Original Investigation

# Breast Cancer Screening Using Tomosynthesis in Combination With Digital Mammography

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**IMPORTANCE** Mammography plays a key role in early breast cancer detection. Single-institution studies have shown that adding tomosynthesis to mammography increases cancer detection and reduces false-positive results.

**OBJECTIVE** To determine if mammography combined with tomosynthesis is associated with better performance of breast screening programs in the United States.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective analysis of screening performance metrics from 13 academic and nonacademic breast centers using mixed models adjusting for site as a random effect.

**EXPOSURES** Period 1: digital mammography screening examinations 1 year before tomosynthesis implementation (start dates ranged from March 2010 to October 2011 through the date of tomosynthesis implementation); period 2: digital mammography plus tomosynthesis examinations from initiation of tomosynthesis screening (March 2011 to October 2012) through December 31, 2012.

**MAIN OUTCOMES AND MEASURES** Recall rate for additional imaging, cancer detection rate, and positive predictive values for recall and for biopsy.

**RESULTS** A total of 454 850 examinations (n=281 187 digital mammography; n=173 663 digital mammography + tomosynthesis) were evaluated. With digital mammography, 29 726 patients were recalled and 5056 biopsies resulted in cancer diagnosis in 1207 patients (n=815 invasive; n=392 in situ). With digital mammography + tomosynthesis, 15 541 patients were recalled and 3285 biopsies resulted in cancer diagnosis in 950 patients (n=707 invasive; n=243 in situ). Model-adjusted rates per 1000 screens were as follows: for recall rate, 107 (95% CI, 89-124) with digital mammography vs 91 (95% CI, 73-108) with digital mammography + tomosynthesis; difference, −16 (95% CI, −18 to −14; $P < .001$); for biopsies, 18.1 (95% CI, 15.4-20.8) with digital mammography vs 19.3 (95% CI, 16.6-22.1) with digital mammography + tomosynthesis; difference, 1.3 (95% CI, 0.4-2.1; $P = .004$); for cancer detection, 4.2 (95% CI, 3.8-4.7) with digital mammography vs 5.4 (95% CI, 4.9-6.0) with digital mammography + tomosynthesis; difference, 1.2 (95% CI, 0.8-1.6; $P < .001$); and for invasive cancer detection, 2.9 (95% CI, 2.5-3.2) with digital mammography vs 4.1 (95% CI, 3.7-4.5) with digital mammography + tomosynthesis; difference, 1.2 (95% CI, 0.8-1.6; $P < .001$). The in situ cancer detection rate was 1.4 (95% CI, 1.2-1.6) per 1000 screens with both methods. Adding tomosynthesis was associated with an increase in the positive predictive value for recall from 4.3% to 6.4% (difference, 2.1%; 95% CI, 1.7%-2.5%; $P < .001$) and for biopsy from 24.2% to 29.2% (difference, 5.0%; 95% CI, 3.0%-7.0%; $P < .001$).

**CONCLUSIONS AND RELEVANCE** Addition of tomosynthesis to digital mammography was associated with a decrease in recall rate and an increase in cancer detection rate. Further studies are needed to assess the relationship to clinical outcomes.

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Screening mammography has played a key role in reducing breast cancer mortality. By identifying a subset of cancers diagnosed before they reach clinical presentation, intervention is more likely to result in long-term survival.[1] Despite this benefit, mammography has drawn criticism for excessive false-positive results, limited sensitivity, and the potential of overdiagnosis of clinically insignificant lesions.[2,3]

Incremental improvements in mammography have been realized through development of full-field digital imaging[4] and, recently, through the addition of the 3-dimensional technique of tomosynthesis.[5] Tomosynthesis involves image acquisition from an x-ray source that moves over an arc of excursion with reconstruction into thin slices to minimize the influence of overlapping breast structures. This data set can be acquired simultaneously with a conventional digital mammogram. In 2011, tomosynthesis was approved by the US Food and Drug Administration (FDA) to be used in combination with standard digital mammography for breast cancer screening.[6] This combined mode (digital mammography + tomosynthesis) addresses the primary limitations of conventional screening mammography by increasing conspicuity of invasive cancers while concomitantly reducing false-positive results.[7-9] Total radiation dose when tomosynthesis is added is approximately 2 times the current digital mammography dose but remains well below the limits defined by the FDA.[10] The reconstruction of a generated 2-dimensional image from the tomosynthesis data set, a technology recently approved by the FDA, should further address concerns regarding dose.[11]

Performance metrics for radiologists such as recall and cancer detection rates have been established to monitor screening outcomes, which in turn enable breast centers to assess the effectiveness of mammographic screening.[12,13] Supplemental screening modes such as magnetic resonance imaging and ultrasound have demonstrated the ability to improve cancer detection but have failed to simultaneously reduce false-positive results.[14,15]

In this multicenter analysis, the performance of digital mammography + tomosynthesis was compared with that of digital mammography alone across a spectrum of radiology practices in the United States.

