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Review

Rapid review: Estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts

Nehmat Houssami [a, b, *], Robin M. Turner [c]

[a] Sydney School of Public Health, Sydney Medical School, University of Sydney, Sydney, Australia
[b] Breast Centre, Royal Hospital for Women, New South Wales, Australia
[c] School of Public Health and Community Medicine, University of New South Wales, Australia

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ABSTRACT

High breast tissue density increases breast cancer (BC) risk, and the risk of an interval BC in mammography screening. Density-tailored screening has mostly used adjunct imaging to screen women with dense breasts, however, the emergence of tomosynthesis (3D-mammography) provides an opportunity to steer density-tailored screening in new directions potentially obviating the need for adjunct imaging. A rapid review (a streamlined evidence synthesis) was performed to summarise data on tomosynthesis screening in women with heterogeneously dense or extremely dense breasts, with the aim of estimating incremental (additional) BC detection attributed to tomosynthesis in comparison with standard 2D-mammography. Meta-analysed data from prospective trials comparing these mammography modalities in the same women (N = 10,188) in predominantly biennial screening showed significant incremental BC detection of 3.9/1000 screens attributable to tomosynthesis ($P < 0.001$). Studies comparing different groups of women screened with tomosynthesis (N = 103,230) *or* with 2D-mammography (N = 177,814) yielded a pooled difference in BC detection of 1.4/1000 screens representing significantly higher BC detection in tomosynthesis-screened women ($P < 0.001$), and a pooled difference for recall of −23.3/1000 screens representing significantly lower recall in tomosynthesis-screened groups ($P < 0.001$), than for 2D-mammography. These estimates can inform planning of future trials of density-tailored screening and may guide discussion of screening women with dense breasts.

1. Introduction

High mammographic breast tissue density is associated with increased breast cancer (BC) risk [1–3], and is also associated with an increased risk of an interval BC in women who have mammography screening [4,5]. Although density-tailored screening using adjunct imaging has long been of interest and evaluated in many studies [6] the introduction of breast density legislation in some USA states [7,8]) means that density-tailored screening requires investigation for population screening in the overall context of risk-based screening [9]. There are however drawbacks from application of adjunct imaging to screen women with dense breasts, including but not limited to increased costs, the inconvenience to the individual of having a further layer of testing and inherent risk of further false-positives, and uncertainty regarding the extent that adjunct imaging could enhance screening benefit. Within this evolving scenario of BC screening, the relatively recent emergence of digital breast tomosynthesis (quasi-3D-mammography) provides an opportunity to improve BC screen-detection in women with dense breasts using a new mammography platform, potentially obviating the need for adjunct imaging [10–12].

A rapid review (a streamlined evidence synthesis) was performed to assess the evidence on tomosynthesis screening in women with dense breasts, with the aim of estimating additional or incremental BC detection attributable to tomosynthesis, to provide timely knowledge informing density-tailored screening research and practice.

* Corresponding author. Sydney School of Public Health (A27), Sydney Medical School, University of Sydney, Sydney 2006, Australia.
E-mail address: nehmat.houssami@sydney.edu.au (N. Houssami).

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2. Methods

2.1. Literature search and eligible studies

A rapid review, a streamlined approach to systematically identify and summarise emerging evidence [13], was conducted. An updated literature search of a previously described systematic review [10] was performed: the search consisted of a Medline search (exploded "breast neoplasm", combined with "tomosyn$" or "3D-mammography"in title) at July 2016, and contact with content experts. Literature searching, study identification, and data extraction from eligible studies were performed by one investigator.

Studies eligible for inclusion in this rapid review were those that (a) evaluated tomosynthesis (also referred to as 3D-mammography) for population screening in comparison with standard digital mammography, and (b) provided data on BC detection (detection data or rates and/or incremental BC detection from tomosynthesis) or allowed its calculation, in women with dense breasts. BC detection data were extracted (number of detected BCs for each modality, or additional cancers detected by one modality) or were calculated from reported proportions, and the number of screens in dense breasts was extracted or calculated. Where recall data were also provided for dense breasts for tomosynthesis and for mammography screening, these were extracted. Information on study design, subjects, and screening setting was also obtained. The primary outcome to be estimated in pooled analysis was additional or incremental BC detection attributed to tomosynthesis screening in comparison with standard 2D-mammography screening in women with heterogeneously dense or extremely dense breasts [14] jointly referred to as dense breasts.

