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Early screening outcomes before, during, and after a randomized controlled trial with digital breast tomosynthesis

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ABSTRACT

Purpose: To describe and compare early screening outcomes before, during and after a randomized controlled trial with digital breast tomosynthesis (DBT) including synthetic 2D mammography versus standard digital mammography (DM) (To-Be 1) and a follow-up cohort study using DBT (To-Be 2).

Methods: Retrospective results of 125,020 screening examinations from four consecutive screening rounds performed in 2014–2021 were described and compared for pre-To-Be 1 (DM), To-Be 1 (DM or DBT), To-Be 2 (DBT), and post-To-Be 2 (DM) cohorts. Descriptive analyses of rates of recall, biopsy, screen-detected and interval cancer, distribution of histopathologic tumor characteristics and time spent on image interpretation and consensus were presented for the four rounds including five cohorts, one cohort in each screening round except for the To-Be 1 trail, which included a DBT and a DM cohort. Odds ratios (OR) with 95% CIs was calculated for recall and cancer detection rates.

Results: Rate of screen-detected cancer was 0.90% for women screened with DBT in To-Be 2 and 0.64% for DM in pre-To-Be 1. The rates did not differ for the To-Be 1 DM (0.61%), To-Be 1 DBT (0.66%) and post-To-Be 2 DM (0.67%) cohorts. The interval cancer rates ranged between 0.13% and 0.20%. The distribution of histopathologic tumor characteristics did not differ between the cohorts.

Conclusions: Screening all women with DBT following a randomized controlled trial in an organized, population-based screening program showed a temporary increase in the rate of screen-detected cancer.

1. Introduction

Breast cancer screening with digital breast tomosynthesis (DBT) in combination with digital mammography (DM) or synthetic 2D mammograms (SM), is associated with higher cancer detection rates compared to standard DM alone, while the effect on recall rates varies between studies [1–9]. The effect of DBT on interval cancer rates is still unclear as the relatively low cancer incidence leads to a small number of cancers included in published studies [5,10–15]. In a 2018 *meta*-analysis, pooled data from prospective European trials and observational U.S. studies showed that screening with DBT resulted in a more pronounced increase in screen-detected cancers in Europe than in the U.S., while a decrease in

Abbreviations: CI, Confidence interval; DBT, Digital Breast Tomosynthesis; DCIS, Ductal carcinoma in situ; DM, Digital Mammography; ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; IQR, Interquartile range; OR, Odds ratio; PPV-1, Positive predictive value of recalls; PPV-3, Positive predictive value of performed biopsies; PR, Progesterone receptor; RCT, Randomized Controlled Trial; SM, Synthetic 2D Mammography.

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recall rate was only observed in the U.S. studies, where recall rates are generally higher compared to Europe [16].

Most of the published results on DBT screening are based on prevalent (initial) screening episodes with DBT. Only a few studies have reported on consecutive screening rounds of DBT, showing lower recall rates and a sustained higher rate of screen-detected cancer for DBT compared with DM [17–20]. However, it is unknown how outcomes are impacted in consecutive screening rounds and whether one DBT screening, likely to decrease the recall rates by clarifying areas of breast tissue superimposition, may have beneficial effect on downstream screening interpretation regardless of the subsequent screening modality (DM or DBT).

The Tomosynthesis Trial in Bergen was a randomized controlled trial (RCT) performed within the national screening program for breast cancer in Norway (BreastScreen Norway), 2016–2017 (To-Be 1) [21]. All participating women were randomly assigned to screening with DBT including SM, or DM. To-Be 1 was followed by To-Be 2 during 2018–2019; a follow-up, single group cohort study where all participating women were screened with DBT + SM. Complete results from To-Be 2 have not yet been reported.

In this study, we aimed to describe and compare early screening outcomes before, during, and after the To-Be trials. The comparison between these periods will help elucidate whether there was any lasting impact of the temporary change to DBT + SM screening during trial periods when returning to standard DM as part of the standard screening program. The results will be valuable for evidence-based decisions and in policy discussions about whether DBT + SM should be recommended in screening programs for breast cancer. We hypothesized that early screening outcomes would improve (i.e. reduce rate of recall and increase rate of screen-detected cancer) during the To-Be trials and decline when returning to DM screening.

2. Materials and methods

The To-Be 1 and To-Be 2 trials were approved by the Regional Committee for Medical and Health Research Ethics in Norway (#2015/424), including the use of data collected in the screening round before and after the To-Be trials. To-Be 1 and To-Be 2 are registered at ClinicalTrials.gov (NCT02835625 and NCT03669926, respectively).

2.1. Study settings

BreastScreen Norway is a population-based breast cancer screening program, offering all women in Norway aged 50–69 biennial two-view mammographic screening, using independent double reading with consensus [22]. The To-Be trials were prospective trials performed at the Bergen facilities of BreastScreen Norway [10,21]. Enrollment required written, informed consent.

The study population included women screened in four separate screening rounds, 2014–2021, where the first and fourth round represented standard screening rounds and the second and third rounds included the To-Be trials.

