





# Cost-Effectiveness of Magnetic Resonance Imaging Screening for Women With Extremely Dense Breast Tissue

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## Abstract

**Background:** Extremely dense breast tissue is associated with increased breast cancer risk and limited sensitivity of mammography. The DENSE trial showed that additional magnetic resonance imaging (MRI) screening in women with extremely dense breasts resulted in a substantial reduction in interval cancers. The cost-effectiveness of MRI screening for these women is unknown. **Methods:** We used the MISCAN-breast microsimulation model to simulate several screening protocols containing mammography and/or MRI to estimate long-term effects and costs. The model was calibrated using results of the DENSE trial and adjusted to incorporate decreases in breast density with increasing age. Screening strategies varied in the number of MRIs and mammograms offered to women ages 50-75 years. Outcomes were numbers of breast cancers, life-years, quality-adjusted life-years (QALYs), breast cancer deaths, and overdiagnosis. Incremental cost-effectiveness ratios (ICERs) were calculated (3% discounting), with a willingness-to-pay threshold of €22 000. **Results:** Calibration resulted in a conservative fit of the model regarding MRI detection. Both strategies of the DENSE trial were dominated (biennial mammography; biennial mammography plus MRI). MRI alone every 4 years was cost-effective with €15 620 per QALY. Screening every 3 years with MRI alone resulted in an incremental cost-effectiveness ratio of €37 181 per QALY. All strategies with mammography and/or a 2-year interval were dominated because other strategies resulted in more additional QALYs per additional euro. Alternating mammography and MRI every 2 years was close to the efficiency frontier. **Conclusions:** MRI screening is cost-effective for women with extremely dense breasts, when applied at a 4-year interval. For a willingness to pay more than €22 000 per QALY gained, MRI at a 3-year interval is cost-effective as well.

Approximately 8% of Dutch women aged 50-74 years have extremely dense breast tissue (1). Women with extremely dense breast tissue have approximately a twofold higher risk of developing breast cancer than the average screening population (2). At the same time, dense breast tissue limits the sensitivity of mammography, resulting in high numbers of interval cancers (3,4). In contrast to mammography, the effect of breast density on the sensitivity of magnetic resonance imaging (MRI) is limited (5). However, in most Western countries, women with

average breast cancer risk, including women with dense breast tissue, are currently screened with mammography only.

Recently, the multicenter randomized Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial showed that additional MRI screening for women with extremely dense breast tissue resulted in statistically significantly fewer interval cancers (a difference of 2.5 per 1000 screenings; 95% confidence interval = 1.0 to 3.7;  $P < .001$ ) (6). Furthermore, screen-detected tumors were on average smaller among MRI participants than

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those among women receiving mammography alone. However, MRI screening also resulted in more false-positive results (6), which will lead to additional costs.

Several modeling studies have shown that MRI screening can be cost-effective among high-risk women, especially women with a BRCA1 mutation (7-10). It is unknown whether MRI can be cost-effective for women with extremely dense breasts who are currently screened within the Dutch national mammography screening program. As MRI screening is more expensive than mammography, which can lead to an increase in health-care spending, a cost-effectiveness analysis is needed to evaluate whether the additional effects are worth the money.

In this study, we estimate the cost-effectiveness of MRI screening compared with mammography in women with extremely dense breast tissue by using the results of the DENSE trial and microsimulation modeling. We quantify the effects and costs of several different screening scenarios by varying the screening interval between MRIs and mammograms offered for women aged 50-75 years.

## Methods

### DENSE Trial

The DENSE trial is embedded within the Dutch biennial mammography screening program, for women aged 50-75 years. Women with extremely dense breasts (Volpara density grade 4) and a negative (normal) mammography result (Breast Imaging-Reporting and Data System [BI-RADS] category 1 or 2) were randomly assigned to 2 groups: the MRI invitation group ( $n = 8061$ ) and the control group ( $n = 32\,312$ ) (6). Women assigned to the MRI invitation group were offered additional MRI screening (women who accepted this offer are referred to as the MRI participants;  $n = 4783$ ) (6). Women in the control group did not receive additional screening. Breast density was measured using Volpara imaging software. Volpara density grades (VDG 1 to 4) correspond to the categories of the fourth BI-RADS edition (11). All MRI examinations were performed on 3.0 Tesla MRI systems, and the macrocyclic gadolinium-based contrast agent gadobutrol (Gadovist, Bayer AG, Leverkusen, Germany) was used in all examinations. More details of the DENSE trial have been described previously (6,12). The study has been approved by the Dutch Minister of Health.

