Radiology

A Randomized Trial Comparing Breast Cancer Incidence and Interval Cancers after Tomosynthesis Plus Mammography versus Mammography Alone

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

See also the editorial by Lee and Ray in this issue.

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Background: Adding digital breast tomosynthesis (DBT) to digital mammography (DM) improves breast cancer screening sensitivity, but how this impacts mortality and other end points is unknown.

Purpose: To compare interval and overall breast cancer incidence after screening with DBT plus DM versus DM alone.

Materials and Methods: In this prospective trial (RETomo), women attending screening were randomized to one round of DBT plus DM (experimental arm) or to DM (control arm). All were then rescreened with DM after 12 months (women aged 45–49 years) or after 24 months (50–69 years). The primary outcome was interval cancer incidence. Cumulative incidence up to the subsequent screening round plus 9 months (21- and 33-month follow-up for women aged 45–49 and 50–69, respectively) was also reported. Ductal carcinomas in situ are included. Subgroup analyses by age and breast density were conducted; 95% CIs computed according to binomial distribution are reported.

Results: Baseline cancer detection was higher in the DBT plu DM arm than DM arm (101 of 13 356 women vs 61 of 13 521 women; relative detection, 1.7 [95% CI: 1.2, 2.3]). The mean age ± standard deviation for the women in both arms was 55 years ± 7. Interval cancer incidence was similar in the two arms (21 vs 22 cancers; relative incidence, 0.97 [95% CI: 0.53, 1.8]). Cumulative incidence remained higher in the DBT plus DM arm in women over 50 (153 vs 124 cancers; relative incidence, 1.2 [95% CI: 0.99, 1.6]), while it was similar in the two arms in women aged 45–49 (36 vs 41 cancers; relative incidence, 0.89 [95% CI: 0.57, 1.4]).

Conclusion: In women younger than 50 years, the benefit of early diagnosis seemed to be appreciable, while for women over age 50, the higher sensitivity of tomosynthesis plus mammography was not matched by a subsequent reduction in cancers at the next screening examination or in the intervening interval.

Clinical trial registration no. NCT02698202

Online supplemental material is available for this article.

Digital breast tomosynthesis (DBT) has been shown to be more sensitive than digital mammography (DM) both in double testing studies and randomized trials (2), with only one exception (3). On the other hand, specificity improved in programs where the recall rate with mammography was high, as in most studies in the United States. However, specificity was unaffected or slightly higher where recall rates were low, as in most European studies (2). Thus, higher sensitivity provides the opportunity to improve the desirable effects of screening by way of earlier diagnosis and possibly improved prognosis without more false-positive results. DBT is used in screening practice in the United States (in around 50% of screening tests in 2017) (4) and is considered an option by most guidelines (5,6), but not all (7). What is still unknown is the impact of DBT on subsequent incidence and mortality. Ideally, to assess the real benefits and harms of screening with DBT, we should compare the outcomes in two cohorts of women (one screened with DBT and one with mammography, until all women exit the screening age, with subsequent follow-up) to compare cumulative incidence and mortality. Only after this long follow-up can the impact of early diagnosis on mortality be assessed and the additional cancers detected with DBT that were overdiagnosed, if any, be estimated. It will take a number of decades for such a study to provide any answers. This is too long a period to make any decision on whether to implement a new imaging technology, which would already be obsolete by the end of this hypothetical study.

We designed a trial in which women were randomized to one round of screening with DB plus DM or to DM alone and all retested with DM alone at the next round.

Abbreviations

BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis, DM = digital mammography

Summary

In women younger than 50 years, benefits of early diagnosis with tomosynthesis plus mammography screening seemed appreciable and could increase diagnosis of slow-growing, invasive cancers for women over age 50.

Key Results

- In a randomized trial, baseline cancer detection was higher in women undergoing digital breast tomosynthesis (DBT) plus digital mammography (DM) versus DM alone (101 of 13 356 women vs 61 of 13 521 women; 70% more cancer detected).
- Up to rescreening with DM after 12 months (in women aged 45–49 years) or 24 months (in women aged 50–69 years), interval cancer incidence was similar in the two arms (21 vs 22 cancers).
- Cumulative incidence remained higher for women over 50 in the DBT plus DM arm (153 vs 124 cancers; relative incidence, 1.2) but was similar in the two arms for women aged 45–49 (36 vs 41 cancers; 11% less incident cancers occurred).

Herein, we compare the cumulative incidence of cancers after two rounds of screening, including interval and screening-detected cancers. We have previously confirmed that DBT plus DM can help detect more cancers (8). This follow-up addresses the hypothesis that DBT plus DM reduces interval cancers and cancers at the subsequent screening round; if not, the gain in detection would likely be mainly for slow-growing cancers. Thus, our study aim was to compare interval and overall breast cancer incidence after screening with DBT plus DM versus DM alone.

Materials and Methods

Study Design

RETomo is a two-arm prospective randomized superiority trial (*ClinicalTrials.gov* identifier: NCT02698202) comparing DBT plus DM versus DM alone. Women were randomized to undergo DBT plus DM or DM at baseline; in subsequent rounds, both study arms were screened with DM. Women will be followed up for at least 4.5 years, including at least two rounds of follow-up for all. The coprimary end point, for which we report final data herein, is interval cancers; the second coprimary end point (ie, cumulative incidence of cancers greater than 20 mm in maximum diameter in women with negative findings at baseline screening test) is not reported in this analysis because follow-up has not ended. Furthermore, herein we report the final analysis of baseline results and interim analysis on overall cumulative incidence up to the subsequent screening round plus 9 months (21- and 33-month follow up for women aged 45–49 and 50–69, respectively; the 9-month period after the scheduled second round was considered to include cancers detected in women referred to a 6-month early recall after an inconclusive assessment). A previous study (8) reported the baseline results only (ie, cancer detection, referral rate, and false-positive rate) for 19 560 of 26 877 women as a preplanned interim analysis (8).