In the screening round prior to To-Be 1, 2014–2015 (pre-To-Be 1), 29,320 women attended screening in Bergen and were screened with DM (Fig. 1). Women registered with a previous diagnosis of breast cancer (n = 609), or breast symptoms (n = 124) were excluded from the analyses.

Among women screened in To-Be 1 during the study period 2016–2017, 29,453 consented to participate (Fig. 1) [21]. These women were randomly assigned to DBT + SM (n = 14,734), hereafter referred to as DBT, or DM (n = 14,719). Women registered with a previous diagnosis of breast cancer (DBT = 314; DM = 316) or breast symptoms (DBT = 39; DM = 34), and women with metastasis to the breast from melanoma (DBT = 1; DM = 0) were excluded from the analyses. Among the 28,749 included women, 20,111 had a prior screening examination in pre-To-Be 1.

Among women screened in To-Be 2 during the study period 2018–2019, 31,082 consented to participate (Fig. 1) [10]. All women were screened with DBT. Women registered with a previous diagnosis of breast cancer (n = 445) or breast symptoms (n = 55), and women with lymphoma as primary cancer (n = 5) were excluded from the analyses. Among the 30,577 included women, 24,569 had a prior screening examination in pre-To-Be 1 and/or To-Be 1.

In the screening round after To-Be 2, 2020–2021 (post-To-Be 2), 37,731 women attended screening in Bergen and were screened with DM (Fig. 1). Women registered with a previous diagnosis of breast cancer (n = 509), or breast symptoms (n = 115) were excluded from the analyses. Among the 37,107 included women, 27,321 had a prior screening examination in pre-To-Be 1, To-Be 1 and/or To-Be 2.

The screening round including post-To-Be 2 examinations was originally planned to end in December 2021. Due to the Covid-19 pandemic, screening in Bergen was suspended from March 12 to June 8, 2020 [23]. This resulted in a delayed screening round, ending on May 15, 2022. For illustrative purposes, this study period is labeled 2020–2021 in text, tables, and figures. In summary, the study included data from four screening rounds and five cohorts, one cohort for each screening round, except for To-Be 1 which included a DBT and a DM cohort.

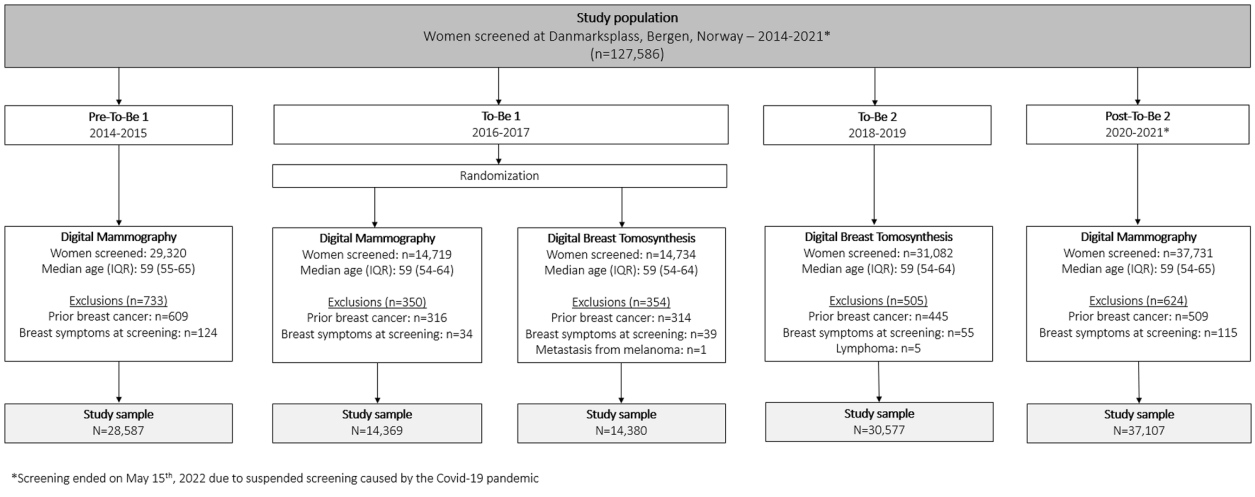

Fig. 1. Study settings and study populations.

2.2. Early screening outcomes

Recall was defined as further assessment due to an abnormal finding on the screening mammogram. Screen-detected breast cancer was defined as breast cancer diagnosed after recall. Interval cancer included breast cancer diagnosed within 24 months after negative screening or 6–24 months after false-positive screening [24]. Due to the delayed screening round post-To-Be 2, women participating in To-Be 2 were followed for interval cancer until May 15, 2022, to ensure adequate cancer follow-up. Data on interval cancer for women screened post-To-Be 2 was not available. Breast cancers included ductal carcinoma in situ (DCIS) and invasive breast cancers. All cancers were histologically verified.

Positive predictive value of recalls (PPV-1) was defined as the percentage of women diagnosed with screen-detected cancer among those recalled. Positive predictive value of performed biopsies (PPV-3) was defined as the percentage of women diagnosed with cancer among those who underwent a biopsy after abnormal screening. Sensitivity was calculated as the number of screen-detected cancers divided by the sum of screen-detected and interval cancers. Specificity was calculated as negative screening examinations without interval cancer divided by the sum of negative and false-positive screening examinations.

