Evidence Synthesis

Number 125

Screening for Breast Cancer With Digital Breast Tomosynthesis

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AHRQ Publication No. 14-05201-EF-2
April 2015

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Chapter 1. Introduction

Purpose

Digital breast tomosynthesis has rapidly been adopted by many providers of mammography screening in the United States. This report summarizes the evidence published through November 2014 on diagnostic tests characteristics of tomosynthesis in screening populations.

Background

Digital breast tomosynthesis, also known as 3-D mammography, uses a computer algorithm to reconstruct multiple low-dose digital images of the breast into thin "slices" spanning the entire breast. These images can be displayed individually or in cine mode. Tomosynthesis has been introduced in radiology as concurrent adjunctive screening with standard two view digital mammography, which more than doubles the total radiation exposure compared to a standard digital mammography screening examination.[1-4] In 2013, the FDA approved the use of synthetic 2-D images to take place of the standard 2-D, two view digital mammograms. This technology eliminates the additional radiation of a digital mammogram, so that the radiation dose is due only the digital breast tomosynthesis exam.[5] There is a substantial cost to acquire this technology; it is currently not known how frequently synthetic views are used. A GE tomosynthesis system was FDA approved in September 2014,[6] and a single 3D view from this system is reported to have similar radiation dose as a standard two-view digital mammography examination.[7] However, it is not yet clear how this system will be used in practice.

Chapter 2. Methods

Key Question

Using the USPSTF's methods[8] (detailed in Appendix A), we addressed the following key question (KQ):

1. What are the test performance characteristics of tomosynthesis as a primary screening modality for breast cancer performed either alone or simultaneously with 2-D digital mammography? How do these performance characteristics differ by age and risk factors?

Data Sources and Searches

We searched MEDLINE, PubMed, Embase, and the Cochrane library from January 2000 through November 2014. To ensure the comprehensiveness of our retrieval strategy, we reviewed the reference lists of included studies and relevant systematic reviews to identify relevant articles. We also supplemented our database searches with suggestions from experts, searched the grey literature for relevant reports and reviewed their references, and searched Clinicaltrials.gov to identify relevant ongoing trials (Appendix B).

Study Selection

Two reviewers independently screened titles and abstracts for relevance, and identified 15 articles for full text review. We required that included studies be conducted in screening populations (asymptomatic women age 40 and older) and evaluate test performance characteristics with a comprehensive reference standard applied to both negative and positive tests results. For breast cancer screening this requires further imaging and/or biopsy of positive results, and a minimum of one year clinical follow-up for negative results to ascertain interval breast cancers not identified by screening.

Quality Assessment and Data Abstraction

Two reviewers independently assessed the full text of each study to assess whether it met our predefined inclusion criteria. No studies met all inclusion criteria. To illustrate the state of available research addressing this key question, results from screening population studies were abstracted into a standard evidence table. A second reviewer checked the data for accuracy. Elements abstracted included population characteristics (e.g., baseline demographics, family or personal history of breast cancer), study design (e.g., inclusion/exclusion criteria, followup, screening rounds), screening test characteristics (e.g., number of readers), and proximate health outcomes, including breast cancer detection rates, invasive breast cancer detection rates, recall rates, and biopsy rates.

Chapter 3. Results

Literature Search

We identified no studies that met our inclusion criteria. To illustrate the state of available research addressing this key question, results from 15 screening studies were abstracted, including a systematic review of the use of breast tomosynthesis for breast cancer screening or diagnosis performed by the Technology Evaluation Center.[9] This review identified one additional study we had not previously located.[10]

Summary of Results

After screening the full-text articles, none met the inclusion criteria. No studies met the required criteria of reporting results on a screening population and employing a comprehensive reference standard; hence, there is no evidence available that addresses the key question regarding the test performance characteristics of tomosynthesis in a screening population. Characteristics of the identified studies conducted are briefly summarized in this report, and those studies reporting on cancer detection rates, recall rates and biopsy rates in a screening population are summarized in Table 1.

One small study from Sweden included both symptomatic and asymptomatic women.[11] This was the only study that applied a comprehensive reference standard including one year clinical follow up. However, of 185 total women, 89 (48%) were diagnosed with breast cancer, so the study sample is not representative of a screening population. Four studies utilized test sets of mammograms with known diagnoses, with and without tomosynthesis images, to evaluate radiologist diagnostic performance.[1, 12-14] All of these test sets were enriched with images of known breast cancers, ranging from 16 percent[13] to 41 percent[1] of the total images.