## Methods

### Study Design

The Health Insurance Portability and Accountability Act–compliant study protocol was approved by the institutional review boards of participating institutions with a waiver of informed consent. This study compared performance of breast cancer screening before and after introduction of tomosynthesis at 13 institutions over 2 periods. Period 1 included 1 full year of screening with digital mammography alone, ending on the date of tomosynthesis introduction at each institution. Period 2 included screening with digital mammography + tomosynthesis until December 31, 2012. Individual institutions' start dates for screening with digital mammography + tomosynthesis ranged from March 2011 to October 2012. The analysis included the following performance metrics: recall rate (proportion of patients requiring additional imaging based on a screening examination result), cancer detection rate (proportion of patients with a screen-detected breast cancer), positive predictive value (PPV) for recall (proportion of patients recalled after screening who were diagnosed as having breast cancer) and PPV for biopsy (proportion of patients undergoing biopsies who were diagnosed as having breast cancer).[12]

### Participating Institutions and Patient Population

Institutions performing screening with tomosynthesis were sent a questionnaire in August 2012. Institutions expecting to complete 5000 or more screening examinations using digital mammography + tomosynthesis by the end of 2012 were invited to participate. All 13 invited sites participated and used the same equipment (Selenia Dimensions, Hologic), the only FDA-approved device at the time.[6]

### Data Collection

Each participating institution provided aggregate data for all screening examinations, additional imaging studies, and relevant biopsy results. Submitted data from each institution were derived from records used to audit annual performance outcomes to maintain FDA compliance for screening mammography facilities.[10]

Recall rates were determined for each institution based on the initial interpretation of screening examinations. If a biopsy was recommended and performed within 120 days of a screening recall, results of the biopsy were used to determine if a cancer was detected. A 120-day interval was chosen to allow reasonable time for patients to complete the diagnostic workup but not include patients who were presenting for a 6-month follow up—a standard interval for short-term reevaluation in breast imaging. Cancers were identified as invasive or ductal carcinoma in situ (DCIS); cancers containing mixed invasive and in situ components were classified as invasive. Cancers not of primary breast origin, such as lymphomas and metastases, were excluded from analysis.

We report the rate of screen-detected cancers and proportion of recalls per 1000 screens before and after tomosynthesis implementation. Because data on interval cancers were not available, absolute sensitivity and specificity could not be calculated.

### Statistical Analysis

Inclusion of 13 sites and expectation of at least 5000 cases per institution in each period would result in a minimum of 65 000 examinations in each time frame for evaluation. A power analysis based on results showing a 28% increase in cancer detection and a 37% reduction in recall rate from a single-institution study using a similar study design[16] was performed to estimate the sample size required. With 65 000 cases in each period and the magnitude of observed change in the single-institution study, the multicenter study would have 80% power for demonstrating change in cancer detection rate and greater than 99% power for demonstrating change in recall rate.

Because sites contributed different numbers of cases during the 2 study periods, the primary analysis adjusts for site effect. Adjusting for site as a random effect allows for the pos-

Table 1. Characteristics of Participating Institutions

| Site | No. of Radiologists | Academic (A) or Nonacademic (N) | Period 1 | | Period 2 | | Total No. of Cases Used for Primary Analysis | Transition to Digital Mammography + Tomosynthesis | No. of Digital Mammography Cases Imaged in Period 2[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | Duration, mo | No. of Digital Mammography Cases | Duration, mo | No. of Digital Mammography + Tomosynthesis Cases | | | |
| 1 | 7 | A | 12 | 10 746 | 16 | 4366 | 15 112 | Hybrid | 16 098 |
| 2 | 10 | N | 12 | 19 830 | 19 | 7909 | 27 739 | Hybrid | 26 105 |
| 3 | 6 | A | 12 | 10 753 | 16 | 14 014 | 24 767 | Complete | 0 |
| 4 | 7 | A | 12 | 12 533 | 17 | 8607 | 21 140 | Hybrid | 10 022 |
| 5 | 13 | N | 12 | 26 502 | 13 | 3640 | 30 142 | Hybrid | 33 112 |
| 6 | 18 | N | 12 | 25 488 | 3 | 5868 | 31 356 | Complete | 0 |
| 7 | 20 | N | 12 | 22 606 | 18 | 2613 | 25 219 | Hybrid | 29 112 |
| 8 | 6 | N | 12 | 16 694 | 18 | 16 149 | 32 843 | Hybrid | 16 098 |
| 9 | 3 | N | 12 | 4801 | 21 | 16 269 | 21 070 | Hybrid | 2178 |
| 10 | 5 | A | 12 | 17 623 | 22 | 5880 | 23 503 | Hybrid | 6416 |
| 11 | 20 | N | 12 | 53 181 | 17 | 24 281 | 77 462 | Hybrid | 56 803 |
| 12 | 12 | A | 12 | 40 382 | 22 | 34 119 | 74 501 | Hybrid | 45 473 |
| 13 | 12 | N | 12 | 20 048 | 20 | 29 948 | 49 996 | Hybrid | 4568 |
| Total | 139 | | | 281 187 | | 173 663 | 454 850 | | 245 985 |

[a] Digital mammography cases imaged during period 2 were used in analysis to address potential selection bias.

sibility that patient outcomes within the same site are correlated, assuming that study patients are not fully independent observations. Specifically, additive and multiplicative mixed models using SAS PROC MIXED and NLMIXED (SAS, version 9.3; SAS Institute Inc) were used to estimate rates with screening method (digital mammography and digital mammography + tomosynthesis) as a fixed effect and site as a random effect. The log link function of the probability was specified. Adjusted rates and 95% confidence intervals were calculated based on the fitted model. All tests were 2-sided and $P < .05$ was considered statistically significant.

