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# A Multimodality Approach to Breast Imaging

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## **Course Description**

Screening and diagnostic breast studies are important services provided by imaging facilities, and require trained medical imaging professionals (MIPs) that are familiar with the modalities used to evaluate the breast and accurately distinguish between benign and malignant disease. While mammography is the most well established imaging modality to screen asymptomatic patients at risk for breast cancer, a multimodality approach is becoming more widely used, encompassing mammography in addition to breast sonography, magnetic resonance imaging (MRI), computed tomography (CT), and, when necessary, surgical and needle biopsy to provide a more thorough analysis of the underlying pathology, and an accurate assessment of a diverse population of women. This article will provide an overview of breast anatomy and pathology, a brief review of each modality, and a discussion of a multimodality approach to imaging and surgical techniques currently used to assess the breast.

## **Learning Objectives**

After reading this article, the participant should be able to:

- Describe the anatomy and physiology of the breast, as well as common benign and malignant breast pathologies
- Understand the respective roles of mammography, breast sonography, magnetic resonance imaging (MRI), , and computed tomography (CT) in breast imaging
- Discuss a multimodality approach to breast imaging in clinical practice
- Identify the sensitivity and specificity of a singular and multimodality approach to breast imaging

Review

A MULTIMODALITY APPROACH TO BREAST IMAGING

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ABSTRACT

Screening and diagnostic breast studies are important services provided by imaging facilities, and require trained medical imaging professionals (MIPs) that are familiar with the modalities used to evaluate the breast and accurately distinguish between benign and malignant disease. While mammography is the most well established imaging modality to screen asymptomatic patients at risk for breast cancer, a multimodality approach is

becoming more widely used, encompassing mammography in addition to breast sonography, magnetic resonance imaging (MRI), computed tomography (CT), and, when necessary, surgical and needle biopsy to provide a more thorough analysis of the underlying pathology, and an accurate assessment of a diverse population of women. This article will provide an overview of breast anatomy and pathology, a brief review of each modality, and a discussion of a multimodality approach to imaging and surgical techniques currently used to assess the breast.

## **Introduction**

Breast cancer has a considerable impact on women's health in the United States. The National Cancer Institute (NCI) has estimated that 1 in 8 American women will be affected by breast cancer in their lifetime.<sup>1</sup> Screening and diagnostic efforts for breast cancer are critical, as the disease has a high rate of successful outcomes with early identification and treatment.<sup>2</sup>

Breast imaging is a critical component for most imaging facilities, and mammography has become a standard screening tool to detect cancer at its earliest stage in an asymptomatic woman. It is therefore critical for Medical Imaging Professionals (MIPs) to have a working knowledge of breast anatomy, physiology, and pathology. In addition, MIPs must be well acquainted with standard mammography studies, recognizing the different benefits and drawbacks of film screen, digital, and computer-assisted detection (CAD) studies. Due to innovations and technical improvements in adjunct imaging modalities, such as breast sonography, magnetic resonance imaging (MRI), and computed tomography (CT), a multimodality approach to breast imaging is

possible and incorporates needle or surgical biopsy of suspicious lesions as the definitive measure of diagnosis and treatment. The accuracy of these individual modalities can be additive and therefore increase the overall breast cancer detection rate. This article will review these topics with a focus on the concept of multimodality breast imaging and its potential to offer individualized strategies that advance women's health.

### **Breast Anatomy and Physiology**

Prior to a discussion about breast imaging techniques, it is important to begin with an overview of the anatomy and physiology of the breast. The breast is situated anterior to the pectoralis major muscle, with fibrous stroma providing the background texture. Cooper's ligaments support the structure of the breast. These ligaments connect the pectoralis major muscle and the fascia of the skin.. Breast tissue is composed of glandular tissue, ducts, connective tissue, and adipose tissue. Most benign and malignant disorders of the breast stem from the network of ducts and glandular lobules.<sup>3</sup> Breast abnormalities are more difficult to detect with clinical breast examination (CBE) or mammography in women with a higher percentage of glandular breast tissue (also referred to dense breast tissue), relative to adipose and fibrous tissue. This is particularly true in premenopausal women.<sup>3</sup>

Breast tissue undergoes cyclical changes dictated by a woman's menstrual cycle. As such, breast cell proliferation increases during the luteal (post-ovulation) phase of the menstrual cycle, and decreases during the follicular (pre-ovulation) phase of the menstrual cycle. This cell proliferation, which is mediated by progesterone and estrogen, results in the breast tenderness that some women experience prior to their monthly period.<sup>4</sup> Likewise, breast anatomy and physiology changes substantially over the course

of a woman's life.<sup>3</sup> These are important factors that can affect the ability to accurately image the breast with available modalities.