In the To-Be trials, time spent on interpreting the screening mammograms and time spent on consensus were recorded (in seconds) for the individual radiologist and per case discussed in consensus. Interpretation times were not recorded in BreastScreen Norway prior to the To-Be trials; however, they were routinely collected after To-Be 2.

Histopathologic tumor characteristics collected for invasive screen-detected and interval breast cancers included histologic type (invasive carcinoma of no special type, invasive lobular carcinoma, invasive tubular carcinoma, and other invasive carcinomas), tumor diameter (mm), histologic grade (Nottingham grade 1–3), and lymph node status (positive/negative). Molecular subtypes of invasive cancers were based on immunohistochemistry according to Goldhirsch et al. [25], classified into five groups: luminal A; luminal B HER2 negative; luminal B HER2 positive; HER2 positive; and triple negative. Tumor diameter and Van Nuys grade (1–3) were reported only for cases of screen-detected DCIS due to a small number of interval DCIS [26].

In women diagnosed with more than one breast cancer, we used a hierarchy of malignancy; invasive tumors were prioritized over DCIS. If two invasive cancers were diagnosed, the tumor with the largest tumor diameter was included in the analyses.

2.3. Statistical analyses

Recall, biopsy, screen-detected and interval breast cancer, PPV-1, PPV-3, sensitivity, and specificity were presented as percentages. Tests of proportions (Z test) were used to test for differences across the cohorts, presented with p-values and 95% confidence intervals. Tumor diameter was described using median and interquartile range (IQR), and all histopathologic tumor characteristics were presented as frequencies and percentages of invasive cancers or DCIS. Interpretation and consensus times were presented in minutes and seconds and described using median values with IQR. We excluded outlier values for interpretation times above 10 min and consensus times above 15 min, assuming that radiologists had been interrupted.

The independency assumption for standard regression models was violated because women could contribute with screening examinations in more than one study cohort. We thus performed multi-level logistic regression taking this dependency into account when calculating odds ratios (OR) with 95% confidence intervals (CI) for recall, screen-detected and interval breast cancer, using those screened in pre-To-Be 1 as reference. ORs were adjusted for screening history (prevalent screen, subsequent screen, or irregular attendance). Software (Stata MP, version 17.0; Stata) was used for data management and statistical analyses.

3. Results

The study sample included 125,020 screening examinations among 53,019 women (Fig. 1). The pre-To-Be 1 cohort included 28,587 women, while the study population of To-Be 1 included 14,369 women screened with DBT and 14,380 screened with DM. The To-Be 2 study population included 30,577 women screened with DBT, with 11,201 previously screened with DBT in To-Be 1, 11,105 previously screened with DM in To-Be 1, and 8,271 women who were either screened for the first time (prevalently) or did not participate in To-Be 1 and thus had no previous DBT. The post-To-Be 2 cohort included 37,107 women screened with DM. Median age was 59 years for all cohorts (Fig. 1).

3.1. Early screening outcomes

Recall rate among women screened with DM in the pre-To-Be 1 cohort was 3.5% (1014/28,587), 4.0% (571/14,369) in the To-Be 1 DM cohort, 3.1% (444/14,380) in the To-Be 1 DBT cohort, 4.8% (1460/30,577) in the To-Be 2 cohort, and 4.0% (1499/37,107) in the post-To-Be 2 cohort (Table 1).

We observed more screen-detected breast cancers among women screened with DBT in To-Be 2 (0.90%, 275/30,577) versus DM pre-To-Be 1 (0.64%, 182/28,587, $p < 0.01$) (Table 1). However, the rate did not significantly differ between those screened prior to To-Be 1 and those screened with DM (0.61%, 87/14,369, $p = 0.70$) or DBT (0.66%, 95/14,380, $p = 0.77$) in To-Be 1, or those screened with DM post-To-Be 2 (0.67%, 249/37,107, $p = 0.59$).

The rate of invasive screen-detected cancers was 0.54% for DM pre-To-Be 1, 0.49% for DM in To-Be 1 and 0.56% for DBT in To-Be 1, 0.76% for DBT in To-Be 2, and 0.52% for DM in post-To-Be 2. PPV-1 was 15.2% (87/571) for DM and 21.4% (95/444) for DBT in To-Be 1. PPV-3 was 33.8% (182/538) for DM in pre-To-Be 1 and 27.5% (249/905) for DM in the post-To-Be 2 cohort.

No statistically significant difference in interval cancer rates were observed between the cohorts; the rate was 0.13% (38/28,587) for women screened prior to To-Be 1 and 0.20% (29/14,369, $p = 0.09$) for women screened with DM in To-Be 1 (Table 1). The sensitivity did not differ between the study cohorts, while the specificity was lower for DM in To-Be 1 (96.6%, 13,798/14,282, $p < 0.01$) and DBT in To-Be 2 (96.1%, 29,177/30,302, $p < 0.01$), and higher for DBT in To-Be 1 (97.6%, 13,936/14,285, $p < 0.01$), compared to DM in pre-To-Be 1 (97.1%, 27,573/28,405).

