Comparison of Digital Screening Mammography and Screen-Film Mammography in the Early Detection of Clinically Relevant Cancers: A Multicenter Study[1]

Adriana M. J. Bluekens, MD
Roland Holland, MD, PhD
Nico Karssemeijer, PhD
Mireille J. M. Broeders, PhD
Gerard J. den Heeten, MD, PhD

Purpose: To compare screen-film mammography with digital mammography in a breast cancer screening program, with a focus on the clinical relevance of detected cancers.

Materials and Methods: The study was approved by the regional medical ethics review board. Informed consent was not required. Before the nationwide transition to digital mammography in the Dutch biennial screening program, the performance of digital mammography was studied in three screening regions. For initial screening examinations, mediolateral oblique and craniocaudal views were obtained of each breast. In subsequent examinations, the mediolateral oblique view was standard. A craniocaudal view was added if indicated. Screening outcomes obtained with screen-film mammography and digital mammography, including radiologic and pathologic characteristics, were compared for initial and subsequent examinations.

Results: A total of 1198493 screening examinations were performed between 2003 and 2007. Recall was indicated in 18896 cases (screen-film mammography: 2.6% at initial examinations, 1.3% at subsequent examinations; digital mammography: 4.4% at initial examinations, 2.1% at subsequent examinations; $P < .001$ for both). Breast cancer was diagnosed in 6410 women (detection rate per 1000 women with screen-film mammography: 5.6 at initial examinations, 5.2 at subsequent examinations; detection rate per 1000 women with digital mammography: 6.8 at initial examinations, 6.1 at subsequent examinations; $P = .02$ and $P < .001$, respectively). Digital mammography depicted significantly more ductal carcinoma in situ (DCIS) lesions, irrespective of screening round. Invasive carcinoma was detected significantly more often in subsequent examinations, particularly when associated with microcalcifications ($P = .047$). The distribution of the histopathologic differentiation grades for DCIS and invasive carcinoma were similar with both modalities. However, with digital mammography more high-grade DCIS lesions were detected at subsequent examinations ($P = .013$).

Conclusion: In a population-based breast screening program, the performance of digital mammography in the detection of DCIS and invasive carcinoma was substantially better than that of screen-film mammography. There is no sign of an increase in detection of low-grade DCIS lesions—indicative of possible overdiagnosis—with digital breast cancer screening. Rather, digital mammography appears to add to the detection of high-grade DCIS.

[1] From the National Expert and Training Centre for Breast Cancer Screening, PO Box 6873, 6503 GJ Nijmegen, the Netherlands (A.M.J.B., R.H., M.J.M.B., G.J.d.H.); Department of Radiology, St. Elisabeth Hospital, Tilburg, the Netherlands (A.M.J.B.); Department of Radiology (N.K.) and Department of Epidemiology, Biostatistics and HTA (M.J.M.B.), Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; and Department of Radiology, Academic Medical Centre, Amsterdam, the Netherlands (G.J.d.H.). Received September 1, 2011; revision requested October 17; revision received April 2, 2012; accepted April 25; final version accepted June 25. **Address correspondence to** A.M.J.B. (e-mail: *a.bluekens@lrcb.umcn.nl*).

The ultimate goal of screening mammography is to reduce the stage at which cancers are detected and treated, resulting in improved survival. With this ambition, population-based breast cancer screening was initiated in the Netherlands in 1989. In the years that followed, the Dutch screening program has proved to be successful (1). Compared with data from the years just before the start of the nationwide screening, breast cancer mortality rates in women aged 55–74 years decreased substantially after 1997, reaching a low of 31% in 2009 (2)—an effect similar to that in other countries in Western Europe and North America (3).

Despite this distinct success, concerns have been raised about possible harms of mammography screening programs—in particular the overdiagnosis of breast cancer; that is, the diagnosis of cancer that, if left undetected and therefore untreated, would never have surfaced clinically in the person's lifetime. The large increase in the incidence of ductal carcinoma in situ (DCIS) in the years after the introduction of population-based screening (4–6) was the basis for this concern. However, the implementation of digital mammography in breast cancer screening seems to be associated with further increases in the incidence of DCIS. Large studies comparing screen-film mammography to digital mammography showed such an effect (7–11), sparking the debate about overdiagnosis in breast cancer screening programs.

Some researchers state that DCIS, as a precursor of invasive breast cancer, is the ideal screening target (12). Critics of breast cancer screening, on the other hand, often argue that high detection rates of DCIS represent overdiagnosis, claiming that many cases are biologically unimportant (13,14).

