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Research article

# Mammographic features and screening outcome in a randomized controlled trial comparing digital breast tomosynthesis and digital mammography

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ABSTRACT

*Purpose:* To compare the distribution of mammographic features among women recalled for further assessment after screening with digital breast tomosynthesis (DBT) versus digital mammography (DM), and to assess associations between features and final outcome of the screening, including immunohistochemical subtypes of the tumour.

*Methods:* This randomized controlled trial was performed in Bergen, Norway, and included 28,749 women, of which 1015 were recalled due to mammographic findings. Mammographic features were classified according to a modified BI-RADS-scale. The distribution were compared using 95 % confidence intervals (CI).

*Results:* Asymmetry was the most common feature of all recalls, 24.3 % (108/444) for DBT and 38.9 % (222/571) for DM. Spiculated mass was most common for breast cancer after screening with DBT (36.8 %, 35/95, 95 %CI: 27.2–47.4) while calcifications (23.0 %, 20/87, 95 %CI: 14.6–33.2) was the most frequent after DM. Among women screened with DBT, 0.13 % (95 %CI: 0.08–0.21) had benign outcome after recall due to indistinct mass while the percentage was 0.28 % (95 %CI: 0.20–0.38) for DM. The distributions were 0.70 % (95 %CI: 0.57–0.85) versus 1.46 % (95 %CI: 1.27–1.67) for asymmetry and 0.24 % (95 %CI: 0.16–0.33) versus 0.54 % (95 %CI: 0.43–0.68) for obscured mass, among women screened with DBT versus DM, respectively. Spiculated mass was the most common feature among women diagnosed with non-luminal A-like cancer after DBT and after DM.

*Conclusions:* Spiculated mass was the dominant feature for breast cancer among women screened with DBT while calcifications was the most frequent feature for DM. Further studies exploring the clinical relevance of mammographic features visible particularly on DBT are warranted.

## 1. Introduction

Mammography is the most common screening tool for breast cancer. During the last decades, standard digital mammography (DM) has replaced screen-film mammography in the Western part of the world [1, 2]. However, digital breast tomosynthesis (DBT) is expected to be the future screening tool for breast cancer [3–5]. European studies have reported higher rates of screen-detected breast cancer when comparing

*Abbreviations:* DBT, digital breast tomosynthesis including synthetic 2D mammography; DM, standard digital mammography; IC, interval cancer; PPV, positive predictive value for recalls; SDC, screen detected cancers; SM, synthetic two-dimensional mammography.

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DBT alone or in combination with DM/synthetic mammograms (SM) versus standard DM [2,6–10]. Recall rates seem to vary in prospective studies [4,8,9,11]. Higher rate of screen-detected breast cancer in DBT is expected to reduce the number of interval cancers although the few published studies on interval cancer have lacked statistical power to conclude on this [12–16]. An increased rate of screen-detected cancer, without a simultaneous reduction in interval cancer rate, might indicate that DBT detects small and biologically less aggressive cancers, potentially representing small, low proliferation tumors, which could represent overdiagnosis and thus cause overtreatment [13,14].

The Tomosynthesis trial in Bergen (the To-Be trial), a randomized controlled trial conducted in Bergen, Norway, compared screening outcome for DBT + SM versus DM [17]. The rates of screen-detected breast cancer did not differ statistically for the two techniques, thus not reproducing results from other studies showing a substantial higher rate of screen-detected cancer among those screened with DBT [4,8,9,11,18,19]. However, the To-Be trial showed that recall rate and rate of false positive screening examinations were lower for DBT than for DM [17]. The somewhat unexpected results from the To-Be trial might relate to the use of first generation equipment, limited experiences in screen-reading DBT among the breast radiologists, or the perception and/or interpretation of mammographic features.

The specific mammographic features that lead to recalls and the diagnosis of screen-detected breast cancer are well documented for DM, and their correlation with histopathological characteristics have been reported [20–23]. Spiculated masses are more often estrogen- and progesterone receptor positive, HER2 negative and with lower proliferative activity compared with other masses, all indicating less aggressive tumors. Calcifications in general are associated with ductal carcinoma in situ (DCIS) and with invasive ductal carcinoma in combination with DCIS, while casting calcifications are associated with non-luminal-cancer, more often histologic grade 3 and decreased overall survival [20–23]. Less is known about mammographic features among women recalled after DBT and most of the published studies have focused on mammographic features of breast cancer while features with benign outcome is less investigated [9,11,24–27].

Overlapping breast tissue might resemble mammographic abnormalities in DM, thereby causing false positive screening results, or the opposite, the overlapping tissue might obscure tumors, resulting in false negative screening results [11,28]. DBT is known to reduce the effect of overlapping breast tissue, thereby improving visualization of both malignant and benign findings [28]. Better understanding of the features, and their association with malignant versus benign/negative outcome is thus warranted.

To gain knowledge about mammographic features of women recalled for further assessment after screening with DBT + SM (hereafter referred as DBT) versus standard DM, we analyzed data collected as a part of the To-Be trial. This study aimed to compare the distribution of mammographic features in women recalled after screening with DBT versus DM, and assess associations between features and final outcome of the screening examination, including immunohistochemically subtypes of the tumours. Our hypothesis was that recalls due to masses would result in a higher percentage of breast cancer for women screened with DBT versus DM.

## 2. Material and methods

The To-Be trial was a randomized controlled trial approved by the Regional Committees for Medical and Health Research Ethics (2015/424) and registered at ClinicalTrials.gov (NCT02835625). Written informed consent from all participating women was obtained. The trial was conducted in Bergen, as a part of BreastScreen Norway during one screening round, in 2016 and 2017. BreastScreen Norway is a population-based screening program for breast cancer, administered by the Cancer Registry of Norway. The program invites women aged 50–69 years to two-view mammography biennially. The screening program and the trial is described in detail elsewhere [17,29–31].

### 2.1. Study sample

A total of 28,749 women were included in the To-Be trial; 14,380 screened with DBT and 14,369 with DM [17]. Among those screened with DBT, 444 (3.1 %) were recalled due to mammographic findings while the corresponding number for DM was 571 (4.0 %). The recalled women comprised the study sample in this study (Fig. 1). We received a pseudonymized dataset from the Cancer Registry of Norway, containing information about the women's screening examination and recall assessment. Data included diagnostic procedures, mammographic features and histopathological findings. The DBT arm included 95 breast malignancies; 80 invasive cancers and 15 ductal carcinoma in situ (DCIS) whereas the DM arm included 87 malignancies; 71 invasive cancers and 16 DCIS (Figs. 2–4). Invasive cancers with DCIS components was considered invasive.

