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Deep Learning in Digital Breast Tomosynthesis: Current Status, Challenges, and Future Trends

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ABSTRACT

The high-resolution three-dimensional (3D) images generated with digital breast tomosynthesis (DBT) in the screening of breast cancer offer new possibilities for early disease diagnosis. Early detection is especially important as the incidence of breast cancer increases. However, DBT also presents challenges in terms of poorer results for dense breasts, increased false positive rates, slightly higher radiation doses, and increased reading times. Deep learning (DL) has been shown to effectively increase the processing efficiency and diagnostic accuracy of DBT images. This article reviews the application and outlook of DL in DBT-based breast cancer screening. First, the fundamentals and challenges of DBT technology are introduced. The applications of DL in DBT are then grouped into three categories: diagnostic classification of breast diseases, lesion segmentation and detection, and medical image generation. Additionally, the current public databases for mammography are summarized in detail. Finally, this paper analyzes the main challenges in the application of DL techniques in DBT, such as the lack of public datasets and model training issues, and proposes possible directions for future research, including large language models, multisource domain transfer, and data augmentation, to encourage innovative applications of DL in medical imaging.

Ruoyun Wang, Fanxuan Chen, Haoman Chen and Chenxing Lin contributed equally to the paper as first authors.

1 | Introduction

Breast cancer has emerged as the leading malignancy threatening women's health worldwide [1–3]. According to the International Agency for Research on Cancer, by 2022, female breast cancer (11.6%) was the second most common cancer in the world [4]. Among women, breast cancer is the most common cancer and is the cause of cancer death, with the highest incidence in 157 countries/areas and the highest mortality in 112 countries/areas worldwide [5]. The high mortality and morbidity rates of breast cancer place a heavy burden on global health [6, 7].

The complexity of breast cancer lies in the diversity and dynamics of its somatic mutations and abnormalities in gene and protein expression profiles [8, 9]. These changes involve numerous genetic elements, including mutations and aberrant amplification of oncogenes, which collectively contribute to the onset and progression of breast cancer [10–14]. Additionally, the interplay among multiple risk factors, such as demographic variables such as sex and age, hormones such as estrogen, genetic predisposition, and modifiable lifestyle factors, further increases the risk of developing breast cancer [15–18].

Therefore, early detection of breast cancer is crucial for reducing the disease burden, enhancing treatment effectiveness, and improving patient prognosis [19]. According to Cancer Research UK, the 5-year survival rate for patients with stage 1 breast cancer is nearly 100%, whereas for stage 4 disease, it drops sharply to 25% [20]. These data underscore the critical role of early diagnosis in improving the outcomes and overall survival of patients with breast cancer. Common imaging modalities for breast cancer include ultrasonography, X-ray, and breast tissue elastography. X-ray-based techniques include conventional mammography, digital mammography (DM), full-field digital mammography (FFDM), and digital breast tomosynthesis (DBT) [21–24]. While screening mammography is widely utilized globally, current mammography techniques have significant limitations, such as high false-positive and false-negative rates and variability in clinician proficiency, which can lead to potential delays and inaccuracies in diagnosis [25]. Additionally, while CT can provide detailed imaging, its clinical application in breast cancer screening and diagnosis remains limited.

Compared with conventional mammography, DM offers superior image quality, faster processing, and more convenient storage [26]. The subsequently developed FFDM, which projects raw three-dimensional (3D) breast tissue data and converts it into a two-dimensional (2D) image, has become widely used in clinical settings because of its utility in early detection and intervention [27]. Compared with the DM, the FFDM provides a wider field of view, results in fewer repeat examination errors, and achieves higher detection rates [28]. Randomized controlled studies have shown that FFDM-assisted screening can reduce the associated mortality rate with breast cancer by approximately 20% [29, 30]. However, FFDM images are 2D and have relatively low specificity [31, 32]. DBT offers superior detection rates, reduced interference from overlapping tissues, and improved accuracy in breast cancer screening with respect to FFDM (Figure 1) [26, 33].

DBT is an innovative advancement in breast imaging based on FFDM [34]. X-ray receivers acquire a series of low-dose X-ray images at various angles around the breast [35–37]. These multiple 2D images are then reconstructed via a computer algorithm to produce a 3D volumetric image of the breast, enabling a more detailed view of the breast tissue and facilitating the detection of abnormalities such as lumps and calcifications [38–40]. The complex reconstruction algorithm minimizes the effects of tissue overlap and structural noise, significantly improving the visualization of lesion edges and thereby the diagnosis of breast cancer; in turn, this improved visualization markedly enhances the sensitivity of DBT [10]. Additionally, DBT reduces diagnostic errors associated with the inherent complexity of fibroglandular breast tissue, thus lowering the false-negative rate [41, 42]. The advantages of DBT in terms of detection efficacy have led to it replacing DM as the imaging modality of choice over the past decade [30]. However, the large number of slices per patient who must be acquired to achieve 3D imaging relative to 2D mammography can influence the efficiency and accuracy of the physician responsible for diagnosing the patient [43].

The development of artificial intelligence (AI) has profoundly impacted the medical field; among the different forms of AI, deep learning (DL) technology has shown powerful automatic image feature extraction capabilities [44–46]. This technology can perform end-to-end feature learning and classification decision-making directly from raw data, eliminating the need for manual feature selection [47–49]. DL has been widely used to improve the early detection and treatment of various types of cancers, leading to substantial increases in patients' chances of survival [50–53]. Researchers have also applied DL to assist in the diagnosis of breast cancer, particularly in detecting and diagnosing lesions with DBT data, with the aim of improving the speed and accuracy of radiologists interpretations [30, 54-56]. In recent years, rapid advances in the field of DL have improved the field of breast imaging, resulting in better performance than traditional mammography-assisted detection methods [57]. However, the application of DL technology in the domain of DBT still faces numerous difficulties and challenges, indicating substantial room for improvement.

Numerous authors have reviewed the application of AI, particularly DL technology, in the field of DBT. For example, Geras et al. [58] introduced the limitations of classical computer-aided detection systems in DBT data, demonstrating how DL systems can enhance the accuracy of malignant tumor detection through neural networks. However, their summary was neither comprehensive nor adequate they propose effective solutions [58]. In 2023, Yoon et al. [59] conducted a systematic review and meta-analysis to comprehensively evaluate the effectiveness of AI technology in DM and DBT. Nevertheless, they did not include sufficient studies assessing the performance of AI systems in interpreting DBT screening examinations and they neglected the collection of publicly available data on mammography [59]. In 2021, Bai et al. [60] discussed the specific technical challenges and solutions faced by DL algorithms in processing DBT data. However, their discussion did not explore algorithmic interpretability, patient privacy protection, and legal and ethical issues in practical clinical applications [60]. In 2023, Zhang et al. [61] provided a comprehensive review of AI in breast cancer imaging analysis, covering aspects such as data augmentation, image segmentation, diagnosis, and prognosis assessment. However,

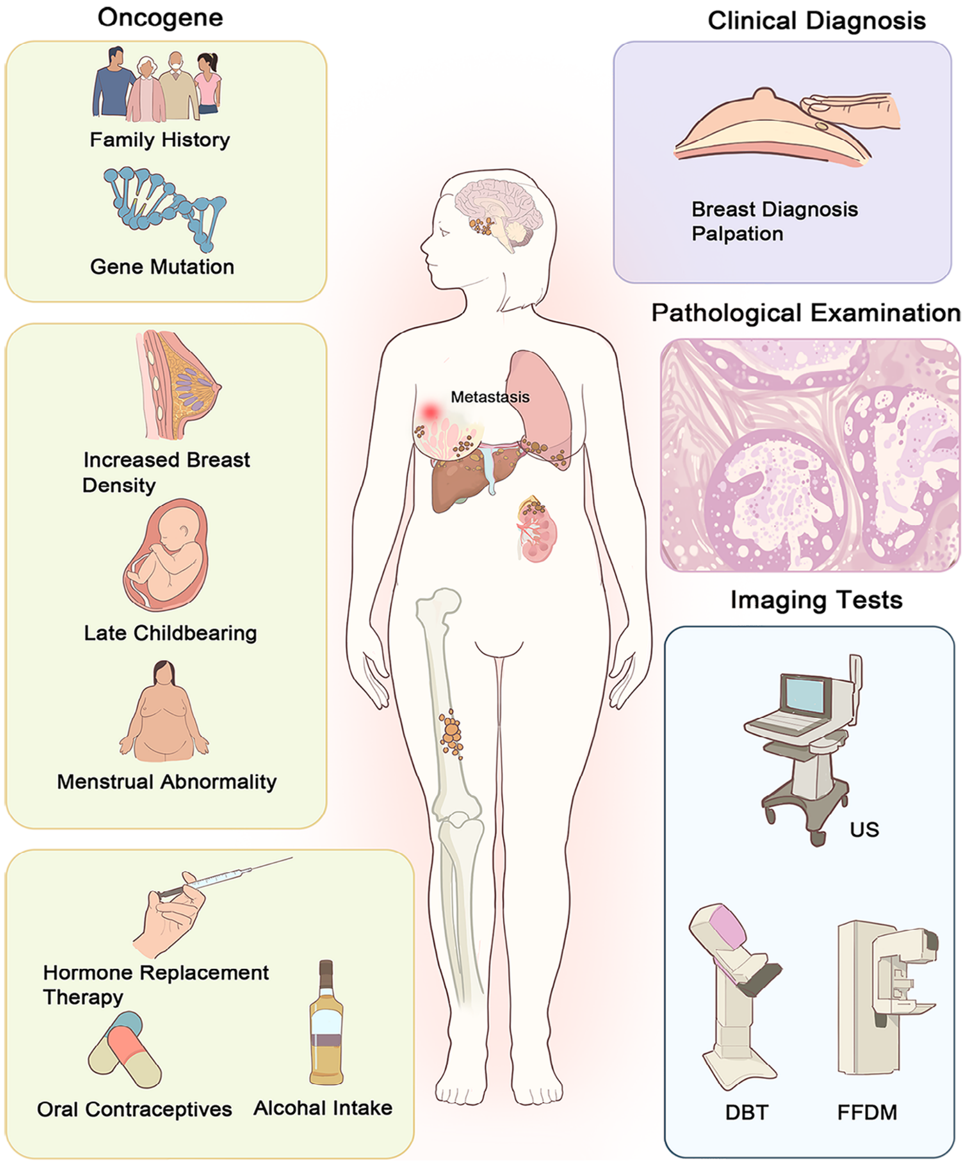

FIGURE 1 | Breast cancer causes, pathogenesis, and screening methods. The causes of breast cancer include family history, gene mutations, increased breast density, late childbearing, menstrual abnormalities, hormone replacement therapy, oral contraceptives, and alcohol intake. The pathogenesis of breast cancer involves mutations in oncogenes within breast cells, leading to abnormal cell proliferation, tumor formation, and invasion of surrounding tissues. Over time, these cancer cells can break through the basement membrane and metastasize to distant sites via the lymphatic and circulatory systems. Screening methods for breast cancer include clinical diagnosis, pathological examination, and imaging tests such as US, FFDM, and DBT.

their review lacked a detailed discussion of DL models in DBT, making it difficult to fully address their applicability for this imaging modality [61]. This review aims to provide a more comprehensive summary and advanced insights into the application of DL technology in DBT to help promote the development and application of AI in this field.

