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Breast Density and Breast Cancer Screening with Digital Breast Tomosynthesis: A TOSYMA Trial Subanalysis

*Stefanie Weigel, MD** • *Walter Heindel, MD** • *Hans-Werner Hense, MD* • *Thomas Decker, MD* • *Joachim Gerß, Dr rer nat*** • *Laura Kerschke, Dr rer medic*** • *for the TOSYMA Screening Trial Study Group*

From the Clinic for Radiology and Reference Center for Mammography Münster, University of Münster and University Hospital Münster, Albert-Schweitzer-Campus 1, Building A1, D-48149 Münster, Germany (S.W., W.H., T.D.); Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany (H.W.H.); and Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany (J.G., L.K.). Received April 22, 2022; revision requested June 8; revision received August 4; accepted August 9. **Address correspondence to** S.W. (email: *weigels@uni-muenster.de*).

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

* S.W. and W.H. contributed equally to this work.

** J.G. and L.K. are co-senior authors.

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

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Background: Digital breast tomosynthesis (DBT) plus synthesized mammography (SM) reduces the diagnostic pitfalls of tissue superimposition, which is a limitation of digital mammography (DM).

Purpose: To compare the invasive breast cancer detection rate (iCDR) of DBT plus SM versus DM screening for different breast density categories.

Materials and Methods: An exploratory subanalysis of the TOmosynthesis plus SYnthesized MAmmography (TOSYMA) study, a randomized, controlled, multicenter, parallel-group trial recruited within the German mammography screening program from July 2018 to December 2020. Women aged 50–69 years were randomly assigned (1:1) to DBT plus SM or DM screening examination. Breast density categories A–D were visually assessed according to the Breast Imaging Reporting and Data System Atlas. Exploratory analyses were performed of the iCDR in both study arms and stratified by breast density, and odds ratios and 95% CIs were determined.

Results: A total of 49 762 women allocated to DBT plus SM and 49 796 allocated to DM (median age, 57 years [IQR, 53–62 years]) were included. In the DM arm, the iCDR was 3.6 per 1000 screening examinations in category A (almost entirely fatty) (16 of 4475 screenings), 4.3 in category B (102 of 23 534 screenings), 6.1 in category C (116 of 19 051 screenings), and 2.3 in category D (extremely dense breasts) (six of 2629 screenings). The iCDR in the DBT plus SM arm was 2.7 per 1000 screening examinations in category A (12 of 4439 screenings), 6.9 in category B (154 of 22 328 screenings), 8.3 in category C (156 of 18 772 screenings), and 8.1 in category D (32 of 3940 screenings). The odds ratio for DM versus DBT plus SM in category D was 3.8 (95% CI: 1.5, 11.1). The invasive cancers detected with DBT plus SM were most often grade 2 tumors; in category C, it was 58% (91 of 156 invasive cancers), and in category D, it was 47% (15 of 32 invasive cancers).

Conclusion: The TOmosynthesis plus SYnthesized MAmmography trial revealed higher invasive cancer detection rates with digital breast tomosynthesis plus synthesized mammography than digital mammography in dense breasts, relatively and absolutely most marked among women with extremely dense breasts.

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Mammography screening is an effective tool for early detection and mortality reduction of breast cancer (1). A meta-analysis of incidence-based mortality studies found a significant reduction in breast cancer mortality by 22% among women invited to screening and by 33% if participating (2).

Mammographic dense breast tissue increases the risk of breast cancer (3). However, studies have demonstrated low breast cancer detection rates in those women screened with digital mammography (DM), especially with extremely dense parenchyma (4,5). Consequently, extremely dense breast parenchyma is associated with an increased interval cancer rate, thus lower screening sensitivity (5,6). Due to the generally poorer prognosis of interval carcinomas, strategies to improve screening performance are of great importance (6–8).

One of these strategies is the use of digital breast tomosynthesis (DBT). In DBT, multiple projections are acquired over an arc, which are reconstructed into a series of stacked images (9). Some studies reported higher invasive cancer detection rates (iCDRs) for DBT plus DM compared with DM alone in women with dense breasts (10,11), while no significant change in iCDR in women with extremely dense breast tissue was found (10,12). Recently, women under 50 years with high breast density screened with DBT plus DM compared with DM only were found to have a higher

Abbreviations

DBT = digital breast tomosynthesis, DM = digital mammography, HER2 = human epidermal growth factor receptor 2, iCDR = invasive cancer detection rate, SM = synthesized mammography, TOSYMA = TOmosynthesis plus SYnthesized MAmmography

Summary

The randomized controlled TOmosynthesis plus SYnthesized MAmmography trial shows higher invasive cancer detection rates with digital breast tomosynthesis plus synthesized mammography compared with digital mammography, mostly marked in extremely dense breasts.