### 2.2. Screen-reading and consensus

All women underwent two-view (cranio-caudal and medio-lateral oblique) DBT or DM of both breasts. We used first generation equipment from GE (Senographe Essential SenoClaire 3D Breast Tomosynthesis™) for imaging. Eight radiologists with varying experience in breast radiology and screen-reading (0–20 years) participated in the screen-reading [29]. All screening mammograms were independently read by two breast radiologists. The hanging protocol included two sets of prior screening mammograms, with even older images available at the workstation, (GE Healthcare MammoWorkstation Version 4.7.0 Image Diagnost). Mammograms with suspicious findings indicated by one or both radiologists (n = 1968) were discussed in a consensus meeting, including two or more radiologists, where 48 % of the cases were dismissed, leaving 1015 women recalled for further assessment, 444 for DBT and 571 for DM (Fig. 1).

### 2.3. Recall assessment

Recall assessments were performed by the same eight radiologists who did the screen-reading. Recalled women underwent additional imaging (ultrasound alone or in combination with DM and/or DBT) and clinical examination before the radiologist decided whether a biopsy was needed. The diagnostic biopsies were performed under ultrasound or stereotactic guidance. MRI was performed in women with lobular cancer confirmed with needle biopsy, highly suspicious findings in combination with mammographic dense breast (Breast Imaging Reporting and Data System, BI-RADS, c or d [32]), and when neoadjuvant treatment was considered, according to national guidelines in Norway [33]. We used contrast-enhanced spectral mammography in women with suspicious MRI-findings without an ultrasound-correlate, and in women with contraindications for MRI (pacemakers or claustrophobia).

### 2.4. Variables of interest

We reported mean age at screening (years) and screening history for the recalled women. Screening history was defined as prevalent (first screening examination in BreastScreen Norway) or subsequent screening examination.

Recall was defined as further assessment due to mammographic findings. The outcome of the recall could be positive or negative. Positive was defined as ductal carcinoma in situ or invasive breast cancer, hereafter referred as breast cancer, while negative was defined as no cancer diagnosed after additional imaging alone or in combination with a needle biopsy. Positive predictive value of the recalls (PPV-1) was defined as breast cancer diagnosed among the women recalled. Positive predictive value of biopsies (PPV-3) was defined as breast cancer diagnosed among those biopsied.

At consensus, before the women were recalled, the radiologists

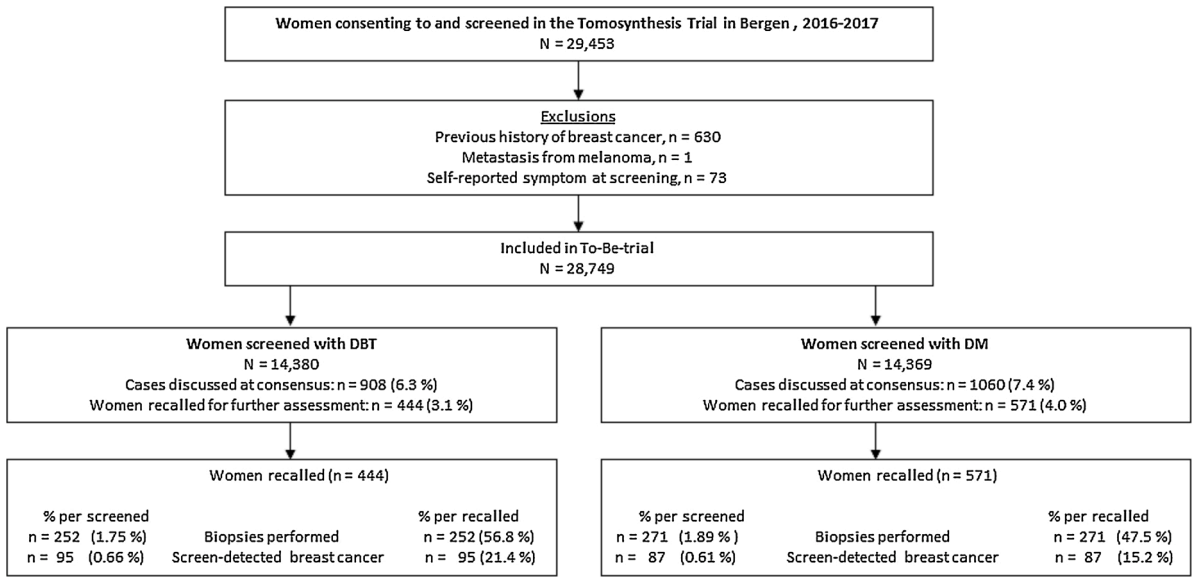


**Fig. 1.** Number (n) and percentage (%) of women included in the To-Be trial 2016–2017, discussed at consensus and recalled for assessment due to mammographic findings, biopsies performed and breast cancer detected, by screening technique.

