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# Cost-effectiveness of digital mammography screening before the age of 50 in The Netherlands

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**In the Netherlands, routine mammography screening starts at age 50. This starting age may have to be reconsidered because of the increasing breast cancer incidence among women aged 40 to 49 and the recent implementation of digital mammography. We assessed the cost-effectiveness of digital mammography screening that starts between age 40 and 49, using a microsimulation model. Women were screened before age 50, in addition to the current programme (biennial 50–74). Screening strategies varied in starting age (between 40 and 50) and frequency (annual or biennial). The numbers of breast cancers diagnosed, life-years gained (LYG) and breast cancer deaths averted were predicted and incremental cost-effectiveness ratios (ICERs) were calculated to compare screening scenarios. Biennial screening from age 50 to 74 (current strategy) was estimated to gain 157 life years per 1,000 women with lifelong follow-up, compared to a situation without screening, and cost €3,376/LYG (3.5% discounted). Additional screening increased the number of LYG, compared to no screening, ranging from 168 to 242. The costs to generate one additional LYG (*i.e.*, ICER), comparing a screening strategy to the less intensive alternative, were estimated at €5,329 (biennial 48–74 *vs.* current strategy), €7,628 (biennial 45–74 *vs.* biennial 48–74), €10,826 (biennial 40–74 *vs.* biennial 45–74) and €18,759 (annual 40–49 + biennial 50–74 *vs.* biennial 40–74). Other strategies (49 + biennial 50–74 and annual 45–49 + biennial 50–74) resulted in less favourable ICERs. These findings show that extending the Dutch screening programme by screening between age 40 and 49 is cost-effective, particularly for biennial strategies.**

Breast cancer is the most commonly diagnosed form of cancer among women aged 30 and older in the Netherlands.[1] Mammography screening allows for early detection and early treatment of breast cancer, with the aim of averting breast cancer death. In the Netherlands, women aged 50 to 74 are invited biennially to screening. Various randomised controlled trials demonstrated a statistically significant breast cancer mortality reduction due to mammography screening in this age group.[2–4] Furthermore, Otto *et al.*[5,6] showed that the Dutch population-based screening programme is effective in reducing breast cancer mortality. The evidence for the benefit of mammography screening for younger women is less conclusive,[7–9] however, an effect for this age group is supported by several studies. Although the UK Age Trial showed a non-significant 17% reduction in breast cancer mortality,[9] a statistically significant breast cancer mortality reduction of 15% to 18% associated with screening for women aged 39 to 49 or 40 to 49 at entry was demonstrated by several meta-analyses of randomised controlled trials.[10–13] In addition, a recent Swedish observational study that compared breast cancer mortality rates between women aged 40 and 49 who were invited to screening and women who were not invited to screening demonstrated a 26% statistically significant breast cancer mortality reduction.[14] Younger women may benefit less from mammography screening because of factors associated with younger age, including a lower breast cancer incidence[1] and a lower test sensitivity of mammography due to higher breast density and, possibly, faster growing tumours.[15,16] However, results from the DMIST trial show that digital mammography improves test sensitivity for younger women with dense breasts compared to film mammography.[17]

Due to the controversy over screening before age 50 there is no consensus on whether or not to offer screening to women aged 40 to 49. The American Cancer Society recommends screening starting at age 40,[18] whereas the U.S. Preventive Services Task Force stated that "the decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context

**Key words:** breast cancer, mammography screening, age, cost-effectiveness, computer simulation

**Abbreviations:** A: annual (screening); B: Biennial (screening); CER: cost-effectiveness ratio; DCIS: ductal carcinoma in situ; ICER: incremental cost-effectiveness ratio; LYG: life-year gained; PPV: positive predictive value; QALY: quality-adjusted life-year

Additional Supporting Information may be found in the online version of this article.

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**What's new?**
**Women in the Netherlands are supposed to start routine mammograms at 50, but that recommendation is under review. Considering advances in technology and increasing cancer rates among younger women, these authors studied the cost-effectiveness of digital mammography starting before age 50. The current protocol, biennial screening from ages 50 to 74, costs €3,376 per life-year-gained (LYG). Extending biennial screening to 48 year olds, the authors found, cost €5,329 per additional LYG, and beginning at age 45 increased the cost to €7,628 per additional LYG. Thus, earlier screening could be a cost-effective strategy.**

into account, including the patient's values regarding specific benefits and harms".[19] There is also no wide agreement in Europe, although the majority of European national screening programmes do not invite women under age 50 years. Routine mammography screening is currently extended to age 47 in the UK, as a result of the outcomes of the UK Age Trial.[20]

Biennial mammography screening for women aged 50 to 74 in the Netherlands has been shown to reduce breast cancer mortality at reasonable cost.[21] Two important reasons to consider a lower starting age of routine screening in the Netherlands are the increasing incidence of breast cancer among women aged 40 to 49 (2.4% annually between 1995 and 2004)[22] and the recent implementation of digital mammography. It is unclear, however, whether extending screening to women younger than 50 years is cost-effective. This study therefore assesses the cost-effectiveness of digital mammography screening between ages 40 and 49 in addition to current screening in the Netherlands.

## Material and Methods

### Model overview

The effects of screening were assessed using the MISCAN microsimulation model.[21,23] MISCAN simulates individual life histories of women and the natural history of breast cancer in a subset of these women. First, breast cancer incidence and breast cancer mortality are estimated in a situation without screening. Subsequently, mammography screening and treatment related improvements in survival are simulated, in order to determine the impact of screening and treatment on the life histories. Breast cancer starts with the onset of a preclinical ductal carcinoma *in situ* (DCIS) and continues with its progression through the invasive successive stages T1A, T1B, T1C and T2+. At each stage, a tumour may become screen-detected (if screening is present), clinically detected (if symptoms are present) or may progress to the next preclinical stage (Fig. 1).[24] Screening leads to the detection of smaller tumours, which may improve survival after diagnosis. Women with a screen- or clinically detected cancer may receive adjuvant treatment, which also improves survival.