2.2. Statistical analyses

For paired data, pooled estimate (and 95%CI) of the incremental effect on detection was calculated using a random effects model for proportions using the Wilson (score) method. For data from independent groups of participants, the pooled difference in proportions (and 95%CI) was calculated using random effects modelling estimated with the DerSimonian and Laird method. Study-specific and pooled estimates of effect were calculated as the effect attributed to tomosynthesis screening, that is the proportion or rate for detection at standard mammography was subtracted from that for tomosynthesis: hence a (+) estimate indicates an increase from tomosynthesis whereas a (−) estimate indicates a reduction. Forest plots were used to display results for the effect on BC detection. All analyses were conducted in Stata SE 14.1 [15].

3. Results

Eight eligible studies [16–23], from 263 screened abstracts, provided data on tomosynthesis for population screening of women with dense breasts, in comparison with 2D-mammography. Additional studies reporting on tomosynthesis for population screening either did not report data in dense breasts or did not report sufficient data to allow calculation of additional BC detection in dense breasts [24–29] hence were not eligible for inclusion, or were earlier or simultaneous reports of the identified eligible studies [30,31]. There were no randomised controlled trials. There were two types of eligible studies with broadly similar study and screening characteristics for each study group, as follows:

3.1. Prospective trials reporting paired screen-detection measures in the same participants

Four studies [16–19], described in Table 1 and also shown in Fig. 1, provided data allowing estimation of *incremental* BC detection for a total of 10,188 women with heterogeneously dense or extremely dense breasts. These studies shared similar characteristics including: prospective design; embedded in European screening programs or imaging centres that operate within the construct of organised population screening services; used double-reading as the standard of care in programmatic screening (one trial used single-reading [19]); and implemented biennial screening (one study included biennial or annual screening [19]). A key characteristic of this group of studies is that tomosynthesis screening was compared with that of standard 2D-mammography

Table 1
Studies comparing tomosynthesis (T) and standard mammography (M) for population breast screening and reporting cancer detection data in women with heterogeneously dense or extremely dense breasts.

Study (author, year published)	Recruitment timeframe	Study population median (or mean) age; range, years	Number of screens with heterogeneously dense or extremely dense breasts	Effect on breast cancer detection in dense breasts attributed to tomosynthesis, per 1000 screens	Effect on recall (or false recall where specified) in dense breasts, per 1000 screens
Prospective trials comparing tomosynthesis (2D+3D[a]) screening with 2D-mammography alone in the same screening participants at the same screening episode: Estimates of effect represent incremental rates in the same women					
Ciatto 2013 [16]	2011–2012	58; 48-71	1215	+2.5/1000	−26.0/1000 (false recall conditional analysis)
Lång 2016[a] [17]	2010–2012	56; 40-76	3150	+3.8/1000	NA[b]
Bernardi 2016 [18]	2013–2015	58; 49-71	2592	+5.4/1000	+10.5/1000 (false recall)
Tagliafico 2016 [19]	2012–2015	51; 38-88	3231	+4.0/1000	NA[b]
Retrospective studies comparing tomosynthesis (2D+3D) screening with 2D-mammography alone in different groups of screening participants: Estimates of effect represent differences in rates between different groups of women					
Rose 2013 [20]	M: 2010 T: 2011–2012	M (mean) 53.8 T (mean) 54.5	M: 7009 T: 4006	+1.4/1000	−36.8/1000
McCarthy 2014 [21]	M: 2010–2011 T: 2011–2013	M (mean) 56.9 T (mean) 56.7	M: 3489 T: 5056	+1.8/1000	−19.4/1000
Conant 2016 [22]	2011–2014	Range: 40–74	M: 35320 [44303][c] T: 9265 [21133][c]	+2.1/1000	−22.1/1000
Rafferty 2016 [23]	2011–2012	Not reported	M: 131996 T: 84243	+1.4/1000	−18.4/1000

[a] The Malmö breast tomosynthesis screening trial, from Lång et al. [17], was the only study reporting screen-detection for stand-alone tomosynthesis (3D-mammography) in comparison with 2D-mammography.
[b] NA = not available, either could not be extracted for subgroups with dense breasts [17], or data for recall at 2D-mammography not distinctly reported [19].
[c] In the Conant study [22], the number of screens with dense breasts differed for cancer detection data (restricted to screens with 1 year follow-up) and for recall data with the latter shown in square brackets.