This work reviews the methods, challenges, and future directions related to the application of DL to DBT data for the early screening of breast cancer. The manuscript can be divided into four parts. First, a brief overview of the basic principles, advantages, and limitations of DBT is provided. Second, based on the application of DL in medical image processing and analysis of breast diseases, DL models are classified into three categories, and their applications in early breast cancer screening are summarized. Third, the application of DL in other areas of DBT, along with the application of other AI techniques in early DBT screening, including the provision of publicly accessible databases, is explored. Finally, the challenges of applying DL in DBT are presented, and future research directions are summarized.

2 | DBT: Basic Knowledge and Importance

Commonly used mammography examinations in clinical practice include DM, FFDM, and DBT. The DM employs digital sensors to capture mammographic images; specifically, the acquired electronic data are transmitted to a computer for processing, producing a breast image [62, 63]. DM has played a key role in reducing breast cancer mortality rates but has faced criticism due to its high number of false-positive results and limited sensitivity, and the potential for overdiagnosing clinically unimportant lesions [64]. FFDM captures X-ray images of the entire breast area with digital sensors, allowing a wider field of view and resulting in a more accurate mammogram [65, 66].

FFDM has long been considered the gold standard for breast cancer screening [67, 68]. However, it exhibits reduced sensitivity and specificity when affected by the "masking effects" of the upper parenchyma mal tissues [69]. These limitations are addressed in DBT through the arc motion of the X-ray generator above the patient, resulting in the emission of low-dose X-rays at predetermined intervals from different angles and allowing the capture of images from various perspectives [70]. After acquisition, the DBT images are reconstructed into slices as thin as 1 mm in a plane parallel to the detector, and 3D reconstruction is performed to help determine the position of the lesion relative to the breast tissue [71, 72].

Studies have shown that for breast lesions, DBT provides better visibility of the mass, areas of structural distortion, and margin characterization [73, 74]. Researchers have shown that models trained on 3D DBT data can help reduce recall rates, improve biopsy patient selection, and increase cancer detection rates, particularly for patients with dense breasts [75–77]. Therefore, DBT is more advantageous for breast cancer screening and diagnosis than DM and FFDM are, facilitating early treatment and prognostic assessment of the disease [78].

Despite the many advantages of DBT over conventional mammography, there are some limitations in integrating this emerging technology into routine clinical practice. DBT, which functions as a pseudotomographic imaging modality, produces a series of 2D slices of the target breast tissue at varying vertical resolutions. This partial tomosynthesis effect significantly reduces the masking effect caused by overlapping tissue and is less effective for women with very dense breasts [79–81]. During screening, the radiosensitivity of the female breast requires careful attention to the radiation dose [82–84]. Barufaldi et al. [85] conducted an empirical assessment using a specialized tracking system to monitor the radiation doses from the DM and DBT. Their findings indicated a statistically discernible increase in the radiation dose associated with DBT in comparison with that associated with DM (2.21 vs. 1.76 mGy, respectively). While the radiation dose from DBT is marginally higher than that from DM, it remains within the acceptable limits prescribed by the Mammography Quality Standards Act [85].

In addition, the workload is increased by the complexity of DBT images and the long interpretation time, which leads to the need for double reading for many screening procedures, further exacerbating the workload [43, 86, 87]. DBT also faces challenges in the detection of calcifications and the need for breast compression during the imaging process, and the long compression time may affect patient tolerance [88] (Figure 2). Therefore, a comprehensive review of the use of computational modeling in DBT to accelerate the diagnostic process is of particular importance.

3 | DL in DBT for the Early Screening of Breast Cancer

Developments in AI have led to its implementation in medical contexts by an increasing number of people to improve the efficiency and accuracy of diagnosis [43, 89-91]. DL plays an important role in the clinical diagnosis and treatment of diseases, covering the fields of serology, imaging, and genomics. In 2023, Chi et al. [92] identified specific pancreatic cancer biomarkers by analyzing serum miRNA expression profiles from the GEO database via machine learning and artificial neural networks and developed a novel artificial neural network model for early diagnosis. Li et al. [93] developed and validated a two-stage DL model based on multichannel MRI for automatic detection and segmentation of brain metastases, which excelled in improving the detection sensitivity and segmentation accuracy of tumors smaller than 5 mm, achieving 90% sensitivity and 56% accuracy on a test set. In 2024, Hoang et al. [94] developed the ENLIGHT-DeepPT framework, which effectively predicts cancer treatment outcomes from pathology images with an overall advantage ratio of 2.28 and an accuracy of 46.5%.

DBT typically requires nearly twice the acquisition and interpretation time of DM, thus increasing the workload of the imaging physician [90]. AI algorithms have been shown to enhance the ability of the imaging physician to recognize cancers in mammograms without prolonging the reading time. Over the past decade, DL-based computer-aided diagnostic (CAD) systems have achieved remarkable success in medical image diagnostics, especially in early screening tasks involving DBT [95–98]. DL techniques have also demonstrated broad application prospects in other medical image analysis fields, such as disease classification [99], segmentation [100, 101], detection [102], and image alignment [103].

3.1 | Diagnostic Classification of Breast Diseases From DBT Data via DL

DL has a wide range of applications in different stages of DBT, including image reconstruction [104], improving image quality [105], and reducing noise. Over the years, several DL-based methods have been developed for performing classification tasks. In the early days, perceptron and multilayer perceptron (MLP) methods were developed to address linear and nonlinear problems [106, 107]. In the 1990s, Yann LeCun's [108] LeNet-5 demonstrated the potential utility of convolutional neural networks (CNNs). The success of AlexNet in 2012 marked the widespread adoption of DL. Subsequently, a visual geometry group network was developed, enhancing classification performance through increased network depth [109–112]. Google neural networks subsequently introduced the inception module to improve efficiency [113, 114], and a residual network (ResNet) resolved the gradient vanishing problem in deep networks through residual connectivity [115, 116]. In recent years, an efficient neural network (EfficientNet) has been developed even higher efficiency and accuracy through composite scaling [117–119], whereas the vision transformer has demonstrated the competitiveness of transformer-based architectures in image classification tasks [120–122]. Continued innovations in these models have driven significant performance improvements in

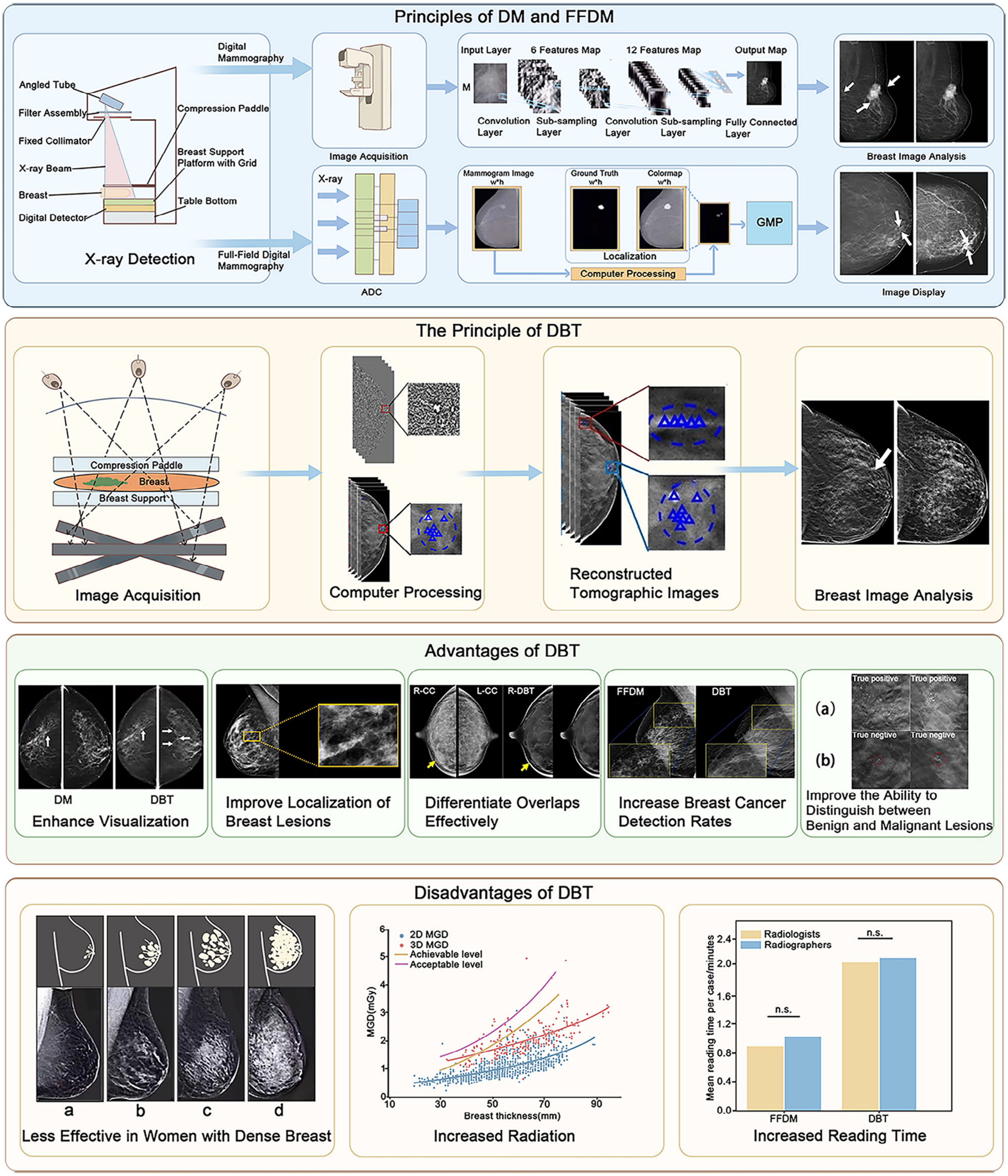

FIGURE 2 | Principles of DM, FFDM, and DBT imaging and the advantages and disadvantages of DBT in clinical applications. DM uses a digital detector to penetrate the breast tissue with X-rays. The sensor then converts X-ray absorption into a digital signal that is then processed by a computer to produce a high-resolution image of the breast. This is achieved through the use of image filtering, feature extraction, and enhancement. FFDM uses a planar detector and a rotating arm to comprehensively scan the breast tissue area, convert the X-ray signals to digital form, and capture high-resolution images of the internal structure of the breast via a fully digital detector. The data are then processed and reconstructed by a computer to produce high-resolution breast images. DBT is based on the imaging principle of obtaining a series of high-resolution, 2D breast images by taking multiple, low-dose exposures of an X-ray tube over a limited angular range. The images are then reconstructed by a computer into high-resolution tomograms parallel to the detector, resulting in 3D tomograms. DBT has several advantages over DM and FFDM, including enhanced visualization, precise localization, effective differentiation of overlap, improved detection of breast cancer, and improved discrimination between benign and malignant lesions. However, DBT also has some disadvantages, such as being less effective in women with dense breasts, higher radiation dose [396], and longer reading time [87], which can impact efficiency. MGD, mean glandular dose.

classification tasks and facilitated the application of DL in other domains.

However, most well-established DL models originally designed to analyze natural images may produce suboptimal results when applied directly to medical imaging tasks [123], in part due to the substantial differences between the two types of images. Additionally, DBT data differ notably from ordinary medical imaging data [124]. For example, in the application of case of DBT data to breast cancer screening, 3D imaging is used to provide higher tissue resolution and contrast via the acquisition of a series of low-dose X-ray images from different angles and their reconstruction into 3D images [125, 126]. While this method reduces the effect of tissue overlap and improves lesion detection, it also introduces a series of challenges [127, 128]. Lesions may appear as different shapes and with different densities in different slices, and the complexity of normal tissues further increases lesion identification difficult [129]. Therefore, DBT data hold great research importance for the classification of breast diseases. Next, we detail the application of various DL models in DBT (Figure 3).

