Introduction

Breast cancer is the most frequently diagnosed cancer in women, accounting for 29% of new cancer cases per year, and is the second cause of death from cancer in women in the USA, accounting for 14% of cancer related deaths (American Cancer Society, 2016). It has been estimated that in 2016 invasive breast cancer will be diagnosed in about 246,660 women, with an additional 61,000 cases of in situ breast cancer. From 2003 to 2012, while incidence trends reveal stable rates, mortality rates decreased by 1.9% per year. Overall, breast cancer death rates declined by 36% from 1989 to 2012 (American Cancer Society, 2016) with substantial credit given to screening (Lee et al., 2013).

Although traditional breast screening with mammography is recognized as the most effective method for detecting early-stage breast cancer, it has a low positive predictive value. Taif et al. found an abnormal mammogram in 6.8% of the population screened but breast cancer was present in only 1% (Taif et al., 2014). This implies that the considerable percentage of recalls for additional imaging or biopsy does not ultimately result in cancer detection, leading to unnecessary burden on women and the healthcare system (Hubbard et al., 2013).

Digital breast tomosynthesis, through the generation of a three-dimensional image of breast during the standard mammographic compression, can reduce interference from breast tissue overlap, removing the conventional digital mammography limitations due to superimposed breast tissue. For this reason, it is a promising mean to differentiate between malignant and non-malignant features and, consequently, decrease false-positive recalls, associated healthcare costs and women anxiety (Gilbert et al., 2015).

In this article, the advantages of DBT as a screening tool in terms of recall rates, cancer detection rates and cost-effectiveness are reviewed.

Materials and Methods

A comprehensive systematic review was conducted independently by all three authors using search terms such as tomosynthesis, breast imaging, 3D-mammography. PubMed, Medline, Google Scholar, Ovid, and Cochrane data search engines were utilized from inception until April 2016. The authors then manually scrutinized reference lists in the recovered articles and relevant abstracts from scientific meetings to identify any further articles.

Studies were considered for review if they evaluated the impact of digital breast tomosynthesis, associated or not with conventional mammography, on recall rates, cancer detection rates and/or costs when compared with conventional mammography alone. This search yielded 18 manuscripts.
Results

Recall rate

The term "recall rate" refers to the percentage of women recommended for additional diagnostic procedures following an abnormal or inconclusive screening mammogram in the 6 months following the index screen. Recall is defined as the performance of a diagnostic mammogram or a breast ultrasound procedure, while other procedures that may follow imaging, such as biopsy or fine needle aspiration, are not required to meet the recall definition (Alcusky et al., 2014). There is a considerable literature regarding recall rate reduction with DBT combined or not with mammogram compared with digital mammography alone (Table 1). Only three studies assess the clinical performance and difference in recall rates