### Model parameters and assumptions

The MISCAN model was updated earlier by de Gelder *et al.* using Dutch screening and treatment data from 1975 to 2008 and international data.[23] We updated this model with regard to test sensitivity of mammography and background breast cancer incidence (described below). Other parameters were adopted from the earlier model, including the mean duration of preclinical screen-detectable cancer, transition probabilities between tumour stages and survival rates after clinical diagnosis and screen-detection (Supporting Information Appendix, Table 1).

All parameters were specified by age (including ages 40–49) and tumour stage and survival rates were also specified by lymph node status. Dutch data from screening organisations and comprehensive cancer centres were used to estimate the mean duration of preclinical screen-detectable cancer and the transition probabilities between tumour stages.[1,25] Survival rates after screen-detection were estimated using data from the Swedish randomised controlled trials.[3,4,26,27] Probabilities of receiving adjuvant treatment (endocrine therapy, chemotherapy or a combination of the two) and survival rates after receiving adjuvant treatment were incorporated using data from Dutch regional comprehensive cancer centers[1,25] (data by age, stage and calendar year) and data from the EBCTCG meta-analysis,[28] respectively.

Test sensitivity of mammography was estimated earlier using Dutch screening data on rates of screen-detected and interval cancers between 1990 and 2007 and between 1990 and 2005, respectively.[23] As digital mammography completely replaced film mammography in 2010 in the Netherlands and women in our analysis are screened from 2014 onwards, we refitted the model for age- and stage-specific test sensitivity of digital mammography. The model was recalibrated using Dutch digital screening data including age-specific detection- and interval cancer rates,[29] stage distribution and stage-specific detection rates[30] and breast cancer incidence between 2007 and 2011.[1] We also incorporated future trends in breast cancer incidence. The trend in background breast cancer incidence (in the absence of screening) between 1975 and 2008 was modelled previously with MISCAN by assuming an annual rise in breast cancer incidence of 1.4%.[23] Because extrapolating this annual rise to the period of time of our analysis would lead to an unlikely high incidence, we assumed that the rise diminished from 2008 to a constant incidence from the year 2028 onwards (Supporting Information Appendix, Table 1).

The effect of screening might be smaller for women aged 40 to 49 due to, amongst others, higher breast density.[15,16] Test sensitivity of mammography and positive predictive value (PPV) of a screening mammogram are therefore likely to be lower for younger women. Recent Dutch data on

