

Archives of Surgical Research | Systematic Literature Review**Artificial Intelligence In Breast Screening: A Systematic Literature Review**

Haseeb Arif, Emaan Tindyala, Hira Ashraf

IMPORTANCE Breast cancer is the most prevalent cancer in women worldwide. Early presentation, detection and prompt treatment limit morbidity and mortality due to breast cancer. Conventionally, breast cancer screening techniques and diagnosis have relied upon interpretation of radiologists and pathologists. However, advancement in artificial intelligence can lead to further enhancement in accuracy and efficiency of these diagnostic techniques, thereby, reducing incidence of morbidity and mortality.

AIM This systemic literature review is conducted to ascertain whether artificial intelligence (AI) can be used to complement existing breast cancer screening techniques. Objective of this review is to determine whether AI can enhance sensitivity of screening techniques, enable more accurate classification of benign and malignant tumors and improve assessment of response to neoadjuvant therapy.

METHODS This systemic review is conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A comprehensive computer literature search in database of PubMed was performed using a combination of search terms: 'Artificial intelligence' OR 'AI' OR 'Machine learning' AND 'Screening' AND 'Breast cancer'. 843 articles were identified through search in PubMed database. Following removal of 4 duplicate papers, titles and abstracts of 839 articles were reviewed. 115 articles with relevant titles and abstracts were analyzed. Following thorough analysis, 15 papers were included in this literature review.

RESULTS AI algorithms exhibited capability in classifying breast lesions and identification of malignancy in otherwise suspicious lesions across different imaging techniques. The integration and assistance of AI algorithms in interpretation of MRI, mammography and thermography has led to significant improvement in diagnostic accuracy and classification of breast lesions. AI complements radiologists and aids in improving performance, thereby, generating better results. AI has the capability to predict response to neoadjuvant chemotherapy in breast cancer patients, leading to safer, more effective and more cost-effective treatment for breast cancer patients.

CONCLUSIONS Artificial intelligence has the potential to revolutionize medicine in 21st century. Artificial intelligence has widespread potential in breast cancer screening. It can aid in improving radiologists' ability to detect cancer on radiograms, classifying breast lesions, and predicting response to neoadjuvant therapy.

KEYWORDS Artificial Intelligence, Machine Learning, Neural Networks, Breast Cancer, Neoadjuvant Therapy, Screening.

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Breast cancer is the second most common cause of cancer related death in women worldwide. Globally, it is one of the most common cancers in women¹.

Despite its high prevalence early detection and prompt treatment are highly effective means of limiting mortality². Screening techniques such as mammography, MRI, ultrasonography and biopsy are the mainstay in breast cancer screening³. Advancement in technology especially in the field of artificial intelligence (AI) has led to further enhancement in accuracy and efficiency of these diagnostic methods. Implementation of artificial intelligence in breast cancer screening can potentially lead to further reduction in mortality in breast cancer patients through early diagnosis⁴⁻⁶.

The concept of AI has been a subject of speculation for many decades. Alan M. Turing proposed the query about machine thinking in his 1950 paper. Turing believed that the ultimate form of AI would be indistinguishable from a human being^{7,8}. Subsequent research led to the creation of IBM's Deep Blue, thereafter, marking the initiation of further advancement and implementation of AI in the field of medicine⁹. A wide range of tools have emerged from the field of AI. These tools are broadly classified into knowledge-based systems (KBS), computational intelligence (CI), and hybrids. In KBS knowledge is explicitly modelled in words and can be interpreted by a human. In CI knowledge is represented by figures. Hybrids find numerous applications in multiple fields such as agriculture,¹⁰ education, economics, medicine and others¹¹. AI has been used to