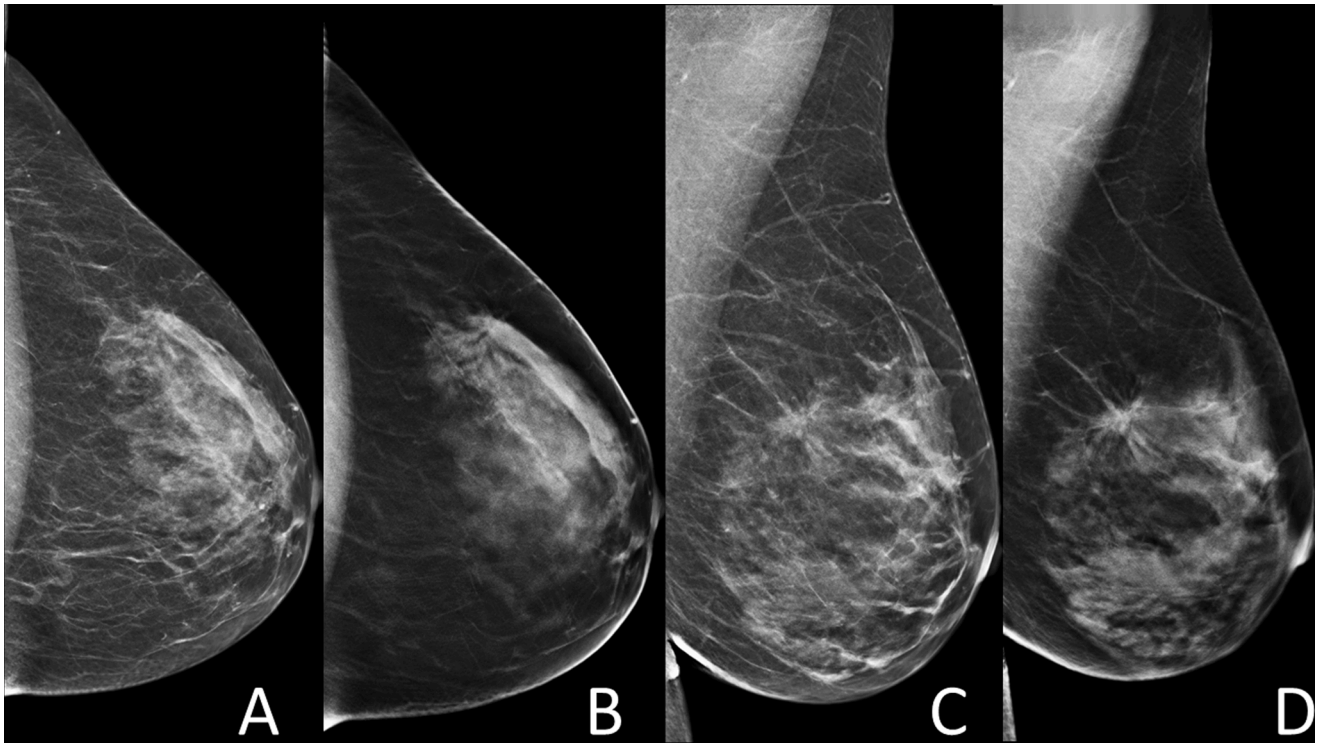


**Fig. 2.** Left craniocaudal synthetic 2D image (A) and 1 mm plane (B), left mediolateral oblique synthetic 2D image (C) and 1 mm plane (D), in a woman recalled after DBT because of spiculated mass in the lateral upper part of left breast. Histologic examination revealed a nonluminal A-like invasive carsinoma, histologic grade 1 and ductal carsinoma in situ grade 2.

classified the women's mammographic density according to BI-RADS and mammographic features to a modified BI-RADS-scale [30,32]. Circumscribed mass was defined as a mass with more than 75 % of the margin being well-defined and no part of the margin appearing indistinct. Obscured mass was defined as a mass with less than 75 % of the margin being well-defined and no part of the margin appearing indistinct. The category indistinct mass was used when the whole or parts of the margin was indistinct (poorly defined) or microlobulated as defined in BI-RADS [32]. We defined a mass including calcifications "mass with calcifications" while spiculated mass, architectural distortion, asymmetry, calcifications, and associated features were defined according to BI-RADS [32].

Invasive cancers were histologically classified into five subtypes based on immunohistochemistry [34] and collapsed into two groups; luminal A-like and non-luminal A-like (Luminal B HER2-, Luminal B HER2+, HER2+, and triple negative. Low Ki67-level was defined as Ki-67 level $<30$ %, high level as Ki-67 $\geq 30$ %).

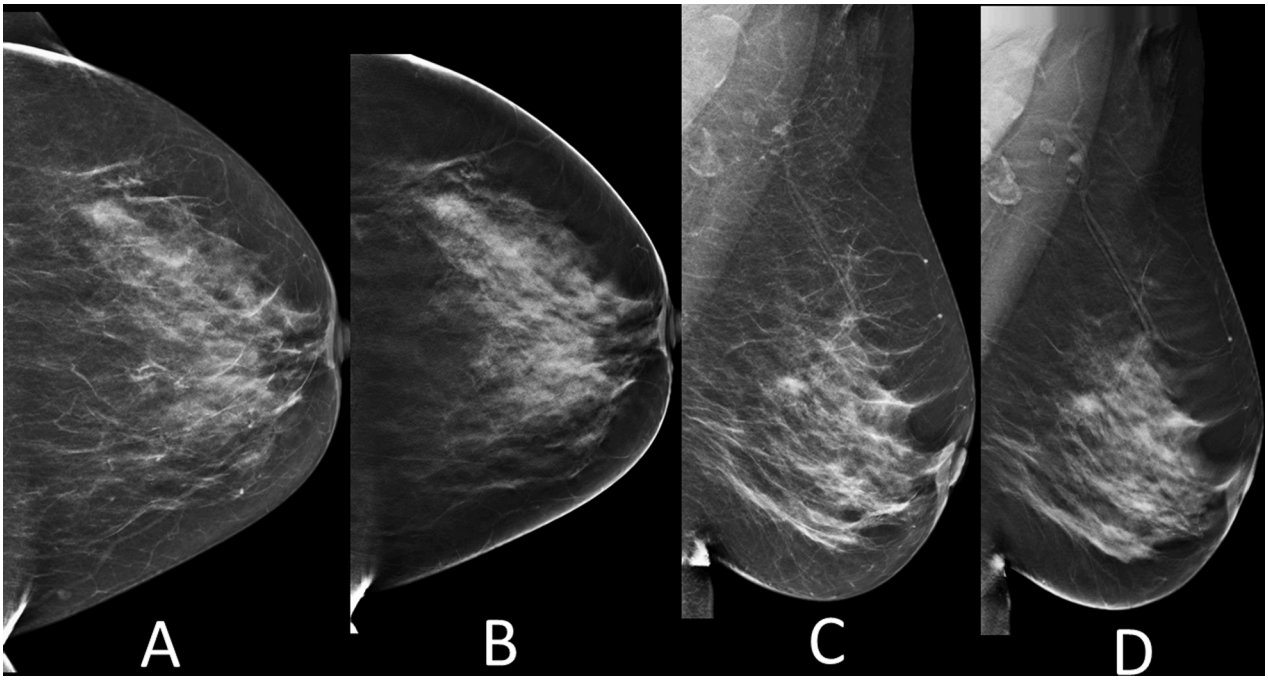


**Fig. 3.** Both readers picked this indistinct tumor in the lateral part of the left breast in this woman screened with DBT. **A and B:** Left craniocaudal synthetic 2D image and 1 mm plane, **C and D:** Left mediolateral oblique synthetic 2D image and 1 mm plane. The tumor measured 18 mm at histology, and was a nonluminal A-like invasive carcinoma NST, histologic grade 3.

