**SUMMARY**

**Objective:** To evaluate the available data of Breast Tomosynthesis as a complementary tool of direct digital mammography. **Methods:** A systematic literature search of original and review articles through PubMed was performed. We reviewed the most important aspects of Tomosynthesis in breast imaging: **Results:** 36 Original articles, 13 Review articles and the FDA and American College of Radiology standards were included. Breast Tomosynthesis has showed a positive impact in breast cancer screening, improving the rate of cancer detection due to visualization of small lesions unseen in 2D (such as distortion of the architecture) and it has greater precision regarding tumor size. In addition, it improves the specificity of mammographic evaluation, decreasing the recall rate. **Limitations:** Interpretation time, cost and low sensitivity to calcifications. **Conclusions:** Breast Tomosynthesis is a new complementary tool of digital mammography which has showed a positive impact in breast cancer diagnosis in comparison to the conventional 2D mammography. Decreased recall rates could have significant impact in costs, early detection and a decrease in anxiety.

**RESUMEN**

**Objetivo:** Evaluar el estado del arte de la tomosíntesis como herramienta complementaria de la mamografía digital directa. **Métodología:** Se realizó una búsqueda sistemática de la literatura de artículos originales y de revisión a través de PubMed. Se revisaron los aspectos más importantes en cuanto a utilidad y limitaciones de la tomosíntesis en las imágenes de mama. **Resultados:** Se incluyeron 36 artículos originales y 33 de revisión, así como los estándares internacionales de la FDA y del American College of Radiology. La tomosíntesis de mama ha demostrado un impacto positivo en el tamizaje de cáncer de seno, al mejorar la tasa de detección de cáncer, permitir la visualización de pequeñas lesiones no vistas en 2D (como la distorsión de la arquitectura) y presentar mayor precisión en el tamaño tumoral. Adicionalmente, mejora la especificidad de la evaluación mamográfica disminuyendo el llamado. El tiempo de lectura, la sensibilidad para detectar microcalcificaciones y el costo del equipo son sus limitaciones. **Conclusiones:** La tomosíntesis es una nueva herramienta complementaria de la mamografía digital y ha generado un impacto positivo en el diagnóstico de cáncer de mama en comparación con la mamografía convencional 2D. La disminución del llamado tendría un valor significativo en costos, detección temprana y disminución en la ansiedad.

**Introduction**

The incidence of breast cancer on a global scale has increased in recent years, with particularly sharp increases in western and northern Europe (1). Since 2008, an estimated 20% increase in global incidence of the disease has been reported, whereas mortality has decreased 14%. Breast cancer is the most frequent cause of death among women and the most frequently diagnosed cancer in 140 out of 184 countries. A lack of early detection and access to proper treatment is the cause of greater breast cancer mortality in developing countries (2).
In Colombia, according to the DANE (Spanish acronym for the National Administrative Department of Statistics), breast cancer mortality has constantly increased for the last two decades, showing an increase of 3.5 per 100,000 population in 1981 to 6.8 per 100,000 in 2000 (3). According to data from the national healthcare monitoring program Así Vamos en Salud, Colombia, the country had a breast cancer mortality rate of 10.01 per 100,000 population, a slight decrease from 2010 (4).

Continuous improvement and implementation of new technologies has paved the way for the development of diagnostic imaging. Mammographic imaging, however, has experienced a slower rate of evolution compared to other imaging techniques, such as computerized tomography or magnetic resonance imaging.

Widespread use of analog mammography began during the sixties, remaining the only method for breast cancer screening. Mammography (MG) is the only effective screening method proven to lower mortality in up to 30% (5); it is an accessible, low-cost, low-radiation method. Nonetheless, cancer is not visualized in 10% to 30% of cases. MG is incredibly useful, but not enough for accurate detection. Ultrasound, along with mammography, can increase breast cancer detection rates particularly among high-risk women and in those with denser breasts (6, 7).

The bidimensional nature of a MG causes image superposition, which poses a great challenge for radiologists and is the leading cause for requesting complementary diagnostic tests (focal compression, magnification, ultrasound, or magnetic resonance) to reach a definitive diagnosis.

Image superposition can cause false positive results due to anatomical noise, which appears as consequence of projecting mammary volume on a bidimensional image, or may darken real lesions giving way to false negative results. This situation is even more critical in denser breasts; not only a diagnostic challenge, such breasts have a relative risk of 5 for contracting breast cancer (8) and a relative risk of 7 for interval breast cancer (9). High breast density decreases the sensitivity of mammography; overall sensitivity of the technique reaches 70%-90% yet, for denser breasts, sensitivity decreases to 30%-48% (10). In addition, according to a study by Cochrane, many women experience significant psychological distress for months as a consequence of a false positive result (11).