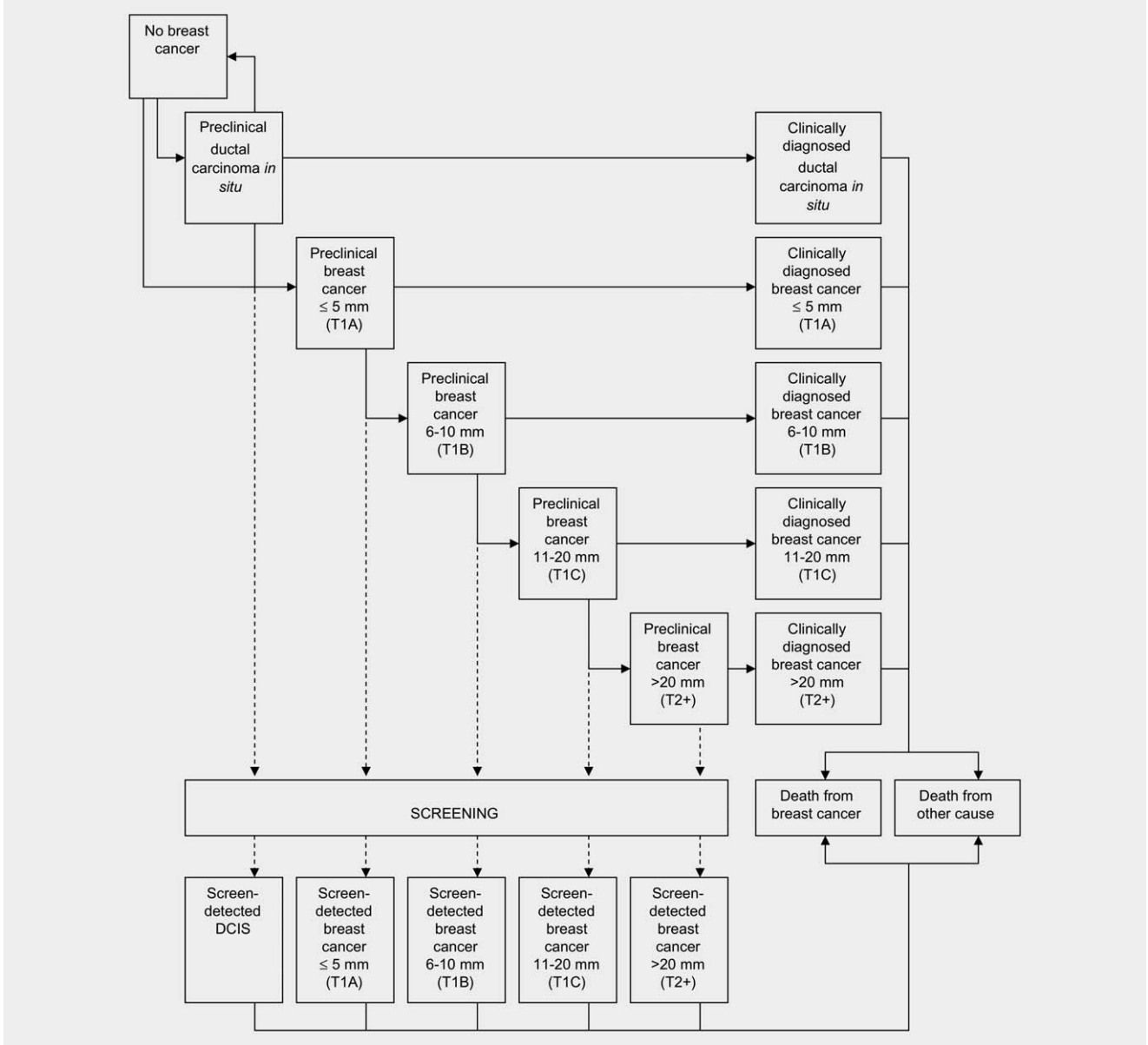


**Figure 1.** Transitions in the MISCAN model.[24] The arrows represent the possible transitions.

screening characteristics of women aged 40 to 49 are unavailable. Based on different trials, we estimated test sensitivity for women aged 40 to 49 to be up to 25% lower than test sensitivity for women aged 55 and older.[31] In order to account for a gradual change, test sensitivity was linearly interpolated between age 50 and 55. Stage-specific test sensitivities are shown in the Supporting Information Appendix in Table 1. The PPV of a digital screening mammogram was estimated to be 30% for women aged 50 and older, based on findings of a recent Dutch study.[30] The PPV for women aged 40 to 49 was assumed to be 12% (40% of the PPV for women aged 50 and older).[17,32,33]

In the Netherlands, mammography is often repeated in the hospital after recall for further assessment because of a suspicious screening mammogram.[34] Therefore, we assumed that all women recalled for further assessment would undergo an additional (diagnostic) mammogram.

### Screening strategies

A cohort of 10 million Dutch women was simulated and women were followed from age 40 to death (from 2014 to 2074). Screening strategies varied in starting age (between 40 and 50) and frequency (annual or biennial). Women were screened biennially between age 50 and 74 in all strategies, in accordance with the current programme. Additional effects of strategies could therefore directly be linked to screening before age 50. Women aged 40 to 49 have been shown to have higher interval cancer rates than older women, due to greater mammographic breast density and higher tumour

**Table 1.** Costs associated with breast cancer screening, diagnosis and treatment[29,37,38]

| Procedure | Costs[1] |
|---|---|
| Screening | |
| Invitation | 2 |
| Digital screening mammogram | 58 |
| Diagnosis | |
| Magnetic resonance imaging (MRI)[2] | 367.59 |
| Consultation after recall[3] | 69.05 |
| Ultrasound | 77.08 |
| Fine needle aspiration (FNA) | 141.73 |
| Biopsy[4] | 175.86 |
| Additional mammogram[5] | 103.23 |
| Treatment by stage[6] | |
| DCIS | 4,569 |
| T1a, N- | 4,333 |
| T1b, N- | 5,057 |
| T1c, N- | 11,146 |
| T2, N- | 10,815 |
| T1a, N+ | 16,103 |
| T1b, N+ | 6,744 |
| T1c, N+ | 20,822 |
| T2, N+ | 15,063 |
| Advanced disease | |
| Palliative therapy | 18,000[7] |

[1]Costs are in Euros.
[2]MRI is assumed to be performed to measure the effect of neo-adjuvant therapy for all T2+ cancers.
[3]The number of consultations after recall in the presence of screening is calculated by using the number of screen-detected cancers and a positive predictive value (PPV) of 30%[30] (ages 50–74) or 12% (ages 40–49). The number of consultations after recall in the absence of screening is calculated by using the number of clinically detected cancers and a PPV of 58.3%.[39]
[4]All biopsies are assumed to be image-guided and therefore coincide with an ultrasound. The number of biopsies is calculated by using the number of breast cancers diagnosed and a PPV of 66.7%.[29] Costs of biopsy are calculated as the mean costs of FNA and biopsy.
[5]All women recalled for further assessment are assumed to undergo an additional mammogram.
[6]Mean treatment costs per tumour stage.
[7]Estimate from de Koning et al. 1992[38] indexed to current price levels.

growth rates.[16,35] Therefore, we considered both biennial and annual screening for women aged 40 to 49. The following strategies were simulated: (*i*) biennial screening from age 50 to 74 (current strategy), (*ii*) one screen at age 49 and biennial screening from age 50 to 74, (*iii*) biennial screening from age 48 to 74, (*iv*) biennial screening from age 45 to 74, (*v*) annual screening from age 45 to 49 and biennial screening from age 50 to 74, (*vi*) biennial screening from age 40 to 74, (*vii*) annual screening from age 40 to 49 and biennial screening from age 50 to 74. In addition, to compare the cost-effectiveness of lowering the starting age of screening to the cost-effectiveness of increasing the stopping age, biennial screening from age 50 to 76 was simulated. An 80% attendance to screening was assumed.[29]

For each strategy, the number of invitations, mammograms, screen- and clinically detected tumours (stage- and age-specific), total life-years and breast cancer deaths were predicted. Results are presented per 1,000 women, aged 40 in 2014, with lifelong follow-up. The number of false-positive findings was calculated using the number of screen-detected cancers and a PPV of 30% (women aged 50 and older) or a PPV of 12% (women aged 40 to 49).

### Costs and effects

We adopted a health care payer perspective[36] and calculated direct medical costs including costs of screening, diagnostics and treatment. Costs of a screening mammogram were based on data from the Dutch screening organisations.[29] We used costs of diagnosis and treatment costs by tumour stage reported by Saadatmand et al. in the MRISC study.[37] An overview of all costs is shown in Table 1.[29,37–39]

Both the effects of screening and adjuvant treatment are simulated in MISCAN. In order to predict the effect of screening, breast cancer mortality is estimated for a scenario with adjuvant treatment and screening and compared to breast cancer mortality in a scenario with adjuvant therapy but without screening. The effect of screening was estimated by predicting life-years gained (LYG). Costs and effects were calculated from the lowest starting age of screening (40 years) until death. Both effects and costs were discounted at 3.5% per year to take time preference into account.[40] In order to meet Dutch standards, we also used a discount rate of 1.5% for effects and 4% for costs (Supporting Information Appendix, Table 2).