Using DM pre-To-Be 1 as the reference, the adjusted OR of recall was 1.1 (95% CI: 1.0–1.3, $p = 0.02$) for DM in To-Be 1, 0.9 (95% CI: 0.8–1.0, $p = 0.02$) for DBT in To-Be 1, 1.4 (95% CI: 1.3–1.5, $p < 0.01$) for DBT in To-Be 2, and 1.1 (95% CI: 1.0–1.2, $p = 0.01$) for DM in post-To-Be 2 (Table 2). Using the same study cohort as the reference, screening with DBT in To-Be 2 was associated with an OR of screen-detected cancer of 1.4 (95% CI: 1.1–1.9, $p = 0.01$), when adjusting for screening history (prevalent screen, subsequent screen, or irregular attendance) and dependency between the study cohorts. No differences in ORs of interval cancer were observed between the study cohorts. Sensitivity analyses, adjusted for either screening history, dependency between study cohorts, or neither, did not change the results (Appendix A1-3).

3.2. Histopathologic tumor characteristics

Overall, the distribution of histopathologic tumor characteristics for screen-detected and interval cancers did not differ among women in the study cohorts (Table 3 and 4). For invasive screen-detected cancers, the percentage of lobular carcinomas varied from 10.5% (16/153) in pre-To-Be 1, 18.3% (13/71) and 7.5% (6/80) in To-Be 1, 16.7% (39/233) in To-Be 2 and 12.5% (24/192) post-To-Be 2 (Table 3). The number of tubular cancers was low and comprised 0.7% (1/153) in pre-To-Be 1, 5.6% (4/71) in To-Be 1 DM, while it was 6.0% (14/233) for To-Be 2. The distribution of histologic grade 3 invasive, screen-detected cancers

Table 1
Early screening outcomes of women screened with Digital Mammography (DM) or Digital Breast Tomosynthesis including synthetic 2D mammograms (DBT) before, during, and after the To-Be trials, 2014–2021.

	2014–2015		2016–2017			2018–2019		2020-2021[€]	
	Pre-To-Be 1 DM (n = 28,587)		To-Be 1 DM (n = 14,369)	To-Be 1 DBT (n = 14,380)		To-Be 2 DBT (n = 30,577)		Post-To-Be 2 DM (n = 37,107)	
	n	%	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Recall	1014	3.5	571	4.0[#] (3.7, 4.3)	444	3.1[#] (2.8, 3.4)	1460	4.8[#] (4.5, 5.0)	1499	4.0[#] (3.8, 4.2)
Biopsy	538	1.9	271	1.9 (1.7, 2.1)	252	1.8 (1.5, 2.0)	853	2.8[#] (2.6, 3.0)	905	2.4[#] (2.3, 2.6)
Screen-detected cancer	182	0.64	87	0.61 (0.48, 0.73)	95	0.66 (0.53, 0.79)	275	0.90[#] (0.79, 1.01)	249	0.67 (0.59, 0.75)
DCIS	29	0.1	16	0.11 (0.06, 0.17)	15	0.10 (0.05, 0.16)	42	0.14 (0.10, 0.18)	57	0.15 (0.11, 0.19)
Invasive	153	0.54	71	0.49 (0.38, 0.61)	80	0.56 (0.43, 0.68)	233	0.76[#] (0.66, 0.86)	192	0.52 (0.44, 0.59)
PPV-1[β]	182/1014	17.9	87/571	15.2 (12.3, 18.2)	95/444	21.4 (17.6, 25.2)	275/1460	18.8 (16.8, 20.8)	249/1499	16.6 (14.7, 18.5)
PPV-3[α]	182/538	33.8	87/271	32.1 (26.5, 37.7)	95/252	37.7 (31.7, 43.7)	275/853	32.2 (29.1, 35.4)	249/905	27.5[#] (23.9, 29.6)
Interval cancer[*]	38	0.13	29	0.20 (0.13, 0.28)	20	0.14 (0.08, 0.20)	49	0.16 (0.12, 0.20)	NA	
DCIS	3	0.01	1	0.01 (0.01, 0.02)	–	–	3	0.01 (0.00, 0.02)	NA	
Invasive	35	0.12	28	0.19 (0.12, 0.27)	20	0.14 (0.07, 0.20)	46	0.15 (0.11, 0.19)	NA	
Sensitivity	182/220	82.7	87/116	75.0 (37.1, 82.9)	95/115	82.6 (75.7, 89.5)	275/324	84.9 (80.9, 88.8)	NA	
Specificity	27,573/28,405	97.1	13,798/14,282	96.6[#] (96.3, 96.9)	13,936/14,285	97.6[#] (97.3, 97.8)	29,177/30,302	96.1[#] (95.8, 96.3)	NA	

β PPV-1: Proportion of screen-detected cancers among those recalled.
α PPV-3: Proportion of screen-detected cancers among those recalled with a biopsy.
* Two years follow up after screening.
€ Screening round lasted to May 2022 due to stop in screening in 2020 caused by the Covid-19 pandemic.
# $p < 0.05$ and 95% CI using pre-To-Be 1 as reference.

varied from 14.3% (21/153) in pre-To-Be 1 to 24.1% (41/170) in post-To-Be 2. The distribution of lymph node positive tumors varied from 14.0% (32/228) in To-Be 2 to 26.8% (19/71) in To-Be 1, DM.

