





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

H. Amarens Geuzinge , MSc,^{1,*} Marije F. Bakker , PhD,² Eveline A.M. Heijnsdijk, PhD,¹ Nicolien T. van Ravesteyn, PhD,¹ Wouter B. Veldhuis , MD,³ Ruud M. Pijnappel, MD,³ Stéphanie V. de Lange, MD,^{2,3} Marleen J. Emaus, PhD,³ Ritse M. Mann , MD,^{4,5} Evelyn M. Monninkhof, PhD,² Petra K. de Koekoek-Doll, MD,⁵ Carla H. van Gils, PhD,² Harry J. de Koning, MD,¹ on behalf of the DENSE trial study group

¹Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands; ²Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; ³Department of Radiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; ⁴Department of Medical Imaging, Radboud University Medical Centre, Nijmegen, the Netherlands and ⁵Department of Radiology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

*Correspondence to: H. A. Geuzinge, MSc, Department of Public Health, Erasmus MC, PO Box 2040 3000 CA Rotterdam, the Netherlands (e-mail: h.geuzinge@erasmusmc.nl).

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

Received: January 7, 2021; Revised: April 5, 2021; Accepted: June 15, 2021

© The Author(s) 2021. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

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^a

| % 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 |

^aReference 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 ^a | No screening | 2Mx | 5MRI | 4MRI | 2Mx/MRI | 3MRI | 2Mx_4MRI | 6Mx_2MRI | 2MRI | 4Mx_2MRI | 2Mx_2MRI |
|---------------------------------------|--------------|------------------|------------|------------|--------------------|------------|--------------------|------------------|------------|--------------------|--------------------|
| Undiscounted results | | | | | | | | | | | |
| 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 ^b | — | 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 |
| Discounted results^c | | | | | | | | | | | |
| 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 |

^aNote 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.

^bBecause 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.

^cDiscounted by 3%.

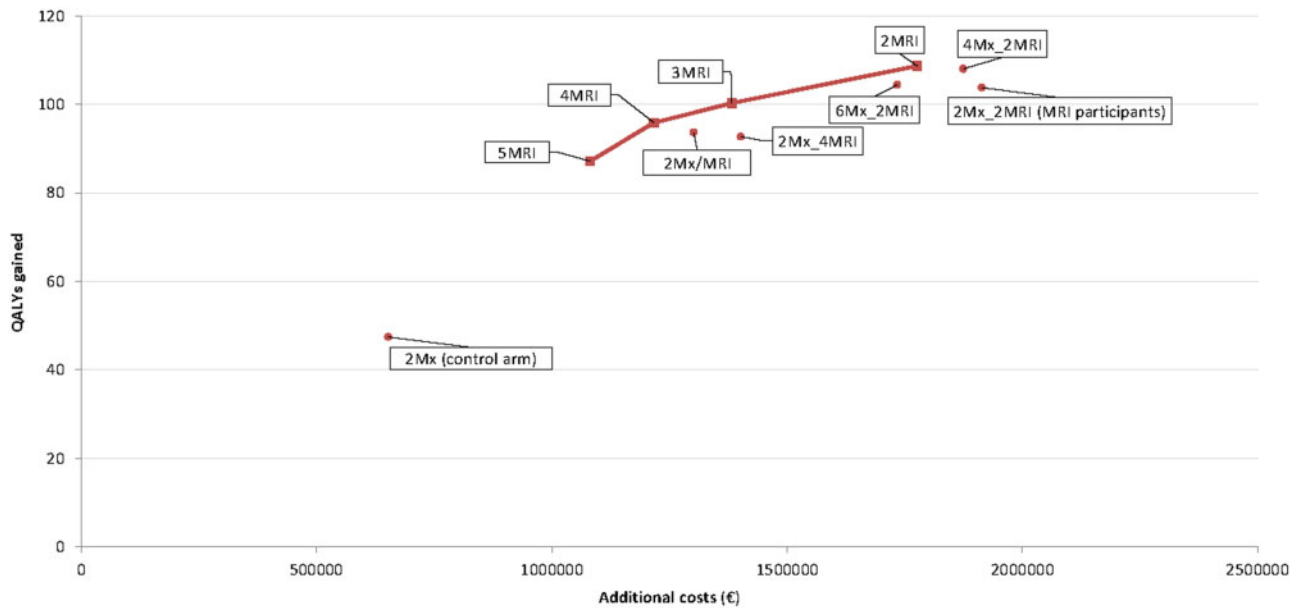


Figure 1. Efficiency frontier (3% discounting). 2MRI = MRI every 2 years; 3MRI = MRI every 3 years; 4MRI = MRI every 4 years; 5MRI = MRI every 5 years; 2Mx = mammography every 2 years; 2Mx/MRI = screening every 2 years with alternating mammography and MRI; 2Mx_2MRI = MRI and mammography every 2 years; 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 |
|--|--|---|-------------------|
| One-way sensitivity analyses | | | |
| 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 |
| Scenario analyses | | | |
| No decrease in breast cancer incidence | NA | 4MRI | 15 467 |
| Different discount rates | Costs: 4% | 4MRI | 9836 ^a |
| | Effects: 1.5% | | |
| Different set of utility values | See Supplementary Table 5 (available online) | 4MRI | 15 955 |

^aThe 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.