### MISCAN Model

To extrapolate the findings of the DENSE trial, we used an updated version of the Microsimulation Screening Analysis (MISCAN) model by Sankatsing et al. (13). The MISCAN model simulates individual life histories from birth to death and the natural history of breast cancer. A subset of women have an onset of breast cancer; the probability of onset increases with age. At each breast cancer stage (ductal carcinoma in situ [DCIS], T1A, T1B, T1C, T2+) (14), the tumor can be preclinical in which it may grow to the subsequent stage or become clinically diagnosed or screen detected. The model structure has been published previously (13).

The MISCAN model was used to model women with extremely dense breast tissue. Incidence, dwelling times (the time between transitions from one stage to the next) and stage-specific sensitivities of MRI and mammography were estimated by calibration. Model predictions were calibrated to the numbers of screen-detected cancers during the first (prevalent)

and second (incident) round and interval cancers during the first round as observed during the DENSE trial among the MRI participants and the control group (further specified in the [Supplementary Methods](#), available online) (6). We aimed to model the predictions with 95% Poisson confidence intervals of the observed numbers.

After calibration, the model was adjusted to incorporate decreases in breast density over time. Based on Dutch data (15), 21.9% of the women with VDG4 at the age of 50 years was modeled to remain at that level. For 78.1% of the women, a decline in breast density was modeled, at the age of 55 and/or 65 years (Table 1). Decreasing breast density over time was assumed to be associated with increasing sensitivity of mammography, decreasing breast cancer incidence, and decreasing numbers of false-positive mammography results (Table 1) (1,16). All other parameters were assumed to be equal across density categories.

Probabilities of additional investigations and false-positive results in the MRI participants were obtained from the DENSE trial (Supplementary Tables 1 and 2, available online). These probabilities were not measured in the control arm. The probability of a false-positive mammogram in extremely dense breasts was based on Wanders et al. (1). Based on published data (17-19) and expert opinion and according to Dutch practice, we assumed that all women with a positive mammogram would be referred to a hospital to undergo tomosynthesis and 88% to undergo an ultrasound, 38% an ultrasound-guided biopsy, and 8% a stereotactic biopsy (for estimations, see [Supplementary Table 3](#), available online).

In the DENSE trial, 22% of the MRI participants with a positive MRI underwent an ultrasound of the axilla. Imaging the axilla is not part of the screening work-up but is performed for efficiency reasons in women receiving a biopsy: if the biopsy is positive, the woman does not have to be recalled for a staging ultrasound of the axilla. We applied an equal probability after a positive mammogram. Based on Dutch guidelines, we assumed all women to undergo a positron emission tomography-computer tomography after a T2+N+ diagnosis (20). Furthermore, we modeled 26%, 27%, and 38% of women with a DCIS, T1A-T1C, and T2+ diagnosis, respectively, to undergo a pre-operative MRI (21,22).

### Costs

We applied a health-care perspective and only considered direct medical costs and costs related to other causes of death. Most unit prices were derived from a previous cost-effectiveness study (10). The price of tomosynthesis was assumed to be equal to mammography within a hospital setting. Unit prices are shown in [Supplementary Table 4](#) (available online). A telephone consult with the general practitioner was modeled after a positive screening result, which reflects current practice in the Netherlands.

Mean treatment costs were calculated using previously published prices (10) and the quantity of each treatment type per T stage in 2011 (Supplementary Table 5, available online). These data were obtained from the Netherlands Comprehensive Cancer Registration. Subsequently, mean treatment costs were multiplied by the modeled numbers of tumors by T stage (Supplementary Table 6, available online). Costs in the last year of life were derived from Polder et al. (23) and converted to the price level of 2018.

