIRADS 1, 2) invited every 2 years. At age 50, all women biennial screening.	Women 44-50 years: Annual mammography vs. Annual/biennial mammography based on breast density.	- Cumulative incidence of T2+/node positive tumors across comparison groups and breast density categories. - Cumulative incidence of interval cancer across comparison groups and breast density categories.
MyPEBS Study	France, UK, Israel, Italy, Bélgium	2018-2025 (started)	Randomized trial, non-inferiority	Women 40-74 years N? 85.000	Age, breast density, family history, previousbiopsies, BMI, genetic markers	Comparison group: Standard screening based on the recommendations in each participating country. Intervention group: Stratification on 4 risk groups based on the 5-year risk of breast cancer.	Standard screening vs. - Low risk women (<1%): mammograhy every 4 years. - Intermediate risk (1-1,66%): biennial mammography (if high density, ABUS every 2 years) - High risk women (1,67-6%): annual mammography (if high density ABUS every year). - Very high-risk women (>=6%): annual mammography + MRI grafía.	- Incidence rate of advance tumor in each strata.

Table 2: Characteristics of mathematical modeling studies assessing risk-based personalized screening strategies

Author	Journal	Year	Country	Type of modeling	Data sources	Reference population	Risk factors [1]	Comparison groups	Strategies	Outcome measures
Trentham-Dietz	Ann Intern Med	2016	USA	CISNET (microsimulation). Three different models	External sources, and previously published evidence	Women 50-74 years	Combination of mammographic density, and 4 levels of relative risk (RR: 1.0, 1.3, 2.0, 4.0) based on previous published evidence.	Reference Relative Risk (RR=1) vs. RR> 1.3, RR>2.0, RR>4.0	- Annual, biennial, triennial screening age 50-74 years vs no screening - Biennial screening age 50-64 years vs biennial screening 65-74 years	Lifetime cost of breast cancer deaths, life expectancy and number of QALY, false-positive results, biopsies with a benign results, overdiagnosis, cost-effectiveness, and ratio of false-positive results among breast cancer deaths avoided by screening
Omahony	Med Decis Making	2014	Ireland	Cost-effectiveness microsimulation, and MISCAN (Monte Carlo microsimulation)	External sources, and previously published evidence. Mostly, screening data from Switzerland	Women 50-70 years	Increase or decrease in breast cancer incidence in the population (continuous value)	Different screening periodicities based on breast cancer annul incidence. Taking as reference a cost-effectiveness threshold of 20.000 € per QALY for average incidence of 0.00225 per women-year (1.9 years screening interval)	Screening periodicity (continuous time measure) according to breast cancer risk (continuous risk measure)	ICER, cost per QALY
Vilaprinyo	PLoS One	2014	Spain	Lee-Zelen probabilistic model (multiestate model)	External sources, and previously published evidence. Mostly, data from population registries, screening programs and clinical studies from Spain	Women 40-79 years	Mammographic density, family history, previous biopsy	Low: BIRADS A + one risk factor (RF) among: family history, or previous biopsies, or BIRADS B without RF Medium-Low: BIRADS A + 2 RF; or BIRADS B + 1 RF; or BIRADS C or D without RF Medium-high: BIRADS B + 2 RF; or BIRADS C or D + 1 RF High: BIRADS C or D + 2 RF	2624 strategies: - Screening start age (40, 45, 50) - Periodicity (annual, biennial, triennial, and quinquenial) - Screening stop age (69, 74)	Benefits: Number of lifes extended, and number of QALY gained. Adverse effects: False-positive results, Interval cancers and false-negatives, overdiagnosis, DCIS due to screening Costs: ICER, incremental benefit-harm ratio
Wu	Br J Cancer	2013	Taiwan	Markov (microsimulation)	External sources, and previously published evidence	Women ≥ 50 years	BRCA, mammographic density, SNPs, BMI, and age at 1st pregnancy	Deciles of risk according to risk score distribution. Percentile 50-60 as reference	a) Start age based on age at which the 10-year risk equals 1% of the 10-year risk of the 50th percentil of the risk score at age 50 (29 to 69 years). b) Screening interval (0.4 to 8 years) based on interval cancer rate that equals the threshold of triennial mammography for the 50th percentil of risk score. c) Mammography and MRI, or mammography and US based on the improvement in sensitivity obtained from decreasing the interval cancer rate until the percentile equals to the median value of the population with triennial mammography alone.	Number of mammograms, incidence of screen-detected cancer, incidence of interval cancer, proportion of interval cancers among breast cancer cases