The remaining nine studies were screening cohort studies that reported on recall rates and cancer detection rates for digital mammography with or without tomosynthesis.[4, 10, 15-19] These studies compared findings from single cohort undergoing both studies[4, 19] or compared 2 screening cohorts, one undergoing digital mammography only compared to a cohort undergoing mammography and tomosynthesis.[10, 15-18] After elimination of reports from the same dataset, findings from 7 studies are summarized in Table 1. In these studies, tomosynthesis was generally associated with an increase in the breast cancer detection rates compared to digital mammography alone. The proportions of invasive cancers with and without the use of tomosynthesis were somewhat higher with tomosynthesis in some studies[4, 16-18] and similar to digital mammography in others. [10, 15, 19] Compared to digital mammography, tomosynthesis was associated with reduced immediate recall rate and higher positive predictive value for an initial positive result (PPV_1).[4, 10, 15-19] In two of four studies reporting biopsy rates, the biopsy rate was slightly higher with tomosynthesis compared to digital mammography alone (Table 1).[15-18]

Chapter 4. Discussion

Current studies do not provide information on diagnostic test characteristics of tomosynthesis for breast cancer screening, as none report on a comprehensive reference standard. Studies are consistent in finding reduced overall recall rates with similar or higher biopsy rates. One factor that may reduce immediate recall rates with tomosynthesis is that the technology obtains additional breast images at the time of initial screening, which for the commonly used current technology more than doubles the breast radiation dose of digital mammography. Technology approved by the FDA in 2013 for synthetic 2-D mammography reduces the radiation dose to that of the tomosynthesis exam alone.[5] Cancer detection rates are somewhat higher, and the proportion of invasive cancers detected is similar to or higher than the proportion detected with digital mammography alone. Ongoing studies registered with clinical trials.gov are listed in Appendix B and descriptions of these studies suggest that results of the application of a comprehensive reference standard to a screening population may become available within a few years. Studies are needed that employ the standard approach to breast imaging interpretation in the United States (single reading), and that report on both interval cancers identified by a comprehensive reference standard and longer term outcomes, including effects of the addition of tomosynthesis to digital mammography on the stage distribution of detected cancers, breast cancer recurrence or 2nd (contralateral) breast cancers and mortality rates.

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Table 1. Screening for Breast Cancer Using Tomosynthesis: Study Characteristics and Reported Outcomes

Author, Year (Location)	Study Design and Setting	Study N	Radiologist/ Population Characteristics	Breast Cancer Prevalence	Cancer Detection Rate (% Invasive)	Recall/Biopsy Rate	Positive Predictive Value
Greenberg, 2014 (Washington, DC area)	Cohort (2 arm) Community-based multi-site radiology practice	DBT+DM: 20,943 exams DM only: 38,674 exams	14 radiologists	DBT+DM: 131/20,943 exams DM only: 190/38,674 exams	DBT: 6.3 per 1,000 exams (73.6%) DM only: 4.9 per 1,000 exams (62.1%)	*Recall* DBT+DM: 13.6% DM only: 16.2% *Biopsy* DBT+DM: 2.6% DM only: 2.2%	*PPV1* DBT+DM: 4.6% DM only: 3.0% *PPV3* DBT+DM: 23.8% DM only: 22.8%
Friedewald, 2014* (Multi-state)	Retrospective cohort (2 arm) 13 academic health centers and community breast diagnostic/screening centers	DBT+DM: 173,663 exams DM only: 281,187 exams	139 radiologists Mean age: DBT+DM: 56.2 y DM only: 57.0 y Limited to screening exams and subsequent follow-ups	DBT+DM: 950/173,663 exams DM only: 1207/281,187 exams	DBT+DM: 5.5 per 1,000 exams (74.5%) DM only: 4.3 per 1,000 exams (67.4%)	*Recall* DBT+DM: 8.9% DM only: 10.6% *Biopsy* DBT+DM: 1.9% DM only: 1.8%	*PPV1* DBT+DM: 6.1% DM only: 4.1% *PPV3* DBT+DM: 29.0% DM only: 24.0%
McCarthy, 2014 (Pennsylvania)	Cohort (2 arm) One academic medical center	DBT+DM: 15,571 exams DM only: 10,728 exams	6 radiologists Mean age: DBT+DM: 56.7 y DM only: 56.9 y Excluded personal hx breast cancer	DBT+DM: 85/15,571 exams DM only: 49/10,728 exams	DBT+DM: 5.5 per 1,000 exams (71%) DM only: 4.6 per 1,000 exams (69%)	*Recall* DBT+DM: 8.8% DM only: 10.4% *Biopsy* DBT+DM: 2.0% DM only: 1.8%	*PPV1* DBT+DM: 6.2% DM only: 4.4% *PPV3* DBT+DM: 25.4% DM only: 24.7%
Ciatto, 2013 (Italy)	Prospective cohort (1 arm) Population screening program	7,294 exams DM+DBT images interpreted independently from DM only images	8 radiologists Median age: 58 y Screen positive if either reader interpreted DM or DBT as abnormal	DBT+DM: 59/7,994 exams DM only: 39/7,994 exams	DBT+DM: 8.1 per 1,000 exams (88.1%) DM only: 5.3 per 1,000 exams (89.7%)	*Recall* DBT+DM: 4.3% DM only: 4.4% *Biopsy* NR	DBT+DM: 18.8% DM only: 12.1%