Such criticism, however, seems to be unfounded without data about the characteristics of the detected lesions. After all, DCIS is considered to be a heterogeneous disease with varying morphology and behavior, ranging from rather indolent lesions to aggressively growing DCIS with invasive components (15,16). To date, standardized analysis of nuclear grade and associated necrosis is used to classify DCIS according to biologic potential and separate it into three risk groups: low, intermediate, and high grade (17,18). Because high-grade DCIS is more aggressive and often associated with invasive disease, the detection of these lesions in screening is likely to be of great importance in the prevention of life-threatening invasive cancer (19).

In population-based screening programs, most detected DCIS lesions are high grade (19,20). However, with the advent of digital mammography in breast screening and the associated increase in DCIS detection, it is uncertain whether this favorable distribution of subtypes in screening-detected DCIS still holds. To our knowledge, detailed data concerning the pathologic characteristics of both in situ and invasive cancers detected at digital mammography screening have not yet been published.

The aim of our large observational study was to compare screen-film mammography and digital mammography in a breast cancer screening program, with a focus on the clinical relevance of cancers.

Advances in Knowledge

- The performance of digital mammography in screening is substantially better than that of screen-film mammography with regard to the detection of both ductal carcinoma in situ (DCIS) (detection rates: 0.2 vs 0.1 per 1000 women in initial examinations, 1.1 vs 0.7 per 1000 women in subsequent examinations) and invasive carcinoma (detection rates: 0.8 vs 0.6 per 1000 women in initial examinations, 4.1 vs 3.8 per 1000 women in subsequent examinations).
- The improved detection of DCIS with digital mammography is seen throughout the histopathologic grading spectrum, without an increase in the proportion of low-grade DCIS (14.4% with either modality).
- Digital mammography seems to add to the detection of high-grade DCIS (58.5% vs 50.5% of DCIS detected with conventional screening).

Implication for Patient Care

- Digital screening mammography demonstrates advantages in the early detection of breast cancer by increasing the detection of clinically relevant cancers while keeping potential overdiagnosis low.

Materials and Methods

The study was approved by a medical ethics review board. To comply with privacy regulations, all women signed a general informed consent form permitting the use of data for evaluation and scientific research. Specific written informed consent for this study was not required.

Setting

In anticipation of the nationwide transition from conventional to digital mammography in the Dutch screening program, three pilot studies were set up in 2003–2004 to test the quality of digital screening and the organizational consequences of implementation.

The results of one of these pilot studies have been used to analyze the screening performance of digital mammography and led to previous publications (10,21). The current observational study encompasses the results of all three digital

Published online before print
10.1148/radiol.12111461 **Content code:** BR

Radiology 2012; 265:707–714

Abbreviation:
DCIS = ductal carcinoma in situ

Author contributions:
Guarantors of integrity of entire study, A.M.J.B., R.H., M.J.M.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final versions approval, all authors; literature research, A.M.J.B., R.H.; statistical analysis, A.M.J.B., R.H.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

mammography pilot studies conducted from October 2003 to December 2007 at the screening centers of Preventicon (Utrecht, the Netherlands), SBBZWN (Rotterdam, the Netherlands), and BBNN (Groningen, the Netherlands).

At the start of the pilot studies, digital mammography was introduced at each participating center by replacing at least one of the conventional units with a digital mammography system. All other conventional units were kept operational. The pilot studies were part of the national screening program in which all women aged 50–75 years receive a personal invitation to participate in screening every 2 years. Women are invited according to postal code and assigned to the nearest screening center. It is not possible for a woman to self-select her screening location. The screening program specifically targets asymptomatic women. The technicians are instructed and trained not to screen symptomatic women but to refer them to their general practitioners instead. Details concerning the Dutch screening program have been reported previously (22,23).

Participants

Between October 2003 and December 2007, all women attending the screening program at the participating centers were included in the study. If both modalities were present at the same screening location, assignment of women to digital mammography or screen-film mammography was based on the availability of the units when participants presented to the screening center. However, women who had previously undergone digital screening mammography were always offered digital mammography. In other cases, the assigned screening location determined the modality used.

All women invited for screening were informed in writing about the possibility of undergoing digital mammography. Refusing digital mammography for any reason did not have any consequences for screening participation and hardly ever occurred.

Procedures

The three screening centers worked independently and were responsible for imaging, reading, and recall for diagnostic work-up.

