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Magnetic Resonance Elastography for Breast Cancer Diagnosis Through the Assessment of Tissue Biomechanical Properties

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ABSTRACT

Background and Aim: Breast cancer and normal breast tissue exhibit different degrees of stiffness, indicating distinct biomechanical properties. Study results reveal that breast cancer tissue is several times stiffer than normal breast tissue. These variations can serve as indicative factors for imaging purposes. Depicting markers can significantly enhance the process of breast cancer diagnosis and treatment. This article provides a brief review of the biomechanical properties of breast cancer tissue, highlighting the role of the magnetic resonance elastography (MRE) technique in utilizing these properties for diagnosing breast cancer.

Methods: In breast MRE, low-frequency shear waves are employed to measure breast stiffness. This method not only offers a quantitative diagnosis but also generates an elastogram, determining the stiffness of each area through its colors.

Results: MRE represents a diagnostic technique with heightened sensitivity, based on depicting the viscoelasticity properties of breast tissue and describing tumors in terms of biomechanical properties. Combining tissue biomechanical properties, such as tissue stiffness, with contrast-enhanced breast Magnetic Resonance Imaging (MRI) leads to tumor diagnosis. The value of MRE in oncological imaging aims at the early detection of tumors and evaluating the prognosis of breast cancer.

Conclusion: Breast MRE can identify the reduction of interstitial pressure in tumors by detecting changes in tissue stiffness, making it an effective tool for monitoring treatment responses. This technique is safe, repeatable, and highly precise, significantly aiding in patient screening.

1 | Introduction

Breast cancer is one of the most common cancers among women, alone accounting for 31% of all new diagnoses [1]. Early diagnosis is a crucial factor in the patient's treatment process, increasing the relative survival rate to 95% [2]. Currently, mammography is the primary method for breast cancer diagnosis. However, this method has limitations in diagnosing some tumors [3, 4]. In dense breasts, the rate of cancer detection using mammography is weak, and approximately 10% to 30% of cases go undetected [5, 6]. Therefore, the use of complementary methods becomes necessary, particularly those providing physical and biological information beyond the tumor's appearance. For many years, oncology imaging, while displaying morphological properties of tumors and cells, has also

reported other essential parameters such as blood flow mapping, water mobility, and cell metabolism. Breast magnetic resonance elastography (MRE) is a medical imaging technique used to determine the stiffness or elasticity of soft tissues. The term "stiffness" fundamentally refers to expressing how a tissue changes its shape under an externally applied force [7]. Stiffness can be assessed using an ultrasound device or MRI. Unlike mammography, which primarily focuses on detecting anatomical changes, elastography evaluates tissue properties, helping distinguish between normal and abnormal breast tissue [8]. MRE combines MRI with gentle vibrations, called shear waves, to create a map that shows how stiff a tissue is. It works by measuring how fast the waves move through the tissue stiffer areas allow the waves to travel faster. This helps physicians get a clear, measurable picture of tissue stiffness, which can be important for diagnosing conditions in the breast and other areas [9–11].

Breast MRE is similar to standard MRI but focuses on assessing the biomechanical properties of breast tissue. In this technique, a modified phase-contrast GRE sequence, synchronized with low-frequency shear waves, captures tissue displacement to measure stiffness. This data is processed into an elastogram, a visual map of tissue stiffness. T1- or T2-weighted sequences may also be used for additional anatomical detail [12].

The advantages of MRE over other MRI techniques that provide more specific physiological and functional information, such as diffusion-weighted (DWI) and dynamic contrast-enhanced (DCE) MRI, include its ability to assess tissue stiffness and detect mechanical changes in tissues. However, MRE's limitations lie in its lower accuracy in detecting detailed physiological changes compared to MRI-DCE and MRI-DWI [13]. As a result, MRE is more commonly used as an adjunct to these techniques rather than as a standalone method, since each technique provides distinct information, and their combination can lead to a more accurate diagnosis.

Breast MRE is essentially the same as noninvasive and risk-free MRI, with the distinction that its primary objective is to depict the biomechanical properties of the breast. In fact, the foundation of breast MRE relies on combining tissue stiffness properties with contrast-enhanced imaging properties in breast MR.