Tomosynthesis introduction at participating sites was nonuniform. Because of budgetary constraints, the majority of sites could not replace all mammography devices with tomosynthesis-capable units at once. Two sites did make a complete conversion, while the remaining sites maintained a hybrid environment with some patients receiving digital mammography alone during the second period. These concurrent digital mammography screening events were not included in the primary analysis. While no participating site intentionally targeted any specific population for tomosynthesis, the possibility of selection bias exists within the hybrid environments. Therefore, the analysis was repeated using all screened women (concurrent digital mammography alone plus digital mammography + tomosynthesis) in the digital mammography + tomosynthesis period to test if a significant change in cancer detection and recall rates was present between the preimplementation and postimplementation time frames.

## Results

**Table 1** summarizes the characteristics of participating institutions. A total of 454 850 screening mammograms were interpreted at 13 sites by 139 radiologists and used for the primary analysis. Of the 454 850 examinations, 281 187 (61.8%) were performed in the first period (digital mammography alone) and 173 663 (38.2%) were performed in the second period (digital mammography + tomosynthesis). The average duration of the second period was 17 months (range, 3-22 months). The volumes of digital mammography + tomosynthesis varied from 2613 to 34 119 cases (mean, 13 359 cases). The mean age of patients undergoing imaging with digital mammography alone was 57.0 years (range of means from 13 sites, 54.4-60.5 years) and with digital mammography + tomosynthesis was 56.2 years (range, 52.6-59.7 years).

**Table 2**, **Table 3**, and **Table 4** summarize recall, biopsy, and cancer detection rates for individual sites and for the entire cohort screened with digital mammography (period 1) and with digital mammography + tomosynthesis (period 2). The statistical model estimate is also shown. The recall rate per 1000 screens with digital mammography alone was 107 (95% CI, 89-124) compared with 91 (95% CI, 73-108) with digital mammography + tomosynthesis. This represents an overall decrease in recall rate of -16 (95% CI, -18 to -14; $P < .001$) per 1000 screens when screening was performed with digital mammography + tomosynthesis compared with digital mammography alone. Eleven of the 13 sites observed a decrease in recall rate when screening with digital mammography + tomosynthesis. Two sites had recall rate increases of 18 per 1000 examinations with digital mammography + tomosynthesis screening. The number of women undergoing biopsy who were recalled based on screening results was 5056 with digital mammography alone and 3285 with digital mammography + tomosynthesis. The model-adjusted biopsy rate per 1000 women screened is shown in Table 3 and was 18.1 (95% CI, 15.4-20.8) with digital mammography and 19.3 (95% CI, 16.6-22.1) with digital mammography + tomosynthesis. This represents an increase in biopsy rate for digital mammography + tomosynthesis of 1.3 (95% CI, 0.4-2.1; $P = .004$) per 1000 screens. Cases recommended for bi-

Table 2. Total No. of Cases Read and Rates of Recall With Digital Mammography Alone and Digital Mammography With Tomosynthesis

| Site | Cases Read | | No. of Recalls | | Recalls per 1000 Cases | | |
|---|---|---|---|---|---|---|---|
| | Digital Mammography | Digital Mammography + Tomosynthesis | Digital Mammography | Digital Mammography + Tomosynthesis | Digital Mammography | Digital Mammography + Tomosynthesis | Change (95% CI)[a] |
| 1 | 10 746 | 4366 | 1394 | 471 | 130 | 108 | -22 (-33 to -10) |
| 2 | 19 830 | 7909 | 1518 | 575 | 77 | 73 | -4 (-11 to 3) |
| 3 | 10 753 | 14 014 | 1118 | 1245 | 104 | 89 | -15 (-23 to -8) |
| 4 | 12 533 | 8607 | 1385 | 679 | 111 | 79 | -32 (-40 to -23) |
| 5 | 26 502 | 3640 | 3436 | 320 | 130 | 88 | -42 (-53 to -30) |
| 6 | 25 488 | 5868 | 2394 | 658 | 94 | 112 | 18 (10 to 27) |
| 7 | 22 606 | 2613 | 1490 | 220 | 66 | 84 | 18 (8 to 28) |
| 8 | 16 694 | 16 149 | 1908 | 1371 | 114 | 85 | -29 (-36 to -23) |
| 9 | 4801 | 16 269 | 836 | 2614 | 174 | 161 | -13 (-25 to -2) |
| 10 | 17 623 | 5880 | 1580 | 456 | 90 | 78 | -12 (-20 to -4) |
| 11 | 53 181 | 24 281 | 8173 | 3349 | 154 | 138 | -16 (-21 to -10) |
| 12 | 40 382 | 34 119 | 2907 | 2032 | 72 | 60 | -12 (-16 to -9) |
| 13 | 20 048 | 29 948 | 1587 | 1551 | 79 | 52 | -27 (-32 to -23) |
| All | 281 187 | 173 663 | 29 726 | 15 541 | 106 | 89 | -17 |
| Model estimate[b] | | | | | 107 | 91 | -16.1 (-18.0 to -14.2) |

[a] $P<.001$ for overall change.