This study was approved by the provincial ethics committee of Reggio Emilia and by the Italian Ministry of Health, Prevention Directorate. All participants signed informed consent. The study was partially funded by the Emilia-Romagna Regional Health Authority for recruitment and by the Italian Ministry of Health for the follow-up; GE Healthcare loaned one piece of tomosynthesis equipment for our study period. The authors had full control of the study design, data collection, and data analysis.

Study Participants

The province of Reggio Emilia is located in Northern Italy. The screening program invites women aged 45–49 years annually and women aged 50–74 years biennially (9). Women aged 45–69 attending screening from March 2014 to August 2017 in one of the three clinics with machines equipped with DBT for a new screening round were eligible for the study. Women aged 70–74 years were not included because they would not have two rounds of follow-up within the screening program for all women. Exclusion criteria were previous breast cancer, inclusion in or eligibility for a hereditary breast cancer surveillance program (10), pregnancy, previous DBT examination, very large breasts (which could require more than one exposure for each projection), augmentation prostheses, or language barriers. For practical reasons (ie, reducing variability in the number of nonattenders in recruitment sessions), only women who had already participated in the previous screening round were asked to participate.

For participating women, after completion of the DM projections, the randomization arm was disclosed to the radiographer and the woman. Women allocated to the DBT plus DM arm proceeded with the DBT projections.

Imaging Protocol

Women in the control arm underwent standard four-projection DM (left and right craniocaudal plus mediolateral oblique); women in the experimental arm underwent the same standard four-projection DM, then four-projection DBT, both performed with Senographe Essential digital systems (GE Healthcare) (8,11).

In both arms, two radiologists independently read the images; in the event of disagreement, arbitration by a third reader was conclusive, as it is for routine screening. Ten radiologists participated in the trial, and each read a balanced number of experimental and control arm images (see Appendix E1 [online] for details).

In the experimental arm, first, the radiologist read the DBT examination and gave a judgment of positive or negative; this judgment was recorded for research only. Then, the workstation presented the DM examination together with previous mammograms. The radiologist made the final decision about recall at this step, using a dichotomous scale. Synthetic two-dimensional images were not available for routine DBT reading. Women with positive results were recalled for assessment (Appendix E1 [online]).

Women were actively re-invited for the subsequent screening round unless diagnosed with breast cancer or with a lesion requiring strict follow-up or if they moved to another province or died.

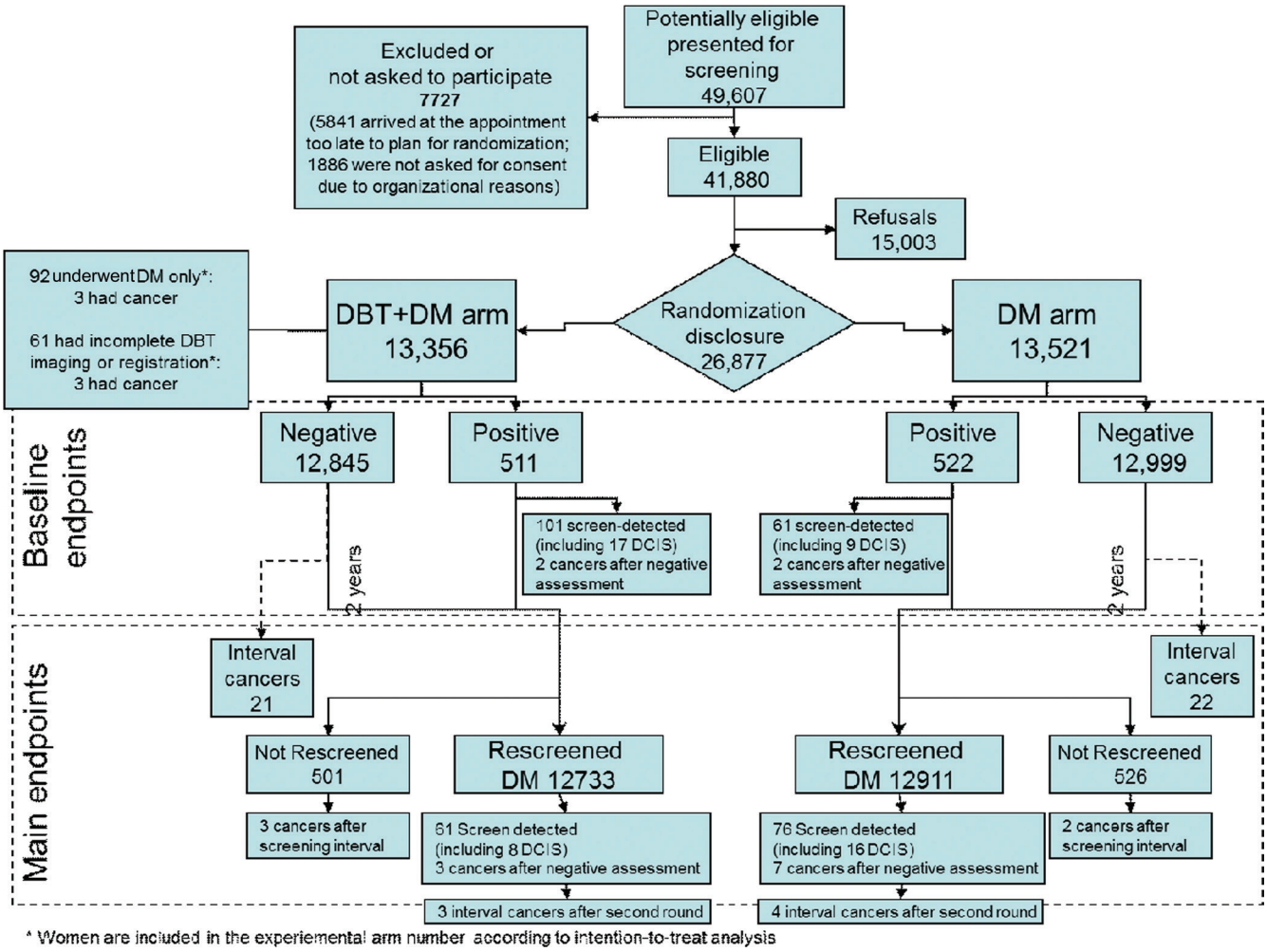

Figure 1: Consort study flow diagram. DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ, DM = digital mammography.