2 | Stiffness of Cancer Cells and Cancer Tissue

Cancer cells and cancer tissue have unique and different biomechanical properties, and understanding these differences is crucial for advancing cancer research. At the cellular level, various studies show that breast cancer cells have a softer structure than normal cells [14, 15]. The expression level of intermediate strand proteins can significantly affect the degree of cancer cell stiffness. In addition, the amount of ATP increases in these cells, and other cell components that change during cancer, such as inner membrane organelles and related molecules, myosin II, or the microtubule network, impact cell stiffness [16, 17]. As shown in Figure 1, actin fibers are significantly less in cancer cells, and this is one of the factors influencing lower stiffness.

However, at the tissue level, it is opposite, and cancerous tissue has higher stiffness than normal breast tissue. Pharmacological inhibition of myosin II has been shown to enhance invasiveness by reducing cell stiffness. Elevated tissue stiffness is a hallmark of solid tumors, often attributed to the heightened density of collagen fibers within the extracellular matrix (ECM) [18]. Tumor growth causes collagen fibers to regenerate and change their direction towards the periphery of the tumor. This, in turn, leads to the stretching of collagen fibers around the tumor, causing tensile stress [19]. This increased stiffness, as illustrated in Figure 2, is due to rapid proliferation of tumor cells, and heightened deposition of ECM components such as collagen in the tumor microenvironment (TME). The collagen density in the microenvironment of normal breast tissue is 1 mg/mL, whereas for tumor tissue, it is 4 mg/mL. This increase in density leads to ECM hardening. ECM provides structural support to tissues, and its composition changes can increase stiffness [20–22]. The sensitivity of breast MRE is attributed to the viscoelastic networks formed by cells and the ECM.

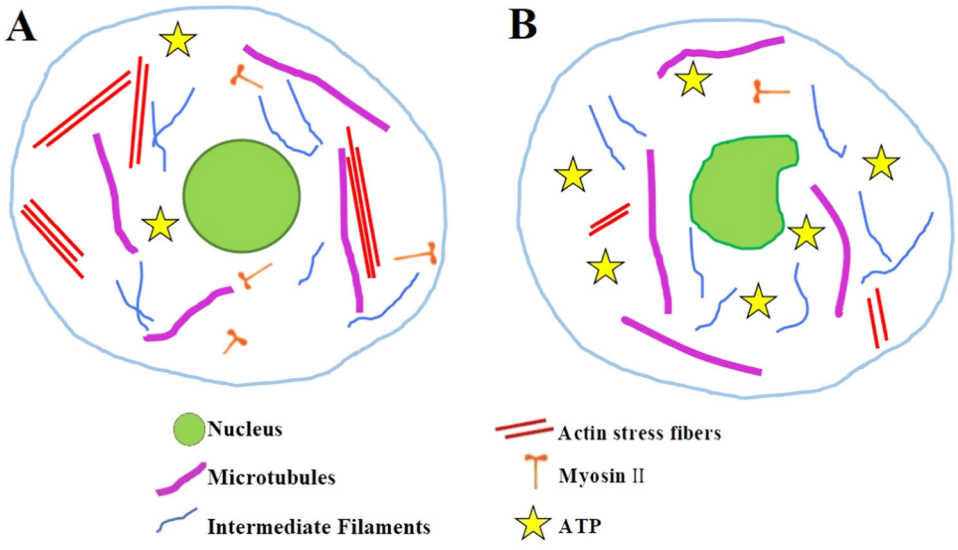

FIGURE 1 | Schematic of cellular constituents. (A) Normal cell. (B) Cancer cell.