Table 1. Screening for Breast Cancer Using Tomosynthesis: Study Characteristics and Reported Outcomes

Author, Year (Location)	Study Design and Setting	Study N	Radiologist/ Population Characteristics	Breast Cancer Prevalence	Cancer Detection Rate (% Invasive)	Recall/Biopsy Rate	Positive Predictive Value
Haas, 2013 (Connecticut)	Cohort (2 arm) Multi-site (1 academic medical center, 2 outpatient radiology clinics, 1 mobile mammography van)	DBT+DM: 6,100 women DM only: 7,058 women	8 radiologists Mean age: DBT+DM: 55.8 y DM 57.5 y Personal hx of breast cancer: DBT+DM: 5.5% DM only: 2.8%	DBT+DM: 35/6,100 women DM only: 37/7,058 women	DBT+DM: 5.7 per 1,000 women (69%) DM only: 5.2 per 1,000 women (68%)	*Recall* DBT: 8.4% DM: 12.0% *Biopsy* NR	DBT+DM: 6.8% DM only: 4.3%
Rose, 2013 (Texas)	Cohort (2 arm) Multisite community-based comprehensive breast cancer center	DBT+DM: 9,499 exams DM only: 13,856 exams	6 radiologists Asymptomatic women	DBT+DM: 51/9,499 exams DM only: 56/13,856 exams	DBT+DM: 5.4 per 1,000 exams (80%) DM only: 4.0 per 1,000 exams (70%)	*Recall* DBT+DM: 5.5% DM only: 8.7% *Biopsy* DBT+DM: 1.4% DM only: 1.5%	*PPV1* DBT+DM: 10.1% DM only: 4.1% *PPV3* DBT+DM: 39.8% DM only: 26.5%
Skaane, 2013 (Norway)	Prospective cohort (1 arm) City-wide (Oslo) breast cancer screening program	12,621 exams DM+DBT images interpreted independently from DM only images	8 radiologists Median age: 58 y Screen positive if either reader interpreted DM or DBT as abnormal	DBT+DM: 101/12,621 exams DM only: 77/12,621 exams	DBT+DM: 8.0 per 1,000 exams (80.2%) DM: 6.1 per 1,000 exams (72.7%)	*Recall* DBT+DM: 6.1% DM only: 6.7% *Biopsy* NR	DBT+DM: 13.1% DM only: 9.1%

*Possible inclusion of data from Rose (2013) and Greenberg (2014).

DBT=digital breast tomosynthesis; DM=digital mammography; hx=history; NR=not reported; PPV=positive predictive value; PPV1=true positives (cancers)/all positives; PPV3=true positives (cancers)/all biopsies.

Appendix A. Detailed Methods

Key Question Literature Search Strategy

Note: The literature search strategy for this supplemental review overlapped with our main evidence review, "Adjunctive Screening for Breast Cancer in Women With Dense Breasts," and is therefore not limited to only tomosynthesis.

Database: Cochrane
Search Strategy:

'*mammogra* AND screen* AND (breast density OR dense breast OR parenchym*) in Title, Abstract, Keywords*

Database: Ovid MEDLINE(R)
Search Strategy:
---
1. "breast densit*".ti,ab.
2. parenchym*.ti,ab.
3. mammo* pattern.ti,ab.
4. mammo* patterns.ti,ab.
5. radiological pattern*.ti,ab.
6. wolfe*.ti,ab.
7. tabar*.ti,ab.
8. mammo* feature*.ti,ab.
9. breast pattern*.ti,ab.
10. mammo* densit*.ti,ab.
11. tissue densit*.ti,ab.
12. or/1-11
13. (negative test result* or false negative).mp. or exp False Negative Reactions/
14. "sensitivity and specificity"/ or "limit of detection"/ or roc curve/ or signal-to-noise ratio/
15. "sensitivity and specificity"/ or "limit of detection"/ or roc curve/ or signal-to-noise ratio/
16. or/13-15
17. ((negative adj4 mammogra*) or negative screen).mp.
18. 16 or 17
19. (supplementa* adj3 screen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
20. (breast or mammogra*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21. 12 and 16 and 18
22. 20 and 21
23. 12 and 19
24. (((supplementa* adj5 ultraso*) or supplementa*) adj5 imag*).mp.
25. 12 and 24
26. 20 and 25
27. 22 or 26