[b] The model estimate adjusted for site as a random effect and treated time period as a fixed effect.

Table 3. Rates of Biopsy With Digital Mammography Alone and Digital Mammography With Tomosynthesis

| Site | No. of Biopsies | | Biopsies per 1000 Cases | | |
|---|---|---|---|---|---|
| | Digital Mammography | Digital Mammography + Tomosynthesis | Digital Mammography | Digital Mammography + Tomosynthesis | Change (95% CI)[a] |
| 1 | 191 | 63 | 18 | 14 | -3.3 (-7.9 to 1.2) |
| 2 | 398 | 130 | 20 | 16 | -3.6 (-7.2 to -0.1) |
| 3 | 187 | 297 | 17 | 21 | 3.8 (0.3 to 7.3) |
| 4 | 267 | 168 | 21 | 20 | -1.8 (-5.7 to 2.1) |
| 5 | 367 | 82 | 14 | 23 | 8.7 (4.5 to 12.9) |
| 6 | 637 | 208 | 25 | 35 | 10.5 (5.9 to 15.0) |
| 7 | 379 | 40 | 17 | 15 | -1.5 (-6.6 to 3.7) |
| 8 | 340 | 227 | 20 | 14 | -6.3 (-9.1 to -3.5) |
| 9 | 155 | 423 | 32 | 26 | -6.3 (-11.5 to -1.0) |
| 10 | 191 | 76 | 11 | 13 | 2.1 (-1.0 to 5.2) |
| 11 | 1124 | 693 | 21 | 29 | 7.4 (5.1 to 9.7) |
| 12 | 527 | 468 | 13 | 14 | 0.7 (-1.0 to 2.3) |
| 13 | 293 | 410 | 15 | 14 | -0.9 (-3.0 to 1.2) |
| All | 5056 | 3285 | 18 | 19 | 0.9 |
| Model estimate[b] | | | 18.1 | 19.3 | 1.3 (0.4 to 2.1) |

[a] $P=.004$ for overall change.

[b] The model estimate adjusted for site as a random effect and treated time period as a fixed effect.

opsy that were lost to follow-up comprised 4.6% of recommended biopsies for digital mammography alone and 3.6% for digital mammography + tomosynthesis.

Cancer was detected in 1207 women (n=815 invasive cancers; n=392 DCIS) with digital mammography and 950 (n=707 invasive cancers; n=243 DCIS) with digital mammography + tomosynthesis. The cancer detection rate per 1000 examinations for the cohort screened with digital mammography was 4.2 (95% CI, 3.8-4.7) compared with 5.4 (95% CI, 4.9-6.0) when screening with digital mammography + tomosynthesis, representing an overall increase in cancer detection rate of 1.2 (95% CI, 0.8-1.6; $P < .001$) with digital mammography + tomosynthesis compared with digital mammography alone. Twelve of the 13 sites increased their cancer detection rates.

When cancers were classified by their maximal histology as either invasive or DCIS (**Table 5** and **Table 6**), the invasive cancer detection rate per 1000 examinations for the cohort screened with digital mammography was 2.9 (95% CI, 2.5-3.2) compared with 4.1 (95% CI, 3.7-4.5) when screening with digital mammography + tomosynthesis, representing an overall

Table 4. Rates of Cancer Detection With Digital Mammography Alone and Digital Mammography With Tomosynthesis

| Site | No. Cancers | | Cancers per 1000 Cases | | |
|---|---|---|---|---|---|
| | Digital Mammography | Digital Mammography + Tomosynthesis | Digital Mammography | Digital Mammography + Tomosynthesis | Change (95% CI)[a] |
| 1 | 44 | 32 | 4.1 | 7.3 | 3.2 (0.7 to 5.7) |
| 2 | 95 | 39 | 4.8 | 4.9 | 0.1 (-1.7 to 1.9) |
| 3 | 47 | 75 | 4.4 | 5.4 | 1.0 (-0.8 to 2.7) |
| 4 | 51 | 50 | 4.1 | 5.8 | 1.7 (-0.2 to 3.6) |
| 5 | 82 | 14 | 3.1 | 3.8 | 0.8 (-1.2 to 2.7) |
| 6 | 156 | 44 | 6.1 | 7.5 | 1.4 (-0.9 to 3.6) |
| 7 | 102 | 8 | 4.5 | 3.1 | -1.5 (-4.1 to 1.2) |
| 8 | 76 | 80 | 4.6 | 5.0 | 0.4 (-1.1 to 1.9) |
| 9 | 11 | 97 | 2.3 | 6.0 | 3.7 (1.4 to 6.0) |
| 10 | 42 | 28 | 2.4 | 4.8 | 2.4 (0.8 to 4.0) |
| 11 | 230 | 150 | 4.3 | 6.3 | 1.9 (0.8 to 2.9) |
| 12 | 189 | 179 | 4.7 | 5.2 | 0.6 (-0.4 to 1.6) |
| 13 | 82 | 154 | 4.1 | 5.1 | 1.1 (-0.2 to 2.3) |
| All | 1207 | 950 | 4.3 | 5.5 | 1.2 |
| Model estimate[b] | | | 4.2 | 5.4 | 1.2 (0.8 to 1.6) |