Key Results

- In a subanalysis of 99 558 women from the TOmosynthesis plus SYnthesized MAmmography trial, digital breast tomosynthesis (DBT) plus synthesized mammography (SM) depicted 2.7 more invasive cancers per 1000 women with dense breast categories (C and D) than digital mammography (DM); odds ratio: 1.48.
- The largest difference of invasive cancer detection rates of all density categories was found in women with extremely dense breasts (category D) (DBT plus SM, 8.1 per 1000 vs DM, 2.3 per 1000; odds ratio: 3.8).

iCDR in the first DBT screening round and a lower iCDR in the subsequent DM screening round, suggesting an advancement of the effective time point of the breast cancer diagnosis (13).

To reduce radiation dose, DM may be replaced by synthesized mammography (SM), which reconstructs two-dimensional images from the DBT data set (9). In line with results of DBT studies in addition to DM, a prospective study showed higher iCDR with DBT plus SM in all women regardless of breast density (14), and a randomized controlled trial showed an increase of screen-detected cancers for DBT plus SM versus DM in women with denser breasts (15). Because of the typically small proportion of women with extremely high breast density in the screening target population (5,16,17), comparative assessment of iCDR for separate density categories is challenging.

The German TOmosynthesis plus SYnthesized MAmmography (TOSYMA) randomized controlled trial has nearly 100 000 participants and demonstrates that iCDR is overall significantly higher with DBT plus SM (7.1 per 1000 women screened) compared with DM (4.8 per 1000 women screened) (18). The purpose of this subanalysis from TOSYMA was to compare the iCDR of DBT plus SM versus DM for women with different breast density categories based on a large randomized controlled trial to support diagnostic superiority of DBT plus SM in women with dense breasts.

Materials and Methods

Study Design

The recruitment of the multicenter, multivendor, randomized clinical trial TOSYMA took place between July 5, 2018, and December 30, 2020. Women underwent individual 1:1 randomization to DBT plus SM (test arm) or DM (control arm) at 17 screening sites in the federal states of North Rhine-Westphalia and Lower Saxony, Germany (ClinicalTrials.gov: NCT03377036).

The protocol has been approved by the local medical ethics committee (2016–132-f-S) and by two further institutional review boards. Written informed consent was obtained from all study participants. The study was monitored by an independent data and safety monitoring committee.

The study protocol (19) and results of the first primary end point, the overall iCDR, and four secondary end points have been published previously (18). The following exploratory analysis of the TOSYMA trial focuses on differences of the iCDR in both study arms among women with different breast densities.

Study Participants

Women aged 50–69 years are eligible for participation in the biennial German mammography screening program (20). Women living in the catchment areas of the TOSYMA units received a study invitation together with their regular invitation letter to initial or subsequent screening. Women with a breast cancer diagnosis up to 5 years before screening invitation or a mammography within the past 12 months were not eligible. Breast implants or previous TOSYMA participation were trial specific exclusion criteria (19).

The modified full analysis set included all randomized participants who underwent either type of mammographic examination after randomization. Examinations corresponding to a second study participation were excluded from the full analysis set.

Imaging Protocol

Mammographic devices of seven different vendors were used by the screening units: Fujifilm, AMULET Innovality (n = 10 075), IMS Giotto, Class Tomo (n = 7970), Hologic, Lorad Selenia Dimensions (n = 10 955), Hologic, Lorad Selenia Dimensions (n = 40 645), Siemens Healthineers, MAMMOMAT Inspiration (n = 6759), Siemens Healthineers, MAMMOMAT Revelation (n = 12 917), and GE Healthcare, Senographe Essential (n = 10 237). All devices had both a DM and a DBT mode. According to the randomized allocation, the examination was either performed with the DM or the DBT mode (ie, at the same mammography system). Examinations in both study arms included the craniocaudal and mediolateral oblique views of each breast. In the DBT plus SM arm, stacked images of 1 mm or less, in addition to SM, were displayed for reading (18). Available prior examinations were obtained with DM technique.

Image Analysis

Independent double reading was performed in both study arms (20) by 83 qualified mammography screening readers (four to eight readers per site; 12 readers with 2–4 years of experience, 22 readers with 5–9 years of experience, and 49 readers with at least 10 years [eg, S.W. and W.H.]). Qualification included at least 5000 screening mammograms per year. Examinations were read in a mixed order of both study

arms, without identification of the arm before retrieving data from MaSc (KV-IT) or from the picture archiving computer system (18). A certified responsible screening physician (27 of 30 physicians with at least 5 years of experience) indicated recall for further diagnostic work-up and performed the assessment (18).