Table 1: Baseline Characteristics and Completeness of Follow-up of Recruited Women according to Arm

Characteristic	Experimental Arm (DBT + DM)	Control Arm (DM)
Recruited	13 356 (49.7)	13 521 (50.3)
Age (y)*	55 ± 7	55 ± 7
45–49	5053 (49.8)	5103 (50.2)
50–69	8303 (49.7)	8418 (50.3)
BI-RADS breast density category		
A	1125 (49.7)	1139 (50.3)
B	5136 (49.9)	5147 (50.1)
C	4738 (49.8)	4773 (50.2)
D	1232 (50.6)	1205 (49.4)
Not available	1125 (47.2)	1257 (52.8)
Invited for a new round	13 105 (49.7)	13 268 (50.3)
Screened for a new round	12 733 (49.7)	12 911 (50.3)

Note.—A total 26 877 women participated in the study. Unless otherwise specified, data are numbers of participants, with percentages in parentheses. BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis, DM = digital mammography.

* Data are means ± standard deviations.

Breast density was retrospectively assessed using validated software (DenSeeMammo version 1.2, Predilife) (12) in December 2018. The system is calibrated to reproduce the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) density classification distribution in the screening age (ie, 45–74 years) (13).

Definition and Ascertainment of Outcomes

The first primary end point was incidence of interval cancers, defined as cancers occurring after a negative screening examination and before the next scheduled screening round (12 months for women aged 45–49 years and 24 months for women aged 50–69 years at recruitment) in all women with negative findings at baseline. Furthermore, overall cumulative incidence up to 21 months and up to 33 months for women aged 45–49 years and 50–69 years, respectively, was considered a safety outcome, as a proxy measure of the excess diagnosis (if any) with DBT plus DM compared with DM screening. Ductal carcinomas in situ are included.

Secondary end points were as follows: *(a)* detection, defined as the number of cancers detected within 9 months of a positive screening examination out of the total number of screened women; *(b)* the proportion of recalled women, defined as

Table 2: Baseline Results and Second Round Results by Arm

Result	Experimental Arm (DBT + DM)	Control Arm (DM)	Relative Effect*	Absolute Effect per 1000 Women Screened*
Baseline results				
Recruited	13 356 (100)	13 521 (100)		
Recalled women	511 (3.83)	522 (3.86)	0.99 (0.88, 1.1)	0 (−5, 4)
With percutaneous biopsy	159 (1.19)	110 (0.81)	1.5 (1.1, 1.9)	4 (1, 6)
Surgery†	116 (0.87)	68 (0.50)	1.7 (1.3, 2.3)	4 (2, 6)
Invasive cancers	84 (0.63)	52 (0.38)	1.6 (1.2, 2.3)	2 (1, 4)
Ductal carcinoma in situ	17 (0.13)	9 (0.07)	1.9 (0.85, 4.3)	1 (0, 1)
Detection rate	101 (0.76)	61 (0.45)	1.7 (1.2, 2.3)	3 (1, 5)
Positive predictive value (%)	19.8	11.7	1.7 (1.3, 2.3)	…
Benign	14 (0.10)	8 (0.06)	1.8 (0.74, 4.2)	0 (0, 1)
Benign to malignant ratio	0.17	0.15	…	…
No. of false-positive results	410 (3.07)	461 (3.41)	0.90 (0.79, 1.0)	−3 (−8, 1)
Interval cancers	21 (0.16)	22 (0.17)	0.97 (0.53, 1.8)	0 (−1, 1)
Invasive cancers	19 (0.14)	20 (0.15)	0.96 (0.51, 1.8)	0 (−1, 1)
Ductal carcinoma in situ	2 (0.02)	2 (0.02)	1.0 (0.14, 7.2)	0 (0, 0)
Second round results				
Screened women	12 733 (100)	12 911 (100)		
Recalled women	464 (3.64)	506 (3.92)	0.93 (0.82, 1.1)	−3 (−7, 2)
With percutaneous biopsy	78 (0.61)	104 (0.81)	0.76 (0.57, 1.0)	−2 (−4, 0)
Surgery†	68 (0.53)	83 (0.64)	0.83 (0.60, 1.1)	−1 (−3, 1)
Invasive cancers	53 (0.42)	60 (0.46)	0.90 (0.62, 1.3)	0 (−2, 1)
Ductal carcinoma in situ	8 (0.06)	16 (0.12)	0.51 (0.22, 1.2)	−1 (−1, 0)
Detection rate	61 (0.48)	76 (0.59)	0.81 (0.58, 1.1)	−1 (−3, 1)
Overall cumulative incidence‡	189 (1.42)	165 (1.22)	1.2 (0.94, 1.4)	2 (−1, 5)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. DBT = digital breast tomosynthesis, DM = digital mammography.

* Data in parentheses are 95% CIs.

† All surgical procedures, including open biopsy, for malignant and benign lesions.

‡ Cumulative incidence also includes cancers occurring after negative assessment, cancers detected in symptomatic women overdue for their mammogram, and interval cancers occurring after the second round before the end of follow-up.

women recalled for an assessment out of the total number of screened women; *(c)* false-positive results, defined as women recalled for assessment but without a cancer (invasive or in situ) out of the total number of screened women; and *(d)* the positive predictive value, defined as the proportion of women with a screening-detected cancer out of those recalled for and attending assessment.

