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Digital mammography screening: Weighing reduced mortality against increased overdiagnosis

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ABSTRACT

Objective: Digital mammography has been shown to increase the detection of ductal carcinoma *in situ* (DCIS) compared to screen-film mammography. The benefits and risks of such an increase were assessed.
Methods: Breast cancer detection rates were compared between 502,574 screen-film and 83,976 digital mammograms performed between 2004 and 2006 among Dutch screening participants. The detection rates were then modeled using a baseline model and two extreme models that respectively assumed a high rate of progression and no progression of preclinical DCIS to invasive cancer. With these models, breast cancer mortality and overdiagnosis were predicted.
Results: The DCIS detection rate was significantly higher at digital mammography (1.2 per 1000 mammograms (95% C.I. 1.0–1.5)) than at screen-film mammography (0.7 per 1000 mammograms (95% C.I. 0.6–0.7)). Consequently, 287 (range progressive- non progressive model: 1–598) extra breast cancer deaths per 1,000,000 women (a 4.4% increase) were predicted to be prevented. An extra 401 (range: 165–2271) cancers would be overdiagnosed (a 21% increase).
Conclusion: Modeling predicted that digital mammography screening would further reduce breast cancer mortality by 4.4%, at a 21% increased overdiagnosis rate. The consequences of digital screening, however, are sensitive to underlying assumptions on the natural history of DCIS.

Introduction

Because of its improved contrast resolution, digital mammography has the potential to improve test accuracy compared to screen-film mammography (Lewin et al., 2002; Lewin et al., 2001; Pisano et al., 2005; Skaane et al., 2003). Digital mammography in women aged 45–69 resulted in significantly higher referral and cancer detection rates than screen-film mammography (Skaane et al., 2007). Other trials, however, showed that an improved accuracy was limited to women under the age of 50, women with dense breasts and pre- or peri-menopausal women (Lewin et al., 2002; Pisano et al., 2005). The long term benefits and risks of digital mammography in population-based screening have not yet been assessed.

In 2004, a feasibility study of screening women with digital mammography was started in the Netherlands. Here, the results were modeled and used to predict the benefits and risks of implementing digital mammography as compared to screen-film mammography. Because various digital mammography studies observed an increased detection of ductal carcinoma *in situ*[1] (DCIS) and micro-calcifications frequently related to DCIS (Del Turco et al., 2007; Vigeland et al., 2008), our study focused on the benefits and risks of an increased detection of DCIS. However, the extent to which such lesions have the potential to become invasive cancers remains uncertain (National Institutes of Health State-of-the-Science Conference Statement). Detecting DCIS may prevent progression to invasive cancer, but may also imply that a lesion is diagnosed that would not have progressed to invasive cancer during the woman's lifetime (i.e. 'overdiagnosis'). The main purpose of this study is to assess the consequences of an increased detection of DCIS by digital mammography relative to screen-film mammography screening.

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[1] List of abbreviations: Ductal carcinoma in situ (DCIS); Medio-lateral oblique (MLO); Cranio-caudal (CC); Micro-simulation screening analysis (MISCAN); Invasive tumor diameter ≤5 mm (T1a); Invasive tumor diameter 6–10 mm (T1b); Invasive tumor diameter 11–20 mm (T1c); Invasive tumor diameter >20 mm (T2+); Screen-film mammography (SFM); Digital mammography (DM).

