Overview of tomosynthesis (3D mammography) for breast cancer screening

Nehmat Houssami[1], Kylie Hunter[2], Sophia Zackrisson[3]

1-Sydney School of Public Health, Sydney Medical School, University of Sydney, Sydney, Australia

2-NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia

3- Diagnostic Radiology, Department of Translational Medicine, Lund University, Skåne University Hospital Malmö, 20502 Malmö, Sweden

Correspondence

Professor Nehmat Houssami

Sydney School of Public Health (A27), Sydney Medical School, University of Sydney, Sydney 2006, Australia.

Phone +61 0419 273510

Email: nehmat.houssami@sydney.edu.au

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Abstract

This review of the evidence on digital breast tomosynthesis, a 3D mammography technology, for breast cancer (BC) screening, describes two types of studies. Prospective trials comparing tomosynthesis (combined with 2D-mammography) screening with 2D-mammography alone in the same participants were based on double-reading practice in mostly biennial screening. These showed incremental BC detection attributed to use of tomosynthesis ranging from 2.2-2.7 per 1000 screens. Retrospective studies reported the *difference* in BC detection between women screened with tomosynthesis (2D plus 3D-mammography) or with 2D-mammography alone, using single-reading and mostly annual screening. Differences in cancer detection ranged between 0.2-2.1 per 1000 screens favouring tomosynthesis. The impact of using tomosynthesis on recall was heterogeneous, however significant reduction in recall rates was observed amongst the retrospective studies.

Keywords: breast cancer; digital breast tomosynthesis; mammography; population screening

Executive summary:

- Prospective non-randomised trials, embedded in European population screening programs, show that using tomosynthesis (3D-mammography) in addition to, or as replacement to, standard 2D-mammography screening of the same women significantly increases breast cancer detection
- A growing number of retrospective studies have compared groups of women who were screened using tomosynthesis (2D plus 3D-mammography) or with 2D-mammography alone – these show some improvement in BC detection in the tomosynthesis-screened groups however the estimated effect varied considerably between studies
- The effect of using tomosynthesis on recall was heterogeneous across studies, however significant reduction in recall rates was observed amongst all the retrospective studies.
- The longer-term effect of tomosynthesis on screening benefit remains unclear and warrants further research.

Introduction

The use of digital breast tomosynthesis, a near three-dimensional (3D) mammography technology, for early detection of breast cancer (BC) has gathered momentum. Although evidence on various clinical applications of tomosynthesis is accumulating [1-3], none is emerging as rapidly as the evidence on its population screening capability. In this work, we review the evidence on tomosynthesis or 3D-mammography in the population breast screening setting. In doing so, we highlight current knowledge as well evidence gaps on this new technology for BC screening.

Background on the technology

The development of digital breast tomosynthesis has its background in the well-known limitation of 2D mammography, namely the projection of a three-dimensional structure (the breast) on two-dimensional images, mammograms. This implies that normal breast tissue and parenchymal structures may hide or simulate a tumour on the mammogram, a situation more pronounced in the denser breast. In screening up to 30% of cancers may not be visible on mammography due to overlapping tissue effect and the sensitivity may be as low as 50% in women with dense breasts [4, 5].

The tomographic principle described in the early 20th century was adapted for breast imaging during the 1970's [6, 7]. With the development of digital detectors in mammography in the 1990's, the tomosynthesis concept was further refined and the modern concept of digital breast tomosynthesis was established [8, 9]. In tomosynthesis, the X-ray tube moves along a limited arc and a number of low-dose images are acquired of the compressed breast from different angles, typically between 15 and 50 degrees. The low-dose projection images are then mathematically reconstructed into usually 1mm thin slices, that can be viewed sequentially by scrolling in an image stack or as a cine loop. The technique minimizes the effect of overlapping tissue and tumours are hence better visualized [10]. Without any additional radiation exposure, it is possible to derive a so-called synthetic mammogram from the tomosynthesis volume. The synthetic mammogram may be useful to obtain an overview of the breast, to judge microcalcification clusters, and to facilitate comparison with prior mammograms. The radiation dose of tomosynthesis varies between vendors, although is usually comparable or somewhat higher than mammography [10]. The reading time for tomosynthesis is approximately double compared to standard mammography alone, and efforts are being made to improve the screen-reading work flow.