Table 1. Studies assessing the impact of tomosynthesis on recall rates

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Modality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciatto et al., 2013</td>
<td>2013</td>
<td>Prospective, population-based study</td>
<td>7,235</td>
<td>DBT+DM vs DM. Independent double reading.</td>
<td>Potential 17.2% reduction in recall rate using DBT.</td>
</tr>
<tr>
<td>Conant et al., 2016</td>
<td>2016</td>
<td>Retrospective</td>
<td>198,881</td>
<td>DBT+DM (n=55,998) vs DM (n=142,883)</td>
<td>CDR 8.1/1000 in DBT+DM vs 5.3/1000 in DM alone. Recall rate 8.7% in DBT+DM vs 10.4% in DM. CDR 5.9/1000 in DBT+DM vs 4.4/1000 in DM. PPV 1.6% in DBT+DM vs 4.1% in DM. No significant difference in FN screening exams (0.46/1000 DBT+DM vs 0.60/1000 DM).</td>
</tr>
<tr>
<td>Destounis et al., 2014</td>
<td>2014</td>
<td>Retrospective</td>
<td>1,048</td>
<td>DBT+DM (n=524) vs DM (n=524)</td>
<td>Recall rate 4.5% in DBT+DM vs 11.45% in DM. CDR 5.7/1000 in DBT+DM vs 3.8/1000 in DM. Recall rate 7.8% in DBT+DM vs 12.3% in DM. CDR 5.9/1000 in DBT+DM vs 5.7/1000 in DM. Recall rate 9.1% in DBT+DM vs 10.7% in DM alone. CDR 5.4/1000 in DBT+DM vs 4.2/1000 in DM alone. The difference in CDR is only true for invasive cancers, whereas for DCIS diagnosis both methods score 1.4/1000. Sensitivity (Cancer recalled/total cancer) 89% in DBT+DM arm, vs 87% in DM arm. The difference in sensitivity is higher for women aged 50-59 years old, for cancer size 11-20 mm, and for breast density exceeding 50%. Specificity (Not cancers not recalled/not cancers) 69% in DBT+DM vs 58% in DM alone.</td>
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<tr>
<td>Durand et al., 2014</td>
<td>2014</td>
<td>Retrospective</td>
<td>17,955</td>
<td>DBT+DM (n=8,591) vs DM (n=9,364)</td>
<td>PPV recall 16.2% in DBT+DM vs 6% in DM. CDR 5.9/1000 in DBT+DM vs 4.4/1000 in DM. PPV 1.6% in DBT+DM vs 4.1% in DM. No significant difference in FN screening exams (0.46/1000 DBT+DM vs 0.60/1000 DM).</td>
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<tr>
<td>Friedewald et al., 2014</td>
<td>2014</td>
<td>Retrospective study</td>
<td>454,850</td>
<td>DBT+DM (n=173,663) vs DM (n=281,187)</td>
<td>PPV recall 39.8% in DBT+DM vs 26.5% in DM. CDR 5.4/1000 in DBT+DM vs 4.2/1000 in DM alone. The difference is even more significant in dense breasts and in women &lt; 40. CDR 5.4/1000 in DBT+DM vs 4.2/1000 in DM alone.</td>
</tr>
<tr>
<td>Gilbert et al., 2015</td>
<td>2015</td>
<td>Prospective, population-based study</td>
<td>8,662</td>
<td>DBT+DM vs DM. Independent double reading.</td>
<td>Recall rate 13.6% in DBT vs 16.2% in DM. CDR 6.3/1000 in DBT vs 4.9/1000 in DM. PPV 4.6% in DBT vs 2.0% in DM (i.e. a positive DBT scan ins more likely to ultimately result in cancer diagnosis). Recall rate 8.4% in DBT+DM vs 12% in DM alone. This difference is even more significant in dense breasts and in women &lt; 40. CDR 5.4/1000 in DBT+DM vs 4.2/1000 in DM alone.</td>
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<tr>
<td>Greenberg et al., 2014</td>
<td>2014</td>
<td>Retrospective</td>
<td>77,833</td>
<td>DBT+DM (n=23,149) vs DM (n=54,684)</td>
<td>PPV recall 39.8% in DBT+DM vs 26.5% in DM. CDR 8.9/1000 in DBT vs 6.3/1000 in DM.</td>
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<tr>
<td>Haas et al., 2013</td>
<td>2013</td>
<td>Retrospective study</td>
<td>13,158</td>
<td>DBT+DM (n=6,100) vs DM alone (n=7,058)</td>
<td>PPV recall 39.8% in DBT+DM vs 26.5% in DM. CDR 8.9/1000 in DBT vs 6.3/1000 in DM.</td>
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<tr>
<td>Láng et al., 2015</td>
<td>2015</td>
<td>Prospective</td>
<td>7,500</td>
<td>DBT+DM vs DM. Independent double reading.</td>
<td>Overall recall rate 6.4% in DBT vs 9.3% in DM. Recall rate was higher in DBT than in DM for masses (26.8% vs 8.9%), distortions (5.3% vs 0.6%), calcifications (20.3% vs 13.4%), whereas it was lower for asymmetries (13.3% vs 32.2%) and focal asymmetries (18.2% vs 32.2%). No significant differences were found regarding biopsy PPV and CDR.</td>
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<tr>
<td>Lourenco et al., 2015</td>
<td>2015</td>
<td>Retrospective</td>
<td>25,948</td>
<td>DBT (n=12,921) vs 2D (n=12,577)</td>
<td>PPV 4.6% in DBT vs 2.0% in DM (i.e. a positive DBT scan ins more likely to ultimately result in cancer diagnosis). Recall rate 8.4% in DBT+DM vs 12% in DM alone. This difference is even more significant in dense breasts and in women &lt; 40. CDR 5.4/1000 in DBT+DM vs 4.2/1000 in DM alone.</td>
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<tr>
<td>McDonald et al., 2015</td>
<td>2015</td>
<td>Prospective study</td>
<td>26,299</td>
<td>DBT (n=15,571) vs DM (n=10,726)</td>
<td>Recall rate 16% in DBT, 20.5% in DM at baseline screening (the difference was higher in patients &lt;50); 7.8% in DBT vs 9.1% in DM for previously screened patients. CDR 5.9/1000 in DBT, vs 4.2/1000 (baseline screening); 5.4/1000 in DBT, vs 4.6/1000 (previously screened). Recall rate 5.5% in DBT+DM vs 8.7% in DM.</td>
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<tr>
<td>Rose et al., 2013</td>
<td>2013</td>
<td>Retrospective</td>
<td>23,355</td>
<td>DBT+DM (n=9,499) vs DM (n=13,856)</td>
<td>CDR 5.37/1000 in DBT+DM vs 4.04/1000 in DM. PPV recal 39.8% in DBT+DM vs 26.5% in DM. No significant difference in the stage, grade, size or nodal status of the diagnosed cancer according to the two methods.</td>
</tr>
<tr>
<td>Skaane et al., 2013</td>
<td>2013</td>
<td>Prospective</td>
<td>12,621</td>
<td>DBT+DM vs DM. Independent double reading, divided into 4 arms.</td>
<td>FP 53.1/1000 in DBT+DM vs 61.1/1000 in DM. CDR 8.0/1000 in DBT+DM vs 6.1/1000 in DM. PPV recall 16.2% in DBT+DM vs 6% in DM. Recall rate 25.5% in DBT+DM vs 38.4% in DM.</td>
</tr>
<tr>
<td>Sumkin et al., 2015</td>
<td>2015</td>
<td>Prospective</td>
<td>1,074</td>
<td>DBT+DM vs DM. Independent reading.</td>
<td>Overall recall rate 6.4% in DBT vs 7.2% in DM. CDR 5.37/1000 in DBT+DM vs 4.04/1000 in DM. PPV recal 39.8% in DBT+DM vs 26.5% in DM. No significant difference in the stage, grade, size or nodal status of the diagnosed cancer according to the two methods.</td>
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</table>