Before TOSYMA started, all readers took part in a training course at the Reference Center for Mammography Münster. According to the study arm, breast density was assessed at DM or SM, with use of the fourth (American College of Radiology categories 1 to 4) and fifth editions (categories A to D) of the Breast Imaging and Reporting Data System, or BI-RADS, (see Appendix S1 [online] for definitions) (16,17,21). In the BI-RADS fifth edition (17), category A is defined as almost entirely fatty, B is defined as scattered areas of fibroglandular density, C is defined as heterogeneously dense, which may obscure small masses, and D is defined as extremely dense, which lowers the sensitivity of mammography scans. If both breasts differed in density, readers were advised to record the category of the denser breast. If discordant density categorization during the independent double reading process was documented, the highest density category was used.

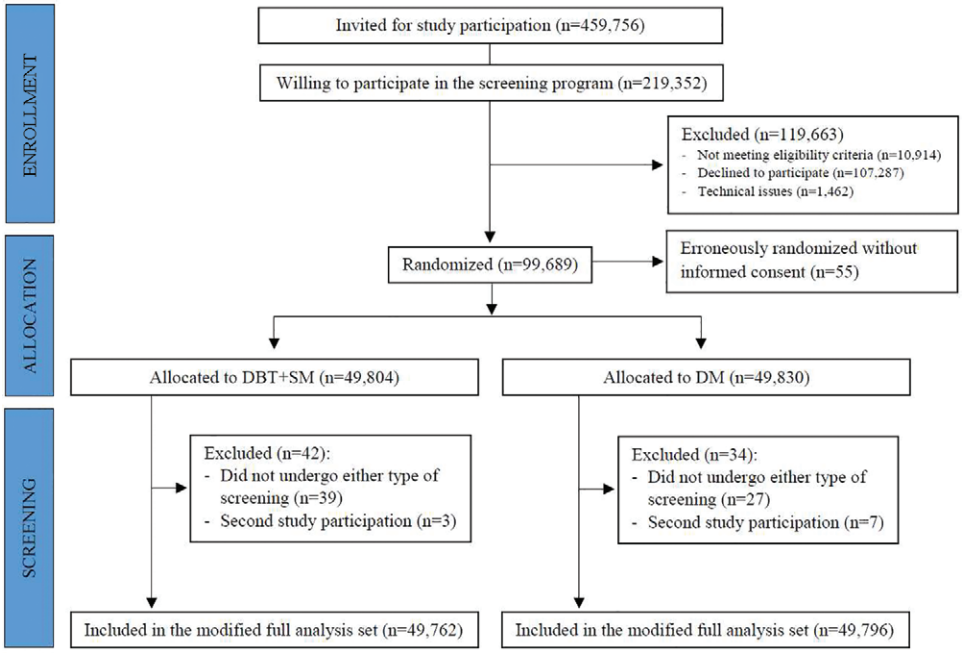

Figure 1: Flowchart shows the randomized allocation of the TOmosynthesis plus SYnthesized MAmmography trial participants. DBT = digital breast tomosynthesis, DM = digital mammography, SM = synthesized mammography.

Histologic Assessment

All 32 certified screening pathologists related to study sites had to take part at a teaching session of the reference pathologist (T.D., a dedicated breast pathologist with 29 years of experience, serving as a reference pathologist in screening since program launch) to be informed about obligatory assessments and documentations of tumor-related histopathologic parameters. Per protocol, each pathologist was given the option of asking the responsible reference pathologist for advice if needed.

Outcome Parameters

The primary outcome in this subanalysis was the screen-detected iCDR per 1000 women screened. In examinations of more than one manifestation per patient, the most advanced tumor stage was used. Invasive breast cancers were stratified according to their histologic sizes or according to their clinical and/or imaging sizes if neoadjuvant treatment was performed.

Secondary outcomes were the detection rate of ductal carcinoma in situ per 1000 women screened, the recall rate of assessment (women recalled per 100 women screened), and the positive predictive value of recall (women with screen-detected invasive breast cancers and ductal carcinoma in situ per 100 women recalled).

Histopathologic subtypes, tumor stage II+ according to Union for International Cancer Control (tumor size ≥20 mm and/or occurrence of local or distant metastases), histopathologic grading (grade 1, grade 2, grade 3), estrogen and progesterone receptor status (<1%, 1%–9% vs ≥10%), human epidermal growth factor receptor 2 (HER2) expression (HER2-negative versus HER2-positive: immunohistochemically detected protein overexpression with a score of 3 or gene amplification), and Ki67 value (<10%: low proliferation, 10%–25%: intermediate proliferation vs >25%: highly proliferating tumors) were determined.

Data on invasive interval cancers, provided by the regional cancer registries, are not yet available, as the follow-up period of the TOSYMA study of 2 years after a negative screening examination is still ongoing. These data will be reported later.