Conventional images were acquired with one of five different systems: GE 600 and 800T (GE Healthcare, Buc, France), Instrumentarium Alpha RT (Instrumentarium, Tuusula, Finland), Planmed Nuance (Planmed, Helsinki, Finland)—all of which used the Min-R 2000/Min-R 2250 screen-film combination (Kodak, Rochester, NY)—and Mammomat 3000 (Siemens, Erlangen, Germany), which used the Agfa HDR/MR Detail-R screen-film combination (Agfa-Gevaert, Mortsel, Belgium). Three different systems were used to acquire digital images: Lorad Selenia (Hologic, Danbury, Conn), Embrace DM1000 (Agfa-Gevaert), both of which used a 70-μm pixel size and a 24 × 29-cm field of view, and Lorad M-IV (Hologic) with a Profect CS reader and HR-BD screens (Fuji, Tokyo, Japan), which used a 50-μm pixel size and 18 × 24-cm and 24 × 30-cm fields of view.

For initial screening examinations, mediolateral oblique and craniocaudal views were obtained. The standard subsequent examination consisted of mediolateral oblique views only. A craniocaudal view was added when indicated (in 40%–50% of cases) by using criteria based on breast density and visible abnormality. One screening center, however, routinely obtained both views in first as well as subsequent screening examinations. In case of a subsequent screening examination, previously obtained mammograms were available for comparison at all times in all three screening centers. Computer-aided diagnosis was optional in one of the screening centers, as described in our previous report (10).

Only certified and well-trained radiologists, who read 3000–5000 screening mammograms per year, performed the readings throughout the study period. Two radiologists read and rated the images independently. According to the current Dutch screening protocol, recall was indicated in cases of incomplete examination (Breast Imaging Reporting and Data System [BI-RADS] score 0) or suspicious findings (BI-RADS score ≥4). In cases of discordance, the final decision on recall was attained by consensus.

Data Collection

Study data were collected from the database of the national breast cancer screening program, which included radiology reports and pathologic tumor characteristics and staging data.

Radiologic abnormalities were classified as a mass, a mass with calcifications, microcalcifications only, or other (eg, architectural distortion and asymmetry). In one of the pilot studies, part of the radiology reports from the screen-film mammography group was not stored electronically. For the same reason, a small part of the radiologic digital mammography data was missing as well. Because these data could not be retrieved otherwise, we compared the distribution of radiologic features for the screen-film mammography group, both including and excluding the data from this pilot study, and found them to be remarkably similar. We therefore believe the missing data to be random and included the pilot study's data in the overall analysis.

The source of data about pathologic tumor characteristics was the original pathology report. Central pathologic review was not carried out. Pathologic characteristics of two pilot studies could be assembled from the screening database complemented by data from PALGA, the nationwide network and archive of pathology reports. One pilot region, however, was not connected to PALGA. Therefore, detailed pathology data had to be extracted from reports obtained from the individual pathology laboratories. To make this practically feasible, we chose to retrieve the data for all digital mammography cases and a random sample of the screen-film mammography cases (equal in size to the number of digital mammography cases). The sample of screen-film mammography cases was appropriately weighted by initial and subsequent examinations. Histologic type and grade of the tumors were recorded. In situ carcinomas were classified on the basis of nuclear grade and necrosis (17,18), whereas invasive

Table 1

Screening Performance of Screen-Film Mammography and Digital Mammography at Initial and Subsequent Examinations

Variable	Screen-Film Mammography	Digital Mammography	*P* Value
Screened women*	1 045 978	152 515	
Initial screening examination	127 521 (12.2)	22 860 (15.0)	<.001
Subsequent screening examination	918 457 (87.8)	129 655 (85.0)	<.001
Recalled women*	15 238	3658	
Initial screening examination	3278 (2.6)	1002 (4.4)	<.001
Subsequent screening examination	11 960 (1.3)	2656 (2.0)	<.001
No. of breast cancers detected†	5468	942	
Initial screening examination	711 (5.6)	156 (6.8)	.022
Subsequent screening examination	4757 (5.2)	786 (6.1)	<.001
Positive predictive value of recall (%)‡	35.9	25.8	
Initial screening examination	21.7	15.6	<.001
Subsequent screening examination	39.8	29.6	<.001

* Data are numbers of women. Numbers in parentheses are percentages (values have been rounded).

† Data are numbers of women. Numbers in parentheses are rates per 1000 women screened.

‡ Data are the proportion of recalled patients with cancer.

carcinoma was classified on the basis of the Bloom and Richardson grading system modified by Elston and Ellis, all according to the World Health Organization classification system (24). Staging data were recorded according to the TNM classification system developed by the International Union against Cancer (25). In addition to separate T and N staging, two categories were created: T1N0 (small tumors without lymph node involvement) and >T1N0 (tumors >20 mm and/or those with lymph node involvement).