### *Common benign breast pathologies*

A wide variety of benign disorders of the breast can occur when different elements of breast tissue exhibit exaggerated growth. Most neoplastic breast pathologies arise from the terminal ductal lobular units (TDLUs) within the lobules of the breast, and may or may not be associated with an increased risk of subsequent breast cancer.<sup>3</sup> The most common benign breast condition is characterized by fibrocystic changes that result in an increased amount of fibrous tissue within breasts that are considered healthy. Since these types of changes have been found in 60% of North American women, the condition is not considered a disease state. Meanwhile, women may be diagnosed with fibrocystic breast disease if pain, nipple discharge, or fibrocystic lumps that are suspicious of cancer accompany these changes.<sup>4</sup>

Increased cell proliferation in the breast can also result in benign breast lesions and may signal an increased risk of subsequent breast cancer. The diagnostic categories for these lesions can include ductal hyperplasia, diffuse papillomatosis, or complex fibroadenoma. Women diagnosed with atypical hyperplasia of the ducts or lobules may have a higher risk of developing breast cancer later in life, especially if they have a strong family history of breast cancer. Cases of more progressive atypical hyperplasia are diagnosed as carcinoma in situ, and women with this condition have a 4 to 5 times greater risk of breast cancer compared with the general population. Those with lobular breast cancer have a 10-fold greater risk compared with other women.<sup>5</sup> Guidelines have attempted to define the absolute risk of breast cancer associated with benign breast

disease, particularly atypical hyperplasia and fibrocystic disease, to help guide clinicians in their recommendations for breast biopsy and long-term follow-up schedule of mammography and clinical examinations.<sup>6,7</sup>

### *Breast cancer presentation and diagnosis*

Invasive breast cancer can be characterized as infiltrating lobular carcinoma or infiltrating ductal carcinoma. Infiltrating ductal carcinoma is the most common presentation of invasive breast cancer, and represents 50% to 75% of all invasive breast cancers.<sup>3</sup> It is important to identify breast cancer early with regular clinical examination, self-examination, and available breast imaging modalities. Intraductal breast carcinomas that have not invaded the surrounding breast tissue are highly curable, and smaller invasive tumors are more curable than larger invasive tumors.<sup>4</sup> Mammography is a well-established modality for annual breast cancer screening. Women are encouraged to receive a baseline mammogram at age 35, followed by a regular schedule of annual mammograms that can be determined by the individual's relative risk profile.<sup>4</sup> While some women may require monitoring at an earlier age due to genetic factors that increase breast cancer risk or a strong family history of breast cancer, mammography is less conclusive in younger women due to their denser breast tissue.<sup>4</sup> The radiation delivered with mammography has not been considered a problem when adhering to the screening schedule suggested for older women, but this radiation exposure may pose a higher risk in younger women, and mammography is therefore more controversial in these patients.<sup>4</sup>

Only 10-15% of breast cancers appear mammographically malignant; the use of physical findings, such as visual inspection and CBE, are therefore important to help in raising the



accuracy of the mammographic diagnosis.<sup>5</sup> An additional concern is the risk of providing a false-positive mammographic result. A false positive result indicates that the abnormality or disease being investigated is present when in fact it is not.<sup>8</sup> Research has been conducted to ascertain the level of false positives associated with mammography and it has been reported as high as 50% in a 10 year period.<sup>8</sup> Accuracy in mammographic reporting is dependent on a number of factors such as the sophistication of the radiologists, patient volume, and the availability of feedback on patient outcomes. Since mammography can have an inherent lack of accuracy, it becomes important to determine methods to refine each practice's ability to confidently provide an early stage diagnosis. A practice will post a higher accuracy for detection of breast cancer among those women who are coming in systematically for mammography, rather than those who only have a single screening mammography study.<sup>8</sup> Reviewing previous sets of screening mammograms allows for the detection of subtle architectural changes that might otherwise have been missed. Having the ability to follow-up areas of concern on the mammographic image with a compatible imaging modality allows for further study of area in question and has the potential to raise diagnostic accuracy. Ideally, specificity is a measure of diagnostic accuracy by determining that the imaging diagnosis is benign and the patient is indeed disease free.<sup>8</sup> Screening mammography is devoted to sorting out those women who are disease free and capturing those that are questionable for further imaging or biopsy to provide an accurate diagnosis of potential disease.