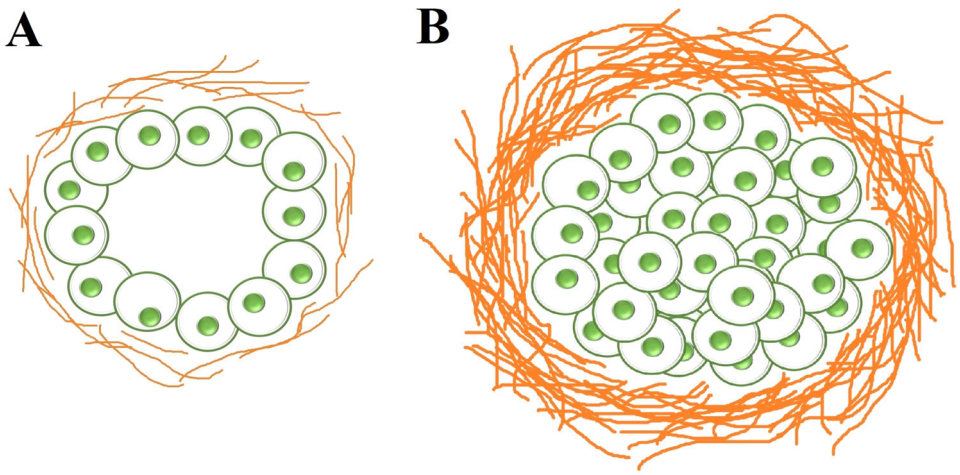

FIGURE 2 | Schematic of cancer cells mechanism and contribution of collagen fibers in ECM stiffness. (A) Normal tissue. (B) Cancer tissue.

To express the stiffness of the tissue, the modulus of elasticity (E) or Young's modulus is used, which according to the following formula, quantifies the relationship between tensile or compressive stress σ (force per unit area) and axial strain ε (proportional deformation) in the linear elastic region:

$$E = \frac{\sigma}{\varepsilon}.$$

The unit of modulus of elasticity is Pascal (Pa) [23]. The greater the tissue stiffness, the higher the numerical value of E will be. This relationship underscores the direct correlation between tissue rigidity and the resulting elevated numerical expression represented by E. Figure 3 illustrates that the stiffness of normal breast tissue is lower in comparison to malignant tumors. This difference and heterogeneity in the mechanical properties of normal tissue and cancer tissue are significant noninvasive imaging markers.

2.1 | Principle of MRE

MRE is an imaging technique that uses MRI to measure the mechanical properties, such as stiffness of biological tissues. The measurements of tissue stiffness are ultimately converted into images known as elastograms, which depict the mechanical maps of the tissue. MRE employs complex wave fields that originate from multiple point sources or are reflected from various angles, creating elastograms [24]. Due to its reliance on detecting changes in tissue structure and mechanical properties, MRE plays a crucial role in evaluating and diagnosing breast masses and detecting changes not identifiable by other imaging modalities, even having the ability to accurately reveal normal tissue changes at the onset of tumorigenesis [25].

To determine the biomechanical properties of tissue by MRE, several hypotheses should be considered such as tissue compressibility, tissue elasticity pores, attenuation, and so on [26]. In this technique, for easier understanding, the tissue is considered linearly elastic, homogeneous, and isotropic. In this case, considering these hypotheses, it leads to an equation called shear modulus:

$$\mu = \rho \times C_T^2,$$

Where μ is shear modulus, ρ is the tissue density (considered as $1\,\mathrm{gr/cm^3}$) and C_T is the shear wave speed in the tissue. The degree of tissue stiffness is determined by measuring the speed of the shear modulus. In soft tissue, Young's modulus is considered to be three times the value of the shear modulus:

$$E = 3\mu.$$

This means Young's modulus and shear modulus provide the same information, albeit with different coefficients. A higher shear modulus speed indicates greater tissue stiffness, while softer tissues exhibit a lower speed of the shear modulus [27]. In MRE, the speed of the shear modulus is calculated by meeting the specified requirements. Subsequently, upon data processing and estimating the shear modulus speed, an elastogram is generated.