Screening strategies were ranked according to their effectiveness (number of LYG). The cost-effectiveness ratio was calculated for the current screening strategy (biennial 50–74), the least effective scenario, as the difference in costs between current screening and no screening divided by the number of LYG by current screening. Subsequently, in order to compare screening scenarios, incremental cost-effectiveness ratios (ICERs) were calculated for strategies that screen additionally between ages 40 and 49 as the difference in costs divided by the difference in LYG between a strategy and the previous, less effective, strategy in the ranking. The ICER of a strategy therefore reflects the costs required to generate one additional LYG, compared to the previous strategy. Strategies were defined as dominated if an alternative, more effective strategy existed that required lower costs to generate an additional LYG. Non-dominated strategies were considered to be efficient. We compared ICERs to a cost-effectiveness threshold of £20,000–£30,000 (approximately €24,000–€36,000) per quality-adjusted life-year (QALY) gained.[40] Strategies that did not exceed this threshold were considered to be cost-effective.

### Sensitivity analyses

Univariate sensitivity analyses were performed in order to assess to what extent parameter values and assumptions

affected the costs per LYG and the ranking of efficient screening strategies. First, we varied the test sensitivity of digital mammography for women aged 40 to 49 (50% and 100% of the test sensitivity for women aged 55 and older). Second, we varied the PPV of digital mammography for women aged 40 to 49 (9% and 15%). Third, we simulated a constant background breast cancer incidence (equal to incidence in 2008) as well as an annual increase in incidence of 1%. Fourth, in our analysis, all women who are screened and recalled for further assessment were assumed to undergo an additional mammogram (in addition to the screening mammogram) in the hospital. This may, however, not always be true in practice and we therefore also tested the assumption that instead of all women, only 50% of the women would undergo an additional mammogram in the hospital.

Finally, in order to assess the effect of screening strategies on quality of life we estimated quality-adjusted life-years (QALYs), using utility estimates with a value between 0 (worst imaginable health state) and 1 (healthy state). We included reductions in utility associated with screening participation and a positive screen of 0.006 for 1 week and 0.105 for 5 weeks, respectively.[41] To take into account reductions in utility from breast cancer treatment, we used adjusted health utilities reported by Stout *et al.*,[42] with minor adjustments in the application of these utilities as our model cannot discriminate between regional and distant breast cancer stages (Supporting Information Appendix, Table 1). Women who do not die of breast cancer were assumed to experience a loss in quality of life of 0.1 for 2 years from diagnosis if diagnosed with *in situ* or localised breast cancer and a loss of 0.25 for 2 years from diagnosis if diagnosed with regional or distant breast cancer. For women who die of breast cancer, a reduction of 0.4 was calculated from diagnosis until breast cancer death.

## Results

### Model validation

As women in our analysis are screened and followed in the future (2014–2074), we were not able to compare model predictions to observed data. However, our model predicted trends in breast cancer incidence and mortality from 1989 to 2011 quite well (Supporting Information Appendix, Figs. 1 and 2).

### Effects of screening

Without screening, 135 cases of breast cancer and 45 breast cancer deaths were predicted to occur among 1,000 women, aged 40, followed over their lifetimes (undiscounted) (Table 2).

Screening these women biennially from age 50 to 74 (current strategy) averted 12 breast cancer deaths and gained 157 life-years (13 LYG per breast cancer death averted), compared to no screening. In total, 138 breast cancer cases were diagnosed, of which 53 were screen-detected and 3 were overdiagnosed (138–135). Screening led to 124 false-positive findings.

Strategies that screened additionally before age 50 gained life-years ranging from 168 (49 + biennial 50–74) to 242 (annual 40–49 + biennial 50–74), compared to no screening. Offering annual screening from age 40 to 49, in addition to the current strategy, would lead to three additional deaths averted, 85 additional LYG and 105 additional false-positive findings (Table 2), by performing 7,842 additional mammograms, per 1,000 women, 40 years of age, followed over their lifetimes.

Biennial screening from age 50 to 76 gained 161 undiscounted life-years and averted 12 breast cancer deaths (data not shown).

### Incremental cost-effectiveness

Additional screening at age 49 and additional annual screening from age 45 to 49 were dominated by biennial strategies that were more effective and required lower costs to generate an additional LYG. Biennial screening from age 50 to 76 was dominated by biennial screening from age 48 to 74, which gained more additional life-years for similar costs (data not shown). All other strategies were on the efficiency frontier (Fig. 2).

Total costs due to breast cancer diagnosis, treatment and death in the absence of screening were estimated at €1,161,008 per 1,000 women, followed over their lifetime (3.5% discounted) (Table 2). The estimated costs of the current screening program were €3,376 per LYG (3.5% discounted) (Table 3). One additional screening round at age 48 was predicted to gain five additional life-years, per 1,000 women, and to cost €5,329 per additional LYG. Biennial screening from age 45 instead of 48 would gain six more life-years that cost €7,628 per LYG. Lowering the starting age of biennial screening from age 45 to age 40 would gain nine additional life-years that would cost €10,826 each. Screening annually instead of biennially from age 40 would result in a gain of nine more life-years that cost €18,759 per LYG. All ICERs were below the cost-effectiveness threshold.