classify skin cancers with accuracy on par with certified dermatologists¹¹. In addition, it has been used in intraoperative margin assessment of breast tissue to identify breast cancers¹². A study at Children's National Medical Center in Washington, showed that a supervised autonomous robot could perform soft-tissue surgery¹³. Conventionally, breast cancer screening and diagnosis has relied upon interpretation of radiological images and biopsy specimens by radiologists or pathologists. However, significant research is being conducted so that this task can be handed over to AI for greater effectiveness¹⁴. Artificial intelligence is the ability possessed by sophisticated software to analyze information critically with a higher degree of efficiency⁸. Unlike a human being, it is devoid of fatigability and emotionality¹⁵. Deep learning is a type of AI that refers to an algorithm that uses multilayered 'neural networks' to learn information and feed it into network¹⁶. After sufficient learning this algorithm can be used to detect similar patterns in any new data presented to it. Deep learning convolutional neural networks contains neural networks with many layers. It has already been used in detection of breast cancer and mitosis on histological images¹⁷.

Past research has also demonstrated that implementation of AI in the detection of breast cancer led to greater sensitivity and specificity when compared to the results produced by human professionals alone^{18,19}. In this systemic literature review we seek to analyze the potential role of artificial intelligence in improving breast cancer screening in women.

METHODS:

This systemic review is conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Objective of conducting this review is to ascertain whether artificial intelligence can be used to complement existing breast cancer screening techniques.

Search strategy: A comprehensive computer literature search in database of PubMed was performed. The search algorithm was based on a combination of keywords: 'Artificial intelligence' OR 'AI' OR 'Machine learning' AND 'Screening' AND 'Breast cancer'. All search papers were reviewed according to the selected criteria.

Inclusion of articles: Computer literature search on PubMed database using the aforementioned keywords and additional filters yielded 843 articles. Additional filters applied during search included 'Species: Human', 'Sex: Female', 'Subject: Cancer', 'Average age of participants: ≥40 year'. All articles from 1/1/2019 till 1/5/2021 were included in the search process. Clinical studies, clinical trials, randomized control trials, systemic reviews and meta-analyses were reviewed during detailed analysis. Following removal of 4 duplicate papers, titles and abstracts of remaining 839 papers were reviewed. Papers with relevant

titles and abstracts were filtered, yielding 115 papers. Full text versions of 115 papers were reviewed and 26 papers were analyzed thematically. Following detailed analysis for suitability of inclusion, 15 papers were included in this literature review. Exclusion criteria included duplicate papers, papers with irrelevant titles, papers with irrelevant abstract, papers with irrelevant themes and papers not available in English language. Article selection process is given in Diagram 1.

Data synthesis: Thematic analysis of 26 papers was done. Following evaluation of suitability for inclusion 15 papers were used in this review. Data about author name, year of origin, type of AI used, purpose of study, screening method and key findings was collected and coded. These themes identified through data analysis are given in table.

RESULTS

843 articles were identified through search in PubMed database. Following removal of 4 duplicate papers, titles and abstracts of 839 articles were reviewed. Full text versions of 115 articles with relevant titles and abstracts were thoroughly analyzed. Thematic analysis of 26 papers was done. Following detailed analysis 15 papers were included in this review. Themes identified through analysis of data are coded in table 1.

Classification of breast lesions: MRI has a high diagnostic accuracy for detecting calcified and non-calcified breast lesions^{13,20,21}. Hence, application of AI to enhance this highly effective screening technique results in even greater sensitivity and accuracy. P.Herent et al, proposed a 50 layer residual neural network (ResNet-50) that used two-step system of detecting a lesion and classifying it into: normal tissue, other benign lesions, invasive ductal carcinoma (IDC), other malignant lesions and malignancy²². This exhibited an overall AUC (area under the curve) of 0.817 across all classifications, being particularly capable of identifying malignancy (AUC: 0.869)²². Another paper used a SVM (support vector machine) using machine learning to identify malignancy, achieving an AUC of 0.90, hence, accurately identifying malignant lesions²³. However, both of these systems relied on significant pre-processing of MRI prior to interpretation by the AI algorithm. The residual neural network devised by P.Herent et al, relied on an 'attention block' which was trained to initially detect area of anomaly and feed this data to a second branch that averaged features maps over selected areas²². The second study involved pre-analysis of the image by a clinical post-processing platform, performed by a radiologist, which generated quantifiable characteristics of that image (i.e., lesion size, diffusion restriction, T2w signal intensity and vascularity). These characteristics served as predictors of malignancy once entered into the algorithm. This study also implemented machine learning (ML) algorithm into an open access internet application that could predict whether a lesion on

MRI image was benign or malignant, upon entering the aforementioned characteristics of MRI image. Further research is required for the validation of these algorithms with additional 3D image information and morphological data²².