Statistical Analysis

Groups were compared for baseline characteristics such as age and screening interval. Screening intervals longer than 36 months were not taken into account because they were indicative of a missed screening round. We compared the two screening modalities with respect to breast cancer detection rate, recall rate, and positive predictive value for recall. Furthermore, differences in radiologic and pathologic characteristics of detected cancers were evaluated. Study results were evaluated separately for initial and subsequent screening examinations, thereby avoiding possible bias caused by any imbalance in the number of initial and subsequent examinations between both groups.

Software was used for data management and analysis (SPSS, version 16.0 for Windows; SPSS, Chicago, Ill). Descriptive statistics were applied to explore the radiologic and pathologic characteristics of the lesions. Means were compared with an independent two-sample *t* test, whereas categorical variables were compared by using the Pearson χ^2 test. $P \leq .05$ was considered indicative of a statistically significant difference.

Results

During the study period, 1 198 493 screening examinations were performed, which consisted of 1 045 978 screen-film mammography examinations (87.3%) and 152 515 digital mammography examinations (12.7%). Recall was indicated in 18 896 cases.

The mean age of recalled women at the time of the screening examination was 60.5 years for the screen-film mammography group and 59.3 years for the digital mammography group ($P < .001$). The mean age of women diagnosed with cancer was also lower in the digital mammography group than in the screen-film mammography group (61.4 and 62.3 years, respectively). This trend was true for both patients with in situ carcinoma (mean age, 60.1 and 60.9 years) and those with invasive carcinoma (mean age, 61.7 and 62.6 years). The screening interval (range, 18–36 months) was comparable for the digital mammography and screen-film mammography groups, with means of 24.9 and 24.3 months, respectively ($P < .001$).

A total of 15 238 women in the screen-film mammography group and 3658 women in the digital mammography group were recalled. Overall rates are not presented because an imbalance in the number of initial and subsequent examinations between both groups might create a bias. Recall rates were lower for screen-film mammography (2.6% for initial examinations, 1.3% for subsequent examinations) than for digital mammography (4.4% for initial examinations, 2.1% for subsequent examinations), and both differed significantly ($P < .001$) (Table 1).

Significantly more cancers were detected with digital mammography than with screen-film mammography, both for initial ($P = .022$) and subsequent ($P < .001$) screening examinations. For initial screening examinations, the detection rate per 1000 women was 5.6 with screen-film mammography and 6.8 with digital mammography. The difference in detection for subsequent screening examinations was also in favor of digital mammography, with respective rates of 5.2 and 6.1 per 1000 women.

The positive predictive value of recall was significantly lower for digital mammography than for screen-film mammography in both initial (15.6% vs 21.7%, respectively) and subsequent (29.6% vs 39.8%, respectively) screening examinations.

The proportion of lesions recalled on the basis of microcalcifications was significantly higher in the digital mammography group, with relatively fewer recalls based on mammographic masses (Table 2). With conventional mammography, 19.6% of all recalled lesions were based on microcalcifications withoutan associated density, whereas with digital

mammography 31.1% were based on microcalcifications alone.

Overall, a mass with microcalcifications was the radiologic feature with the highest positive predictive value for recall. With digital mammography, 48.1% were positive at diagnostic work-up, of which 86.3% concerned invasive carcinoma and 13.7% DCIS. Conversely, approximately one-fourth of recalled masses only or microcalcifications only were true positive (24.6% and 23.3%, respectively).

The detection of invasive carcinoma based on masses associated with microcalcifications was significantly better with digital mammography than with screen-film mammography ($P = .047$). The detection of DCIS on the basis of microcalcifications tended to be better as well.

With digital mammography, in both initial and subsequent examinations, significantly more DCIS was detected ($P = .002$ and $P < .001$, respectively). In addition, relatively more invasive cancers were detected with digital mammography, but the difference was only significant for initial screening examinations ($P < .001$) (Table 3). This higher detection of invasive cancers was completely accounted for by ductal carcinoma ($P = .010$), whereas the detection of lobular carcinoma and other subtypes was similar for both modalities ($P = .527$ and $P = .105$, respectively). Table 4 shows that most invasive cancers were small and nonadvanced, as judged by the proportion classified as T1N0. In this category, marginally more cancers were detected with digital mammography than with screen-film mammography (63.6% vs 61.7%, respectively; $P = .347$). In general, tumor stages were comparable.