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28. 23 or 27
29. limit 28 to ((abstracts or english language) and yr="2000 -Current")

Database: Ovid MEDLINE(R)
Search Strategy:
---

1. exp "Sensitivity and Specificity"/
2. sensitivity.tw.
3. specificity.tw.
4. ((pre-test or pretest) adj probability).tw.
5. post-test probability.tw.
6. post-test probability.tw.
7. likelihood ratio$.tw.
8. or/1-7
9. Breast Neoplasms/
10. (breast adj (neoplasm or neoplasms or tumour or tumor or tumors or tumours or cancer or carcinoma or carcinomas or oncologic or oncology)).mp.
11. 9 or 10
12. exp Mammography/
13. Mammograph$.ti,ab.
14. 12 or 13
15. 8 and 14
16. "breast densit*".ti,ab.
17. parenchym*.ti,ab.
18. mammo* pattern.ti,ab.
19. mammo* patterns.ti,ab.
20. radiological pattern*.ti,ab.
21. wolfe*.ti,ab.
22. tabar*.ti,ab.
23. (birad* or bi-rad*).ti,ab.
24. mammo* feature*.ti,ab.
25. breast pattern*.ti,ab.
26. mammo* densit*.ti,ab.
27. tissue densit*.ti,ab.
28. "breast imaging reporting and data system".ti,ab.
29. or/16-28
30. 8 and 11 and 14 and 29
31. limit 30 to english language

1. 65. Image Processing, Computer-Assisted/ or Radiographic Image Interpretation, Computer-Assisted/ or Tomography, X-Ray Computed/ or Radiographic Image Enhancement/ or Tomography, X-Ray/ or tomosynthesis.mp. or Imaging, Three-Dimensional/
2. 66. 64 and 65
3. 67. Ultrasonography, Mammary/ or automated ultrasound.mp.
4. 68. whole breast ultrasound.mp.
5. 69. hand help ultrasound.mp.
6. 70. magnetic resonance imaging.mp. or Magnetic Resonance Imaging/

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7. 71. mri.mp.
8. 72. Technetium Tc 99m Sestamibi/ or scintimammography.mp.
9. 73. or/67-72
10. 74. 31 and 73
11. 75. limit 74 to (english language and yr="2000 -Current")
12. 79. or/76-78
13. 80. 62 and 79
14. 81. limit 80 to (english language and yr="2000 -Current")
15. 82. 81 not 75
16. 83. 65 or 73
17. 84. 82 and 83

Database: Embase
Search Strategy:
---

1. 'mammography'/exp OR 'mammography' OR 'mammography system'/exp OR 'mammography system' OR mammograph*:ab,ti AND [2000-2014]/py
2. 'dosimetry'/exp OR 'dosimetry' OR 'radiation protection'/exp OR 'radiation protection' OR 'radiation measurement'/exp OR 'radiation measurement' AND [2000-2014]/py
3.
4. 'radiation exposure'/exp OR 'radiation exposure' OR 'radiation induced neoplasm'/exp OR 'radiation induced neoplasm' OR 'radiation injury'/exp OR 'radiation injury' AND [2000-2014]/py
5. 'morbidity'/exp OR 'morbidity' OR 'mortality'/exp OR 'mortality' OR 'adverse effect':ab,ti OR 'adverse effects':ab,ti OR harm:ab,ti OR harms:ab,ti OR contraindic*:ab,ti AND [2000-2014]/py
6. #2 OR #4
7. #1 AND #5 AND #6

8.1 'breast tumor'/exp/dm_pc,dm_di
8.2 (breast NEXT/5 (neoplasm* OR tumour* OR tumor* OR cancer* OR carcinom* OR oncolog*)):ab,ti
8.3 #8.1 OR #8.2
8.4 'mass screening'/exp OR 'mass radiography'/exp
8.5 'neoplasm'/exp/dm_pc,dm_di
8.6 'mammography'/exp OR 'mammography system'/exp OR mammograph*:ab,ti
8.7 screen*:ab,ti
8.8 #8.4 OR #8.5 OR #8.6 OR #8.7
8.9 #8.3 AND #8.8
8.10 'sensitivity and specificity'/exp OR sensitivity:ab,ti OR specificity:ab,ti
8.11 (('pre test' OR pretest) NEAR/5 probability):ab,ti
8.12 (('pre test' OR pretest) NEAR/5 probability):ab,ti
8.13 'likelihood ratio':ab,ti OR 'likelihood ratios':ab,ti
8.14 #8.10 OR #8.11 OR #8.12 OR #8.13
8.15 #8.9 AND #8.14
8.16 'breast density':ab,ti OR 'dense breasts':ab,ti OR 'dense breast':ab,ti OR parenchym*:ab,ti OR 'mammographic feature':ab,ti OR 'mammographic features':ab,ti OR (mammography