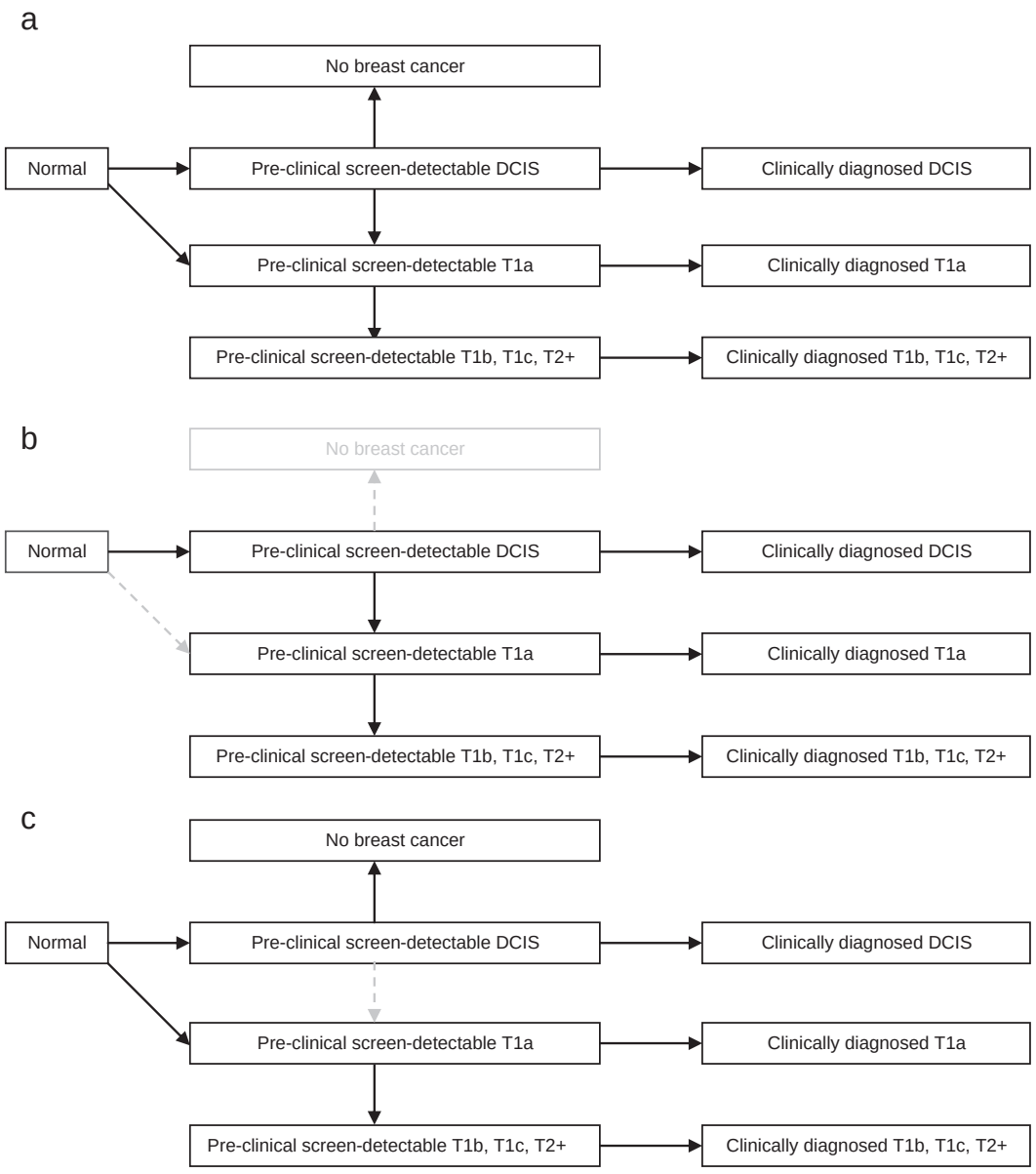

Fig. 1. a-c. Preclinical tumor stage transitions in the absence of mammography screening in the baseline (a), the progressive (b) and the non-progressive (c) screen-film and digital mammography models. In the state 'no breast cancer', a woman does not develop a breast malignancy during her lifetime anymore. In the progressive model variant (b), no transition between normal and preclinical screen-detectable T1a, and between preclinical screen-detectable DCIS and 'no breast cancer' occurs. In the non-progressive model variant (c), no transition between preclinical screen-detectable DCIS and preclinical screen-detectable T1a occurs.

Three scenarios for the natural history of DCIS were considered, that assumed that 1) a part would progress and another part would not, 2) all cases would progress to invasive cancer, or 3) all would be overdiagnosed.