3.1.1 | Convolutional Neural Network

CNN extract local features from data through convolutional operations, construct high-level semantic information layer by layer, and are commonly used to process structured data such as images. In 2019, Samala et al. developed a CNN using multistage transfer learning (MSTL) for classifying malignant and benign masses on DBT images. They first fine-tuned an ImageNet-trained CNN using more readily available mammography data and then performed a second stage of fine-tuning using a small, available DBT dataset. This article employs a MSTL approach to feature extraction, in particular applying pretrained knowledge of CNNs in relevant ancillary domains to the task of classifying breast cancer. They compared multistage fine-tuned CNNs with single-stage CNNs fine-tuned directly with DBT data and assessed how the different fine-tuning strategies affected the performance of the CNNs when the available mammography and DBT data varied over a wide range. Additionally, the impact of different migration learning strategies on classification performance was evaluated via statistical methods with restricted sample sizes, such as area under the curve (AUC) and paired *t*-tests. In the single-stage transfer learning (STRL) test set, the view-based AUC was 0.85 ± 0.05, whereas in the MSTL test set, the AUC significantly improved to 0.91 ± 0.03. The study demonstrated that when the target domain has a limited number of training samples, using data from similar auxiliary domains for additional stages of training is effective [130].

In 2021, Aswiga et al. [131] developed an innovative, two-tier framework for classifying the data in DBT datasets. Initially, they built a basic framework based on multilevel transfer learning, whose main goal was to utilize knowledge gained from five other datasets (including a general nonmedical imaging dataset and a specialized mammography dataset) for feature extraction and subsequent classification of the target DBT dataset. By progressively fine-tuning the model, they enhanced the classification performance. Notably, the AUC for the fine-tuned MedCNN using the CNCF fusion algorithm reached an impressive value of 0.89.

3.1.2 | Deep Convolutional Neural Network

The deep CNN (DCNN) is based on CNNs and is suitable for more complex tasks by increasing the depth and number of layers of the network to improve the feature extraction and representation capabilities of the model. In 2018, Samala et al. [132] proposed a layered pathway evolution method to compare multiple DCNNs for breast cancer classification via DBT. Initially, transfer learning was employed with 19,632 augmented regions of interest (ROIs) from 2454 lesions identified on mammograms to further train a DCNN pretrained on ImageNet. Subsequently, 9120 DBT ROIs from 228 lesions were used in the second stage to further train the pretrained DCNN. The results demonstrated substantial network simplification; the number of neurons decreased by 87%, the number of parameters was reduced by 34%, and the required multiplications and additions in the convolutional layer were diminished by 95%. The AUC in the test increased from 0.88 to 0.90 in the evaluation of 89 lesions identified on mammograms from 94 independent DBT cases before and after pruning, respectively. The results of that study suggest that the features learned by a DCNN from mammography can be effectively transferred to DBT.

3.1.3 | Graph Convolutional Network

The graph convolutional network (GCN) is a neural network for graph-structured data that extracts node features and captures node relationships through neighborhood aggregation. In 2018, Zhang et al. [133] developed a novel method called boundary-aware dense region CNN with a GCN (BDR–CNN–GCN), which integrates two state-of-the-art neural networks. This study used a combination of a CNN and a GCN through feature extraction to increase the performance of breast cancer detection, and the performance was evaluated via statistical metrics such as sensitivity, specificity, and accuracy. The experimental results indicate that compared with the five proposed neural network models and 15 state-of-the-art breast cancer detection methods, the BDR–CNN–GCN method achieves superior performance, with a sensitivity of $96.20 \pm 2.90\%$, a specificity of $96.00 \pm 2.31\%$, and an accuracy of $96.10 \pm 1.60\%$. These findings demonstrate that BDR–CNN–GCN is an effective method for improving malignant breast mass detection. However, importantly, both the training and test sets in that study were derived from the Mini-Mammographic Image Analysis Society dataset, and no independent external validation was conducted. Therefore, the reliability of the model requires further verification. Future studies are planned to test the proposed AI model by expanding the dataset to include mammography X-ray images from diverse sources and with varying resolutions.

3.1.4 | Dense Convolutional Network Model

Dense convolutional network (DenseNet) enhances feature reuse and improves training efficiency by directly using the output

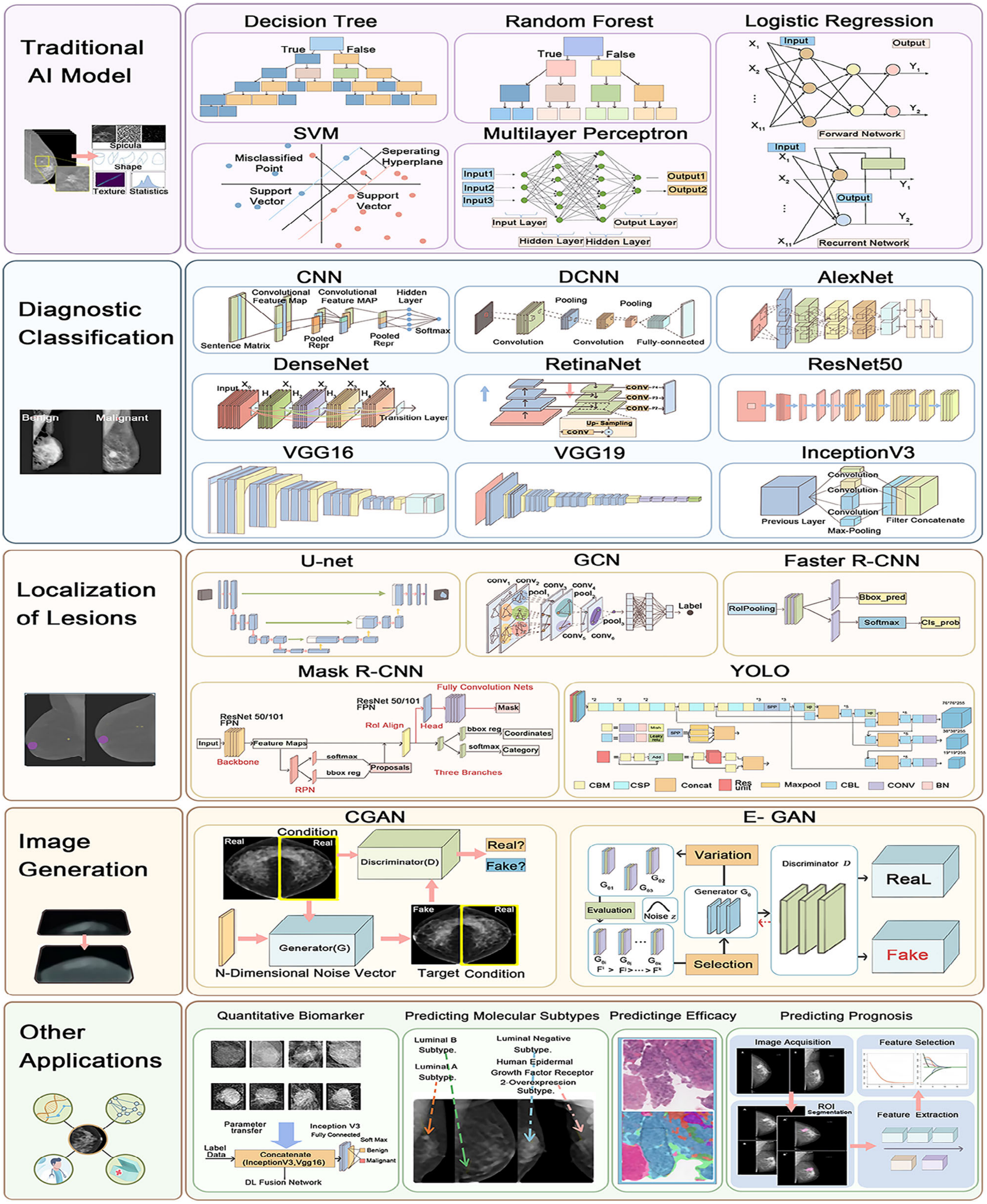

FIGURE 3 | Applying DL models and other AI techniques to DBT data. The traditional AI models applied to DBT include decision trees, random forests, logistic regression, SVM, and multilayer perceptron. Deep learning models for the diagnostic classification of breast diseases on DBT data include CNN, DCNN, AlexNet, DenseNet, RetinaNet, ResNet50, VGG16, VGG19, and Inception V3. The deep learning models used for breast lesion segmentation and detection on DBT data include U-Net and GCN. Other DL models used for medical image generation from DBT data include Faster R-CNN, Mask R-CNN, and YOLO. In addition, a GAN has been used for this purpose. The applications of DL in DBT go beyond early detection and diagnosis of breast cancer. It can also act as a quantitative biomarker, predict molecular subtypes, assess treatment efficacy, and predict patient prognosis.

of each layer as the input for all subsequent layers. In 2022, Pawar et al. [134] proposed a multichannel DenseNet architecture for breast cancer detection. This architecture consists of a four-channel transfer learning architecture that extracts important features from two medial oblique views and two craniocaudal views of digital mammograms of a single patient. An evaluation of 800 digital mammograms with different breast imaging reporting and data system (BI-RADS) density levels revealed that the architecture achieved statistically good performance: 96.67% accuracy in the training set and 90.06% accuracy in the test set, with a mean AUC of 0.9625. These findings suggest that the proposed architecture can achieve state-of-the-art results with a relatively small number of images and low computational power. Additionally, DenseNet enhances the propagation of features throughout the network and facilitates feature reuse, significantly reducing the number of parameters needed and thus simplifying the network's computational requirements. Compared with most advanced network architectures, the DenseNet architecture yields superior breast cancer detection models with less computational effort.

3.1.5 | RetinaNet Model

RetinaNet enhances the detection of small and challenging objects by introducing focal loss, which balances positive and negative samples while maintaining both efficiency and accuracy. In 2023, Habeeb et al. [135] achieved efficient breast cancer detection with a two-stage transfer learning approach combined with RetinaNet. For feature extraction, the first stage of transfer learning employs the curated breast imaging subset of the digital database for screening mammography (CBIS-DDSM) dataset for pretraining, whereas the second stage fine-tunes the model on the INbreast dataset, resulting in substantial performance improvements. Specifically, the model achieves true positive (TP) rates of 0.99 ± 0.02 and 1.67 false positives (FPs) per image, indicating a substantial enhancement over the STRL methods. This approach provides an innovative framework and serves as a successful example for breast cancer detection.

3.1.6 | ResNet50 model

ResNet50 is a 50-layer deep ResNet that alleviates the vanishing gradient problem in deep networks by introducing residual connections, enhancing training efficiency and accuracy. In 2022, Chen et al. [136] employed the ResNet50 architecture in DBT to diagnose breast cancer in patients with structural distortions, employing gradient-based class activation mapping (Grad-CAM) to visualize suspicious areas in 298 patients. In that study, feature extraction was performed via radiomic and DL methods, radiological features were extracted by manually outlining the ROI, key features were identified via support vector machines (SVMs), and finally, the diagnostic performance of the different models was assessed via the DeLong test. The AUC of the imaging radiomics model, which incorporated CC + MLO features, was 0.82, with a sensitivity of 0.78, a specificity of 0.68, and an accuracy of 0.74, whereas the AUC of the DL model was 0.61. Despite its lower accuracy, the trained model allows Grad-CAM to highlight suspicious areas of structural distortion, facilitating automatic ROI depiction. The results of the study suggest that the developed CAD tool can initially detect subtle pathologic textures on DBT images and subsequently perform further characterization to make a diagnosis.