It is foreseen that tomosynthesis will be useful in both the screening and diagnostic settings where it may improve screening sensitivity, potentially decrease recall rates as well as improving lesion size

measurement and characterization, although many of these issues are yet to be proven in prospective trials.

Review Methods

We used a literature search methodology that updates a previously described systematic review [1]: a Medline search (exploded "breast neoplasm", combined with "tomosyn$" or "3D-mammography"in title) was performed at July 2016 by one investigator (NH). Studies that evaluated tomosynthesis (3D-mammography) for population BC screening in comparison with standard (2D) digital mammography and that provided data for screening detection measures were identified. Studies were summarised in evidence tables including study design and setting, and data reported for cancer detection, and recall or false-recall. The range of comparative estimates for cancer detection and for recall was described.

Results

The literature search did not identify any randomised controlled trials of tomosynthesis for population breast screening. There were two types of studies reporting data on tomosynthesis screening, with generally similar study and screening setting characteristics within each group; therefore these are summarised separately by study design.

Prospective non-randomised trials reporting comparative screening detection measures in the same participants

Four prospective trials reported in 6 publications [11-16], shown in Table 1, compared tomosynthesis (usually in combination with acquired or synthetic 2D-mammography) screening with standard 2D-mammography alone in the same screening participants. These studies shared similar characteristics of a prospective design, were based on double-reading practice, provided mostly biennial screening, and were undertaken in European population-based screening programs. In three of these trials, tomosynthesis (3D-mammography) was integrated with 2D-mammography (2D with 3D) and was compared with 2D-mammography alone, whereas the Malmö tomosynthesis trial compared stand-alone 3D with 2D [15]. The STORM-2 trial compared two different 3D-mammography screen-readings, one combining 2D with 3D, and another using 3D with synthesized 2D images (whereby 2D images are reconstructed from the 3D acquisitions) [16]. These trials had different reading sequences

and two used arbitration meetings (Oslo, Malmö) whereas the STORM trials did not, as noted in study characteristics in table 1.

All four trials showed that using tomosynthesis significantly increased BC detection rates, as shown in the study-specific data in Table 1. These studies provided data that allow calculation of *incremental* ('extra') BC detection attributable to use of 3D-mammography, which was in the range of an additional 1.9 to 2.7 cancers per 1000 screening examinations, or in the range of an additional 2.2 to 2.7 cancers per 1000 screening examinations excluding the Oslo study interim analysis based on single-reading [13]. The data for recall or false-positive recall were heterogeneous across studies, and also within each study (for 2 studies) according to the analytic approach used, as well as whether arbitration was practiced and whether recalls were reported before or after arbitration. Recall data varied from an increase attributable to use of tomosynthesis in the range of 0.55-1.03% in the proportion of overall recall, to an estimated reduction of up to 2% in the absolute false-recall proportion using pre-arbitration results (shown in Table1).

Retrospective studies comparing screening detection measures in different groups of women

Ten retrospective studies [17-26], summarised in Table 2, reported data on the *difference* in BC detection rates between groups of women who were screened with tomosynthesis (using 2D and 3D mammography) *or* were screened with standard 2D-mammography alone, at different timeframes and/or imaging services. In addition to being conducted retrospectively, these studies shared characteristics of screening practice in the USA, comprising mostly annual screening and using single-reading as the standard practice in that setting.

Almost all the above-described studies showed that cohorts screened with tomosynthesis (2D with 3D) had higher BC detection rates than those screened with 2D-mammography alone. However, many studies did not report statistically significant differences between compared groups, and one study [24] showed lower cancer detection for use of tomosynthesis screening (Table 2). Excluding that one study, there was broad variability in the difference in cancer detection rates, ranging between 0.2 and 2.1 per 1000 screens favouring tomosynthesis (2D with 3D) screening (without excluding any studies the range is -0.8 to 2.1 per 1000 screens). A consistent finding from the retrospective studies is significant reduction in recall amongst tomosynthesis-screened cohorts, ranging between a reduction of 1.4% and 7.3% in the *absolute* proportion of recalls relative to 2D-mammography screening alone.

