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# Safety and cost-effectiveness of shortening hospital follow-up after breast cancer treatment

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**Background:** In the Netherlands, the first 5 years of follow-up after treatment for breast cancer are carried out in hospital with yearly mammography. After this, for patients aged over 60 years who have undergone mastectomy, there is a shift of care to the National Screening Programme (NSP) for mammography every 2 years. After breast-conserving therapy follow-up is performed by the general practitioner (GP), with mammography every second year and physical examination annually. The aim of this study was to evaluate the clinical effects and costs of four different strategies for follow-up after breast cancer treatment.

**Methods:** An extended and validated simulation model for breast cancer follow-up was used. The current guidelines for follow-up (baseline strategy) and three less intensive follow-up strategies were evaluated. The main outcome measure was the detection rate of small tumours (2 cm or smaller) and associated costs for each strategy.

**Results:** Shortening the follow-up time in hospital by shifting care to the NSP or GP after 2 years instead of 5 years of hospital follow-up, lowering the age of referral to the NSP or GP from 60 to 50 years, and termination of annual physical examination by the GP after hospital follow-up did not decrease the detection of small tumours. In addition, a substantial decrease in costs was observed with simplified follow-up.

**Conclusion:** Decreasing hospital follow-up time, lowering the age of referral to the NSP or GP, and termination of annual physical examinations would lead to a substantial reduction in costs while maintaining the possibility of detecting small breast cancers.

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## Introduction

Breast cancer is the most common malignancy in women in North America and Western Europe, accounting for more than one in four diagnosed cancers<sup>1,2</sup>. Substantial improvements in survival have been achieved and the 5-year age-adjusted relative survival rate for patients with breast cancer in European countries increased from 74 per cent in 1988 to 83 per cent in 1999<sup>3</sup>.

Routine follow-up for early detection of new primary breast cancer is recommended after primary treatment and constitutes the major part of healthcare for breast cancer survivors<sup>4,5</sup>. There are several potential ways in which hospitals can reduce this workload<sup>6,7</sup>. First, less frequent

follow-up including mammography and a shorter duration of follow-up can be implemented<sup>8,9</sup>. Second, follow-up can be provided by nurses or general practitioners (GPs). These strategies have shown acceptable patient satisfaction and comparable quality of life outcomes to those associated with hospital follow-up<sup>10–12</sup>. Third, tailored approaches can be developed, including individual risk assessment of new primary breast cancers, age and co-morbidities, and even psychological preferences<sup>13</sup>. A few randomized controlled trials have evaluated these alternative follow-up models, but none had enough statistical power to establish the ideal frequency and safety of alternative follow-up methods<sup>7</sup>.

In the absence of adequate trial data, simulation modelling can provide guidance on the risks, benefits and resources required for routine follow-up to detect early primary breast cancers. The aim of the present study was to evaluate the effectiveness and costs of different follow-up strategies for women with a previous breast cancer. For this simulation, a previously validated simulation-based decision model was extended<sup>14,15</sup>. The main outcome of the study was the detection rate of early breast cancer and the associated additional costs.

