



Original article

Should women with a BRCA1/2 mutation aged 60 and older be offered intensified breast cancer screening? – A cost-effectiveness analysis



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ABSTRACT

Objectives: This study aimed to investigate the cost-effectiveness of intensified breast cancer (BC) screening for women with a BRCA1/2 mutation aged 60–74. Simulated strategies were: (0) annual mammography as reference, (1) alternating annual mammography and MRI for women with dense breasts only; (2) addition of annual MRI for women with dense breasts only; (3) addition of annual MRI for all women.

Materials and methods: A validated micro-simulation model of invasive BC was updated and validated for interval BC rates and tumor size distribution. Incremental cost-effectiveness ratios (ICER) of all three intensified strategies were compared to the next best strategy and stratified for BRCA1 and BRCA2. Discount rates for costs and life years gained (LYG) were 1.5% and 4% for the Dutch situation; 3% and 3% for international comparison. A threshold of €20,000 per LYG was applied.

Results: All intensified strategies showed more detected BCs and LYG, reduced BC deaths, and increased false positives. The Dutch discounted ICER of intensified strategy 1 compared to annual mammography was €38,000 per LYG in BRCA1 mutation carriers and €18,000 per LYG in BRCA2 mutation carriers. Further intensified strategies showed an ICER above the threshold when compared to this strategy. With international discount rate, the ICERs of all intensified strategies were above the threshold.

Conclusion: Of the three alternative strategies, only alternating annual MRI and mammography for BRCA2 mutation carriers and dense breasts aged 60–75 is cost-effective compared to annual mammography. For BRCA1 mutation carriers, none of the alternative strategies is cost-effective compared to the next best strategy.

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1. Introduction

Women with a BRCA1 or BRCA2 mutation are at relatively high risk of developing breast cancer (BC) with a cumulative risk by the age of 70 ranging from 55 to 66% for BRCA1 carriers and 55–64% for BRCA2 carriers [1–3]. In mutation carriers, of all ages, tumors grow faster than those in women from the general population at the same age [4,5]. These women are recommended to have an

intensified screening program, usually with annual MRI and mammography, outside of the general population screening program. However, guidelines for screening BRCA mutation carriers with annual MRI and mammography vary between countries with respect to the age of continued screening using both modalities. Adding MRI to mammography screening is recommended until age 50–60 but in some settings the same approach is recommended for older women or without an upper age limit [6–8].

Intensive screening with MRI in BRCA1 or a BRCA2 mutation carriers aged 60 and above is an on-going and relevant issue for several reasons. The risk of developing BCs in women with a BRCA1/2 mutation continues to increase after the age of 60 [1,2,9]. A substantial proportion of women with a BRCA1/2 mutation remains

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at risk of developing BC from the age of 60 even after risk-reducing strategies [10]. Annual mammography may not be sufficiently accurate for women with a gene mutation aged 50 and older, hence MRI should be considered for screening these women [11]. No guidelines for the upper age limit for screening with MRI could be identified in a recent meta-analysis [11]. In prospective screening trials, *BRCA* mutation carriers above age 60 represented relatively small numbers which makes it difficult to assess the effectiveness of screening in this age-group [11]. In the absence of data from clinical trials, a model study is an alternative and appropriate approach to evaluate the benefits and costs of screening this age-group in the long term and in an economic point of view.

Using a validated breast cancer micro-simulation model, we aimed to investigate the cost-effectiveness of screening strategies that add MRI to mammography in women with a *BRCA1/2* mutation aged 60–74. We estimated the additional benefits, harms, and costs and hence cost-effectiveness of adding MRI to mammography in this older population of *BRCA* mutation carriers.

2. Methods

This study is reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [12]. A validated micro-simulation model [13,14] was applied to simulate asymptomatic women with *BRCA1* or *BRCA2* mutations throughout their life-time. Intensified screening strategies adding from age of 60 onwards MRI were simulated and compared to the next most effective strategy. All strategies were simulated with the same screening regime before age 60. Direct costs were derived from the perspective of the payer including costs of screening for the total simulated population, costs of diagnosis in case of positive test, and costs of treatment and hospital stay. Both Dutch and international discount rates were applied. The Dutch discount rates were 1.5% and 4% for costs and LYG while the international discount rates were 3% and 3% respectively [15].