Statistical Analysis

All analyses were performed on the modified full analysis set according to the intention-to-treat principle. Categorical data are presented as absolute and relative frequencies and continuous data as medians and IQRs. With use of standard descriptive statistical measures, the iCDR was assessed within each breast density subgroup, A–D, according to BI-RADS fifth edition (17) and within the combined density subgroups (A plus B defined as non-dense breasts, C plus D defined as dense breasts), additionally stratifying by age (50–59 years and 60–70 years). To quantify differences in the iCDR be-

Table 1: Demographics and Distribution of Breast Density Categories according to BI-RADS Fourth and Fifth Edition

Parameter	Control Arm (*n* = 49 796)	Test Arm (*n* = 49 762)
Age group (y)		
50–59	30 994 (62)	30 941 (62)
60–70	18 802 (38)	18 821 (38)
Screening round		
Initial round	8653 (17)	8613 (17)
Subsequent round	41 143 (83)	41 149 (83)
BI-RADS breast density category: fourth edition*		
ACR 1	4829 (10)	4921 (10)
ACR 2	24 020 (48)	22 956 (46)
ACR 3	18 678 (38)	18 530 (37)
ACR 4	2261 (5)	3341 (7)
Missing†	8 (<0.1)	14 (<0.1)
ACR 1 plus 2	28 849 (58)	27 877 (56)
ACR 3 plus 4	20 939 (42)	21 871 (44)
Total (evaluable)	49 788 (100)	49 748 (100)
BI-RADS breast density category: fifth edition*		
A	4476 (9)	4440 (9)
B	23 549 (47)	22 343 (45)
C	19 062 (38)	18 791 (38)
D	2634 (5)	3946 (8)
Missing†	75 (0.2)	242 (0.5)
A plus B	28 025 (56)	26 783 (54)
C plus D	21 696 (44)	22 737 (46)
Total (evaluable)	49 721 (100)	49 520 (100)

Note.—Data are numbers of participants with percentages in parentheses. For the 41 examinations (0.04%) with missing breast density evaluation from one of the readers, the available assessment was used. Control arm represents digital mammography, and test arm represents digital breast tomosynthesis plus synthesized mammography. ACR = American College of Radiology, BI-RADS = Breast Imaging Reporting and Data System.

* The highest breast density category of the independent double reading was used per examination.

† Missing evaluation of both readers.

tween study arms, common odds ratios (adjusted for study site) and corresponding 95% CIs were calculated with use of conditional maximum likelihood estimation.

Statistical analyses were performed with use of SAS (version 9.4) and R (version 4.0.2) softwares by biostatisticians (J.G. and L.K., with 18 and 6 years of experience, respectively, in the statistical design and analysis of clinical trials). As this was an exploratory analysis, no significance tests were performed. Instead, effect sizes are reported with use of point estimates and CIs.

Results

Study Participants

A total of 99 689 women underwent individual 1:1 randomization. The median age of the 49 762 women allocated to DBT plus SD and 49 796 women allocated to DM alone who were included in the modified full analysis set (Fig 1) was 57 years (IQR, 53–62 years); approximately two-thirds of women in each study arm (30 994 and 30 941, respectively) were between 50 and 59 years old (Table 1). About 17% of women in each study arm (8653 of 49 796 women with DM and 8613 of 49 762 women with DBT plus SM) attended the mammography screening for the first time (ie, in an initial screening round), while all others participated in a subsequent round. The four categories of breast density were similarly distributed among women allocated to DBT plus SM or to DM, irrespective of the BI-RADS edition employed. Therefore, only the fifth edition was used in all following analyses.

Dense breasts (ie, category C and D) were present in 21 696 women screened with DM (44%) and 22 737 women screened with DBT plus SM (46%) (Table 1). The majority of women with dense breasts (67%) (ie, 14 622 and 15 317, respectively) were aged 50–59 years (Table 2).