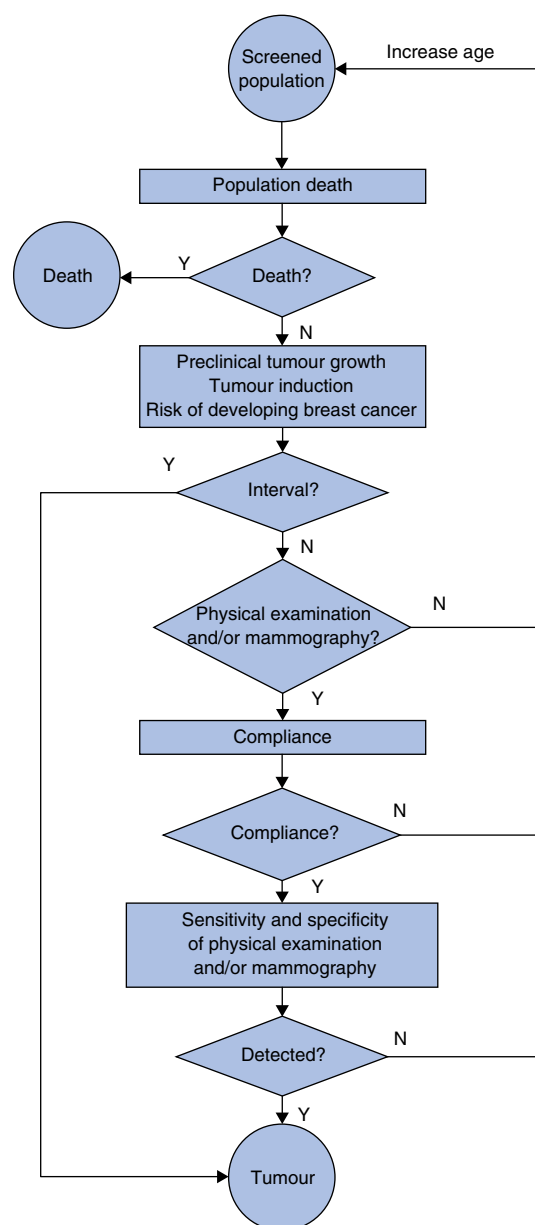
## Methods

### Population screened by the model

The input population screened by the model was based on a database of women with a history of breast cancer that was representative of the Dutch breast cancer population with respect to age at diagnosis, tumour stage, nodal status and treatment of the first tumour. The women were diagnosed with breast cancer between January 1989 and January 2003, and treated in four hospitals in the North Netherlands. Data were extracted from the patients' medical records in all hospitals using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centres.

### Description of the simulation model

The structure of the model is shown in *Fig. 1*. The life of each woman is simulated for each year from the moment of detection of the first breast cancer until death or until a second breast cancer is detected. For each woman it is simulated whether or not she dies. If she does not die, the event 'second breast cancer' and the event 'detection of this second breast cancer' are simulated. The probability of a second breast cancer is calculated based on the current age of the patient and the number of years since primary breast cancer treatment. Tumours are selected randomly based on this probability and are presumed to grow according to the preclinical growth model. When a tumour is diagnosed based on symptoms, it is considered as an interval tumour. Otherwise it is checked whether a physical examination and/or mammography is scheduled based on the selected scenario and, if so, whether the woman will undergo this examination based on her expected compliance. If physical examination and/or mammography is performed, a possible tumour can be detected based on the sensitivity of the method. If a tumour is detected during that year, the woman is diagnosed with a second breast cancer, the screening is terminated and the simulation ends. If no new cancer is detected, the woman's age is increased, and the loop starts over again.



**Fig. 1** Structure of the simulation model for follow-up after curative treatment for breast cancer. The circles correspond to the clinical state of the patient, the diamonds to decisions made in the simulation programme, and the rectangles to the different model components with parameters given in *Tables 1* and *2*. Y, yes; N, no

### Clinical parameters in the simulation model

The clinical parameters of the simulation model have been described in previous publications<sup>14,15</sup>. For the purpose of follow-up of women after primary breast cancer, the input parameters of the model were adapted to the

**Table 1** Guideline recommendations for hospital follow-up during the first 5 years after primary treatment of breast cancer (current strategy)

	Physical breast examination	Mammography
Year 1	Every 3 months	Yearly
Year 2	Every 6 months	Yearly
Years 3–5	Yearly	Yearly

current Dutch screening scenario (Tables 1 and 2), and in addition the model was extended and subsequently validated. Compared with previous publications<sup>14,15</sup>, the model was extended to include population death rates, the risk of developing a second primary tumour, the sensitivity of physical examination, the specificity of mammography and physical examination, and patients' compliance. In addition, the input parameters of the model were changed in accordance with the literature (Table S1, supporting information)<sup>14–16</sup>.

The population death rate model used cumulative death rates derived from Dutch data (<http://www.rivm.nl>). The risk of developing a second primary breast cancer was based on a publication on the incidence of breast cancer among female cancer survivors diagnosed in the 1990s, which was about 1 per cent per year<sup>17</sup>. The parameters of the compliance model were estimated from a database of 669 women with a history of breast cancer<sup>18</sup>. Finally, the sensitivity and specificity model was extended with an estimate for an age-dependent sensitivity of physical examination, and was derived from data published by Fryback and colleagues<sup>16</sup>. The specificity of physical examination, 97.1 per cent, was added<sup>19</sup>. The sensitivity of screening mammography depends on tumour size and was based on the results of screening mammography in women with a personal history of breast cancer<sup>20</sup>. The specificity of mammography, 98.3 per cent, was added<sup>21</sup>.