### Utilities

Utility values (quality of life) were obtained from the literature (Supplementary Table 7, available online). A disutilities of 10%

Table 1. Adjustments to the Microsimulation Screening Analysis model to simulate decreases in breast density<sup>a</sup>

% of women with VDG4 at age 50 y	VDG density according to age			Factor difference of the sensitivity of mammography (1)			Factor difference of the onset of breast cancer (16)			Factor difference of the probability of a false-positive mammogram (1)		
	50-54 y	55-64 y	≥65 y	50-54 y	55-64 y	≥65 y	50-54 y	55-64 y	≥65 y	50-54 y	55-64 y	≥65 y
	21.9	4	4	4	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
18.8	4	4	3	Referent	Referent	1.14	Referent	Referent	Referent	Referent	Referent	Referent
40.8	4	3	3	Referent	1.14	1.14	Referent	Referent	Referent	Referent	Referent	Referent
18.4	4	3	2	Referent	1.14	1.27	Referent	Referent	Referent	Referent	Referent	Referent

<sup>a</sup>Reference values were calibrated. VDG = Volpara density grade.

was applied for DCIS and localized breast cancer, and a disutility of 25% was for regional breast cancer (24), with durations of 5 years. A disutility of 50% was applied for metastasized breast cancer until death (24). We applied a disutility associated with screening participation of 0.006 for 1 week and a disutility associated with a positive screen of 0.105 for 5 weeks (25).

### Screening Strategies

Several screening strategies were simulated with varying intervals (see [Supplementary Figure 1](#), available online). The MRI participants and control group of the DENSE trial correspond with 2Mx\_2MRI (mammography plus MRI at a 2-year interval) and 2Mx (mammography at a 2-year interval), respectively.

Each modeled strategy started with mammography at age 50 years, because women always undergo mammography as their first screening (as density is unknown). In case of a decrease in breast density from category 4 to 3, women switched to mammography at a 2-year interval. This switch was assumed to take place after the first screening following the modeled breast density drop. We assumed that breast density can be measured with mammography and MRI. In the screening strategies containing mammography and MRI together in 1 screening round, we assumed women would undergo the mammogram first and the MRI 1 month later, which allows for a cancellation of the MRI when a drop in breast density was shown on the mammogram. A screening attendance rate of 100% was modeled.

### Analyses

A cohort of 10 million Dutch women, born in 1965, was simulated from age 25 years until death. Outcomes were the number of screening mammograms, screening MRIs, screen-detected cancers, interval cancers, life-years, quality-adjusted life-years (QALYs), deaths from breast cancer, and deaths from other causes. Overdiagnosis was defined as detected cancers that would not have been diagnosed in a woman's lifetime in a situation without screening. Strategies were ranked by total costs. A strategy with fewer QALYs than the previous strategy in the ranking was considered "strongly dominated." The incremental cost-effectiveness ratio (ICER) of a strategy in comparison with the previous strategy was calculated by dividing incremental costs by incremental life-years and incremental QALYs. A strategy with a higher ICER than the next strategy was considered "weakly dominated." All results were scaled to 1000 women. Both costs and effects were discounted at 3%. A willingness-to-pay threshold of €22 000 (£20 000) was applied, based on the lower bound of the The National Institute for Health and Care Excellence (NICE) threshold range (26).

One-way sensitivity analyses were performed by varying utility values  $\pm 10\%$ , probabilities of diagnostic procedures after a positive mammogram  $\pm 25\%$ , and the price and false-positive rate of MRI  $\pm 25\%$ . Furthermore, we adjusted the price of tomosynthesis by increasing the price with 25% (or one could say 125%) because tomosynthesis may be more expensive. Because axillary ultrasound is relatively often performed in the Netherlands, we performed a sensitivity analysis in which this was only performed after a proven malignancy. We applied these adjustments separately to all strategies to analyze the effect on the ICERs.

Three scenario analyses were performed to quantify methodological uncertainty. First, we applied a discount rate of 4.0% for costs and 1.5% for effects, based on Dutch guidelines (27).

Second, we assumed breast cancer incidence would not decrease with decreasing breast density (28). Third, we applied different utility values (see [Supplementary Table 8](#), available online).

## Results

### Calibration Results

[Supplementary Figures 2-7](#) (available online) show the numbers observed and simulated screen-detected and interval cancers by T stage. Most of the simulated numbers fell within the 95% confidence intervals of the observed numbers. Overall, the simulated tumor size in the model was slightly larger than observed. The number of screen-detected T2+ tumors in the MRI group was overestimated, as well as the number of interval T2+ tumors in the control group. The number of interval T1C tumors in the control group was underestimated.

