

## Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts: Interim Report of a Prospective Comparative Trial

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### ABSTRACT

#### Purpose

Debate on adjunct screening in women with dense breasts has followed legislation requiring that women be informed about their mammographic density and related adjunct imaging. Ultrasound or tomosynthesis can detect breast cancer (BC) in mammography-negative dense breasts, but these modalities have not been directly compared in prospective trials. We conducted a trial of adjunct screening to compare, within the same participants, incremental BC detection by tomosynthesis and ultrasound in mammography-negative dense breasts.

#### Patients and Methods

Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts is a prospective multicenter study recruiting asymptomatic women with mammography-negative screens and dense breasts. Eligible women had tomosynthesis and physician-performed ultrasound with independent interpretation of adjunct imaging. Outcome measures included cancer detection rate (CDR), number of false-positive (FP) recalls, and incremental CDR for each modality; these were compared using McNemar's test for paired binary data in a preplanned interim analysis.

#### Results

Among 3,231 mammography-negative screening participants (median age, 51 years; interquartile range, 44 to 78 years) with dense breasts, 24 additional BCs were detected (23 invasive): 13 tomosynthesis-detected BCs (incremental CDR, 4.0 per 1,000 screens; 95% CI, 1.8 to 6.2) versus 23 ultrasound-detected BCs (incremental CDR, 7.1 per 1,000 screens; 95% CI, 4.2 to 10.0),  $P = .006$ . Incremental FP recall occurred in 107 participants (3.33%; 95% CI, 2.72% to 3.96%). FP recall (any testing) did not differ between tomosynthesis (FP = 53) and ultrasound (FP = 65),  $P = .26$ ; FP recall (biopsy) also did not differ between tomosynthesis (FP = 22) and ultrasound (FP = 24),  $P = .86$ .

#### Conclusion

The Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts' interim analysis shows that ultrasound has better incremental BC detection than tomosynthesis in mammography-negative dense breasts at a similar FP-recall rate. However, future application of adjunct screening should consider that tomosynthesis detected more than 50% of the additional BCs in these women and could potentially be the primary screening modality.

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### INTRODUCTION

Mammography is the primary modality for the early detection of breast cancer (BC), and is recommended for population breast screening on the basis of evidence of mortality reduction.<sup>1,2</sup> Radiologically-dense breasts are associated with decreased mammography sensitivity and increased risk of an interval cancer in screened women, and

density is also an independent risk factor for BC.<sup>3-5</sup> Various breast imaging modalities have been evaluated as adjunct screening for women with mammography-dense breasts. However, interest in applying adjunct screening on a population level has intensified after legislative measures in some US states, requiring that women be informed about their breast density and about adjunct screening,<sup>4,6</sup> such as ultrasound.<sup>7-9</sup> Adjunct ultrasound in women

with dense breasts detects additional cancers not found on mammography, although estimates of ultrasound's incremental BC detection are heterogeneous (approximate range, 1.9 to 4.2 per 1,000 screens).<sup>7-16</sup> Ultrasound screening for dense breasts is also resource intensive and increases false recalls and costs, while producing debatable benefit.<sup>7,8</sup>

Digital breast tomosynthesis (quasi three-dimensional [3D] mammography) is a relatively novel technique. It creates thin-slice reconstructions of the breast from low-dose digital mammographic images acquired at multiple angles. This evolution of mammography improves lesion visibility by reducing overlapping tissue; hence, it has the potential to increase BC detection and to reduce false-positive (FP) findings. Screening studies have shown that adjunct tomosynthesis yields incremental BC detection in the range of 1.2 to 2.7 per 1,000 screens.<sup>17-21</sup> On the basis of these data, tomosynthesis is being touted as a potential adjunct screening modality for dense breasts; however, there are no trials that have directly compared tomosynthesis and ultrasound for adjunct screening of mammography-dense breasts.

We performed a prospective multicenter screening trial of tomosynthesis and ultrasound for adjunct screening in women with dense breasts. We hypothesized that tomosynthesis or ultrasound would each detect approximately two to three cancers per 1,000 screens in women with dense breasts and negative two-dimensional (2D) mammograms.<sup>7,13,18</sup> Our aim was to estimate the comparative incremental BC detection for these adjunct modalities in women with mammography-negative screens and dense breasts.