Methods

Since 1990, all women in the Netherlands aged 49–69 (since 1998: aged 49–74) are offered biennial screening. In 2004, digital mammography screening was implemented in three screening units in Utrecht, Drechtsteden and Heerenveen. During the same period, screen-film mammography was performed in 20 other screening units in these regions. In 10 of these screening units, the mammograms were interpreted by the same radiologists who read the digital mammograms. We only included those in our analysis. Referral and TNM stage-specific (International Union against Cancer, 1987) detection rates at digital mammography screening between 2004 and 2006 were compared to the referral and detection rates at screen-film mammography during the same period. To test statistical differences between digital mammography and screen-film mammography, 95% confidence intervals around the mean referral and detection rates were calculated. The rates were age-standardized to the Dutch female population in 2000.

Screen-film and digital mammography differed in the number of views made at subsequent screening examinations. Standard practice at subsequent screen-film mammograms was a medio-lateral oblique (MLO) view, with an additional cranio-caudal (CC) view on indication (in approximately 30%–40% of the examinations). Utrecht and Heerenveen used the same protocol for subsequent digital mammograms, but subsequent digital examinations in Drechtsteden all included a MLO and CC view. The digital screening units in Utrecht and Heerenveen used Full Field Digital Mammography, while the digital unit in Drechtsteden used digital phosphor storage plate mammography. In Heerenveen and Utrecht, prior screen-film mammograms were digitized and directly available at reading for comparison with the new digital images. In Drechtsteden, only screen-film mammograms were available at reading.

The benefits and risks of screen-film and digital mammography screening were predicted using the MIcro-simulation Screening Analysis model MISCAN (Rijnsburger et al., 2004). With MISCAN, individual life histories of women are generated, and the impact of screening on these life histories is

assessed. The simulated life histories together represent the observed female population aged 0–100 years in 1989. Some women in the simulated population develop breast cancer. Its natural course is modeled as a Markov-like progression through the successive preclinical invasive tumor stages T1a, T1b, T1c and T2+(≤5 mm, 6–10 mm, 11–20 mm, >20 mm, respectively). T1a may or may not be preceded by preclinical screen-detectable DCIS (Fig. 1a). A fraction of preclinical DCIS may also regress spontaneously. Each preclinical tumor may progress into the next stage, become clinically diagnosed, or become screen-detected. Transition probabilities, durations of tumor stages and test sensitivity were estimated using data from the Dutch cancer registry and the nation-wide screening program (Vereniging Integrale Kankercentra VIKC, 2010; National Evaluation Team for Breast cancer screening (NETB), 2009). These data included the age-, stage-, and calendar year specific incidence of clinically diagnosed and screen-detected breast cancer (at screen-film mammography), breast cancer detection rates, and interval cancer rates between 1990 and 2006.

In the "baseline model", the fraction of breast tumors that has a screen-detectable preclinical DCIS stage was estimated to be 18%. Of these lesions, 11% progress to invasive cancer, 5% is clinically diagnosed and 2% regress. The mean duration of preclinical screen-detectable DCIS was estimated to be 5.2 years; the mean duration of preclinical invasive breast cancer 2.6 years. The estimated test sensitivity of screen-film mammography, defined as the fraction of screen-detectable tumors that become screen-detected, was 47%, 47%, 62%, 90% and 98% for DCIS, T1a, T1b, T1c and T2+ respectively (Appendix 1).

Because breast cancer is a heterogeneous disease for which the development from preclinical lesion to invasive cancer is unclear (Vargo-Gogola and Rosen, 2007), and because model predictions depend on the assumed natural history of the disease, two extreme alternatives to the baseline model were also explored:

1) The 'progressive model' in which all breast tumors pass through a preclinical screen-detectable DCIS stage, none of which regress. An estimated 96% of all screen-detectable DCIS would progress to invasive cancer if no screening would take place, and 4% would be clinically diagnosed. (Fig. 1b),
2) The 'non-progressive model', in which none of the invasive breast tumors pass through a preclinical screen-detectable DCIS stage, and in which the majority of preclinical DCIS would regress. An estimated 2% of preclinical DCIS would be clinically diagnosed (Fig. 1c).

