Maturitas 109 (2018) 81–88

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

A modelling study to evaluate the costs and effects of lowering the starting age of population breast cancer screening

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ARTICLE INFO

Keywords:
Breast neoplasm
Mass screening
Mammography
Age
Cost-effectiveness analysis
Computer simulation

ABSTRACT

Background: Because the incidence of breast cancer increases between 45 and 50 years of age, a reconsideration is required of the current starting age (typically 50 years) for routine mammography. Our aim was to evaluate the quantitative benefits, harms, and cost-effectiveness of lowering the starting age of breast cancer screening in the Dutch general population.

Methods: Economic modelling with a lifelong perspective compared biennial screening for women aged 48–74 years and for women aged 46–74 years with the current Dutch screening programme, which screen women between the ages of 50 and 74 years. Tumour deaths prevented, years of life saved (YOLS), false-positive rates, radiation-induced tumours, costs and incremental cost-effectiveness ratios (ICERs) were evaluated.

Results: Starting the screening at 48 instead of 50 years of age led to increases in: the number of small tumours detected (4.0%), tumour deaths prevented (5.6%), false positives (9.2%), YOLS (5.6%), radiation-induced tumours (14.7%), and costs (4.1%). Starting the screening at 46 instead of 48 years of age increased the number of small tumours detected (3.3%), tumour deaths prevented (4.2%), false positives (8.8%), YOLS (3.7%), radiation-induced tumours (15.2%), and costs (4.0%). The ICER was €5600/YOLS for the 48–74 scenario and €5600/YOLS for the 46–74 scenario.

Conclusions: Women could benefit from lowering the starting age of screening as more breast cancer deaths would be averted. Starting regular breast cancer screening earlier is also cost-effective. As the number of additional expected harms is relatively small in both the scenarios examined, and the difference in ICERs is not large, introducing two additional screening rounds is justifiable.

1. Introduction

Breast cancer screening has been implemented in many European countries to detect breast cancer at an early stage and decrease breast cancer mortality. In these programmes, usually the age of 50 is considered optimal for starting regular screening due to the increasing incidence of the disease afterwards [1]. There are, however, some countries (United Kingdom, Czech Republic) and regions (e.g. in Sweden and Italy) that invite women younger than 50 years to be screened despite the controversy in the benefit-harm balance [1,2].

Arguments in favour of lowering the starting age of screening are based on the potential breast cancer specific mortality decrease for

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https://doi.org/10.1016/j.maturitas.2017.12.009
Received 13 April 2017; Received in revised form 9 October 2017; Accepted 8 December 2017

women as there is evidence of an increased incidence of breast cancer above the age of 40 and more prominently between 45 and 50 years, and there is a great potential number of years of life gained for deaths averted [3]. Results from the United Kingdom Age Trial [4] suggest that regular mammographic screening in the age group 40–49 could reduce the risk of dying from breast cancer (relative risk (RR) 0.88 (95% confidence interval (CI) 0.74–1.04), although the reduction was less pronounced as compared to results from meta-analyses for older age groups [5,6]. On the other hand, there are also studies showing that potential harms as overdiagnosed breast cancers [7], radiation-induced breast cancer deaths [8,9], false positive test results [10–15], unnecessary biopsies [11,12], and costs of false positive biopsies [16] accompany regular screening, though their estimated numbers varied largely. Such potential harms have been considered to outweigh the benefits of regular screening for women 40–49 years old and thus regular breast cancer screening in this age group is generally not recommended [17].

There are a number of recent modelling studies [7,8,10–15,18] which tried to balance the expected benefits and harms of breast cancer screening but these evaluations were partial, i.e. focused only on mortality reduction, radiation-induced tumours and tumour deaths, or overdiagnosis and only three of them analysed the Dutch setting [7,8,18]. The most recent study focused on the cost-effectiveness of digital mammography screening before the age of 50 in the Netherlands and concluded that additional screening between age 40 and 49 was cost-effective, however, their model only considered age as a risk factor for breast cancer and did not incorporate other factors as breast density which is important in younger age groups [18].