Primary and Secondary Outcomes

In the DM arm, the iCDR was 3.6 per 1000 women screened in category A (16 of 4475 screenings), 4.3 in category B (102 of 23 534 screenings), 6.1 in category C (116 of 19 051 screenings), and 2.3 in category D (six of 2629 screenings). The iCDR in the DBT plus SM arm was 2.7 per 1000 women screened in category A (12 of 4439 screenings), 6.9 in category B (154 of 22 328 screenings), 8.3 in category C (156 of 18 772 screenings), and 8.1 in category D (32 of 3940 screenings) (Table 2). Of note, women screened with DBT plus SM showed consistently higher iCDR in breast density categories B–D than women screened with DM. In particular, they did not show the distinctly low iCDR for women in category D that was found in the DM group. Thus, in women with extremely dense breasts, the difference in iCDR between DBT plus SM screened and DM screened was 5.8 per 1000, corresponding to an odds ratio of 3.8 (95% CI: 1.5, 11.1), or a relative increase of 256%. In women with dense breasts (ie, combining C and D categories), DBT plus SM still depicted 2.7 per 1000 women screened more invasive cancers than DM, corresponding to an odds ratio of 1.48 (95% CI: 1.17, 1.87) and a relative increase of 47% (8.3 per 1000 divided by 5.6 per 1000). This effect was more prominent in women aged 60–70 years than 50–59 years (Table 2). The detection rate of ductal carcinoma in situ did not notably differ between study arms in all density categories (Table S1 [online]).

The recall rates for further assessment were consistently higher with higher breast density but not different between DM and DBT plus SM (Table 3). In contrast, the positive predictive value of recall was higher in women with denser breasts who were screened with DBT plus SM (17.3% in density category C) as compared with DM (12.7%). Of note, the positive predictive value of recall was lowest in both study arms (13.5% for DBT plus SM and 8.0% for DM) for women with extremely dense breasts.

Tumor Characteristics

A descriptive analysis (Table 4) was performed to compare the characteristics of cancers detected with DBT plus SM

Table 2: Screen-detected Invasive Breast Cancers per Study Arm by Breast Density and Age Group

BI-RADS Breast Density Category: Fifth Edition*	Control Arm				Test Arm				Difference of iCDR	Odds Ratio‡
	Total	Outcome Missing†	Invasive BC	iCDR	Total	Outcome Missing†	Invasive BC	iCDR		
A	4476	1	16	3.6	4440	1	12	2.7	−0.9	0.79 (0.34, 1.78)
B	23549	15	102	4.3	22343	15	154	6.9	2.6	1.61 (1.24, 2.08)
C	19062	11	116	6.1	18791	19	156	8.3	2.2	1.37 (1.07, 1.76)
D	2634	5	6	2.3	3946	6	32	8.1	5.8	3.8 (1.5, 11.1)
A plus B	28025	16	118	4.2	26783	16	166	6.2	2.0	1.48 (1.16, 1.90)
50–59 years of age	16324	12	59	3.6	15485	13	61	3.9	0.3	1.09 (0.75, 1.59)
60–70 years of age	11701	4	59	5.0	11298	3	105	9.3	4.3	1.87 (1.34, 2.62)
C plus D	21696	16	122	5.6	22737	25	188	8.3	2.7	1.48 (1.17, 1.87)
50–59 years of age	14622	14	72	4.9	15317	15	102	6.7	1.8	1.36 (0.99, 1.86)
60–70 years of age	7074	2	50	7.1	7420	10	86	11.6	4.5	1.64 (1.14, 2.37)

Note.—Data are numbers of participants, besides invasive cancer detection rates (iCDRs), which are percentages per 1000 women screened. For examinations with missing breast density evaluations from one of the readers (<0.1%), the available assessment was used. Control arm represents digital mammography, and test arm represents digital breast tomosynthesis plus synthesized mammography. BC = breast cancer, BI-RADS = Breast Imaging Reporting and Data System.

* The highest breast density category of the independent double reading was used per examination.

† Numbers of women without evaluable outcome data (ie, data on invasive breast cancer detection).

‡ Adjusted for study site (ie, screening unit). Data in parentheses are 95% CIs.

Table 3: Recall Rate and PPV1 per Study Arm by Breast Density

BI-RADS Breast Density Category: Fifth Edition*	Control Arm				Test Arm			
	A	B	C	D	A	B	C	D
Recall								
Total	4476	23549	19062	2634	4440	22343	18791	3946
Recalls	89	1092	1176	155	93	950	1102	303
Recall rate (%)	2.0	4.6	6.2	5.9	2.1	4.3	5.9	7.7
Difference (%)	NA	NA	NA	NA	0.1	−0.3	−0.3	1.8
PPV1								
Recalls	89	1092	1176	155	93	950	1102	303
Outcome missing†	1	15	11	5	1	15	19	6
Invasive breast cancer plus ductal carcinoma in situ	17	129	148	12	14	175	187	40
PPV1 (%)	19.3	12.0	12.7	8.0	15.2	18.7	17.3	13.5
Difference (%)	NA	NA	NA	NA	−4.1	6.7	4.6	5.5

Note.—Data are numbers of participants, unless otherwise noted. For examinations with missing breast density evaluation from one of the readers (<0.1%), the available assessment was used. Control arm represents digital mammography, and test arm represents digital breast tomosynthesis plus synthesized mammography. BI-RADS = Breast Imaging and Reporting Data System, NA = not applicable, PPV1 = positive predictive value of recall.