The parameters of the two extreme models described above were estimated in the same way as the baseline model parameters, using incidence and detection rates from the period in which screen-film mammography was only used. To assess the consequences of digital screening, variants to these models were developed with a higher test sensitivity for DCIS than their screen-film counterparts, using detection rates of DCIS and invasive breast cancer at digital mammography screening between 2004 and 2006. In the baseline model, the sensitivity of digital mammography for DCIS was estimated to be 100%. In the progressive and non-progressive model, the sensitivity was estimated to be 94% and 72%, respectively (Appendix 1).

Using these models, we predicted the number of prevented breast cancer deaths and overdiagnosed breast cancers after a 30 year period of biennial screening, starting in 1990. An 82% participation rate was assumed, corresponding to the current participation rate in the Netherlands (National Evaluation Team for Breast cancer screening (NETB), 2007). The number of prevented breast cancer deaths was calculated by comparing the predicted breast cancer mortality in the presence and absence of screening. Overdiagnosis was calculated similarly, by comparing the predicted breast cancer incidence in the presence and absence of screening. All effects were calculated for 1,000,000 women aged 0–100 in 1989 with at least one screening examination between 1990 and 2020, measured during the lifespan of this population.

Results

Screen-film and digital mammography screening

Between 2004 and 2006, 83,976 digital and 502,574 screen-film mammograms were made. Referral rates were significantly higher at digital than at screen-film mammography screening: 14.9 per 1000 screen-film (95% C.I.: 14.6–15.3) versus 23.8 per 1000 digital mammograms (95% C.I.: 22.8–24.9) (Table 1). Referral rates peaked at the start of digital screening in 2004 to a rate twice that of screen-film mammography, but decreased from 2005 on (Fig. 2a). The breast cancer detection rate at digital mammography remained stable over the years (Fig. 2b). The average detection rate between 2004 and 2006 was significantly higher at digital than at screen-film mammography: 4.8 per 1000 screen-film (95% C.I.: 4.6–5.0) compared to 5.6 per 1000 digital examinations (95% C.I.: 5.1–6.1) (Table 1). The relative increase in detection rates was similar between first and subsequent screening examinations (Table 1).

The increase in breast cancer detection was mainly attributable to an 80% increase in the detection of DCIS, from 0.7 per 1000 screen-film (95% C.I.: 0.6–0.7) to 1.2 per 1000 digital mammograms (95% C.I.: 1.0–1.5). The detection rate of invasive cancers did not significantly differ between screen-film and digital mammography (3.9 per 1000 screen-film (95% C.I.: 3.8–4.1) versus 4.4 per 1000 digital mammograms (95% C.I.: 3.9–4.8). DCIS constituted 14% of all tumors detected at screen-

Table 1
Referral advices, screen-detected in situ and invasive carcinomas between 2004 and 2006, by type of mammography.

2004–2006	First screening examinations			Subsequent screening examinations (<2,5 years interval)			All screening examinations		
	Age 49–54			Age 50–74			Age 49–74		
	Screen-film	Digital	+/− (%)	Screen-film	Digital	+/− (%)	Screen-film	Digital	+/− (%)
Screening examinations (n)	61 038	12 078		434 743	70 635		502 574	83 976	
Referral advice (n)	1 815	553		5 411	1 421		7 445	2 023	
Age-standardized referral rate per 1000 examinations (95% C.I.)	30.2 (28.8–31.6)	49.4 (45.5–53.7)	+64*	12.6 (12.2–12.9)	20.3 (19.3–21.4)	+63[a]	14.9 (14.6–15.3)	23.8 (22.8–24.9)	+61[a]
Screening carcinomas[d] (n)	301	74		1 998	381		2 365	463	
Age-standardized detection rate per 1000 examinations (95% C.I.)	5.1 (4.6–5.7)	6.8 (5.5–8.5)	+33	4.6 (4.4–4.8)	5.4 (4.9–6.0)	+18[b]	4.8 (4.6–5.0)	5.6 (5.1–6.1)	+19[b]
Screen-detected DCIS[d] (n)	47	19		278	83		335	102	
Age-standardized detection rate per 1000 examinations (95% C.I.)	0.8 (0.6–1.1)	1.7 (1.1–2.6)	+103	0.6 (0.6–0.7)	1.2 (0.9–1.4)	+81[c]	0.7 (0.6–0.7)	1.2 (1.0–1.5)	+80[c]
Screen-detected invasive[d] (n)	238	54		1654	296		1946	358	
Age-standardized detection rate per 1000 examinations (95% C.I.)	4.1 (3.6–4.6)	5.0 (3.9–6.5)	+23	3.8 (3.6–4.0)	4.2 (3.8–4.7)	+11	3.9 (3.8–4.1)	4.4 (3.9–4.8)	+12