Overall, the histopathologic grade distribution of DCIS did not differ significantly between the two modalities ($P = .105$). The share of low-grade (grade 1) DCIS was the same for both screening modalities (14.4%). The relative amount of high-grade DCIS was higher with digital mammography, primarily in subsequent screening examinations ($P = .013$, Table 5). The poorly differentiated type of DCIS (grade 3) occurred most often and accounted for 58.5% of all digitally detected in situ carcinomas (compared with 50.5% at conventional screening). High-grade DCIS lesions most often manifested as microcalcifications (90.0%).

The overall distribution of the subtypes of invasive carcinoma was similar for both modalities ($P = .122$). In screening-detected invasive carcinoma, the moderately differentiated type (grade 2) was most frequent. The proportion of well-differentiated grade 1 invasive carcinoma was higher with digital mammography than with screen-film mammography (33.2% vs 29.7%, respectively) owing to the detection of significantly more grade 1 lesions in initial screening examinations ($P < .001$, Table 5).

Table 2

Radiologic Characteristics of All Recalled Lesions and Detected Cancers

Variable	Screen-Film Mammography*	Digital Mammography*	*P* Value
Recalled lesions (benign and malignant)			
Mass	6820 (65.4)	1883 (57.3)	<.001
Mass with microcalcifications	953 (9.1)	266 (8.1)	.067
Microcalcifications only	2047 (19.6)	1022 (31.1)	<.001
Other	603 (5.8)	113 (3.4)	<.001
Detected DCIS			
Mass	59 (11.4)	18 (9.9)	.598
Mass with microcalcifications	46 (8.9)	17 (9.4)	.830
Microcalcifications only	409 (78.8)	144 (79.6)	.831
Other	5 (1.0)	2 (1.1)	.869

* Data are numbers of women. Numbers in parentheses are percentages (values have been rounded). Missing values were ignored when estimating percentages.

Table 3

Histopathologic Characteristics of Detected Cancers at Initial and Subsequent Examinations

Variable	Screen-Film Mammography	Digital Mammography	*P* Value
DCIS*	679 (15.4)	195 (20.9)	
Initial screening examination†	104 (0.1)	34 (0.2)	.002
Subsequent screening examination†	575 (0.7)	161 (1.1)	<.001
Invasive carcinoma*	3732 (84.6)	740 (79.1)	
Initial screening examination†	474 (0.6)	121 (0.8)	<.001
Subsequent screening examination†	3258 (3.8)	619 (4.1)	.185

Note.—Missing values (positive findings without a specified diagnosis) were as follows: SBBZWN screening center: 0.5% screen-film mammography, 0.8% digital mammography; BBNN screening center: 0.2% screen-film mammography, 0% digital mammography; Preventicon screening center: 0.6% screen-film mammography, 0.6% digital mammography.

* Data are numbers of women. Numbers in parentheses are percentages.

† Data are numbers of women. Numbers in parentheses are rates per 1000 women screened.

Discussion

Results of our study showed that digital mammography is superior to screen-film mammography in the screening setting in the early detection of clinically relevant cancers. Similar to what was found in other studies, the sensitivity of digital mammography was higher than that of screen-film mammography (8–10,26). More DCIS and invasive ductal carcinomas were detected with digital screening, the latter particularly when associated with microcalcifications. Therefore, the enhanced depiction of microcalcifications on digital images has most likely added to its higher

Table 4

Staging Data for Detected Invasive Cancers

Variable	Screen-Film Mammography	Digital Mammography	*P* Value*
T stage			
T1	3519 (79.3)	595 (80.8)	.335
T2	866 (19.5)	132 (17.9)	
T3	48 (1.1)	9 (1.2)	
T4	5 (0.1)	0 (0)	
Missing values	69	10	
N stage			
N0	3044 (71.6)	535 (71.4)	.943
N1 (mic)	981 (23.1)	190 (25.4)	
N2	153 (3.6)	20 (2.7)	
N3	76 (1.8)	4 (0.5)	
Missing values	96	19	
Tumor category			
T1N0	2709 (61.7)	463 (63.6)	.327
>T1N0	1682 (38.3)	265 (36.4)	

Note.—Tumor stage was determined with the TNM classification system developed by the International Union against Cancer. Data are numbers of women. Numbers in parentheses are percentages (values have been rounded).
* Calculated for all detected invasive carcinomas.