Therefore, in the current analysis we performed a comprehensive evaluation regarding the proper balance of harms and benefits of regular breast cancer screening starting from a younger age, including breast density variation as a function of age. The aim of our study was to evaluate the quantitative benefits, harms, and cost-effectiveness of lowering the starting age of breast cancer screening in the Dutch general population given the already available biennial screening among women aged 50–74. The following outcomes were considered: tumour deaths prevented, years of life saved (YOLS), number of false positives, radiation-induced tumours, costs and cost-effectiveness. Qualitative outcomes (such as quality of life) were not included.

2. Methods

This study was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [19]. We applied the Simulation Model on Radiation Risk and breast cancer Screening (SiMRiSc) in the current analysis. The model was previously published and externally validated in women with BRCA mutations [20–22]. For the purpose of this analysis, the SiMRiSc model was extended by including a breast density parameter (Table 1) and externally validated (Table 2) for the general population of women by comparing the outcomes to empirical data from the Dutch national screening programme. As this model was restricted to invasive breast cancer only, ductal carcinoma in situ (DCIS) was not included.

The current breast cancer screening scheme in the Netherlands was included: biennial population screening in women aged 50–74 years as a reference scenario. Scenarios were developed for two alternative screening regimens with earlier starting ages: biennial screening from 48 to 74 years and from 46 to 74 years. The outcomes of the model consisted of potential benefits: tumour deaths prevented, YOLS; and potential harms of screening: number of false positives and radiation-induced tumours.

2.1. Description of the model and its components

SiMRiSc is a micro-simulation Markov model (Fig. 1). An extensive description of the model can be found in previous publications [20–23]. Women were simulated during their lifetime taking into account their life expectancy, chance of developing a tumour, tumour growth and survival from breast cancer, breast density and mammographic sensitivity and specificity, and risk of tumour induction due to diagnostic radiation. If a tumour was present at the screening moment, the chance of detection was dependent on the mammographic sensitivity. If the tumour was found, either by screening or self-detection, the woman was removed from the simulation and the breast cancer specific death age of the woman was calculated based on the life expectancy after breast cancer diagnosis depending on the tumour size at clinical detection.

The model parameters are presented in Table 1. In the simulation, every woman was given a predetermined natural death age which was sampled from the life expectancy in the Netherlands [20]. The breast cancer incidence rate was sampled to assign an individual probability to develop breast cancer during the lifetime of the women and the age at which the tumour would be clinically detected [24]. A systematic literature search was performed to estimate the parameters in the tumour growth model and the tumour size at clinical (self-) detection. The history of the tumour was calculated by applying an exponential growth model with an age-dependent tumour volume doubling time sampled from a population log-normal distribution. The preclinical period of the tumour was defined as the time from which the tumour size was larger than the minimal detection threshold for mammography (5 mm) until the time of clinical detection without screening [25]. The specificity of mammography was based on a single RCT which was considered the best source for mammographic specificity for the current analysis since the screened women were in the age group 45–69 years [26].

Finally, a systematic error was introduced which referred to a fraction of breast cancer cases that could not be detected by mammography mainly due to lobular carcinomas, dense breast tissue and tumours located close to the thorax wall. Based on expert opinion (RMP), we assumed this fraction to be 10%, that is, 10% of all cases that should be detected based on tumour volume would not be detected due to their characteristics.

2.2. Modelling the effect of breast density

In the model the chance of tumour detection at screening was modelled to be dependent on the mammographic sensitivity given the breast density of the woman at certain age. Systematic literature searches were performed to find estimates for the distribution of breast density in the population and the relation between breast density and mammographic sensitivity [27–29]. A meta-analysis based on calculating the weighted average value from the reported sample sizes [27–29] was performed to estimate the baseline values and the 95% CI for breast density. The same method of meta-analysis was applied for estimating the sensitivity of mammography as a function of breast density and age, based on the resulting literature [30–38].

2.3. Screening scenarios

Two alternative screening scenarios in which women were subjected to systematic mammographic screening were simulated according to different starting ages, i.e. 46 and 48 years of age. The screening interval was biennial and the end age was set at 74 years. The current population breast cancer screening programme, i.e. biennial screening in the age group 50–74 years, was set as a reference scenario and was compared to the alternative scenarios.