Another uncommon method of breast cancer screening called thermography relies on infrared radiation to detect breast lesions. One paper argued that the heterogeneity of the IR (infrared) signal emanating from the breast can be used to accurately detect possible lesions. It elaborated on the increased amount of heat generated by malignant lesions appreciable on the IR image. This increased amount of heat is generated due to angiogenesis, Nitric Oxide vasodilatory phenomenon, inflammation or action of estrogen in estrogen receptor positive malignancies,²³. The study aimed to incorporate a deep learning algorithm (ResNet-50) with thermography (deep thermionics) to detect breast lesions in suspected patients. However, main obstacle faced was generation of very high dimensionality using the algorithm alone. It identified 2048 dimensions of IR image which would inevitably lead to overfitting and 'curse of dimensionality'²³. The paper addressed this issue through use of an auto encoder reducing high dimensionality of the images. The autoencoder was trained specifically to reduce dimensionality hierarchically to lower dimension, reducing the dimensionality from 2048 to 16 compressed descriptors. This system captured the predominant features of IR images

with breast lesions, eliminating variations due to background 'noise'²³. The 'deep thermionics' system of lesion detection yielded an accuracy of 78.16%. It was proposed as a viable adjunct to pre-existing breast cancer screening techniques such as CBE (Clinical breast exam), MRI, Mammography, USG etc. This autonomous system had no need for human annotated features but its inability at accurately detecting deeper lesions with a more inconspicuous cutaneous IR signature was noted²³.

Breast micro calcifications (MC)s exhibit a strong correlation with the type of breast lesion present. In malignant lesions MC appear more scattered, smaller in size and greater in number²⁴. One paper aimed to elaborate use of a deep convolutional neural network (CNN) to classify breast MCs detected on mammography images. The research used a 5-layered deep CNN architecture to identify MC descriptors. This was compared to lesion classification using traditional manually extracted MC descriptors (e.g., shape, texture and morphology). It was concluded that CNN generated MC features were more accurate in classifying lesions (CNN accuracy: 0.8768 VS Manual features accuracy: 0.8667). It was also verified that traditional morphological features could be useful in guiding artificial neural network (CNN) to achieve higher accuracy for classification of MCs. CNN features filtered by morphological features achieved the greatest accuracy of 0.8859²⁴.