Aiming to overcome these limitations, mammographic technology has moved forward. In 2000, the FDA approved digital mammography and the use of both of its components: indirect converted digital mammography (CR, for Computed Radiography) and full-field direct digital mammography (DR, for Digital Radiography) (12).

Several investigations have assessed the efficiency of digital MG for breast cancer diagnosis. In 2005, Pizano et al. found that no significant statistical differences existed between analog and digital MG. However, results stemming from a specific patient sample of under 50 years of age, premenopausal, with high breast density (dense, heterogeneous breast tissue) provided statistically significant evidence that the sensitivity of digital MG was greater (78%) than that of analog MG (61.1%) and CR (5.34%). Cancer detection rates were also high using DR (0.71%), compared to analog (0.66%) and CR (0.55%) (14).

Tomosynthesis

Aiming to improve mammography specificity while maintain sensitivity, new technological developments have been approved for use. In 2011, the FDA approved the use of tomosynthesis for breast cancer screening (15), a technique developed with the purpose of improving specificity and sensitivity of mammography considering that normal breast structures may hide malignant tumors.

What Is Tomosynthesis?

Tomosynthesis is a complementary tool for full-field direct digital mammography, different from conventional MG in that its movable X-ray tube that performs multiple low-radiation doses to capture information, which is then reconstructed with algorithms similar to those in 1-mm slice tomography (16). The first tomosynthesis images of the breast were obtained by Niklason et al. in 1997 (17).

How Does It Work?

Conventional 2D MG consists of a fixed tube that generates X-rays, which are in turn absorbed by a photosensitive phosphorus screen that emits light onto a plate, creating an analog image, or onto a digital detector, creating a direct digital image. Tomosynthesis uses a X-ray tubes that moves continuously across an arc that varies in angle and number of cuts, such as 15°, 25° and 45°. The tube emits multiple low-radiation doses that are absorbed by the breast (18). The receiving surface is a digital detector, usually containing selenium. The detector may remain fixed or move along with the tube (19, 20).

This difference may lower image superposition of the breast tissue and lesions, providing a clearer visualization of clinical findings and enabling the radiologist to detect hidden or smaller lesions that would not appear on conventional MG imaging. Furthermore, tomosynthesis allows for a better evaluation of mammographic findings such as asymmetries and distortions that, using 2D MG, may require complementary information from other imaging methods. Tridimensional images are reconstructed with algorithms similar to those used in computerized tomography and are sent to the workstation, where the can be visualized one by one or as a slideshow (figure 1) (20).

Pain arising from breast compression associated with 2D MG is a major issue that may affect screening attendance (21). Compression exerted for a tomography is similar to a conventional MG; however, compression lowers the absorbed radiation (disperse radiation) (22).

There are no universal consensus or protocols for tomosynthesis, and these vary from one institution to another. Tomosynthesis may be single mediolateral oblique (MLO) only, cranio-caudal (CC) only, or both. Most physicians use tomosynthesis in two projections. Nonetheless, 3D images are always accompanied by digital CC and MLO mammography images (23). Recent research may favor using tomosynthesis in all screening patients (24).

The number of images acquired varies with breast thickness; common values range from 25 to 90 per projection on each breast.
Advantages

- Better definition of tumor size (25): in breast cancer diagnosis and management, lesion size is a major factor for prognosis and stage prediction (26). Studies have shown that digital MG with tomosynthesis is more accurate than digital MG alone for establishing tumor measurements, in both fatty and dense breasts. When compared with pathology examination results, size is significantly overestimated in digital MG of dense breasts (p < 0.001), in contrast with digital MG with tomosynthesis (p = 0.068) (27). Tomosynthesis is arguably superior to digital MG for the evaluation of overall lesion size, particularly of small lesions and lesions in dense breasts. Parenchymal density is directly correlated with the superiority of tomosynthesis (28).

- Better asymmetry assessment (figure 2): one of the main causes of recall for MG is asymmetries. Most asymmetries correspond to breast tissue superposition (29). Evaluating these findings using 2D MG would require additional projections such as focal compression and ultrasound. There is evidence that tomosynthesis’ usefulness is equivalent to that of several projections (17,25).

- Architectural distortion (figure 3): tomosynthesis has increased the detection of breast architecture distortions, not visualized under 2D techniques (25,27,30). This finding is one of the main causes of false negatives in MG. Implementing tomosynthesis allows for identification of this type of anomalies, which are not clearly detected using 2D MG.