DBT, digital breast tomosynthesis; DM, digital mammography; CDR, cancer detection rate; DCIS, ductal carcinoma in situ; PPV, positive predictive value; FP, false positive.
of DBT alone versus digital mammography (Lourengo et al., 2015; McDonald et al., 2015; Lang et al., 2016). Lang et al. (Lang et al., 2016) reported a cancer detection rate of 8.9/1000 screens for DBT alone and of 6.3/1000 for digital mammography, although the recall rate was slightly higher in the DBT group (3.8%) compared to the DM group (2.6%). Similar conclusions but with different findings were drawn by Lourenco et al. (2015) who reported a non-significant superior cancer detection rate for DM (5.4/1000) compared to DBT (4.6/1000) but a significant difference of 31% in recall rates favouring DBT (6.4% vs 9.3%). The recall rate was lower with DM than with DBT for masses, distortions, and calcifications and lower with DBT than with DM for asymmetries and focal asymmetries. Another prospective study (McDonald et al., 2015) with similar patient size as Lourenco et al. found a 22% reduction in recall in the baseline screening group when using DBT (16.0% recall rates) compared to DM (20.5% recall rates), and a 14.3% reduction in the previously screened patients (DBT: 7.8%; DM: 9.1%). Cancer detection rate and PPV were increased too with DBT both in the baseline and in the previously screened groups leading to the conclusion that DBT alone could be more beneficial than DM alone especially for women undergoing baseline screening.

