Objective: To compare the performance of two-dimensional synthetic mammography (SM) combined with digital breast tomosynthesis (DBT) (SM/DBT) and full-field digital mammography (FFDM) including women with DBT (FFDM/DBT) undergoing secondary examination for breast cancer.

Material and Methods: Out of 186 breasts, including 52 with breast cancers; FFDM/DBT and SM/DBT findings were interpreted by four expert clinicians. Radiation doses of FFDM, SM/DBT, and FFDM/DBT were determined. Inter-rater reliabilities were analyzed between readers and between FFDM/DBT and SM/DBT by Cohen's Kappa coefficients. Diagnostic accuracy was compared between SM/DBT and FFDM/DBT by Fisher's exact tests. Two representative cancer cases were examined for differences in the interpretation between FFDM and SM.

Results: A higher radiation dose was required in FFDM/DBT than in SM/DBT (median: 1.50 mGy vs. 2.95 mGy). Inter-rater reliabilities were similar between both readers and modalities. Both sensitivity and specificity were equivalent in FFDM/DBT and SM/DBT (p = 0.874–1.00). Compared with FFDM, SM did not clearly show abnormalities with subtle margins in the two representative cancer cases.

Conclusion: SM/DBT had a similar performance to FFDM/DBT in detecting breast abnormalities but requires less radiation. DBT complements SM to improve accuracy to a level equivalent to that of FFDM. Taken together, SM/DBT may be a good substitute for FFDM/DBT for the secondary examination of breast cancer.
INTRODUCTION

Previous studies have shown favorable results regarding full-field digital mammography (FFDM), combined with digital breast tomosynthesis (DBT) (FFDM/DBT) for breast cancer screening [1–8]. DBT provides an added diagnostic advantage of breast imaging from different angles with less breast tissue superimposition [9]. As the radiation dose for DBT is similar to or slightly higher than the dose required for FFDM, FFDM/DBT requires approximately double the radiation dose required by FFDM alone [10]. Two-dimensional synthetic mammography (SM) images can be reconstructed from DBT images. SM combined with DBT (SM/DBT) reduces the radiation dose required due to the elimination of FFDM, while maintaining a high sensitivity [11–15]. DBT is currently used for secondary examination of symptomatic women or women recalled after initial screening in several countries [16, 17]. In this study, we compared the performance of FFDM/DBT and SM/DBT for secondary examination of breast cancer. We hypothesized that FFDM/DBT and SM/DBT would display similar sensitivity, specificity, and accuracy, while SM/DBT would require less radiation than FFDM/DBT.

MATERIALS AND METHODS

STUDY SUBJECTS

This retrospective study received ethics approval from the relevant Institutional Review Board and informed consent was obtained from all subjects. A series of 93 nationality women who were undergoing their first outpatient visit to the Breast Cancer Clinic of the hospital in April 2015 were enrolled. They had visited the hospital upon referral regarding their symptoms or recalled after initial screening in several countries [16, 17]. In this study, we compared the performance of FFDM/DBT and SM/DBT for secondary examination of breast cancer. We hypothesized that FFDM/DBT and SM/DBT would display similar sensitivity, specificity, and accuracy, while SM/DBT would require less radiation than FFDM/DBT.

TABLE 1

| AGE            | BREAST COMPOSITION | CANCER (N = 52) | HISTOLOGICALLY BENIGN (N = 28) |
|----------------|--------------------|-----------------|--------------------------------|
| 31–82 years (median: 45 years) | A: 1 / B: 22 / C: 57 / D: 13 | DCIS 9 (17.3%) | Fibroadenoma 7 |
|                | Dense breast 70 (75.3%) | IDC 43 (82.7%) | Intraductal papilloma 2 |
|                | DCIS, ductal carcinoma in situ | Apocrine metaplasia 1 | Phyllodes tumor 1 |
|                | IDC, extremely dense | Hemangioma 1 | Negative 16 |

Table 1 Characteristics of the breasts analyzed.

186 breasts in 93 nationality women.