3.1.7 | Visual Geometry Group-16 Model

Visual geometry group-16 (VGG16) is a 16-layer CNN that enhances feature extraction and classification performance via small convolutional kernels and a deep architecture. In 2024, Esposito et al. [137] developed a preprocessing tool called the digital breast imaging tool (DBIT) and evaluated its performance in improving DL-based CAD systems for cancer detection. They extracted over 200 DBT volumes from a public repository, dividing them into negative and positive (benign and malignant) tumors to form the "original dataset" (raw images) and the "processed dataset" (images processed with DBIT). In the study, 214 features were extracted via PyRadiomics, a SVM was used for feature selection and model construction, and the model performance was evaluated via fivefold cross-validation and the DeLong test. The classification performance of VGG16 in the original and processed datasets was evaluated in terms of the AUC, accuracy, F1 score, precision, sensitivity, and specificity. The average classification accuracy of VGG16 increased by approximately 12% with the processed dataset. The results demonstrate that DBIT effectively preprocesses images to serve as suitable inputs for DL-based CAD systems, thereby assisting imaging physicians in the diagnosis of breast cancer.

3.1.8 | Visual Geometry Group-19 Model

Visual geometry group-19 (VGG19) is a 19-layer CNN that extends VGG16 with additional convolutional layers, offering enhanced feature representation for more complex image classification tasks. In 2018, Mendel et al. [138] used an ImageNet pretrained VGG19 model to extract features from DBT images for the classification of malignant and benign lesions. Features were selected from the VGG19 model after each maxpool layer, and mean pooling was applied to reduce feature dimensionality. To avoid feature redundancy, a "leave-one-out" stepwise feature selection method was used to identify the most frequently selected features, followed by an estimation of the likelihood of malignancy. The study utilized 78 lesion images, including 30 images of malignant lesions and 48 images of benign lesions. The results revealed a significant improvement in classification accuracy when combined with the use of anterior and posterior images from DBT, with DBT images having an AUC as high as 0.98 in the classification of mass and architectural distortion (ARD) lesions, compared with 0.88 in FFDM ($p = 0.024$), highlighting the advantages of DBT in the detection of breast malignancies.

In 2023, Mukhlif et al. [139] proposed a novel method called dual transfer learning, which is based on pattern convergence between the source and target domains. Four pretrained models (VGG16, Xception, ResNet50, and MobileNetV2) were fine-tuned on sufficient unclassified breast cancer images by adjusting the corresponding final layers. A small number of already classified images of the same disease and target task were also used, and data augmentation techniques were employed to balance the categories and increase the sample size. The experimental results indicate that the proposed method enhances the performance of all the models, whereas data augmentation further improves the performance of the VGG16, Xception, ResNet50, and MobileNetV2 models by 19.66, 34.76, 31.76, and 33.03%, respectively. Notably, the Xception model achieved an accuracy of 99%, a precision of 99.003%, a recall of 98.995%, an F1 score of 99%, a sensitivity of 98.55%, and a specificity of 99.14%.

3.1.9 | InceptionV3 Model

InceptionV3 uses a modular Inception architecture and factorized convolutions to improve computational efficiency and feature extraction, making it suitable for various image recognition tasks. In 2023, Harron et al. [140] conducted a comparative investigation of various pretrained CNN models for feature extraction in fuzzy detection with DBT images. The CNN models assessed included ResNet18, ResNet50, AlexNet, VGG16, and InceptionV3. These pretrained CNN models, combined with a SVM classifier, yield promising results in the fuzzy classification of DBT images. Specifically, deep feature extraction methods were used for feature extraction, with InceptionV3 having the highest accuracy of 97% and a maximum AUC of 0.9961.

3.2 | Breast Lesion Segmentation and Detection with DL on DBT Data

In the task of lesion detection and classification, the development of DL has significantly changed the traditional methods of image segmentation and detection [141–144]. In 2012, AlexNet marked the rise of DL in computer vision [145, 146], followed by the region-based CNN (R-CNN) family [147, 148] (including Fast R-CNN and Faster R-CNN) and the You Only Look Once (YOLO) model from 2016 onward, which drove further developments in object detection [149–152]. For semantic segmentation, models such as the fully convolutional network and U-shaped network (U-Net) have achieved breakthroughs in pixel-level prediction [153, 154], and the Mask R-CNN and DeepLab series have resulted in further improvements in instance and semantic segmentation [155–159]. In 2021, transformer architectures, such as the detection transformer and swin transformer, were introduced to perform visual tasks [160, 161]. In 2023, Xia and Wang [162] systematically reviewed transformer-based approaches, noting that models such as vision transformer and swin transformer have been widely used for image segmentation tasks for brain tumors, stroke, and other diseases. The article summarizes a variety of architectures that fuse convolution with transformer, including SwinUNet, TransBTS, and so on. These methods utilize the global modeling capability of transformer, which significantly improves the segmentation effect in multimodal medical images, and especially show strong adaptive ability under small sample conditions [162]. These advancements have led to significant progress in image segmentation and detection techniques [163, 164].

For segmentation and detection tasks, DBT data present unique advantages and disadvantages compared with other medical data [165–167]. The higher resolution of DBT allows the capturing of fine structures and lesions in breast tissue, providing clearer images than traditional 2D mammography methods and enhancing the accuracy of detection and segmentation algorithms [168–170]. However, the high resolution also results in substantial storage requirements and increased computational resources for processing and analysis [171]. The volume of 3D imaging data grows exponentially with respect to that of 2D imaging data, placing greater demands on hardware [172]. Additionally, DBT images usually contain hundreds of slices, making manual lesion labeling extremely time consuming and error prone [173–175]. Consequently, the segmentation and detection tasks for DBT data are highly complex.

3.2.1 | U-Net Model

U-Net achieves multiscale feature fusion through an encoder–decoder structure with symmetric skip connections. In 2020, Lai et al. [176] proposed an algorithm for automatically segmenting DBT-detected images masses using the U-Net architecture. This approach can be divided into six stages: DBT image preprocessing, patch extraction, data augmentation, voting scheme fusion, segmentation via the U-Net architecture, and postprocessing. The authors employed a 23-layer U-Net model for segmentation, after which they compared the performance of their model with that of linear discriminant analysis, SVM and CNN. Their model outperformed the other methods, with accuracies, sensitivities, specificities, and AUCs for the entire experimental dataset of 0.871, 0.869, 0.882, and 0.859, respectively. The results demonstrate that the proposed U-Net-based system is an effective solution to the problem of DBT mass segmentation.

3.2.2 | Faster R-CNN

Faster R-CNN is an efficient object detection framework that integrates an RPN for generating region proposals and a CNN for object classification and localization. In 2019, Fan et al. [177] designed a CAD system for DBT masses via Faster R-CNN. They first collected a dataset comprising 89 patients and 105 masses. The detection architecture employs a CNN with a region proposal network to generate region proposals (e.g., bounding boxes) with mass likelihood scores for each slice. The masses detected on consecutive 2D slices are then merged into a 3D DBT volume through a slice fusion procedure. The performance of the CAD system was evaluated with free-response ROC curve analysis, and the results indicated that, in a comparison between R-CNN-based CAD systems and DCNN-based CAD systems, the AUCs were 0.96 and 0.92, respectively [178]. The results demonstrated the utility of faster R-CNN for pretesting ROIs and distinguishing true masses from FPs in DBT. They further compared the performance of this method with that of a previous DCNN-based CAD system, showing that the faster R-CNN could improve prescreening and reduce FPs in mass CAD systems.

3.2.3 | Mask R-CNN

Mask R-CNN is an extension of Faster R-CNN that adds a parallel branch, such as segmentation, to achieve object classification, localization, and pixel-level segmentation. Additionally, in 2022, Fan et al. [178] proposed the Mask R-CNN CAD system framework for breast lump detection and segmentation of DBT images, which uses ResNet-50 as a feature extractor. The study was based on a 364-sample design divided into a training set ($n = 201$) and a test set ($n = 163$). In lesion detection, the 3D-Mask R-CNN achieves a sensitivity of 90% and an FP rate of 0.8 per lesion, which outperforms the performance of the 2D-Mask R-CNN and Faster R-CNN. Statistical analysis revealed that the 3D-mask R-CNN significantly outperformed 2D-based detection in patients with different features ($p < 0.05$).

3.2.4 | YOLO Model

YOLO is an end-to-end object detection framework that reformulates object detection as a single neural network regression problem, enabling real-time object detection and localization. In 2022, Hossain et al. [179] presented a novel algorithm for detecting breast lesions on DBT images using multidepth level convolutional models. They employed YOLOv5 as the base network and enhanced the detection algorithm through data augmentation and fine-tuning, ultimately developing an integrated algorithm for medium-to-large models. The integrated model achieves an average sensitivity of 0.786 FPs per DBT volume on the DBTex independent test set, with a 2 FP per image sensitivity of 0.743. The results indicate that the FP outcomes of nonbiopsied benign lesions provide valuable information for the lesion detection algorithm and that the integrated detection model improves lesion detection.

3.3 | Breast Medical Image Generation with DL on DBT Data

Since 2012, DL has achieved tremendous progress in the field of image generation. In 2013, autoencoder and variational autoencoder (VAE) improved the quality of image generation through unsupervised learning [180–182]. In 2014, the generative adversarial network (GAN) was proposed by Ian Goodfellow et al. [183]; this system significantly enhanced the quality of generated images through adversarial training between a generator and discriminator. Subsequent variants, such as deep convolutional GAN, Pix2pix, and cycle GAN, further advanced image transformation and style migration [184–187]. After 2017, the Wasserstein GAN, big GAN, and style GAN families demonstrated notable improvements in training stability and image quality [188–191]. Since 2020, generative transformation models such as vector quantized VAE 2, diffusion models for autoregressive language learning-E, and contrastive language-image pretraining, which combine VAE and transformer architectures, have substantially improved image quality and consistency in multimodal generation tasks [192–197].

The applications of generative models in the field of medical images primarily include image enhancement and restoration [198, 199], image segmentation [200, 201], image synthesis [202, 203], image transformation [204], and anomaly detection [205]. A prominent challenge with DBT data in the context of DL is the high cost of manual delineation and annotation. DBT images typically consist of hundreds of slices, and manually annotating lesions in each slice requires medical experts to spend substantial time and effort, resulting in fewer publicly available DBT datasets with annotations such as outlining [36]. Therefore, image synthesis, dataset extension, and improvements in the generalization ability of the model through data augmentation techniques and GANs have become important areas of research.

3.3.1 | Generative Adversarial Network

GAN achieves high-quality data generation through adversarial training between a generator and a discriminator. Although primarily used for image generation, GANs have also played significant roles in improving breast cancer detection through various innovative approaches [206–208]. GANs can augment DBT datasets by generating synthetic images that closely resemble real cases, even when trained on a small dataset [209, 210]. These synthetic images can be integrated into the original dataset, enriching and diversifying the available training data and improving the robustness and generalizability of machine learning models dedicated to breast cancer detection, greatly facilitating the development of more accurate and reliable detection algorithms [211, 212].