The main principles of MRE include three steps:

1. **Propagating Shear Waves and Optimal Frequency**

   MRE uses different techniques to send shear waves into the breast tissue. The way of sending the shear wave should be chosen carefully because, otherwise, the wave may not spread well in the breast tissue, and the resulting image may lack quality due to the artifacts it creates. In general, there are two methods for sending a shear wave to the breast: using an active stimulator, which is not a priority due to compressing the breast tissue, and using passive stimulators, which is a newer and more common method [26, 28]. Since the shear wave is a mechanical wave, the stiffness of the breast tissue affects the propagation speed of the shear wave. More density in the breast tissue leads to an increase in the propagation speed of the shear wave. The critical factor in sending a shear wave is its frequency. The higher the frequency of the transmitted wave, the more likely it is to identify tumors with smaller dimensions. However, one limitation of applying high frequency is that it reduces the MRE image signal. Different studies have used frequencies ranging from 37.5 to

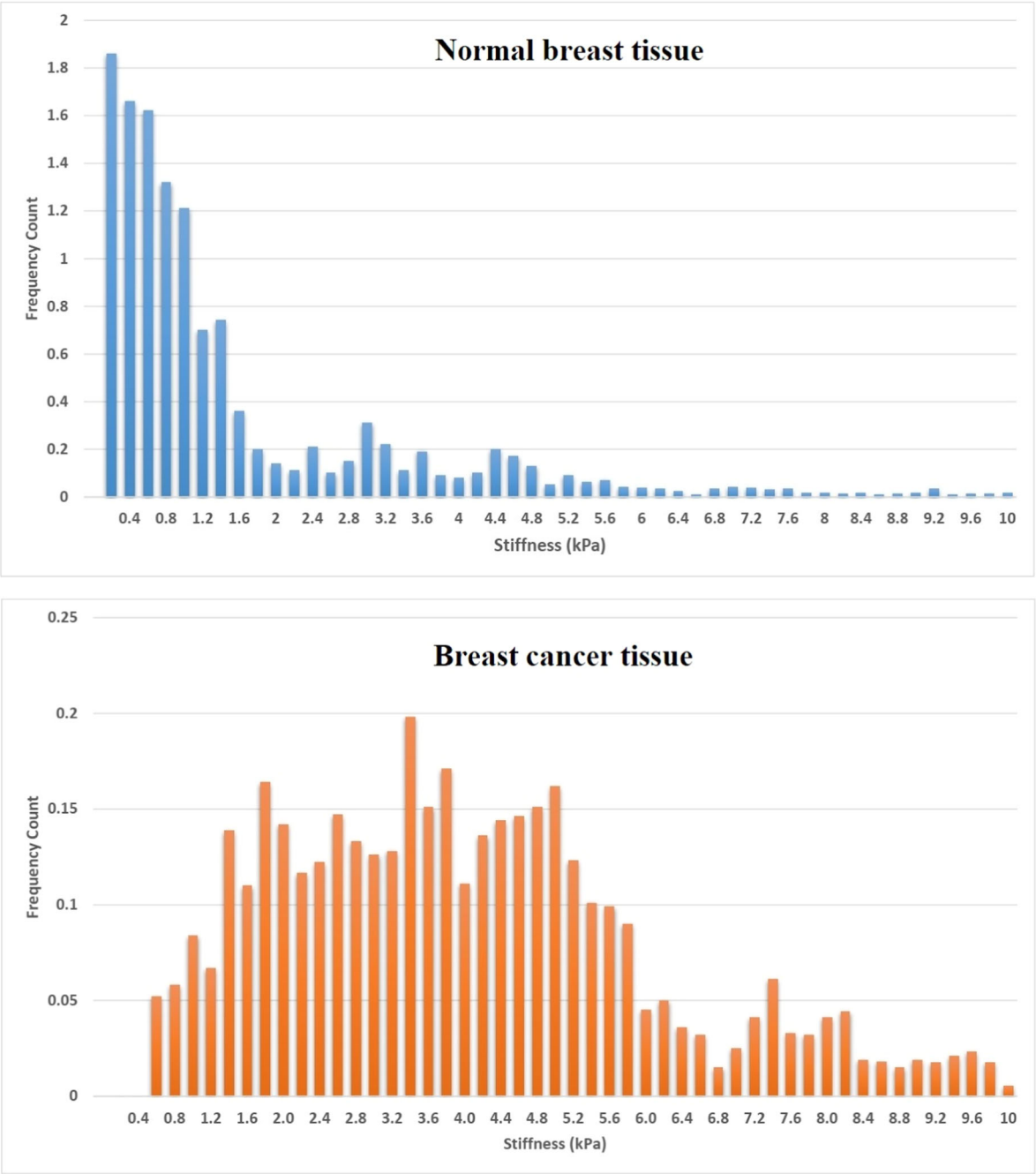

FIGURE 3 | Stiffness distribution for normal glandular breast tissue and cancer tissue.