* The highest breast density category of the independent double reading was used per examination.

† Numbers of recalled women without evaluable data on breast cancer detection.

and DM in women with density categories C and D. The small numbers of cancers detected with DM in extremely dense breasts (n = 6) limited in-depth statistical comparisons between study arms in this subcategory. Generally, the proportion of small invasive cancers and Union for International Cancer Control stage I tumors detected with DBT plus SM was higher than with DM. The invasive cancers detected by DBT plus SM were most often grade 2 tumors; category C had 58% (91 of 156 invasive cancers), and category D had 47% (15 of 32 invasive cancers) (Fig 2). In density category C, DBT plus SM depicted a higher proportion of invasive lobular cancers (Fig 3). When comparing cancers detected with DBT plus SM, a higher proportion of cancers with estrogen and progesterone receptor status less than 10% was observed in category D versus category C. HER2-positive tumors were less prevalent among cancers detected with DBT plus SM, and the Ki67 status was slightly more favorable.

Table S2 (online) shows the corresponding description of breast cancers with density categories A and B.

Table 4: Tumor Characteristics of Screen-detected Invasive Breast Cancers per Study Arm by Breast Density

BI-RADS Breast Density Category: Fifth Edition*	C		D	
	Control Arm	Test Arm	Control Arm	Test Arm
No. of invasive breast cancers	116	156	6	32
T category†				
pT1 plus cT1 (≤20 mm)	72 + 13 (73)	111 + 17 (82)	1 + 2 (50)	25 + 4 (91)
pT2+ plus cT2+ (>20 mm)	24 + 7 (27)	20 + 8 (18)	2 + 1 (50)	2 + 1 (9)
Median size (mm)‡	15.0 (9.0–22.0)	13.0 (9.0–18.0)	22.5 (14.0–30.3)	11.00 (5.8–15.0)
UICC category†				
UICC I (%)§	60 + 10 (65)	99 + 12 (73)	1 + 1 (40)	20 + 3 (82)
UICC II+ (%)‖	29 + 9 (35)	32 + 9 (27)	2 + 1 (60)	4 + 1 (18)
Missing	8	4	1	4
Grading				
Grade 1	34 (29)	48 (31)	1 (17)	10 (31)
Grade 2	69 (59)	91 (58)	3 (50)	15 (47)
Grade 3	13 (11)	17 (11)	2 (33)	7 (22)
Morphology				
NST	94 (81)	107 (69)	6 (100)	27 (84)
Lobular	17 (15)	37 (24)	0 (0)	4 (13)
Other	5 (4)	12 (8)	0 (0)	1 (3)
Estrogen receptor				
≤10%	7 (6)	9 (6)	0 (0)	4 (14)
>10%	109 (94)	144 (94)	6 (100)	25 (86)
Missing	0	3	0	3
Progesterone receptor				
≤10%	24 (21)	30 (20)	0 (0)	10 (34)
>10%	91 (79)	123 (80)	6 (100)	19 (66)
Missing	1	3	0	3
HER2				
Negative	95 (82)	138 (92)	3 (50)	26 (87)
Positive	21 (18)	12 (8)	3 (50)	4 (13)
Missing	0	6	0	2
Ki67				
<25%	89 (77)	124 (81)	3 (50)	22 (73)
≥25%	26 (23)	29 (19)	3 (50)	8 (27)
Missing	1	3	0	2

Note.—Data are presented as numbers of women with percentages in parentheses, unless otherwise noted. Control arm represents digital mammography, and test arm represents digital breast tomosynthesis plus synthesized mammography. cT = clinical tumor size, HER2 = human epidermal growth factor receptor 2, NST = invasive carcinoma of no special type, pT = histologic tumor size, UICC = Union for International Cancer Control.

* The highest breast density category of the independent double reading was used per examination. For examinations with missing breast density evaluation from one of the readers (<0.1%), the available assessment was used.

† Data based on pT or cT when neoadjuvant therapy was applied. For women with neoadjuvant therapy, tumor size, regional lymphnode metastasis, and distant metastasis were prospectively assessed by the responsible physician at the study site.

‡ Data in parentheses are IQRs.

§ UICC I = tumor size of 20 mm or smaller, no regional or distant metastasis. Based on pT + cT.

‖ UICC II+ = tumor size of at least 20 mm, or any regional or distant metastasis. Based on pT + cT.

Discussion

The present analyses focused on a masking of radiologic tumor signs by dense breast tissue (17). We found that in women with extremely dense breasts (category D), the use of digital breast tomosynthesis (DBT) plus synthesized mammography (SM) resulted in an invasive cancer detection rate (iCDR) of 8.1 compared with 2.3 per 1000 women screened with digital mammography, a relative increase of over 250%. In fact, with DBT plus SM, the iCDR for breast density category D achieves detection rates comparable to those in category C.