- Evaluation of a dense breast and lesion contour (figures 4-7): tomosynthesis is 15% more sensitive than MG in dense breasts. In some patients, this may be explained by tomosynthesis’ capacity to outline lesion contours better. It also allows for making changes to BI-RADS categories without further projections (25, 28,30,31).

- Reduces recall rates: this in turn decreases patient distress and screening program costs (19). Tomosynthesis lowers recall rates in 10%-30% when contrasted with digital MG. Some studies report recall rate drops of up to 50% (24,32-34).

- Increases PPV (positive predictive value) for biopsy recommendations: digital MG with tomosynthesis has shown a greater specificity than focal compression (100%), compared with digital focal compression (94%), causing a reduction in non-malignant lesion biopsies (35).

- Increases PPV for recalls: increases from 4.7% (digital MG) to 10% in digital MG with tomosynthesis (36). In addition, false positive rates may decrease in up to 15%, compared to a mammography with no tomosynthesis (24). Some studies have demonstrated that tomosynthesis can cause a 9% decrease in false positives, compared to MG and additional projections (p < 0.01), directly affecting recall rates (37).

- Increases cancer detection rates (figures 8-9): tomosynthesis sensitivity is 90%, and its specificity 79% (38). Cancer detection rates using tomosynthesis is 8 cases per 1000 studies, while digital MG reaches 6.1 cases per 100 studies, a 31% increase (24). A study by Svahn showed that an average of 10.4 cancer diagnoses were possible using tomosynthesis, in contrast to digital MG. Results showed a greater diagnostic accuracy using tomosynthesis, suggesting that breast cancer detection can be improved with this technique (31,39).

- Detects invasive cancer better (figure 10): overdiagnosis is the detection of breast cancer that would never reach a clinically evident stage, and therefore would not be potentially lethal (40, 41). Recent studies have determines that approximately 30% of breast cancers are overdiagnosed in screening mammographies (42). Non-onvasive tumors may affect the diagnosis. Before the implementation of mammography, ductal carcinoma in situ (DCIS) corresponded to 2%-5% of breast cancers, which jumped to 20%-30% of detected cancers nowadays; this has generated a debate on its importance regarding pathology, progression potential, overdiagnosis and overtreatment, as there is no way to determine which cases will not progress to invasive lesions. This leads to patient stress, additional tests, and treatments that can even be unnecessary in certain cases (41).

- Tomosynthesis may detect up to 40% more cancers than simple MG. The Skaane study revealed that additional abnormal findings detected with tomosynthesis did not correspond to high-risk lesions nor to DCIS, but rather to invasive cancer, which implies a 26% increase in high-grade cancer detection rates (24). Findings suggest that tomosynthesis may decrease overdiagnosis. The Michell study included 204 cancer cases; 34.3% classified as malignant (BI-RADS 5) using analog MG, improving to 39.7% with digital MG and to 58.3% with digital MG with tomosynthesis (43).

Recall

A recall is the situation arising from a radiologist’s interpretation of a mammography as positive or abnormal, requiring complementary images for a definitive diagnosis and final recommendation.

A recall depends on three variables: the radiologist (experience, specific mammography training, affiliation to a medical academic center); the population (mammary density, age, hormonal replacement, risk factors); and the system (annual number of analyzed mammographies, single versus dual analysis, CAD) (44). The technology used to evaluate the breast has a major impact on the recall; on the other hand, the availability of prior studies for comparison reduces recalls in up to 51% (45).

![Figure 1. Physical principles. a) Mammography. b) Tomosynthesis. Created by the authors.](image-url)
Figure 2. a) Bilateral MLO projection. 2D image of a right prepectoral asymmetry; b) Right MLO magnification, upper quadrants. Image obtained from 3D video, evidencing that the asymmetry corresponds to superposed glandular tissue, with no underlying lesion. No additional projections were required.

Figure 3. Left retroareolar CC magnification. a) 2D image, dense breast, no significant finding; b) 3D image, clearly showing a distortion of mammary architecture not seen in 2D. Radial scar.

Figure 4. Left MLO magnification. a) 2D image of a node with darkened contours; b) 3D image clearly showing lesion contours, categorizing it as confined nodule.

Figure 5. Left MLO projection. a) 2D image, dense breast, prepectoral asymmetry; b) 3D image clearly three nodules, not seen in 2D; c) 3D image following the previous one, showing a fourth nodule not seen in 2D or the last 3D image.
Figure 6. Left MLO projection. a) 2D image, dense breast, no nodules observed; b) 3D image, showing a confined nodule in the lower quadrants not visible in 2D images.

Figure 7. Right MLO magnification. a) 2D image of a confined nodule; b) 3D image of the same nodule, showing microlobulation and placing it in a different BI-RAIDS category.