## PATIENTS AND METHODS

The Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND) study was implemented prospectively as a multicenter study in Italy. Our aim was to estimate the comparative incremental detection for these adjunct modalities using methods that allow independent test interpretation. We also aimed to assess false recalls for each adjunct screening modality. The study received institutional review board approval (514REG2014), and written informed consent was obtained from participants.

ASTOUND is a registered study (NCT02066142) sponsored by the University of Genoa, which was responsible for governance and coordination of the five collaborating breast imaging centers. These screening centers, according to conventional practice in Italy, are performing supplemental imaging in women with mammography-dense breasts using physician-performed ultrasound, and more recently using tomosynthesis. Therefore, in ASTOUND, a mix of prevalent and incident ultrasound screening, and prevalent tomosynthesis screening, are compared in one screening round.

### Study Participants

Asymptomatic women ( $\geq 38$  years old) presenting for mammography screening to public hospital-based radiologic services with dedicated breast imaging were eligible if standard 2D digital mammography was classified as Breast Imaging-Reporting and Data System<sup>22</sup> density categories three (heterogeneously dense) or four (extremely dense)<sup>22,23</sup> and was negative for BC, as shown in the flow diagram (Fig 1). Women who had a personal history of BC, were pregnant or lactating, or had breast prostheses were ineligible for the study. All participants had both tomosynthesis and ultrasound; Fig 1 shows the study schema.

### Image Acquisition

Mammography and tomosynthesis images were acquired using digital mammography units with tomosynthesis capability (Hologic, Selenia Dimensions; Bedford, MA). Standard 2D-mammography and then 3D-mammography (tomosynthesis) acquisitions were performed in women with dense breasts per the study schema (Fig 1). Immediate check of the 2D acquisition was performed to determine density, and 3D images were acquired at the same breast compression, consisting of bilateral two-view (mediolateral oblique and craniocaudal) mammograms (Appendix, online only).

Live mammography reporting supported immediate categorization of 2D-mammography density before proceeding to the tomosynthesis acquisitions (Fig 1; Appendix). Hence, the second sequence in screen reading was based on tomosynthesis with availability of 2D mammography. The same radiologist reported the 2D and the tomosynthesis (3D) images. Screens showing lesions requiring recall for additional work up (usually with a score of four to five, according to a categorical scale used in European practice<sup>12</sup>) were deemed positive and recalled for further investigation. Lesions considered probably benign were not routinely recalled for assessment but could be recommended for early (6-month) imaging follow up.

Ultrasound was then performed by another radiologist who was blinded to the tomosynthesis (3D) images (but who was aware that standard 2D mammography was negative). This methodology ensured that radiologists were blinded to the tomosynthesis findings if they were reporting the ultrasound and vice versa. Bilateral handheld breast ultrasound was performed using 10 MHz as the lowest maximum frequency of the transducer (Appendix). Screens classified as suspicious (as outlined above for mammography) were further investigated. All ultrasound examinations were performed by physicians with breast imaging experience.