### Sensitivity analyses

Estimated costs per (additional) LYG were only slightly influenced by varying the PPV for women under the age of 50 or by assuming that only 50% of women recalled for further assessment would undergo an additional mammogram (Supporting Information Appendix, Table 3). Assuming a constant breast cancer incidence or a lower test sensitivity of digital mammography for women aged 40 to 49 led to more unfavourable ratios of costs and effects (maximum €21,459) whereas a constant annual increase in incidence or a higher test sensitivity led to more favourable ratios. Adjustment for quality of life resulted in a slightly higher reduction in life-years in the absence of screening than in the presence of screening, which led to a higher number of QALYs gained than the number of life-years gained for the different screening scenarios (Table 2). ICERs calculated by dividing the

**Table 2.** Effects and costs[1] of screening

| | No screening | B 50–74 (current) | 49 + B 50–74 | 48 + B 50–74 | B 45–74 | A 45–49 + B 50–74 | B 40–74 | A 40–49 + B50–74 |
|---|---|---|---|---|---|---|---|---|
| Undiscounted | | | | | | | | |
| Screening data | | | | | | | | |
| Women invited to screening | | +10,710 | +11,604 | +11,671 | +13,129 | +15,471 | +15,591 | +20,385 |
| Screening tests | | +8,653 | +9,377 | +9,431 | +10,613 | +12,511 | +12,608 | +16,495 |
| Effects | | | | | | | | |
| Breast cancers diagnosed[2] | 135 | +3 | +3 | +3 | +3 | +3 | +3 | +4 |
| Screen-detected cancers | | +53 | +56 | +55 | +59 | +62 | +62 | +67 |
| Breast cancer deaths | 45 | −12 | −12 | −13 | −13 | −14 | −14 | −15 |
| Life-years (%)[3] | 41,382 | +157 (0.4) | +168 (0.4) | +173 (0.4) | +191 (0.5) | +205 (0.5) | +215 (0.5) | +242 (0.6) |
| Quality-adjusted life-years | 41,171 | +198 | +211 | +217 | +239 | +256 | +268 | +300 |
| False-positive findings | | +124 | +139 | +147 | +171 | +189 | +198 | +229 |
| Costs (€) | | | | | | | | |
| Invitations | | +21,420 | +23,208 | +23,342 | +26,258 | +30,942 | +31,181 | +40,770 |
| Screening mammograms | | +501,848 | +543,847 | +547,017 | +615,531 | +725,639 | +731,280 | +956,713 |
| Diagnosis | 117,839 | +5,090 | +7,067 | +8,493 | +11,667 | +14,041 | +15,414 | +19,458 |
| Treatment | 1,714,552 | −173,202 | −180,836 | −181,749 | −192,980 | −207,184 | −207,062 | −230,906 |
| Breast cancer deaths | 814,882 | −212,256 | −222,712 | −225,364 | −239,243 | −252,526 | −255,868 | −278,564 |
| Total (%)[3] | 2,647,273 | +142,900 (5) | +170,574 (6) | +171,740 (6) | +221,232 (8) | +310,912 (12) | +314,945 (12) | +507,470 (19) |
| 3.5% Discounted | | | | | | | | |
| Total costs | 1,161,008 | +137,057 | +158,680 | +163,704 | +210,234 | +281,643 | +306,590 | +475,420 |
| Life-years | 20,834 | +41 | +44 | +46 | +52 | +56 | +61 | +70 |

[1]Results represent the difference in effects or costs between a screening strategy and a situation without screening and are presented per 1,000 women, 40 years of age, followed over their lifetimes.
[2]The additional cancers diagnosed by screening, compared to no screening, reflect overdiagnosis.
[3]Percentage change compared to no screening.
Abbreviations: B: biennial screening; A: annual screening.

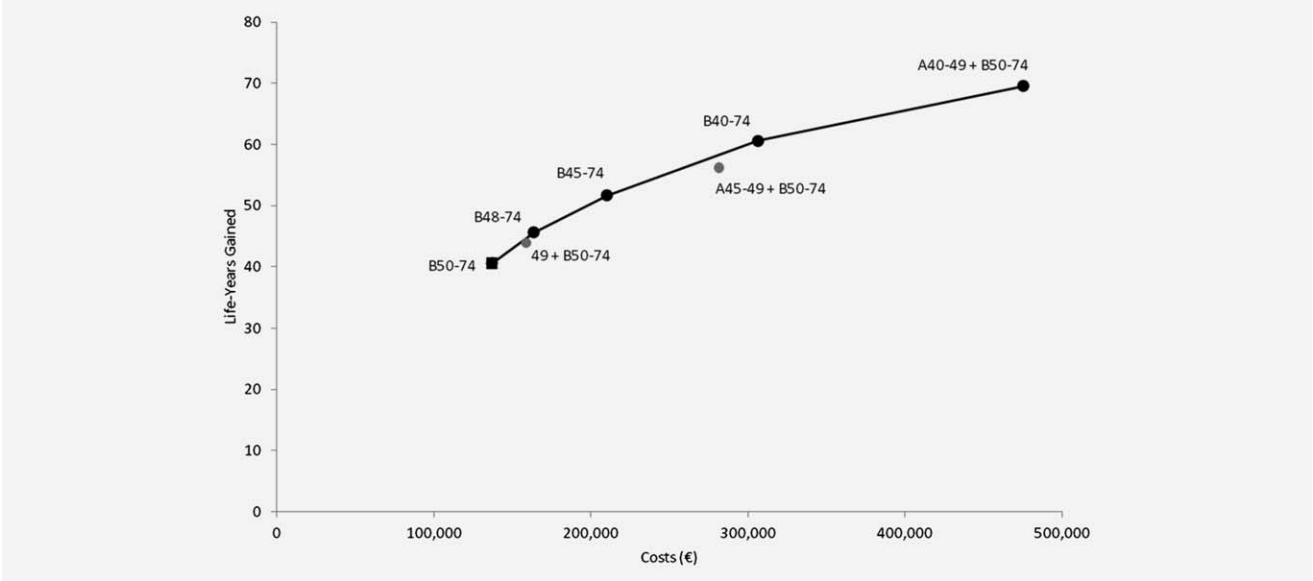


**Figure 2.** Efficiency frontier of screening strategies. Both costs and LYG are relative to a situation without screening and are presented per 1,000 women (3.5% discounted).The current screening strategy (B 50–74) is displayed by a square, all other points reflect ICERs of additional screening strategies. Points on the frontier represent efficient strategies (*i.e.*, no alternative strategy exists that gains more life years for fewer costs per additional LYG). Dominated strategies are represented by gray dots. Strategies consist of annual (A), biennial (B) or combined (A + B) screening.