Funding

This work was supported by the University Medical Center Utrecht (project number UMCU DENSE); the Netherlands Organization for Health Research and Development (project number ZONMW-200320002-UMCU); the Dutch Cancer Society (project numbers DCS-UU-2009-4348 and UU-2014-6859); the Dutch Pink Ribbon/A Sister's Hope (project number Pink Ribbon-10074); Bayer HealthCare Medical Care (project number BSP-DENSE); Stichting Kankerpreventie Midden-West. For research purposes, Matakina (Wellington, New Zealand) provided Volpara Imaging Software, version 1.5, for installation on servers in the screening units of the Dutch screening program.

Notes

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

Disclosures: HAG, MFB, EAMH, NTvR, WBV, SVdL, MJE, RMM, EMM, RMM, PKdK-D disclosed no relevant relationships. RMM: disclosed no relevant relationships related to the present article. Activities not related to the present article: institution has received compensation for consultancy from Bayer, Siemens Healthineers, ScreenPoint Medical, BD, Seno Medical, and Transonic Imaging; institution has received or will receive grants from Siemens Healthineers, ScreenPoint Medical, Medtronic, BD, Konig, and Seno Medical; received compensation for lectures from Bayer, Siemens Healthineers, ScreenPoint Medical, BD, Seno Medical, and Transonic Imaging. CHvG received funding from Bayer HealthCare; Volpara Health Technologies has provided Volpara Imaging Software for use in the DENSE trial; consultant Bayer Healthcare. RMP: Patient advocacy breast cancer group of the Netherlands (no payment); received a speakers fee for Hologic.

Author contributions: Conceptualization: CHvG, HJdK, MFB; Methodology: HJdK, EAMH, NTvR, MFB, CHvG, RMP, WBV, RMM, PKdK-D, HAG; Validation: NTvR, EAMH; Formal analysis: HAG, MFB, EAMH, NTvR; Resources: RMP, WBV, RMM, PKdK-D, MFB, SVdL, MJE; Data Curation: MFB, SVdL, MJE; Writing—original draft preparation: HAG; Writing—review and editing: HAG, MFB, EAMH, NTvR, WBV, RMP, SVdL, MJE, RMM, EMM, PKdK-D, CHvG, HJdK; Visualization: HAG; Supervision: MFB, EAMH, NTvR, CHvG, HJdK; Project administration: CHvG, HJdK; Funding acquisition: CHvG.

Prior presentations: Part of this work was presented at the European Congress of Radiology (ECR) in March 2021.

Acknowledgements: We thank the trial participants for their contributions and the regional screening organizations, Volpara Health Technologies, the Dutch Expert Center for Screening, and the National Institute for Public Health and the Environment for their advice and in-kind contributions.

Data Availability

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

References

- Wanders JO, Holland K, Veldhuis WB, et al. Volumetric breast density affects performance of digital screening mammography. *Breast Cancer Res Treat*. 2017;162(1):95–103.
- Price ER, Hargreaves J, Lipson JA, et al. The California breast density information group: a collaborative response to the issues of breast density, breast cancer risk, and breast density notification legislation. *Radiology*. 2013;269(3):887–892.
- Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356(3):227–236.
- Kerlikowske K. The mammogram that cried Wolfe. *N Engl J Med*. 2007;356(3):297–300.
- Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med*. 2008;148(9):671–679.
- Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI screening for women with extremely dense breast tissue. *N Engl J Med*. 2019;381(22):2091–2102.
- Pataky R, Armstrong L, Chia S, et al. Cost-effectiveness of MRI for breast cancer screening in BRCA1/2 mutation carriers. *BMC Cancer*. 2013;13:339.

