

Interval and Consecutive Round Breast Cancer after Digital Breast Tomosynthesis and Synthetic 2D Mammography versus Standard 2D Digital Mammography in BreastScreen Norway

Tone Hovda, MD • Åsne S. Holen, MSc • Kristina Lång, MD, PhD • Judy Lynn Albertsen, MD • Hilde Bjørndal, MD • Siri H. B. Brandal, MD • Kristine Kleivi Sahlberg, MSc, PhD • Per Skaane, MD • Pål Suhrke, MD, PhD • Solveig Hofvind, PhD

From the Departments of Radiology (T.H., H.B.) and Research (K.K.S.), Vestre Viken Hospital Trust, Drammen, Norway; Institute of Clinical Medicine, University of Oslo, Oslo, Norway (T.H.); Cancer Registry of Norway, Oslo, Norway (Å.S.H., S.H.); Department of Diagnostic Radiology, Department of Translational Medicine, Lund University, Malmö, Sweden (K.L.); Institute for Biomedical Engineering, Zurich, Switzerland (K.L.); Departments of Radiology (J.L.A.) and Pathology (P. Suhrke), Vestfold Hospital Trust, Tønsberg, Norway; Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway (S.H.B.B., P. Skaane); and Department of Life Sciences and Health, Faculty of Health Science, Oslo Metropolitan University, PO 5313 Majorstuen, 0304, Oslo, Norway (S.H.). Received June 20, 2019; revision requested August 7; revision received September 25; accepted October 11. **Address correspondence to** S.H. (e-mail: solveig.hofvind@krefregisteret.no).

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

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Background: Screening that includes digital breast tomosynthesis (DBT) with two-dimensional (2D) synthetic mammography (SM) or standard 2D digital mammography (DM) results in detection of more breast cancers than does screening with DM alone. A decrease in interval breast cancer rates is anticipated but is not reported.

Purpose: To compare rates and characteristics of (a) interval breast cancer in women screened with DBT and SM versus those screened with DM alone and (b) screen-detected breast cancer at consecutive screenings with DM.

Materials and Methods: This prospective cohort study from BreastScreen Norway included women screened with DBT and SM (study group) or DM alone (control group) between February 2014 and December 2015 (baseline). All women, except nonattendees, women with breast cancer, and those who exceeded the upper age limit, were consecutively screened with DM after 2 years. Interval breast cancer, sensitivity, and specificity were estimated for women screened at baseline. Recall, screen-detected breast cancer, and positive predictive value were analyzed for consecutively screened women. A χ^2 test, t test ($P < .001$ after Bonferroni correction indicated a significant difference), and binomial regression model were used to analyze differences across groups.

Results: A total of 92 404 women who underwent baseline screening (mean age, 59 years \pm 6 [standard deviation]) were evaluated; 34 641 women in the study group (mean age, 59 years \pm 6) were screened with DBT and SM and 57 763 women in the control group (mean age, 59 years \pm 6) were screened with DM. A total of 26 474 women in the study group (mean age, 60 years \pm 5) and 45 543 women in the control group (mean age, 60 years \pm 5) were consecutively screened with DM. Rates of interval breast cancer were 2.0 per 1000 screened women in the study group and 1.5 per 1000 screened women in the control group ($P = .12$). No differences in histopathologic characteristics of interval breast cancer were observed. In the consecutive screening round, rates of screen-detected breast cancer were 3.9 per 1000 screened women (study group) and 5.6 per 1000 screened women (control group) ($P = .001$). Rates of histologic grade 1 invasive cancer were 0.5 per 1000 screened women (study group) and 1.3 per 1000 screened women (control group) ($P = .001$).

Conclusion: No differences in interval breast cancer rates or tumor characteristics were observed in women screened with DBT and SM compared with women screened with DM. Higher rates of low-grade screen-detected tumors were observed in the control group at consecutive screening.

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Breast cancer is the most common type of cancer among women worldwide, with almost 2.1 million new cases in 2018, and early detection with mammographic screening is considered beneficial to reduce mortality from this disease (1,2). Studies using a paired design have demonstrated a higher rate of screen-detected breast cancer when using standard two-dimensional (2D) digital mammography (DM) in combination with digital breast tomosynthesis (DBT) versus DM alone (3,4), and a randomized controlled trial from Italy reported a 90% increase in breast cancer detection when using DM and DBT together versus DM alone (5).

However, the radiation dose of DBT and DM is nearly double that of DM. Thus, radiation concerns make this technique less suitable for population-based screening. Reconstruction algorithms creating 2D synthetic mammograms (SMs) from DBT image volume have become available, making the radiation dose acceptable for DBT and SM in screening (6–8). A higher rate of screen-detected breast cancer also has been observed for DBT and SM when compared with DM in nonrandomized studies (9–12), while a randomized controlled trial from Norway reported no statistical difference in detection rate for

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Abbreviations

DBT = digital breast tomosynthesis, DM = digital mammography, OVVV = Oslo-Vestfold-Vestre Viken, PPV-1 = positive predictive value of recalls, SM = synthetic mammography, 2D = two-dimensional

Summary

Women screened with digital breast tomosynthesis (DBT) in combination with two-dimensional (2D) synthetic mammography (SM) versus standard 2D digital mammography (DM) showed no differences in rates and characteristics of interval breast cancer, despite a 50% increase in detection of cancer with DBT and SM versus DM alone at baseline screening.