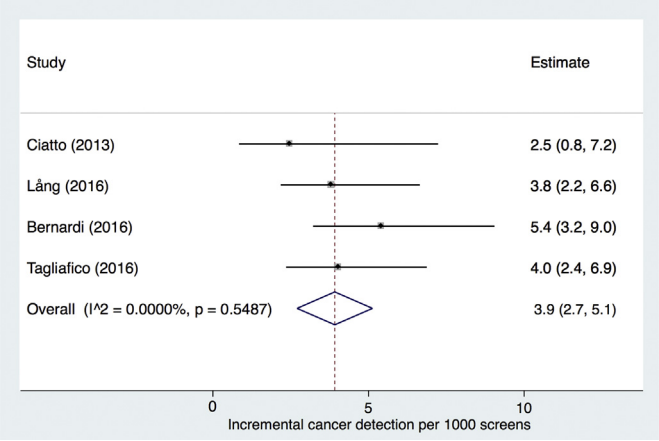

Fig. 1. Study-specific and pooled *incremental* cancer detection attributed to tomosynthesis screening, in comparison with mammography screening, in prospective population screening studies providing data on women with heterogeneously dense or extremely dense breasts.

in the same screening participants at the same screening episode, allowing reliable estimation of the incremental (additional) BC detection that is attributable to tomosynthesis since each woman formed her own 'control'. In three of these studies, tomosynthesis was integrated with 2D-mammography (hence 2D with 3D) and was compared with 2D-mammography alone [16,18,19], whereas the Malmö tomosynthesis trial compared stand-alone 3D with 2D [17]. The pooled *incremental* BC detection from tomosynthesis, shown in Fig. 1, was 3.9 cancers (95%CI 2.7 to 5.1) per1000 screening examinations representing significant additional BC detection above that from 2D-mammography alone ($P < 0.001$). Because only two of these studies reported comparative recall data in dense breasts [16,18] with inconsistent direction of estimates of effect (Table 1) pooled analysis of recall rates was not performed.

3.2. *Retrospective studies reporting screen-detection measures in different groups of women*

Four studies [20–23], described in Table 1 and also shown in Fig. 2, reported data allowing estimation of the *difference* in BC detection rates between different groups of women who were

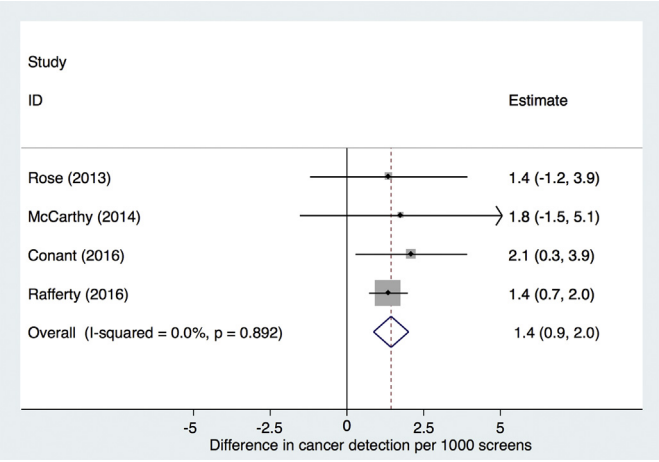

Fig. 2. Study-specific and pooled difference in cancer detection for studies comparing tomosynthesis screening with mammography screening in different groups of participants, and providing data on women with heterogeneously dense or extremely dense breasts (estimates reflect increased detection rates for the tomosynthesis-screened groups).

screened with tomosynthesis (2D with 3D-mammography) *or* were screened with standard mammography alone, at different timeframes and/or radiology services. In addition to having a retrospective design, these studies also shared characteristics inherent in BC screening practice in the USA, namely use of annual screening and single-reading, and were mostly in the context of community-based radiology services. Three studies [20–22] may have contributed data into the larger study from Rafferty [23]. Meta-analysis of BC detection in dense breasts (103,230 tomosynthesis screens versus 177,814 mammography screens) showed a pooled difference of 1.4 cancers/1000 screens (95%CI 0.9 to 2.0), shown in Fig. 2, representing significantly higher BC detection ($P < 0.001$) in the tomosynthesis-screened women than those screened with 2D-mammography alone. Meta-analysis of recall data in dense breasts from these studies (115,098 tomosynthesis versus 186,797 mammography screens) showed a pooled difference of −23.3 recalls/1000 screens (95%CI −29.9 to −16.8) representing a significant *reduction* in recall rates for screening with tomosynthesis ($P < 0.001$) in comparison with 2D-mammography alone screens.