**Table 3.** Incremental cost-effectiveness ratios of additional screening before age 50

| Screening strategy | Additional screening rounds | Costs[1] in € | Life-years gained[1] | Incremental cost-effectiveness ratio[2] |
|---|---|---|---|---|
| No screening | | 1,161,008 | | |
| B 50–74 (current) | | 137,057 | 41 | 3,376 |
| 49 + B 50–74 | 1 | 158,680 | 44 | Dominated |
| B 48–74 | 1 | 163,704 | 46 | 5,329 |
| B 45–74 | 2.5 | 210,234 | 52 | 7,628 |
| A 45–49 + B 50–74 | 5 | 281,643 | 56 | Dominated |
| B 40–74 | 5 | 306,590 | 61 | 10,826 |
| A 40–49 + B 50–74 | 10 | 475,420 | 70 | 18,759 |

[1]Both costs and life-years gained are relative to a situation without screening, 3.5% discounted and presented per 1,000 women, 40 years of age, followed over their lifetimes.
[2]Additional costs per additional LYG; calculated as the difference in costs divided by the difference in life-years gained between a strategy and the previous, less effective, non-dominated strategy in the ranking (no screening for the current strategy).

change in costs by the change in QALYs gained are therefore slightly more favourable than the ICERs based on the change in life-years gained (Supporting Information Appendix, Table 4).

The ranking of strategies was not affected by any of the sensitivity analyses performed and ICERs were below the cost-effectiveness threshold (£20,000; €24,000) in all scenarios.

## Discussion

This study shows that digital mammography screening between age 40 and 49 in the Netherlands, in addition to the current screening strategy, is cost-effective. Our results indicate that, from a cost-effectiveness perspective, biennial screening from age 40 to 49 is more efficient in addition to current screening than annual screening from age 45 to 49. Furthermore, our analysis suggests that one additional screening round is more efficient at age 48 than at age 49 and that extending the lower age-limit of screening by one additional screening round is more effective and will result in lower costs per additional LYG than extending the upper age-limit by one screening round.

Our model predicted that both the number of LYG and breast cancer mortality reduction due to screening would increase with decreasing starting age. However, aside from benefits, additional screening before age 50 years is also associated with additional harms. We estimated that the number of false-positive findings would increase by 74 per 1,000 women (60%), if biennial screening starts at age 40 instead of

age 50. A higher false-positive rate may result in more unnecessary biopsies. However, false-positive rates of current screening in the Netherlands are considerably lower than rates in other countries[43] and will therefore probably remain relatively low if women are screened from age 40, despite the substantial increase in absolute number of false-positive findings. False-positive mammograms were recently shown to increase short-term anxiety.[44] However, long-term anxiety and health utility scores did not differ between women with false-positive mammograms and women with negative mammograms. The number of overdiagnosed cancers was estimated to increase by 0.33 per 1,000 women (11%) if biennial screening starts at age 40 instead of age 50 (cannot be read from Table 2 because numbers are rounded). Overdiagnosis is defined as screen-detection of a cancer that would never have presented clinically in the absence of screening, during a woman's lifetime. As overdiagnosed cancers would not have led to symptoms in the absence of screening, treatment of these cancers is considered to be harmful.

This study shows that the current screening programme in the Netherlands is highly cost-effective (€3,376 per LYG), which corresponds with findings of an earlier conducted Dutch study.[21] Our model predicted a 26% breast cancer mortality reduction due to screening from age 50 to 74, which is in line with the outcomes of randomized controlled trials.[4] Our results show that lowering the starting age of biennial screening to age 40 would reduce breast cancer mortality additionally by 5%. This finding is comparable to results of a previous modelling study in which the additional mortality reduction due to biennial screening from age 40 was determined using six different models (range, 1–6%).[45] This previous study also showed that most strategies on the efficiency frontier are biennial strategies. Correspondingly, in our analysis four of the five efficient strategies have a biennial screening interval. The only annual strategy on the frontier, annual screening from age 40 (+ biennial 50–74), is efficient because it is the most intensive strategy that we simulated and it therefore yields the largest effect (*i.e.,* could not be dominated by an alternative strategy). However, the ICER increases considerably shifting from biennial to annual screening between ages 40 and 49 (from €10,826 per LYG to €18,759 per LYG), which has been reported before.[46]

A microsimulation study based on data from the US showed that biennial mammography screening from age 40 to 79 is cost-effective only for women with either BIRADS breast density categories 3 or 4 or a previous breast biopsy as well as a family history of breast cancer and that annual mammography from age 40 to 49 is not cost-effective for any high-risk group (using a threshold of $100,000 per QALY gained).[47] In contrast, we found that both annual and biennial mammography screening from age 40 are cost-effective, regardless of risk factors. However, Schousboe *et al.*[47] focused on film mammography, which has been shown to be less cost-effective than digital mammography for younger women.[48] Furthermore, sensitivity analyses showed that results were sensitive to the proportion of false-positive findings assumed and false-positive rates in the Netherlands are significantly lower than in the US.[43] This probably (partly) accounts for the more favourable ratio of costs and effects in our analysis. A more recent US modelling study showed that extending biennial digital mammography screening to all women aged 40 to 49, regardless of breast density, is cost-effective,[49] which is in line with our findings. However, results were sensitive to decreases in quality of life associated with screening and false-positives.

Although our results are primarily based on Dutch screening data, outcomes regarding the efficiency of screening strategies are likely to be translatable to other countries.

To our knowledge, our study is the first cost-effectiveness analysis, using Dutch population data and including digital mammography screening from age 40 to 49. One of the strengths of our study is that we used digital mammography screening data for the calibration of our model. An advantage of using a model to determine the effectiveness of screening is that long-term effects are predicted, as women are followed over their lifetime.