For interval cancers, the proportion of invasive, histologic grade 3 cancers was 48.4% (15/35) for pre-To-Be 1, 37.0% (10/27) for To-Be 1 DM, 37.5% (6/16) for To-Be 1 DBT, and 25.6% (10/39) for To-Be 2 (Table 4). We found 22.9% (8/35) of the lesions in pre-To-Be 1 to be triple negative, while the percentage was 7.4% (2/27) in To-Be 1 DM, 20% (4/20) in To-Be 1 DBT, and 17.4% (8/46) in To-Be 2.

Median tumor diameter of screen-detected DCIS varied between 18.5 mm (To-Be 1, DM) and 28.0 mm (To-Be 1, DBT) (Appendix B). For pre-To-Be 1, 48.3% (14/29) of DCIS cases were classified as van Nuys grade 3 compared to 70.7% (29/41) of DCIS cases in To-Be 2.

3.3. Interpretation time

Median time (minutes:seconds) spent on initial screen interpretations [consensus] was generally higher for DBT in To-Be 1 (00:48 [02:21]) and To-Be 2 (00:36 [02:06]) compared with DM in To-Be 1 (00:23 [01:42]) and post-To-Be 2 (00:24) (Appendix C).

4. Discussion

In this study, we compared results of early screening outcomes from a population-based breast cancer screening program before, during, and after a randomized controlled trial (To-Be 1) using digital breast tomosynthesis including synthetic 2D images (DBT) with a return to standard digital mammography (DM) screening upon trial completion. Recall rate was 4.8% and rate of screen-detected cancer 0.90% for women screened with DBT in To-Be 2, representing the highest rates for the study cohorts. Interval cancer rates did not differ statistically between the five screening cohorts, but the number of cancer cases was small, and the study setting was not designed to assess this outcome.

The absence of a statistically significant increase in cancer detection with DBT versus DM in the To-Be 1 trial has been questioned, and several possible explanations have been proposed, including use of first generation equipment, insufficient experience among radiologists in interpreting DBT images, short interpretation times, and differences in hanging protocols [10,21,27–29]. The increased frequency of screen-detected cancer in To-Be 2 [10] supported the skepticism of the validity of the To-Be 1 findings.

Results from To-Be 1 were not communicated to the radiologists before all image interpretations and consensus meetings had been completed, in contrast to a normal screening setting where radiologists are given continuous feedback with possibilities for adjustment [10]. This issue represents a challenge in the study and in general, when running RCTs in population-based screening programs with continuous monitoring. However, when the To-Be 1 RCT finished recruitment, and before To-Be 2 started, mammograms were reviewed, and the results were presented and discussed with the radiologists involved in To-Be 1. In addition, the mammography equipment used in To-Be 1, SenoClaire (GE Healthcare), was replaced with Senographe Pristina (GE Healthcare) in To-Be 2, due to ergonomic aspects. It is unknown whether these changes affected image quality and cancer detection in To-Be 2.

Our study was performed in an everyday screening setting, including data from an RCT (To-Be 1), a cohort study (To-Be 2) and two regular screening rounds (pre- and post-To-Be). Data from four consecutive screening rounds were analyzed, resulting in the inclusion of women contributing with data in up to four of the studied cohorts. The To-Be trials were not powered to show statistical differences in interval cancer rates or differences in the distribution of histopathologic tumor characteristics. We found an increased rate of screen-detected cancer for DBT screening in To-Be 2, while the rate of interval cancer in To-Be 2 did not differ, compared to pre-To-Be 1. Similar findings have been reported from the RETomo trials subsequent screening round, suggesting that the introduction of DBT in screening could lead to a higher detection of

Table 2
Odds ratios (OR) with 95% confidence intervals (CI) and p-values for recall, screen-detected and interval cancer rate, with Digital Mammography (DM) or Digital Breast Tomosynthesis including synthetic 2D mammograms (DBT) before, during, and after the To-Be trials. The analyses are adjusted for screening history and dependency between the study cohorts. Data in parentheses are 95% CI.

	Recall		Screen-detected cancer		Interval cancer	
	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	p-value
Pre-To-Be 1	ref		ref		ref	
To-Be 1 DM	1.1 (1.0, 1.3)	0.02	1.0 (0.7, 1.3)	0.77	1.5 (0.9, 2.4)	0.10
To-Be 1 DBT	0.9 (0.8, 1.0)	0.02	1.0 (0.8, 1.4)	0.73	1.0 (0.6, 1.8)	0.88
To-Be 2 DBT	1.4 (1.3, 1.5)	<0.001	1.4 (1.1, 1.9)	0.01	1.2 (0.8, 1.8)	0.40
Post-To-Be 2	1.1 (1.0, 1.2)	0.01	1.0 (0.8, 1.4)	0.80	*Data not available*	

Table 3
Histopathologic tumor characteristics of invasive screen-detected cancers performed with Digital Mammography (DM) or Digital Breast Tomosynthesis including synthetic 2D mammograms (DBT) before, during, and after the To-Be trials. IQR = Interquartile range; HER2 = Human Epidermal Growth Factor Receptor 2.