### Screen Readers

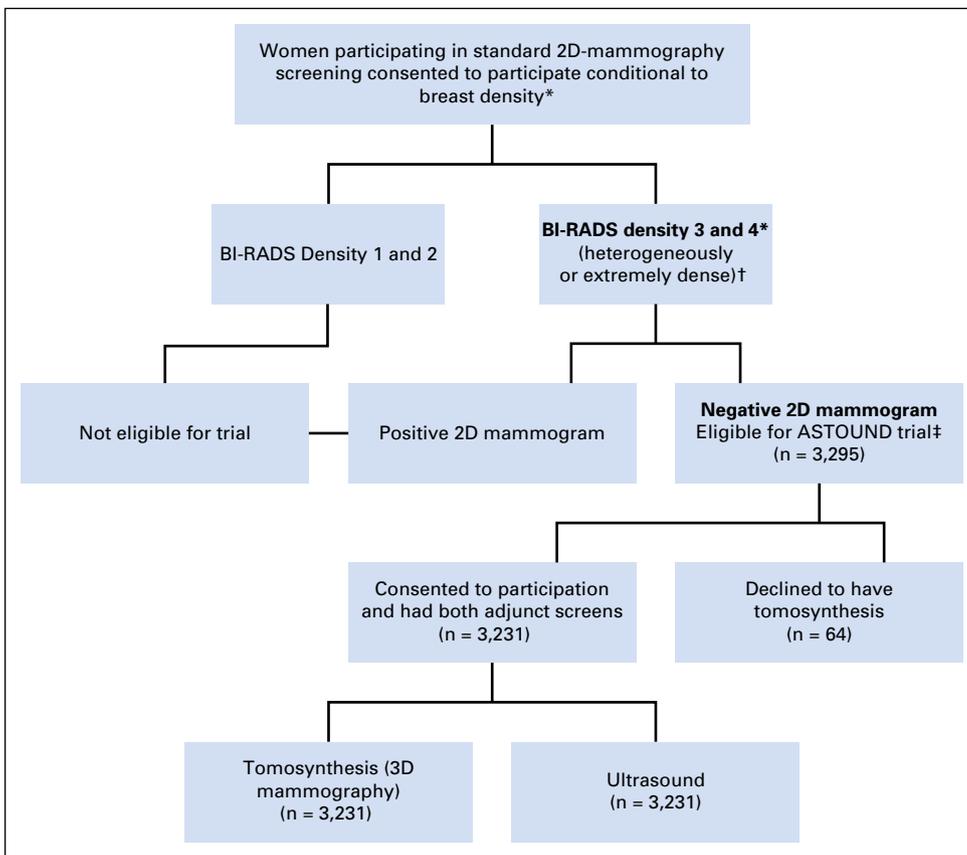
Dedicated breast radiologists, who read at least 5,000 mammograms per annum (in line with European screening standards<sup>24</sup>), interpreted tomosynthesis (experience range, 3 to 5 years) and breast ultrasound (experience range, 7 to 20 years). Hologic SecurView workstations, which were optimized to read both 2D and 3D images, were used for screen reading. Each reader was blinded to the sequential adjunct test results, meaning that the radiologist reporting tomosynthesis did not know the ultrasound report, and the radiologist reporting ultrasound was blinded to the tomosynthesis result. Prior mammograms were provided, where available, at time of interpretation of all modalities.

### Outcome Measures

Our outcome measures were the number and rates of cancers detected per 1,000 screens, the number and percentage of FP recalls, and the incremental cancer detection rate (CDR) for each screening modality. Outcomes were ascertained on the basis of excision histopathology in those who received surgery, or on the basis of the completed assessment inclusive of work-up imaging (with or without core-needle biopsy) in all recalled subjects. Benign core-needle histopathology was considered an ascertained outcome if the diagnosis was consistent with the recalled imaging finding; otherwise, excisional histopathology was required. Given that the study focused on comparative detection at screening, without 1-year follow up, some cancers may be missed by both methods. However, this does not affect estimates of our primary outcomes (screen detection measures). This issue could be assessed at future follow up to identify interval cancers, but it does not affect estimates of the outcome measures for this interim report.

### Statistical Plan and Analysis

For sample size estimation, we hypothesized that the most sensitive imaging technique would show an incremental CDR of three per 1,000 screens, on the basis of knowledge from adjunct screening.<sup>7,12,13,18</sup> We



**Fig 1.** Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND): Study flow diagram. \*Breast Imaging-Reporting and Data System (BI-RADS) breast density category three (heterogeneously dense) or four (extremely dense),<sup>22</sup> which correspond to breast density C and D, respectively, in the most recent Breast Imaging-Reporting and Data System lexicon.<sup>23</sup> †Progress to tomosynthesis acquisitions actioned at this point immediately following density classification using the first 2D-mammography views. Women with negative 2D mammography proceeded as part of the ASTOUND trial, whereas those with positive standard 2D mammography proceeded to work up inclusive of the tomosynthesis acquisitions and were ineligible to be part of the ASTOUND trial. ‡Women who had a personal history of breast cancer, were pregnant or lactating, or had breast prostheses were not eligible to participate.

estimated that 6,000 screens would be needed to have an 80% power to detect a sufficient number of additional cancers with adjunct screening to yield incremental detection rates significantly greater than 1.5 per 1,000 screens at a 95% CI. The estimated sample of 6,000 screens would also give 80% power to detect a difference in CDR of two per 1,000 between imaging techniques (according to McNemar's test at a significance level of 5%). We also planned an interim analysis at approximately 3,000 screens to reassess sample estimates using an adaptive sampling approach informed by incremental detection in the study population (Appendix).