8. Plevritis SK, Kurian AW, Sigal BM, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *JAMA*. 2006;295(20):2374–2384.
9. Lee JM, McMahon PM, Kong CY, et al. Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. *Radiology*. 2010;254(3):793–800.
10. Geuzinge HA, Obdeijn IM, Rutgers EJ, et al.; for the Familial MRI Screening (FaMRisc) Study group. Cost-effectiveness of breast cancer screening with MRI in women at familial risk: the randomized FaMRisc trial. *JAMA Oncol*. 2020;6(9):1381–1389.
11. American College of Radiology. *Breast Imaging Reporting and Data System Atlas (BIRADS Atlas)*. Reston: American College of Radiology, 2003.
12. Emaus MJ, Bakker MF, Peeters PH, et al. MR imaging as an additional screening modality for the detection of breast cancer in women aged 50–75 years with extremely dense breasts: the DENSE trial study design. *Radiology*. 2015; 277(2):527–537.
13. Sankatsing VDV, Heijnsdijk EAM, van Luijt PA, van Ravesteyn NT, Fracheboud J, de Koning HJ. Cost-effectiveness of digital mammography screening before the age of 50 in the Netherlands. *Int J Cancer*. 2015;137(8): 1990–1999.
14. American Joint Committee on Cancer (AJCC). *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
15. Wanders JOP. 2017. Automatically assessed volumetric breast density and breast cancer risk - The era of digital screening mammography [doctoral dissertation]. the Netherlands: Utrecht University. dspace.library.uu.nl/handle/1874/350502.
16. Roman M, Sala M, Bare M; for the BELE study group, et al. Changes in mammographic density over time and the risk of breast cancer: an observational cohort study. *Breast*. 2019;46:108–115.
17. Netherlands Comprehensive Cancer Organisation (IKNL). Monitor bevolkingsonderzoek borstkanker 2017/2018. Published 2018. <https://www.rivm.nl/documenten/monitor-bevolkingsonderzoek-borstkanker-2017-2018>.
18. Timmers JMH, Van Doorne-Nagtegaal HJ, Zonderland HM, et al. The Breast Imaging Reporting and Data System (BI-RADS) in the Dutch breast cancer screening programme: its role as an assessment and stratification tool. *Eur Radiol*. 2012;22(8):1717–1723.
19. Weigel S, Decker T, Korsching E, Hungermann D, Böcker W, Heindel W. Calcifications in Digital Mammographic Screening: Improvement of Early Detection of Invasive Breast Cancers?. *Radiology*. 2010;255(3):738–745.
20. NABON. Borstkanker, landelijke richtlijn, versie 2.0. <https://richtlijndatabank.nl/richtlijn/borstkanker/algemeen.html>. Accessed December 15, 2021.
21. Keymeulen KBIM, Geurts SME, Lobbes MBI, et al. Population-based study of the effect of preoperative breast MRI on the surgical management of ductal carcinoma in situ. *Br J Surg*. 2019;106(11):1488–1494.
22. Lobbes MB, Vriens IJ, van Bommel AC, et al. Breast MRI increases the number of mastectomies for ductal cancers, but decreases them for lobular cancers. *Breast Cancer Res Treat*. 2017;162(2):353–364.
23. Polder JJ, Barendregt JJ, van Oers H. Health care costs in the last year of life—the Dutch experience. *Soc Sci Med*. 2006;63(7):1720–1731.
24. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst*. 2006;98(11):774–782.
25. de Haes JC, de Koning HJ, van Oortmarssen GJ, van Agt HM, de Bruyn AE, van Der Maas PJ. The impact of a breast cancer screening programme on quality-adjusted life-years. *Int J Cancer*. 1991;49(4):538–544.
26. Appleby J, Devlin N, Parkin D. NICE's cost effectiveness threshold. *BMJ*. 2007; 335(7616):358–359.
27. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Tan S. *Kostenhandleiding: Methodologie Van Kostenonderzoek En Referentieprijzen Voor Economische Evaluaties in de Gezondheidszorg*. Diemen: Zorginstituut Nederland; 2015.
28. Kerlikowske K, Ichikawa L, Miglioretti DL, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. *J Natl Cancer Inst*. 2007;99(5):386–395.
29. Froelich MF, Kaiser CG. Cost-effectiveness of MR-mammography as a solitary imaging technique in women with dense breasts: an economic evaluation of the prospective TK-study. *Eur Radiol*. 2021;31(2):967–974.
30. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med*. 2011;155(1):10–20.
31. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med*. 2015;162(3):157–166.
32. Lee CI, Cevik M, Alagoz O, et al. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. *Radiology*. 2015;274(3):772–780.
33. Kuhl CK, Schradning S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection—a novel approach to breast cancer screening with MRI. *J Clin Oncol*. 2014;32(22):2304–2310.
34. Verburg E, van Gils CH, Bakker MF, et al. Computer-aided diagnosis in multiparametric magnetic resonance imaging screening of women with extremely dense breasts to reduce false-positive diagnoses. *Invest Radiol*. 2020;55(7):438–444.