[a] P-value<0.0001.
[b] P-value<0.02.
[c] P-value<0.001.
[d] The difference between the number of screening carcinomas and the number of DCIS and invasive cancers is the number of unclassified cancers and cancers with unknown TNM stage.

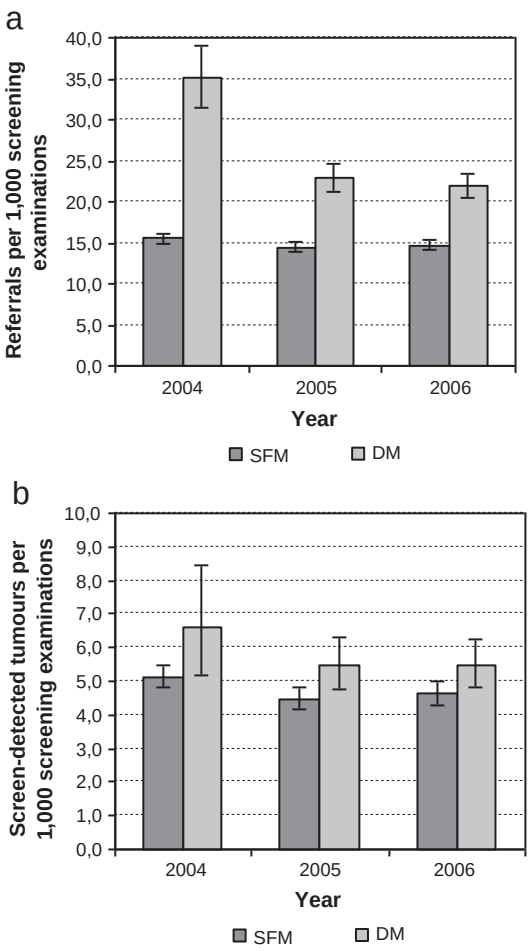

Fig. 2. a–b. Observed referral (a) and breast cancer detection rates (b), by year and screening modality.

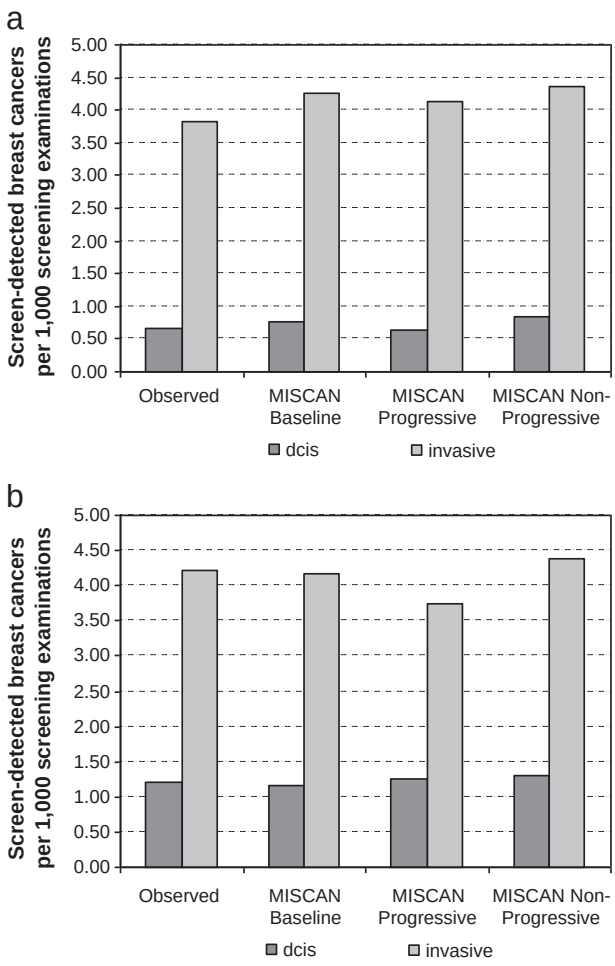

Fig. 3. a–b. Observed and predicted detection rates of DCIS and invasive breast cancer in the period 2004–2006, at screen-film mammography screening (a) and digital mammography screening (b).