Schousboe	Ann Intern Med	2011	USA	Markov (cost-utility model)	External sources, and previously published evidence. Data from SEER (Surveillance, Epidemiology, and End Results) and BCSC (Breast Cancer Surveillance Consortium)	Women 40-79 years	mammographic density, family history, previous biopsy	Risk groups based on cost-effectiveness thresholds (100.000$ and 50.000$ per QALY), and 10-year age groups (40-49, 50-59, 60-69, 70-79), breast density (BI-RADS), and number of risk factors (family history, previous biopsy)	Periodicity (no screening, annual, biennial, every 3-4 years) Strategy re-evaluation every ten years (40-49, 50-59, 60-69, 70-79)	Cost per QALY gained. Number of women screened during ten years to prevent a breast cancer death
Ahern	Br J Cancer	2014	USA	Markov (Monte Carlo microsimulation)	External sources, and previously published evidence. Data from SEER (Surveillance, Epidemiology, and End Results) and BCSC (Breast Cancer Surveillance Consortium)	Women 30-90 years with > 25% lifetime breast cancer risk	N.S.	Women with lifetime breast cancer risk ? 25%, vs. women with lifetime risk ? 50% and ? 75%	12 strategies: MRI (annual, biennial), mammography + clinic examination (none, 6 months, 1 year, 2 years), screening stop age (50, 74)	Cost, survival (life years), and QALY ICERs
Pashayan	Br J Cancer	2011	UK	Probabilistic model	Office for National Statistics (England), and DevCan 6.4.1 (National Cancer Institute, USA)	Women 35-79 years	Poligenic risk score (18 loci)	Women aged 47-79 years with 10 years absolute risk ? 2.5% vs women 35-79 years with 10 years absolute risk = 2.5%	Mammography in women 47-79 years (absolute 10-year risk ? 2.5%) vs. Mammography age 35-79 years with a 10-year absolute risk= 2.5% based on age + SNPs	Number of women in the target population, number of breast cancers potentitally detectable at screening
Gray	Value Health	2017	UK	Discrete Event Simulation	External sources, and previously published evidence. Data from NBSP (National Breast Screening Program) in UK, and expert panel from ASSURE	Women 50-70 years	Cuzick-Tyrer IBIS risk calculator (fenotype, age at menarque, number of pregnancies, age at first birth, age at menopause, atypical hiperplasia, carcinoma lobulillar in situ, BMI) improved with mammographic density	Four interventions: 1) 3 strata based on 10-year risk: < 3.5%, 3.5%-8%, y >8%; 2) 3 strata based on 10-year risk terciles: lowest risk, middle risk, highest risk; 3) Masking in women with high mammographic density (Volpara density 3 or 4); 4) Masking in women with high mammographic density + 3 strata based on intervention 1. Comparison group: Current screening mammography every 3 years in women aged 50-70 years, and no-screening strategy.	Interventions 1 and 2: Mammography every 3, 2, or 1 year for the low, intermediate, and high-risk groups, respectively; Intervention 3: Additional US for women with high breast density. If high risk woman (10-year risk >8%) additional MRI instead of US; Intervention 4: triennial, biennial, yearly mammography based on risk group for intervention 1. Additional US If high breast density	QALY of each strategy, Cost, and ICERs
Van Dyck	Health Policy Technol	2012	Belgium	Markov (cost-efectiveness)	External sources, and previously published evidence. Mostly data from UK.	Women ≥ 50 years	SNPs, breast cancer risk calculator, and risk factors available through the electronic health records system.	High and low risk [2]	High frequency vs low frequency screening strategy [3]	Total cost, and QALYs

NS: Not specified; RR: Relative Risk; QALY: Quality-adjusted life years; SNPs: Single Nucleotide Polymorphism; ASSURE (Adapting Breast Cancer Screening Strategy Using Personalised Risk Estimation). BI-RADS, Breast Imaging Reporting and Data System: A, almost entirely fat; B, scattered fibroglandular density; C, heterogeneously dense; D, extremely dense
1 Age is a risk factor in all models, except in Omahony et al that assumes a constant incidence rate of breast cancer in the 50-70 years age group. 2 The study does not specify how the risk groups are build. 3 The study does not specify the high and low frequenzy strategies.

(1) Venturini E, Losio C, Panizza P, et al. Tailored breast cancer screening program with microdose mammography, US, and MR imaging: short-term results of a pilot study in 40-49-year-old women. Radiology 2013; 268:347-355.

CONCLUSION

Randomized controlled trials will assess personalized strategies, but have not yet presented results. Mathematical modeling studies and the observational study showed evidence in favour of screening personalization. However, they do not consider the feasibility nor the acceptance by the target population.

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