2.1. Description of the SIMRISC model and its components

Women entered the model at the age of 20 and were followed till the end of their life. Annual screening with MRI was simulated from age 25 along with annual mammography from age 30. Women left the model when they died or developed primary BC. The model only simulated primary invasive cancer (not ductal carcinoma in situ) and did not simulate preventive BC surgery. The input parameters as shown in Table 1 apply to all women of all ages used in the simulation.

Initially women were randomly assigned a breast density with a distribution according to age as given in Table 1 [16–19], with a decreasing breast density over life. For all women it was determined, based on incidence data, whether they would develop BC or not [1,13,20], what the age of clinical BC diagnosis would be, and what the age of death by all causes would be [<http://statline.cbs.nl>]. Women could develop BC or die before the start of screening, or during or after the screening period. Tumor growth was determined based on age [4,21]. The tumor doubling time and tumor size at self-detection [30] were assigned randomly from a log-normal distribution with a mean and standard deviation as shown in Table 1. In this way an age of tumor onset was assigned for every woman who would develop BC during her lifetime. This breast cancer incidence curve is in line with data observed in the literature [1].

Between the age of tumor onset and age at self-detection of the tumor, existing tumors could be screen-detected by mammography or MRI based on the sensitivity of these modalities as derived from a systematic literature search [22–29]. Based on the length of the preclinical phase, the tumor doubling time and time of detection or clinical manifestation, the tumor size at diagnosis was calculated. If a developing BC was not screen-detected, it could become clinically manifest between two screening years, and was considered an interval cancer.

A systematic error of 10% was used for mammography [14],

Table 1
Input parameters.

Parameters	Mean values (standard deviation)				Reference		
Tumor induction model							
Dose [mSv]	3 (1)				(20,30)		
Probability of tumor induction [%]	0.51 (0.14)						
Tumor doubling time (log transformed values of days)					(4,21)		
	<i>BRCA1</i>		<i>BRCA2</i>				
<40 years	3.33 (0.17)		3.80 (0.19)				
40–50 years	4.22 (0.21)		4.69 (0.23)				
>50 years	4.39 (0.22)		5.18 (0.26)				
Cumulative incidence rate	<i>BRCA1</i>		<i>BRCA2</i>		(1)		
Life time risk [%]	55 (2.8)		64 (3.8)				
Mean age [years]	43.2 (0.37)		47.9 (0.47)				
s [years]	10.7 (0.53)		10.9 (0.55)				
Self-detection diameter (cm)	3.0 (0.01)				(30)		
Distribution of breast densities	Age/BI-RADS density score	1	2	3	4	(16–19)	
	<40 years [%]	4.4	30.2	48.2	17.2		
	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 of mammography [%]	87 (5.9)		84 (6.8)		73 (9.1)	65 (15.5)	(22–27)
Specificity of mammography [%]	96.5 (0.23)				(28)		
Sensitivity of MRI [%]	95 (5.9)				(29)		
Specificity of MRI [%]	90 (0.21)						
Systematic error of mammography (%)	10				Expert opinion		
Cost in euro (Year 2017)							
Mammography (hospital)	68				(35)		
MRI	168						
Biopsy*	176				(36)		
Treatment and hospitalization by tumor size [€]	<=2 cm	2–5 cm	>5 cm		(37)		
	6367	7050	7616				

which accounted for tumors which could not be detected by mammography due to their characteristics (lobular carcinomas, and location near the thorax wall). The probability of false positive findings was determined by the modality's specificity [28,29]. The model simulated mammography screening first and only when no BC was detected, MRI was performed subsequently. The probability of BC survival was dependent on tumor size based on the work of Michaelson et al. [31].

2.2. Screening strategies

We simulated the reference strategy of annual MRI age 25–60 and subsequent annual mammography age 30–74 as the Dutch guideline (<https://www.oncoline.nl/>), and three intensified screening strategies for women with a *BRCA1/2* mutation age 60 onwards (Supplementary Table 1). Strategy 1 consisted of annual mammography for women with non-dense breasts and alternating annual MRI and mammography for women with dense breasts only; strategy 2 consisted of annual mammography and annual MRI for women with dense breasts only; and strategy 3 consisted of annual mammography plus MRI for all women.