2.4. Expected benefits and harms of regular breast cancer screening

The results from the model simulations were reported in terms of potential benefits: tumour deaths prevented, YOLS; and potential harms of screening: number of false positives and radiation-induced tumours. Tumour deaths prevented, YOLS and radiation-induced tumours were

Table 1
Baseline estimations and 95% confidence intervals (CI) of input parameters.

Parameters		Value (95% CI)				Reference
Tumour induction model	Dose [mSv]	3 (1–5)				[22]
	Probability of tumour induction [%]	0.51 (0.28–0.83)				
Tumour growth model	Tumour doubling time	Days		Geometric mean, log transformed	Spread	
	< 50 years	80		4.38 (3.78–4.99)	0.43	[25]
	50–70 years	157		5.06 (4.80–5.32)	0.17	
	> 70 years	188		5.24 (4.79–5.69)	0.23	
Self-detection model	Self-detection diameter [cm]	Mean		3 (2.9–3.1)		[39]
		standard deviation		0.65 (0.55–0.74)		
Cumulative incidence rate	f [%]	24.0 (22.4–25.6)				[24]
	m [years]	74.5 (72.3–76.7)				
	s [years]	21.4 (19.6–23.2)				
Distribution of breast densities	BI-RADS density score	1	2	3	4	
	< 40 years [%]	4.4	30.2	48.2	17.2	[27–29]
	40–50 years [%]	5.9	34.1	46.9	13.1	
	50–60 years [%]	8.5	50.3	36.6	4.6	
	60–70 years [%]	14.9	53.4	29.4	2.3	
	> 70 years [%]	17.4	54.3	26.2	2.1	
Sensitivity [%]		87 (75.2–98.8)	84 (80.1–87.9)	73 (54.8–91.2)	65 (34.0–96.0)	[30–38]
Specificity [%]		96.5 (96.0–96.9)				[26]
Systematic error [%]		10				Expert opinion

Table 2
Validation of the simulation results.

	simulated	observed
Number of screen detected tumours		
First screening round/age/		
50–54	284	259 (227–291)
55–59	26	22 (12–32)
60–64	18	20 (12–28)
65–69	13	17(3–31)
70–74	9	8(2–14)
Subsequent screening rounds/age/		
50–54	728	405 (371–439)
55–59	1052	710 (660–760)
60–64	1083	800 (751–849)
65–69	927	762 (711–813)
70–74	775	734 (680–788)
Tumour size distribution of screen-detected tumours		
< 2 cm	96.7%	78.3%
2–5 cm	3.2%	18.9%
> 5 cm	0.1%	2.7%
Number of interval cancers per 1000 screens	2.7	1[a]
Number of false positive mammograms per 1000 screens	53.5	10.2

[a] Including DCIS.

calculated for both alternative scenarios, biennial screening from 48 to 74 and from 46 to 74 with respect to the reference biennial screening from 50 to 74 years of age and for the two scenarios compared to each other.

2.5. Cost-effectiveness analysis

Only direct medical costs related to screening and treatment of breast cancer were considered (Table 3). The costs of a screening test were based on data from the Dutch national screening programme, valued in Euros (€) [39]. The costs of a biopsy were based on a study in a similar population group [18]. The costs of treatment were dependent on tumour size and based on the Dutch cancer registry [20], indexed to 2014 [40]. Incremental cost-effectiveness was estimated as the ratio of the incremental costs for screening and the incremental gain in life years for the alternative screening strategies compared to no screening. Discounting of 4% for costs and 1.5% for health effects (YOLS) was applied according to the Dutch guidelines [41]. In order to allow for international comparison, we also applied a discount rate of 3% for both costs and effects [42].

2.6. Validation of the model

The model was validated by comparing the point estimates of the simulated outcomes (screen detected tumours, tumour size distribution,