A. fatty, B. scattered fibroglandular densities, C. heterogeneously dense, D. extremely dense, DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; Negative, no indication of cancer.
61.3% heterogeneously and 14.0% extremely dense) (Table 1). Abnormalities included masses, calcifications, focal asymmetric densities, and distortions. For each image classification, no malignancy required both the readers to interpret the breast as without any lesions or with obvious benign lesions. A probability of malignancy required that one of the readers interpreted the breast as probably benign, suspicion of malignancy, or highly suggestive of malignancy. FFDM, DBT, and SM were interpreted in two sequential modes, which were FFDM followed by FFDM/DBT (Group 1) and SM followed by SM/DBT (Group 2). The four readers were divided as follows: readers I and II interpreted Group 1 images, and readers III and IV interpreted Group 2 images (Figure 1).

EVALUATION OF FFDM AND SM IMAGES
To demonstrate the limitations of SM, the conspicuity of those lesions which were not seen on SM (70 micron pixel size), but were visible on FFDM (100 micron pixel size), were evaluated. The comparison was performed side-by-side for FFDM and SM.

STATISTICAL AND IMAGING ANALYSIS
Inter-rater reliability was analyzed with Cohen’s Kappa coefficients. In Group 1, the coefficient between readers I and II was analyzed for FFDM/DBT. Similarly, in Group 2, the coefficient between readers III and IV was analyzed for SM/DBT. The coefficient was analyzed between FFDM/DBT by Group 1 and SM/DBT by Group 2 (Figure 1). Cohen’s Kappa coefficients were classified as follows: (a) slight agreement, less than 0.20; (b) fair agreement, 0.20 to 0.40; (c) moderate agreement, 0.40 to 0.60; (d) substantial agreement, 0.60 to 0.80; (e) almost perfect or perfect agreement, 0.80 to 1.00 [18].

Regarding the interpretation methods, the coefficient was 0.745 (substantial agreement) between FFDM/DBT and SM/DBT (Table 3). FFDM/DBT and SM/DBT had similar sensitivity (73.1% (38/52) and 71.2% (37/52), p = 1.000), specificity (81.3% (109/134) and 82.8% (111/134), p = 0.874), and accuracy (79.0% (147/186) and 79.6% (148/186), p = 1.00) (Table 4).

In two IDC cases, abnormalities with subtle margins were compared between FFDM and SM images. One representative case had an ill-defined mass identified by FFDM was unclear on SM (Figure 2). Another case had segmental amorphous microcalcifications detected by FFDM whilst on SM, they were interpreted as diffuse coarse calcifications (Figure 3).

![Figure 1](image-url) Two sequential modes were full-field digital mammography (FFDM) followed by FFDM/digital breast tomosynthesis (DBT) (Group 1), and two-dimensional synthetic mammography (SM) followed by SM/DBT (Group 2). FFDM/DBT and SM/DBT were compared using Fisher’s exact test.
### Table 2 Radiation dose for image acquisition.

|            | RADIATION DOSE (MGY) | MEDIAN |
|------------|----------------------|--------|
| FFDM MLO   | 0.69–6.29            | 1.47   |
| CC         | 0.70–6.18            | 1.47   |
| DBT (=SM/DBT) MLO | 0.92–5.43       | 1.50   |
| CC         | 0.93–5.03            | 1.50   |
| FFDM/DBT MLO | 1.64–11.72         | 2.95   |
| CC         | 1.63–11.21           | 2.95   |

**FFDM**, full-field digital mammography; **DBT**, digital breast tomosynthesis; **SM**, two-dimensional synthetic mammography; **MLO**, mediolateral oblique; **CC**, craniocaudal.

### Table 3 Inter-rater reliability with Cohen’s Kappa coefficients.

| COMPARISON                     | COHEN’S KAPPA COEFFICIENTS |
|--------------------------------|-----------------------------|
| Readers I and II reading FFDM/DBT | 0.780 (substantial agreement) |
| III and IV reading SM/DBT       | 0.773 (substantial agreement) |
| Interpretation FFDM/DBT and SM/DBT | 0.745 (substantial agreement) |

**FFDM**, full-field digital mammography; **DBT**, digital breast tomosynthesis; **SM**, two-dimensional synthetic mammography.