[a] $P<.001$ for overall change.

[b] The model estimate adjusted for site as a random effect and treated time period as a fixed effect.

Table 5. Detection Rates for Invasive Cancers

| Site | No. of Invasive Cancers | | Invasive Cancers per 1000 Cases | | |
|---|---|---|---|---|---|
| | Digital Mammography | Digital Mammongraphy + Tomosynthesis | Digital Mammography | Digital Mammongraphy + Tomosynthesis | Change (95% CI)[a] |
| 1 | 32 | 23 | 3.0 | 5.3 | 2.3 (0.2 to 4.4) |
| 2 | 71 | 30 | 3.6 | 3.8 | 0.2 (-1.4 to 1.8) |
| 3 | 32 | 55 | 3.0 | 3.9 | 0.9 (-0.5 to 2.4) |
| 4 | 34 | 34 | 2.7 | 4.0 | 1.2 (-0.3 to 2.8) |
| 5 | 52 | 10 | 2.0 | 2.7 | 0.8 (-0.8 to 2.4) |
| 6 | 104 | 35 | 4.1 | 6.0 | 1.9 (-0.0 to 3.8) |
| 7 | 80 | 7 | 3.5 | 2.7 | -0.9 (-3.2 to 1.5) |
| 8 | 52 | 61 | 3.1 | 3.8 | 0.7 (-0.6 to 1.9) |
| 9 | 7 | 72 | 1.5 | 4.4 | 3.0 (1.0 to 4.9) |
| 10 | 25 | 18 | 1.4 | 3.1 | 1.6 (0.4 to 2.9) |
| 11 | 147 | 112 | 2.8 | 4.6 | 1.8 (1.0 to 2.7) |
| 12 | 129 | 123 | 3.2 | 3.6 | 0.4 (-0.4 to 1.2) |
| 13 | 50 | 127 | 2.5 | 4.2 | 1.7 (0.7 to 2.8) |
| All | 815 | 707 | 2.9 | 4.1 | 1.2 |
| Model estimate[b] | | | 2.9 | 4.1 | 1.2 (0.8 to 1.6) |

[a] $P<.001$ for overall change.

[b] The model estimate adjusted for site as a random effect and treated time period as a fixed effect.

increase of 1.2 (95% CI, 0.8-1.6; $P<.001$) per 1000. Twelve of 13 sites increased detection of invasive cancer; the single site showing a decrease in both overall and invasive cancer detection rates (site 7) had the lowest screening volume using digital mammography + tomosynthesis, accruing only 8 total cancers with the combined mode. The DCIS detection rate per 1000 examinations was 1.4 (95% CI, 1.2-1.6) for both methods with the estimated difference in the detection rate of DCIS between the 2 periods of 0.0 (95% CI,-0.2 to 0.2; $P = .95$) per 1000.

The mean PPV for recall at all sites was 4.3% (95% CI, 3.4%-5.3%) with digital mammography alone vs 6.4% (95% CI, 5.5%-7.4%) with digital mammography + tomosynthesis, a 2.1% increase (95% CI, 1.7%-2.5%; $P < .001$) with digital mammography + tomosynthesis (**Table 7**). The mean PPV for biopsy at all sites was 24.2% (95% CI, 21.1%-27.1%) with digital mammography alone vs 29.2% (95% CI, 26.0%-32.3%) for digital mammography + tomosynthesis, a 5.0% increase (95% CI, 3.0%-7.0%; $P < .001$) when screening was performed with digital mammography + tomosynthesis (Table 7).

**Table 8** shows the histology of the cancers detected in the first period (digital mammography alone) and second period (digital mammography + tomosynthesis). There was an increase in detection rates from 2.46 to 3.27 for invasive ductal carcinoma and from 0.27 to 0.55 for invasive lobular carcinoma when tomosynthesis was added.