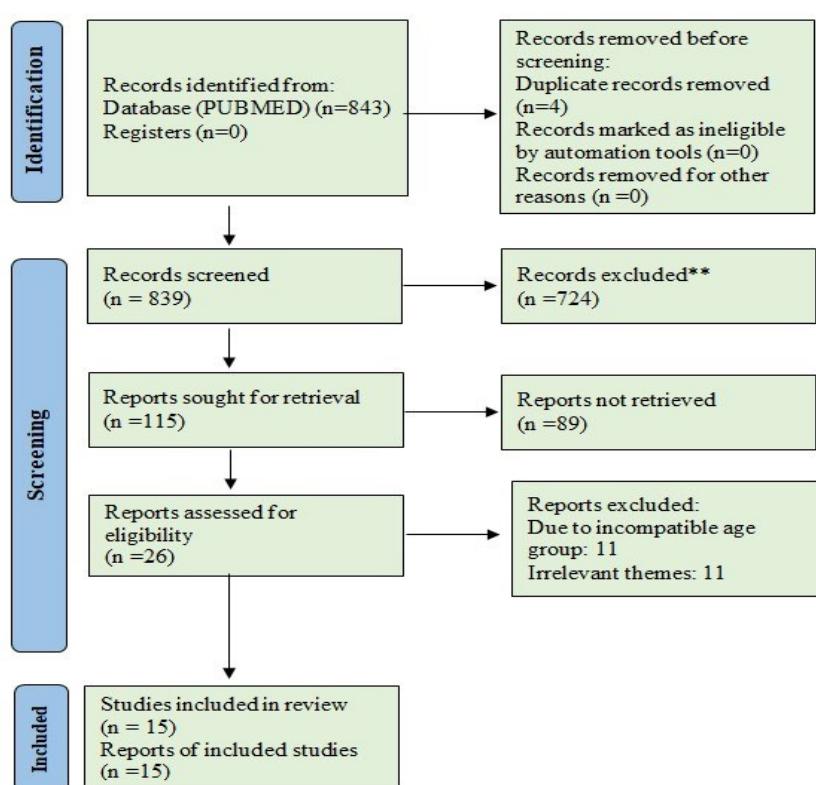


Diagram 1: Article selection process through computer literature search:

Author Name + Year of Origin	Type of AI Used	Purpose of Study	Method of Screening	Key Findings
P. Herent, 2019	DL	Differentiate b/w benign and malignant lesions	MRI (gadolinium chelate-enhanced)	Study showed good performance of the DL system in detecting lesions on MRI
Amirhessam Tahmassebi, 2019	ML	To assess complete response to NAC	MRI	ML with breast MRI enabled early prediction of pCR to NAC as well as survival outcomes
Elizabeth Hope Cain, 2019	ML, Multivariate	To assess pCR to NAC	MRI	The ML model was able to predict pCR through pre-treatment MRI features
Hongmin Cai, 2019	DL (Deep CNN)	Classification of Calcifications on Mammograms	Mammography	CNN is capable of discriminating between malignant and benign cancers using microcalcifications
Alejandro RodriguezRuiz, 2019	DL(DNN)	Identifying normal mammograms to reduce radiologist workload	Mammography	It was found to be feasible to pre-select mammograms using AI to reduce workload with minimum error
Alyssa T Watanabe, 2019	'CmAssist' DL (AI-CAD)	To retrospectively detect missed cancers on mammography	Mammography	There was an improvement in radiologist accuracy with use of cmAssist
Alejandro RodriguezRuiz, 2019	DL (CNN)	To compare the stand-alone performance of AI with 101 radiologists in detecting breast CA	Mammography	The AI had higher AUC than most of the radiologists (61% of radiologists)
Eduardo Fleury, 2019	5 different ML models used (MLP, DT, RF, LDA, SVM)	To evaluate computable BI-RADS radiomic features to classify breast masses	Ultrasonography	ML can aid in distinguishing malignant and benign lesions on ultrasound images with SVM having the highest accuracy
Ji Soo Choi, 2019	DL(CAD)	To investigate whether a CAD system improves the ability of radiologists to differentiate between malignant and benign masses on breast ultrasound (US)	Ultrasonography	Radiologists' performance improved through the use of AI, with more experienced radiologists benefitting more
Stephan Ellmann, 2020	ML, polynomial kernel function support vector machine	Accurate decision rules for the management of suspicious lesions	MRI (between BI-RADS IV or V rating)	Use of ML to interpret MRI images led to improved decision rules for management of suspicious lesions
Qiyuan Hu, 2020	DL(CAD)	To aid Breast cancer diagnosis using mpMRI	MRI	The diagnostic performance was improved by lowering false positives and increasing positive predictive values
Michael Z Liu, 2020	CNN	To predict response to NAC	MRI	The CNN algorithm proved to be feasible to predict NAC
Thomas Schaffter, 2020	Ensemble of AI's; CEM (Challenge ensemble method)	To assess whether AI could 'meet or beat' radiologists' performance	Mammography	The CEM could not beat radiologist's performance on its own but improved performance when used to complement the radiologists' interpretation
Nan Wu, 2020	DL (DNN)	Classification of screening images	Mammography	DNN model was as accurate as human radiologists
Bardia Yousefi, 2020	'ResNet-50' (DNN)	To use Infrared heterogeneity of the breast to detect potential lesions	Thermography	The AI successfully classified the normal and abnormal subjects with an accuracy of 78.16%