	2014–2015		2016–2017				2018–2019		2020–2021	
	Pre-To-Be 1 DM (n = 153)		To-Be 1 DM (n = 71)		To-Be 1 DBT (n = 80)		To-Be 2 DBT (n = 233)		Post-To-Be 2 DM (n = 192)	
	n	%	n	%	n	%	n	%	n	%
Histologic type										
Invasive carcinoma of no special type	125	81.7	51	71.8	62	77.5	167	71.7	161	83.9
Invasive lobular carcinoma	16	10.5	13	18.3	6	7.5	39	16.7	24	12.5
Invasive tubular carcinoma	1	0.7	4	5.6	2	2.5	14	6.0	3	1.6
Other invasive carcinomas	11	7.2	3	4.2	10	12.5	13	5.6	4	2.1
Tumor diameter (mm)										
Median (IQR)	13.5	9.0–20.0	14.5	9.0–20.0	15.0	12.0–20.0	14.0	10.0–22.0	13	8.2–20.0
Data not available	*5*		*3*		*2*		*13*		*18*	
Histologic grade										
Grade 1	57	38.8	24	34.8	22	27.8	80	36.9	54	31.8
Grade 2	69	46.9	35	50.7	39	49.4	97	44.7	75	44.1
Grade 3	21	14.3	10	14.5	18	22.8	40	18.4	41	24.1
Data not available	*6*		*2*		*1*		*16*		*22*	
Lymph node status										
Positive	29	19.0	19	26.8	15	18.8	32	14.0	33	17.2
Data not available	–		–		–		*5*		–	
Subtypes										
Luminal A	84	57.1	44	62.0	48	60.8	141	61.6	94	50.3
Luminal B HER2-	27	18.4	18	25.4	18	22.8	59	25.8	26	13.9
Luminal B HER2+	23	15.6	7	9.9	5	6.3	14	6.1	48	25.7
HER 2+	7	4.8	1	1.4	3	3.8	6	2.6	8	4.3
Triple Negative	6	4.1	1	1.4	5	6.3	9	3.9	11	5.9
Data not available	*6*		–		*1*		*4*		*5*	

slow-growing invasive cancers [15]. However, the Malmö Breast Tomosynthesis Screening Trial observed a statistically significant reduction in the rate of interval cancer when comparing with a contemporary DM screened control group [13]. The number of cases were though limited. A 2021 *meta*-analysis of prospective non-randomized studies evaluating breast cancer detection and interval cancer rates for DBT versus DM, provided consistent evidence that DBT screening significantly increased the cancer detection rate compared to DM screening [30]. The expected decrease in the rate of interval cancers was not observed in the prospective studies of DBT versus DM screening, but the studies were few and none of them were powered to show a statistically significant decrease. A retrospective study from the U.S., comparing results of DBT and DM screening over three screening rounds, showed lower recall rates and higher cancer detection rates for DBT versus DM after subsequent screening [31]. No differences in the rate of interval cancer were however observed.

In BreastScreen Norway, the rates of interval cancer have been stable at about 18/10,000 screened since its inception in 1996 [22]. In this study, the interval cancer rate did not differ between the five study cohorts screened with either DM, DBT, DBT after DM or DM after DBT. For To-Be 2, the DBT sensitivity was comparable to the pre-To-Be 1 DM sensitivity (84.9% versus 82.7%, respectively). However, the DBT specificity was lower in To-Be 2 compared to pre-To-Be 1 DM specificity (96.1% versus 97.1%, respectively).

No firm conclusions can be drawn regarding potential differences in histopathologic tumor characteristics in our study. Some potential prevalence effects due to DBT visualizing spiculated soft tissue components better than DM might however be worth noticing. Tubular carcinomas are of a favorable biologic phenotype and prognosis, normally accounting for about 1–2% of lesions detected on DM screening [32]. Among the small number of cancers in our study, we found a higher proportion of this histologic type among screen-detected cancers in the DBT versus DM cohorts. On the other hand, the proportion of lobular carcinomas and DCIS cases of Van Nuys grade 3 was also highest in To-Be 2 compared to the other cohorts, implying that DBT might help identify more aggressive tumors.

As expected [33], the interpretation time for DBT was longer than for DM in our study. However, 36 s (To-Be 2) compared to 23 s (To-Be 1 DM) does not constitute a big difference in a clinical setting for the individual examination, but with 15,000 examinations to be interpreted at the actual breast center annually by two radiologists, it amounts to 108 [(13 sec × 2 × 15,000)/3600] working hours for a breast radiologist. Our study did not interpret the DBT images according to a more extensive study protocol, all images were interpreted per standard protocol in BreastScreen Norway. Shorter interpretation times for DBT in To-Be 2 compared to DBT in To-Be 1 could possibly be due to a learning curve among the radiologists.