In 2021, Lee and Nishikawa [213] developed a conditional GAN (CGAN) model to simulate normal-appearing mammograms based on mammograms of the opposite breast and processed the images with a CNN. After testing, the fusion AUC of the CNN reached 0.77, which was significantly better than that of the CNN model when only real mammograms were used (AUC of 0.70) and that of the CNN model when only simulated mammograms were used (AUC of 0.68). These results indicate that the CGAN model could aid in the detection of breast cancer [213]. In addition, the study trained a deep image-to-image network for feature segmentation on DBT images and subsequently constructed a task-driven GAN model for simultaneous synthesis and parsing of unseen real DBT images. In 2022, Staffa et al. [214] proposed an evolutionary GAN (E-GAN) to augment and balance DBT image datasets. The quality of the synthetic images generated by the E-GAN was significantly improved at a later stage of the learning process, especially in terms of detail and fidelity, with the structure and texture of the breast becoming more visible [214].

Breast disease classification and diagnosis, lesion segmentation and detection, and medical image generation can be achieved on DBT data via DL models. The integration of image data obtained from DBT is essential for developing an intelligent early breast cancer screening system based on DL. A comprehensive and in-depth exploration of the application of DL in the field of DBT is particularly necessary to fully realize its potential.

3.4 | Application of DL to Other Areas of DBT

DL has various potential applications in the field of DBT [58]. It has already been widely used in breast disease diagnosis and classification, lesion segmentation and detection, and medical image generation [215]. Additionally, in combination with DBT, DL has shown great promise in predicting breast cancer molecular subtypes, chemotherapy response, and recurrence risk [216–218]. DL can also be applied in various clinical environments, suggesting unprecedented opportunities for its application in DBT. Table 1 illustrates several potential applications of DL in

TABLE 1 | Summary of other applications of DL in DBT.

Paper/ reference	Core algorithm	Model application	Evaluation metric	Best results
Shimokawa et al. [219]	DL	Predict the presence of stromal invasion	AUC	0.750
Schmitgen et al. [220]	Random forest	Individualized treatment prediction	Sensitivity	0.770
Rigaud et al. [221]	DL	Automated assessment of breast density	Binary classifications	0.750
Michielsen et al. [222]	CNN	Improve accuracy and precision of iodine quantification in contrast-enhanced tomosynthesis	Dice similarity coefficient	0.975
Jang et al. [223]	CNN	Signal known statistically and background known statistically detection tasks in breast tomosynthesis images	Optimal detection performance	Signal known exactly: 0.912 Signal known statistically: 0.824
Gao et al. [224]	DCNN	Improve the image quality of DBT in terms of image noise and MC conspicuity	AUC	0.970
Su et al. [225]	DL	Improve the DBT imaging performance	Azimuthal symmetry function curves/the image reconstruction time	5.900 mm/9.300 s
Lee et al. [56]	Deep neural network	Improved breast cancer classification performance	AUC	0.910
Yang et al. [226]	Convolutional inception style transfer module	Classify lesion malignancy in DBT	AUC	0.802
Wang et al. [49]	Multiscale feature deep neural network	Breast mass classification using DBT	AUC	0.870
Wang et al. [227]	CNN	Alleviate the impacts for the accurate and rapid detection of microcalcification clusters in DBT	Sensitivity	93.51%
Samala et al. [228]	DCNN	Masses in DBT volume	AUC	0.900
Mota et al. [229]	CNN	An automatic classification of a complete DBT image for the presence or absence of MCs	AUC	94.19%
Lai et al. [176]	U-Net	Improve the automatic segmentation accuracy of breast masses in DBT images	Specificity/AUC	0.882/0.859
Conant et al. [230]	DCNN	Shorten DBT reading time while maintaining or improving accuracy	AUC	0.852
Xiao et al. [231]	CNN	Improve the classification performance of benign and malignant MCs in DBT	AUC	0.8837
Teuwen et al. [104]	CNN	Predictions of breast density	Structural similarity index	0.910
Whitney et al. [232]	CNN	Distinguish between benign or malignant lesions	AUC	0.930

(Continues)

Paper/ reference	Core algorithm	Model application	Evaluation metric	Best results
Matthews et al. [233]	DL	Predict breast density	AUC	0.980
Kim et al. [234]	CNN	Characterize malignant masses in DBT	AUC	0.910

Note: Aside from the source code of Ref. 133 and the database of Ref. 143, none of the source codes or databases of the papers listed in Table 1 are publicly available.
Abbreviations: AUC, area under the curve; CNN, convolutional neural network; DBT, digital breast tomosynthesis; DCNN, deep convolutional neural network; DL, deep learning; MC, microcalcification cluster; U-Net, U-shaped network.
Source code: https://www.mdpi.com/article/10.3390/cancers14205003/s1.
Database: https://wiki.cancerimagingarchive.net/pages/viewpage.action?pageId=39879200.

DBT in addition to those described previously.

DBT has the potential to allow the extraction of quantitative biomarkers of breast cancer [235]. In 2019, Tagliafico et al. [236] extracted a set of 106 quantitative features from DBT images, including morphological features, grayscale/scaling statistics, and texture features. They then applied the least absolute shrinkage and selection operator method to select the most predictive features, yielding 34 features that were significantly correlated with Ki-67, with correlation coefficients exceeding 0.5 for five of them. The quantitative radiographic features of the breast tumors extracted from the DBT images were associated with Ki-67 expression in breast cancer [236].

DL also provides a way for DBT to predict molecular subtypes of breast cancer. This involves the detailed exploration of specific molecular subtype features visualized on DBT images, which can help classify lesions based on receptor status and molecular subtype [237–239]. In 2019, Cai et al. [240] retrospectively analyzed 234 breast cancer patients with surgical, complete pathological, and immunohistochemical data, classified the patients' tumors into four molecular subtypes and then assessed the associations between the clinical features of each molecular subtype and DBT features. The results revealed that the calcification score and lymph node size significantly differed among the four molecular subtypes. Subgroup analyses based on tumor size, calcification score, and lymph node size revealed a significant difference in the distribution of patients with a lymph node size ≥1.5 cm versus those with a lymph node size <1.5 cm. In summary, diagnostic imaging features such as the calcification score and lymph node size determined by DBT can be used as auxiliary diagnostic indicators for the molecular subtype of breast cancer [240].

DL has shown promise for risk prediction and prognosis in DBT [241]. In 2020, Conant et al. [242] compared the resection rate, complete dissection rate, and biopsy recommendation rates; positive predictive value of recall; positive predictive value of biopsy; false-negative rates; and biology, size, and lymph node status of screen-detected and interval cancers in patients consecutively screened with DBT versus DM. The results suggested that DBT screening detects a greater proportion of cancers with a poor prognosis than does DM screening. The combination of DL with DBT, together with other clinical indicators, aims to facilitate early prediction of patient and survival outcomes [243]. The potential application of combining DBT with DL could also be extended to predicting cancer recurrence, as demonstrated through some recent developments in breast imaging [244]. This includes combining AI with imaging genomics, using the features of the latter to predict the risk of recurrence in patients with breast cancer.

DL has demonstrated a wide range of applications in the field of DBT, significantly improving the accuracy of breast disease diagnosis and lesion segmentation and detection and offering the potential for fully automated detection. When combined with DL, DBT technology excels in predicting the molecular subtypes of breast cancer, assessing the response to chemotherapy, and predicting the risk of recurrence, thereby greatly improving the sensitivity in diagnosing breast cancer.

4 | Machine Learning in the Field of DBT

Using the enhanced features extracted from DBT images, different research teams have significantly improved the effectiveness and diagnostic accuracy of early breast cancer screening by combining various techniques, including logistic regression models and machine learning methods [245–247]. In 2022, Eriksson et al. [248] developed a logistic regression model based on DBT information, producing a fundamental machine learning-based classification algorithm that has been widely studied in the field of early breast cancer screening. This model uses enhanced image features extracted from DBT images to predict the risk of breast cancer in women who undergo annual screening [248].

Similarly, Johnson et al. [249] reported a decrease in the incidence of interstitial cancer following DBT screening. Their findings, derived from a prospective, population-based DBT screening trial, indicated a rate of 1.6 interval cancers per 1000 women screened, a reduction from the accepted value that suggests the potential benefits of their method, such as enhanced early detection, leading to reduced breast cancer mortality rates [249]. Additionally, Sharpe et al. [76] analyzed the effect of DBT on recall and cancer detection rates in breast cancer screening. By combining single- and mixed-effects logistic regression models, their results demonstrated that the implementation of DBT significantly improved cancer detection rates, markedly increasing the efficacy of breast cancer screening [76].

In the medical field, machine learning techniques have been widely used for feature extraction from DBT images, as well as for screening and diagnosing breast cancer, as shown in Table 2.

TABLE 2 | Non-DL AI models in DBT.

Paper/ reference	Core algorithm	Model type	Evaluation metric	Best results
Conant et al. [64]	Logistic regression	DBT-based logistic regression model	Sensitivity specificity	0.909 0.913
Niu et al. [250]	Multivariate logistic regression	DBT-based radiomics model	AUC	0.980
Wang et al. [251]	Logistic regression	DBT-based combined radiomics nomogram	AUC	0.905
Eriksson et al. [248]	Elastic net logistic regression, nested cross-validation	DBT-based risk model	AUC	0.820
Bahl et al. [252]	Multivariable logistic regression	DBT-based DL models	Adjusted odds ratio	0.880–1.140
Kim et al. [253]	Multivariable logistic regression	DBT-based logistic regression model	TP, FP	18.7 vs. 21.7% 75.9 vs. 77.6%
Peng et al. [254]	Random forest	DBT-based random forest classifier	AUC	0.834
Sakai et al. [255]	Support vector machine	DBT-based support vector machine classifier	Correct identification rate	0.840
Wels et al. [256]	Multiple multivariate random forest regression	DBT-based machine learning methods	Localization error	22.480 ± 8.670 mm
Samala et al. [132]	Feature selection, random forest classification	DBT-based deep DCNN	AUC	0.900

Note: None of the source codes or databases of the papers listed in Table 2 are publicly available.
Abbreviations: AUC, area under the curve; DBT, digital breast tomosynthesis; DCNN, deep convolutional neural network; DL, deep learning; FP, false positive; SVM, support vector machine; TP, true positive.

In 2022, Niu et al. [250] developed a nomogram that combines radiomic features with clinically important factors. Compared with the classical mammography-DBT assessment method, their nomogram demonstrated superior diagnostic ability and was recommended as a valuable tool for assisting clinicians in the early screening of breast cancer [250].

In 2020, Sakai et al. [255] explored the use of various classifiers, including SVM, naive Bayes, random forest, and MLP classifiers, to classify a variety of extracted radiomic features, with a particular focus on comparing their accuracy. Among these classifiers, the SVM-based classifier was the most effective, achieving accuracies of 55 and 84% in detecting benign and malignant tumors, respectively. These results indicate that the proposed method can assist imaging physicians in diagnosing lesions more accurately [255].

Radiomics employs machine learning technology to analyze and interpret medical images, as demonstrated by numerous studies applying such methods to this field [257–260]. Radiomic methods can extract specific imaging features (e.g., first-order features, textural elements, intensities, gradients, and curvatures) from DBT images to identify ROIs [251, 255, 261]. This capability plays a key role in all aspects of breast cancer management, including diagnosis, subtype differentiation, treatment response assessment, and prognosis.