Table 5

Histopathologic Grade of Differentiation of Detected Cancers at Initial and Subsequent Examinations

Variable	Screen-Film Mammography*	Digital Mammography*	*P* Value
DCIS	679	195	
Grade 1	98 (14.4)	28 (14.4)	
Initial screening examination	22	10	.216
Subsequent screening examination	76	18	.436
Grade 2	221 (32.5)	49 (25.1)	
Initial screening examination	33	13	.319
Subsequent screening examinations	188	36	.009
Grade 3	343 (50.5)	114 (58.5)	
Initial screening examination	49	10	.306
Subsequent screening examination	294	104	.013
Missing/not assessed	17 (2.5)	4 (2.1)	
Overall distribution	…	…	.105
Invasive carcinoma	3732	740	
Grade 1	1110 (29.7)	246 (33.2)	
Initial screening examination	130	50	<.001
Subsequent screening examination	980	196	.898
Grade 2	1734 (46.5)	330 (44.6)	
Initial screening examination	225	44	.931
Subsequent screening examination	1509	286	.365
Grade 3	777 (20.8)	139 (18.8)	
Initial screening examination	106	23	.691
Subsequent screening examination	671	116	.133
Missing/not assessed	111 (3.0)	25 (3.4)	
Overall distribution	…	…	.122

* Data are numbers of women. Numbers in parentheses are percentages (values have been rounded).

detection performance. The histologic profile of these cancers, however, did not differ between the two screening modalities.

Consistent with our previous work (10) as well as with other studies evaluating screening programs (8,26,27), we found recall rates to be higher with digital mammography. This in turn led to lower positive predictive values of recall in initial and subsequent screening examinations. It is noteworthy, however, that the recall rates might be slightly overestimated because calculations were based on the complete study period, including the first months after the introduction of digital mammography—which are typically characterized by disproportionately high rates of recall (21). Nevertheless, the recall rates remain relatively low in comparison to those of other breast cancer screening programs. Considering the work by Otten et al (28), the high recall rates might have had a positive effect on cancer detection at digital mammography, but it is very unlikely that the high detection rates seen with digital mammography in our study were caused by this effect alone.

The aim of screening is not to detect cancer as such, although that is its mechanism: The point of screening is to prevent tumor progression to disseminating, metastatic cancers (29). Hence, depending on the biologic potential of cancers, early detection is only beneficial as long as it contributes to a decrease in cancer mortality and morbidity. All other diagnoses of malignancies could be termed overdiagnosis, which is the diagnosis of cancer that, if left undetected and therefore untreated, would never have surfaced clinically in a person's lifetime.

Overdiagnosis is an inevitable side effect of every screening program. In breast cancer screening, it is accepted because the benefits clearly outweigh the harms (30,31). However, overdiagnosis continues to be cited by critics of screening who assume that with the introduction of digital mammography in screening even more clinically unimportant cancers will be detected (32).

Potential candidates for overdiagnosis are present predominantly in the group of noninvasive cancers (DCIS), typically

of the well-differentiated, low-grade type. Although all grades have potential to progress and become invasive (33), the development of low-grade DCIS can extend over more than 3 decades (34), whereas high-grade DCIS is associated with far more rapid cancer invasion (16).

Although the biologic indolence of low-grade DCIS makes detection of this subtype less important in mass screening, the detection of high-grade DCIS might contribute to mortality reduction by preventing development of life-threatening invasive carcinoma.

We did not find a significant difference in the overall distribution of differentiation subtypes of both DCIS and invasive cancers detected with digital mammography and screen-film mammography. This similarity indicates that the increased detection with digital mammography covers the complete spectrum of breast cancer. According to our data, there is no sign of a disproportionate increase in low-grade DCIS lesions—indicative of possible overdiagnosis—with the transition to digital mammography in breast cancer screening.

When observed as separate entities, low-grade DCIS accounted for 14.4% of all DCIS cases with both modalities in our study. This means that although detection rates increased with digital mammography, still only 3.0% of all digital screening–detected cancers involved low-grade DCIS. Consistent with previous studies, screening-detected DCIS predominantly concerned high-grade lesions (5,19). We observed the detection of high-grade DCIS to be higher with digital mammography than with screen-film mammography (58.5% vs 50.5%, respectively), particularly as a result of a significantly better detection at subsequent screening examinations. Although the overall distribution did not change significantly, this might imply a more favorable subtype profile of screening-detected DCIS with digital mammography.

Because cancers associated with microcalcifications are more often detected with digital mammography, our findings suggest that the improvement in detection performance with digital mammography is primarily due to better depiction of microcalcifications. Recently, other researchers have reported similar results (35,36).