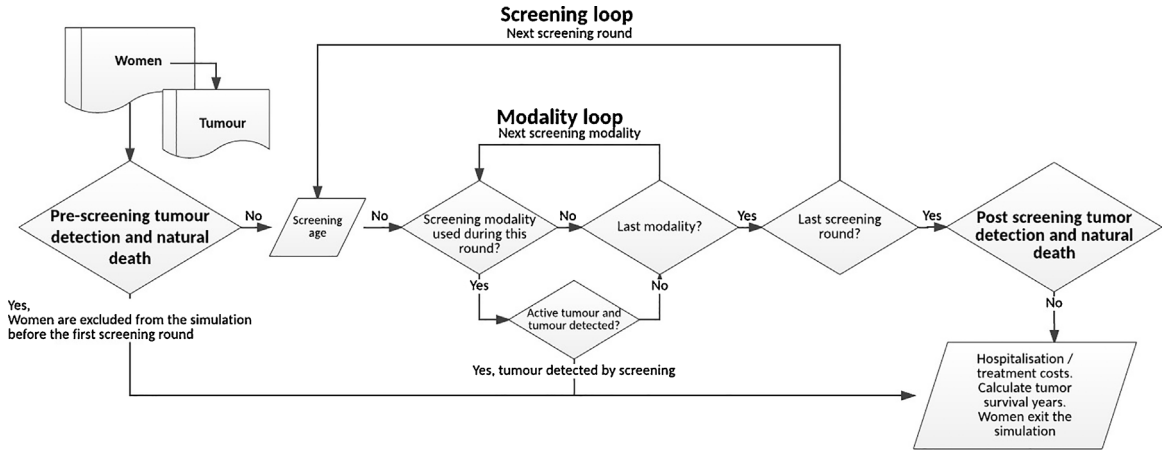

Fig. 1. Flowchart of the model.

Table 3
Costs of screening, diagnosis and treatment of breast cancer in the Netherlands.

Procedure	Costs (in Euro/2013)	References
Screening and diagnosis		
Mammogram	64	[39]
Biopsy	176	[18]
Treatment by tumour size		
Treatment < 2 cm	6438	[20,40]
Treatment 2–5 cm	7128	[20,40]
Treatment > 5 cm	7701	[20,40]

number of interval cancers, number of false positive tests) in the reference scenario to the empirical CI of the observed data from the report [39] of the Dutch national screening programme. The number of simulated screen detected tumours was compared to the observed incidence separately for the initial and the subsequent screening rounds for the age groups 50–54, 55–59, 60–64, 65–69, and 70–74. The simulated results were considered valid when the simulated point estimates fell within the estimated empirical CI.

2.7. Sensitivity analyses

A univariate sensitivity analysis was performed for practical reasons. Since the model has been shown to be predominantly sensitive to the input parameters related to lifetime breast cancer risk and sensitivity of mammography and to a much lesser extent to the other input parameters [22], it was considered that a sampling-based sensitivity analysis where all the input parameters were changed at the same time would not provide essentially different information. Therefore, univariate sensitivity analyses with minimum and maximum values of the 95% CI for the input parameters listed in Table 1 for the entire cohort of 10,000 women were performed to evaluate the effects of parameter uncertainty. Tornado plots were constructed to visualise the impact of parameter uncertainty on the ICER.

3. Results

3.1. Validation of the model

Table 2 shows the comparison between the numbers of detected breast tumours as simulated by the model and as reported in the Dutch national screening programme for the initial and the subsequent screening rounds, the tumour size distribution, the number of interval cancers and the number of false positive mammograms.

The model estimated the amount of screen detected tumours for the initial screening round very well, but overestimated the number of screen detected tumours in the age group 50–69 for the subsequent screening rounds. In the remainder age group, the number of simulated screen detected tumours fell well within the estimated empirical 95% CI. The proportion of small detected tumours was overestimated. The number of the interval cancers and the number of false positive mammograms were also overestimated.

3.2. Expected benefits and harms of regular breast cancer screening, costs and cost-effectiveness

The results from the simulations of the three screening scenarios are presented in Table 4. The addition of one extra screening round led to increase in the number of small screen detected tumours (4.0%), tumour deaths prevented (5.6%), false positives (9.2%), YOLS (5.6%), radiation-induced tumours (14.7%), and costs (4.1%) as compared to the reference scenario.

A further increase in the number of small screen detected tumours (3.3%), tumour deaths prevented (4.2%), false positives (8.8%), YOLS (3.7%), radiation-induced tumours (15.2%), and costs (4.0%) was observed when one extra screening round was added and compared to the 48–74 screening scheme. The ICER was €5600 per YOLS for biennial screening 48–74 as compared to no screening and €5600 per YOLS for biennial screening 46–74 as compared to no screening. The ICERs discounted according to the Dutch guidelines were slightly above the threshold of €20000 per YOLS.