### Outcomes of Different Screening Strategies

Discounted and undiscounted results are shown in [Table 2](#), in order of lowest to highest total costs. Biennial mammography alone resulted in 69 screen-detected breast cancers and 43 breast cancer deaths per 1000 women. Adding MRI every other screening round (2Mx\_4MRI) resulted in 24 additional screen-detected cancers and 7 fewer breast cancer deaths. The addition of MRI every screening round (2Mx\_2MRI) resulted in another 4 additional screen-detected cancers and 1 fewer breast cancer deaths. Leaving out mammography, MRI alone every 2 years yielded 100 screen-detected cancers and 97 screen-detected cancers when offered every 3 years. Numbers of overdiagnosis were similar across all strategies containing MRI: equaling 20-21 cases, compared with 17 with biennial mammography. When moving from the strategy consisting of alternating mammography and MRI at a 2-year interval (2Mx/MRI) to a more expensive strategy, no additional breast cancer deaths were averted.

Screening every 2 years with mammography alone (2Mx) resulted in the lowest total costs and the lowest number of QALYs compared with all other screening strategies ([Figure 1](#)). Additional MRI every 2 years (2Mx\_2MRI) resulted in the highest costs but not the highest number of QALYs and was therefore strongly dominated. Most strategies containing mammography were dominated, because of the limited sensitivity of mammography compared with MRI. However, alternating mammography and MRI every 2 years was close to the efficiency frontier. Screening with MRI alone was efficient with various intervals. Lengthening the intervals resulted in lower total costs and only a few cancers not being screen-detected. When applying the NICE threshold, quadrennial MRI (4MRI) had the highest acceptable ICER with €15 620 per QALY. Screening every 3 years with MRI alone resulted in an ICER of €37 181 per QALY.

### Sensitivity and Scenario Analyses

In all one-way sensitivity analyses, MRI screening every 4 years remained cost-effective with the highest acceptable ICER ([Table 3](#)). The ICERs were most sensitive to the unit price of MRI.

When applying discount rates of 1.5% for effects and 4.0% for costs, the ICERs became lower ([Table 3](#)). The strategy consisting of quadrennial MRI screening remained the highest acceptable ICER of €9836 per QALY gained.

[Supplementary Table 9](#) (available online) shows the results when the breast cancer incidence was assumed not to decrease with decreasing breast density. Overall, more cancers were detected among all strategies, but the ICERs were fairly similar as those presented in [Table 2](#). When applying a different set of utility values, the ICERs remained similar as well ([Table 3](#)).

## Discussion

The aim of this study was to evaluate the cost-effectiveness of several screening strategies containing (additional) MRI screening for women with extremely dense breast tissue. We found that using screening with MRI alone every 4 years resulted in the highest acceptable ICER when applying the NICE threshold. When applying a higher threshold, MRI at an interval of 2 or 3 years can be considered cost-effective as well. Strategies containing mammography were dominated because of more clinically diagnosed cancers, resulting in more breast cancer deaths and less QALYs, compared with strategies with MRI.

To our knowledge, this is the first study evaluating the cost-effectiveness of MRI screening for women with extremely dense breasts. One previous study evaluated costs and QALYs associated with MRI, but there was no comparison strategy, and they used a relatively short time horizon (29). In prior cost-effectiveness studies, either the target groups were high-risk women (7-10) or the cost-effectiveness of screening modalities other than MRI were evaluated (30,31). Shortening the screening interval of mammography from 2 years to 1 year was shown not to be cost-effective for women with dense breasts (30). Additional ultrasonography after a negative mammogram was also not cost-effective because of relatively small benefits and high costs (31). A study by Lee et al. (32) concluded that a combination of tomosynthesis and mammography is likely to be cost-effective for this group of women, with an ICER of \$54 000 (€45 830) per QALY gained.