2.3. Expected benefits and harms of intensified screening

For each *BRCA* status, 100,000 women were simulated 10 times and means and standard deviation (SD) were estimated. The benefits of intensified screening with MRI were calculated as a relative change in comparison with the next best strategy in terms of effectiveness: number of detected BCs, number of interval BCs, number of small tumors (<10 mm), and number of deaths due to BCs. The harms of intensified screening were the relative difference with respect to the reference values in number of false-positive (FP) tests, and number of screens.

2.4. Cost effectiveness analysis

Direct costs of screening, diagnosis and treatment of BCs were considered (Table 1). All analyses were performed in Euro (€) at the 2017 price-level (<http://statline.cbs.nl>). The discounted incremental cost-effectiveness ratio (ICER) representing the additional cost for one life-year gained (LYG), was estimated as compared to the next most effective strategy. If the incremental cost per LYG was ≤ €20,000 the screening strategy was considered cost-effective [19].

2.5. External validation of the model

The model was previously validated for BC screening of women with a *BRCA1/2* mutation and women from the general population [13,14]. Because some of the parameters (risk of developing BC, tumor growth and sensitivity/specificity of MRI) were updated, we performed another external validation on two independent databases regarding the number of interval cancers and the tumor size distribution. The first database included women with a *BRCA1/2* mutation that underwent biennial and annual mammography from age 60 to 81 [10] and the second database included women with a *BRCA1/2* mutation that underwent annual MRI plus mammography from age 25 to 80 [11]. Only BCs in subsequent screening rounds and that were larger than 5 mm were considered.

2.6. Sensitivity analyses

A univariate sensitivity analysis was performed using as minimum and maximum values the lower and upper limit of the 95% confidence intervals for selected input parameters. The impact of the parameters' uncertainty on the ICERs was plotted in Tornado

graphs.

3. Results

3.1. Validation of the model

Considering women who underwent annual mammography plus MRI from age 60 onwards, the model showed a tumor size distribution close to the observed data (Fig. 1a). The proportion of interval cancers estimated by the model was slightly higher than that observed for women with *BRCA1* mutations and comparable for women with a *BRCA2* mutation (Fig. 1a). Regarding women who underwent biennial or annual mammography from age 60, the model showed a comparable proportion of interval cancers, whereas a higher proportion of small size tumors was estimated (Fig. 1b and c).

3.2. Benefits and harms of applying intensified strategies

All three intensified strategies showed an increase in the number of screen-detected BCs and the number of small tumors, while the number of interval cancers and BC deaths both in *BRCA1* and *BRCA2* mutation carriers decreased. The changes in the number of screen-detected BCs, small tumors and BC deaths were similar for women with a *BRCA1* and women with a *BRCA2* mutation. For interval cancers, intensified screening in women with a *BRCA2* mutation yielded a larger change compared to that in women with a *BRCA1* mutation. For both women with a *BRCA1* or *BRCA2* mutation, intensified strategies increased the number of false-positives and the number of MRI screens (Table 2).

3.3. Incremental cost effectiveness ratio

For women with a *BRCA1* mutation, the more intensive the screening, the higher the ICER: all ICERs were above the threshold of €20,000 per LYG whether applying Dutch or international discount rates (Table 2).

For women with a *BRCA2* mutation intensified strategy 1 had an ICER of €18,500 per LYG when Dutch discounting was applied. All other intensified strategies had ICERs above the threshold of €20,000 per LYG compared to the next most effective strategy. When applying international discount rates, the ICER of all intensified strategies remained above €20,000 per LYG (Table 2).

3.4. Sensitivity analysis

The ICERs of all intensified strategies were most sensitive to the uncertainty in self-detection size, tumor doubling time age >50 and cumulative life-time risk (Supplementary Figure 1, Supplementary Figure 2). The uncertainty in sensitivity/specificity of MRI, specificity of mammography, and sensitivity of mammography in BI-RADS1, 2 and 4 only had a minor impact on ICERs.