Table 4
Simulated outcomes, benefits and harms, costs and cost-effectiveness of breast cancer screening for two screening scenarios, biennial screening from 48 to 74 years of age, and biennial screening from 46 to 74 years of age. All number are given for a cohort of 10000 women.

	Scenario (start age-end age)	
	46–74 vs 48–74	48–74 vs 50–74
Outcomes		
Number of screen detected tumours	+3.3% (641)	+4.0% (620)
Detected tumours' size distribution		
< 2 cm	+3.2% (610)	+4.4% (591)
2–5 cm	+6.2% (29)	−2.6% (27)
≥5 cm	+3% (1.4)	−23.3% (1.3)
Number of interval cancers	+8.5% (271)	+8.9% (250)
Recall rates	−2.8%	−3.5%
Expected benefits		
Number of tumour deaths prevented	+4.2% (128)	+5.6% (123)
YOLS	+3.7% (3259)	+5.6% (3143)
YOLS (discounted)	+4.5% (1182)*/ +0.5% (534)**	+8.6% (1131)*/ +5% (531)**
Expected harms		
False positives	+8.8% (4085)	+9.2% (3754)
Number of radiation-induced tumours	+15.2% (39)	+14.7% (33)
Costs and cost-effectiveness		
Total costs/million €	+4.0% (17.4)	+4.1% (16.7)
Total costs (discounted)/ million €	+4.8% (14.5)*/ +5.6% (12.6)**	+4.8% (13.8)*/ +5.5% (11.9)**
ICER	5.6/16.0*/27.1**	5.6/15.5*/26.0**

ICERs are discounted according to:
*International (costs 3% and YOLS 3%).
*Dutch guidelines (costs 1.5% and YOLS 4.5%).

3.3. Sensitivity analyses

The sensitivity analyses revealed that the ICERs for the breast cancer screening scenarios starting at the age of 46 and 48 years were most sensitive to the uncertainty in the lifetime risk of breast cancer, the growth rate of tumours for ages under 50 and the sensitivity of mammography (Fig. 2a/b) and were least sensitive to the uncertainty in the specificity of mammography, the self-detection diameter and the growth rate of tumours for ages over 70. For the 48–74 scenario, the lowest ICER found in the sensitivity analyses was €4000 per YOLS and the highest was €6100 per YOLS. The lowest ICER found in the sensitivity analyses for the scenario 46–74 was €5100 per YOLS and the highest was €6100 per YOLS.

4. Discussion

The aim of this study was to evaluate the benefits, harms, and cost-effectiveness of lowering the starting age of breast cancer screening in the Dutch general population given the already available biennial screening among women aged 50–74. For the purpose of this analysis, a previously published and validated simulation model (SiMRiSc) was extended with a breast density input parameter and externally re-validated for the current application. The model reproduced the observed data for the first screening round with sufficient validity. The model