Discussion

This descriptive review of published evidence highlights that the application of tomosynthesis for population breast screening, generally as an integrated modality with 2D-mammography, improves screening detection measures, either through increased BC detection or reduced recalls, or both [11-26]. The finding of improved BC detection from using tomosynthesis screening was apparent across the two groups of studies summarised in this work – prospective screening trials and also retrospective evaluations. However, additional BC detection attributed to use of tomosynthesis was more consistent and much more evident in the prospective trials, with estimated *incremental* BC detection in the range of an additional 2.2 to 2.7 cancers per 1000 screening examinations. The differences in findings between the two types of studies may be due, at least in part, to the screening frequency, given that the retrospective studies had annual screening whereas mostly biennial screening was implemented in the prospective studies, with less scope for tomosynthesis to increase BC detection in the setting of more frequent (annual) screening.

It is noteworthy that two prospective studies investigated alternate screening strategies to the commonly used 2D with 3D acquisitions, namely one-view stand-alone tomosynthesis in the Malmo study [15], and 3D acquisitions enabling synthetic 2D images in STORM-2 [16]. These studies showed comparable results from using tomosynthesis screening, in terms of BC detection, as the other prospective trials that used dual-acquisition 2D and 3D mammography. The results from these two trials [15, 16] are very relevant to adoption of this mammography technology in that they provide insights into the potential to reduce radiation burden or the potential to reduce the number of views for interpretation and hence the screen-reading time burden, associated with combined 2D and 3D mammography. There are challenges to the adoption of 3D-mammography technology for population screening, including the increased screen-reading time from interpreting both 2D and 3D images, and the increased radiation from dual-acquisition (2D with 3D) – hence the findings of the Malmo and the STORM-2 trials are particularly timely for implementation studies. An additional challenge is the increased demands on information technology infrastructure to support tomosynthesis technology, which needs to be factored into evaluation studies and health-economics analysis.

The effect of tomosynthesis on radiologists' recall rates was heterogeneous when considering the prospective studies, with evidence that it may cause a modest decrease or increase in recall. However, the most striking finding amongst the retrospective studies was that cohorts screened with tomosynthesis (2D with 3D) experienced substantially lower recall rates than those screened with 2D-mammography (Table 2). The underlying recall rates at 2D-mammography amongst the retrospective studies were generally well above those for 2D-mammography in the prospective trials, as shown in Tables 1 and 2. Hence it appears that tomosynthesis may be of more value in a screening context

where there is a relatively high recall rate at 2D-mammography, where it has the effect of reducing radiologists' unnecessary recall. Reductions in the absolute recall rates from tomosynthesis, shown in Table 2, approximate reductions of around a quarter or a third or more of overall recall in some studies.

The above-described data should be considered in the context that enhanced BC detection from adding tomosynthesis for BC screening, in comparison with 2D-mammography alone, does not equate with increased screening efficacy, or increased screening sensitivity; it is possible that the increased BC detection from adding tomosynthesis contributes to overdiagnosis. The International Agency for Research on Cancer (IARC) reported, in its viewpoint on breast screening [27], that there is inadequate evidence that adding tomosynthesis to 2D-mammography improves BC mortality outcomes above that expected from 2D-mammography screening; it also stated that there is insufficient evidence that tomosynthesis reduces interval cancer rates compared to 2D-mammography alone. These evidence gaps remain unaddressed in relation to tomosynthesis screening, despite a growing body of evidence that its use improves detection measures as highlighted in this review. Therefore, future studies should focus on tackling evidence gaps related to the efficacy of integrating tomosynthesis with mammography screening, in particular the effect this would have on surrogates for screening benefit, such as reducing interval BC rates. In addition, randomised trials would be valuable in strengthening the evidence-base on tomosynthesis, and although none were identified for this review, several are currently in early progress.