Although the three previously mentioned studies compare DBT alone versus DM alone, allowing a better discrimination and identification of DBT advantages, the majority of studies on the topic take into account DBT combined with DM versus DM only. In general, articles report that integrated tomosynthesis and digital mammography improves breast-cancer detection and has the potential to reduce false positive recalls (Table 1). Four of these studies were prospective, population-based studies, and all came up with similar findings. The Italian STORM trial (Ciatto et al., 2013) found a 17.2% reduction in recall rate using combined DBT+2DM with respect to traditional screening, with a higher cancer detection rate (8.1/1000 vs 5.3/1000); the British TOMMY trial (Gilbert et al., 2015), demonstrated similar sensitivity in the two groups (89% in DBT+DM, vs 87% in DM alone). Interestingly, the difference in sensitivity was shown to be greater in dense breasts women aged 50-59, and cancers measuring 11-20 mm in greatest diameter. The study also found a significant difference in specificity (69% DBT+DM vs 58% DM). The Oslo trial (Skaane et al., 2013), reported reduction in false positives (53.1/1000 in DBT+DM, vs 61.1/1000 in DM), increase in cancer detection rate (8.0/1000 in DBT+DM, vs 6.1/1000 in DM), and increase in positive predictive value of recall, i.e., the likelihood of additional diagnostic procedures following a screening recall to eventually find a cancer (16.2% in DBT+DM, vs 6% in DM). Furthermore, it demonstrated a significant increase in detection of invasive, node-negative cancers, with respect to traditional screening. One prospective study (Sumkin et al., 2015), also reported reduction in recall rate with the combined screening approach, although with higher overall rates compared to the other studies (25.5% in DBT+DM, vs 38.4% in DM.). Conant et al. 2016 showed reduction in recall rate from 10.4% to 8.7% by adding DBT, with a higher cancer detection rate (5.9/1999 vs 4.4/1000 in 2DM alone).

Table 2. Studies Assessing the Cost-Effectiveness of Tomosynthesis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Modality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonafe de et al., 2015</td>
<td>2015</td>
<td>Economic model</td>
<td>1,000,000 (hypothetical)</td>
<td>DBT+DM vs DM, with evaluation of screening costs, follow-up services rates and costs, post-diagnosis cancer costs.</td>
<td>$28.53 savings per woman screened with DBT + DM. Overall cost savings $550 million per year.</td>
</tr>
<tr>
<td>Kalra et al., 2012</td>
<td>2012</td>
<td>Prospective</td>
<td>5,780</td>
<td>DBT+DM (n=1,602) vs DM (n=4,178)</td>
<td>Direct cost savings $10,185 per 1,000 women screened with DBT. Relative cost savings of 17.1% with tomosynthesis screening. Larger cost savings were seen in patients &lt;40 (50.9%) and in patients with dense breasts (46.6%). Older patients demonstrated increased diagnostic workup costs in the tomosynthesis group.</td>
</tr>
<tr>
<td>Kalra et al., 2013</td>
<td>2013</td>
<td>Prospective</td>
<td>13,174</td>
<td>DBT+DM (n=6,116) vs DM (n=7,058)</td>
<td>Incremental cost by adding DBT adjusted per quality life-year gained is $53.893. Combined screening remained cost-effective (less than 100,000 per quality-adjusted life year gained) over a wide range of incremental improvement in test performance (taken from the Oslo trial).</td>
</tr>
<tr>
<td>Lee et al., 2015</td>
<td>2015</td>
<td>Economic model</td>
<td>-</td>
<td>Biennial DBT+DM vs DM screening program, taking into account women with breast density score ACR 3-4</td>
<td></td>
</tr>
</tbody>
</table>