Our study has some limitations. Because digital mammography was used in a pilot setting, most of the screening examinations were performed with conventional units. This was reflected in our study population, where screen-film mammography represented 87.3% of the cases. Because the study was not to interfere with the ongoing screening program, matching all baseline characteristics in the three digital pilot studies was not feasible. Regional differences in screening setup were foreseen and accepted because this study had to be purely observational to evaluate the digital program in daily practice. Even though the results for each screening center showed similar trends, this site-to-site variability might have had an influence on screening performance. It is unlikely, however, that this had any effect on the distribution of detected cancer subtypes. Another drawback is the missing radiology data for screen-film examinations in one pilot study. However, because we found the results to be quite similar whether including or excluding the data from this pilot study, we felt reassured that the missing values represent a random sample and do not compromise the validity of our study. The source of data on pathologic tumor characteristics was the original pathology report. No central pathologic review was carried out, which may influence the consistency of histologic grading. One pilot region was not connected to the nationwide network and archive of pathology reports. Therefore, detailed pathology data had to be extracted from reports obtained from the individual pathology laboratories. To make this practically feasible, we chose to retrieve the data for all digital mammography cases and an equal random sample of the screen-film mammography cases.

The setup of the Dutch screening program differs in some aspects (eg, number of views, screening interval, and low recall rate) from other screening programs such as that in the United States. For the Dutch program, the focus is on a financially and socially acceptable balance between detection, recall, and false-positive rate, whereas the U.S. approach focuses more on a high detection rate, resulting in higher recall and false-positive rates. This is also reflected in the types of lesions that are detected (eg, higher detection of low-grade DCIS) (37). These differences should be kept in mind when comparing results among the Dutch, U.S., and other screening programs.

This large multicenter study, similar to previous studies, showed digital mammography to have a significantly better detection performance than screen-film mammography in population-based breast cancer screening. This gain is largely due to enhanced depiction of microcalcifications, resulting in improved detection of both DCIS and invasive carcinoma. Although, as with screen-film mammography, digitally detected DCIS predominantly consisted of high-grade lesions, the detection of low-grade DCIS in digital screening remained fairly uncommon. The overall distribution of subtypes according to differentiation grade did not change significantly with use of digital mammography. This finding suggests that presumed overdiagnosis does not increase with the use of digital mammography in breast cancer screening programs.

Acknowledgments: Special thanks to A. Bartels-Kortland (Preventicon), J. Reijerink (SB-BZWN), and J. H. Sangers (BBNN), as the then directors of the participating screening centers, for facilitating the digital pilots.

Disclosures of Conflicts of Interest: A.M.J.B. No relevant conflicts of interest to disclose. **R.H.** No relevant conflicts of interest to disclose. **N.K.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution has a grant or grant pending from Matakina Technology and Riverain Medical; institution received money for patent (planned, pending, or issued) from Mevis Medical Solutions; has stock in Matakina Technology. Other relationships: none to disclose. **M.J.M.B.** No relevant conflicts of interest to disclose. **G.J.d.H.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution received money for consultancy from Philips ICT Research; received payment for lectures including service on speakers bureaus from Philips ICT Research. Other relationships: none to disclose.

References

1. Fracheboud J, Otto SJ, van Dijck JA, et al. Decreased rates of advanced breast cancer due to mammography screening in the

Netherlands. Br J Cancer 2004;91(5):861–867.