4. Discussion

We report the results of a cost-effectiveness study comparing intensive screening strategies screening in older *BRCA1/2* mutation carriers. Using a micro-simulation model, validated in terms of interval cancers and tumor size distribution in this work, we estimated that intensified breast cancer screening after age 60 in women with *BRCA1/2* mutations increased the number of screen-detected BCs, the number of small tumors, and the number of life-years gained, and decreased the number of BC deaths. However, these gains were at a trade-off of increased financial costs and substantially more false-positives and MRI screens. Compared to

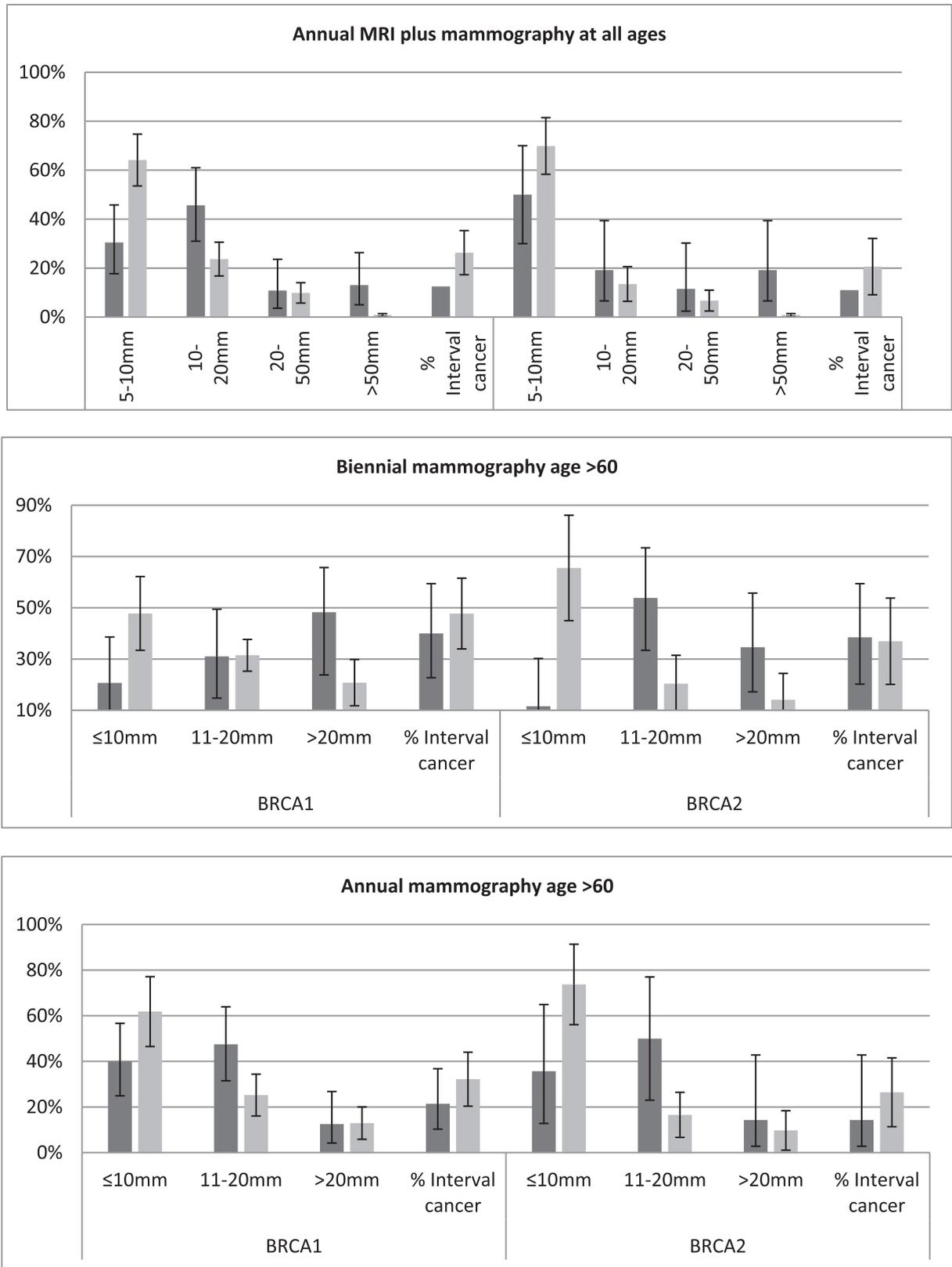


Fig. 1. Comparison of the proportion of interval cancers and the tumor size distribution between the model (light grey) and independent data (dark grey) for *BRCA1* (left) and *BRCA2* (right).