For example, Tagliafico et al. [262] used radiomics in DBT to assess dense breasts, extracting 104 different features from the images of 20 patients and analyzing the differences in three specific features between healthy individuals and cancer patients, achieving an AUC of 0.567. Moreover, Fusco et al. [263] utilized radiomics to differentiate between malignant and benign lesions, focusing on the morphological features distinguishable on DBT, and achieved an AUC of 0.74 following univariate analysis. Together, these studies illustrate the ability of radiomics to identify ROIs by extracting specific imaging features from DBT images. Advances in machine learning technology are critical for improving the early screening and diagnosis of breast cancer.

5 | Public Mammography Databases

DL models in the field of DBT require a substantial amount of data and comprehensive databases [264]. Currently, DM research benefits from numerous datasets sourced from multiple medical centers, but the limited availability of public datasets hampers the development of the DBT field [265–267].

In this subsection, we present several key databases that allow researchers access to DBT-related data. These databases can be categorized into two types: DM datasets and DBT datasets. Notably, the DM and FFDM datasets are relatively abundant in

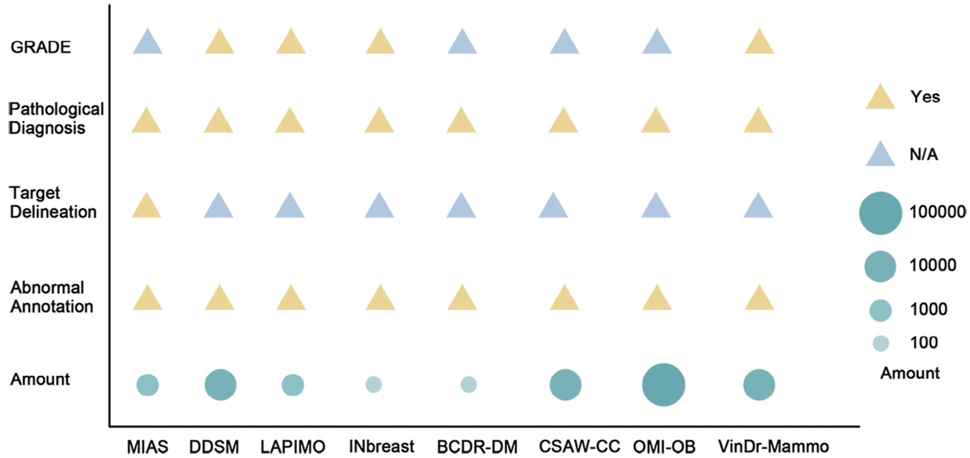

FIGURE 4 | Detailed comparison of breast cancer image databases. We make detailed comparisons between databases based on several key attributes, including GRADE, that is, whether information on the severity grading of breast cancer is included; pathological diagnosis, that is, whether benign and malignant information is included; target delineation, that is, whether the delineation of target regions for breast cancer is included; abnormal annotation, that is, whether abnormal annotations are included; and amount, that is, the number of images in the dataset. The yellow triangles indicate that the attribute is present, whereas the blue triangles represent "not applicable," that is, the data are not provided. The size of the circle indicates the order of magnitude of the images in the dataset. For example, the largest circle represents an order of magnitude of more than 100,000 images, whereas the smallest circle represents an order of magnitude of fewer than 100 images. The representative breast cancer image databases include MIAS, DDSM, LAPIMO, INbreast, BCDR-DM, CSAW-CC, OMI-OB, and VinDr-Mammo.

publicly available sources. We list 11 widely used public datasets with data sizes ranging from a few hundred to hundreds of thousands of samples. Most of these datasets contain detailed regional-level annotations.

We summarize the currently available mammography databases, including DM and FFDM databased. The MIAS and INbreast databases are specifically dedicated to mammography image analysis. The MIAS database was constructed from Joyce-Loebl scanning of films from the UK National Breast Screening Program [268]. It includes images of women of various ages and ethnicities, with annotations detailing lesion location, size, and morphology. INbreast comprises data from 115 women (410 images), including patients with both breasts and those who had undergone mastectomy and lesion types including masses, calcifications, asymmetries, and deformities [269]. The DDSM [270], LAPIMO [271], BCDR-DM [272], CSAW-CC [273], OMI-DB [274], and VinDr-Mammo [273] databases provide extensive collections of mammography and FFDM images. These databases offer not only conventional X-ray images but also ultrasound images and a rich array of images with BI-RADS classification annotations to support the development, training, and performance testing of mammography CAD programs.

The DDSM, LAPIMO, INbreast, and VinDr-Mammo databases contain grading of recommendations, assessment, development, and evaluation annotations. The OMI-DB and VinDr-Mammo databases, containing 148,461 and 5000 four-view FFDM images, respectively, are annotated with detailed assessments and lesion findings at the breast level, providing high-quality resources for research and clinical diagnosis (Figure 4).

In contrast, few publicly available DBT datasets exist because of the relative recency of DBT technology. The main shortcomings of DBT databases with respect to other databases (e.g., DM databases) are their small number of datasets, insufficient detailed annotations, and lack of patient diversity. This limits the options available to researchers and clinicians for training and evaluating DL models. Currently, DBT databases are widely used in training tumor detection and classification algorithms, evaluating their effectiveness in the diagnosis of various conditions, improving image reconstruction and enhancement techniques, conducting multimodal image research, training and educating clinicians, and developing optimized CAD systems [275–277]. These applications not only enhance the early detection and diagnosis of diseases such as breast cancer but also promote the advancement of related technologies and algorithms.

However, most datasets constructed in these studies are not publicly available. The BCS-DBT dataset, consisting of 5060 samples, is currently the only publicly accessible DBT dataset [167, 278]. Two imaging physicians annotated these samples, documented the presence of masses and ARDs, and assessed whether the findings were benign or malignant lesions [279, 280]. However, the details of their regional-level annotations are very limited. This discrepancy highlights the scarcity of comprehensive DBT datasets, especially considering the volume and depth of information needed. Therefore, the development and availability of large-scale, well-annotated public DBT databases is highly important. A comparison between the DBT and DM databases is shown in Table 3.

6 | Challenges and Prospects of DL Applications in DBT Imaging

Although DL techniques have shown great potential in analyzing breast cancer images, their application in the DBT field remains limited. Next, we review the three main challenges faced in the application of DL techniques in DBT research and propose

TABLE 3 | DBT and DM databases.

Dataset	Modality	Samples	Short description	Uniform resource locator
Yonsei University	DBT	173	Malignant breast lesions were included in 169 patients.	Unavailable
Duke University	DBT	4348	The data consist of 19,230 reconstructed volumes from 4348 patients. Cancerous lumps and building distortions are marked by the radiologist with bounding boxes.	Unavailable
The TOMMY trial	DBT	7060	Provides women (47–73 years of age) recalls for further evaluation after routine breast screening and women (40–49 years of age) who participate in annual mammograms.	Unavailable
BCS-DBT	DBT	5060	DBT dataset consists of a collection of patients who has a DBT exam at Duke Health system within January 1, 2014 to January 30, 2018.	https://sites.duke.edu/mazurowski/resources/digital-breast-tomosynthesis-database/
MIAS	DM	322	Provides an organization of UK research groups interested in the understanding of mammograms and generates a database of digital mammograms.	http://peipa.essex.ac.uk/pix/mias/all-mias.tar.gz
DDSM	DM	10,480	Provides a database established by medical institutions in the United States to store breast cancer images, including: cancer, normal, benign, benign without callback.	http://marathon.csee.usf.edu/Mammography/Database.html
LAPIMO	DM	320	Development of a database with significant number of cases and digitized mammographic images forward to the development, training, and performance tests of mammography CAD schemes.	http://lapimo.sel.eesc.usp.br/bancoweb/english/index.php
INbreast	DM	115	Provides a total of 115 patients (410 images), of which 90 are from women with both breasts (four images each) and 25 from mastectomy patients (two images each). Including several types of lesions (lumps, calcifications, asymmetry, and deformation).	http://medicalresearch.inescporto.pt/breastresearch/index.php/Get_INbreast_Database
BCDR-DM	DM	116	Provides 724 (723 female and one male) Portuguese patients cases (with ages between 27 and 92 years old), including 1042 studies, 3612 MLO and/or CC mammography incidences, and 452 lesions clinically described (already identified in MLO and CC views).	https://bcdr.eu/information/about
CMMD	DM	1775	Provides 3728 mammograms performed by 1775 patients between July 2012 and January 2016 are presented, and the biopsy confirmed to be of benign or malignant tumor type. For 749 of these patients (1498 mammography), we also include the molecular subtypes of the patients.	https://www.cancerimagingarchive.net/collection/cmmd/
CSAW-CC	DM	65,240	CSAW includes 499,807 women invited to be screened between 2008 and 2015, with a total of 1,182,733 completing screening tests. Approximately 2 million mammogram images have been collected, including images of all women with breast cancer.	https://link.springer.com/article/10.1007/s10278-019-00278-0

(Continues)

TABLE 3 | (Continued)

Dataset	Modality	Samples	Short description	Uniform resource locator
OMI-DB	FFDM	172,282	Consists of several relational databases and cloud storage systems, containing mammography images and associated clinical and pathological information. The database contains over 2.5 million images from 173,319 women collected from three UK breast screening centers.	https://medphys.royalsurrey.nhs.uk/omidb/
DMID	DM	510	Detailed radiological reports and pathology information via pixel-level annotations and associated segmentation masks to support mammography for DL systems.	https://figshare.com/articles/dataset/_b_Digital_mammography_Dataset_for_Breast_Cancer_Diagnosis_Research_DMID_b_DMID_rar/24522883
VinDr-Mammo	FFDM	5000	A Vietnamese digital mammography dataset with mammal-level assessment and extensive lesion-level annotations, each examination has four standard views and is a double reading, and provides categories, locations, and BI-RADS assessments of nonbenign findings.	https://vindr.ai/datasets/mammo

Abbreviations: BI-RADS, breast imaging reporting and data system; CAD, computer-aided diagnostic; DBT, digital breast tomosynthesis; DL, deep learning; DM, digital mammography; FFDM, full-field digital mammography.

directions for future development. Figure 5 provides an overview of the deployment of DL and machine learning in the DBT domain, highlighting their advantages and challenges.

6.1 | Challenges and Perspectives Related to DBT Datasets

The training of DL models relies on large, high-quality annotated training sets [281, 282], and public datasets provide a foundation for researchers to develop and evaluate models. However, the lack of public DBT datasets remains a significant challenge, with existing well-known mammography datasets (e.g., DDSM and OMI-DB) not applicable to DBT and the sharing of image data severely restricted owing to privacy policies [283–285]. Therefore, further development of DL-based DBT models requires the collection of a large amount of accessible data. Typically, DL models perform best on large amounts of highly annotated data, but DBT typically produces more than 100 times more images than DM does; however, malignant features are usually only visible in a few slices [286, 287]. Previous studies have improved model performance by collating and annotating DBT image datasets, applying multi-instance learning, and so on [288, 289]. Buda et al. [167] collated data from more than 22,000 3D-DBT volumes from 5060 patients to facilitate the development of a breast cancer screening model. Lotter et al. [287] also developed a new method to efficiently train a model using DBT data labeled with breast-level labels while maintaining the interpretation of lesion location. while maintaining interpretability of the lesion location, thereby significantly reducing the need for detailed annotated data without sacrificing performance.