film mammography, and 22% of all tumors detected at digital mammography screening. As a consequence, the stage distribution of digitally detected tumors was slightly more favorable than that of tumors detected at screen-film mammography, with 84% against 78% of all detected breast cancers being non-invasive or 20 mm or smaller. No differences were observed between screen-film mammography and digital mammography in interval cancers and the sensitivity and specificity of mammography (data not shown).

Model validation and parameter estimates

Each model predicted the incidence of clinically diagnosed DCIS and invasive breast cancers, the stage- and age- specific tumor detection rates, interval cancer rates and breast cancer mortality reasonably well. Fig. 3 shows the observed and modeled detection rates of DCIS and invasive cancer.

Breast cancer mortality

In a population of 1,000,000 women aged 0–100 in 1989 with at least 1 screening examination, 5,632,810 screen-film mammograms were predicted to be performed between 1990 and 2020 (Table 2, using the baseline model). Screening would prevent 6577 breast cancer deaths in this population. Digital mammography was predicted to prevent 287 more breast cancer deaths than screen-film mammography: a relative increase of 4.4%.

In the progressive and non-progressive models, a predicted 6753 and 5982 breast cancer deaths per 1,000,000 women were prevented by screen-film mammography screening (Table 2). Digital mammography screening would prevent 598 more breast cancer deaths in the progressive model. In the non-progressive model, however, digital screening had no additional benefits over screen-film mammography screening.

Overdiagnosis

The baseline model predicted that 1926 tumors per 1,000,000 screened women would be overdiagnosed at screen-film mammography (i.e. 2.1% of all diagnosed breast cancers in screened women, or 7.2% of all screen-detected cancers; Table 2). Digital mammography screening would increase the number of overdiagnosed tumors by 21%, to 2527 per 1,000,000 screened women (2.5% of all diagnosed breast cancers in screened women or 8.2% of all screen-detected tumors).

Using the progressive model, digital screening would increase the number of overdiagnosed tumors by 14% (from 1168 cases at screen-film to 1333 cases at digital mammography). In the non-progressive model, on the contrary, digital screening would raise the number of overdiagnosed tumors by 43% (from 5336 cases at screen-film to 7607 cases at digital mammography).

Discussion

Digital mammography led to a statistically significant 80% increase in the number of screen-detected DCIS cases compared to screen-film

Table 2
Predicted breast cancer incidence, overdiagnosis and breast cancer deaths at screen-film and digital mammography screening.