DBT, digital breast tomosynthesis; DM, digital mammography; ACR, American College of Radiology
and a higher PPV (6.4% vs 4.1%). The difference in FN screening exams was instead not significant (0.46/1000 vs 0.60/1000). Destounis et al. (2014) demonstrated a significant decrease in recall rate (4.5% vs 11.45%) and increased Cancer Detection Rate (CDR) (5.7/1000 vs 3.8/1000); Durand et al. (2015) also reported similar data (recall rate: 7.8% vs 12.3%; CDR 5.9/1000 vs 5.7/1000), as well as Friedewald et al. (Friedewald et al., 2014) (recall rate 9.1% vs 10.7%, CDR 5.4/1000 vs 4.2/1000).

The same study also reported a significant increase in invasive cancer detection but not for ductal carcinoma in situ. Greenberg et al. 2014 demonstrated reduction in recall rate (13.6% vs 16.2%), increase in CDR (6.3/1000 vs 4.9/1000), and increase in PPV (4.6% vs 2.0%). Rose et al. (2013) showed similar results (recall rate 5.5% vs 8.7%, CDR 5.37/1000 vs 4.04/1000, PPV of recall 39.8% vs 26.5%), with non-significant differences in stage, grade or nodal studies in the cancers diagnosed according to the two methodologies. Finally, Haas et al. (2013) demonstrated a reduction in recall rate (8.4% vs 12%), getting even stronger in patients younger than 40 and in dense breasts.

Cost reduction

Literature treating the topic of cost-effectiveness, budget impact and comparative costs of DBT is limited (Table 2). An economic model estimating the financial impact of DBT within an hypothetical US managed care plan with one million members compared screening with full field digital mammography versus mammography plus tomosynthesis (Bonafede et al., 2015). In this study, tomosynthesis has been proven to be both economically and clinically favorable with an overall benefit of $78.53 per woman screened. Using an hypothetical $50 incremental cost of the DBT examination, the adjusted savings per woman screened is $28.53. Since in the US around half of the 39 million mammograms performed each year is for screening, the use of DBT could allow to save more than $550 million annually. Different savings value was found by Kalra et al. (Kalra et al., 2012), who estimated a direct cost savings of $10.19 per woman screened when adding DBT to digital mammography compared to digital mammography alone. In this 2012 conference abstract cost advantages of DBT where determined based on direct radiology costs resulting from differences in recall rate. Incremental cost of the DBT examination, non-radiologic diagnostic tools (e.g. open biopsy), cost savings due to earlier cancer detection were not accounted in this research, making it subjected to some limitations when considering the overall cost-effectiveness of DBT.

Similar results were confirmed by a following conference paper (Kalra et al., 2013), showing a relative cost savings of 17.1% when adding DBT resulting from reduction in unnecessary diagnostic workups. Larger cost savings were seen in younger patients (50.9%) and dense breast women (46.6%). Lee at al. (Lee et al., 2015) focused their cost-analysis specifically on women with dense breast between the ages of 50-74. They concluded that biennial combined DBT added to digital mammography is likely to be cost-effective when appropriately priced (up to $226 for DBT plus digital mammography versus $139 for digital mammography alone). Incremental cost per quality-adjusted life year gained by adding DBT to conventional mammography was estimated to be $53,893.