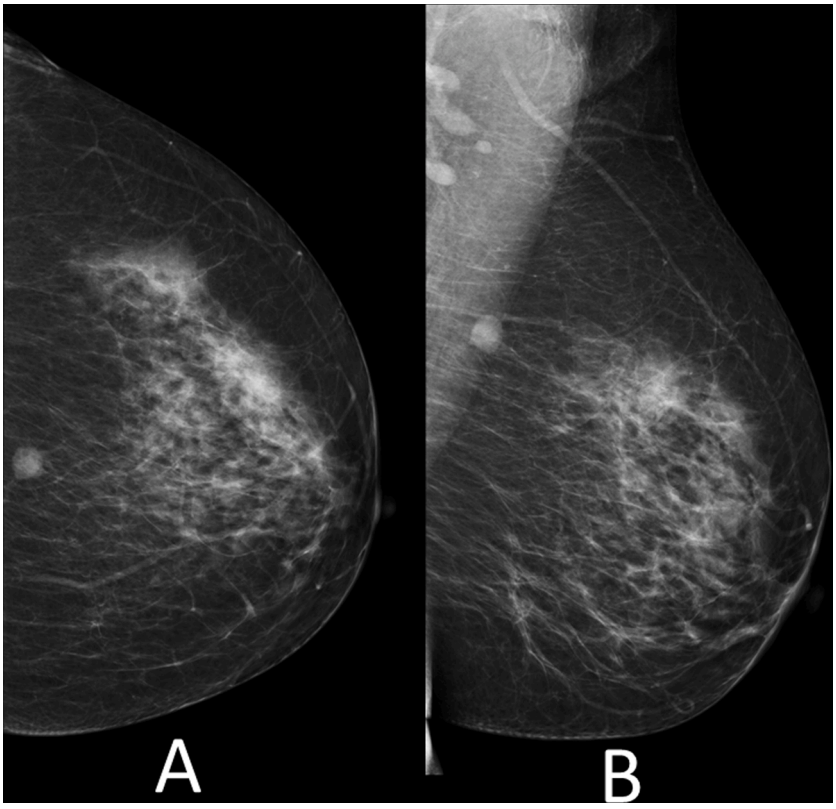


**Fig. 4.** Left craniocaudal (A) and left mediolateral oblique (B) image in woman recalled after screening with digital mammography. This was a 13 mm luminal A-like invasive carcinoma NST, histologic grade 1.

### 2.5. Statistical analyses

Descriptive results were presented for DBT and DM separately. Mean and standard deviations of the age for recalled women was described in years. Screening history, mammographic density, assessment method used at recall, use of needle biopsy and mammographic features were presented as numbers and percentages with 95 % confidence intervals (CI) among the recalled women.

Number and percentage of mammographic features were presented with different denominators; a) positive and negative recall assessment; b) mammographic feature; and c) number of screened women, for DBT and for DM. The distribution of mammographic features for luminal A-like or non-luminal A-like cancers were presented as number and percentage by a) subgroups and b) mammographic feature, for DBT and DM. We tested for differences between the two screening techniques using 95 % CI. The statistical package Stata (version 15; Texas, USA) was used for all data analyses.

## 3. Results

Age, screening history and mammographic density did not differ statistically for women recalled after screening with DBT (n = 444) versus DM (n = 571) (Table 1). All recalled women irrespective of screening technique underwent ultrasound as a part of their assessments, whereas 85.6 % (380/444) and 89.0 % (508/571) of those recalled after DBT and DM, respectively, had other imaging modalities in addition to ultrasound. A higher proportion of the women recalled after DBT 56.8 % (252/444, 95 %CI: 52.0−61.4) had a needle biopsy compared to those screened and recalled after DM, 47.5 % 271/571 (95 %CI: 43.3−51.6). PPV-1 was 21.4 % for DBT versus 15.2 % for DM, while PPV-3 was 37.7 % and 32.1 %, respectively.

The most common mammographic feature among the recalled women was asymmetry, 24.3 % for DBT (108/444, 95 %CI: 20.4−28.6) and 38.9 % for DM (222/571, 95 %CI: 34.9−43.0) (Table 2). A higher percentage of women were recalled due to circumscribed mass and architectural distortions after screening with DBT compared to DM; for circumscribed mass; 18.7 % (83/444, 95 %CI: 15.2−22.6) versus 8.1 % (46/571, 95 %CI:6.0−10.6) and architectural distortion; 15.8 % (70/444, 95 %CI: 12.5−19.5) versus 7.9 %, (45/571, 95 %CI:5.8−10.49) for DBT and DM, respectively. An obscured mass was less frequently observed after DBT (7.9 %, 35/444, 95 %CI: 5.6−10.8) compared with DM (14.2 %, 81/571, 95 %CI: 11.4−17.3).

Among the recalled women with positive outcome/breast cancer 36.8 % (35/95, 95 %CI: 27.2−47.4) cases diagnosed after screening with DBT were classified as spiculated mass while it was 18.4 % (16/87, 95 %CI: 10.9−28.1) for DM (Table 3a). Indistinct mass was the second most frequent feature among the cancer cases both for DBT, 16.8 % (16/95, 95 %CI: 9.9−25.9) and DM, 18.4 % (16/87, 95 %CI: 10.9−28.1). Calcifications was observed in 13.7 %, (13/95, 95 %CI: 7.5−22.3) of the cancer cases for DBT and 23.0 % (20/87, 95 %CI: 14.6−33.2) for DM. Among the recalled cases with negative outcome, asymmetry (Figs. 5 and 6) and obscured mass were less common features in DBT compared to DM. Asymmetry was found in 28.9 % (101/349, 95 %CI: 24.2−34.0) of the negative cases after recall screening with DBT versus 43.4 % (210/484, 95 %CI:38.9−47.9) after DM, and obscured mass in 9.7 % (34/349, 95 %CI: 6.8−13.3) after DBT versus 16.1 % (78/484, 95 %CI: 13.0−19.7) after DM.

Among women recalled due to asymmetry, negative outcome was observed in 93.5 % (101/108, 95 %CI: 87.1−97.4) for those screened with DBT and 94.6 % (210/222, 95 %CI: 90.7−97.2) for DM (Table 3b). Negative outcome after recall for indistinct mass was observed in 54.3 % (19/35, 95 %CI: 36.6−71.2) for DBT and 71.4 % (40/56, 95 %CI: 57.8−82.7) for DM.

Using the number of screened women in the denominator, the percentage of breast cancer classified as spiculated mass was 0.24 % (35/14,380, 95 %CI: 0.17−0.34) for DBT compared to 0.11 % (16/14,369, 95 %CI: 0.06−0.18) for DM (Table 3c). The percentage of benign outcome was 0.13 % (19/14380, 95 %CI: 0.08−0.21) for indistinct mass among women screened with DBT versus 0.28 % (40/14369, 95 %CI: 0.20−0.38 for DM, asymmetry 0.70 % (101/14380, 95 %CI:0.57−0.85) versus 1.46 % (210/14369, 95 %CI: 1.27−1.67) and obscured mass 0.24 % (34/14380, 95 %CI:0.16−0.33) versus 0.54 % (74/14369, 95 %CI: 0.43−0.68).