Key Results

- Rates of interval breast cancer were 2.0 per 1000 screened women in women screened with digital breast tomosynthesis (DBT) and two-dimensional (2D) synthetic mammography (SM) and 1.5 per 1000 screened women in women screened with standard 2D digital mammography (DM) ($P = .12$).
- At baseline, tumors detected with DBT and SM (study group) were smaller and of lower grade than those detected with DM (control group); meanwhile, in the consecutive screening round in which all women were screened with DM, tumors in the control group (DM after DM) were of a lower grade and more favorable molecular subtype.
- Total cancer detection for two consecutive screening rounds, including interval breast cancer, was 8.1 per 1000 screening examinations (495 of 61 115) in the study group (DM after DBT and SM) and 6.7 per 1000 screening examinations (697 of 103 306) in the control group (DM after DM) ($P = .002$).

DBT and SM versus DM (13). Studies reporting early screening outcomes, such as recall rate, rates of screen-detected and interval breast cancer, and positive predictive values, are needed to make evidence-based recommendation for or against use of DBT as a screening tool for breast cancer. Further, there is limited knowledge about interval breast cancer, the sustainability of cancer detection over several screening rounds, and the clinical importance of the results in terms of histopathologic findings and mammographic features of the additional tumors (14–17).

We have previously reported results from the prospective population-based Oslo-Vestfold-Vestre Viken (OVVV) study, which compared early screening outcomes and histopathologic characteristics in women screened with DBT and SM in Oslo County (study group) with those in women screened with DM in Vestfold County and Vestre Viken County (control group) (11). We observed a 50% higher (348 of 37 185 vs 379 of 61 742) rate of screen-detected breast cancer in women screened with DBT and SM compared with the rate of screen-detected breast cancer in women screened with standard DM. In this study, we followed the women screened in the OVVV study for 2 years for interval breast cancer and screen-detected breast cancer in the consecutive screening round.

The main aim of this study was to compare rates and characteristics of interval breast cancer after 2 years of follow-up in women screened with digital breast tomosynthesis (DBT) and synthetic mammography (SM) versus those screened with digital mammography (DM) at baseline. We hypothesized there would be a decrease in interval cancer rate for DBT and SM versus DM after the reported increase in screen-detected cancer (11).

Further, we investigated rates and histopathologic characteristics of screen-detected cancer among women who were consecutively screened with DM.

Materials and Methods

The data protection official at the Cancer Registry of Norway approved this prospective study. The Cancer Registry Regulation waived the requirement to obtain written informed consent for use of screening data for quality assurance and research (18). We received deidentified data from the Cancer Registry of Norway.

BreastScreen Norway is an organized population-based screening program administered by the Cancer Registry of Norway. This program offers all women aged 50–69 years biennial two-view mammographic screening (19). The program performs independent double reading with consensus with random pairs of breast radiologists. Breast biopsy and surgical specimens are examined by pathologists working in close collaboration with the radiologists who performed the screen reading and who assessed the recalled women.

This study is based on data from the OVVV study, in which 37 185 women were screened with DBT and SM in Oslo County and 61 742 women were screened with DM in Vestfold County and Vestre Viken County for one complete screening round from February 2014 to January 2016 (11). Selected results from that study are presented in Table E1 (online).

Study Sample

Our study sample was based on the study population described earlier. The women were screened with DBT and SM in Oslo County and with DM in Vestfold County and Vestre Viken County. The screening technique at baseline was determined by county of residence, with no options to choose the technique. We excluded women with breast cancer diagnosed before baseline screening ($n = 1671$) and women who were screened in January 2016, as complete data on interval breast cancer were not yet available at the time of data extraction. The final study sample consisted of 34 641 women screened with DBT in Oslo County (study group) at baseline and 57 763 women screened with DM in Vestfold County and Vestre Viken County (control group) (Fig 1).

The women were followed for 2 years after baseline screening for interval breast cancer. All women who reported for consecutive screening 2 years after the baseline screening examination (February 2016 to December 2017) were screened with DM since screening with DBT is allowed only within studies in BreastScreen Norway due to a lack of evidence about the benefits and harms (20). In our study, 76% (26 474 of 34 641) of women screened at baseline in the study group and 79% (45 543 of 57 763) of women screened at baseline in the control group were consecutively screened (Fig 1).

A total of 10 176 women in Oslo County and 13 493 women in Vestfold County and Vestre Viken County were screened in the consecutive screening round but not at baseline because of age (prevalently screened) or irregular attendance. These women were not part of the study sample, but the results of screening are shown in Figure 2.