2. National Evaluation Team for Breast Cancer Screening. Interim report 2011. Main results 2008–2009 breast cancer screening programme in the Netherlands. Rotterdam, the Netherlands: Department of Public Health, Erasmus University, 2011.
3. de Koning HJ, Draisma G, Fracheboud J, de Bruijn A. Overdiagnosis and overtreatment of breast cancer: microsimulation modelling estimates based on observed screen and clinical data. Breast Cancer Res 2006;8(1):202.
4. Ernster VL, Ballard-Barbash R, Barlow WE, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. J Natl Cancer Inst 2002;94(20):1546–1554.
5. Sørum R, Hofvind S, Skaane P, Haldorsen T. Trends in incidence of ductal carcinoma in situ: the effect of a population-based screening programme. Breast 2010;19(6):499–505.
6. van Steenbergen LN, Voogd AC, Roukema JA, et al. Screening caused rising incidence rates of ductal carcinoma in situ of the breast. Breast Cancer Res Treat 2009;115(1):181–183.
7. Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005;353(17):1773–1783.
8. 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(3):708–717.
9. Vigeland E, Klaasen H, Klingen TA, Hofvind S, Skaane P. Full-field digital mammography compared to screen film mammography in the prevalent round of a population-based screening programme: the Vestfold County Study. Eur Radiol 2008;18(1):183–191.
10. Karssemeijer N, Bluekens AM, Beijerinck D, et al. Breast cancer screening results 5 years after introduction of digital mammography in a population-based screening program. Radiology 2009;253(2):353–358.
11. Domingo L, Romero A, Belvis F, et al. Differences in radiological patterns, tumour characteristics and diagnostic precision between digital mammography and screen-film mammography in four breast cancer screening programmes in Spain. Eur Radiol 2011;21(9):2020–2028.
12. Cady B. How to prevent invasive breast cancer: detect and excise duct carcinoma in situ. J Surg Oncol 1998;69(2):60–62.
13. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2009;(4):CD001877.
14. Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. BMJ 2009;339:b2587.
15. Patchefsky AS, Schwartz GF, Finkelstein SD, et al. Heterogeneity of intraductal carcinoma of the breast. Cancer 1989;63(4):731–741.
16. Lagios MD. Heterogeneity of duct carcinoma in situ (DCIS): relationship of grade and subtype analysis to local recurrence and risk of invasive transformation. Cancer Lett 1995;90(1):97–102.
17. Holland R, Peterse JL, Millis RR, et al. Ductal carcinoma in situ: a proposal for a new classification. Semin Diagn Pathol 1994;11(3):167–180.
18. Silverstein MJ, Lagios MD, Craig PH, et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer 1996;77(11):2267–2274.
19. Evans AJ, Pinder SE, Ellis IO, Wilson AR. Screen detected ductal carcinoma in situ (DCIS): overdiagnosis or an obligate precursor of invasive disease? J Med Screen 2001;8(3):149–151.
20. Kessar P, Perry N, Vinnicombe SJ, Hussain HK, Carpenter R, Wells CA. How significant is detection of ductal carcinoma in situ in a breast screening programme? Clin Radiol 2002;57(9):807–814.
21. Bluekens AM, Karssemeijer N, Beijerinck D, et al. Consequences of digital mammography in population-based breast cancer screening: initial changes and long-term impact on referral rates. Eur Radio. 2010;20(9):2067–2073.
22. Fracheboud J, de Koning HJ, Beemsterboer PM, et al. Nation-wide breast cancer screening in the Netherlands: results of initial and subsequent screening 1990–1995. National Evaluation Team for Breast Cancer Screening. Int J Cancer 1998;75(5):694–698.
23. Holland R, Rijken H, Hendriks J. The Dutch population-based mammography screening: 30-year experience. Breast Care 2007;2(1):12–18.
24. Devilee P, Tavassoli FA. World Health Organization: tumours of the breast and female genital organs. Oxford, England: Oxford University Press, 2003.
25. Sobin LH, Wittekind C. TNM classification of malignant tumours. 6th ed. New York, NY: Wiley, 2002.
26. Hambly NM, McNicholas MM, Phelan N, Hargaden GC, O'Doherty A, Flanagan FL. Comparison of digital mammography and screen-film mammography in breast cancer screening: a review in the Irish breast screening program. AJR Am J Roentgenol 2009;193(4):1010–1018.
27. Del Turco MR, Mantellini P, Ciatto S, et al. Full-field digital versus screen-film mammography: comparative accuracy in concurrent screening cohorts. AJR Am J Roentgenol 2007;189(4):860–866.
28. Otten JD, Karssemeijer N, Hendriks JH, et al. Effect of recall rate on earlier screen detection of breast cancers based on the Dutch performance indicators. J Natl Cancer Inst 2005;97(10):748–754.
29. Smith RA, Duffy SW, Gabe R, Tabar L, Yen AM, Chen TH. The randomized trials of breast cancer screening: what have we learned? Radiol Clin North Am 2004;42(5):793–806, v.
30. Duffy SW, Tabar L, Olsen AH, et al. Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England. J Med Screen 2010;17(1):25–30.
31. Kopans DB, Smith RA, Duffy SW. Mammographic screening and "overdiagnosis". Radiology 2011;260(3):616–620.
32. Jørgensen KJ, Keen JD, Gøtzsche PC. Is mammographic screening justifiable considering its substantial overdiagnosis rate and minor effect on mortality? Radiology 2011;260(3):621–627.
33. Jones JL. Overdiagnosis and overtreatment of breast cancer: progression of ductal carcinoma in situ: the pathological perspective. Breast Cancer Res 2006;8(2):204.
34. Sanders ME, Schuyler PA, Dupont WD, Page DL. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer 2005;103(12):2481–2484.
35. 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(4):676–682.
36. Feeley L, Kiernan D, Mooney T, et al. Digital mammography in a screening programme and its implications for pathology: a comparative study. J Clin Pathol 2011;64(3):215–219.
37. Hofvind S, Vacek PM, Skelly J, Weaver DL, Geller BM. Comparing screening mammography for early breast cancer detection in Vermont and Norway. J Natl Cancer Inst 2008;100(15):1082–1091.