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INCLUDING DECISION-ANALYTIC BENEFIT-HARM EVALUATION IN HTA - DIFFERENT AGE RANGES AND SCREENING INTERVALS IN BREAST CANCER SCREENING IN GERMANY

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Introduction

In Germany, the organized breast cancer (BC) screening program includes biennial mammography for women in the age of 50-69 years. To complement an IQWiG benefit assessment, we conducted a decision-analytic modelling study to evaluate the long-term benefits and harms of extending the age ranges for breast cancer screening with mammography in Germany compared to current biennial BC screening age 50-69 years.

Methods

Study design

Model type / Time horizon: Markov state-transition model (Figure 1.) with cohort simulation / lifetime.
Population: Women eligible for mammography screening in Germany.
Strategies: Mammography screening. Different age at start and end, screening intervals. Current screening: biennial mammography age 50-69 years.
Outcomes: Detected ductal carcinoma in situ (DCIS), cancer and cancer deaths, life years gained (LYG), quality-adjusted life years (QALY), number mammograms, number positive / false-positive mammograms, overdiagnosis, incremental harm-benefit ratio (IHBR).
Perspective: Women in Germany.

Calibration / Validation

Selected progression probabilities calibrated to observed data (e.g., detected DCIS / cancer by age, cancer stage) from the German statistics agency (DESTATIS) and cancer registries (Robert-Koch Institute). Internal and external model validation using published observed data.

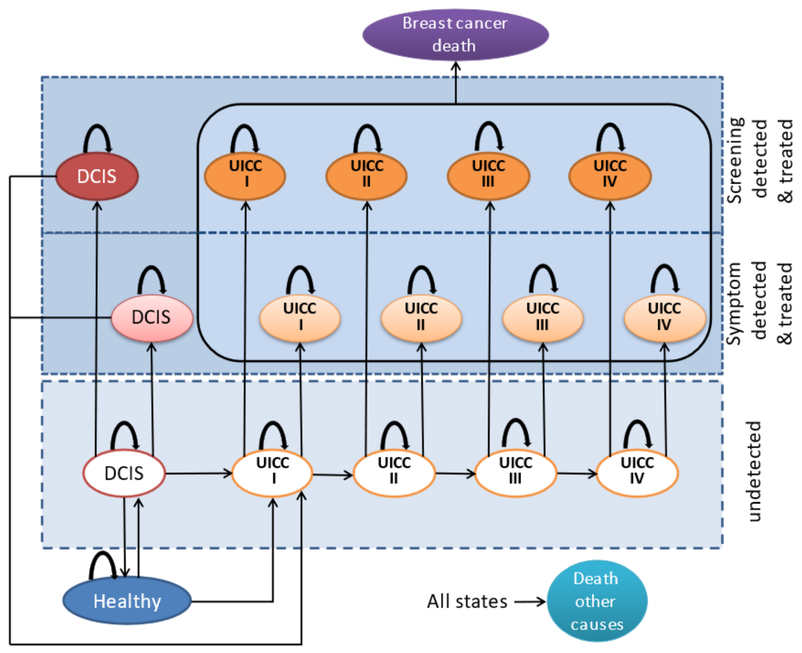


Figure 1. Schematic illustration: Natural history model of breast cancer.
DCIS: Ductal Carcinoma in situ, UICC: Union for International Cancer Control classification, Death other causes: Death by age, sex, race

Sensitivity analysis

Deterministic one-way and multi-way sensitivity analyses: utilities, test characteristics (sensitivity / specificity).

Data

Clinical & epidemiological data: German literature including guidelines and original German data. Data from German cancer registries and the German Statistical Office (DESTATIS).
Transition probabilities: international literature, calibration.
Test characteristics: international data (Mandelblatt et al. 2015) dependent on breast density, age and screening interval (Table 1.).
Quality of life data: German quality-of- life data (QoL) related to age (Jansen et al. 2015) along with published international data on QoL reduction related to detected and treated DCIS, cancer, mammography or positive screening results.