Conclusions and future perspectives

Tomosynthesis undoubtedly appears to be a "better mammography" and its transition into the clinical and screening setting is already taking place in some countries. Organised population-based screening programs are underpinned by evidence from the randomised trials of mammography screening; the issues most often discussed regarding BC screening, such as the actual effect on BC mortality, overdiagnosis and false-positives, need to be carefully evaluated also in screening with tomosynthesis. Moving forward, it will be important to determine to what extent digital breast tomosynthesis changes the balance between the benefits and harms of BC screening, in particular research needs to establish the effect this new technology will have on interval BC rates, and whether it changes estimates of BC overdiagnosis. Nonetheless, the call for better early detection methods for women with dense breasts [28, 29] combined with the anticipated benefits of enhanced BC detection with tomosynthesis from the studies reported so far, points towards a likely future introduction of tomosynthesis for BC screening more broadly. Depending on the final results from the prospective

trials, and the ongoing randomised trials using tomosynthesis, it seems likely that digital breast tomosynthesis may be implemented either for all women or in subgroups of women stratified by BC risk and breast density rather than conventional age-based screening. To minimise radiation exposure to women and to help manage the screen-reading burden (from using acquired 2D and 3D), we believe that tomosynthesis with synthetic 2D images, or tomosynthesis alone, may be the most acceptable way forward for future BC screening practice.

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Table 1: Prospective trials evaluating 3D-mammography (digital breast tomosynthesis) for population breast screening

Study (first author)	Study characteristics	Breast cancer detection			Recall measures	
	Study design (number of screens); screen-reading practice and context	Cancer detection rates (CDR) / 1000 screens for 2D	CDR / 1000 screens for 2D/3D	Absolute effect of 3D on CDR compared to 2D-alone	Recall rates (overall recall, or false-positive (FP) data where specified)	Absolute effect of 3D on FPR compared to 2D-alone
Ciatto [11] [STORM]	Prospective trial (7,292) population-based, Italy, compares 2D and 2D/3D screening (paired data); sequential double-reading, recall by either reader	5.3	8.1	↑ **2.7/1000** P<0.001	Recall for 2D-alone or 2D/3D: 5.5% Recall conditional to 2D/3D-positive: 3.5% (analytic estimate 17% ↓ in FP recalls)	↓ **2.0%‡** (increased overall recall in trial by approximately 1%)
Houssami [12]	Extended analysis of STORM trial includes first year follow-up for interval cancers	5.3 (double-read)	7.5 (single-read)	↑ **2.2/1000** P<0.001	(modelling of recall data from STORM)	↓ **1.2%‡**
Skaane [13]	Prospective trial (12,631) population- based, Norway, comparing 2D and 2D/3D screening (paired data: double-reads with arbitration meeting).	6.1	8.0 (reader-adjusted)	↑ **1.9/1000** P =0.001	2D: 6.1% 2D/3D: 5.3% (15% decrease of FP, adjusted for reader)	↓ **0.8%**
Skaane [14]	Analysis based on standard double-reading practice in Oslo trial	7.1	9.4	↑ **2.3/1000** P<0.001	(pre-arbitration FP scores)	↓ **1.8%** of FP scores but ↑ *overall* recall rate by **0.8%**
Lång [15] [MBTST]	Prospective trial (7,500 from target 15,000) random sample invited in population-based program, Sweden: 2D-mammog (2 views) versus **stand-alone 1-view 3D-mammog (DBT).** Independent double-reads with arbitration meeting)	6.3 (2-view)	3D alone: 8.9 (1-view only)	↑ **2.6/1000** P<0.001	Overall recall rate (after arbitration): 2D: 2.6% 3D: 3.8% P<0.0001	↑ **0.9%**

Bernardi [16] [STORM 2]	Prospective trial (9,672) population-based, Italy, compares 2D with 2D/3D screening *or* 2D synthetic/3D; sequential double-reading x 2 parallel arms (paired data x 2) , recall at any read	6.3 6.3	8.5 2Dsynthetic/3D: 8.8	↑ **2.2/1000** P<0.001 ↑ **2.5 /1000** P<0.001	2D: 3.42% 2D/3D: 3.97% P<0.001 2D: 3.42% 2Dsynthetic/3D: 4.45% P<0.001	↑ **0.55%** ↑ **1.03%**

Table 1 is a modified and updated version of data reported by Zackrisson & Houssami [3].

Key: ↑refers to increase; ↓ refers to decrease; 2D refers to digital mammography acquisition of 2-view mammographic images, 3D refers to digital breast tomosynthesis acquisitions for 2-views except where otherwise specified (see Lång [15]); STORM= *S*creening with *T*omosynthesis *or M*ammography trial; MBTST= *M*almo *B*reast *T*omosynthesis *S*creening *T*rial.