The lack of a common DBT dataset limits the generalization of DL models because their repeatability relies on consistent results under similar conditions, a problem exacerbated by differences in the range of angles, acquisition methods, and reconstruction techniques from different vendors [61, 290, 291]. In addition, DBT images vary significantly from the appearance of normal breast tissue, so image standardization is critical in DBT applications [292, 293]. Researchers use different datasets and evaluation strategies, making results difficult to evaluate and compare. The test sets of many studies tend to come from a single institution and exclude specific data, which obscures the true performance of the algorithm [60]. To this end, data augmentation techniques can be used to improve the learning and generalization capabilities of deep networks [294–297]. For example, Garrucho et al. [298] used synthetic high-density FFDM as data enhancement in the training of a breast mass detection model, and the results showed that this method improved the sensitivity and accuracy of the model on small datasets and enhanced the domain generalization ability of the training model on large databases.

Another important reason for the lack of DBT public datasets is patient privacy protection and ethical issues [299, 300]. Due to data privacy and regulatory issues, data are usually retained within the hospital host server and cannot be easily shared [301, 302]. Ethical requirements to ensure the security and confidentiality of patient data. Failure to properly protect patient privacy can lead to data breaches and legal liabilities, undermining patient confidence in the healthcare system [303, 304]. This ethical consideration has led healthcare organizations to take

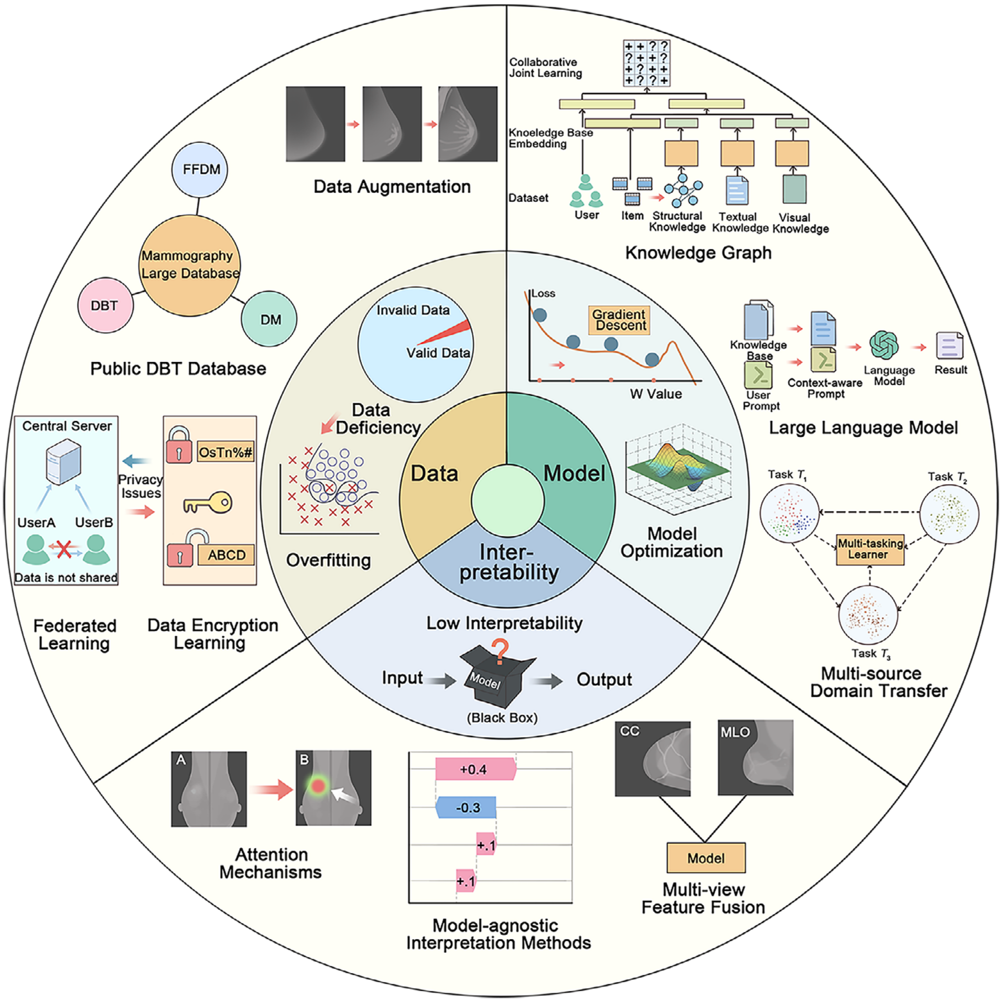

FIGURE 5 | Challenges and future prospects of DL techniques for DBT applications. The challenges are grouped into three categories: data challenges, model challenges, and interpretability challenges. The training of DBT-DL models depends on the availability of a substantial, high-quality annotated training set, as there is a paucity of publicly available datasets for DBT. A lack of data can lead to model overfitting. In addition to building public databases, the use of data augmentation, federated learning, encrypted data learning, and other methods is expected to improve model generalizability across different datasets. In addition, the training process of DL models presents numerous challenges. Multisource domain migration, LLM, and knowledge graphs are expected to facilitate the implementation and dissemination of DBT techniques in clinical settings. Since DL models are opaque, resulting in low interpretability. Attention mechanism networks, multiperspective feature fusion, and in-model interpretation approaches are expected to improve interpretability.

a more cautious approach to sharing sensitive data, limiting the construction of and access to DBT public databases. Data privacy protection methods range from data anonymization and obfuscation to federated learning and encrypted data learning. Federated learning is a private, distributed, and decentralized machine learning method that uses private data to train shared models locally without exchanging original patient data [305–307]. In 2019, Sheller et al. [308] demonstrated federated learning on clinically acquired brain tumor segmentation data for an interagency segmentation task. Their study revealed that federated semantic segmentation models (Dice = 0.852) performed similarly to models trained on shared data (Dice = 0.862) and outperformed two alternative collaborative learning methods [308].

In summary, the challenges faced by datasets during the training of successful models are related to the generalization ability of the model and data privacy protection. In the future, data privacy-preserving methods such as federated learning and encrypted data learning are expected to improve the generalization ability of models for different datasets while meeting the requirements of data privacy preservation. In addition, we encourage research teams to make DBT datasets publicly available to promote the further application of DL models in the field of DBT.

6.2 | Challenges and Perspectives Related to Modeling

New developments in DL models in the DBT field continue to emerge, which we categorize into three parts. We also outline the challenges associated with model training and present prospects for the application of multiple-source domain transfer (MSDT), large language models (LLMs), and knowledge graphs in the DBT domain.

In the field of the diagnosis and classification of breast cancer, DL has made significant progress, with multimodal data fusion achieving encouraging results [309–311]. The synergistic application of DM, DBT, and contrast-enhanced magnetic resonance imaging has been demonstrated to enhance the identification of malignant tumors and reduce the incidence of interstitial cancer [312, 313]. A groundbreaking study by Shoshan et al. [86] used an ensemble of 50 DL and machine learning classifiers to combine DBT data with numerous clinical parameters, including patient age, ethnic background, hormonal status, and family history of breast cancer. Their findings highlighted the efficacy of AI in enhancing breast cancer screening programs. Notably, the AI-driven approach resulted in a significant reduction in the clinical workload by 39.6% and a 25% reduction in patient recall without compromising sensitivity [86]. Thus, this multimodal screening paradigm shows great promise in enhancing DBT by improving diagnostic accuracy and streamlining the screening process.

In the field of early screening and diagnosis, Rodriguez-Ruiz et al. [314] introduced a DL-enhanced interactive tool for imaging students that calculates a localized cancer likelihood score after selecting a specific breast region. This innovation significantly improved the AUC, increasing sensitivity while maintaining specificity and accuracy without prolonging the reading time [314]. In addition, the application of AI in the design and implementation of clinical trials is equally significant. Dong et al. [315] aimed to analyze the characteristics of registered AI trials for cancer diagnosis by searching the ClinicalTrials.gov database to statistically and analytically analyze the design and outcomes of 97 clinical trials involved. The results revealed that most of the trials were observational in design and that the number of interventional trials was low, indicating that the field is in dire need of more high-quality clinical validation [315]. The use of AI in clinical trials is still in its infancy, but it is a rapidly evolving field. As regulators provide more guidance on the acceptability of AI in specific areas, its use will expand, and its implementation will increase rapidly.

Important breakthroughs in lesion segmentation and detection have also been achieved by DL [316–318]. Advanced segmentation models can accurately identify and segment structures and lesions in the breast, aiding in diagnosis and treatment. U-Net and its variants, as well as the DeepLab family, are advanced segmentations models that have been applied to DBT [319–323]. In 2023, Bobowicz et al. [324] proposed a clustering-based constrained attention multiple instance learning (CLAM) classifier that can be trained efficiently despite a relative scarcity of data. A feature extractor pretrained on ImageNet (ResNet18, ResNet34, ResNet50, and EfficientNetB0) was used, resulting in an AUC of 0.848. The attention map of the CLAM algorithm highlights the features in the image most relevant for the algorithm [324].

The field of medical image generation has also benefited from developments in DL, particularly through the application of GANs and VAEs. In 2019, Cogan et al. [325] presented a comprehensive mammogram screening solution consisting of three main components: a machine learning algorithm to accept or reject images as valid mammograms, an artificial neural network to locate potential malignancies, and a web service for uploading images and viewing results. The image receiver is primarily a class of SVMs constructed based on features derived from a VAE. If an image is accepted as a mammogram, the malignant tumor recognizer (ResNet-101 Faster R-CNN) will locate the tumor in the mammogram. In the test data, the malignant tumor recognizer achieved an AUC of 0.951 [325]. In 2023, Balaji [326] proposed a 3D Connected-UNet based on an encoder–decoder architecture for tumor segmentation from 3D MR images and evaluated it on the INbreast and private datasets. The experimental results show that the proposed model outperforms existing breast tumor segmentation methods [326].

MSDT may be a potential optimization approach for integrating DM, FFDM, and DBT data, mitigating variability between datasets and enhancing the generalization ability and diagnostic accuracy of models in the DBT field [327–329]. Specifically, MSDT can reduce data bias, resulting in more stable and accurate models when processing images from various sources, thereby improving the sensitivity and specificity of early breast cancer detection [330, 331]. Additionally, MSDT can significantly reduce the need for and cost of labeled data, as models can be effectively trained using multiple unlabeled datasets. This approach not only addresses the challenge of data scarcity but also accelerates the adoption of DBT technology in clinical settings [332, 333].

In the future, with advancements in transfer learning algorithms and computational resources, the application of the MSDT in DBT is expected to further enhance image quality, diagnostic efficiency, and patient outcome prediction. Regularization methods (e.g., dropout) and the development of more robust model architectures (e.g., transformer) have been proposed for improving model adaptability across different sets of data and tasks [334–338]. In 2019, Aslani et al. [339] proposed the use of secondary networks and corresponding regularized loss terms to learn domain-specific knowledge. Their study demonstrated that networks with independent branches produced more accurate segmentation, such as a dice similarity coefficient (DSC) of 0.7649, than did single-branch networks with all modalities stacked, highlighting the importance of the fluid-attenuated inversion recovery modality for multiple sclerosis lesion segmentation (DSC $>$ 0.65) [339].

These secondary networks learn to predict the class of the input scanner domains, encouraging the backbone segmentation network to ignore domain-specific information and helping it outperform other baseline networks in generalizing to new data points. In 2022, Sendra-Balcells et al. [340] evaluated the potential of domain generalization for increasing the number of images with data augmentation, domain blending, transfer learning, and domain adaptation techniques. Their results indicated that combining data augmentation with transfer learning can produce single-center models that generalize well to new clinical centers not included in the training data [340]. Single-domain neural networks enriched with appropriate generalization procedures can meet or exceed the performance of multicenter, multivendor models for augmented imaging, thereby eliminating the need for comprehensive multicenter datasets for training generalizable models [340, 341].