screening women with a *BRCA1* mutation, intensified screening in *BRCA2* mutation carriers over age 60 yielded more LYG and had less costs. Compared to annual mammography, using a threshold of

€20,000 per LYG and Dutch discount rates, intensified strategy 1 was cost effective in *BRCA2* women but not in *BRCA1* women. Intensified strategy 2 and 3 were not cost-effective for either group

Table 2
Effectiveness and cost-effectiveness of intensified strategies as compared to the next best strategy per 100,000 women.

	BRCA1			BRCA2		
	Strategy 1 vs reference	Strategy 2 vs 1	Strategy 3 vs 2	Strategy 1 vs reference	Strategy 2 vs 1	Strategy 3 vs 2
Relative change in Screen detected BC	5% (83)	5% (82)	14% (252)	5% (188)	2% (73)	10% (428)
Interval BCs	–12% (82)	–13% (80)	–47% (247)	–21% (175)	–10% (64)	–68% (396)
Small tumors detected during screening	4% (52)	6% (80)	14% (198)	5% (185)	4% (156)	11% (500)
BC deaths	–5% (18)	–9% (18)	–23% (56)	–6% (35)	–9% (56)	–23% (56)
Number of mammograms	–15% (74,169)	17% (74,081)	0% (134)	–15% (59,257)	17% (58,664)	0% (893)
Number of MRI examinations	NA (74,130)	114% (84,176)	214% (338,798)	NA (58,910)	112% (66,054)	214% (267,317)
Number of false positives	21% (4814)	40% (10,989)	88% (33,944)	21% (3783)	40% (8638)	88% (26,737)
LYG (undiscounted)	218	229	748	388	209	905
Additional cost x €1000 (undiscounted)	8226	21,515	64,108	6524	16,594	49,448
ICER x €1000 (undiscounted)	37.7	94	85.7	16.8	79.5	54.6
LYG (discounted 1.5%)	169	175	568	290	156	673
Additional cost x €1000 (discounted 4%)	6428	16,495	49,095	5206	13,134	39,141
ICER x €1000 (discounted 1.5–4%)	38	94	86.4	18	84.4	58.2
LYG (discounted 3%)	132	136	438	219	118	508
Additional cost x €1000 (discounted 3%)	6816	17,466	51,989	5490	13,871	41,343
ICER x €1000 (discounted 3–3%)	51.6	128.3	118.6	25.1	117.8	81.4

NA: not applicable; In brackets: absolute difference.

Reference strategy: annual mammography alone; Strategy 1: alternating annual mammography and MRI for women with dense breasts only; Strategy 2: addition of annual MRI for women with dense breasts only; Strategy 3: addition of annual MRI for all women.

of *BRCA1/2* women.

Breast cancer screening in women with a *BRCA1/2* mutation has been implemented in several countries. The age at which MRI screening is recommended to end differs across guidelines, usually within the age range of 50–60 [6–8] with the argument that mammography sensitivity improves with age and MRI is relatively more expensive. In contrast, prospective studies investigating the effectiveness of screening with annual MRI as an adjunct to mammography support screening with annual MRI both in women younger and older than 50, from the perspective of enhanced cancer detection [11]. In general, screening women with a *BRCA1/2* mutation with annual MRI plus mammography compared to annual mammography alone is considered to be cost-effectiveness [32–34]. However, studies have focused on screening of women below the age of 60 or throughout the whole screening period, and there is no comparative data for women older than 60 [32–34]. Our study addresses this evidence gap by specifically comparing different screening strategies in women with a *BRCA1/2* mutation aged 60–74 year in the Dutch context and considered breast density as a determinant for different screening modalities.