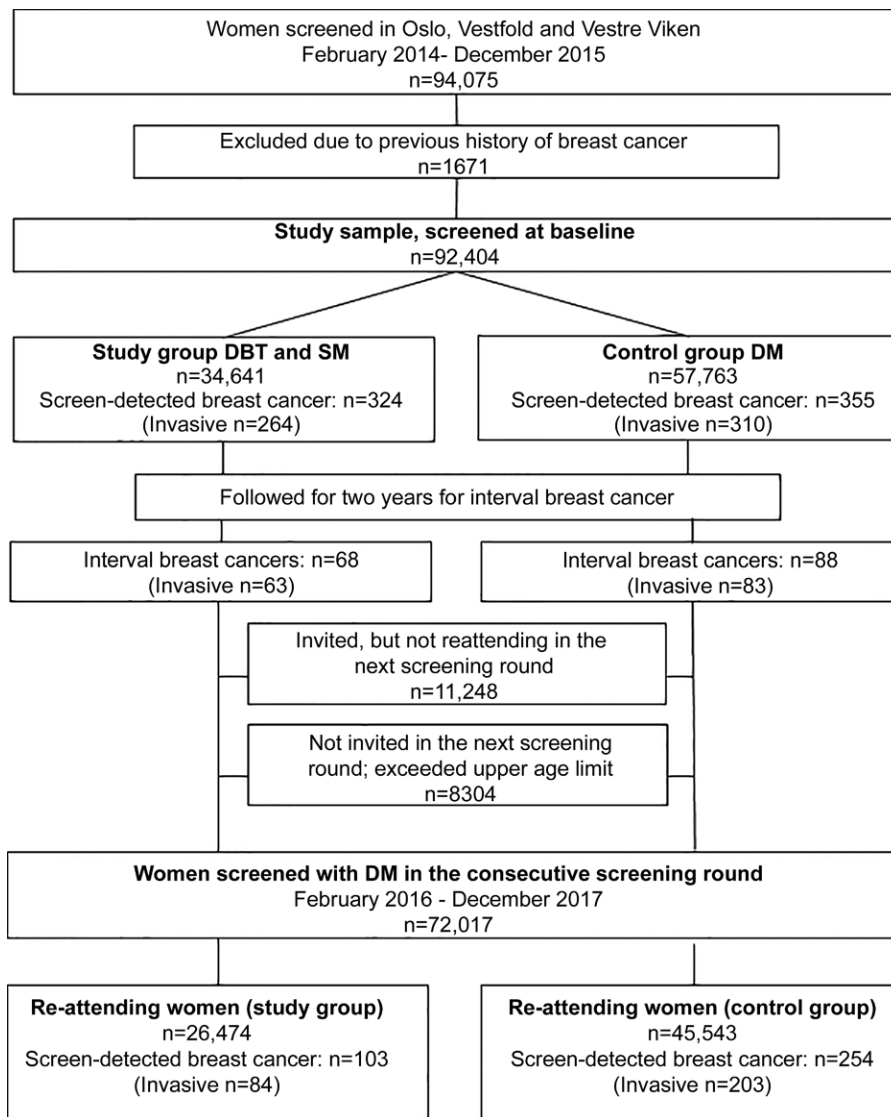


Figure 1: Flowchart shows women screened at baseline (February 2014 to December 2015) and in the consecutive screening round (February 2016 to December 2017) in Oslo County (study group, digital breast tomosynthesis [DBT] including synthetic mammography [SM] at baseline and digital mammography [DM] in the consecutive round) and in Vestfold County and Vestre Viken County (control group, DM in both rounds).

Women screened in Oslo County and Vestfold County were screened at stationary screening units (Dimensions; Hologic, Bedford, Mass). In Vestre Viken County, women were screened at stationary units (Mammomat Inspiration; Siemens, Erlangen, Germany) or a mobile unit (Seno Essential; GE Healthcare, Buc, France).

Definition of Measures

Recall was defined as further assessment due to abnormal mammographic findings. Screen-detected breast cancer was breast cancer diagnosed after recall. We included ductal carcinoma in situ and invasive breast cancer as breast cancer. Interval breast cancer was defined as breast cancer diagnosed 0–24 months after negative screening findings or 6–24 months after false-positive baseline screening findings. Positive predictive value of recalls (PPV-1) was the percentage of women with a diagnosis of screen-detected cancer among those women who were recalled.

Prognostic tumor characteristics included histologic type (ductal carcinoma in situ, invasive ductal carcinoma, invasive lobular carcinoma, tubular carcinoma, and other). Further characteristics, such as mean and median tumor diameter, lymph node involvement (negative or positive), and histologic grade (grade 1–3), were described for invasive breast cancer. Predictive tumor characteristics for invasive breast cancer were presented as subtypes based on immunohistochemistry results. These subtypes were as follows: (a) luminal A (estrogen receptor [ER]- and progesterone receptor [PR]-positive findings, human epidermal growth factor 2 [HER2]-negative findings, and low Ki-67 level [$<30\%$]), (b) luminal B HER2 negative (HER2-negative findings, ER-positive findings, PR-positive findings, and/or Ki-67 level $>30\%$), (c) luminal B HER2 positive (ER- and HER2-positive findings, any PR findings, any Ki-67 level), (d) HER2 positive (HER2-positive findings, ER- and PR-negative findings), and (e) triple negative findings (ER-, PR-, and HER2-negative findings) (21).

Women with true-positive (TP) findings were those in whom screen-detected breast cancer was diagnosed. Women with false-negative (FN) findings were those with an interval breast cancer diagnosis. Women with negative findings at screening who did not receive an interval breast cancer diagnosis were considered to have true-negative (TN) findings, and screened

women who were recalled but who did not receive a breast cancer diagnosis were considered to have false-positive (FP) findings. Sensitivity is presented as a percentage and was defined as $TP/(TP+FN)$. Specificity is also presented as a percentage and was defined as $TN/(TN+FP)$.

Statistical Analyses

Analyses were stratified by screening technique. Both age and tumor diameter were described as mean \pm standard deviation and median and interquartile range. Recall screening-detected breast cancer, interval breast cancer, and histopathologic tumor characteristics were presented as rates per 1000 screened women within defined periods.

We used a binomial regression model with a log link function to estimate the unadjusted and adjusted risk ratios with 95% confidence intervals for interval breast cancer for screening with DBT and SM, with DM as the reference standard. Covariates in