Breast density	Age (years)	Screening Interval	Sens (BC) (%)	Sens (DCIS)	Spec
ACR A - D	40-49	initial	74.6-92.1	94.3-95.4	**76.0**-87.2
		annual	**51.2**-80.6	**90.2**-91.9	88.4-93.0
		biennial	65.2-88.1	92.9-94.2	87.6-92.5
	50-64	initial	82.2-94.8	94.4-95.5	84.3-90.3
		annual	62.3-86.8	90.4-92.1	91.2-94.8
		biennial	74.7-92.1	93.0-94.3	90.6-94.4
	≥65	initial	86.8-**96.3**	94.4-**95.5**	86.3-91.6
		annual	70.2-90.3	90.4-92.2	92.4-**95.5**
		biennial	80.8-94.3	93.1-94.4	91.9-95.2

Table 1. Mammography performance by breast density, age and screening interval.
ACR – American College of Radiology, BC – invasive breast cancer, DCIS - Ductal Carcinoma in situ, Sens – sensitivity, Spec – specificity. The range (minimum and maximum values) of variation of test sensitivity and specificity across all subgroups are shown in red. Source: Mandelblatt et al. 2015

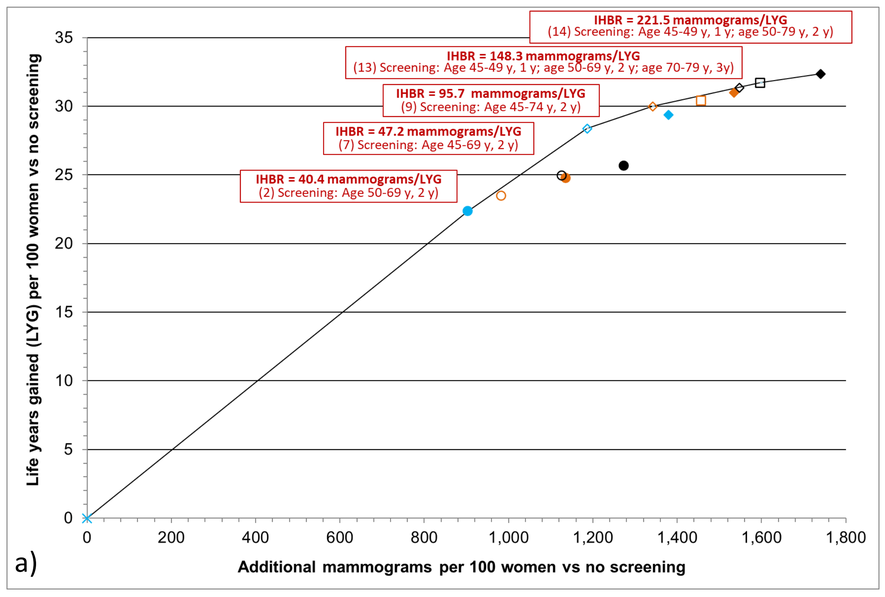
Results

Base-case analyses: *Clinical effectiveness*

The highest potential gain in life years was achieved with mammography at age 45-79 years (annual, age 45-49y; biennial, 50-79y) with 10.0 LYG per 100 participating women compared with current screening.
The highest gain in QALYs is expected by biennial mammography at ages 45-74 years (3.5 QALYs gained/100 women vs. current screening).

Base-case analyses: *Benefit-harm trade-offs*

Figure 2 shows the benefit - harm frontiers including the IHBRs in
a) number of additional mammograms,
b) number of false-positive mammograms, per LYG
for non-dominated strategies on the harm-benefit frontier efficiency line.