The results of our simulation showed that screening women with a *BRCA2* mutation age 60–74 was more beneficial and less costly than screening the same-age women with a *BRCA1* mutation. This can be explained by the input parameters including relatively higher cumulative life-time risk, older age of onset and slower tumor growth rate in *BRCA2* women. Since women with a *BRCA2* mutation tend to develop BC at an older age and are at higher risk compared to women with a *BRCA1* mutation, more women with a *BRCA2* mutation remain at risk when they enter screening at age 60, thus more cancers were screen-detected in this group. Due to the slower growth rate, *BRCA2*-associated BCs are more likely to be detected by screening and there were fewer interval cancers, the treatment cost was therefore also lower. More detected cancer and less interval cancers as well in proportion as in absolute number lead to higher LYG in women with a *BRCA2* mutation. This emphasizes the need for different screening strategies based on *BRCA* mutation type.

Although the SIMRISC model has been applied in previous works and is well validated [13,14], updated values for some of the input parameter (life-time risk, tumor doubling time and accuracy of MRI) were applied. Firstly, the life-time risk to develop BCs in women with a *BRCA1/2* mutation was updated [1]. The life-time risk

we applied is lower than estimates from a recent prospective cohort [3]. The main explanation for this higher estimate is the case selection in the prospective study, as in this study only incidence cases were included [3]. As these proven carriers are usually from a family with higher risk and have more follow-up than unaffected relatives, which is probably associated with higher risk estimates, we stick to estimates based on a Kaplan Meier method including index cases and proportion of untested first degree relatives which was shown to be the most consistent method for carriers counseled in the clinic [1]. In addition, sensitivity analysis showed that the uncertainty in life-time risk did not have a large impact on ICERs. Secondly, the tumor doubling time used in our model was based on a relatively small number of tumors in mostly *BRCA1* carriers together with results from a simulation study [4,21]. There is little data on the tumor doubling time of *BRCA1/2* associated BCs. Although sensitivity analysis showed that the model is sensitive to the uncertainty in the tumor doubling time, all ICERs remained not cost-effective and well above the threshold of €20,000. Further, the accuracy data of MRI was obtained from literature which may underestimate the accuracy of MRI in current practice. However, the uncertainty in MRI sensitivity or specificity did not significantly alter estimated ICERs (Supplementary Figure 1 and Supplementary Figure 2).

This study has some limitations. Firstly, we modeled invasive BCs and not ductal carcinoma in-situ (DCIS), which may have underestimated the benefits of screening. DCIS accounts for about 20% of the BCs diagnosed in *BRCA1/2* carriers [35]. However, because knowledge about the progression of DCIS to invasive is not conclusive, we only modeled growth of invasive cancers. Secondly, the sensitivity of mammography was determined by the woman's breast density, and not as a function of tumor size. Thus, the chance of detecting a small or large size tumor was equal given a certain breast density, which might possibly overestimate the benefits of screening, although validation of the model was reasonably good. Thirdly, although we incorporated radiation induction risk in the model, the lag-time (time interval between exposure and the development of BC) was not specifically modeled. When applying lag-time, induced tumors will develop at older age (15–20 years after exposure), which will increase the ICER. This effect will be small and does not change the outcomes of our study since the impact of tumor induction on the ICER was only minor according to the sensitivity analysis. Finally, we evaluated intensified screening

in women age 60–74 but modeled the same screening program during age 25–60 years for both *BRCA1* and *BRCA2* mutation carriers. If different screening strategies were applied by *BRCA* status during age 25–60, the population entering screening after age 60 will be different for each *BRCA* status. However, for each *BRCA* status, the population entering intensified screening will be the same for all the intensified strategies. The model results are not expected to be altered since we only consider differences from age 60 onwards.

Using this validated model, alternating MRI and mammography annually for women with a *BRCA2* mutation and dense breasts age 60–75 was cost-effective compared to annual mammography but it was not cost-effective for women with a *BRCA1* mutation. Adding MRI to annual mammography in women with *BRCA1/2* mutations, whether restricted to women with dense breasts or for all women, was not cost-effective. Screening guidelines should consider different recommendations for older women with *BRCA1* and *BRCA2* mutations. Our study indicates that women with a *BRCA2* mutation age 60–74 should be offered annual mammography if they have non-dense breasts, and alternating MRI and mammography annually if they have dense breasts. Women with a *BRCA1* mutation aged 60–74 should continue to be screened with annual mammography.

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Conflicts of interest

The authors declare no potential conflict of interest.

Ethical approval

Ethical approval is not needed for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2019.03.004>.

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