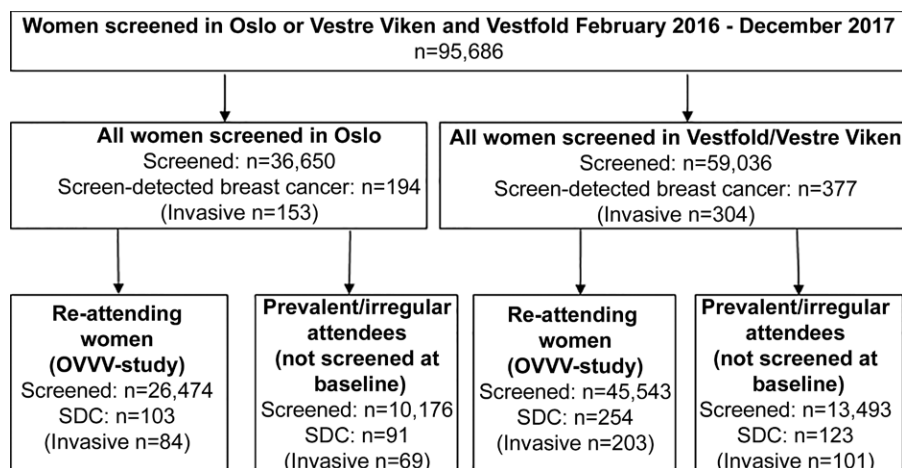


Figure 2: Flowchart shows women screened in Oslo County (study group) and in Vestfold County and Vestre Viken County (control group) in the consecutive screening round (February 2016 to December 2017), including women screened and not screened at baseline. OVVV study = Oslo-Vestfold-Vestre Viken study, SDC = screen-detected breast cancer.

the adjusted models were age (continuous) and screening history. Screening history was defined as prevalent (first time screened in the program) or subsequent (previously screened in the program). The rate of all breast cancer detected (baseline screen-detected, interval, and consecutive round screen-detected breast cancer) per 1000 screened women at baseline was estimated for the two groups. Differences across categories were tested with two-sample *t* and χ^2 tests. After Bonferroni correction, $P < .001$ was considered to indicate a significant difference.

An in-house version of Stata, version 15.0 (Stata, College Station, Tex), was used for statistical analyses.

Results

Study Sample

At baseline, 34641 women were screened with DBT and SM (mean age, 59 years \pm 6) and 57763 were screened with DM (mean age, 59 years \pm 6). A total of 72017 women were consecutively screened with DM; there were 26474 women (mean age, 60 years \pm 5) in the study group and 45543 (mean age, 60 years \pm 5) in the control group ($P < .001$ for both).

Baseline Screening

After baseline screening, the interval breast cancer rate was 2.0 per 1000 women (68 of 34641) in the DBT group and 1.5 per 1000 women (88 of 57763) in the DM group ($P = .12$) (Table 1). Sensitivity was 82.7% (324 of 392) in the DBT group and 80.1% (355 of 443) in the DM group ($P = .35$); specificity was 97.6% (33415 of 34249) in the DBT group and 97.4% (55802 of 57320) in the DM group ($P = .048$) (Table 1, Fig 3). The adjusted risk ratio of interval breast cancer was 1.30 (95% confidence interval: 0.95, 1.78) for women in the DBT group relative to the DM group after adjusting for age and screening history (Table 2). In terms of tumor diameter ($P = .51$), histologic grade ($P = .03$ to $P = .53$), lymph node status ($P = .90$), and subtype ($P = .06$ to $P = .95$), no statisti-

cal difference was observed between interval breast cancer after baseline screening with DBT versus baseline screening with DM (Table 3).

Mean tumor diameter was 15 mm \pm 12 for screen-detected cancers and 21 mm \pm 13 for interval breast cancers among all women screened at baseline (both study and control group) ($P < .001$). The proportion of histologic grade 1 cancers was 31% (178 of 574) for screen-detected cancers versus 16% (23 of 146) for interval breast cancers ($P < .001$), and the proportion of luminal A subtypes was 59% (332 of 574) for screen-detected cancers at baseline versus 43% (61 of 146) for interval cancers ($P < .001$) (Table E2 [online]).

Consecutive Screening

For consecutively screened women, the recall rate was 23 per 1000 women (621 of 26474) in the study group and 31 per 1000 women (1408 of 45543) in the control group ($P < .001$) (Table 1). The rate of screen-detected breast cancer was 3.9 per 1000 women (103 of 26474) and 5.6 per 1000 women (254 of 45543) ($P = .001$), respectively. PPV-1 was 16.6% (103 of 621) in the study group and 18.0% (254 of 1408) in the control group ($P = .43$).

In women diagnosed with screen-detected breast cancer in the consecutive screening round, the rate of histologic grade 1 cancer was 0.5 per 1000 women (13 of 26474) in the study group and 1.3 per 1000 women (58 of 45543) in the control group ($P = .001$). The rates of luminal A subtype were 1.3 per 1000 women (35 of 26474) in the study group and 2.7 per 1000 women (124 of 45543) in the control group ($P < .001$) (Table 3). No difference was observed between the study and control groups with respect to tumor diameter ($P = .50$) or lymph node status ($P = .78$) (Fig 4).

Baseline and Consecutive Screening

The overall rate of breast cancers in two screening rounds for the study sample was 8.1 per 1000 screening examinations (495 of 61115) among those screened with DBT at baseline and 6.7 per 1000 screening examinations (697 of 103306) for those screened with DM at baseline ($P = .002$), resulting in a difference of 1.4 per 1000 screening examinations (Table 4).