### Table 4 FFDM/DBT compared with SM/DBT for the detection of breast cancer.

| INTERPRETATION | FISHER’S EXACT TEST |
|----------------|---------------------|
| Sensitivity FFDM/DBT | 38/52 (73.1%)     | p = 1.000 |
| SM/DBT           | 37/52 (71.2%)      |             |
| Specificity FFDM/DBT | 109/134 (81.3%)   | p = 0.874  |
| SM/DBT           | 111/134 (82.8%)    |             |
| Accuracy FFDM/DBT | 147/186 (79.0%)   | p = 1.000  |
| SM/DBT           | 148/186 (79.6%)    |             |

**FFDM**, full-field digital mammography; **DBT**, digital breast tomosynthesis; **SM**, two-dimensional synthetic mammography.

---

**Figure 2** An ill-defined mass was detected with subtle margins in the lower area of the full-field digital mammography (FFDM) mediolateral oblique (MLO) image (a) and the inner area of the FFDM craniocaudal (CC) image (b). The mass was rated unclear on the two-dimensional synthetic mammography (SM) MLO (c) and CC (d) images.
DISCUSSION

The present study demonstrated that SM/DBT has a similar performance to FFDM/DBT in the secondary examination of breast cancers. This is consistent with previous studies regarding secondary examination and have shown similar accuracies for FFDM/DBT and SM/DBT [16]. Several studies on breast cancer screening have demonstrated the diagnostic advantage of FFDM/DBT [1–8]. Regarding specific subgroups of women, it has been observed that FFDM/DBT offers a significant improvement in sensitivity in women aged 50–59 years and with breast density of 50% or more, however, this improved sensitivity is not seen with SM/DBT [19]. In the present study, 75.3% of cases were classified as having a dense breast composition. However, the diagnostic accuracy of SM/DBT was not inferior to FFDM/DBT. The two representative cases presented in this study highlight the effectiveness of SM/DBT and demonstrate the limitations of SM. The FFDM images could be used to detect the ill-defined masses from MLO and CC (two-view findings) whereas, the SM image could only show the noticeable density from MLO (one-view finding). This downgraded result is consistent with that of a previous study [20]. Normal structures superimposed on glandular tissue, such as ligaments, can be accentuated [21]; grouped amorphous calcifications on FFDM were interpreted as diffuse coarse calcifications on SM in the present study. These were interpreted as probable malignancies on SM/DBT. Since ill-defined margins of masses delineate the invasive area of breast cancer and amorphous microcalcifications warrant a biopsy for the histological diagnosis, they are important in the detection of abnormalities related to malignancies in clinical judgement. Recently, advancements in SM and DBT have been carried out, including Clarity HD high-resolution 3D™ (70 micron pixel size) for DBT and Intelligent 2D™ (Hologic, Marlborough, MA) for SM [22]. The contrast resolution of the digital image depends on the number of pixel values. Advanced implement is expected to overcome the limitations of SM.

As previously shown [14], the present study demonstrated that SM/DBT required half the radiation dose of FFDM/DBT, similar to the dose required for FFDM alone. Taken together, the present study suggests that DBT complements SM and that SM/DBT produces useful images for secondary examination.

CONCLUSION

SM/DBT has a similar performance to FFDM/DBT for secondary examination of breast cancer, while requiring less radiation.

ETHICS AND CONSENT

The present study received Ethics Committee approval from the Institutional Review Board of the hospital and written informed consent to participate was obtained from the women.
FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR AFFILIATIONS

Eiji Nakajima orcid.org/0000-0002-9847-6810
Tokyo Medical University Ibaraki Medical Center, JP

Hiroko Tsunoda
St. Luke’s International Hospital, JP

Mariko Ookura
St. Luke’s Medilocus, JP

Kanako Ban orcid.org/0000-0002-7244-2436
Tokyo Health Service Association, JP

Yuko Kawaguchi
Tokyo Health Service Association, JP

Mami Inagaki
Inagaki breast clinic, JP

Kanako Ban
Tokyo Medical University Hospital, JP

Norihiko Ikeda
Inagaki breast clinic, JP

Mami Inagaki
Tokyo Health Service Association, JP

Kanako Ban
Tokyo Health Service Association, JP

Yuko Kawaguchi
Tokyo Health Service Association, JP

Mami Inagaki
Inagaki breast clinic, JP

Norihiko Ikeda
Tokyo Medical University Hospital, JP

Kinya Furukawa
Tokyo Medical University Ibaraki Medical Center, JP

Takashi Ishikawa orcid.org/0000-0003-3450-4533
Tokyo Medical University, JP

REFERENCES

1. Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology. 2013; 267(1): 47–56. DOI: https://doi.org/10.1148/radiol.12121373

2. Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014; 311(24): 2499–2507. DOI: https://doi.org/10.1001/jama.2014.6095

3. Conant EF, Beaber EF, Sprague BL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography compared to digital mammography alone: A cohort study within the PROSPR consortium. Breast Cancer Res Treat. 2016; 156(1): 109–116. DOI: https://doi.org/10.1007/s10549-016-3695-1

4. McDonald ES, Oustimov A, Weinstein SP, et al. Effectiveness of digital breast tomosynthesis compared with digital mammography: Outcomes analysis from 3 years of breast cancer screening. JAMA Oncol. 2016; 2(6): 737–743. DOI: https://doi.org/10.1001/jamaoncol.2015.5536

5. Ciato S, Houssami N, Bernardi D, et al. Integration of 3D digital mammography with tomosynthesis for population breast–cancer screening (STORM): A prospective comparison study. Lancet Oncol. 2013; 14(7): 583–589. DOI: https://doi.org/10.1016/S1470-2045(13)70134-7

6. McCarthy AM, Kontos D, Synnestvedt M, et al. Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program. J Natl Cancer Inst. 2014; 106(11): dju316. DOI: https://doi.org/10.1093/jnci/dju316

7. Skaane P. Breast cancer screening with digital breast tomosynthesis. Breast Cancer. 2017; 24(1): 32–41. DOI: https://doi.org/10.1007/s12282-016-0699-y

8. Houssami N. Digital breast tomosynthesis (3D-mammography) screening: data and implications for population screening. Expert Rev Med Devices. 2015; 12(4): 377–379. DOI: https://doi.org/10.1586/17434440.2015.1028362

9. Diekmann F, Buck I. Tomosynthesis and contrast-enhanced digital mammography: Recent advances in digital mammography. Eur Radiol. 2007 Dec; 17(12): 3086–3092. DOI: https://doi.org/10.1007/s00330-007-0715-x

10. Swahn TM, Houssami N, Sechopoulos I, et al. Review of radiation dose estimates in digital breast tomosynthesis relative to those in two-view full-field digital mammography. Breast. 2015; 24(2): 93–99. DOI: https://doi.org/10.1016/j.breast.2014.12.002

11. Gur D, Zuley ML, Anello MI, et al. Dose reduction in digital breast tomosynthesis (DBT) screening using synthetically reconstructed projection images: An observer performance study. Acad Radiol. 2012; 19(2): 166–171. DOI: https://doi.org/10.1016/j.acrad.2011.10.003

12. Skaane P, Bandos AI, Eben EB, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: Comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology. 2014; 271(3): 655–663. DOI: https://doi.org/10.1148/radiol.13131391

13. Bernardi D, Macaskill P, Pellegrini M, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): A population-based prospective study. Lancet Oncol. 2016; 17(8): 1105–1113. DOI: https://doi.org/10.1016/j.lancro.2016.03.008

14. Zuckerman SP, Conant EF, Keller BM, et al. Implementation of synthesized two-dimensional mammography in a population-based digital breast tomosynthesis screening program. Radiology. 2016; 281(3): 730–736. DOI: https://doi.org/10.1148/radiol.2016160366

15. Aujero MP, Gavenonis SC, Benjamin R, et al. Clinical performance of synthesized two-dimensional mammography combined with tomosynthesis in a large screening population. Radiology. 2017; 281(1): 70–76. DOI: https://doi.org/10.1148/radiol.2017162674

16. Zuley ML, Guo B, Catullo VJ, et al. Comparison of two-dimensional synthesized mammograms versus original digital mammograms alone and in combination with
Nakajima et al. Digital Breast Tomosynthesis Complements Two-Dimensional Synthetic Mammography for Secondary Examination of Breast Cancer. Journal of the Belgian Society of Radiology. 2021; 105(1): 63, 1–7. DOI: https://doi.org/10.5334/jbsr.2457

Submitted: 26 February 2021  Accepted: 29 August 2021  Published: 05 November 2021

COPYRIGHT:
© 2021 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See http://creativecommons.org/licenses/by/4.0/.

Journal of the Belgian Society of Radiology is a peer-reviewed open access journal published by Ubiquity Press.