Figure 8. Right MLO magnification, upper quadrants. a) 2D image, dense breast, no significant findings; b) 3D image showing a clear distortion of mammary architecture, not seen in 2D image. Invasive ductal cancer.
One of the largest evaluations in scientific research has been the change in recall percentage following the implementation of tomosynthesis; a great number of such studies reported a significant reduction (10%-50%) while some studies found percentages up to 50% (19,32-34).

In Latin America, there is no information on the actual recall rates due to a lack of publications on the subject. It could be, however, well above the recommended maximum of 10% of the American College of Radiology (46) due to issues such as lack of access to healthcare, availability of past studies for comparison, and the lack of organization of population screen programs.

Tomosynthesis has been proven to have the same or greater accuracy as MG with projections involving compression, improving lesion characterization, administering an adequate radiation dose, providing benefits and comfort if no complementary 2D projections are required (35,47,48).

### Disadvantages

- **Cost of equipment**: implementation of tomosynthesis technology implies modifying a conventional digital mammography unit’s software, which results in greater cost compared to a conventional 2D MG, than using computerized tomography. Average cost of a digital MG with tomosynthesis is higher than a 2D MG (32,49,50).
- **Reimbursement policies**: given the recent approval of this technology in social security systems worldwide, including Colombia, there are no procedure codes that allow for coverage of the majority of the cost of equipment and professional labor.
- **Time investment**: breast radiologists went from analyzing four conventional MG projections to hundreds of images using MG with tomosynthesis. A conventional MG usually comprises two images (CC and MLO) on each breast and occasionally up to two additional ones (Eklund or focal compressions); on rarer occasions, six or more are required. MG with tomosynthesis significantly increases image analysis time: 35%-65% longer than conventional MG, a time directly correlated with the radiologist’s experience (49). An average, 5 cm breast requires approximately 50 images per projection. Analysis and report preparation times are long when using tomosynthesis alone or combined with 3D MG, due to the great number of generated images for each individual case (32,49).
- **Some authors point out that the time required to analyze and report tomosynthesis findings is offset by a lower recall rate (19,32). Currently, many radiologists have limited experience with tomosynthetic MG images, but analysis times decrease significantly as they gain experience (51,52).
• Microcalcification visualization: 2D is the reference standard for microcalcification detection (47). Up until today, microcalcifications are still best viewed using digital MG than tomosynthesis, with latter are reported to have lower sensitivity (72%) for detecting microcalcifications than the former (76%) (32); this may be due to movement artifacts resulting from a relatively longer procedure time in tomosynthesis (53). Nonetheless, some studies have reported greater sensitivity for individual and intraductal calcifications for MG with tomosynthesis (54). On the other hand, new FDA-approved developments, such as C-View synthesized imaging, may increase microcalcification visualization in 30%.

Radiation Dosage in Tomosynthesis
Radiation dosage is a major concern for the International Commission on Radiological Protection (ICRP) due to potential risks of ionizing radiation in unauthorized doses (55). For a breast with a thickness of around 5 cm and 50% glandular fraction, tomosynthesis imaging only requires 8% more radiation than digital MG or analog MG (1.3 mGy and 1.2 mGy, respectively) (56). Tomosynthesis is considered a safe procedure as radiation doses it requires are within parameters established by the Mammography Quality Standard Act (MQSA) (57).

The Future of Tomosynthesis
Synthetic imaging
The ability to reconstruct 2D images from data from digital MG with tomosynthesis could potentially eliminate 2D mammography examinations, which would lead to 30%-50% reductions in radiation dosages. However, this would imply that reconstructed 2D images are equivalent in quality to those from a direct 2D MG (26). A study suggested that synthesized 2D images from tomosynthesis data offer a lower sensitivity than a 2D MG with tomosynthesis (0.772 compared to 0.826, respectively) (56).

Generation synthetic 2D images from projections acquired through digital MG with tomosynthesis is presented as a possible solution to the need for 2D images while reducing absorbed radiation in at least 30%. Synthetic image construction algorithms have been optimized throughout the present year, reaching FDA approval following a clinical trial that evidenced the equal or superior capacity of synthetic imaging (C-View) to detect lesions in certain cases (12).

Other advances with evidence under development are contrast and subtraction tomosynthesis, which may generate new clinical alternatives. Preliminary results are very promising.

Conclusions
Tomosynthesis is a new digital mammography tool, with safe radiation doses within the allowed parameters, that is changing breast cancer diagnosis thanks to its better performance (improved sensitivity and specificity) in comparison with traditional 2D mammography. Recall reduction through the use of this technology shall have significant value in terms of cost reduction, timely attention, and reduction of patient distress.

References

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