For all women screened in the consecutive round with or without baseline screening, we observed recall rates of 37 per 1000 women (1370 of 36650) in Oslo County (DM after DBT, $P = .004$ compared with baseline) and 44 per 1000 women (2590 of 59036) in Vestfold County and Vestre Viken County (DM after DM, $P < .001$ compared with baseline) (Table E3 [online]). The rate of screening-detected breast cancer in the consecutive screening round, including those with and those without baseline screening, was 5.3 per 1000 women (194 of 36650) in Oslo County, which was lower than at baseline (P

Table 1: Age and Rates of Interval Breast Cancer, Sensitivity and Specificity in Women Screened in the Oslo-Vestfold-Vestre Viken Study at Baseline Screening, and Rates of Recall and Screen-detected Breast Cancer and PPV-1 in Women Reattending in the Consecutive Screening Round

| Variable | Women Screened from February 2014 to December 2015 | | | | Reattending Women Screened from February 2016 to December 2017 | | | |
|-------------------------------|--|--|---|-------------------|--|---|---|-------------------|
| | Total (<i>n</i> = 92 404) | Study Group (DBT and SM) (<i>n</i> = 34 641) | Control Group (DM) (<i>n</i> = 57 763) | <i>P</i> Value | Total (<i>n</i> = 72 017) | Study Group (DM after DBT and SM) (<i>n</i> = 26 474) | Control Group (DM after DM) (<i>n</i> = 45 543) | <i>P</i> Value |
| Age (y) | | | | | | | | |
| Mean* | 59.3 ± 5.9 | 59.1 ± 5.8 | 59.4 ± 5.9 | <.001† | 60.4 ± 5.3 | 60.3 ± 5.2 | 60.5 ± 5.3 | <.001† |
| Median‡ | 59.0 (54.0–64.0) | 59.0 (54.0–64.0) | 59.0 (54.0–65.0) | ... | 60.0 (56.0–65.0) | 60.0 (56.0–65.0) | 60.0 (56.0–65.0) | ... |
| Interval breast cancer | 156 (1.7) | 68 (2.0) | 88 (1.5) | .12 | ... | ... | ... | ... |
| DCIS | 10 (0.1) | 5 (0.1) | 5 (0.1) | .41 | ... | ... | ... | ... |
| Invasive | 146 (1.5) | 63 (1.8) | 83 (1.4) | .16 | ... | ... | ... | ... |
| Sensitivity (%)§ | 81.3 (679/835) | 82.7 (324/392) | 80.1 (355/443) | .35 | ... | ... | ... | ... |
| Specificity (%)§ | 97.4 (89,217/91,569) | 97.6 (33,415/34,249) | 97.4 (55,802/57,320) | .048 | ... | ... | ... | ... |
| Recall | ... | ... | ... | ... | 2029 (28) | 621 (23) | 1408 (31) | <.001† |
| Screen-detected breast cancer | ... | ... | ... | ... | 357 (5.0) | 103 (3.9) | 254 (5.6) | .001 |
| DCIS | ... | ... | ... | ... | 70 (1.0) | 19 (0.7) | 51 (1.1) | .10 |
| Invasive | ... | ... | ... | ... | 287 (4.0) | 84 (3.1) | 203 (4.5) | .008 |
| PPV-1 (%)§ | ... | ... | ... | ... | 17.6 (357/2029) | 16.6 (103/621) | 18.0 (254/1408) | .43 |

Note.—Unless otherwise indicated, data are number of women, and data in parentheses are rates per 1000 women screened. DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ, DM = digital mammography, PPV-1 = positive predictive value of recall, SM = synthetic mammography. *P* value was calculated for study group versus control group with the Pearson χ^2 test.

* Data are mean ± standard deviation.

† Statistically significant after Bonferroni correction.

‡ Data in parentheses are the median and interquartile range.

§ Data in parentheses were used to calculate sensitivity, specificity, or PPV-1.

< .001), and 6.4 per 1000 women (377 of 59 036) in Vestfold County and Vestre Viken County, which was not significantly different from the rate at baseline (*P* = .60).

Consecutive Screening Only (No Baseline Screening)

For women not screened at baseline but in the second screening round only, no significant differences were observed in rates of screen-detected breast cancer (8.9 per 1000 women [91 of 10 176] in Oslo County and 9.1 per 1000 women [123 of 13 493] in Vestfold County and Vestre Viken County, *P* = .89), PPV-1 (12.1% [91 of 749] in Oslo County and 10.4% [123 of 1182] in Vestfold County and Vestre Viken County, *P* = .23) (Table E3 [online]), or in histologic type, mean tumor diameter, tumor grade, lymph node status, or molecular subtypes (*P* > .05 for all) (Table E4 [online]).

Discussion

As increased rates of screen-detected breast cancer are reported for screening with digital breast tomosynthesis (DBT) versus standard two-dimensional (2D) digital mammography (DM),

a decline in interval breast cancer may be anticipated. In our study, the interval breast cancer rate did not differ (*P* = .12) between women screened with DBT and synthetic mammography and those screened with DM, despite a 50% higher rate of screen-detected cancer for DBT. No differences in rates of histopathologic tumor characteristics among interval breast cancers were observed (*P* > .03 or higher for all characteristics). In the consecutive screening round, the rate of screen-detected breast cancer decreased in the study group from 9.4 per 1000 women to 3.9 per 1000 women (*P* < .001). No change was observed in the control group (from 6.1 per 1000 women to 5.6 per 1000 women, *P* = .42). Recall was lower in the study group than in the control group among consecutively screened women (23 per 1000 women vs 31 per 1000 women, *P* < .001), while no difference was observed at baseline (*P* = .41).