All recruited women were followed up in the screening program and the cancer registry. The evaluation of the surgical specimen was considered the final diagnosis of the lesion. Malignant lesions were classified as invasive cancer or ductal carcinoma in situ. In cases of bilateral cancer, the more severe diagnosis was considered. Lesions were classified according to maximum dimension, lymph node involvement, stage, grade, hormone receptors, human epidermal growth factor receptor 2, and Ki67 positivity (see Appendix E1 [online] for details) (14). Pathologists were not informed of the study arm. For women who underwent neoadjuvant therapy, TNM classification at diagnosis was considered; in these examinations, the radiologic tumor size was assessed by three external radiologists who were blinded to study arm information (Appendix E1 [online]).

Statistical Analyses

For primary and secondary outcomes, we present the relative risk between the two arms and an absolute risk difference per 1000 screened women, with 95% CIs computed using Stata (version 13.0, StataCorp). $P < .05$ was considered indicative of statistically significant difference. Nelson-Aalen cumulative hazard estimates are reported. All analyses are presented according to age group (women aged 45–49 years and 50–69 years) and breast density (ie, nondense [BI-RADS categories A and B] and dense [categories C and D]). We report data for all cancers, including ductal carcinoma in situ. Sample size calculation is reported in Appendix E1 (online).

Results

Participant Characteristics

A total of 26 877 women consented to participate and were randomized: 13 356 to the DBT plus DM experimental arm and 13 521 to the DM control arm. The mean participant age ± standard deviation was 55 years ± 7 in both arms. Among those randomized to the experimental arm, 153 did not undergo DBT

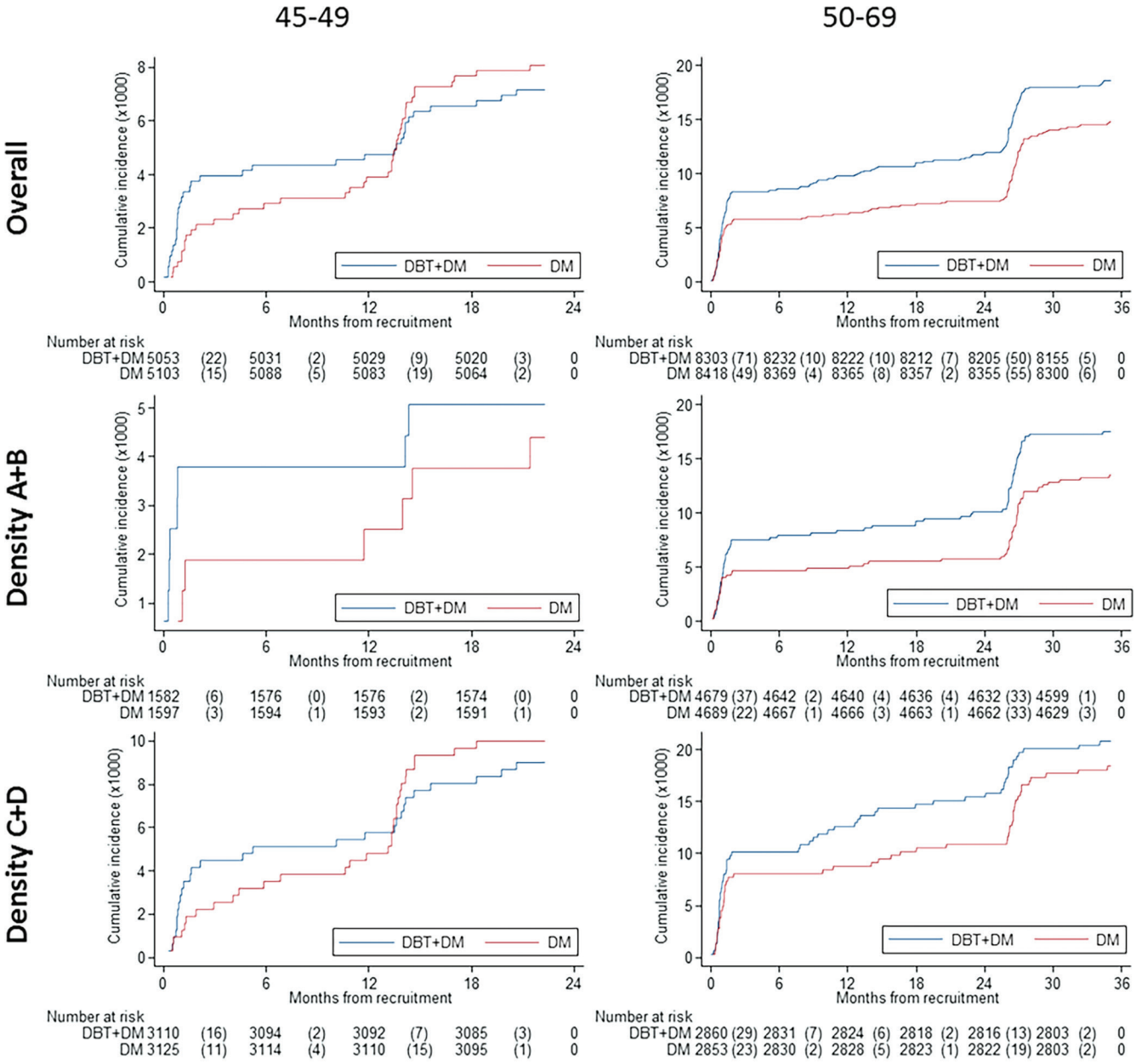

Figure 2: Nelson-Aalen hazard plots show cumulative incidence of breast cancer (invasive and ductal carcinoma in situ) by age at recruitment (in years) and breast density (according to Breast Imaging Reporting and Data System category). Women aged 45–49 years at recruitment were followed up for 21 months (12-month screening interval plus 9 months to complete assessment); women aged 50–69 years at recruitment were followed up for 33 months (24-month screening interval plus 9 months to complete assessment). DBT = digital breast tomosynthesis, DM = digital mammography.

or had incomplete data (Fig 1). According to the intention-to-treat approach, all these women were included in the DBT plus DM arm in all analyses. Women's age, breast density, and completeness of follow-up were similar in the two arms, except for a higher number of DM examinations in the control arm for which density assessment was not possible due to technical reasons (Table 1).