Among women diagnosed with invasive breast cancer after screening with DBT, 58.7 % (44/75, 95 %CI: 46.7–69.9) were luminal A-like compared to 61.4 % (43/70, 95 %CI: 49.0–72.8) of the women screened with DM (Table 4). For DBT, 52.3 % (23/44, 95 %CI: 36.7−67.5) of the luminal A-like cancers were classified as spiculated mass compared to 20.9 % (9/43, 95 %CI: 10.0−36.0) after DM. Spiculated mass was the most frequent feature among non-luminal A-like cancers, 29.0 % (9/31, 95 %CI: 14.2−48.0) after screening with DBT and 25.9 % (7/27, 95 %CI: 11.1−46.3) after screening with DM. Among malignant indistinct masses, 53.3 % (8/15, 95 %CI: 26.6−78.7) were non-luminal A-like for DBT versus 31.3 % (5/16, 95 %CI: 11.0−58.7) for DM.

**Table 1**
Characteristics of women recalled for assessment due to mammographic findings, methods used in the assessment, numbers (n) and percentages (%) of women who had a needle biopsy, positive predictive value of recalls (PPV-1) and of performed biopsies (PPV-3) after screening with digital breast tomosynthesis (DBT) or digital mammography (DM), in the To-Be trial.

| | **DBT** (N = 444) | | **DM** (N = 571) | |
|---|---|---|---|---|
| | n | % (95 % CI) | n | % (95 % CI) |
| Age (mean, standard deviation) | 444 | 58.5 (6.4) | 571 | 59.0 (6.3) |
| Screening history | | | | |
| Prevalent screens (n, %) | 128 | 28.8 (24.7−33.3) | 136 | 23.8 (20.4−27.5) |
| Subsequent screens (n, %) | 316 | 71.2 (66.7−75.3) | 435 | 76.2 (72.5−79.6) |
| Mammographic density | | | | |
| BIRADS a (n, %) | 17 | 3.8 (2.2−6.1) | 21 | 3.7 (2.3−5.6) |
| BIRADS b (n, %) | 281 | 63.3 (58.6−67.8) | 348 | 60.9 (56.8−65.0) |
| BIRADS c (n, %) | 137 | 30.9 (26.6−35.4) | 193 | 33.8 (29.9−37.8) |
| BIRADS d (n, %) | 9 | 2.0 (0.9−3.8) | 9 | 1.6 (0.7−3.0) |
| Assessment | | | | |
| Ultrasound alone | 64 | 14.9 (11.3−18.0) | 63 | 11.0 (8.6−13.9) |
| Ultrasound and other imaging[a] | 380 | 85.6 (82.0−88.7) | 508 | 89.0 (86.1−91.4) |
| Biopsy (n, %) | 252 | 56.8 (52.0−61.4) | 271 | 47.5 (43.3−51.6) |
| PPV-1 | 95/444 | 21.4 (17.7−25.5) | 87/571 | 15.2 (12.4−18.5) |
| PPV-3 | 95/252 | 37.7 (31.7−44.0) | 87/271 | 32.1 (26.6−38.0) |

[a] DM, DBT, contrast enhanced spectral mammography and/or Magnetic resonance imaging.

**Table 2**
Distribution (n and %) of mammographic features in women recalled for assessment due to mammgraphic findings, by screening technique (digital breast tomosynthesis, DBT, or digital mammography, DM), in the To-Be trial, 2016-2017.

| | **DBT (N = 444)** | | **DM (N = 571)** | |
|---|---|---|---|---|
| Mammographic features | n | % (95 % CI) | n | % (95 % CI) |
| Asymmetry | 108 | 24.3 (20.4−28.6) | 222 | 38.9 (34.9−43.0) |
| Circumscribed mass | 83 | 18.7 (15.2−22.6) | 46 | 8.1 (6.0−10.6) |
| Architectural distortion | 70 | 15.8 (12.5−19.5) | 45 | 7.9 (5.8−10.4) |
| Calcifications | 49 | 11.0 (8.3−14.3) | 78 | 13.7 (10.9−16.8) |
| Spiculated mass | 37 | 8.3 (5.9−11.3) | 16 | 2.8 (1.6−4.5) |
| Indistinct mass | 35 | 7.9 (5.6−10.8) | 56 | 9.8 (7.5−12.5) |
| Obscured mass | 35 | 7.9 (5.6−10.8) | 81 | 14.2 (11.4−17.3) |
| Mass with calcifications | 22 | 5.0 (3.1−7.4) | 21 | 3.7 (2.3−5.6) |
| Associated features | 4 | 0.9 (0.2−2.3) | 5 | 0.9 (0.3−2.0) |
| No information | 1 | 0.2 (0.0−1.2) | 1 | 0.2 (0.0−1.0) |

**Table 3**
Number and distribution (n,%) of mammographic features for recalled women with positive (invasive breast cancer and/or ductal carcinoma in situ) and negative (benign after assessment with or without needle biopsy) outcome by a) recall outcome, b) by mammographic features, c) by rates of screened women, stratified by screening technique (digital breast tomosynthesis, DBT and digital mammography, DM) in the To-Be trial, 2016-2017.