## Follow-up strategies studied

In the Netherlands, current guidelines recommend hospital follow-up for 5 years with yearly mammography (Table 1). After this follow-up, women aged over 60 years who have undergone mastectomy are referred to the National Screening Programme (NSP) for mammography every second year. After breast-conserving therapy women are referred to the GP for mammography every other year, and annual physical examination. For the present study, the current guidelines are indicated as the current strategy. In the first alternative strategy, follow-up time in hospital was shortened by a shift of care from the hospital to the NSP or GP after 2 years of follow-up. In the second alternative strategy, hospital follow-up time was reduced by a shift of care from the hospital to the NSP or GP after 2 years of follow-up and by lowering the referral age from 60 to 50 years. In the third alternative strategy, hospital follow-up time was reduced by shifting care from the hospital to the NSP or GP after 2 years of follow-up, by lowering the referral age from 60 to 50 years, and by terminating yearly physical examination in general practice. The simulation model ran until every woman had left the model owing to death or detection of a secondary primary breast cancer.

## Economic evaluation

A cost-effectiveness analysis was undertaken to evaluate the balance between costs and effects of the various follow-up strategies. The analysis considered the additional costs associated with an increase of 1 per cent in the number of early breast cancers detected (the percentage of second primary tumours diagnosed with a size of 2 cm or less). The cost of mammography was €92 in hospital<sup>22</sup> and €53 in the NSP<sup>23</sup>. The cost per false-positive result for pathological evaluation was €75<sup>24</sup>. The cost of a specialist visit, including consultation and physical examination, was

**Table 2** Differentiated follow-up proposed (at least) 5 years after primary treatment of breast cancer (current strategy)

	After mastectomy	After breast-conserving therapy
Age ≤ 60 years		
Coordination	Hospital	Hospital
Physical breast examination	–	Yearly
Mammography	Yearly	Yearly
MRI	–	–
Age 60–75 years		
Coordination	National screening programme	General practitioner
Physical breast examination	–	Yearly
Mammography	Every 2 years	Every 2 years
Age > 75 years	Follow-up can be ended	Follow-up can be ended

MRI, magnetic resonance imaging.

€25. The total costs of treatment were estimated at €5857 for tumours of 2 cm or smaller, €6485 for tumours larger than 2 cm up to 5 cm in size, and €7006 for tumours larger 5 cm at diagnosis<sup>25</sup>.

### Statistical analysis

Values in parentheses presented in the text are 95 per cent confidence intervals. The model estimates were based on 1000 replications of the simulation performed for each scenario.

### Results

The input population screened by the model was based on a database of 5073 women with a history of breast cancer (Table 3). The model was validated by comparison of simulation results with observed numbers in the database regarding the following parameters: number of deaths, number of tumours, and the number and percentage of small, medium and large tumours. Only 384 (95 per cent c.i. 347 to 421) deaths were simulated, whereas 518 deaths were recorded in the database (Fig. S1a, supporting information). However, the database recorded all deaths, including those after detection of a second primary breast cancer, whereas in the simulation women left the model when a second primary breast cancer was detected. A total of 141 (114 to 167) tumours were found in the simulation, which corresponded well with the 136 tumours in the database (Fig. S1a, supporting information). The number and percentage of small, medium and large tumours in the simulation corresponded well with tumours in the database (Fig. S1a,b, supporting information). The confidence

**Table 3** Characteristics of the population screened by the model presented

	No. of women (n = 5073)
Age at diagnosis (years)*	61.1(4.4)
Follow-up time (years)†	7.2 (0.03–18.2)
Pathological tumour category	
Tis	324 (6.4)
T1	2463 (48.6)
T2	1842 (36.3)
T3	184 (3.6)
T4	202 (4.0)
Unknown	58 (1.1)
Pathological node category	
N0	2962 (58.4)
N1	1946 (38.4)
N2/N3	75 (1.5)
Unknown	90 (1.8)
Surgery	
Mastectomy	3297 (65.0)
Breast-conserving therapy	1776 (35.0)
Radiotherapy	
Yes	2374 (46.8)
No	2699 (53.2)
Chemotherapy	
Yes	976 (19.2)
No	4097 (80.8)

Values in parentheses are percentages unless indicated otherwise; values are \*mean(s.d.) and †median (range).

interval for the mean tumour size in the simulation, 1.4 to 2.1 cm, included the observed mean tumour size of 1.5 cm in the database. Finally, the mean age of the women diagnosed with a second tumour was 67.0 (41.5 to 92.5) years in the simulation, which was somewhat higher than the mean age of 61.1 years for women included in the database, but within the confidence interval (32.9 to 89.3).