Discussion

Digital breast tomosynthesis as breast cancer screening modality addresses the primary limitations of conventional mammography by increasing conspicuity of invasive cancers while concomitantly reducing false-positive results. This has a direct effect on the number of recalls due to inconsistent or uncertain screening tests, implying limitation of patient anxiety and a significant overall cost reduction. Intuitively, recall rate reduction after breast cancer screening could have great benefits, including decrease in patient anxiety and in health care system financial burden.

It has been reported that addition of tomosynthesis to digital mammography significantly reduced false positives and consequently recall rates. A target recall rate of approximately 10.0 % for first mammograms and 6.7% for subsequent mammograms is usually recommended, because these rates keep the estimated number of additional work-ups per additional cancer detected or, in other words, the estimated number of additional women needed to be recalled at a given rate to detect one additional cancer, lower than 100 (Schell et al., 2007).

Although a single mammogram is less expensive than a combined mammogram plus DBT screening examination, the cost of diagnostic evaluation for abnormal mammograms is significant. It has been estimated that the annual cost to Medicare for additional diagnostic work-up after suspicion of breast cancer was approximately $679 million in 2009, while $250 million were spent due to false positive mammograms (Lee et al., 2009).

The cost of recalls for follow-up is the core element when analyzing the added value of DBT, due to the abovementioned advantages of tomosynthesis in reducing overdianoses and working up due to false positive screens. In 2015, the national breast-care costs in the year following false positive screening mammograms in the US have been estimated to be around $4 billion (Ong et al., 2015), much more than the data from 2009.

In conclusion, adding DBT to digital mammogram substantially reduces unnecessary diagnostic services, especially in younger and dense-breast women and allows for earlier, less costly treatment strategies. Overall, cost-effectiveness of DBT is most sensitive to the additional cost of tomosynthesis.

One additional, yet debated, point in favor of DBT screening is the detection of invasive breast cancers at earlier stages compared to traditional mammogram, with the direct consequence of cheaper therapeutic approaches (Mittmann et al., 2011; Skane et al., 2013). On the contrary, Rose et al. (2013) showed no difference in distribution of cancers’ stages diagnosed according to the two methods.

Further studies are needed to assess the effects of better detection and characterization of breast cancer allowed by
DBT on clinical outcomes.

Since DBT was found superior in terms of detection rate and equal in terms of positive predictive value Lang et al. suggestion is that DBT might be feasible as a stand-alone screening modality. The data from the literature (Lang et al., 2016; Lourenco et al., 2015) are promising, in that they showed DBT to be superior to DM alone in diagnostic accuracy. However, data from the McDonald study (2015) do not seem that encouraging, especially in a baseline screening setting, since the recall rate from DBT alone lie far beyond the ideal 10.0% threshold.

Intuitively, the advantages of performing DBT alone rely mainly on the lower costs and decreased reading time. While no literature is present to quantify the incremental cost of mammogram added to tomosynthesis, it has been proven that the combined screening modality with DBT and digital mammography significantly prolongs image acquisition and screen-reading times when compared with digital mammography alone and, intuitively, with DBT alone (Bernardi et al., 2012).

Since the literature concerning this emerging topic is still quite limited and the results vary among different studies, it is to date not possible to give an answer to this question, but further studies are needed in order to better ascertain whether a screening with tomosynthesis alone would be a feasible choice for the future.

In conclusion, Digital breast tomosynthesis addresses the primary limitations of conventional screening mammography by increasing conspicuity of invasive cancers while concomitantly reducing false-positive results. This results in a significant reduction in recall rates, preventing unnecessary burden on women and the healthcare system. Overall, adding DBT to digital mammogram substantially reduces unnecessary diagnostic services, especially in younger and dense-breast women and allows for earlier, less costly treatment strategies.

Further research is needed to evaluate the potential impact of DBT on longer-term outcomes, such as interval cancer rates and mortality, to better understand the broader clinical and economic implications of adoption of DBT. Moreover, lack of randomized trial design of the present studies limits the full generalization of the findings.

References