| a) By recall outcome | DBT (N = 444) | | | | DM (N = 571) | | | |
|---|---|---|---|---|---|---|---|---|
| | Positive n = 95 | | Negative n = 349 | | Positive n = 87 | | Negative n = 484 | |
| | n | % (95 % CI) | n | % (95 % CI) | n | % (95 % CI) | n | % (95 % CI) |
| Spiculated mass | 35 | 36.8 (27.2–47.4) | 2 | 0.6 (0.1–2.1) | 16 | 18.4 (10.9–28.1) | – | |
| Indistinct mass | 16 | 16.8 (9.9–25.9) | 19 | 5.4 (3.3–8.4) | 16 | 18.4 (10.9–28.1) | 40 | 8.3(6.0–11.1) |
| Calcifications | 13 | 13.7 (7.5–22.3) | 36 | 10.3 (7.3–14.0) | 20 | 23.0 (14.6–33.2) | 58 | 12.0 (9.2–15.2) |
| Architectural distortion | 10 | 10.5 (5.2–18.5) | 60 | 17.2 (13.4–21.6) | 7 | 8.0 (3.3–15.9) | 38 | 7.9 (5.6–10.6) |
| Asymmetry | 7 | 7.4 (3.0–14.6) | 101 | 28.9 (24.2–34.0) | 12 | 13.8 (7.3–22.9) | 210 | 43.4 (38.9–47.9) |
| Mass with calcifications | 7 | 7.4 (3.0–14.6) | 15 | 4.3 (2.4–7.0) | 11 | 12.6 (6.5–21.5) | 10 | 2.1 (1.0–3.8) |
| Circumscribed mass | 5 | 5.3 (1.7–11.9) | 78 | 22.3 (18.1–27.1) | 2 | 2.3 (0.3–8.1) | 44 | 9.1 (6.7–12.0) |
| Obscured mass | 1 | 1.1 (0.0–5.7) | 34 | 9.7 (6.8–13.3) | 3 | 3.4 (0.7–9.7) | 78 | 16.1 (13.0–19.7) |
| Associated features | 1 | 1.1 (0.0–5.7) | 3 | 0.9 (0.2–2.5) | – | | 5 | 1.0 (0.3–2.4) |
| No information | – | | 1 | 0.3 (0.0–1.6) | – | | 1 | 0.2 (0.0–1.1) |
| **b) By mammographic feature** | **DBT (N = 444)** | | | | **DM (N = 571)** | | | |
| | n | % (95 % CI) | n | % (95 % CI) | n | % (95 % CI) | n | % (95 % CI) |
| Spiculated mass | 35 | 94.6 (81.8–99.3) | 2 | 5.4 (0.7–18.2) | 16 | 100 (79.4–1) | – | |
| Indistinct mass | 16 | 45.7 (28.8–63.4) | 19 | 54.3 (36.6–71.2) | 16 | 28.6 (17.3–42.2) | 40 | 71.4 (57.8–82.7) |
| Calcifications | 13 | 26.5 (14.9–41.1) | 36 | 73.5 (58.9–85.1) | 20 | 25.6 (16.4–36.8) | 58 | 74.4 (63.2–83.6) |
| Architectural distortion | 10 | 14.3 (7.1-–24.7) | 60 | 85.7 (75.3–92.9) | 7 | 15.6 (70.5–93.5) | 38 | 84.4(70.5–93.5) |
| Asymmetry | 7 | 6.5 (2.6–12.9) | 101 | 93.5 (87.1–97.4) | 12 | 5.4 (2.8–9.3) | 210 | 94.6 (90.7–97.2) |
| Mass with calcifications | 7 | 31.8 (13.9–54.9) | 15 | 68.2 (45.1–86.1) | 11 | 52.4 (29.8–74.3) | 10 | 47.6(25.7–70.2) |
| Circumscribed mass | 5 | 6.0 (2.0–13.5) | 78 | 94.0 (81.9–95.7) | 2 | 4.3 (0.5–14.8) | 44 | 95.7 (85.2–99.5) |
| Obscured mass | 1 | 2.9 (0.1–14.9) | 34 | 97.1 (85.1–99.9) | 3 | 3.7 (0.8–10.4) | 78 | 96.3 (89.6–99.2) |
| Associated features | 1 | 25.0 (0.6–80.6) | 3 | 75.0 (19.4–99.4) | – | | 5 | 100 (47.8–1) |
| No information | | | 1 | 100 (2.5–1) | – | | 1 | 100 (2.5–1) |
| **c) By screened women** | **DBT (N = 14,380)** | | | | **DM (N = 14,369)** | | | |
| | n | % (95 % CI) | n | % (95 % CI) | n | % (95 % CI) | n | % (95 % CI) |
| Spiculated mass | 35 | 0.24 (0.17–0.34) | 2 | 0.01 (0.00–0.05) | 16 | 0.11 (0.06–0.18) | – | |
| Indistinct mass | 16 | 0.11 (0.06–0.18) | 19 | 0.13 (0.08–0.21) | 16 | 0.11 (0.06–0.18) | 40 | 0.28 (0.20–0.38) |
| Calcifications | 13 | 0.09 (0.05–0.15) | 36 | 0.25 (0.18–0.35) | 20 | 0.14 (0.09–0.21) | 58 | 0.40 (0.31–0.52) |
| Architectural distortion | 10 | 0.07 (0.03–0.13) | 60 | 0.42 (0.32–0.54) | 7 | 0.05 (0.02–0.10) | 38 | 0.26 (0.19–0.36) |
| Asymmetry | 7 | 0.05 (0.02–0.10) | 101 | 0.70 (0.57–0.85) | 12 | 0.08 (0.04–0.15) | 210 | 1.46 (1.27–1.67) |
| Mass with calcifications | 7 | 0.05 (0.02–0.10) | 15 | 0.10 (0.06–0.17) | 11 | 0.08 (0.04–0.14) | 10 | 0.07 (0.03–0.13) |
| Circumscribed mass | 5 | 0.03 (0.01–0.08) | 78 | 0.54 (0.43–0.68) | 2 | 0.01 (0.00–0.05) | 44 | 0.31 (0.22–0.41) |
| Obscured mass | 1 | 0.01 (0.00–0.04) | 34 | 0.24 (0.16–0.33) | 3 | 0.02 (0.00–0.06) | 78 | 0.54 (0.43–0.68) |
| Associated features | 1 | 0.01 (0.00–0.04) | 3 | 0.02 (0.00–0.06) | – | | 5 | 0.03 (0.01–0.08) |
| No information | – | | 1 | 0.01 (0.00–0.04) | – | | 1 | 0.01 (0.00–0.04) |

## 4. Discussion

In this study, we observed differences in the distribution of mammographic features for women recalled after screening with DBT versus DM. Asymmetry was the most common feature of all recalls for DBT and for DM, although less frequent for DBT compared to DM. Spiculated mass was the most common feature among women recalled and diagnosed with breast cancer after screening with DBT, while calcification was most frequent for recalled women diagnosed with breast cancer after screening with DM. Further, spiculated mass was the most common feature among women diagnosed with a non-luminal A-like cancer after DBT and after DM. The percentage of asymmetries, indistinct and obscured masses in women with a negative outcome after recall was lower for DBT versus DM.

Our finding of spiculated mass being the most common mammographic feature (36.8 %) for cancers detected after screening with DBT is in line with other studies. The Oslo Tomosynthesis Screening Trial showed a comparable rate (37 %) [25], while it was 68 % in the Malmö Breast Tomosynthesis Screening Trial [11]. The higher percentage in the Malmö trial might be due to use of different classification systems; To-Be 2 used five categories of masses, the Oslo study three (circumscribed, mass with calcifications and spiculated), while the Malmö-trial used two; circumscribed and spiculated. The distribution of immunohistochemical subtypes did not differ for DBT versus DM in our study, which was in line with results from the Malmö-trial [35]. Some studies have reported that spiculated masses are associated with less aggressive luminal A-like cancers [7,36,37]. However, both in our and the Malmö study, spiculated masses were the most common mammographic feature among the non-luminal A-like cancers, after DBT as well as after DM [35].