1) No screening
2) Screening: Age 50-69 y, 2 y (Ref)
3) Screening: Age 50-69 y, 2 y; age 70-74 y, 3 y
4) Screening: Age 50-74 y, 2 y
5) Screening: Alter 50-69 y, 2 y; age 70-79 y, 3 y
6) Screening: Age 50-79 y, 2 y
7) Screening: Age 45-69 y, 2 y
8) Screening: Age 45-49 y, 1 y; age 50-69 y, 2 y
9) Screening: Age 45-74 y, 2 y
10) Screening: Age 45-49 y, 1 y; age 50-69 y, 2 y; age 70-74 y, 3 y
11) Screening: Age 45-49 y, 1 y; age 50-74 y, 2 y
12) Screening: Age 45-79 y, 2 y
13) Screening: Age 45-49 y, 1 y; age 50-69 y, 2 y; age 70-79 y, 3 y
14) Screening: Age 45-49 y, 1 y; age 50-79 y, 2 y
Harm-benefit frontier

Legend Figure 2.

Figure 2. Harm-benefit efficiency frontier for mammography screening.
Life years gained per 100 women compared with a) number of additional mammograms per 100 women, b) Number additional false-positive mammograms per 100 women for different mammography screening strategies in women in Germany. IHBR – incremental harm-benefit ratio; BC – breast cancer; vs – versus; pos. – positive; y - year

Overdiagnosis

Overdiagnoses occurred mainly due to DCIS and was highest in strategies with mammography age 45-79 years (Figure 3).

Sensitivity analysis

No significant changes, when varying utility parameters.
Simultaneous variation of sensitivity and specificity in opposite directions showed an effect on the harm-benefit ratios:

- Scenario 1 (reduced specificity/increased sensitivity): IHBRs were significantly higher compared to the base-case analysis results.
- Scenario 2 (increased specificity/reduced sensitivity): IHBRs were lower compared to the base-case analysis results.

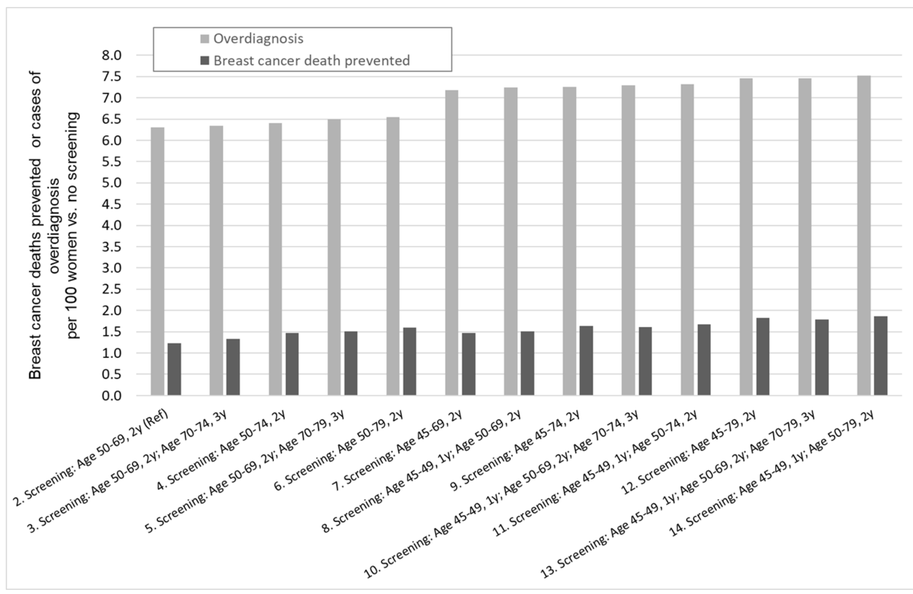


Figure 3. Overdiagnosis versus prevented cancer deaths from mammography.
y – year

Conclusion

Based on our results, extension of the age range for mammography may prevent additional deaths from breast cancer and increase remaining life expectancy. Considering quality of life and harm-benefit ratios, biennial mammography from age 45 to 74 years may provide a good balance between additional benefits and harms. In future research, evidence-based personal information on the acceptance of harms per additional unit of benefit should be used. This decision-analytic framework is suited for HTAs on cancer screening.

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