The number of cancers detected by adjunct screening, the true-positive rate, and the number of FP recalls (for any additional testing and for testing that included biopsy) were cross tabulated and compared between the two techniques using McNemar's test for paired binary data and exact *P* value. The incremental CDR for each screening modality and the 95% CI were estimated. The positive predictive value for recall with biopsy was calculated.

## RESULTS

There were 3,295 screening participants with negative 2D mammography and dense breasts, with a median age of 51 years (interquartile range, 44 to 78 years; range, 38 to 88 years) invited into the study between December 2012 and March 2015. Of these, 64 declined to have tomosynthesis (Fig 1); therefore, 3,231 participants were included.

### Incremental BC Detection and Cancer Characteristics

Among screening participants with negative 2D mammography, tomosynthesis or ultrasound detected suspicious findings warranting further investigation in 131 of 3,231 women. Twenty-

four of these participants had screen-detected lesions that yielded malignant outcomes at assessment and histopathology, comprising invasive ductal (*n* = 18), invasive lobular (*n* = 4), mixed invasive type (*n* = 1), and ductal carcinoma in situ (*n* = 1).

As shown in cross-tabulated data (Table 1), of these 24 additional screen-detected BCs, 12 were detected on both tomosynthesis and ultrasound, one was only detected on tomosynthesis, and 11 were only detected on ultrasound. Of the 24 screen-detected cancers (Table 1), 13 were detected with tomosynthesis (incremental CDR, 4.0 per 1,000 screens; 95% CI, 1.8 to 6.2) versus 23 that were detected with ultrasound (incremental CDR, 7.1 per 1,000 screens; 95% CI, 4.2 to 10.0), *P* = .006. The incremental CDR for tomosynthesis and ultrasound differed by a CDR of 3.1 per 1,000 screens (95% CI, 1.2 to 3.1), favoring ultrasound. The incremental CDR for adjunct screening with tomosynthesis and ultrasound (where either was positive) was 7.4 per 1,000 screens (95% CI, 4.4 to 10.4).

Table 2 shows the radiologic and pathologic characteristics, and mode of detection, of the cancers detected in ASTOUND. The mean tumor size was 15.2 mm (standard deviation, 6.1 mm) for tomosynthesis-detected cancers and 15.1 mm (standard deviation, 4.8 mm) for ultrasound-detected cancers; axillary nodes were metastatic in seven of 22 (32%) cancers with known nodal pathology, with a further patient reported to have axillary node micrometastases.

### FP Screens

There were 3.33% (95% CI, 2.72% to 3.96%) FP screens (107 FP recalls for any testing) from adjunct screening. Table 3 reports

**Table 1.** Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND): Incremental Breast Cancer Detection in Women With Negative Two-Dimensional-Mammography Screening

Adjunct Breast Screening Modality	Ultrasound Positive	Ultrasound Negative	Total, n (%)
Tomosynthesis positive	12	1	13 (54.2%)
Tomosynthesis negative	11	0*	11 (45.8%)
Total, n (%)	23 (95.8%)	1 (4.2%)	24

NOTE.  $P = .006$  for McNemar's test for paired binary data.

\*On the basis of cancers detected in the study population at adjunct screening and does not include follow-up data on interval cancers; hence, cell has a value of zero. This does not affect the comparative detection data shown in this cross tabulation.

cross-tabulated data for tomosynthesis and ultrasound in women who did not have BC, inclusive of FP recalls at assessment; no significant differences were found between the two modalities ( $P = .26$ ). Table 4 reports cross-tabulated data for women who did not have BC, inclusive of FP recalls leading to biopsy (needle biopsy, with two women also requiring excisional biopsy); no significant differences were found between tomosynthesis and ultrasound ( $P = .86$ ). Of the 38 subjects who had biopsy and were subsequently classified as FP recalls (1.18% of adjunct screens), 22 were FP at tomosynthesis and 24 were FP at ultrasound (Table 3). FP recalls were generally resolved with core-needle biopsy; two women underwent surgical biopsy, which showed radial scars (both were FP at tomosynthesis).