An important strength of this study is the use of data of incident and prevalent screening rounds of a large, randomized, controlled trial. In addition, we used a well-established microsimulation model to extrapolate the findings of this trial. By calibration, dwell times and sensitivities of mammography and MRI were estimated, which allowed us to model several screening strategies, expanding the DENSE trial. An important limitation is that most of our MRI detection estimates were higher than the observed numbers. However, most numbers were within the confidence limits of the observed data. This was not the case for T2+ and T1C tumors. We overestimated the number of screen-detected T1C tumors and underestimated the number of screen-detected T2+ tumors by mammography in the control arm. Also, we overestimated the number of MRI-detected T2+ tumors, although the number of estimated T2+ interval tumors was within the confidence limits. Overall, we expect this to result in conservative model predictions for the effects of MRI screening, mainly because of the overestimated number of screen-detected T2+ tumors by MRI, because T2+ tumors are associated with a relatively poor survival. The fact that numbers of interval cancers during the second round were unknown is also a limitation. By varying dwelling times and sensitivities of mammography and MRI, we performed several calibrations of which the fit closest to the target outcomes was used in our analyses. Another limitation may be that we assumed that pre-operative MRIs were performed in 26%-38% of the detected tumors (21,22), independent of the detection mode. However, in reality, when a tumor is detected by MRI, a pre-

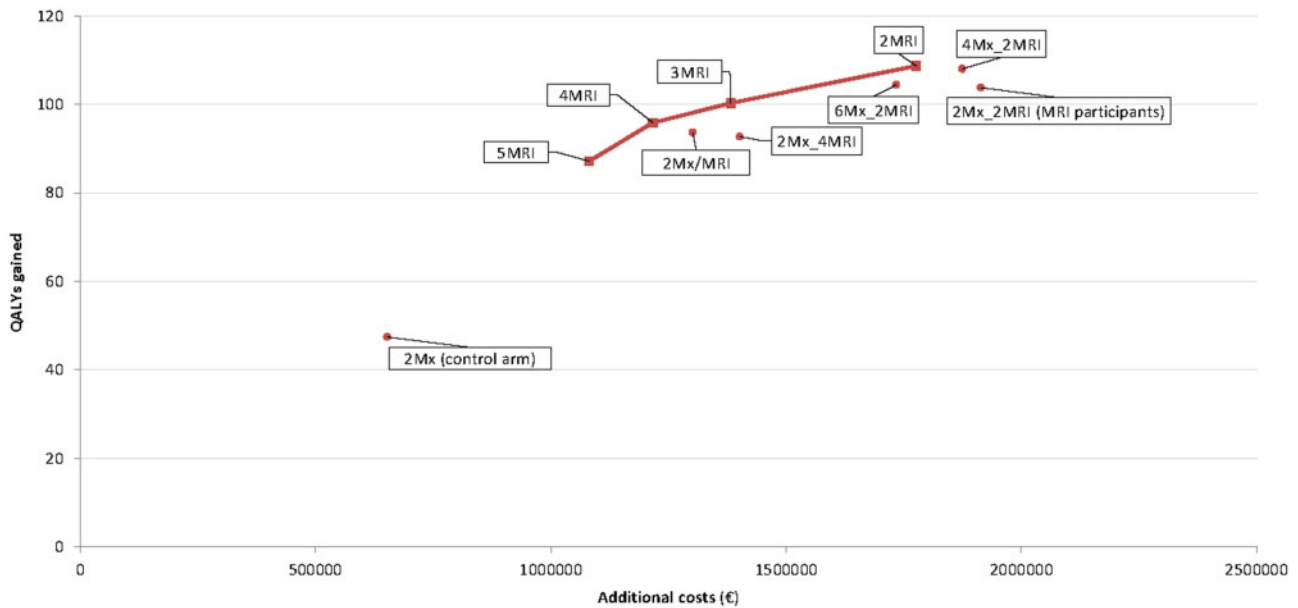
Table 2. Results of all screening strategies, per 1000 women from age 25 years until death