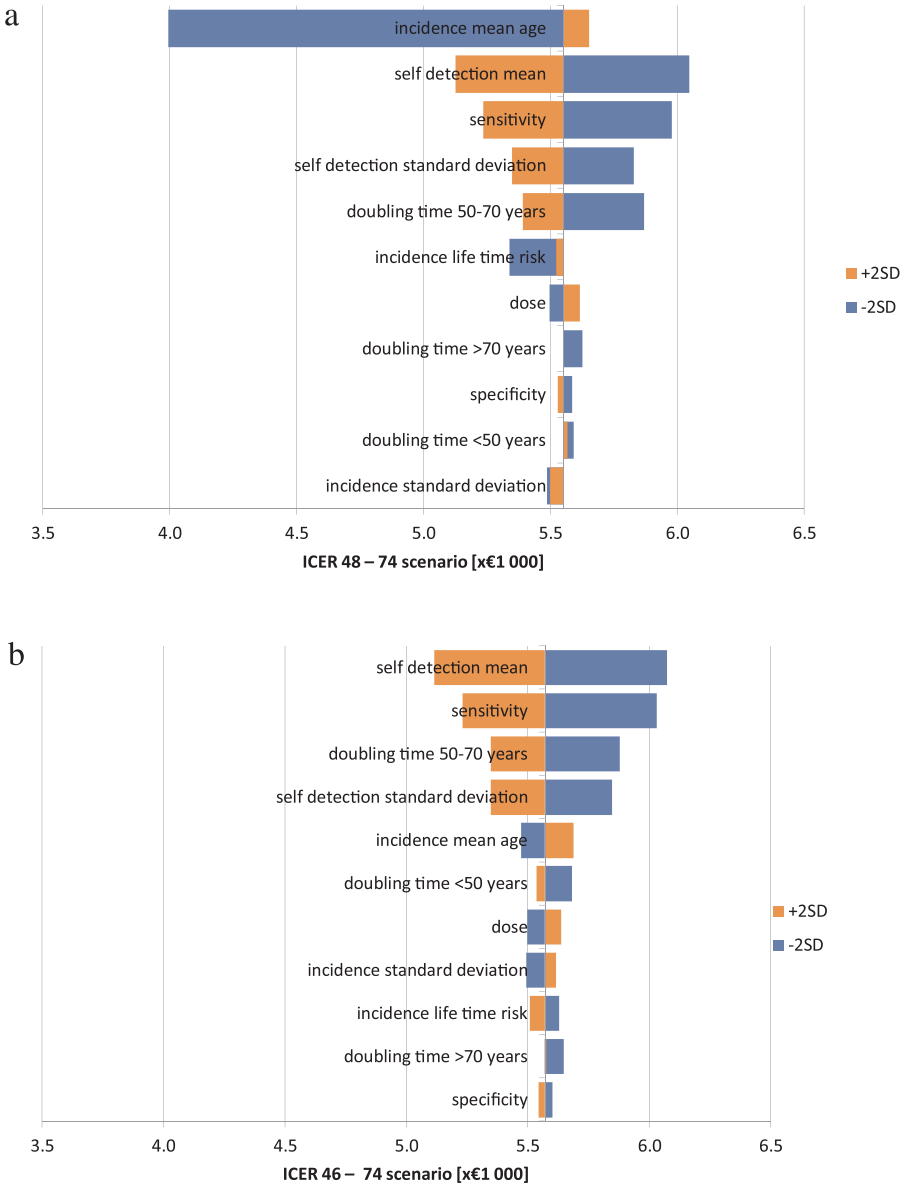

Fig. 2. Tornado diagram for univariate sensitivity analyses.

overestimated the number of tumours in the subsequent screening round as well as the proportion of small tumours, interval cancers and false positive mammograms. However, since we were mainly interested in the relative effect of lowering the starting age of screening, we conclude that although the absolute outcome of the validation showed an overestimation, the relative outcomes of lowering the starting age of screening were correct. Our analysis revealed that starting the regular breast cancer screening at earlier ages could result in increased expected benefits in terms of YOLS and tumour deaths prevented, and was cost-effective in terms of costs per YOLS. However, the number of expected harms, i.e. false positives and radiation-induced tumours also increased. The two alternative scenarios showed ICERs that would generally be considered cost-effective with values below €20000 per YOLS. Only the ICERs discounted in accordance with the Dutch guidelines were slightly above the threshold of €20000/YOLS.

Starting breast cancer screening at an earlier age expectedly increased the number of prevented tumour deaths due to the increased number of small screen detected tumours which could be potentially curable and thus prolonged the survival of breast cancer patients and increased their YOLS. However, expanding the lower age limit also increased the potential harms of screening in terms of number of radiation-induced tumours and false positives thus affecting negatively the number of YOLS and the mortality reduction from breast cancer. In addition, false positive results from screening could increase the distress on patients and bring to unnecessary referrals to further testing. The reported ICERs (except for the ones discounted according to the Dutch guidelines) were below a commonly referred ceiling threshold of €20000 for cost-effectiveness of preventive care programmes in the Netherlands [43]. Our analysis suggested that lowering the screening age for breast cancer seems to show slightly declining marginal returns. From a decision-makers' point of view lowering the starting age of breast cancer screening of the general population could be considered as adding one and two additional rounds of screening is cost-effective. However, expanding the starting age of breast cancer screening even lower would further increase the expected harms and thus costs of screening and it is not supported by epidemiological evidence which shows prominent increase in the breast cancer incidence above 45 years of age [3].