Table 6. Detection Rates for Ductal Carcinoma In Situ (DCIS) Cancers

| Site | No. of DCIS Cancers | | DCIS Cancers per 1000 Cases | | |
|---|---|---|---|---|---|
| | Digital Mammography | Digital Mammography + Tomosynthesis | Digital Mammography | Digital Mammography + Tomosynthesis | Change (95% CI)[a] |
| 1 | 12 | 9 | 1.1 | 2.1 | 0.9 (-0.4 to 2.3) |
| 2 | 24 | 9 | 1.2 | 1.1 | -0.1 (-1.0 to 0.8) |
| 3 | 15 | 20 | 1.4 | 1.4 | 0.0 (-0.9 to 1.0) |
| 4 | 17 | 16 | 1.4 | 1.9 | 0.5 (-0.6 to 1.6) |
| 5 | 30 | 4 | 1.1 | 1.1 | -0.0 (-1.2 to 1.1) |
| 6 | 52 | 9 | 2.0 | 1.5 | -0.5 (-1.8 to 0.7) |
| 7 | 22 | 1 | 1.0 | 0.4 | -0.6 (-1.8 to 0.6) |
| 8 | 24 | 19 | 1.4 | 1.2 | -0.3 (-1.0 to 0.5) |
| 9 | 4 | 25 | 0.8 | 1.5 | 0.7 (-0.5 to 1.9) |
| 10 | 17 | 10 | 1.0 | 1.7 | 0.7 (-0.3 to 1.7) |
| 11 | 83 | 38 | 1.6 | 1.6 | 0.0 (-0.6 to 0.6) |
| 12 | 60 | 56 | 1.5 | 1.6 | 0.2 (-0.4 to 0.7) |
| 13 | 32 | 27 | 1.6 | 0.9 | -0.7 (-1.3 to -0.1) |
| All | 392 | 243 | 1.4 | 1.4 | 0.0 |
| Model estimate[b] | | | 1.4 | 1.4 | 0.0 (-0.2 to 0.2) |

[a] $P$=.95 for overall change.

[b] The model estimate adjusted for site as a random effect and treated time period as a fixed effect.

Table 7. Positive Predictive Values (PPVs) for Recall and Biopsy

| Site | Recall | | | Biopsy | | |
|---|---|---|---|---|---|---|
| | PPV for Digital Mammography, % | PPV for Digital Mammography + Tomosynthesis, % | Change, % (95% CI) | PPV for Digital Mammography, % | PPV for Digital Mammography + Tomosynthesis, % | Change, % (95% CI) |
| 1 | 3.2 | 6.8 | 3.6 (1.6 to 5.7) | 23 | 51 | 27.8 (15.1 to 40.5) |
| 2 | 6.3 | 6.8 | 0.5 (-1.8 to 2.9) | 24 | 30 | 6.1 (-2.5 to 14.8) |
| 3 | 4.2 | 6.0 | 1.8 (0.0 to 3.6) | 25 | 25 | 0.1 (-7.9 to 8.1) |
| 4 | 3.7 | 7.4 | 3.7 (1.7 to 5.7) | 19 | 30 | 10.7 (2.5 to 18.8) |
| 5 | 2.4 | 4.4 | 2.0 (0.2 to 3.8) | 22 | 17 | -5.3 (-15.1 to 4.6) |
| 6 | 6.5 | 6.7 | 0.2 (-2.0 to 2.3) | 25 | 21 | -3.3 (-10.0 to 3.3) |
| 7 | 6.8 | 3.6 | -3.2 (-6.7 to 0.3) | 27 | 20 | -6.9 (-21.3 to 7.5) |
| 8 | 4.0 | 5.8 | 1.9 (0.4 to 3.3) | 22 | 35 | 12.9 (5.4 to 20.3) |
| 9 | 1.3 | 3.7 | 2.4 (1.0 to 3.7) | 7 | 23 | 15.8 (8.8 to 22.9) |
| 10 | 2.7 | 6.1 | 3.5 (1.6 to 5.4) | 22 | 37 | 14.9 (3.2 to 26.5) |
| 11 | 2.8 | 4.5 | 1.7 (0.9 to 2.4) | 21 | 22 | 1.2 (-2.7 to 5.0) |
| 12 | 6.5 | 8.8 | 2.3 (0.8 to 3.8) | 36 | 38 | 2.4 (-3.6 to 8.4) |
| 13 | 5.2 | 9.9 | 4.8 (2.9 to 6.6) | 28 | 38 | 9.6 (2.5 to 16.6) |
| All | 4.1 | 6.1 | 2.0 | 24 | 29 | 5.1 |
| Model estimate[a] | 4.3 | 6.4 | 2.1 (1.7 to 2.5) | 24.2 | 29.2 | 5.0 (3.0 to 7.0) |
| $P$ value | | | <.001 | | | <.001 |

[a] The model estimate adjusted for site as a random effect and treated time period as a fixed effect.

The **Figure** demonstrates the combined change (recall and cancer detection rates) for digital mammography alone vs digital mammography + tomosynthesis at each site as well as overall mean and model estimates. Eleven of 13 sites simultaneously increased cancer detection and decreased recall rates with the addition of tomosynthesis.