This study has limitations. The short trial period of the To-Be trials resulted in a relatively small study population, leading to a low number of cancers, hampering our ability to detect significant differences in

Table 4
Histopathologic tumor characteristics of invasive interval cancers performed with Digital Mammography (DM) or Digital Breast Tomosynthesis including synthetic 2D mammograms (DBT) before, during, and after the To-Be trials. IQR = Interquartile range; HER2 = Human Epidermal Growth Factor Receptor 2.

	2014–2015		2016–2017				2018–2019	
	Pre-To-Be 1 DM (n = 35)		To-Be 1 DM (n = 28)		To-Be 1 DBT (n = 20)		To-Be 2 DBT (n = 46)	
	n	%	n	%	n	%	n	%
Histologic type								
Invasive carcinoma of no special type	24	68.6	21	75.0	13	65.0	38	82.6
Invasive lobular carcinoma	8	22.9	5	17.9	2	10.0	7	15.2
Invasive tubular carcinoma	1	2.9	–	–	1	5.0	–	–
Other invasive carcinomas	2	5.7	2	7.1	4	20.0	1	2.2
Tumor diameter (mm)								
Median (IQR)	25.5	14.5–35.0	20.0	15.0–25.0	16	12.0–24.0	18	11.0–30.0
Data not available	*3*		*2*		*3*		*8*	
Histologic grade								
Grade 1	6	19.4	7	25.9	3	18.8	2	5.1
Grade 2	10	32.3	10	37.0	7	43.8	27	69.2
Grade 3	15	48.4	10	37.0	6	37.5	10	25.6
Data not available	*4*		*1*		*4*		*7*	
Lymph node status								
Positive	9	25.7	8	29.6	6	30.0	14	30.4
Data not available	–		*1*		–		–	
Subtypes								
Luminal A	13	37.1	12	44.4	6	30.0	16	34.8
Luminal B HER 2-	5	14.3	11	40.7	5	25.0	14	30.4
Luminal B HER 2+	6	17.1	–	–	3	15.0	6	13.0
HER 2+	3	8.6	2	7.4	2	10.0	2	4.4
Triple negative	8	22.9	2	7.4	4	20.0	8	17.4
Data not available	–		*1*		–		–	

screen-detected and interval cancer rates and histopathologic tumor characteristics between the cohorts. Including results from the screening round prior and post To-Be provided a real-life comparison of women within the same age range, however, interval cancers from the screening round post-To-Be 2 were not yet available to include in these analyses due to the required follow-up time. It should also be mentioned that the included women in part were offered and participated in screening over consecutive screening rounds, meaning that the same women were included in more than one cohort. This is a representation of a real-life screening program and has been shown to not be of influence for the outcome of the study when compared in adjusted and unadjusted analyses.

In summary, screening all women with DBT following an RCT in an organized breast cancer screening program led to a temporary increase in the rate of screen-detected cancer. Based on a limited number of cases, no difference in interval cancer rates was observed across the four consecutive screening rounds, regardless of screening technique. Larger studies or pooled analyses are needed to have the power to conclude on interval cancers and differences in cancer characteristics.

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Data statement

Data from the Cancer Registry of Norway (CRN) has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by CRN is intended nor should be inferred.

Research data used in the analyses can be made available on request to https://helsedata.no/, given legal basis in Articles 6 and 9 of the GDPR and that the processing is in accordance with Article 5 of the GDPR.

CRediT authorship contribution statement

Åsne S. Holen: Data curation, formal analyses, writing original draft, editing, investigation, project administration. **Marie B. Bergan:** Formal analyses, writing original draft, editing, investigation. **Christoph I. Lee:** Writing, editing, investigation. **Sophia Zackrisson:** Writing, editing, investigation. **Nataliia Moshina:** Writing, editing, investigation. **Hildegunn S. Aase:** Writing, editing, investigation. **Ingrid S. Haldorsen:** Writing, editing, investigation. **Solveig Hofvind:** Analyses, writing, editing, investigation, project administration and conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Åsne Sørlien Holen: None. Marie Burns Bergan: None. Christoph Lee: personal fees from the American College of Radiology for journal editorial board work and textbook royalties from McGraw Hill, Inc., Oxford University Press, and UpToDate, Inc., all outside the submitted work. Sophia Zackrisson: None. Hildegunn Siv Aase: None. Ingfrid Salvesen Haldorsen: None. Solveig Hofvind: Head of BreastScreen Norway but has permanent employment as a researcher at the Cancer Registry of Norway, independent of her job as administrative leader of BreastScreen Norway.

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Appendix A

Appendix A1

Odds ratios (OR) with 95% confidence intervals (CI) and p-values for recall, screen-detected and interval cancer rate, with Digital Mammography (DM) or Digital Breast Tomosynthesis including synthetic 2D mammograms (DBT) before, during, and after the To-Be trials. The analyses are adjusted for screening history but not dependency between the study cohorts. Data in parentheses are 95% CI.