Primary and Secondary End Point Results

Recall at the first round was similar in the two arms (3.8% vs 3.9%; relative recall for DBT plus DM vs DM, 0.99 [95% CI: 0.88, 1.1]), while detection was 70% higher in the DBT plus DM arm, with 101 versus 61 cancers found (relative detection, 1.7 [95% CI: 1.2, 2.3]). Consequently, the positive predictive value was higher in the DBT plus DM arm (19.8%) than in the DM arm (11.7%). Twenty-one interval cancers were identified in the DB plus DM arm and 22 in the DM arm (relative incidence, 0.97 [95% CI: 0.53, 1.8]). Detection at second round was 19% lower in the DBT plus DM arm than in the DM arm (61 vs 76 cancers; relative detection, 0.81 [95% CI: 0.58, 1.1]). The cumulative incidence was 189 cancers in the DBT plus DM arm and 165 in the DM arm, including screening-detected cancer at the first and second rounds, interval cancers, and cancers detected after negative assessments in women overdue for screening, as well as interval cancers occurring in the first 9 months after the second round. This corresponded to about 20% more tumors in DBT plus DM arm (relative risk, 1.2 [95% CI: 0.94, 1.4]) (Table 2, Fig 2).

Table 3: Baseline Results and Second Round Results by Arm in Women Aged 45–49 Years

Result	Experimental Arm (DBT + DM)	Control Arm (DM)	Relative Effect*	Absolute Effect per 1000 Women Screened*
Baseline results				
Recruited	5053 (100)	5103 (100)		
Recalled women	200 (3.96)	206 (4.04)	0.98 (0.81, 1.2)	−1 (−8, 7)
With percutaneous biopsy	47 (0.93)	31 (0.61)	1.5 (0.97, 2.4)	3 (0, 7)
Surgery†	29 (0.57)	14 (0.27)	2.1 (1.1, 4.0)	3 (0, 6)
Invasive cancers	19 (0.38)	10 (0.20)	1.9 (0.89, 4.1)	2 (0, 4)
Ductal carcinoma in situ	2 (0.04)	2 (0.04)	1.0 (0.14, 7.2)	0 (−1, 1)
Detection rate	21 (0.42)	12 (0.24)	1.8 (0.87, 3.6)	2 (0, 4)
Positive predictive value (%)	10.5	5.8	1.8 (0.91, 3.6)	…
No. of false-positive results	179 (3.54)	194 (3.80)	0.93 (0.76, 1.1)	−3 (−10, 5)
Interval cancers	3 (0.06)	8 (0.16)	0.38 (0.10, 1.4)	−1 (−2, 1)
Invasive cancers	3 (0.06)	7 (0.14)	0.43 (0.11, 1.7)	−1 (−2, 1)
Ductal carcinoma in situ	0 (0)	1 (0.02)	…	0 (−1, 0)
Second round results				
Screened women	4813 (100)	4855 (100)		
Recalled women	163 (3.39)	195 (4.02)	0.84 (0.69, 1.0)	−6 (−14, 1)
With percutaneous biopsy	15 (0.31)	30 (0.62)	0.50 (0.27, 0.94)	−3 (−6, 0)
Surgery†	11 (0.23)	22 (0.45)	0.50 (0.24, 1.0)	−2 (−5, 0)
Invasive cancers	7 (0.15)	14 (0.29)	0.50 (0.20, 1.2)	−1 (−3, 0)
Ductal carcinoma in situ	2 (0.04)	4 (0.08)	0.50 (0.09, 2.8)	0 (−1,1)
Detection rate	9 (0.19)	18 (0.37)	0.50 (0.23, 1.1)	−2 (−4, 0)
Overall cumulative incidence‡	36 (0.71)	41 (0.80)	0.89 (0.57, 1.4)	−1 (−2, 0)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. DBT = digital breast tomosynthesis, DM = digital mammography.

* Data in parentheses are 95% CIs.

† All surgical procedures, including open biopsy, for malignant and benign lesions.

‡ Cumulative incidence also includes cancers occurring after negative assessment, cancers detected in symptomatic women overdue for their mammogram, and interval cancers occurring after the second round before the end of follow-up.

Subgroup Analyses

For the first round, data were substantially similar for the 45–49 and 50–69 age groups (Tables 3, 4). In the 45–49 age group, interval cancers (three vs eight) and cancers detected at the second round (nine vs 18) were fewer in the DBT plus DM arm than in the DM arm (relative incidence of interval cancer, 0.38 [95% CI: 0.10, 1.4]; relative detection, 0.50 [95% CI: 0.23, 1.1]) (Table 3). Cumulative incidence after 21 months was slightly lower in the DBT plus DM arm (36 vs 41 cancers; relative incidence, 0.89 [95% CI: 0.57, 1.4]) (Table 3, Fig 2).

In the 50–69 age group, we found no difference in interval cancers (18 vs 14; relative incidence, 1.3 [95% CI: 0.65, 2.6]) and cancers detected at the second round (52 vs 58; relative detection, 0.91 [95% CI: 0.66, 1.3]) between the two arms. Thus, the cumulative incidence at 33 months remained 25% higher in the DBT plus DM arm (153 vs 124 cancers; relative incidence, 1.2 [95% CI: 0.99, 1.6]) (Table 4, Fig 2).