300 Hz, but usually, the range of 50 to 100 Hz can be an ideal choice [25, 29].

2. **MR Image Acquisition**

In breast MRE, a tailored MRI pulse sequence is imperative for optimal imaging. Key sequences such as planar spin-echo-echo imaging (SE-EPI), gradient echo (GRE), spin-echo (SE), and balanced steady-state free precession play pivotal roles in acquiring images across diverse medical applications. Among these, SE-EPI emerges as a frontrunner, celebrated for its advantages. SE-EPI distinguishes itself with its remarkable imaging speed, operating swiftly within milliseconds. This rapid pace expedites image acquisition and yields a high signal-to-noise ratio (SNR), a cornerstone of MRI imaging quality. A robust SNR enhances the precision of detection and diagnosis, underscoring SE-EPI's significance in clinical practice [30, 31].

Furthermore, to extend spatial coverage and alleviate artifacts, SE-EPI can be enriched through a three-dimensional (3D) imaging paradigm. Integration of 3D imaging bolsters the accuracy of measurement values, elevating the diagnostic efficacy of SE-EPI [32]. In MRE, a prevalent technique involves harmonic mechanical excitation, typically oscillating between 20 and 100 Hz [33]. This method harnesses oscillating motion-sensitizing gradients to encode tissue displacement within the phase of acquired data during the harmonic cycle [34, 35].

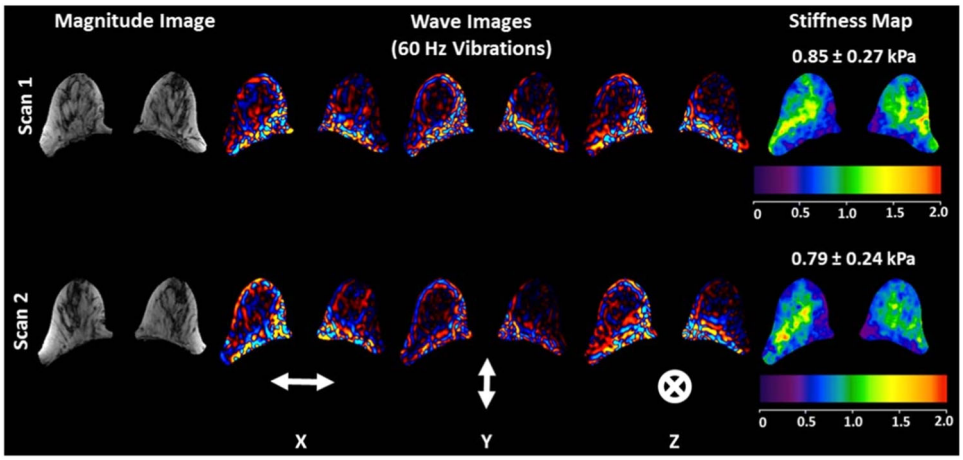

FIGURE 4 | Magnitude image, wave images and the corresponding stiffness map. Reprinted from Hawley et al. [38], Copyright (2024), with permission from John Wiley and Sons.

3. **MR Elastogram Generation**

Following the acquisition of images from the source phase, post-processing techniques are applied to transform them into visual representations that depict the displacement of waves. Multiple inversion algorithms have been developed to extract material properties from the acquired MRE data. After the imaging process, raw images are obtained [27]. This process consists of three main steps [36, 37]:

1. Preprocessing: Includes noise reduction, heterogeneity correction to make images uniform, and increasing image resolution.
2. Registration: Includes image alignment and map deformation.
3. Quantitative analysis: Includes elastogram generation, region of interest (ROI) analysis, and statistical analysis.