Analysis of results from the first period using digital mammography alone compared with the entire population during the second period (concurrent digital mammography alone plus digital mammography + tomosynthesis) was performed to address the potential for selection bias. This analysis assessed associations with the availability of tomosynthesis at a site as opposed to a direct association with tomosynthesis. There were 245 985 concurrent cases with digital mammography alone (58.6%) imaged in the second period (Table 1) at hybrid sites compared with 173 663 cases with digital mammography + tomosynthesis examinations (41.4%). Despite the fact that nearly 60% of cases in the second period were imaged with digital mammography alone, there was still a statistically significant improvement in cancer detection of 0.6 (95% CI, 0.3-1.0; $P$ < .001) per 1000 screens and a decrease in recall rate of −5.4 (95% CI, −6.9 to −4.0; $P$ < .001) per 1000 screens.

Table 8. Histology of Cancers Detected

| Histology | No. of Cancers | | Cancers per 1000 Cases | | |
|---|---|---|---|---|---|
| | Digital Mammography | Digital Mammography + Tomosynthesis | Digital Mammography | Digital Mammography + Tomosynthesis | Change (95% CI) |
| Invasive | | | | | |
| IDC | 693 | 568 | 2.46 | 3.27 | 0.81 (0.49 to 1.14) |
| ILC | 75 | 95 | 0.27 | 0.55 | 0.29 (0.17 to 0.41) |
| ILC/IDC | 39 | 29 | 0.14 | 0.17 | 0.03 (-0.04 to 0.10) |
| Other[a] | 5 | 5 | 0.02 | 0.04 | 0.01 (-0.02 to 0.04) |
| Unspecified[b] | 3 | 10 | 0.01 | 0.05 | 0.04 (0.01 to 0.07) |
| Total | 815 | 707 | 2.90 | 4.07 | 1.20 (0.83 to 1.56) |
| Ductal carcinoma in situ | 392 | 243 | 1.39 | 1.40 | 0.01 (-0.22 to 0.24) |
| Total | 1207 | 950 | 4.29 | 5.47 | 1.20 (0.77 to 1.63) |

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

[a] Cancers labeled as other included 2 papillary, 2 mucinous, and 1 malignant phyllodes in the digital mammography group and 2 papillary, 1 mucinous, 1 spindle cell, and 1 breast sarcoma in the digital mammography + tomosynthesis group.

[b] Cancers labeled as unspecified are invasive breast cancers reported without a subcategory.

## Discussion

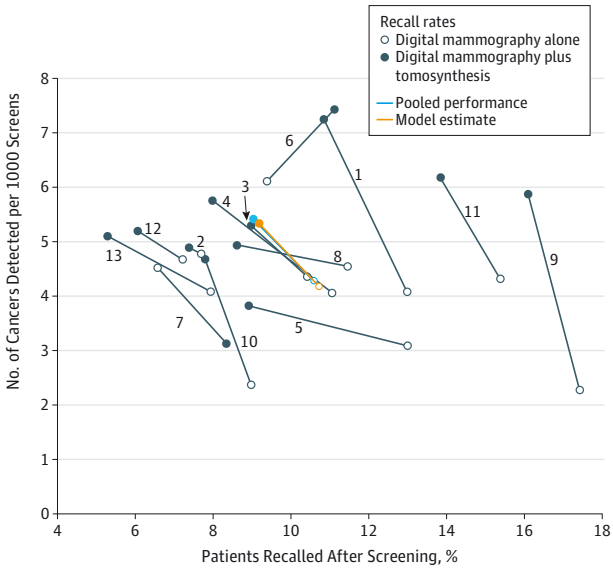
Success of mammography screening programs is achieved by meeting specific performance benchmarks that directly relate to patient outcomes.[12,13] Adherence to established guidelines provides the appropriate balance between early detection and generation of false-positive findings that result in unnecessary additional testing, anxiety, and expense.[2,3] Application of these metrics to new technology can allow objective assessment of that technology's potential value for breast cancer screening.

Recently, 2 prospective single-site European studies have demonstrated the efficacy of digital mammography + tomosynthesis in breast cancer screening. Skaane et al[17] reported a 40% increase in detection of invasive cancers with a simultaneous 15% reduction in false-positive results in 12 621 screening examinations with the use of digital mammography + tomosynthesis compared with digital mammography alone. In an analysis of 7292 screening examinations, Ciatto et al[18] demonstrated a significant increase in cancer detection rate from 5.3 to 8.1 cancers per 1000 women screened, with 20 of 59 cancers seen only after addition of tomosynthesis to conventional digital mammography. A 17% reduction in recall rate was also reported.

In the United States, 2 single-site observational studies have shown improved screening outcomes with tomosynthesis imaging. Rose et al[16] and Haas et al[19] showed statistically significant relative reductions in recall rate of 37% and 30%, respectively. Although both groups demonstrated an increase in cancer detection, neither achieved statistical significance, possibly because of limited patient volumes.

In 173 663 examinations, the addition of tomosynthesis to digital mammography was associated with significantly better performance outcomes when compared with 281 187 screens using digital mammography alone. A reduction in recall rate of 16 per 1000 (relative decrease of 15%) was observed across the cohort screened with tomosynthesis. Of the 13 screening sites, 11 showed a substantial decrease (range, 4-42 per 1000) in the number of patients recalled from screening. The 2 sites that experienced increases in recall rate after the introduction of tomosynthesis had either a short duration of implementation (site 6) or low volume of examinations per radiologist (site 7), underscoring the importance of adequate radiologist experience in tomosynthesis interpretation.