Density data were available for 24 495 women (91% of the total). In the 12 547 women with fatty tissue or scattered density (BI-RADS category A or B), results were similar to the overall data, with higher detection in the DBT plus DM arm than in the DM arm at baseline (46 vs 25 cancers; relative detection, 1.9 [95% CI: 1.1, 3.0]) and similar interval cancer incidence (seven vs six cancers; relative incidence, 1.2 [95% CI: 0.40, 3.5]) and second round detection in the two arms (35 vs 37 cancers; relative detection, 0.95 [95% CI: 0.60, 1.5]). Cumulative incidence in the women with nondense breasts remained 27% higher in the DBT plus DM arm than the DM arm (90 vs 71 cancers; relative incidence, 1.3 [95% CI: 0.93, 1.7]) (Table 5).

In the 11 948 women with dense or very dense breast tissue (BI-RADS category C or D), detection at baseline was higher in the DBT plus DM arm than the DM arm (49 vs 31 cancers; relative detection, 1.6 [95% CI: 1.0, 2.5]); during follow-up, interval cancers (14 vs 15 cancers; relative incidence, 0.93 [95% CI: 0.45, 1.9]) and cancers detected at the second round (19 vs 34 cancers; relative detection, 0.56 [95% CI: 0.32, 0.98]) were lower in the DBT plus DM arm. The cumulative incidence in this group was similar in the two arms (88 vs 83 cancers; relative incidence, 1.1 [95% CI: 0.79, 1.4]) (Table 6).

Characteristics of Identified Cancers

Cancers detected in the DBT plus DM arm were smaller and more often node-negative, grade I or II, hormone receptor–positive, human epidermal growth factor receptor 2–negative, and Ki67-negative. Interval cancers following the first round did not show substantial differences between the two arms. Finally, screening-detected cancers in the DM arm were smaller

Table 4: Baseline Results and Second Round Results by Arm in Women Aged 50–69 Years

Results	Experimental Arm (DBT + DM)	Control Arm (DM)	Relative Effect*	Absolute Effect per 1000 Women Screened*
Baseline results				
Recruited	8303 (100)	8418 (100)		
Recalled women	311 (3.75)	316 (3.75)	1.0 (0.86, 1.2)	0 (−6, 6)
With percutaneous biopsy	112 (1.35)	79 (0.94)	1.4 (1.1, 1.9)	4 (1, 7)
Surgery†	87 (1.05)	54 (0.64)	1.6 (1.2, 2.3)	4 (1, 7)
Invasive cancers	65 (0.78)	42 (0.50)	1.6 (1.1, 2.3)	3 (0, 5)
Ductal carcinoma in situ	15 (0.18)	7 (0.08)	2.2 (0.89, 5.3)	1 (0, 2)
Detection rate	80 (0.96)	49 (0.58)	1.7 (1.2, 2.4)	4 (1, 6)
Positive predictive value (%)	25.7	15.8	1.7 (1.2, 2.3)	…
No. of false-positive results	231 (2.78)	267 (3.17)	0.88 (0.74, 1.0)	−4 (−9, 1)
Interval cancers	18 (0.22)	14 (0.17)	1.3 (0.65, 2.6)	1 (−1, 2)
Invasive cancers	16 (0.20)	13 (0.16)	1.2 (0.60, 2.6)	0 (−1, 2)
Ductal carcinoma in situ	2 (0.02)	1 (0.01)	2.0 (0.18, 22)	0 (−1, 0)
Second round results				
Screened women	7920 (100)	8056 (100)		
Recalled women	301 (3.8)	311 (3.86)	0.98 (0.84, 1.1)	−1 (−7, 5)
With percutaneous biopsy	63 (0.80)	74 (0.92)	0.87 (0.62, 1.2)	−1 (−4, 2)
Surgery†	57 (0.72)	61 (0.76)	0.95 (0.66, 1.4)	0 (−3, 2)
Invasive cancers	46 (0.58)	46 (0.57)	1.0 (0.68, 1.5)	0 (−2, 2)
Ductal carcinoma in situ	6 (0.08)	12 (0.15)	0.51 (0.19, 1.4)	−1 (−2, 0)
Detection rate	52 (0.66)	58 (0.72)	0.91 (0.66, 1.3)	−1 (−3, 2)
Overall cumulative incidence‡	153 (1.84)	124 (1.47)	1.2 (0.99, 1.6)	4 (−2, 8)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. DBT = digital breast tomosynthesis, DM = digital mammography.

* Data in parentheses are 95% CIs.

† All surgical procedures, including open biopsy, for malignant and benign lesions.

‡ Cumulative incidence also includes cancers occurring after negative assessment, cancers detected in symptomatic women overdue for their mammogram, and interval cancers occurring after the second round before the end of follow-up.

and more often node-negative, hormone receptor–positive, and Ki67-negative (Table 7).

Discussion

In this study, we aimed to assess the downstream consequences of digital breast tomosynthesis (DBT) plus digital mammography (DM) screening in terms of interval cancers and cumulative cancer incidence in a randomized trial comparing DBT/ plus DM with DM alone. Despite DBT plus DM helping detect 70% (95% CI: 20, 130) more cancer at baseline, very similar numbers of interval cancers occurred in the two arms, and screening-detected cancers at the following round were similar, leading to a +16% difference in cumulative incidence (95% CI: −6, +43) in the DBT plus DM arm. However, in younger women (45–49 years) and in women with dense breast tissue (Breast Imaging Reporting and Data System [BI-RADS] category C or D), the higher cancer detection obtained using DBT plus DM at baseline was followed by a lower incidence of interval cancers and by lower rate of detection at the following round, leading to −11% (95% CI: −43, +39) and +6% (95% CI: −21, +43) differences in cumulative incidence, respectively. Our results suggest that DBT plus DM in these women primarily advanced the time of diagnosis of cancers that would have occurred in the near future. In women over age 50 and in women with nondense breast tissue (BI-RADS category A or B), cumulative incidence was 25% (95% CI: −1, +58) and 27% (95% CI: −35, +73) higher, respectively. Our results suggest that tumors detected with use of DBT plus DM but undetectable at DM in these age and density groups would not have progressed to symptomatic disease in the next 2 years or to cancer detected at screening with DM after 2 years. Cancers detected with DBT plus DM at the first round were smaller and had more favorable prognostic factors (ie, node-negative, grade I, and hormone receptor–positive). At the second round, the opposite occurred, with higher proportions of smaller and better-prognosis cancers detected in the DM arm. No changes were observed in the absolute incidence of cancers with unfavorable prognostic factors at baseline or for interval cancers or second round cancers.