Our finding of no difference in interval breast cancer rates between the DBT and DM groups (2.0 per 1000 women vs 1.5 per 1000 women) is in line with results from previous studies, and the rates are also consistent with the overall rate of interval breast cancer of 1.8 per 1000 women in BreastScreen Norway from

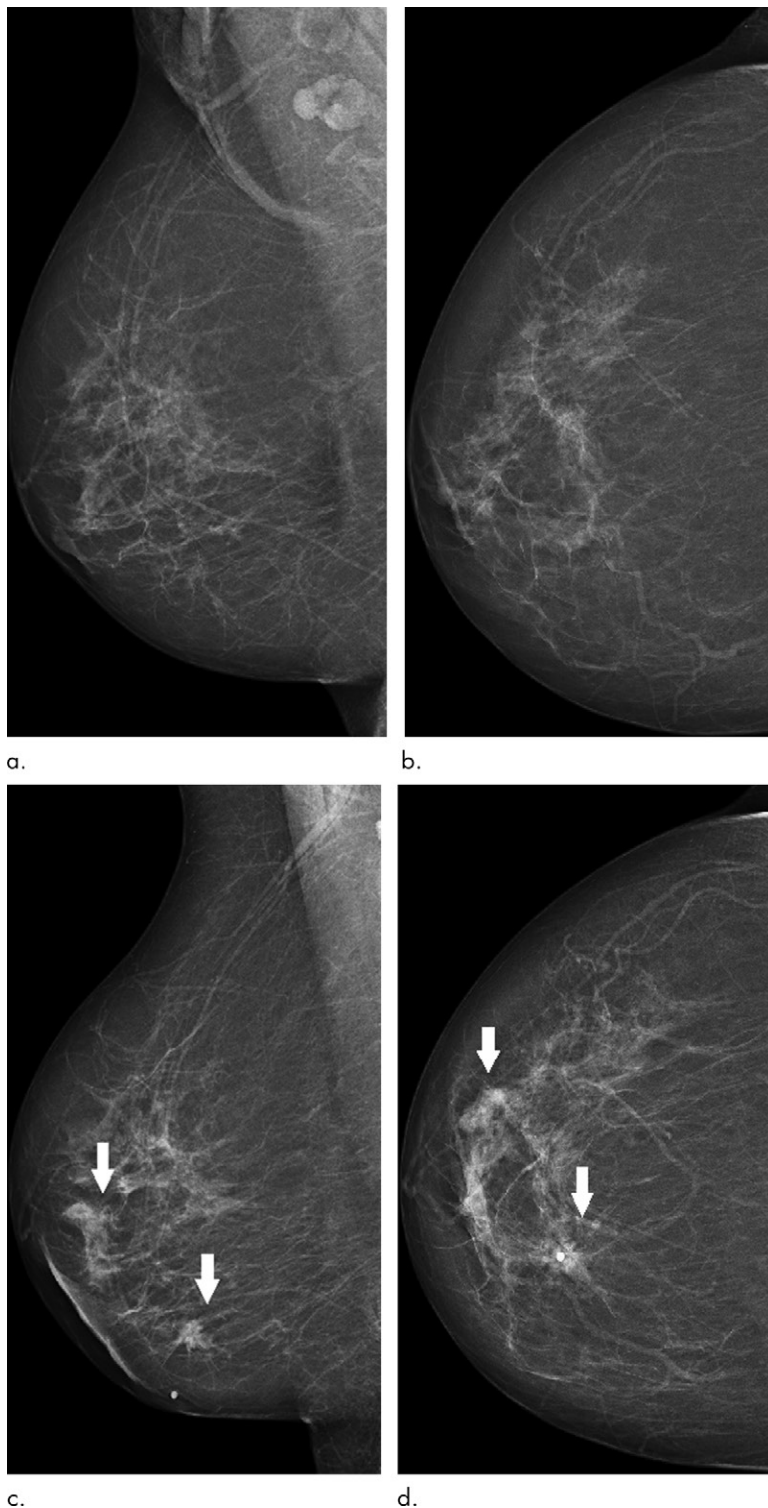


Figure 3: Images in a 67-year-old woman diagnosed with bifocal interval breast cancer (arrows in **c** and **d**) in the right breast 23 months after baseline screening with standard two-dimensional digital mammography. Right (**a**) mediolateral oblique and (**b**) craniocaudal baseline screening mammograms. Right (**c**) mediolateral oblique and (**d**) craniocaudal diagnostic mammograms. Final histopathologic examination revealed bifocal invasive carcinoma NST (no special type).

1996 to 2014 (19). The interval cancer rate was 2.1 per 1000 screens in the Oslo Tomosynthesis Screening Trial (or OTST) compared with 2.0 per 1000 screens prior to the OTST (22).

The Screening with Tomosynthesis or Standard Mammography (or STORM) trial reported interval breast cancer rates of 1.2 per 1000 screens and 1.6 per 1000 screens for DBT and DM, respectively; however, the numbers are small, and only nine interval cancer cases were observed in the DBT group (16). In the Malmö Breast Tomosynthesis Screening Trial (or MBTST), the interval breast cancer rate was 1.5 per 1000 screens in the DBT group (23). The screening regimen in the United States differs from that in Europe, with annual screening, generally higher recall rates, and lower rates of interval breast cancer (3). Still, no differences in interval cancer rate were observed for screening with DBT versus screening with DM in two U.S. studies; McDonald observed rates of 0.5 per 1000 screens for DBT and 0.7 per 1000 screens for DM ($P = .60$) (14), while Bahl et al observed rates of 1.1 per 1000 screens for both DBT and DM ($P = .84$) (24). Thus, in keeping with other studies, our study did not enable us to confirm an anticipated reduction in interval breast cancer after increased cancer detection at screening with DBT. Our findings support results from other studies, indicating that interval breast cancers are mammographically or biologically different from screen-detected breast cancers and are thus not affected by increased screening sensitivity or technique. This assumption is also supported by the discrepancy of histopathologic tumor characteristics in screen-detected and interval breast cancer, as described previously.