### Positive Predictive Value

The positive predictive value for recall leading to biopsy was 13 per 35 screens (37%; 95% CI, 21.3 to 55.4) for tomosynthesis, and 23 per 47 screens (48%; 95% CI, 34.1 to 63.9) for ultrasound.

### Additional Findings

Findings that were probably benign, which were not recalled for work up but recommended for short-term imaging review, were due to tomosynthesis in 150 (4.7%) screens, and were due to ultrasound in 57 (1.8%) screens.

## DISCUSSION

We report interim results of ASTOUND, a prospective screening trial that compares the detection capability of breast tomosynthesis and ultrasound in women with dense breasts, whose conventional 2D-mammography screening was negative. To the best of our knowledge, this is the first prospective trial to directly compare these adjunct modalities in the same women. We found that each of these imaging modalities, reported independently of each other, yielded additional BC detection. However, adjunct ultrasound led to significantly higher incremental BC detection than tomosynthesis (CDR per 1,000 screens: 7.1 [95% CI, 4.2 to 10.0]  $\nu$  4.0 [95% CI, 1.8 to 6.2],  $P = .006$ ). Although incremental BC detection was observed with each imaging modality, tomosynthesis detected approximately half of the additional cancers identified through adjunct screening in dense breasts, whereas ultrasound detected almost all, with similar

additional false recall for the two modalities in this mammography-negative population.

These results should be interpreted with caution given that this is an interim analysis, and that the study population comprised women who self-referred to breast screening and who had dense mammograms. Although self-referral to breast screening at the participating centers is intended for women at population (average) risk, we are unable to quantify the risk profile of participating women. However, we can confirm that we did not include women with *BRCA* gene mutations. Results of ASTOUND can be used to inform adjunctive screening studies because we provide the first within-subject comparative estimates of CDRs for tomosynthesis and ultrasound. A major strength of our study's comparative methodology is the independent interpretation of the two adjunctive modalities; only knowledge from the standard 2D mammogram was known to each interpreting radiologist at the time that adjunct screening was reported. A further strength is the high participation rate in the study, with fewer than 2% of eligible women declining to have adjunct tomosynthesis.

Our results could be taken to suggest that tomosynthesis is detecting BCs that would have been otherwise masked (on 2D mammography) by overlapping breast parenchyma, but seems less capable than ultrasound at finding cancers that are entirely masked by mammography-dense tissue. Although it is difficult to pinpoint the reasons for the observed difference in BC detection in the study, we assume that some cancers are visible to only one of the physical principles of imaging modalities (x-ray for tomosynthesis  $\nu$  ultrasound). The case-by-case data shown in Table 2 highlight that the majority of ultrasound-detected cancers that were not detected on tomosynthesis were masses, whereas the one tomosynthesis-detected cancer missed on ultrasound was an architectural distortion.

Our study showed that tomosynthesis and ultrasound had similar false recall for any testing (1.7% and 2.0%, respectively), and for recall leading to biopsy (0.7% and 0.7%, respectively), which did not differ statistically between the two adjunct modalities (Tables 3 and 4). Overall, FPs represented 3.33% of all adjunct screens, with 1.18% of participants having biopsy (mostly needle biopsy) for FP recall. Although these FP data may seem surprising given that high FP rates have been reported for adjunct ultrasound,<sup>7,8,11,13,15</sup> one should consider that adjunct ultrasound's FP-recall rates vary substantially between studies (approximate range, 1% to 7% or higher if additional testing is included),<sup>2,7-11,13-16</sup> and that probably benign findings were not routinely recalled for work up in our setting (these led to a recommendation of early imaging in 1.8% of adjunct ultrasounds).