Our results are in line with an earlier modelling study by de Gelder et al. [8] which also reported increase in prevented tumour deaths with lowering the starting age of screening. The number of screen detected tumours in our simulations are comparable to the ones reported by

Sankatsing et al. [18]: 3.8% additional screen detected tumours in a screening scenario commencing from 48 up to 74 years of age vs. 4.0% additional screen detected tumours in our simulations, which resulted in averting 13 breast cancer deaths and adding 10.2% YOLS as compared to 123 averted breast cancer deaths and 5.6% increase in YOLS in our scenario. False positive screening findings in our analysis are more favourable than the ones from Sankatsing et al. [18] who reported 18.5% increase in women screened regularly from the age of 48 to the age of 74, while we found 9.2% increase in false positives in the same age group.

Our results regarding radiation-induced tumours are higher than the ones reported by de Gelder et al. [8] who revealed that decreasing the starting age of population breast cancer screening increased the induced breast cancer incidence and the numbers varied for the different scenarios depending on variation of the radiation dose (1–5 mSv), i.e. 5.9–29.6 for biennial screening in a simulated cohort of 100 000 women aged 50–74 years, 7.0–35.2 for ages 48–74 and 8.3–41.5 for ages 46–74. They concluded that the risk of radiation-induced tumours was negligible compared to the number of prevented deaths, however, they assumed an average absorbed glandular dose of 1.3 mGy per view (of both breasts) and their calculations were based on one-view mammography at subsequent screening rounds [8] while in our estimations we utilised the 3 mSv glandular dose which is still state-of-the-art for a two-way view mammography screening. The cost-effectiveness ratios of both alternative screening scenarios are in line with the findings of other studies which also reported the lowering of starting age for breast cancer screening to be cost-effective [18].

Model simulations predicted the empirical data of the first screening round with sufficient validity. Variances between simulated results and empirical 95% CI were observed in the number of screen detected tumours in the age group 60–74 for the subsequent screening rounds, the size distribution, and in the number of interval cancers and false positives. Since the model is most sensitive to the tumour doubling time we calculated that a 15% lower tumour doubling time gives a reduction of almost 50% in the number of screen detected tumours in the subsequent screening rounds which is well within the empirical 95% CI of the observed data. In addition, the proportion of small screen detected tumours (< 2 cm) reduced by 10% whereas the number of interval cancers, due to the decreased tumour doubling time, increased even further to 4.5. In the SiMRiSc model women will develop breast cancer at specific age and the tumour will grow according to the predefined tumour doubling time, therefore, there will be no length time bias. In addition, the study evaluates the relative effect of lowering the starting age of breast cancer screening from 50 to 48 and from 48 to 46, and the possible effects of lead time bias will cancel out. A possible explanation for the overestimation of the false positive mammograms is that the programme specificity in the Netherlands is amongst the highest reported [39]. Another explanation could be the double reading which lowers the number of false referrals. However, as seen from the sensitivity analyses the specificity of mammography has very little influence on the ICERs (Fig. 2a/b). The analyses showed that the model is most sensitive to the uncertainty in the lifetime risk of breast cancer, the growth rate of tumours for ages under 50 and the sensitivity of mammography. However, the highest discounted ICERs found €26000 per YOLS for the 48–74 scenario and €27100 per YOLS for the 46–74 scenario were still slightly above the cost-effectiveness threshold of €20000/YOLS.

Our analysis has clearly demonstrated that regular breast cancer screening with earlier starting ages could be beneficial for women despite the relevant increase in harms. However, recent studies have suggested that the contribution of mass mammography to mortality reduction from breast cancer might be overestimated. A drawback of the early detection of breast cancer is the diagnosis of cancers which would never become clinically detected (overdiagnosis). According to a comprehensive review on European breast cancer screening programmes this overdiagnosis accounts on average for 6.5% of all screen detected breast cancers [1]. A recent analysis estimated 11% overdiagnosed tumours in the Dutch breast cancer screening programme [44]. With the introduction of national breast cancer screening programmes, the rate of detection of large tumours decreased in favour of small tumours. However, these small tumours are more likely to be overdiagnosed than to become large [45]. Overdiagnosis causes patient harm and overtreatment, increases the costs for the healthcare system and decreases the cost-effectiveness of mass breast cancer screening.