	Screen-film mammography	Digital mammography
Baseline model		
Population aged 0–100 in 1990, with at least 1 screening examination between 1990 and 2020 (n)	1,000,000	1,000,000
Screening examinations, 1990–2020 (n)	5,632,810	5,628,930
Breast cancers, measured during the whole lifespan of the population (n)	92,413	92,801
Screen-detected breast cancers (n)	26,720	28,258
Overdiagnosed breast cancers (n)	1926	2327
Fraction of overdiagnosed breast cancers of all diagnosed breast cancers (%)	*2.1%*	*2.5%*
Fraction of overdiagnosed breast cancers of all screen-detected breast cancers (%)	*7.2%*	*8.2%*
Predicted breast cancer deaths, without screening, during the whole lifespan of the population (n)	28,971	28,971
Predicted breast cancer deaths, with screening, during the whole lifespan of the population (n)	22,394	22,106
Reduction in breast cancer deaths (n, %)	*6577 (22.7%)*	*6864 (23.7%)*
Progressive model	Screen-film mammography	Digital mammography
Population aged 0–100 in 1990, with at least 1 screening examination between 1990 and 2020 (n)	1,000,000	1,000,000
Screening examinations, 1990–2020 (n)	5,637,820	5,635,370
Breast cancers, measured during the whole lifespan of the population (n)	94,517	94,676
Screen-detected breast cancers (n)	25,279	26,674
Overdiagnosed breast cancers (n)	1168	1333
Fraction of overdiagnosed breast cancers of all diagnosed breast cancers (%)	*1.2%*	*1.4%*
Fraction of overdiagnosed breast cancers of all screen-detected breast cancers (%)	*4.6%*	*5.0%*
Predicted breast cancer deaths, without screening, during the whole lifespan of the population (n)	29,668	29,668
Predicted breast cancer deaths, with screening, during the whole lifespan of the population (n)	22,914	22,316
Reduction in breast cancer deaths (n, %)	*6753 (22.8%)*	*7351 (24.8%)*
Non-progressive model	Screen-film mammography	Digital mammography
Population aged 0–100 in 1990, with at least 1 screening examination between 1990 and 2020 (n)	1,000,000	1,000,000
Screening examinations, 1990–2020 (n)	5,628,200	5,620,920
Breast cancers, measured during the whole lifespan of the population (n)	96,504	98,778
Screen-detected breast cancers (n)	27,838	30,209
Overdiagnosed breast cancers (n)	5336	7607
Fraction of overdiagnosed breast cancers of all diagnosed breast cancers (%)	*5.5%*	*7.7%*
Fraction of overdiagnosed breast cancers of all screen-detected breast cancers (%)	*19.2%*	*25.2%*
Predicted breast cancer deaths, without screening, during the whole lifespan of the population (n)	28,758	28,758
Predicted breast cancer deaths, with screening, during the whole lifespan of the population (n)	22,777	22,776
Reduction in breast cancer deaths (n, %)	*5982 (20.8%)*	*5983 (20.8%)*

mammography, as observed in other studies (Del Turco et al., 2007; Vigeland et al., 2008). Using our baseline model we found an increased detection of DCIS could raise the number of prevented breast cancer deaths by 4.4%, and the number of overdiagnosed tumors by 21%. Such predictions, however, depend on the assumed progression and regression rate and the mean duration of preclinical screen-detectable DCIS.

DCIS is a heterogeneous disease and its natural history is poorly understood. The prevalence of DCIS observed in autopsy studies (0.2%–18%) suggests that not all cases become invasive (McCann et al., 2004). Most argue that all DCIS have the potential to progress, but that some cases are destined to grow faster and are associated with recurrence after local excision (Erbas et al., 2006; Tsikitis and Chung, 2006), invasion of the basement membrane (Feig, 2000), distant metastases after recurrence (Jones, 2006), and poor survival (Jones, 2006; Evans et al., 2001). Studies in the Netherlands found that between 47% and 54% of screen-detected DCIS are the more progressive, poorly differentiated 'high grade' type (Meijnen et al., 2005; Schouten van der Velden et al., 2007; de Roos et al., 2007); somewhat less than the 61% (11%/18%) progression rate used in our baseline model. The most direct evidence for DCIS progression comes from the follow-up of under-treated DCIS initially misdiagnosed as benign, in which 11%–60% women develop invasive cancer within 10–20 years (McCann et al., 2004). Further indication for DCIS progression consists of microscopic studies on DCIS, that showed basement membrane invasion in 15%–28% of the cases, and microscopy on invasive lesions that showed that DCIS was present in 20%–30% of the carcinomas (Feig, 2000). Because genetic and histological similarities were found between DCIS and recurrent invasive cancer (Erbas et al., 2006; Jones, 2006), it is thought that they share a common etiology. Because our two alternative models with extreme assumptions on progression and regression fit equally well to the observed breast cancer incidence and detection rates as the baseline model, our study could not provide information about the 'true' natural history of breast cancer.