Also, our findings reflect that interpreting radiologists had breast ultrasound screening expertise. In addition, radiologists had access to prior breast ultrasound screens for many participants because ultrasound screening included prevalent and incident screens. FP recall is likely to be variable in adjunct screening practice and might be higher for less experienced radiologists. Although ASTOUND's participating radiologists also had experience with tomosynthesis (see Patients and Methods), this modality has been applied for screening only in recent years. Hence, the adjunct screening round represented prevalent tomosynthesis screening (which might account for some of the additional FP recall caused by tomosynthesis). Comparison of our

**Table 2.** Characteristics and Mode of Detection of Breast Cancers Detected at Adjunct Screening in the Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND) Trial

Case No.	Age, Years	Density	Tomosynthesis	Ultrasound	Radiologic Sign	Final Histology	Tumor Size (Pathology), mm	Tumor Grade	Axillary Nodes	ER/PR*	HER2†
1	46	3	Positive	Positive	Architectural distortion	IDC	5	NA	Negative	NA	NA
2	47	3	Positive	Positive	Mass	IDC	15	G2	Metastases	NA	NA
3	39	3	Negative	Positive	Mass	IDC	19	G2	Negative	Positive	0
4	43	3	Negative	Positive	Mass	IDC	14	G2	Negative	Positive	0
5	44	3	Negative	Positive	Mass	ILC	18‡	NA	Negative	Positive	0
6	51	4	Positive	Positive	Mass	IDC	13	G3	Metastases	Positive	1+
7	64	3	Positive	Positive	Mass	IDC	7	G2	Metastases	Positive	NA
8	52	4	Positive	Negative	Architectural distortion	IDC	15	G1	Negative	NA	NA
9	41	4	Negative	Positive	Mass	IDC	14	G1	Negative	NA	NA
10	61	4	Positive	Positive	Mass	IDC	19	G3	Metastases	Negative	0
11	67	4	Positive	Positive	Architectural distortion	ILC	25	G3	Metastases	Positive	3+
12	49	4	Positive	Positive	Architectural distortion	ILC	15	G1	Negative	Positive	0
13	51	4	Positive	Positive	Asymmetric density	IDC	17	G2	Negative	Positive	1+
14	78	3	Negative	Positive	Architectural distortion	DCIS	14	Low-grade DCIS	NA	NA	NA
15	60	3	Negative	Positive	Mass	Mixed invasive	15	G2	Negative	NA	NA
16	49	4	Negative	Positive	Mass	IDC	19	G3	Micrometastases	Positive	1+
17	49	3	Negative	Positive	Mass	IDC	14	G2	Negative	Positive	1+
18	53	4	Negative	Positive	Mass	IDC	11	G1	Negative	Positive	1+
19	38	3	Negative	Positive	Mass	IDC	17	G3	Metastases	Positive	0
20	43	3	Negative	Positive	Mass	ILC	13	G2	Negative	Positive	0
21	58	4	Positive	Positive	Mass	IDC	15	G2	Metastases	Positive	0
22	43	3	Positive	Positive	Architectural distortion	IDC	25	NA	NA	Negative	NA
23	54	3	Positive	Positive	Asymmetric density	IDC	11	G2	Negative	Positive	0
24	53	3	Positive	Positive	Architectural distortion	IDC	19‡	NA	Negative	NA	NA

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal cancer; ILC, invasive lobular cancer; PR, progesterone receptor; NA, not available (ie, not known or not done).  
 \* ER/PR considered positive if either ER and/or PR positive.  
 †HER2 scores were based on immunohistochemistry testing.  
 ‡Tumor size was based on imaging size.

**Table 3.** Screening Examinations Classified as Not Having Breast Cancer, Inclusive of False-Positive Recalls,\* in the Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND) Study

Adjunct Breast Screening Modality	Ultrasound Positive	Ultrasound Negative	Total, n (%)
Tomosynthesis positive	11	42	53 (1.7)
Tomosynthesis negative	54	3,100	3,154 (98.3)
Total, n (%)	65 (2.0)	3,142 (98.0)	3,207

NOTE.  $P = .26$  for McNemar's test with continuity correction.

\*Recall for any testing (imaging with or without needle biopsy).