**Table 4** Outcomes for breast cancer survivors with different follow-up strategies

	Current strategy	First alternative strategy	Second alternative strategy	Third alternative strategy
No. of second tumours	1043(9)	1047(10)	1042(9)	1053(9)
Programme sensitivity (%)	58.0(0.5)	57.9(0.6)	58.0(0.6)	58.4(0.6)
Sensitivity of clinical examination (%)	10.5(0.4)	10.3(0.3)	10.5(0.4)	9.7(0.3)
Sensitivity of mammography (%)	47.5(0.6)	47.6(0.6)	47.3(0.6)	48.7(0.6)
Total no. of clinical examinations (×1000)	41.9(0.2)	36.3(0.2)	36.3(0.1)	24.7(0.1)
Total no. of mammographies (×1000)	33.9(0.2)	32.1(0.2)	27.2(0.1)	26.6(0.1)
Mean invasive tumour size (cm)	1.80(0.05)	1.86(0.05)	1.95(0.04)	1.94(0.04)
Small tumours (%)	51.7(0.6)	51.5(0.6)	50.6(0.6)	50.6(0.6)
Medium tumours (%)	30.2(0.5)	30.3(0.5)	30.7(0.5)	29.6(0.5)
No. of false-positive findings (×1000)	1.82(0.02)	1.66(0.02)	1.51(0.02)	1.27(0.02)
No. of tumours in patients aged > 75 years	259(6)	261(6)	257(6)	266(6)
Screening cost (€ million)	4.30(0.02)	3.98(0.02)	3.52(0.02)	3.16(0.01)
Cost per 1% increase in small tumours (€ ×1000)	83.1(1.0)	77.3(0.9)	69.4(0.8)	62.1(0.8)
Total cost (€ million)	11.3(0.1)	11.0(0.1)	10.5(0.1)	10.2(0.1)

Values are mean(s.d.) from 1000 simulations.

The strategy for follow-up based on the current guidelines as well as the three alternative strategies showed no substantial differences in the number of second tumours detected, in the programme sensitivity, and in the sensitivity of physical examination or mammography (Table 4). Applying the current strategy for follow-up, 51.7 (50.5 to 52.9) per cent of second tumours detected were small and mean diameter was 1.80 (1.70 to 1.90) cm. The first alternative strategy produced a comparable rate of small tumours (51.5 (50.3 to 52.7) per cent) and a similar mean tumour size (1.86 (1.76 to 1.96) cm). With the second strategy a comparable rate of small tumours (50.6 (49.4 to 51.8) per cent) and mean tumour size (1.95 (1.87 to 2.03) cm) was found, and the third strategy yielded similar results (50.6 (49.4 to 51.8) per cent and 1.94 (1.86 to 2.02) cm respectively).

There were appreciable differences in number of clinical examinations, number of mammographies and number of false-positive findings on mammography between strategies. Consequently, there were substantial differences in costs. Applying the current guidelines, the total screening cost was estimated at €4.30 (4.26 to 4.34) million. The three alternative strategies were associated with lower mean screening costs: €3.98 (3.94 to 4.02), 3.52 (3.48 to 3.56) and 3.16 (3.14 to 3.18) million respectively. The third alternative strategy was the least expensive, with an estimated cost of €62 100 (60 500 to 63 700) for increasing the detection of small tumours by 1 per cent.

## Discussion

Shortening the follow-up time in hospital by shifting to the NSP or GP after 2 years instead of 5 years, lowering the age of referral from 60 to 50 years, and terminating annual physical examination in general practice did not decrease the percentage of small tumours detected during follow-up. In addition, a substantial decrease in costs was observed.