Results <sup>a</sup>	No screening	2Mx	5MRI	4MRI	2Mx/MRI	3MRI	2Mx_4MRI	6Mx_2MRI	2MRI	4Mx_2MRI	2Mx_2MRI
<b>Undiscounted results</b>											
All tumors	152	169	173	173	173	173	172	173	173	173	173
Screen-detected tumors	—	69	94	96	94	97	93	98	100	99	97
Overdiagnosis <sup>b</sup>	—	17	21	21	21	21	20	21	21	21	21
Breast cancer deaths	54	43	37	35	36	35	36	34	34	34	35
False-positives	—	141	203	217	245	239	270	288	283	308	330
No. of mammograms	—	11 114	6483	5328	8735	6006	11 024	7446	5865	8137	11 006
No. of MRIs	—	—	2891	3779	3242	4324	3079	5542	6088	5926	5383
Screening, €	—	768 004	1 234 301	1 395 979	1 485 393	1 591 067	1 599 214	2 022 061	2 061 187	2 174 171	2 224 690
Diagnostics, €	207 544	222 857	238 966	244 556	260 337	256 639	273 806	284 184	280 881	294 094	298 100
Treatment, €	1 230 641	1 338 814	1 374 366	1 366 305	1 362 604	1 362 531	1 360 721	1 355 903	1 355 403	1 354 624	1 354 264
Breast cancer death, €	1 512 425	1 209 474	1 030 535	994 921	1 009 505	982 002	1 014 825	966 768	949 821	952 233	969 311
Death other causes, €	20 281 602	20 512 479	20 648 984	20 676 144	20 665 053	20 685 991	20 660 998	20 697 618	20 710 555	20 708 688	20 695 666
<b>Discounted results<sup>c</sup></b>											
Total costs, €	10 029 132	10 681 842	11 110 699	11 246 367	11 330 895	11 411 722	11 431 163	11 763 234	11 805 633	11 903 811	11 943 649
Life-years	57 816	57 870	57 913	57 921	57 919	57 926	57 918	57 929	57 933	57 933	57 929
QALYs	49 473	49 520	49 560	49 569	49 566	49 573	49 565	49 577	49 581	49 581	49 576
ICER, €/QALY	NA	Weakly dominated	12 410	15 620	Strongly dominated	37 181	Strongly dominated	Weakly dominated	46 971	Strongly dominated	Strongly dominated

<sup>a</sup>Note that some differences in outcomes between strategies do not seem logical, but these are caused by mammography showing a possible drop in breast density: in strategies containing mammography and magnetic resonance imaging (MRI) in 1 screening round, a decrease in density was detected by mammography, resulting in dropping the subsequent MRI in that same screening round. In strategies not containing mammography, a drop in density was observed on the MRI. Therefore, in strategy 2MRI, more MRIs were performed compared with 2Mx\_2MRI. 2MRI = MRI every 2 years; 2Mx\_2MRI = MRI every 2 years; 2Mx = mammography every 2 years; 2Mx\_2MRI = MRI and mammography every 2 years; 2Mx\_4MRI = mammography every 2 years and MRI every 4 years; 3MRI = MRI every 3 years; 4MRI = MRI every 4 years; 5MRI = MRI every 5 years; 2Mx/MRI = screening every 2 years with alternating mammography and MRI; 4Mx\_2MRI = mammography every 4 years and MRI every 2 years; 6Mx\_2MRI = mammography every 6 years and MRI every 2 years. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years.

<sup>b</sup>Because of rounding, the numbers of overdiagnosis may not be precisely the difference in the numbers of tumors with and without screening as shown in this table.

<sup>c</sup>Discounted by 3%.



**Figure 1.** Efficiency frontier (3% discounting). 2MRI = MRI every 2 years; 3MRI = MRI every 3 years; 4MRI = MRI every 4 years; 5MRI = MRI every 5 years; 2Mx = mammography every 2 years; 2Mx/MRI = screening every 2 years with alternating mammography and MRI; 2Mx\_2MRI = MRI and mammography every 2 years; 2Mx\_4MRI = mammography every 2 years and MRI every 4 years; 4Mx\_2MRI = mammography every 4 years and MRI every 2 years; 6Mx\_2MRI = mammography every 6 years and MRI every 2 years. MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