Several reports on interval cancers in DBT studies have been published in the past 6 years (15–21), including two meta-analyses (22,23). All suggest a small, if any, impact of DBT screening on interval cancers. However, most of these studies, consistent with our results, found an improvement in detection with DBT at baseline (15–21). Our results suggest no reduction of interval cancers for women aged 50 years or over but a reduction in interval cancers in women aged 45–49. For the moment, other large

Table 5: Baseline Results and Second Round Results by Arm in Women with Nondense Breasts (BI-RADS Category A or B)

Result	Experimental Arm (DBT + DM)	Control Arm (DM)	Relative Effect*	Absolute Effect per 1000 Women Screened*
Baseline results				
Recruited	6261 (100)	6286 (100)		
Invasive cancers	39 (0.62)	22 (0.35)	1.8 (1.1, 3.0)	3 (0, 5)
Ductal carcinoma in situ	7 (0.11)	3 (0.05)	2.3 (0.61, 9.1)	1 (0, 2)
Detection rate	46 (0.73)	25 (0.40)	1.9 (1.1, 3.0)	3 (1, 6)
Positive predictive value (%)	21.9	13.0	1.7 (1.1, 2.6)	…
Interval cancers	7 (0.11)	6 (0.10)	1.2 (0.40, 3.5)	0 (−1, 1)
Invasive cancers	6 (0.10)	4 (0.06)	1.5 (0.43, 5.3)	0 (−1, 1)
Ductal carcinoma in situ	1 (0.02)	2 (0.03)	0.50 (0.05, 5.6)	0 (−1, 0)
Second round results				
Screened women	5970 (100)	6002 (100)		
Invasive cancers	31 (0.52)	32 (0.53)	0.97 (0.60, 1.6)	0 (−3, 2)
Ductal carcinoma in situ	4 (0.07)	5 (0.08)	0.80 (0.22, 3.0)	0 (−1, 1)
Detection rate	35 (0.59)	37 (0.62)	0.95 (0.60, 1.5)	0 (−3, 2)
Overall cumulative incidence†	90 (1.44)	71 (1.13)	1.3 (0.93, 1.7)	3 (−1, 7)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis, DM = digital mammography.

* Data in parentheses are 95% CIs.

† Cumulative incidence also includes cancers occurring after negative assessment, cancers detected in symptomatic women overdue for their mammogram, and interval cancers occurring after the second round before the end of follow-up.

Table 6: Baseline Results and Second Round Results by Arm in Women with Dense Breasts (BI-RADS Category C or D)

Result	Experimental Arm (DBT + DM)	Control Arm (DM)	Relative Effect*	Absolute Effect per 1000 Women Screened*
Baseline results				
Recruited	5970 (100)	5978 (100)		
Invasive cancers	40 (0.67)	26 (0.43)	1.5 (0.94, 2.5)	2 (0, 5)
Ductal carcinoma in situ	9 (0.15)	5 (0.08)	1.8 (0.60, 5.4)	1 (−1, 2)
Detection rate	49 (0.82)	31 (0.52)	1.6 (1.0, 2.5)	3 (0, 6)
Positive predictive value (%)	18.4	10.8	1.5 (0.97, 2.3)	…
Interval cancers	14 (0.23)	15 (0.25)	0.93 (0.45, 1.9)	0 (−2, 2)
Invasive cancers	13 (0.22)	15 (0.25)	0.86 (0.41, 1.8)	0 (−2, 2)
Ductal carcinoma in situ	1 (0.02)	0 (0)		0 (0, 1)
Second round results				
Screened women	5686 (100)	5706 (100)		
Invasive cancers	16 (0.28)	25 (0.44)	0.64 (0.34, 1.2)	−2 (−4, 1)
Ductal carcinoma in situ	3 (0.05)	9 (0.16)	0.33 (0.09, 1.2)	−1 (−2, 0)
Detection rate	19 (0.33)	34 (0.60)	0.56 (0.32, 0.98)	−3 (−5, 0)
Overall cumulative incidence†	88 (1.47)	83 (1.39)	1.1 (0.79, 1.4)	1 (−3, 5)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. BI-RADS = Breast Imaging Reporting and Data System, DBT = digital breast tomosynthesis, DM = digital mammography.

* Data in parentheses are 95% CIs.

† Cumulative incidence also includes cancers occurring after negative assessment, cancers detected in symptomatic women overdue for their mammogram, and interval cancers occurring after the second round before the end of follow-up.

studies have suggested greater benefits from introducing DBT in terms of screening performance in women younger than age 50 (4,24). Data from the BreastScreen Norway cohort study showed, consistent with our data, that the increase in detection obtained with DBT at the first round, compared with DM detection, is not compensated by a decrease at the following round (25).

Our findings are also consistent with the evidence produced by the UK Age trial, suggesting no effect on overdiagnosis at annual screening in young women in addition to screening from age 50 (26), and with the estimation of a longer sojourn time of cancers in older women obtained from modeling data in the Swedish Two-County Study (27).