The results from three alternative strategies evaluated in the present study suggest that women with breast cancer can be referred to the NSP for mammography or to general practice for follow-up by physical examination after an initial 2-year hospital-based follow-up. These findings are consistent with the results from a randomized clinical trial in which follow-up in general practice of women with breast cancer did not increase the time to diagnosis of recurrence<sup>11,26</sup>.

In the second and third alternative strategies, the age for referral from hospital-based follow-up to the NSP or general practice was lowered from 60 to 50 years.

Mammography every second year instead of annually would be recommended in these women. This would lead to the number of mammographies for women aged between 50 and 60 years being reduced from ten to five. In the present simulation, this strategy was as safe as the one proposed by the current guidelines. These results are in agreement with studies demonstrating no adverse effects associated with a 2-year screening interval among women in their 50s or older<sup>27,28</sup>.

In the third alternative strategy, physical examination was no longer performed after 2 years of follow-up. This also turned out to be a safe strategy, with a comparable mean tumour size and a similar percentage of small tumours detected. These results are in agreement with a recent meta-analysis indicating that few relapses are detected by physical examination, and that patients diagnosed clinically with a relapse may do less well<sup>29</sup>.

The model used in this study is an extension of a validated model for the simulation of effects of breast cancer screening<sup>14,15</sup>. There was no difference between the expected results obtained using the current strategy in the model and the observed results of the follow-up database and published findings for the Dutch breast cancer population<sup>30,31</sup>.

The impact of shortening follow-up was studied in the Dutch situation in which women are screened in the NSP every other year. If the study had been performed in the context of annual screening or screening every third year, as in the UK, all strategies would have been expected to show an increase or decrease respectively in the percentage of small tumours detected. Only a small decrease in the percentage of small tumours detected was observed in the different strategies for screening every second year. Therefore, if the screening frequency were increased from every other year to annually, a difference between the strategies in the detection of small tumours would be unlikely. However, if the screening frequency were decreased from every other year to every third year, the detection of small tumours would decrease. This would be especially true if the patients' age for referral to the NSP or GP were lowered from 60 to 50 years, as in the second and third alternative strategies.

This study has some limitations. The percentage of small tumours was used as an outcome instead of quality-adjusted life years (QALYs). It is generally accepted that early detection of second breast cancer will result in improved survival<sup>32</sup>. A population-based study revealed that women with stage II or higher breast cancer had worse survival, whereas women with stage I breast cancer did not<sup>31</sup>. A previous systematic review concluded that early detection of isolated recurrences in patients without symptoms

during follow-up was associated with substantially better survival than late detection of recurrence<sup>32</sup>. It is unlikely that the relative cost-effectiveness of the present four strategies would change if QALYs were simulated as the outcome. Another potential limitation of the present study could be the use of the estimated preclinical tumour growth derived from the general population instead of a population of women with a history of breast cancer. The tumour doubling times were based on data from Peer and colleagues<sup>33</sup> and these data are still considered to be applicable. However, it is uncertain whether tumour growth in women with a history of breast cancer differs from that in the general population. As an example, adjuvant treatment could influence tumour growth, which may lower the detection rate in follow-up programmes. The model incorporated Dutch cumulative death rates. However, it is well known that women who survive breast cancer are at an increased risk of death. Finally, the local recurrence rate was not taken into account in the present model used for simulation owing to the lack of conclusive information on local recurrences. The model would be improved by extending it to include the early detection of locoregional recurrences. This would lead to a decrease in sensitivity for tumour detection during follow-up. However, as this would be the case for all follow-up scenarios, it would not be expected to have a major impact on the conclusions based on the present investigation.

The results of the present simulation-based study indicate that a decrease in hospital follow-up time, lowering the age of referral to the NSP or GP, and terminating yearly physical examination after 2 years would lead to a substantial reduction in costs while maintaining the detection rate of early breast cancer.

## Disclosure

The authors declare no conflict of interest.

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### Supporting information

Additional supporting information may be found in the online version of this article:

**Fig. S1** Validation of the simulation programme. **a** Comparison of number of deaths, total number of tumours, and small, medium and large tumours in the simulation compared with numbers observed in the database. **b** Comparison of percentages of small, medium and large tumours in the simulation compared with those in the database (Word document)

**Table S1** Input parameters of the screening model (Word document)

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