Our study had some limitations. First, we included data from women screened at three different breast centers with different equipment and screening techniques. Further, the breast radiologists and pathologists were dedicated to the breast center, and the study design hampers adjustment for these factors, as the screening technique was related to the breast center. However, the centers had comparable cancer detection rates prior to the study period (11,19), and no differences in cancer detection rate, PPV-1, or histopathologic characteristics were observed in the subsequent screening round among those not screened at baseline. Second, some women in the study group were previously screened with DBT in the Oslo Tomosynthesis Trial (10). Among reattending women in the study group, prior DBT images were available for comparison at screening or consensus reading, which may have caused increased confidence among radiologists when determining whether to recall women. The higher recall rate among consecutively screened women in the control group might be a poststudy effect caused by the lower cancer detection rate at baseline screening or a random variation (19). Another limitation is the sample size and thus the number of interval breast cancers: there were

Table 2: Risk Ratio for Interval Breast Cancer in Women Screened with DBT or DM in the Oslo-Vestfold-Vestre Viken Study

| Variable | Unadjusted | | | Adjusted* | | |
|---------------------|------------|------------|---------|------------|------------|---------|
| | Risk Ratio | 95% CI | P Value | Risk Ratio | 95% CI | P Value |
| Screening technique | | | | | | |
| Control group (DM) | 1.00 | ... | ... | 1.00 | ... | ... |
| Study group (DBT) | 1.29 | 0.94, 1.77 | .12 | 1.30 | 0.95, 1.78 | .11 |
| Age | 1.01 | 0.98, 1.03 | .61 | 1.01 | 0.98, 1.04 | .60 |
| Screening history | | | | | | |
| Prevalent | 1.00 | ... | ... | 1.00 | ... | ... |
| Subsequent | 1.02 | 0.67, 1.55 | .93 | 0.97 | 0.59, 1.60 | .89 |

Note.—Unadjusted and adjusted risk ratios for interval breast cancer in baseline screened women (February 2014 to December 2015) by age and screening history. CI = confidence interval, DM = digital mammography, DBT = digital breast tomosynthesis including synthetic mammography.

* Adjusted for age and screening history.

Table 3: Histopathologic Tumor Characteristics for Interval Breast Cancer and Screen-detected Breast Cancer in the Consecutive Screening Round by Screening Technique

| Variable | Interval Breast Cancer | | | Breast Cancer Discovered at Consecutive Screening | | |
|-------------------------|--------------------------|---------------------------|---------|---|----------------------------|---------|
| | Study Group DBT (n = 63) | Control Group DM (n = 83) | P Value | Study Group DM (n = 84) | Control Group DM (n = 203) | P Value |
| Histologic type | | | | | | |
| IDC | 53 (1.5) | 64 (1.1) | .08 | 69 (2.6) | 157 (3.5) | .05 |
| ILC | 7 (0.2) | 9 (0.2) | .61 | 9 (0.3) | 25 (0.6) | .21 |
| Tubular | 2 (0.1) | 0 | .07 | 3 (0.1) | 5 (0.1) | .97 |
| Other | 1 (0.03) | 10 (0.2) | .05 | 3 (0.1) | 16 (0.4) | .06 |
| Tumor diameter (mm) | | | | | | |
| Mean* | 21.5 ± 16.9 | 19.9 ± 9.1 | .51 | 15.4 ± 13.0 | 14.3 ± 8.2 | .50 |
| Median† | 17.0 (13.0–25.0) | 19.0 (14.0–25.0) | ... | 12.0 (7.5–18.0) | 13.0 (9.0–19.0) | ... |
| NA | 2 | 7 | ... | 2 | 5 | ... |
| Histologic grade | | | | | | |
| 1 | 11 (0.3) | 12 (0.2) | .31 | 13 (0.5) | 58 (1.3) | .001 |
| 2 | 34 (1.0) | 34 (0.6) | .03 | 52 (2.0) | 115 (2.5) | .13 |
| 3 | 18 (0.5) | 36 (0.6) | .53 | 19 (0.7) | 30 (0.7) | .77 |
| NA | 0 | 1 | | | | |
| Lymph node positive | 15 (0.4) | 24 (0.4) | .90 | 16 (0.7) | 30 (0.7) | .78 |
| NA | 0 | 3 | ... | 1 | 5 | ... |
| Subtype | | | | | | |
| Luminal A | 27 (0.8) | 34 (0.6) | .27 | 35 (1.3) | 124 (2.7) | <.001‡ |
| Luminal B HER2 negative | 22 (0.6) | 21 (0.4) | .06 | 35 (1.3) | 48 (1.1) | .31 |
| Luminal B HER2 positive | 3 (0.1) | 10 (0.2) | .35 | 2 (0.1) | 15 (0.3) | .03 |
| HER2 positive | 2 (0.1) | 3 (0.1) | .83 | 5 (0.2) | 4 (0.1) | .24 |
| Triple negative | 8 (0.2) | 13 (0.3) | .95 | 3 (0.1) | 10 (0.2) | .31 |
| NA | 1 | 2 | ... | 4 | 2 | ... |

Note.—Histopathologic tumor characteristics for invasive interval breast cancer in women screened between February 2014 and December 2015 and screen-detected breast cancer in women consecutively screened between February 2016 and December 2017. Unless else otherwise specified, data are numbers of women, and data in parentheses are rates per 1000 women screened. DBT = digital breast tomosynthesis including synthetic mammography, DM = digital mammography, HER2 = human epidermal growth factor 2, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, NA = information not available.

* Data are mean ± standard deviation.

† Data in parentheses are the interquartile range.

‡ Statistically significant after Bonferroni correction.