	Recall		Screen-detected cancer		Interval cancer	
	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	p-value
Pre-To-Be 1	ref		ref		ref	
To-Be 1 DM	1.1 (1.0, 1.3)	0.02	1.0 (0.7, 1.2)	0.74	1.5 (0.9, 2.4)	0.10
To-Be 1 DBT	0.9 (0.8, 1.0)	0.02	1.0 (0.8, 1.3)	0.74	1.0 (0.6, 1.8)	0.88
To-Be 2 DBT	1.4 (1.3, 1.5)	<0.001	1.4 (1.2, 1.7)	<0.001	1.2 (0.8, 1.8)	0.40
Post-To-Be 2	1.1 (1.0, 1.2)	0.01	1.0 (0.8, 1.2)	0.79	*Data not available*	

Appendix A2

Odds ratios (OR) with 95% confidence intervals (CI) and p-values for recall, screen-detected and interval cancer rate, with Digital Mammography (DM) or Digital Breast Tomosynthesis including synthetic 2D mammograms (DBT) before, during, and after the To-Be trials. The analyses are adjusted for dependency between the study cohorts, but not screening history. Data in parentheses are 95% CI.

	Recall		Screen-detected cancer		Interval cancer	
	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	p-value
Pre-To-Be 1 DM	ref		ref		ref	
To-Be 1 DM	1.1 (1.0, 1.3)	0.02	1.0 (0.8, 1.3)	0.94	1.5 (0.9, 2.5)	0.09
To-Be 1 DBT	0.9 (0.8, 1.0)	0.01	1.1 (0.8, 1.4)	0.51	1.0 (0.6, 1.8)	0.87
To-Be 2 DBT	1.4 (1.3, 1.5)	<0.001	1.6 (1.3, 1.9)	<0.001	1.2 (0.8, 1.8)	0.39
Post-To-Be 2 DM	1.1 (1.1, 1.2)	0.001	1.2 (0.9, 1.5)	0.17	*Data not available*	

Appendix A3

Crude odds ratios (OR) with 95% confidence intervals (CI) and p-values for recall, screen-detected and interval cancer rate, with Digital Mammography (DM) or Digital Breast Tomosynthesis including synthetic 2D mammograms (DBT) before, during, and after the To-Be trials. The analyses are not adjusted for dependency between the study cohorts nor screening history. Data in parentheses are 95% CI.

	Recall		Screen-detected cancer		Interval cancer	
	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	p-value
Pre-To-Be 1	ref		ref		ref	
To-Be 1 DM	1.1 (1.0, 1.2)	0.03	1.0 (0.7, 1.2)	0.70	1.5 (0.9, 2.5)	0.09
To-Be 1 DBT	0.9 (0.8, 1.0)	0.01	1.0 (0.8, 1.3)	0.77	1.0 (0.6, 1.8)	0.87
To-Be 2 DBT	1.4 (1.3, 1.5)	<0.001	1.4 (1.2, 1.7)	<0.001	1.2 (0.8, 1.8)	0.39
Post-To-Be 2	1.1 (1.0, 1.2)	0.001	1.1 (0.9, 1.3)	0.59	*Data not available*	

Appendix B

Histopathologic tumor characteristics of screen-detected Ductal Carcinoma in Situ (DCIS) with standard digital mammography (DM) or digital breast tomosynthesis (DBT) before, during, and after the To-Be trials. IQR = Interquartile range.

	2014–2015		2016–2017				2018–2019		2020–2021	
	Pre-To-Be 1 DM (n = 29)		To-Be 1 DM (n = 16)		To-Be 1 DBT (n = 15)		To-Be 2 DBT (n = 42)		Post-To-Be 2 DBT (n = 57)	
	n	%	n	%	n	%	n	%	n	%
Tumor diameter (mm)										
Median (IQR)	20.0	10.0–36.0	18.5	9.3–34.5	28.0	20.0–30.0	27.0	16.0–41.0	24.0	14.0–35.0
Data not available	*3*		–		*2*		*1*		1	
Van Nuys Grade										
Grade 1	8	27.6	1	6.7	2	13.3	4	9.8	15	26.3
Grade 2	7	24.1	5	33.3	5	33.3	8	19.5	7	12.3
Grade 3	14	48.3	9	60.0	8	53.3	29	70.7	35	61.4
Data not available	–		*1*		–		*1*		–	

Appendix C

Median time (minutes:seconds) with inter-quartile range (IQR) spent on initial screen-readings and consensus with standard digital mammography (DM) or digital breast tomosynthesis (DBT) before, during, and after the To-Be trials

	2016–2017				2018–2019		2020–2021	
	To-Be 1 DM		To-Be 1 DBT		To-Be 2 DBT		Post-To-Be 2 DM	
Screen-reading (min:sec)	n = 28,738		n = 28,760		n = 61,154		n = 74,142	
Median (IQR)	00:23	00:12–00:43	00:48	00:33–00:78	00:36	00:24–00:57	00:24	00:15–00:43
Data not available	*2*		–		*2*		*887*	
*Excluded**	*15*		*21*		*30*		*164*	
Consensus (min:sec)	n = 2,106		n = 1,806		n = 5,320			
Median (IQR)	01:42	01:15–02:25	02:21	01:42–03:32	02:06	01:34–02:51	*Data not available*	
*Excluded***	*2*		–		*26*			

* Screen-readings lasting > 600 s were excluded.
** Consensus lasting > 900 s were excluded.

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