Table 1 : Author name, year of origin, type of AI used, purpose of study, screening method and key findings identified following thorough analysis of 15 included papers: **Important terms:** ML: Machine learning, DL: Deep learning, AI: Artificial intelligence, MRI: Magnetic resonance imaging, BI-RADS: Breast imaging reporting and data system, NAC: Neoadjuvant chemotherapy, PCR: Pathological complete response, CNN: Convolutional neural network, DNN: deep neural network, CAD: computer aided diagnosis, MLP: Multilayer perceptron, DT: Decision tree, RF: Random Forest, LDA: Linear discriminant analysis, SVM: Support vector machine, AUC: area under the curve

AI complementing radiologists and reducing workload:

Many papers have sought to evaluate performance of AI in aiding radiologists for detection of breast cancer on mammograms. 'DM DREAM', concluded that superior results were achieved when AI was used to complement radiologists' interpretation. The 8 finalist algorithms from this challenge were aggregated to increase effectiveness and performance thus forming the CEM (Challenge ensemble model). This model failed to surpass radiologists in their performance alone. However, CEM model gave

more accurate results when used to complement radiologist interpretation¹⁵.

Another study used a deep learning AI algorithm called cmAssist to classify mammograms as 'actionable' or 'non-actionable', assigning a score to each lesion for likelihood of malignancy. 7 radiologists with different years of experience were provided the assistance of cmAssist for evaluating different mammograms. It was found that AI improved radiologists' performance by an average of 11% especially benefitting the inexperienced radiologists. It

enhanced their performance up to par with more experienced radiologists. The workload was reduced while the accuracy was increased²⁵. Alejandro R-R et. al. implemented a deep convolutional neural network (dCNN) to evaluate likelihood of malignancy using a 1-10 scale. A threshold could be set anywhere along the scale to include/exclude lesions. When the threshold was set at 2 the workload reduced by 17% whereas only 1% true positive cases were missed. 2 cases were also missed by the radiologists due to their poor visibility on the mammogram²⁶.

AI shows promising results when used with ultrasonography (USG). It improves specificity and sensitivity when used to augment and improve radiologist interpretation^{27,28}. Two studies aimed at improving radiologist interpretation of USG images and both showed improvement in performance of radiologists through the use of AI^{27,28}. They used BIRADS lexicon to extract features from USG images to use for classification of malignant or benign lesions. One study showed that radiologists performed better with use of deep learning AI algorithm while interpreting ultrasonograms, especially benefitting experienced radiologists. 10.1% of previously misidentified benign cases were correctly identified and prevented from unnecessary biopsy²⁸.

Ai vs radiologists: A possibility and requirement exist for creation of a system that can interpret radiograms with accuracy on par with or greater than radiologists. Such a system can be used in areas with limited medical facilities to quickly screen for potential breast cancer lesions, double check results and provide accurate medical diagnoses. One such deep learning CNN algorithm proposed by Rodriguez R.A. et al, proved to be more accurate than majority of radiologists²⁹. Performance of this AI construct in detecting breast CA on mammograms was compared with 101 radiologists having different experience levels. It was concluded; while AI could not outperform most experienced radiologists, yet its AUC was higher than 61% of the radiologists²⁹. Therefore, this stands as a testament to potential of AI in outperforming human professionals in breast cancer detection, an area where future iterations might substitute or replace inexperienced radiologists.

Predicting response to neoadjuvant therapy: Neoadjuvant therapy (NAT) in cancer patients is a significant therapeutic modality that reduces cancer burden and improves prognosis. Research has shown that MRI is highly effective in assessing response to neoadjuvant therapy^{30,31}. However, predicting a patient's response to therapy beforehand is important since only 30% of the patients benefit from NAT⁶. Early prediction of patients' response to therapy can therefore help use targeted treatment, minimize toxicity from ineffective therapies and reduce cost of unnecessary therapies. One study concluded that; CNN could predict response to NAC with an accuracy of 72%⁶.