This study also had a few limitations. First, our model outcomes depend on assumptions and input values. We assumed a constant PPV for women aged 40 to 49 and a higher constant PPV for women aged 50 and older. In reality there may be a gradual increase in PPV with increasing age and changes in PPV over time. However, sensitivity analyses showed that differences in PPV were of little influence on our results. Differences in test sensitivity did affect model outcomes. We estimated test sensitivity for women aged 40 to 49 to be up to 25% lower, using studies that were based on the use of film mammography,[31] because digital data on age-specific test sensitivity is scarce. The ratio in sensitivity of digital mammography between younger and older women may be different due to improved sensitivity associated with digital mammography for younger but not for older women.[17] The estimated difference in sensitivity may therefore be overestimated and the number of additional LYG by screening before age 50 could be a conservative estimate. Model outcomes were also sensitive to the assumed trend in background breast cancer incidence. Extrapolating the earlier trend in incidence to the time period of our analysis would lead to an extremely high and unlikely incidence. We therefore assumed that the earlier constant annual rise in incidence would decrease over time. Although differences in test sensitivity and background breast cancer incidence were of influence on costs per additional LYG, the ranking of strategies and whether a strategy was efficient or dominated remained unchanged. Furthermore, in the worst-case scenarios (low test sensitivity or constant background breast cancer incidence) ICERs did not exceed the cost-effectiveness threshold (£20,000; €24,000).

Another limitation is that we compare costs per LYG to a threshold expressed as costs per QALY gained, in our base case analysis. However, our sensitivity analysis showed that adjusting for quality of life has little impact on cost-

effectiveness estimates, which is in line with earlier findings.[41,50] In addition, when we adjust for quality of life, the incremental cost-effectiveness ratios are slightly more favourable and therefore remain below the threshold of £20,000 per QALY gained (approximately €24,000 per QALY gained). When we compare the ICERs to the willingness-to-pay threshold of €20,000 per QALY gained, often cited in Dutch cost-effectiveness analyses,[51–53] all screening scenarios remain cost-effective.

Apart from age, we did not consider risk factors for breast cancer (*e.g.,* breast density). The cost-effectiveness of risk-based screening strategies that start before age 50 is therefore an important area for further research.

Finally, the effect of adjuvant treatment was modelled using the most recent data of the EBCTCG trial.[28] Future improvements in therapy may reduce the effectiveness and therefore the cost-effectiveness of screening.

In conclusion, our results indicate that additional screening between age 40 and 49 in the Netherlands is cost-effective. However, the decision about whether or not to implement screening before age 50 years will also depend on the balance of benefits and harms. If it is decided to extend the screening programme, our findings provide information that could be useful for selecting an appropriate screening strategy, by taking into account the cost-effectiveness of different starting ages between age 40 and 49 and suggesting that biennial strategies have more favourable ratios of costs and effects.

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## References

1. Nederlandse Kankerregistratie. http://www.cijfersoverkanker.nl/. Last accessed January, 2014.
2. Shapiro S. Periodic screening for breast cancer: the HIP randomized controlled trial. Health insurance plan. *J Natl Cancer Inst Monogr* 1997; 27–30.
3. Tabar L, Vitak B, Chen HH, et al. The Swedish two-county trial twenty years later. Updated mortality results and new insights from long-term follow-up. *Radiol Clin North Am* 2000;38:625–51.
4. Nystrom L, Andersson I, Bjurstam N, et al. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002;359:909–19.
5. Otto SJ, Fracheboud J, Looman CW, et al.; National Evaluation Team for Breast Cancer. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet* 2003;361:1411–17.
6. Otto SJ, Fracheboud J, Verbeek AL, et al.; National evaluation team for breast cancer. Mammography screening and risk of breast cancer death: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2012;21:66–73.
7. Alexander FE, Anderson TJ, Brown HK, et al. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *Lancet* 1999;353:1903–8.
8. Miller AB, To T, Baines CJ, Wall C. The Canadian national breast screening study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* 2002;137:305–12.
9. Moss SM, Cuckle H, Evans A, et al. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* 2006;368:2053–60.
10. Hendrick RE, Smith RA, Rutledge JH, III, et al. Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. *J Natl Cancer Inst Monogr* 1997;22:87–92.
11. Smith RA, Duffy SW, Gabe R, et al. The randomized trials of breast cancer screening: what have we learned? *Radiol Clin North Am* 2004;42:793–806.
12. Nelson HD, Tyne K, Naik A, et al. Force USPST. Screening for breast cancer: an update for the U.S. preventive services task force. *Ann Intern Med* 2009;151:727–37, W237-W242.
13. Magnus MC, Ping M, Shen MM, et al. Effectiveness of mammography screening in reducing breast cancer mortality in women aged 39–49 years: a meta-analysis. *J Womens Health (Larchmt)* 2011;20:845–52.
14. Hellquist BN, Duffy SW, Abdsaleh S, et al. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish mammography screening in young women (SCRY) cohort. *Cancer* 2011;117:714–22.
15. Carney PA, Miglioretti DL, Yankaskas BC, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med* 2003;138:168–75.
16. Buist DS, Porter PL, Lehman C, et al. Factors contributing to mammography failure in women aged 40–49 years. *J Natl Cancer Inst* 2004;96: 1432–40.
17. Pisano ED, Hendrick RE, Yaffe MJ, et al. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology* 2008;246:376–83.
18. American Cancer Society. http://www.cancer.org/. Last accessed: February, 2014.
19. U. S. Preventive Services Task Force. Screening for breast cancer: U.S. preventive services task force recommendation statement. *Ann Intern Med* 2009;151:716–26, W-236.
20. NHS Breast Cancer Screening Programme. Available at: http://www.cancerscreening.nhs.uk. Last accessed May, 2014.
21. Groenewoud JH, Otten JD, Fracheboud J, et al. Netb. Cost-effectiveness of different reading and referral strategies in mammography screening in the Netherlands. *Breast Cancer Res Treat* 2007; 102:211–18.
22. Louwman WJ, Voogd AC, van Dijck JA, et al. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: a long-term population-based study in southeastern Netherlands. *Cancer Causes Control 2008*;19:97–106.
23. de Gelder R, Heijnsdijk EA, Fracheboud J, et al. The effects of population-based mammography screening starting between age 40 and 50 in the presence of adjuvant systemic therapy. *Int J Cancer* 2015; 137:165–72.
24. de Gelder R, Bulliard JL, de Wolf C, et al. Cost-effectiveness of opportunistic versus organised mammography screening in Switzerland. *Eur J Cancer* 2009; 45:127–38.
25. National Evaluation Team for Breast cancer screening (NETB). National evaluation of breast cancer screening in the Netherlands 1990-2007. Twelfth evaluation report. Rotterdam, The Netherlands: Erasmus MC University Medical Center Rotterdam, Radboud University Nijmegen Medical Centre, 2009.
26. de Koning HJ, Boer R, Warmerdam PG, et al. Quantitative interpretation of age-specific mortality reductions from the Swedish breast cancer-screening trials. *J Natl Cancer Inst* 1995;87:1217–23.
27. Bjurstam N, Bjorneld L, Warwick J, et al. The Gothenburg breast screening trial. *Cancer* 2003; 97:2387–96.
28. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365:1687–717.
29. National Evaluation Team for Breast cancer screening (NETB). National evaluation of breast cancer screening in the Netherlands 1990-2011/2012. Thirteenth evaluation report. Rotterdam, The Netherlands: Erasmus MC University Medical Center Rotterdam, Radboud University Nijmegen Medical Centre, 2014.
30. van Luijt PA, Fracheboud J, Heijnsdijk EA, et al.; Team for breast cancer screening in Netherlands study. Nation-wide data on screening performance during the transition to digital mammography: observations in 6 million screens. *Eur J Cancer* 2013;49:3517–25.
31. International Agency for Research on Cancer. Breast cancer screening, vol. 7. In: Vainio H,