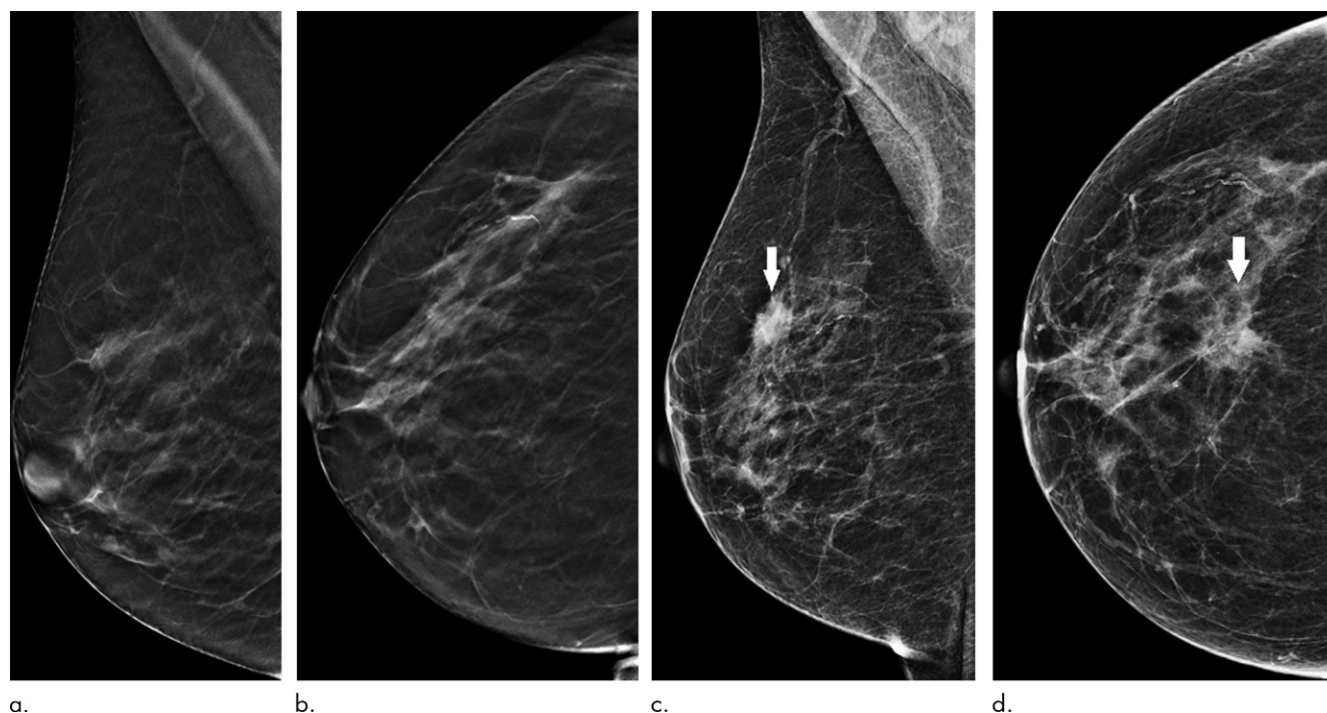


Figure 4: Images in a 63-year-old woman diagnosed with screen-detected breast cancer (arrow in **c** and **d**) in the right breast at consecutive screening with standard two-dimensional (2D) digital breast mammography (DM) after baseline screening with digital breast tomosynthesis (DBT) and 2D synthetic mammography. Right (**a**) mediolateral oblique and (**b**) craniocaudal baseline screening DBT mammograms. Right (**c**) mediolateral oblique and (**d**) craniocaudal consecutive screening DM mammograms. Final histopathologic examination revealed invasive carcinoma NST (no special type).

Table 4: Total Cancer Detection for Oslo-Vestfold-Vestre Viken Study Participants from 2014 to 2017

| Variable | Study Group | Control Group | <i>P</i> Value |
|---|----------------------|----------------------|----------------|
| Screening examinations | | | |
| Baseline (February 2014 to December 2015) | 34 641 | 57 763 | ... |
| Consecutive screening round (February 2016 to December 2017) | 26 474 | 45 543 | ... |
| Total | 61 115 | 103 306 | ... |
| Cancer detection (n) | | | |
| SDC at baseline (February 2014 to December 2015) | 324 | 355 | ... |
| IBC 2-year follow-up | 68 | 88 | ... |
| SDC at consecutive screening (February 2016 to December 2017) | 103 | 254 | ... |
| Total | 495 | 697 | ... |
| Total cancer detection rate | 8.1 per 1000 screens | 6.7 per 1000 screens | .002 |

Note.—Data are number of women screened, number of breast cancers detected at screening (SDC), and number of interval breast cancers (IBC) at baseline and in the consecutive screening round. Women in the study group were screened with digital breast tomosynthesis and synthetic mammography at baseline and digital mammography (DM) in the consecutive screening round. Women in the control group were screened with DM in both screening rounds.

68 cancers detected with DBT and 88 cancers detected with DM. However, we consider the results trustworthy, as they are highly comparable with those of other studies and are in line with the rates in BreastScreen Norway and at the participating breast centers (19).

In conclusion, we did not observe a statistical difference in interval breast cancer rates between women screened with digital breast tomosynthesis (DBT) and synthetic mammography and those screened with standard two-dimensional (2D) digital mammography (DM), despite a 50% higher rate of screen-detected cancer for DBT versus DM at baseline. Our findings are in line with those of other studies. Further, the cancers detected

at baseline with DBT were mainly small low-grade invasive cancers, and the cancer detection rate declined significantly in the consecutive screening round with DM. This may indicate a prevalence effect of DBT screening with increased lead time and detection of less aggressive tumors. Our findings may question whether the additional tumors have the potential to progress and become life-threatening cancers in the women or if they are small, low-proliferation cancers representing overdiagnosis with little or no clinical importance (3,14). More, larger, and aggregated studies on interval breast cancer and DBT, including results from consecutive screening rounds and analyses of mammographic features of screen-detected and interval breast

cancers, are needed to understand the benefits and harms of implementing DBT in population-based screening programs for breast cancer (25).

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