As expected from randomization, the frequencies of women with dense breasts (American College of Radiology categories 3 and 4; categories C and D) were similar in the two study arms. Extremely dense breasts (American College of Radiology category 4 or category D) accounted for less than 10% in each study arm. This is consistent with previous reports (5,22,23), suggesting that the transition from DM to DBT does not change the reporting of breast density.

Previous DBT plus DM studies stratified screened women into those with nondense (ie, categories A and B) versus dense breasts (ie, categories C and D) and reported significantly higher iCDR with DBT for the latter (10,11,24). For women with extremely dense breasts (ie, category D), comparative studies did not find significantly higher iCDR for DBT plus DM (10,12). Due to the low prevalence of extremely dense breasts, most studies had difficulties estimating the effect of DBT on cancer detection

precisely (11,24). DBT might be effective in women with extremely dense breasts combined with further risk factors leading to a significantly lower risk of advanced breast cancers over a period of 12 months (25).

TOSYMA as a large randomized controlled trial identified a clearly higher iCDR with DBT plus SM among women from category D (14,15). Although there is no consensus on the optimal approach (12), the TOSYMA trial results may suggest that especially women with extremely dense breasts could benefit from a transition from DM to DBT plus SM screening (26,27). Of note, the higher iCDR was achieved with a higher positive predictive value of recall in the DBT plus SM arm. The detection rate of breast cancer overall, that is, of invasive breast cancer plus ductal carcinoma in situ, was solely due to the higher iCDR and not related to higher ductal carcinoma in situ detection, irrespective of breast density.