**Table 3.** Results of the 1-way sensitivity analyses and scenario analyses

Input parameter	Value in sensitivity analysis	Strategy with the highest acceptable ICER	ICER, €/QALY
<b>One-way sensitivity analyses</b>			
Unit cost MRI +25 %	€340	4MRI	21 267
Unit cost MRI -25%	€204	4MRI	10 074
Utility value DCIS/localized breast cancer +10%	0.849	4MRI	14 722
Utility value DCIS/localized breast cancer -10%	0.695	4MRI	16 749
Utility value regional breast cancer +10%	0.708	4MRI	16 243
Utility value regional breast cancer -10%	0.579	4MRI	15 137
Utility value metastasis +10%	0.566	4MRI	15 983
Utility value metastasis -10%	0.463	4MRI	15 369
Probabilities of a false-positive MRI result +10%	First MRI: 9.8%	4MRI	16 013
Probabilities of a false-positive MRI result -10%	Subsequent MRIs: 3.3%	4MRI	15 331
	First MRI: 5.9%		
Unit cost tomosynthesis +25%	Subsequent MRIs: 1.9%	4MRI	15 590
	€115		
Probability diagnostic ultrasound after a positive mammogram +25%	100%	4MRI	15 602
Probability diagnostic ultrasound after a positive mammogram -25%	66%	4MRI	15 653
Probability stereotactic biopsy after a positive mammogram +25%	11%	4MRI	15 608
Probability stereotactic biopsy after a positive mammogram -25%	6%	4MRI	15 632
Probability ultrasound-guided biopsy after a positive mammogram +25%	48%	4MRI	15 590
Probability ultrasound-guided biopsy after a positive mammogram -25%	29%	4MRI	15 650
Ultrasound axilla only after a proven malignancy	17%	4MRI	15 627
<b>Scenario analyses</b>			
No decrease in breast cancer incidence	NA	4MRI	15 467
Different discount rates	Costs: 4%	4MRI	9836 <sup>a</sup>
	Effects: 1.5%		
Different set of utility values	See <a href="#">Supplementary Table 5</a> (available online)	4MRI	15 955

<sup>a</sup>The ICER of the next strategy (3MRI) on the frontier was just above the threshold with a value of 24 835/QALY. 4MRI = MRI every 4 years ; ICER= incremental cost-effectiveness ratio; MRI= magnetic resonance imaging; QALY = quality-adjusted life year.

operative MRI may no longer be necessary. We also had to make several assumptions on diagnostic procedures after a positive mammogram, but these hardly affected the ICERs.

Based on our results, screening with MRI alone every 4 years would be recommended from a cost-effectiveness perspective. However, when women know they have extremely dense breasts and thereby an elevated breast cancer risk, they may want to be screened more than once every 4 years. This may result in opportunistic screening. Opportunistic screening, however, was not incorporated in our model. In case a 2-year interval is preferred by policy makers, alternating mammography and MRI can be an alternative.

Approximately 8% of women aged 50-75 years have extremely dense breasts (1). Even though we showed MRI screening is cost-effective for these women, it would create a burden on health-care budgets. Furthermore, screening these women within a hospital setting may lead to capacity problems. Implementation of MRI screening would lead to a need of more MRI machines and more (trained) personnel.

We modeled only women with extremely dense breasts receiving an MRI screening, but the sensitivity of mammography is also low among women with heterogeneously dense breasts (VDG3) (1). However, also expanding MRI screening to these women will create a larger burden on health-care budgets and screening capacities, as 29% of the screening population falls in this category (1). Also, the benefit of MRI may be lower for this group because the sensitivity of mammography is higher among women with heterogeneously dense breasts compared with women with extremely dense breasts (1).

We modeled Dutch women with extremely dense breasts within the Dutch health-care setting, but we assume that relative differences in health outcomes between the modeled screening strategies will be approximately similar in other countries. Because health-care prices and cost-effectiveness thresholds vary per country, this should be kept in mind when translating our ICERs to other countries.

In our analyses, the unit cost of MRI was €272, and the ICER was highly sensitive to this. In the near future, we expect several technological developments, such as artificial intelligence and abbreviated MRI, which could reduce false-positive diagnoses as well as acquisition and reading time (33,34). Therefore, we expect MRI screening to become less expensive in the future.

In conclusion, this study showed that MRI screening every 4 years for women with extremely dense breast tissue was cost-effective and had the highest acceptable ICER. If decision makers are willing to pay more than €22 000 per QALY gained, MRI every 2 or 3 years can also become cost-effective.

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## Notes

**Role of the funders:** The funding sources had no role in the design, conduct, analysis, or reporting of this study.

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## Data Availability

Model data can be made available on request. Trial data will be made available after the study has been closed.

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