In Figure 4, the magnitude images, wave images, and the MRE are shown, respectively. These raw images are essentially unprocessed information of shear wave motion in the tissue. Various techniques are employed in the subsequent processing of this data: inverse algorithms, phase unwrapping, and regularization techniques. After these image processing techniques are applied, the final MRE images are created, resulting in a visual map of tissue stiffness [39, 40].

2.2 | MRE Studies in Breast Cancer

The initial investigations into MRE in cancer patients primarily concentrated on assessing the biomechanical properties of breast cancer. However, subsequent MRE studies have demonstrated that tissue stiffness in cancer patients is altered in vivo, providing a potential imaging marker for enhanced tumor detection and properties when combined with clinical multiparametric MRI. MRE studies in breast tumors are summarized in Table 1. In general, the findings indicate that malignant lesions tend to be stiffer and display more viscous behavior than benign lesions.

According to the results described in Table 1, the elasticity of the tumor is higher than that of the normal breast tissue. The results of Balleyguier et al. [10] showed that using the MRE method to diagnose breast cancer results in a sensitivity of 79% and a specificity of 90%, demonstrating the excellent statistical value of this method. Sinkus et al. [47] reported an increase in specificity in breast MRE from 40% to 60%, while Siegmann et al. [25] observed an increase from 75% to 90% in their study. These findings indicate that combining MR with elastography methods, which reveal the viscoelastic properties of tissues, significantly enhances the accuracy of diagnosis. The results of studies confirm that this method, aside from its ability to detect tumors in normal tissue, can also serve as an important screening and predictive tool [28]. Breast MRE can identify the reduction of interstitial pressure in tumors by detecting changes in tissue stiffness, allowing it to monitor treatment responses effectively.

Generally, with age, the density of breast tissue increases, diminishing the screening efficacy of mammography. Since MRE is a safe, repeatable, and high-precision method, it significantly aids patient screening. Unlike mammography, its detection power remains unaffected by increasing density, and it is a nonionizing method. However, this method has limitations and challenges, including motion artifacts during imaging, spatial resolution limitations, and a lack of a standard for determining the optimal frequency. By addressing these limitations and refining protocols, a high standard can be achieved in performing all the steps. Introducing artificial intelligence into this field can further broaden the clinical application of this method [44, 52].

2.3 | Limitations and Challenges

Despite the numerous advantages of this method, there are limitations and challenges in its clinical application, with the most significant being limited accessibility. Many diagnostic and screening centers for breast cancer lack access to this modality. Currently, no standard protocol has been established for this diagnostic method, and the conducted studies do not adhere to the same protocol and imaging conditions. Therefore,

TABLE 1 | Summary of breast MRE studies.