Table 7: Histologic and Molecular Characteristics of Cancers by Arm, Round, and Mode of Diagnosis

Characteristic	Baseline		Interval Cancers		Second Round	
	DBT/DM	DM	DBT/DM	DM	DBT/DM	DM
No. of cancers	101	61	21	22	61	76
Lesion dimension*						
<10 mm	31 (37)	19 (37)	4 (21)	4 (20)	13 (25)	31 (52)
≥10 to <20 mm	45 (54)	21 (40)	10 (53)	8 (40)	31 (58)	25 (42)
≥20 mm	8 (9)	12 (23)	5 (26)	8 (40)	9 (17)	4 (7)
Lymph nodes*						
N0	67 (80)	43 (83)	13 (68)	10 (50)	38 (72)	52 (87)
N1mic	3 (4)	0 (0)	0 (0)	3 (15)	4 (8)	4 (7)
N1	12 (14)	7 (13)	6 (32)	5 (25)	9 (17)	1 (2)
N2	1 (1)	2 (4)	0 (0)	1 (5)	2 (4)	2 (3)
N3	1 (1)	0 (0)	0 (0)	1 (5)	0 (0)	1 (2)
Stage						
Ductal carcinoma in situ	17 (17)	9 (15)	2 (10)	2 (9)	8 (13)	16 (21)
I	63 (62)	35 (57)	9 (43)	12 (55)	38 (62)	54 (71)
II	18 (18)	15 (25)	9 (43)	4 (18)	13 (21)	2 (3)
III, IV	3 (3)	2 (3)	1 (5)	4 (18)	2 (3)	4 (5)
Grade						
I	16 (16)	7 (11)	0 (0)	2 (9)	3 (5)	5 (7)
II	71 (72)	40 (66)	14 (70)	11 (50)	46 (77)	57 (76)
III	12 (12)	14 (23)	6 (30)	9 (41)	11 (18)	13 (17)
Not available	2	0	1	0	1	1
Estrogen receptor						
≥10%	94 (94)	56 (92)	15 (71)	18 (82)	53 (88)	68 (91)
<10%	6 (6)	5 (8)	6 (29)	4 (18)	7 (12)	7 (9)
Not available	1	0	0	0	1	1
Progesterone receptor						
>10%	76 (76)	41 (67)	12 (57)	13 (59)	40 (67)	55 (73)
≤10%	24 (24)	20 (33)	9 (43)	9 (41)	20 (33)	20 (27)
Not available	1	0	0	0	1	1
HER2*						
Positive	7 (8)	12 (23)	3 (17)	3 (15)	7 (13)	5 (9)
Negative	77 (92)	40 (77)	15 (83)	17 (85)	45 (87)	50 (91)
Not available	0	0	1	0	1	5
Triple-negative	2 (2)	2 (3)	5 (24)	1 (5)	2 (3)	2 (3)
Ki67*						
Positive (≥20%)	21 (25)	17 (33)	10 (53)	11 (55)	20 (38)	7 (12)
Negative (<20%)	63 (75)	35 (67)	9 (47)	9 (45)	33 (62)	49 (88)
Not available	0	0	0	0	0	4
Breast density†						
A	5 (5)	4 (7)	0 (0)	0 (0)	3 (6)	7 (10)
B	41 (43)	21 (38)	7 (33)	6 (29)	32 (59)	30 (42)
C	39 (41)	22 (39)	12 (57)	11 (52)	15 (28)	28 (39)
D	10 (11)	9 (16)	2 (10)	4 (19)	4 (7)	6 (8)
Not available	6	5	0	1	7	5

Note.—Data are numbers of cancers, with percentages in parentheses. Percentages are reported only for valid values. The Table does not include cancers that occurred after negative assessment, cancers detected in symptomatic women overdue for their mammogram, or interval cancers that occurred after the second round. DBT = digital breast tomosynthesis, DM = digital mammography, HER2 = human epidermal growth factor receptor 2.

* Excluding ductal carcinoma in situ.

† Breast density is categorized according to the Breast Imaging Reporting and Data System.

Consistent with a recent meta-analysis (28), the improvement in relative detection in our trial was similar in BI-RADS categories B and C; a recent study suggests scarce improvement in detection for BI-RADS category D (29), and our findings, even if limited by small numbers, go in the same direction. On the other hand, our results suggest that DBT plus DM in dense breasts may result in earlier detection of cancers that would otherwise be detected with DM in the following round or would occur as interval cancers.

Our study had limitations. First, the small numbers limit the power of preplanned subgroup analyses. Second, in the attempt to obtain results on the impact of DBT screening on interval cancers and estimate excess diagnosis in a limited time span, our trial only compared one round of DBT plus DM with one round of DM. An ongoing trial in the United Kingdom is recruiting 100 000 women, randomizing them to two rounds of DBT or DM, with regular DM screening for all thereafter. Results from the UK study will provide information on the types of breast cancers that are diagnosed at DM versus DBT (30). The effects of screening mammography on breast cancer mortality, whether that screening is with DM or DBT, will require decades of long-term follow-up. Finally, the use of the synthesized two-dimensional image from DBT allows similar diagnostic accuracy while almost halving the radiation dose (31–36). This led the European Union Guidelines Development Group to recommend against the use of DBT in addition to DM (22). Nevertheless, our data on interval cancers and cumulative incidence can also be applied to any screening with DBT, with or without DM. In fact, at baseline, the proportion of cancers that were DBT-negative and were detected only on the basis of DM was very small (2), consistent with the results of previous studies comparing DBT and DM in the same women (31,37–39).

Our results suggest that introducing digital breast tomosynthesis in screening could lead to diagnosis of slow-growing invasive cancers that would

not occur in the next 3 years. Early diagnosis of fast-growing cancers seems to be appreciable in women under 50 years and in women with dense breasts, but larger studies and pooled analyses of ongoing trials are needed.

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