Figure. Combined Change in Cancer Detection Rate and Recall Rate for Each Institution After Implementation of Tomosynthesis




Lines demonstrate combined change in performance for each institution, labeled by site number. Pooled performance across all institutions is shown in blue. The model estimate is shown in orange.

This marked reduction in recall rate becomes even more notable when viewed in conjunction with the simultaneous increase in cancer detection of 1.2 per 1000 women screened (relative increase of 29%) after the introduction of tomosynthesis. In recent years, considerable attention has been drawn to the number of women recalled from mammographic screening, with particular emphasis placed on the "harms" resulting from false-positive examination results.[2,3] However, the focus on recall rate has frequently failed to recognize the interplay between the number of women recalled and the number of cancers detected. Ideally, false-positive findings would be limited while cancer detection is maintained (or increased) to preserve the overall goals of screening.[12,13] Thus, the association

of implementation of tomosynthesis with simultaneous improvement in both of these fundamental metrics of breast cancer screening indicates a potential advantage of incorporation into screening.

Recalling fewer women after screening yet finding additional cancers implies that the relative yield for each recall will increase. The PPV for recall (likelihood of cancer diagnoses in women recalled for additional imaging) is routinely measured to assess the ongoing performance of all mammographic screening programs in the United States.[12] When tomosynthesis was added, the PPV for recall increased from 4.3% to 6.4% (relative increase of 49%). Similarly, PPV for biopsy reflects the proportion of cancers found in women undergoing biopsies based on screen-detected findings. Although an overall increase was observed in the biopsy rate in patients screened with digital mammography + tomosynthesis (19.3 vs 18.1 per 1000 cases for the digital mammography cohort), there was a concomitant 21% relative increase in PPV for biopsy, reflecting the higher yield of malignancy in women undergoing biopsy from the digital mammography + tomosynthesis group. The association with fewer unnecessary tests and biopsies, with a simultaneous increase in cancer detection rates, would support the potential benefits of tomosynthesis as a tool for screening. However, assessment for a benefit in clinical outcomes is needed.

After implementation of tomosynthesis, the invasive cancer detection rate increased from 2.9 to 4.1 per 1000, a relative increase of 41%, while detection of DCIS was unchanged at 1.4 per 1000. The success of mammographic screening in reducing mortality is predicated on the principle of detecting and treating small, asymptomatic cancers before they have metastasized. Accordingly, the preferential increase in invasive cancer detection with addition of tomosynthesis may be of particular value in optimizing patient outcomes from mammographic screening.

A specific strength of our study was the diversity of practices represented. Previous single-institution reports of tomosynthesis implementation have the potential to be influenced by local factors. Additionally, lower volumes in these studies have limited the ability to show statistical significance for some measures of mammographic screening performance. The participating sites in this study are geographically diverse, reflect academic and nonacademic settings, and include specialist and nonspecialist radiologists. Adoption of the technology was also nonuniform, including complete and partial conversion to tomosynthesis. Despite this diversity, there was remarkably consistent improvement in measured screening outcomes when tomosynthesis was implemented. Moreover, the large volume of patients reflected collectively in this study provided statistical significance to critical measures of screening mammography performance not easily achievable in prior single-site studies given the relatively low prevalence of cancer in the screening population.

This study had several limitations. First, lack of a randomized trial design, in which 2 cohorts are concurrently enrolled and screened, introduces the possibility that results were not purely due to the addition of tomosynthesis. The data used in this retrospective analysis are routinely captured by all screening facilities (required for regulatory compliance for mammography centers in the United States) and do not extend to variables that could measure potential confounding effects of disparate patient characteristics or variability in diagnostic evaluation between the 2 periods. However, there were no differences in mean age between the 2 periods, and the use of the same sites in both periods was intended to provide comparable populations in the 2 cohorts. We would not expect the risk profile at any given site to change meaningfully between the 2 periods, and our statistical models adjusting for site effects were consistent with the unadjusted results. The fact that sites converted incrementally to tomosynthesis further introduces the possibility of selection bias. However, sensitivity analysis including the concurrent digital mammograms in the tomosynthesis period suggested that selection bias alone could not account for the significant performance gains. Another limitation of this study is that only population-level (rather than patient-level) statistics were available from each site. Therefore, we were not able to evaluate the number of repeat examinations and, as a consequence, avoided statistical assumptions of independent observations. While implementation of tomosynthesis in our study was associated with a reduction in recall rate from screening, follow-up data were not available that would allow evaluation of false-negative result rates. The study did not assess clinical outcomes, so whether the increase in cancer detection rates is of benefit is not known.

## Conclusions

The addition of tomosynthesis to digital mammography was associated with a decrease in recall rate and an increase in cancer detection rate. Further studies are needed to assess the relationship to clinical outcomes.

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