In addition, the available adjuvant and targeted therapies have an impact on the mortality reduction from breast cancer. The 25-year follow-up of the Canadian National Breast Screening Study concluded that in the presence of freely available adjuvant therapy for breast cancer, annual mammography in women aged 40–59 years did not exceed mortality reduction achieved by physical examination [46]. The study of Autier et al. found that factors other than screening, amongst which breast cancer management, contributed to the reduction of breast cancer death risks [47]. A widely criticised and disputed study [45], mainly for its methodological considerations [48], concluded that, after the implementation of screening mammography, breast cancer mortality reduction was predominantly attributable to the improved systemic therapies. Modelling studies have also analysed the issue and reported that advances in systemic therapies for breast cancer have decreased the absolute benefit of regular screening but not the relative benefit due to their impact on survival from the disease [49], and estimated the contribution of adjuvant therapies to breast cancer mortality reduction to be ranging from 12% to 20.9%, while the reduction in the mortality rates attributable to screening was predicted to be from 7.5% to 22.7% [50,51], concluding that adjuvant systemic therapy and screening reduced breast cancer mortality in similar amounts [51]. These recent developments suggested that systemic treatments could have synergistic and even competitive effects to regular screening on the mortality reduction from breast cancer. If the effects from systemic therapies are so considerable, then evaluations of lowering the intensity of mass screening by introducing longer screening intervals are warranted. In addition, costs of systemic therapies which increase more rapidly than effects need further consideration.

Current modelling studies were found to carry high risk of bias in their results due to the lack of transparency in the selection of sources for input data and assumptions, and the lack of external validation [52]. As compared to these recently reviewed simulation models [52] the SiMRiSc had the following advantages: external validation, systematically selected and evaluated independent sources for sampling of the input parameters, reporting on both expected benefits and harms of regular breast cancer screening. The systematic selection of input data and the external validation allow to compare and translate the results from our simulation to other Western countries. Another advantage of this analysis is that it included breast density variation as a function of age. Breast density is an important factor influencing negatively the sensitivity of mammography in younger ages [27] and thus the cost-effectiveness of breast cancer screening. A limitation of the model is that DCIS was not included and thus disregarded from the validation and the cost-effectiveness analyses. Inclusion of DCIS, which accounted for nearly 20% of screen-detected tumours in the Dutch population in 2011 [39], could have an impact on the number of screen detected tumours and thus increase YOLS and cost-effectiveness, especially in the era of digital mammography. Another limitation is that the assumed tumour growth model does not account for tumour regression or growth stagnation; however, very slow growing tumours (on the edge of growth stagnation) are allowed in the model. In addition, the breast density parameter used in this model was derived from USA data, but it can be considered a good proxy for estimating breast density. However, as seen from the validation results these limitations did not seem to have large impact on the outcomes of the model. The validation of the SiMRiSc model was limited to the data available from the Dutch screening programme, which included screen detected tumours, tumour

size distribution (of the screen detected tumours), number of interval cancers, number of false positive tests but not the distribution of breast density amongst the screened women nor size of the interval cancers. Breast density is a factor which influences the sensitivity of mammography and tumour size is a predictor of survival and an argument in choosing a specific treatment. Our analysis focused only on quantitative outcomes and qualitative outcomes (such as quality of life) were not evaluated. It is known that regular breast cancer screening can have a negative impact on the quality of life in terms of pain from mammography, anxiety, and distress from false positive results in the short line, however, this has not been shown to affect generic health-related quality of life [53].

In conclusion, given the results from the simulation model, women could benefit from lowering the starting age of screening in terms of prevented cancer deaths due to the early diagnosis and treatment of the disease at reasonable additional costs and relatively low additional risks. Starting regular breast cancer screening earlier is also cost-effective. As the number of additional expected harms is relatively small in both alternative scenarios and the difference in ICERs is not large, introducing two additional screening rounds to the current biennial breast cancer screening in the Netherlands is justifiable from a cost-effectiveness and benefit-harms point of view.

Contributors

Rositsa G Koleva-Kolarova was responsible for formal analysis, validation, investigation, data curation, drafting and editing the manuscript, visualisation and project administration.

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Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for this study.

Ethical approval

This study did not involve human subjects.

Provenance and peer review

This article has undergone peer review.

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