	Research group	Results	Year	References
1	Reeves et al. The Institute of Cancer Research, London, UK.	MRE can measure increases in tumor stiffness as imaging biomarkers of treatment response.	2023	[41]
2	Patel et al. Mayo Clinic, USA.	Mean stiffness, elasticity, and viscosity were significantly higher in high-risk patients with dense breasts compared to average-risk patients.	2022	[42]
3	Pagé et al. Université Paris Cité, France.	Breast malignant tumors, have high stiffness and high visco-elastic ratio.	2022	[43]
4	Jin et al. The Institute of Cancer Research, London, UK.	Breast MRE enables noninvasive detection of tumor stiffness and will aid in the development of ECM-targeting therapies.	2019	[44]
5	Bohte et al. Department of Radiology and Nuclear Medicine, Amsterdam, Netherlands.	Breast MRE can be used for preoperative tumor delineation, staging, and monitoring.	2018	[45]
6	Balleyguier et al. Radiology Department, Villejuif, France.	Breast MRE differentiateed malignant from benign breast tumors.	2018	[10]
7	Hawley et al. The Ohio State University Wexner Medical Center Columbus, USA.	Dense breasts had significantly higher stiffness measurements compared with nondense breasts.	2017	[28]
8	Chen et al. Mayo Clinic, USA.	The stiffness of normal adipose tissue ranged from 0.25 to 0.41 (mean = 0.33) kPa and glandular tissue ranged from 0.46 to 0.9 (mean = 0.64) kPa.	2013	[46]
9	Siegmann et al. University Hospital Tuebingen, Germany	Malignant lesions had higher elasticity and viscosity compare benign lesions.	2010	[25]
10	Sinkus et al. Waves and Acoustics Laboratory, (ESPCI), Paris, France	Viscoelastic properties of breast lesions can differentiate between malignant and benign tumors.	2007	[47]
11	Xydeas et al. Department of Radiology, University Tuebingen, Germany	Malignant tumors were stiffer than benign lesions and surrounding breast tissue.	2005	[48]
12	McKnight et al. Mayo Clinic, USA	The mean elasticity values for normal tissue, fibroglandular tissue, and tumor tissue were 3.3, 7.5, and 33 kPa, respectively. When comparing these values, it's noteworthy that breast cancer tissue is four times stiffer than normal fibroglandular tissue.	2002	[49]
13	Lorenzen et al. Eppendorf University Hospital, Hamburg, Germany	Malignant tumors had higher elasticity values compared to benign lesions. Mean elasticity of breast adipose tissue, breast parenchyma, benign tumor tissue, and malignant tumor tissue were 1.7, 2.5, 7.0, and 15.9 kPa, respectively.	2002	[50]
14	Sinkus et al. Philips Research Laboratories, Hamburg, Germany	MRE provides new diagnostic information for distinguishing between benign and malignant breast diseases.	2000	[51]

to address this issue, more studies should be conducted by researchers. This will not only fulfill all diagnostic needs but also validate it as a standard and routine modality, similar to MRI or mammography. Another significant limitation of MRE is its low spatial resolution, making it challenging to detect lesions with dimensions smaller than 5 mm [53]. One of the perspectives of breast MRE development can be related to introducing artificial intelligence. Unlike other procedures of breast cancer imaging, there have been relatively few studies in this field, and artificial intelligence algorithms for breast cancer diagnosis using the MRE method have not yet been introduced. Conducting more studies can draw researchers' attention to this method, leading to more published results and, ultimately, a fundamental step toward creating standardized protocols.

3 | Conclusion

The tissue stiffness parameter, derived from the biomechanical properties of tissue, stands as a crucial biomarker in investigating and differentiating normal tissue from cancerous tissue, including both benign and malignant tumors. MRE emerges as a rapid and highly accurate diagnostic method for breast tumor diagnosis, contributing significantly to breast cancer detection by measuring tissue stiffness through the magnetic field of the MRI machine and low-frequency shear waves. This method not only offers a quantitative diagnosis but also generates an elastogram, determining the stiffness of each area through its colors. The positioning of these colors aids in identifying both the extent and range of the tumor. In addition to the applications of elastography in diagnosing breast cancer with MRI, which were comprehensively discussed in this article, this technique, when combined with other imaging procedures, can also have significant diagnostic value. For instance, combining gastrointestinal ultrasound with elastography can aid in diagnosing intestinal fibrous structures in patients with ulcerative colitis or Crohn's disease [54, 55]. Therefore, it is recommended that the elastography method and its applications in diagnosing other diseases be further explored, with careful consideration of the challenges, limitations, and clinical aspects, to provide a comprehensive guide to its use in clinical diagnosis.

Author Contributions

Mohammad Hossein Jamshidi: conceptualization, investigation, writing–original draft, writing–review and editing, validation, project administration, supervision, data curation, methodology. **Aida Karami:** data curation, writing–review and editing, writing–original draft, investigation, methodology, visualization. **Amirhesam Keshavarz:** investigation, writing–original draft, writing–review and editing, data curation, conceptualization. **Ali Fatemi:** writing–original draft, writing–review and editing, conceptualization. **Sepehr Ghanavati:** writing–review and editing, data curation, writing–original draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data are available in the main text. All authors have read and approved the final version of the manuscript. Mohammad Hossein Jamshidi had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. No data set available as no new data were generated.

Transparency Statement

The lead author Mohammad Hossein Jamshidi affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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