Indistinct mass might be easier to classify "correctly" with DBT compared to DM because the thin planes visualize tumor margins more clearly than DM. In the Malmö-trial, circumscribed mass was the second most common non-luminal-A-like cancer, which again differ from our results probably due to their limited number of feature-categories. Our study indicated that indistinct mass is an important feature for detecting cancers; it was the second most common feature among the breast cancers and about half of these cases were non-luminal A-like after screening with DBT.

In the To-Be trail, a low percentage (7.4 %) of the cancers detected at DBT was classified as asymmetry, which correspond to results reported from Spain (1% (1/92)) [9] and from the Oslo Tomosynthesis Trial (4% (4/101)) [25]. This finding supports the notion that overlapping tissue is less of a challenge in DBT compared to DM; soft tissue lesions are frequently visible in both views and correctly classified as a mass rather than asymmetry if real. This might indicate that use of DBT has the

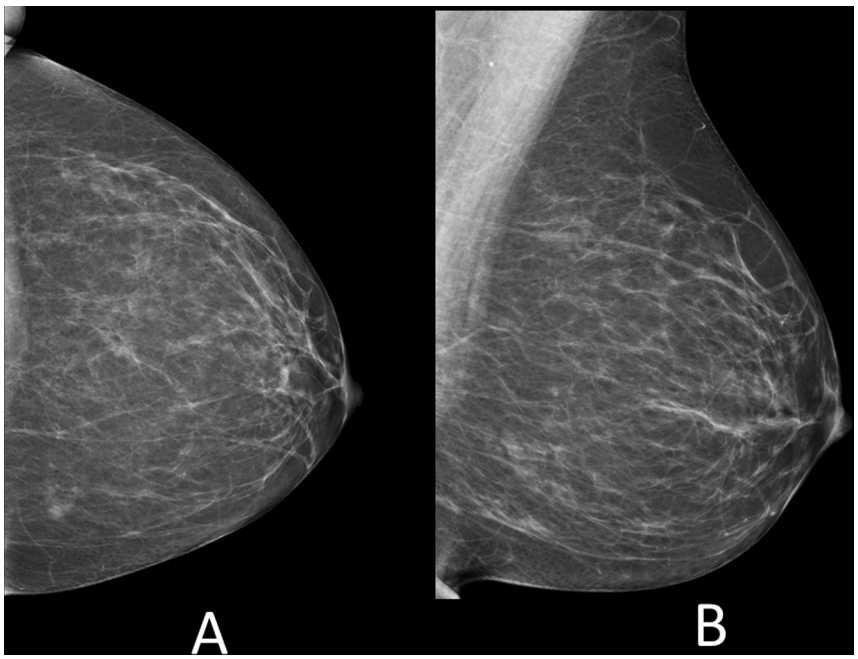


**Fig. 5.** Left craniocaudal (A) and left mediolaterale oblique image (B) in a woman recalled because of asymmetry in the medial part of the craniocaudal image. Assessment was performed with negative outcome, without biopsy.

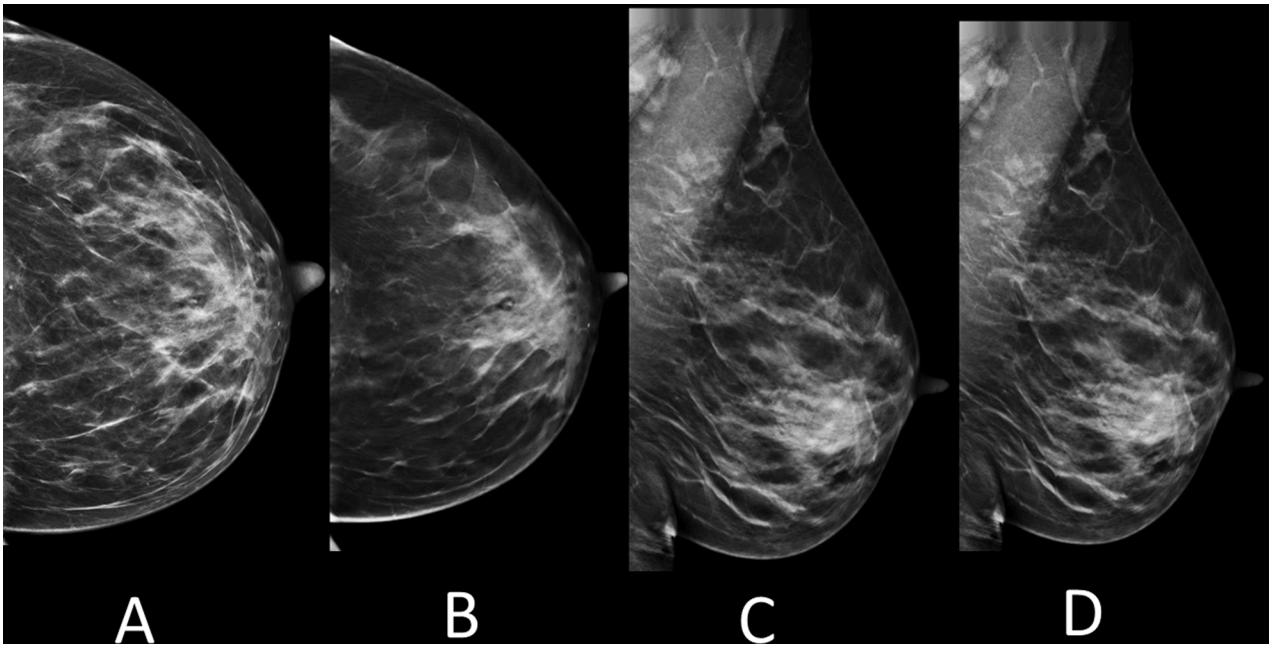


**Fig. 6.** Left craniocaudal synthetic 2D image (A) and 1 mm plane (B), left mediolateral oblique synthetic 2D image (C) and 1 mm plane (D), in a woman recalled after DBT, because of asymmetry in the upper part of left breast. Additional imaging at recall revealed no malignancy.

potential to reduce recalls due to asymmetry.

Calcifications were the most common feature for breast cancers detected by DM, statistically not different compared to DBT. In DBT, images are reconstructed from raw-data and calcifications are enhanced and visible, but the characterization of the calcifications might be different in DBT compared to DM [38]. The use of first-generation equipment may also have influenced our results; optimized versions of equipment are now available, which is said to visualize calcifications differently compared to first generation.