**Table 4.** Screening Examinations Classified as Not Having Breast Cancer, Inclusive of False-Positive Recalls With Biopsy,\* in the Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts (ASTOUND) Study

Adjunct Breast Screening Modality	Ultrasound Positive	Ultrasound Negative	Total, n (%)
Tomosynthesis positive	8	14	22 (0.7)
Tomosynthesis negative	16	3,169	3,185 (99.3)
Total, n (%)	24 (0.7)	3,183 (99.3)	3,207

NOTE.  $P = .86$  for McNemar's test with continuity correction.

\*Biopsy refers to needle biopsy; however, two cases also required surgical biopsy (both were false-positive at tomosynthesis).

findings with those from other studies is limited by the lack of prospective screening trials that directly compare these adjunct modalities in women with mammography-negative dense breasts.

Evidence reviews of adjunct screening technologies for women with mammography-negative dense breasts have concluded that ultrasound shows substantial but heterogeneous incremental BC detection.<sup>2,7</sup> Although the incremental CDR for ultrasound in our study is higher than reported CDRs for ultrasound,<sup>7,9,10,15</sup> as outlined earlier, our interim estimate has wide CIs, and it seems likely that women who self-referred to screening may have additional risk factors, such as a family history of BC, and may be above the average population risk. However, other than age and density, we did not have detailed characteristics of the women screened as part of ASTOUND because risk-related data were not routinely collected at participating imaging centers; we acknowledge this limitation of the study. Although it could be said that the CDR in our study overestimates incremental detection from adjunct screening (due to the possibility that we may have included women who were above population risk), we point out that this does not invalidate the comparative CDR between tomosynthesis and ultrasound, which is the focus of the trial.

If the final results from ASTOUND confirm those of the interim analysis, it could be argued that breast tomosynthesis has little value in a setting where adjunct ultrasound is frequently used for screening women with mammography-dense breasts. Furthermore, many centers using tomosynthesis are performing dual acquisitions (both 2D and 3D mammogram acquisitions); therefore, the increase in radiation<sup>2</sup> from tomosynthesis may not be justifiable. However, given the recent availability of tomosynthesis acquisitions that also provide reconstructed 2D mammography,<sup>25</sup> concerns regarding increased radiation will become less relevant. Hence, the remaining issue for adjunct screening is whether tomosynthesis is justifiable on the basis of our data. If adjunct ultrasound is systematically performed for dense breasts (as practiced in our screening setting), the incremental CDR from tomosynthesis is negligible, on the basis of our data.

On the other hand, if adjunct ultrasound is not routinely performed in mammography-negative dense breasts, then our results could be taken to support use of adjunct tomosynthesis despite its lower incremental CDR relative to ultrasound. The rationale is that through tomosynthesis-based mammography (assuming that it also provided the reconstructed 2D images), a

substantial proportion of the additionally detected BCs on adjunct ultrasound would be identified through the primary tomosynthesis screen. Ultrasound is time and resource intensive; therefore, a comprehensive cost-effectiveness evaluation is needed to define the comparative costs of these adjunct screening methods, factoring in screen-detection metrics and the potential for tomosynthesis to eliminate the 2D-mammography acquisition, which would significantly impact resource utilization.

There are several limitations to this study, including the absence of risk-related data (outlined above), and the modest number of cancers in the interim report. Hence, our incremental CDRs are associated with relatively large CIs; we plan to continue the study to provide more precise estimates at its conclusion. Another limitation is that we compared a mix of prevalent and incident ultrasound screening with prevalent tomosynthesis screening, which might give more favorable FP-recall data for ultrasound relative to tomosynthesis. Also, biomarker (eg, estrogen receptor/progesterone receptor and human epidermal growth factor receptor 2) data were not available for all of the detected cancers (Table 2). However, given the interest in adjunct screening of women with dense breasts and the emerging transition to tomosynthesis screening,<sup>18,19,26</sup> we think that these interim data are of interest and may guide others in planning future evaluations and recommendations on adjunct screening. We also acknowledge that ASTOUND focused on screen-detection measures, and specifically on incremental BC detection; we do not have longer-term data to determine screening benefit because this was not within the scope of the study. The value of adjunct screening could be potentially assessed by follow up of screened subjects and comparing interval cancer rates between those who had adjunct screening and those who did not receive adjunct screening.<sup>27</sup>