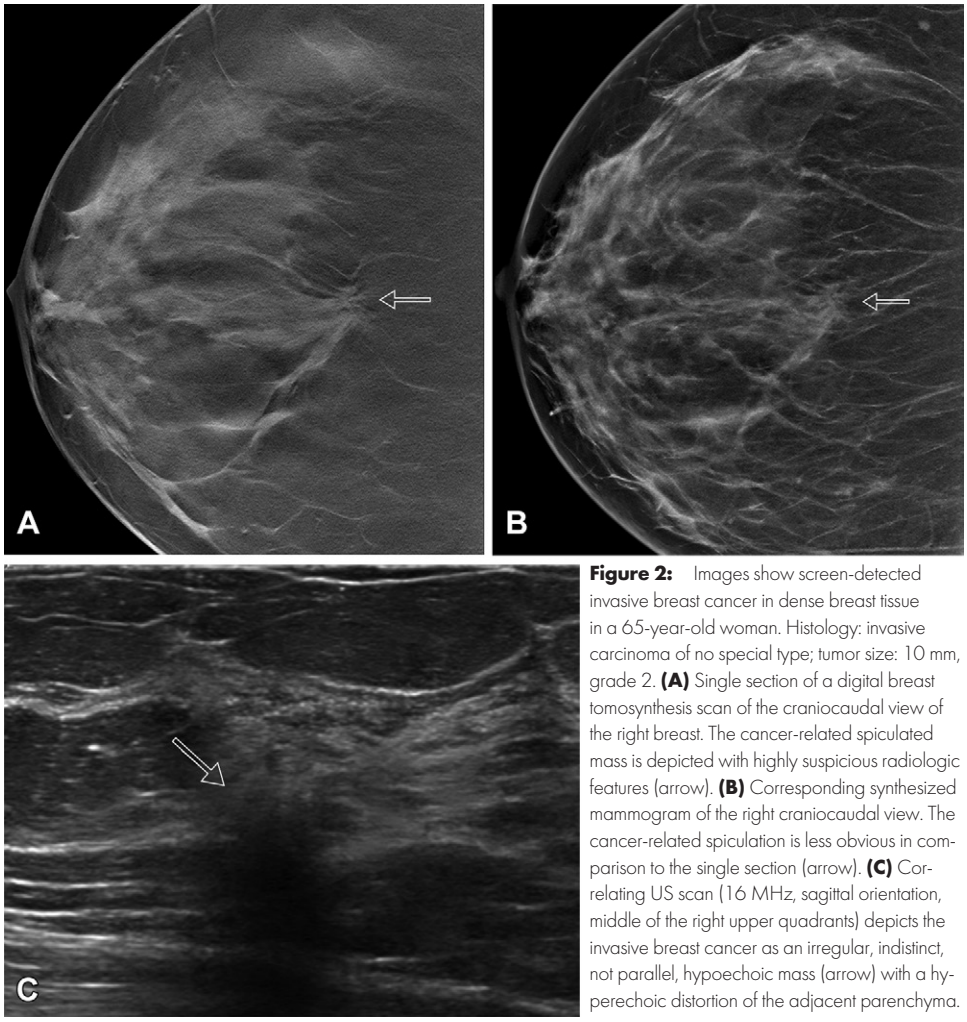

Figure 2: Images show screen-detected invasive breast cancer in dense breast tissue in a 65-year-old woman. Histology: invasive carcinoma of no special type; tumor size: 10 mm, grade 2. **(A)** Single section of a digital breast tomosynthesis scan of the craniocaudal view of the right breast. The cancer-related spiculated mass is depicted with highly suspicious radiologic features (arrow). **(B)** Corresponding synthesized mammogram of the right craniocaudal view. The cancer-related spiculation is less obvious in comparison to the single section (arrow). **(C)** Correlating US scan (16 MHz, sagittal orientation, middle of the right upper quadrants) depicts the invasive breast cancer as an irregular, indistinct, not parallel, hypoechoic mass (arrow) with a hyperechoic distortion of the adjacent parenchyma.

Among the few women with category A breast density, who typically have the lowest breast cancer incidence, the iCDR of DBT plus SM was not higher than that of DM, consistent with other estimates (12,23). There was also no increase in positive predictive value of recall. Thus, it appears that DM alone could be sufficient for screening category A breasts.

The number of category D cancers in the DM arm is low; this precluded a more detailed comparison of tumor characteristics. As compared with DM, the cancers detected with DBT plus SM in the numerically more robust category C show a high proportion of grade 2 tumors, a higher proportion of lobular cancers but no marked differences in tumors greater than 20 mm in diameter or tumors with grade 3 or hormone receptor–negative or HER2-positive status. This is consistent with reports and supports that higher sensitivity of DBT for architectural abnormalities improves the diagnosis of invasive carcinomas overall and invasive lobular carcinomas in particular (24,26).

As a strength, this large randomized controlled trial was embedded into a population-based screening program (18). Demographic characteristics of study participants and outcomes in the control arm are consistent with data from the program outside the study (28). Patient-level information

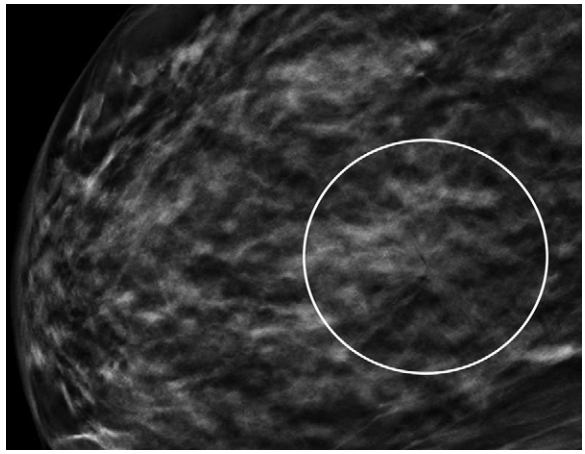

Figure 3: Image shows screen-detected invasive breast cancer in dense breast tissue in a 61-year-old woman without a correlate in the synthesized mammogram as well as in the US examination during assessment. Histology: invasive lobular carcinoma; tumor size: 6 mm, grade 2. Single section of a digital breast tomosynthesis scan of the craniocaudal view of the right breast depicts the tumor-related architectural distortion (circle).

allowed exploratory subgroup analyses. The multicenter, multivendor approach with a mix of readers and mammography devices should confer high feasibility and external transferability of the employed methods.

This study had certain limitations. The analyses are exploratory and hypothesis generating but did not confirm or reject hypotheses in terms of confirmatory statistical results. Study results are based on only one screening round in an ongoing screening program (ie, in women from prevalence and incidence screens); a detailed analysis of iCDR by breast density to distinguish between prevalence and incidence screens with DBT plus SM was not possible (12). Furthermore, readers' attention to the test arm may have been increased.

The TOSYMA study protocol includes a prospective follow-up of the participants by cancer registries (19); this may help to further assess sources of potential over- as well as underdiagnosis (13,29–33). In addition, the calculation of cumulative incidence rates, sensitivity, and specificity per breast density are expected to consolidate the view on diagnostic performance and clinical benefit of DBT plus SM.

In conclusion, the TOmosynthesis plus SYnthesized MAmmography trial shows that the higher invasive cancer detection rate found for digital breast tomosynthesis (DBT) plus synthesized mammography (SM), as compared with digital mammography (DM) screening, is present in all density categories apart from women with predominantly fatty parenchyma. The strongest absolute and relative differences were observed among women with extremely dense breasts. This suggests that the limited sensitivity of DM in women with extremely dense breasts may be compensated with DBT plus SM.

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