Distortion of normal architecture is a part of spiculated masses and architectural distortions [26,32]. Our results support the notion that architectural distortions are better visualized in DBT versus DM [26,39]. However distortions did not reveal a higher rate of breast cancers for DBT compared to DM. In other studies [19,24,40], higher proportions of tumors with favorable characteristics were observed for screening with DBT compared with DM. In our study, the proportion of luminal A-like cancers, a subtype known to be associated with a more favorable prognosis, did not differ between DBT and DM. This may be explained by the use of prior mammograms in the screen-reading; in the To-Be-trial priors up to 10 years back in time were available. If similar distortions or densities were identified on priors, the findings were often dismissed either at the screen-reading or at consensus. Hanging protocols are

**Table 4**
Distribution (n and %) of mammographic features for subgroups by screening technique (digital breast tomosynthesis, DBT, and digital mammography, DM) among invasive breast cancer cases in each subgroup (a) and among the specific features (b) in the To-Be trial, 2016-2017.

| | DBT (N = 75) | | | | DM (N = 70) | | | |
|---|---|---|---|---|---|---|---|---|
| | Luminal A-like | | Non-luminal A-like | | Luminal A-like | | Non-luminal A-like | |
| | n = 44 (58.7 %) | | n = 31 (41.3 %) | | n = 43 (61.4 %) | | n = 27 (38.6 %) | |
| | n | % (95 % CI) | n | % (95 % Cl) | n | % (95 % Cl) | n | % (95 % Cl) |
| **a) By subgroups** | | | | | | | | |
| Spiculated mass | 23 | 52.3 (36.7–67.5) | 9 | 29.0 (14.2–48.0) | 9 | 20.9 (10.0–36.0) | 7 | 25.9 (11.1–46.3) |
| Indistinct mass | 7 | 15.9 (6.6–30.1) | 8 | 25.8 (11.9–44.6) | 11 | 25.6 (13.5–41.2) | 5 | 18.5 (6.3–38.1) |
| Circumscribed mass | 2 | 4.5 (0.6–15.5) | 3 | 9.7 (2.0–25.8) | 1 | 2.3 (0.1–12.3) | – | |
| Architectural distortion | 7 | 15.9 (6.6–30.1) | 3 | 9.7 (2.0–25.8) | 2 | 4.7 (0.6–15.8) | 3 | 11.1 (2.4–29.2) |
| Mass with calcifications | 2 | 4.5 (0.6–15.5) | 3 | 9.7 (2.0–25.8) | 4 | 9.3 (2.6–22.1) | 4 | 14.8 (4.2–33.7) |
| Asymmetry | 3 | 6.8 (1.4–18.7) | 2 | 6.5 (0.8–21.4) | 8 | 18.6 (8.4–33.4) | 3 | 11.1 (2.4–29.2) |
| Calcifications | – | | 2 | 6.5 (0.8–21.4) | 7 | 16.3 (6.8–30.7) | 4 | 14.8 (4.2–33.7) |
| Associated features | – | | 1 | 3.2 (0.1–16.7) | – | | – | |
| Obscured mass | – | | – | | 1 | 2.3 (0.1–12.3) | 1 | 3.7 (0.1–19.0) |
| **b) By mammographic feature** | | | | | | | | |
| Spiculated mass | 23 | 71.9 (53.3–86.3) | 9 | 28.1 (13.7–46.7 | 9 | 56.3 (29.9–80.2) | 7 | 43.8 (19.8–70.1) |
| Indistinct mass | 7 | 46.7 (21.3–73.4) | 8 | 53.3 (26.6–78.7) | 11 | 68.8 (41.3–89.0) | 5 | 31.3 (11.0–58.7) |
| Circumscribed mass | 2 | 40.0 (5.3–85.3) | 3 | 60.0 (14.7–94.7) | 1 | 100 (2.5–1) | – | |
| Architectural distortion | 7 | 70.0 (34.8–93.3) | 3 | 30.0 (6.7–65.2) | 2 | 40.0 (5.3–85.3) | 3 | 60.0 (14.7–94.7) |
| Mass with calcifications | 2 | 40.0 (5.3–85.3) | 3 | 60.0 (14.7–94.7) | 4 | 50.0 (15.7–84.3) | 4 | 50.0 (15.7–84.3) |
| Asymmetry | 3 | 60.0 (14.7–94.7) | 2 | 40.0 (5.3–85.3) | 8 | 72.7 (39.0–94.0) | 3 | 27.3 (39.0–94.0) |
| Calcifications | – | | 2 | 100 (15.8–1) | 7 | 63.6 (30.8–89.1) | 4 | 37.4 (10.9–69.2) |
| Associated features | – | | 1 | 100 (2.5–1) | – | – | – | – |
| Obscured mass | – | | – | – | 1 | 50.0 (2.5–1) | 1 | 50.0 (2.5–1) |

Information not available for 6 cases (5 DBT, 1 DM) due to neoadjuvant treatment.

usually based on "expert opinion" as evidence based guidelines are not available. Research aimed at identifying efficient hanging protocols is therefore desired.

Our finding of a higher proportion of circumscribed mass among women recalled after DBT (19 %) versus DM (8%) was unexpected since circumscribed mass is usually considered benign, not warranting a recall [32]. Lack of experience in DBT-screening among the screen-readers in the To-Be trial might explain this finding. DBT usually visualizes circumscribed mass clearly while overlapping tissue partially or totally can mask the same lesion when using DM. Notably, even though circumscribed mass represented fewer cancers compared to other features, it still contributed to 9.7 % of non-luminal A-like cancers for DBT which is in line with established knowledge; some aggressive triple negative cancers may present as indistinct-, obscure or, circumscribed masses [23].

This study, based on data from a randomized controlled trial has several limitations. The distribution of mammographic features cannot be directly compared with results from other studies due to use of different classification systems and equipment. Further, the number of cases within each mammographic feature is small and the distribution might be influenced by the absence of higher cancer detection rate for DBT versus DM in our study, contrary to other studies from Europe [2, 6–10]. A review of prior mammograms of interval and consecutive round screen-detected cancer according to features is planned, but delayed due to the covid pandemic. Limited experience in screen-reading DBT among the radiologists and use of first generation equipment from GE might also be of influence of the consensus, recall and detection rates. Further, the To-Be trial was a single center study, in which the generalizability of results should be interpreted with care.

In conclusion, this study identified different distributions of mammographic features among women recalled after screening with DBT or DM in the To-Be trial. Asymmetry was the most common feature of all recalls, however less frequent for DBT versus DM. Spiculated mass was the dominant feature for breast cancer among women screened with DBT while calcifications was the most frequent feature for DM. Further studies exploring the clinical relevance of the different mammographic features are warranted; more knowledge might enable radiologists to improve the benefit-harm-ratio in screening.

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## Declaration of Competing Interest

All the authors declare no conflict of interest.

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