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NEAR/2 feature*):ab,ti OR 'breast pattern':ab,ti OR 'breast patterns':ab,ti OR (breast NEAR/3 pattern):ab,ti OR 'mammographic density':ab,ti OR (mammography NEAR/3 density):ab,ti OR 'mammographic pattern':ab,ti OR 'mammographic patterns':ab,ti OR (mammography NEAR/2 patterns):ab,ti OR 'radiological pattern':ab,ti OR 'radiological patterns':ab,ti OR wolfe*:ab,ti OR tabar*:ab,ti OR birad*:ab,ti OR 'bi rad':ab,ti OR 'breast imaging reporting and data system':ab,ti OR 'tissue density':ab,ti OR (tissue NEAR/3 density):ab,ti

8.17 #8.15 AND #8.16

8.18 #8.17 AND [english]/lim AND [2000-2014]/py

Appendix A. Detailed Methods

Inclusion and Exclusion Criteria

Category	Inclusion	Exclusion
Populations	KQ 1: Women primarily aged 40 years and older receiving tomosynthesis screening	Women with: • Pre-existing breast cancer • Clinically significant BRCA 1/2 mutations • Li-Fraumeni syndrome • Cowden syndrome • Hereditary diffuse gastric syndrome • Other familial breast cancer syndromes • High-risk breast lesions (DCIS, LCIS, ADH, ALH) • Previous doses of chest radiation (>20Gy) before age 30 • Undergoing diagnostic or surveillance mammography
Setting	Conducted in primary care or other setting with primary care-comparable population	Settings not generalizable to primary care
Intervention or Exposure	Tomosynthesis	Digital or full-film mammography alone; other new technologies, such as MRI or ultrasound; use for diagnostic or surveillance purposes; use in a diagnostic or surveillance setting only
Comparisons or Nonexposure	Digital or film mammography	
Outcomes	Test performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios for invasive breast cancers, breast lesions [DCIS], total breast cancers, breast cancers by stage); biopsy rates, recall rates	
Study Designs	Diagnostic accuracy studies with reference standard and more than one radiologist/reader, RCTs, cohort studies with more than one radiologist/reader, and meta-analyses	
Language	English only	Non-English languages
Publication Date	Trials published from January 2000 to present	Trials published before January 2000
Study Quality	Fair- and good-quality studies	Poor-quality studies

Appendix B. Ongoing Studies and Trials Pending Assessment

Investigator (Location) Study Title/Name	Number of Participants/ Estimated Enrollment	Intervention	Outcomes	2014 Status
Sophia Zackrisson (Sweden) *Malmö Breast Tomosynthesis Screening Trial*	15,000	Screening with tomosynthesis compared to digital mammography	Cancer detection; sensitivity; specificity	Study Period: March 2010 – March 2016 Recruiting
Emily Conant (United States) *Comparison of Full-Field Digital Mammography With Digital Breast Tomosynthesis Image Acquisition in Relation to Screening Call-Back Rate*	550	Screening with digital mammography compared to a combination of 2D and 3D tomosynthesis	Recall rates; sensitivity; specificity; lesion characterization; radiation dose	Study Period: December 2012 – June 2012 Status unknown
Jules Sumkin (United States) *Assessment of Digital Breast Tomosynthesis (DBT) in the Screening Environment*	1,080	Screening with digital mammography and tomosynthesis (images interpreted independently)	Recall rates; specificity	Study Period: May 2010 – May 2014 Recruiting
Per Skaane (Norway) *Tomosynthesis in the Oslo Breast Cancer Screening Program (DBT)*	25,000	Screening with digital mammography and tomosynthesis	Screening performance indicators; interval cancer rates	Study Period: November 2010 – September 2015 Ongoing, but not recruiting
Thomas Moritz (Austria) *Digital Breast Tomosynthesis vs. Digital Mammography: A National Multicenter Trial*	600	Screening with digital mammography and tomosynthesis	Specificity; sensitivity	Study Period: January 2012 – December 2012 Status unknown