Recently, LLMs have achieved important milestones in addressing various challenges in the biomedical field [342–345]. For example, in 2024, Huang et al. [346] introduced the clustered rule-interval short palindromic repeats-generative pretrained transformer (CRISPR-GPT) that enhances domain knowledge and external tools to automate the process of designing CRISPR-based gene editing experiments. CRISPR-GPT leverages the reasoning capabilities of LLMs to facilitate the selection of CRISPR systems and experimental design, demonstrating the potential of LLMs in complex biodiscovery tasks [346]. At the same time, LLMs play an important role in clinical trials. In 2024, Jin et al. [347] introduced TrialGPT, an LLM-based framework for assisting in the matching of patients to clinical trials. Evaluated across 183 patients and more than 18,000 trial annotations, TrialGPT not only achieved 87.3% predictive accuracy, but also significantly reduced the time for clinical trial matching, demonstrating its great potential to enhance patient recruitment efficiency [347].

DL models are highly dependent on the amount of data, and the number of mammograms required for a human physician to achieve better diagnostic performance is much less than that required for DL models. Human doctors utilize their extensive experience and comprehensive background knowledge in the diagnostic process and can make accurate diagnoses with fewer images, whereas DL models require large amounts of data for training to ensure their accuracy and generalizability in various situations. However, LLMs have the potential to mitigate the extensive data needs of DL models in medical imaging diagnosis with many mammography images. Like human doctors, LLMs can use textual information to enhance their diagnostic capabilities. By analyzing electronic health records and other textual information, an LLM can acquire more contextual knowledge, improving the accuracy of image diagnosis [348–351]. LLMs can also accumulate a vast amount of medical knowledge and reasoning ability through the pretraining process, enabling them to apply existing knowledge and reasoning strategies when processing new image data, thus improving diagnostic efficiency and accuracy, even in cases of low image data availability [352–354].

In addition, various retrieval augmented generation (RAG) methods have been developed to search for documents from a knowledge corpus and generate responses by attaching them unconditionally or selectively to the input of the LLM [355–357]. In 2024, Jeong et al. [358] introduced self-biomedical RAG (Self-BioRAG), a reliable biomedical text framework that is specialized in generating explanations, retrieving domain-specific documents, and self-reflective generated responses. The experimental results for Self-BioRAG demonstrated significant performance gains, with an average absolute improvement of 7.2% compared with those of state-of-the-art open-base models with parameter sizes of 7B or less [358].

Overall, the application of the RAG score to LLMs enables the models to act like medical experts do, utilizing information from retrieved documents and coded knowledge, thereby enhancing the capabilities of the biomedical and clinical domains.

A retrospective study by Andrea et al. in 2024 demonstrated that, based on breast imaging reports written in three languages, publicly available LLMs such as GPT-4, GPT-3.5, and Google Bard reached moderate agreement with the BI-RADS category assignments given by human readers (AC1 values of 0.52, 0.48, and 0.42, respectively). However, their limitations in processing multilingual breast imaging reports have revealed their performance in complex clinical tasks needs improvement [359]. Additionally, in 2024, Vera et al. evaluated the performance of ChatGPT-3.5 and GPT-4 in clinical note analysis, guideline-based Q&A, and patient management recommendations by searching medical literature analysis and retrieval systems online for relevant studies published before December 22, 2023. The results revealed the potential of LLMs in breast cancer patient care, with high accuracy in structured tasks but demonstrating issues regarding inconsistency and cue dependency, highlighting the importance of careful validation and continuous monitoring of these models [360]. Currently, state-of-the-art models such as GPT-4 and pathway language model 2 occupy a central position in healthcare AI innovation, showing significant potential for DBT screening in the early stages of breast cancer [359, 361, 362]. Incorporating LLMs into this field is expected to help health care professionals more accurately identify and classify breast lesions and shorten consultation times, potentially transforming the landscape of breast cancer diagnosis and screening.

However, the problem of the baselessness of LLMs in generating knowledge highlights the need to incorporate other technological tools to improve the accuracy and reliability of the generated information. Among these, the integration of knowledge graphs into LLMs provides one effective solution [363–365]. Knowledge graphs describe knowledge as a structured and decisive representation in the form of “head entity-relation-tail entity” triples; examples include Wikidata, yet another great ontology, and never-ending language learning [366–368]. Knowledge graphs, an important subfield of knowledge engineering, can provide LLMs with structured medical knowledge and relationships to enhance their comprehension and reasoning capabilities, thus helping the models more accurately and comprehensively consider pathological features and diagnostic information when analyzing and interpreting medical images [369–371].

In 2023, Li et al. [372] designed a workflow centered on a DL model called the bidirectional long short-term memory highway conditional random field. This workflow first establishes the structure of the knowledge graph for breast cancer diagnosis at the conceptual level and then searches for associations through bidirectional long short-term memory while optimizing information flow with a highway network, which optimizes information flow and feature extraction, leading to significant improvements in performance [372]. In 2022, Zhang and Cao [373] combined knowledge graphs with natural language processing to simplify the extraction of breast cancer genetic features, using the Bhattacharyya distance index and Gini index for sample gene selection. These advances are expected to enrich the pathways for breast cancer gene extraction and significantly contribute to disease control and prevention [373].

In conclusion, DL models have broad application prospects in the field of DBT, and their potential to achieve significant advancements in diagnostic classification, lesion segmentation and detection, and medical image generation has been preliminarily verified in various studies. Through multisource domain migration, DL models are expected to integrate data from different sources better and achieve improved generalizability and diagnostic accuracy. AI technologies other than DL, including LLMs and knowledge graphs, are expected to accelerate the application and diffusion of DBT technologies in clinical settings.

6.3 | Interpretability Challenges and Perspectives

One of the main challenges in applying DL and other AI models to DBT is the issue of model interpretability [374–376]. DL models are often regarded as "black boxes" [377] due to a lack of transparency in their decision-making process [378, 379]. If a model makes a mistake, it is difficult for doctors to detect and correct it, potentially resulting in diagnostic errors [380].

Regulatory issues have a profound impact on the interpretability of DL models, and regulatory restrictions have made the development of tools and strategies for interpreting complex models of sophisticated AI a pressing need [381]. On the one hand, regulatory frameworks have driven the development of interpretability standards to ensure that AI meets transparency and compliance requirements in its applications [382]. On the other hand, regulatory requirements enhance model transparency, prompting developers to emphasize interpretability in the design and implementation process, enabling healthcare professionals to understand model decisions and thus increasing trust in AI [383]. Regulation also facilitates the validation and approval process by requiring developers to demonstrate evidence of explainability to gain approval for clinical applications, which drives the development of compliant technologies. Farah et al. [384] emphasized the importance of explainability in enhancing trust among healthcare stakeholders through a review of the existing literature. The specific tools proposed in the article include decision support flowcharts and evaluation methods that incorporate interpretability into the core of algorithm development to help understand how machine learning algorithms work [384].

Strategies for improving the interpretability of DL models applied to DBT include feature visualization, fusion of multiview feature fusion, model-agnostic interpretation, and location annotation. Mohseni et al. [383] presented a multidisciplinary framework that integrates knowledge from different domains to support the design and evaluation of explainable AI (XAI) in clinical workflows. The article categorizes the design goals and evaluation methods of XAI, emphasizing how interpretable tools can be practically applied to enhance physicians' trust and willingness to use them [385]. Lu et al. [386] enhanced the model's application in clinical trial management by employing a selective classification approach in conjunction with a hierarchical interaction network that ensured the retention of prediction decisions at low confidence, thereby enhancing physicians' trust and willingness to use model predictions. The results of the study showed that the method significantly improved the accuracy and interpretability of clinical trial approval prediction [386]. Improving interpretability can be achieved by introducing innovative neural network architectures and visualization techniques, such as models based on attention mechanisms and Grad-CAM. The introduction of the attention mechanism enhanced model interpretability, allowing networks based on this mechanism to represent the significance of features at different spatial locations and guide the information visible in other parts of the network [387]. Fusion of multiview features involves combining image information from different angles and levels and enhancing the interpretability and reliability of the model by integrating features from different viewpoints, thereby making the model's decision more clinically meaningful.

In 2023, Zhong et al. [388] proposed a multiview fusion network with local-global dual-path transformer architecture, for mammography-based breast density classification in breast cancer screening, achieving AUCs of 96.73 and 91.12% on two publicly available mammography datasets, CBIS-DDSM and INbreast, respectively. The designed fusion model utilizes information from multiple views more efficiently than existing models do, outperforming baseline and state-of-the-art methods [388]. In 2016, Gal and Ghahramani [389] developed a new theoretical framework that treats dropout training in deep neural networks as approximate Bayesian inference in a deep Gaussian process.

Model-agnostic interpretation methods, such as LIME and Shapley additive explanations (SHAPs), can reveal the detailed contributions of individual features to the prediction results of a DL model [390–392]. In 2022, Ma et al. [216] built an interpretable machine learning model to distinguish the molecular subtypes of breast cancer, using the SHAP technique to identify important features for predicting the molecular subtypes from many imaging signs. The application of these explanatory methods in DBT can better elucidate the decision-making process of the model for each image segment, identify key lesion features, and enhance physicians' trust in the model's predictions, thereby increasing the clinical application value of DBT [393].

Another intuitive and enhanced interpretability approach is lesion localization annotation [394]. This method can reveal the spatial locations of key features in the model's decision-making process, aiding imaging physicians in understanding and validating the model's diagnostic results, thereby improving trust and clinical usability in the model. The noninterpretability of DL models remains the most significant barrier to their clinical deployment, highlighting the urgent need for models with better interpretability [395].

7 | Conclusion

This review comprehensively analyzes the applications, challenges, and future directions related to DL technology in the field of DBT. First, we analyzed the current status of DBTs, including their principles and applications. Next, we summarize the functions and applications of DL in the treatment of breast diseases and classify the DL models into three main categories. Additionally, we explore the application of DL in other areas of DBT and other AI techniques in addition to DL in early DBT screening, summarizing publicly accessible databases. Finally, we address the challenges and future research directions in the application of DL to DBT, summarize the potential of knowledge graph- and LLM-based applications in DBT, and lay a foundation for advancing DL-based early DBT screening applications. Our work highlights the significant promise of DL applications in DBT and outlines future research trajectories.

Author Contributions

R.Y.W.: Data curation, investigation, and writing—original draft. F.X.C.: Data curation, investigation, and writing—original draft. H.M.C.: Data curation, investigation, and writing—original draft. C.X.L.: Investigation, methodology, and visualization. J.C.S.: Investigation, methodology, and visualization. Y.T.W.: Investigation, methodology, and visualization. L.X.M.: Investigation, methodology, and visualization. X.Q.H.: Investigation, methodology, and visualization. M.W.: Investigation, methodology, and visualization. J.W.: Investigation, methodology, and visualization. Q.Z.: Conceptualization, funding acquisition, project administration, supervision, and writing—review and editing. J.W.S.: Conceptualization, funding acquisition, project administration, supervision, and writing—review and editing. J.Y.P.: Conceptualization, funding acquisition, project administration, supervision, and writing—review and editing. All authors have read and approved the final manuscript.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information