In conclusion, this interim report of the ASTOUND trial indicates that adjunct ultrasound has significantly better incremental BC detection than tomosynthesis in women with dense breasts and negative 2D-mammography screening. Nonetheless, tomosynthesis detected approximately 50% of the additional BCs detected in these women at adjunct screening. Hence, policy on adjunct screening in women with dense breasts should consider whether the screening context routinely provides ultrasound to these women and that tomosynthesis could potentially be the primary imaging modality (without any adjunct imaging). This issue requires careful health-economic evaluation to complement the data we have presented on comparative detection for adjunct tomosynthesis and ultrasound.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Adjunct Screening With Tomosynthesis or Ultrasound in Women With Mammography-Negative Dense Breasts: Interim Report of a Prospective Comparative Trial**

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### **Appendix**

#### **Additional Methods for Imaging**

*Mammography breast density.* Breast tissue density was based on visual check of the standard two-dimensional (2D)-mammography images, and was reported using Breast Imaging-Reporting and Data System density categories. Mammography and tomosynthesis images were acquired using digital mammography units with tomosynthesis capability (Hologic, Selenia Dimensions; Bedford, MA). Standard 2D-mammography and then three-dimensional (3D)-mammography (tomosynthesis) acquisitions were performed (COMBO-mode) only in women with dense breasts (density categories three [heterogeneously dense] or four [extremely dense]). For the trial to be feasible, it was essential that 2D and 3D acquisitions be performed at the same screening episode and at the same breast compression, with minimal delay between acquisitions. Therefore, an immediate live check of the 2D acquisition was performed. A resident physician trained in Breast Imaging-Reporting and Data System density classification determined breast density from the first 2D-mammography acquisition, usually the craniocaudal views. 3D images were acquired within a few seconds at the same breast compression in women with heterogeneously dense or extremely dense breasts.

*Recall for further assessment and biopsy.* Screens showing lesions requiring recall for additional work up (usually a score of four or five, according to a categorical scale used in European practice) were deemed positive and recalled for further assessment. Otherwise, screens showing no abnormalities, or showing lesions considered benign or probably benign, were not recalled for further assessment. Lesions considered probably benign may have been recommended for early imaging follow up at a 6-month interval. Image-guided biopsy was predominantly performed using ultrasound. Tomosynthesis-guided biopsy was available at four participating centers and was accessible to all trial participants when it was required. However, the majority of screen-detected lesions were seen and biopsied under ultrasound guidance.

*Breast ultrasound scanning.* The breast ultrasound scanner had to be equipped with a multifrequency linear array transducer, which was operated at a maximum frequency of 10 MHz or higher. Scanning was performed with radial, sagittal, and transverse approaches, and the axillary and parasternal areas were included. Lesions were evaluated in at least two orthogonal axes, usually according to the radial and antiradial directions of scanning. For each lesion, at least two diameters were measured, including the maximum (widest) diameter. If no lesion was detected, two images (sagittal and coronal) were acquired per quadrant.

#### **Interim Analysis: Adaptive Sampling**

Interim analysis was planned at approximately 3,000 screens to reassess sample estimates using an adaptive sampling approach informed by incremental detection in the study population. A conditional power analysis (which was based on a Monte Carlo resampling technique) was run to estimate the probability of higher cancer detection with tomosynthesis compared with ultrasound at the conclusion of the study (for an initial sample estimate of 6,000 screens), given the observed data and assuming a detection rate of tomosynthesis double that of ultrasound in the remaining part of the study.

On the basis of interim data, the cancer detection rate (CDR) estimates for tomosynthesis and ultrasound indicated that the 95% CIs of both estimates allowed rejection of the hypothesis of an incremental CDR lower than 1.5 per 1,000 screens. The difference between the two techniques was significant ( $P < .01$ ). Hence, assuming that study continuation yielded a CDR of 7.1 per 1,000 screens for ultrasound (the same as that observed) but of eight per 1,000 for tomosynthesis (assuming double the observed CDR at interim analysis), a conditional power analysis revealed that the power to detect significantly higher CDR for tomosynthesis than ultrasound would be less than 10%. Therefore, ongoing recruitment primarily is aimed at providing more precise estimates of comparative incremental CDR.