Bianchini F, eds. IARC handbooks of cancer prevention. IARC handbooks of cancer and prevention. Lyon: IARC Press, 2002.
32. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: follow-up and final results of Oslo II study. *Radiology* 2007;244:708–17.
33. Perry NM, Patani N, Milner SE, et al. The impact of digital mammography on screening a young cohort of women for breast cancer in an urban specialist breast unit. *Eur Radiol* 2011;21:676–82.
34. Timmers JM, 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; 22:1717–23.
35. Bailey SL, Sigal BM, Plevritis SK. A simulation model investigating the impact of tumor volume doubling time and mammographic tumor detectability on screening outcomes in women aged 40–49 years. *J Natl Cancer Inst* 2010;102:1263–71.
36. Neumann PJ. Costing and perspective in published cost-effectiveness analysis. *Med Care* 2009; 47:S28–S32.
37. Saadatmand S, Tilanus-Linthorst MM, Rutgers EJ, et al. Cost-effectiveness of screening women with familial risk for breast cancer with magnetic resonance imaging. *J Natl Cancer Inst* 2013;105: 1314–21.
38. de Koning HJ, van Ineveld BM, de Haes JC, et al. Advanced breast cancer and its prevention by screening. *Br J Cancer* 1992;65:950–5.
39. Huisarts en Wetenschap 2002;4:194-98.
40. National Institute for Health and Care Excellence. Available at: http://www.nice.org.uk/. Last accessed January, 2014.
41. de Haes JC, de Koning HJ, van Oortmarssen GJ, et al. The impact of a breast cancer screening programme on quality-adjusted life-years. *Int J Cancer* 1991;49:538–44.
42. Stout NK, Rosenberg MA, Trentham-Dietz A, et al. Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst* 2006;98:774–82.
43. Otten JD, Fracheboud J, den Heeten GJ, et al. Likelihood of early detection of breast cancer in relation to false-positive risk in life-time mammographic screening: population-based cohort study. *Ann Oncol* 2013;24:2501–6.
44. Tosteson AN, Fryback DG, Hammond CS, et al. Consequences of false-positive screening mammograms. *JAMA Intern Med* 2014;174: 954–61.
45. Mandelblatt JS, Cronin KA, Bailey S, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med* 2009;151: 738–47.
46. Carles M, Vilaprinyo E, Cots F, et al. Cost-effectiveness of early detection of breast cancer in Catalonia (Spain). *BMC Cancer* 2011; 11:192.
47. Schousboe JT, Kerlikowske K, Loh A, et al. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med* 2011;155:10–20.
48. Tosteson AN, Stout NK, Fryback DG, et al., DMIST Investigators. Cost-effectiveness of digital mammography breast cancer screening. *Ann Intern Med* 2008;148:1–10.
49. Stout NK, Lee SJ, Schechter CB, et al. Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. *J Natl Cancer Inst* 2014;106:dju092.
50. Chapman RH, Berger M, Weinstein MC, et al. When does quality-adjusting life-years matter in cost-effectiveness analysis? *Health Econ* 2004;13: 429–36.
51. de Kok IM, van Rosmalen J, Dillner J, et al. Primary screening for human papillomavirus compared with cytology screening for cervical cancer in European settings: cost effectiveness analysis based on a Dutch microsimulation model. *BMJ* 2012;344:e670.
52. de Boer PT, Pouwels KB, Cox JM, et al. Cost-effectiveness of vaccination of the elderly against herpes zoster in the Netherlands. *Vaccine* 2013; 31:1276–83.
53. Verhoef TI, Redekop WK, Hasrat F, et al. Cost effectiveness of new oral anticoagulants for stroke prevention in patients with atrial fibrillation in two different European healthcare settings. *Am J Cardiovasc Drugs* 2014;14:451–62.