‡ Decrease in FPR achieved only if recall *conditional* to 3D-positivity (analytic estimate), actual trial rate shown in table

Table 2: Retrospective studies evaluating 3D-mammography (digital breast tomosynthesis) for population breast screening

Study (first author)	Study characteristics	Breast cancer detection			Recall measures	
	Study design (number of screens); screen-reading practice and context	Cancer detection rates (CDR)/ 1000 screens for 2D	CDR / 1000 screens for 2D/3D	Absolute effect of 3D on CDR compared to 2D-alone	Recall rates	Absolute effect of 3D on recall compared to 2D-alone
Rose [17]	Retrospective: before vs after (13,856 vs 9499) introduction of 3D as adjunct to 2D screening; single-reading (radiology services, USA)	4.0	5.4	↑ **1.4/1000** P=0.18	2D: 8.7% 2D/3D: 5.5% P < 0.001	↓ **3.2%**
Haas [18]	Retrospective: services using 2D vs those using 2D/3D (7,058 vs 6,100) in same year; single-reading (breast or radiology services, USA)	5.2	5.7	↑ **0.5/1000** P=0.70	2D: 12.0% 2D/3D: 8.4% P < 0.01	↓ **3.6%**
Friedewald [19]	Retrospective: before vs after (281,187 vs 173,663) introduction of 3D as adjunct to 2D mammography screening; single-reading (readers from 13 radiology services, USA)	4.2	5.4	↑ **1.2/1000** P <0.001	2D: 10.7% 2D/3D: 9.1% P < 0.001	↓ **1.6%**
Greenberg [20]	Retrospective: women opting for 3D vs not, multiple services concurrent (23,149 vs 54,684; ~30% opted for tomo); single-reading (USA)	4.9	6.3	↑ **1.3/1000** (adjusted) P =0.035	2D: 16.2% 2D/3D: 13.6% P < 0.001	↓ **2.6%**
McCarthy [21]	Retrospective: before vs after introduction of 3D as adjunct to 2D (15,571 vs 10,728); single-reading (USA)	4.6	5.5	↑ **0.9/1000** P =0.32	2D: 10.4% 2D/3D: 8.8% P < 0.001	↓ **1.6%**
Durand [22]	Retrospective: received 2D/3D vs received 2D (8,591 vs 9,364); single-reading (USA)	5.7	5.9	↑ **0.2/1000** P = 0.88	2D: 12.3% 2D/3D: 7.8% P < 0.001	↓ **4.5%**

Sharpe [23]	Retrospective: received 2D/3D vs received 2D (5,703 vs 80,149); single-reading (USA)	3.5	5.4	↑ **1.9/1000** P=0.018	2D: 6.10% 2D/3D: 7.51% P < 0.001	↓ **1.4%**
Lourenco [24]	Retrospective: before vs after (12,577 vs 12,921) introduction of 3D as adjunct to 2D mammography screening; single-reading (USA)	5.4	4.6	↓ **0.8/1000** P = 0.44	2D: 9.3% 2D/3D:6.4% P < 0.001	↓ **2.9%**
Conant [25]	Retrospective (PROSPR multicentre consortium): received 2D/3D vs received 2D (55,998 vs 142,883)	4.4	5.9	↑ **1.5/1000** P>0.05	2D: 10.4% 2D/3D: 8.7% P < 0.001	↓ **1.7%**
Starikov [26]	Retrospective: received 2D/3D vs received 2D (2070 vs 12,157); single-reading (USA)	3.2	5.3	↑ **2.1/1000** P=0.13	2D: 17.5 2D/3D: 10.2 P < 0.001	↓ **7.3%**

Table 2 is a modified and updated version of data reported by Zackrisson & Houssami [3].

Key: ↑refers to increase; ↓ refers to decrease; 2D refers to digital mammography acquisition of 2-view mammographic images, 3D refers to digital breast tomosynthesis acquisitions for 2-views; PROSPR= *P*opulation-based *r*esearch *o*ptimizing *s*creening through *p*ersonalized *r*egimens.