4. Discussion

Timely synthesis of currently available evidence, reported in this rapid review, shows that the integration of tomosynthesis in mammography screening of women with dense breasts improves BC detection: this finding of enhanced detection in dense breasts attributed to tomosynthesis screening was evident across two types of studies that had different research methodologies and screening contexts. Meta-analysed estimate for *incremental* BC detection of 3.9/1000 screens (Fig. 1) attributed to tomosynthesis screening reflects data from prospective trials comparing mammography modalities in the same women in predominantly biennial screening. Studies retrospectively comparing different groups of women screened with the different modalities in annual screening practice, showed a pooled difference in BC detection of 1.4/1000 screens (Fig. 2) for tomosynthesis-screened groups, coupled with a pooled difference of −23.3 recalls per 1000 screens (reduction in recall rate in tomosynthesis-screened women). Although the above-reported estimates of additional BC detection attributed to tomosynthesis screening differ in magnitude, both are statistically significant (in comparison with standard mammography screening) and are in the same direction of effect; the difference between the estimates is at least partly explained by screening frequency whereby a higher potential for additional BC detection from tomosynthesis is evident in biennial screening practice. These estimates can be used to inform planning of future studies of density-tailored screening and may also be used to guide decisions and recommendations on screening women with dense breasts.

Various breast imaging modalities have been used for adjunctive screening of women with mammography-dense breasts; these were systematically and thoroughly reviewed by Melnikow et al. [6] who quantified the detection capability of ultrasound, MRI, and highlighted the limited number of studies reporting tomosynthesis data in dense breasts at that time. Although adjunct screening of women with dense breasts using ultrasound or MRI yields (or may yield) higher BC detection [6] than the estimates reported in this rapid review for tomosynthesis, it is important to note that studies of adjunct imaging for dense breasts have generally included or selected subjects with additional risk factors [6,32], whereas the studies of tomosynthesis summarised in this review were mostly population screening studies. Furthermore, the issue here is not whether ultrasound or MRI could detect more BC than tomosynthesis in dense breasts (these modalities would likely be more sensitive than tomosynthesis as indicated by one interim report

[19]) – the issue of relevance is that tomosynthesis may offer a more feasible and more acceptable approach for density-tailored screening at the population level and in particular for organised breast screening programs such as those implemented in Europe, UK, and Australia.

The purpose of this rapid review was to quantify the effect of tomosynthesis, in terms of additional BC detection, above that which may be expected from standard mammography screening, in women with dense breasts. This work has not examined all the evidence on tomosynthesis screening (for which several reviews have been published [10,12,33]) because it has focused on evidence in women with heterogeneously dense or extremely dense breasts on mammography for the reasons outlined in the introduction, and to provide a timely and concise evidence synthesis of rapidly emerging data for dense breasts.

It is acknowledged that enhanced BC detection from tomosynthesis, in comparison with mammography alone, or indeed from adjunctive screening in dense breasts, has not been investigated in studies assessing screening benefit in terms of mortality reduction; hence increased BC detection can only be taken as indicative of the potential to improve screening outcomes and/or to reduce the risk of interval BC. Although evidence of improved screening benefit is currently lacking for density-tailored screening, what makes the issue of tomosynthesis screening for dense breasts immediately relevant in breast imaging and screening practice is the implementation of density-specific legislation in some settings (with potentially broad ramifications), plus the reality of using tomosynthesis alone for primary screening. Because tomosynthesis acquisitions can now also be used to reconstruct high-definition 2D-images, yielding similar BC detection as that from tomosynthesis plus 2D-mammography acquisitions [18,34], it seems reasonable that the next phase of tomosynthesis research and practice will increasingly adopt tomosynthesis-only acquisitions (with reconstructed 2D images). Hence, a new direction in research is warranted to evaluate tomosynthesis alone as the *primary* screening modality for women known to have mammography-dense breasts, potentially obviating the need to add other imaging tests to screen dense breasts. The estimates we have provided in this review can be used to plan estimates of effect for future studies and trials of tomosynthesis for density-tailored BC screening.

Conflict of interest statement

No conflicts of interest to disclose.

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