Our predicted overdiagnosis rate of 2.1% at screen-film mammography and 2.5% at digital mammography (baseline model) was in line with estimates of between 1% and 3% from previous modeling studies (Duffy et al., 2005; de Koning et al., 2006), but much lower than recent estimates of around 50% (Morrell et al., 2010; Jorgensen and Gotzsche, 2009). Differences between overdiagnosis estimates may be explained by the length follow-up to allow for lead time, or by the denominator that is used to define the population at risk (De Gelder et al., accepted for publication; Puliti et al., this issue).

We may have underestimated the consequences of digital screening, because the 12% increase in the detection of invasive cancers, mostly attributable to T1a and T1b tumors, was not accounted for. However, this increase was non-significant. Recent data (including detection rates in 2007) showed that the detection of invasive cancers, particularly T1a, increased significantly at digital screening compared to screen-film mammography (National Evaluation Team for Breast cancer screening (NETB), 2009). If we would include this increase, the predicted number of breast cancer deaths would be 13% lower than at screen-film mammography, but the number of overdiagnosed cases 26% higher. Our findings may also have been affected by the additional CC views at subsequent digital mammograms in Drechtsteden. The breast cancer referral and detection rates at this unit were higher than in Utrecht or Heerenveen. Because additional CC views at subsequent examinations are increasingly indicated in the Netherlands, the breast cancer mortality reduction and overdiagnosis rate are unlikely to be strongly over-

estimated. In all three regions, referral rates peaked in 2004, while detection rates remained stable. This suggests that our estimates are not affected by a 'learning curve' effect. Our model was based on Dutch incidence and mortality data from 1990 to 2006, a period in which breast cancer patients may be treated by adjuvant systemic therapy (see Jatoi, this issue). This may have affected the screening effects to some extent.

Our analysis focused on the consequences of digital mammography among the targeted age group of 49–74 years old women. The Digital Mammographic Imaging Screening Trial (DMIST) suggested that digital mammography was more accurate than screen-film mammography for pre- and peri-menopausal women younger than 50 years with dense breasts (Pisano et al., 2005; Pisano et al., 2008). Younger women may therefore benefit more from digital mammography than the age group that was studied here. Presently, the effectiveness of screen-film mammography screening for women below age 50 is not sufficiently supported by scientific evidence (see Moss, this issue), but digital screening might change this.

Conclusion

The increased detection of DCIS by digital mammography screening could reduce breast cancer mortality by 4.4%, at a 21% increased overdiagnosis rate, but this is sensitive to assumptions on progression of DCIS.

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Authors' contributions

RdG, JF, GD and HdK were responsible for the conception and design of the study. JF acquired the study data. RdG, JF, EH, GD, HdK performed the study analysis. RdG, JF, EH, GD, HdK interpreted the data. RdG drafted all versions of the article; JF, EH, GdH, AV, MB, GD and HdK critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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Appendix 1. Estimated model parameters

Fraction of preclinical screen-detectable DCIS that progress, regress, or become clinically diagnosed in the absence of screening, and the estimated mean preclinical stage durations and test sensitivities at screen-film and digital mammography. The stage durations and the fraction of preclinical screen-detectable DCIS that progress to invasive cancer, the fraction that is clinically diagnosed and the fraction that regress are age-dependent. The parameters that are presented here are calculated for age 50.

	Baseline model	Progressive model	Non-progressive model
Fraction of tumors with a preclinical screen-detectable DCIS stage (%)	18%	100%	52%
that progress to preclinical invasive cancer in the absence of screening (%)	*11%*	*96%*	*0%*
that will be clinically diagnosed in the absence of screening (%)	*5%*	*4%*	*2%*
that regress in the absence of screening (%)	*2%*	*0%*	*50%*
Fraction of tumors without a preclinical screen-detectable DCIS stage (%)	82%	0%	48%
Duration of preclinical breast cancer per stage at age 50 (year)			
DCIS	5.2	0.4	0.5
invasive	2.6	2.6	2.6
Test sensitivity at screen-film mammography (%)			
DCIS	47	47	47
T1a	47	47	47
T1b	62	62	62
T1c	90	90	90
T2+	98	98	98
Test sensitivity at digital mammography (%)			
DCIS	100	94	72
T1a	47	47	47
T1b	62	62	62
T1c	90	90	90
T2+	98	98	98

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