Tahmassebi A. et. al. used 8 different artificial intelligence machine learning models to pre-assess patient responsiveness to NAC. The study used a wide range of qualitative and quantitative features extracted from MRI images (23 features/ lesion) to ascertain responsiveness of NAC. It was concluded; 'XGBoost' ML model was most effective at detecting responsiveness. Hence, this could be used as a cheaper and more accessible alternative to other methods of ascertaining response to NAC such as Oncotype Dx³⁰.

Cain EH et.al, concluded that using lesser extracted features led to better AI performance. 529 features were originally extracted; however less than 8 features were chosen per image. Greatest performance was exhibited by the model using least number of extracted features (n=2)³¹. Therefore, it can be concluded that AI algorithms, especially those using lesser extracted features, show promising results in the detection of the probability of patients' NAC response. It can potentially lead to the reduction in ineffective therapies, reduced exposure to toxic medication and decreased treatment costs.

DISCUSSION

An alarming rise in breast cancer incidence necessitates the adoption of measures that can help reduce mortality and morbidity³². Regular screening, early presentation, timely diagnosis and prompt treatment play a crucial role in better outcomes^{3,33}. Breast cancer screening and diagnosis have conventionally relied upon the interpretation of radiographs and histological specimens by radiologists and pathologists. This review is aimed towards determining whether AI can enhance the sensitivity of existing screening techniques, enable more accurate classification of benign and malignant tumors and the improve assessment of the patient's response to neoadjuvant therapy in breast cancer patients.

Most of the analyzed studies aimed at assessing role of AI in complementing radiologists in reducing their workload but very few were found to be assessing role of AI in evaluating response to neoadjuvant therapy and even fewer sought to develop AI that could match or outperform radiologists. It leaves much capacity for further research and development of AI that can assess patient response to neoadjuvant chemotherapy. Neoadjuvant chemotherapy is an important part of treatment for breast cancer patients, AI can help eliminate burden of unnecessary therapy and potentially prevent unnecessary exposure to highly toxic therapeutic chemotherapy. In addition, development of autonomously working AI that requires little human input can be highly beneficial in developing countries where medical facilities are limited and patients cannot afford services of qualified practitioners and radiologists.

A self-sufficient and highly sensitive AI construct can also be used in developed countries to 'Double check'

radiologists' interpretations for greater sensitivity. It can also aid in reducing the number of false positives and unnecessary biopsies. This 'double checking' is already practiced in European nations where one radiologist's diagnosis is cross checked and confirmed by another. Using a highly capable and approved AI algorithm can lead to greater sensitivity and specificity with reduced cost and workload for doctors. AI can also be used to train students more efficiently with lower costs.

Several studies have evaluated use of AI to aid radiologists in reducing their workload and increasing efficiency. As we strive to improve cancer detection several steps have been taken to improve performance and sensitivity of radiologists such as computer aided diagnosis (CAD) and double reading. CAD has widespread implementation worldwide. Double reading as mentioned above is used in Europe where two radiologists read the same radiograph to confirm and complement on each other's findings. Research has demonstrated that the aforementioned methods are ineffective in increasing radiologist efficiency. Studies have failed to prove role of CAD in improving screening outcomes, because of the low specificity of these systems²⁶. This review concludes that use of AI to complement radiologists led to superior outcomes in all of the studies. However, more research is required in field of AI. Most of the research done is centered on commonly employed screening techniques such as MRI and mammography; whereas other screening methods such as thermography are found to be underrepresented.

AI algorithms examined exhibited a good capability in classifying breast lesions and identification of malignancy in otherwise suspicious lesions across different imaging techniques. The integration and assistance of AI algorithms in the interpretation of MRI, Mammography and Thermography led to significant improvement in classification and diagnostic accuracy of breast lesions.

LIMITATIONS AND RECOMMENDATIONS

This systematic literature review is limited by use of only one database for collection of resources. It includes studies on female patients only; all studies on male patients were

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