With the advancement of new technologies, mammography has been supplemented by a variety of other imaging modalities, including breast MRI, sonography, and breast CT. In addition, breast biopsy is another important component to

arriving at a definitive diagnosis in many patients presenting with breast abnormalities. The remainder of this article will focus on a multimodality approach to breast imaging and diagnosis accuracy that can be obtained with a multimodality approach.

### **Conventional Breast Imaging and a Multimodality Approach**

A variety of imaging technologies have been established in the evaluation of breast disease, especially in the screening and diagnosis of breast cancer. Each modality is associated with a certain sensitivity and specificity, a multimodality approach to breast imaging has been proposed to increase the detection rate compared with the use of a single modality.<sup>9</sup>

#### *Mammography*

Mammography is the most accepted and widely used imaging technique for the screening of breast cancer, particularly in older and postmenopausal women.<sup>4</sup> Current breast cancer screening guidelines recommend that women of any age should be referred for genetic counseling if they are at an elevated risk of having breast cancer gene mutations, based on family history. In most women, it is recommended that breast cancer screening discussions begins after a baseline at 35 and then another exam at 40 years. The screening mammography routine should occur every 1-2 years between the ages of 40 and 59 years. In women 70 years of age and older and with a life expectancy of at least 10 years, continued regular mammography screening should be considered, but these women should be counseled to understand that the value of mammography is less conclusive in their age group due to fewer clinical studies of mammography in women

over the age of 70 years.<sup>10</sup> An important issue with breast cancer in elderly women is the slow growing nature of their cancers and the screening of these women often demonstrates an advanced breast cancer that has gone unnoticed due to the indolent nature of its growth.

The system under which mammography images are captured can have an important impact on image quality and the value of the study in particular populations of women. Traditional film screen mammography is being supplanted by digital mammography, which is now considered the gold standard for both screening and diagnostic mammography studies, in combination with soft copy reading.<sup>11</sup> Digital mammography may offer a particular advantage to film screen mammography in women who are pre- or perimenopausal, women under the age of 50, and women with dense breasts, as reported in the American College of Radiology Imaging Network (ACRIN) Digital Mammographic Imaging Screening Trial (DMIST) study.<sup>12</sup> One small mammography practice reported an increase in the rate of cancer detection with mammography in women with dense breasts after transitioning the facility from film screen to digital mammography.<sup>13</sup> Clinicians should therefore consider individual patient factors, including age, menopause status, and age, when suggesting mammography screening and facility choice in certain women.

Computer-aided detection (CAD) has also been employed in efforts to improve the screening and diagnostic accuracy of mammography. This technology prompts the reader to re-evaluate suspicious lesions or areas of the mammographic study, and may improve the sensitivity of mammography in breast cancer screening and diagnosis,

resulting in earlier cancer detection and improved outcomes.<sup>14</sup> However, the value of CAD has been found to be variable compared with a standard radiologist's interpretation and has the potential to increase false positives. One evaluation of CAD's influence on the final interpretation of the digital mammogram reading was that CAD failed to increase diagnostic yield; meanwhile, double reading of mammography studies by technologists, as well as the radiologist, was a more effective strategy to improve breast cancer detection.<sup>15</sup> Novel techniques, including defining gray-scale invariant ranklet texture features during the MRI,<sup>16</sup> and combining results from two machine learning classifiers,<sup>17</sup> have demonstrated the ability to reduce false positive rates in CAD-assisted digital mammography. Research must be carefully critiqued relative to CAD, as some evaluations have included small numbers of patients and/or inexperienced radiologists. In addition, critical factors requiring careful consideration when evaluating the utility of CAD in clinical practice include radiologist experience, lesion characteristics, the setting of the radiologist's practice, and the software used to perform CAD.<sup>8</sup>

### *Breast ultrasound*

Breast sonography is a useful modality for breast imaging in both younger and older patients. In younger patients, sonography can be used as an alternative to mammography, and can provide improved visualization in denser breast tissue among younger women. In older women, sonography may be used as an adjunctive imaging tool with mammography. In one study of patients undergoing evaluations in a breast clinic between January 2000 and August 2003, the addition of adjunctive breast sonography with mammography was more sensitive than mammography alone (80.8% vs. 56.6%,

$p < 0.001$ ). Overall, the addition of sonography resulted in a diagnosis of breast cancer in 9 of 14 studies found to be normal on mammography and 16 of 29 studies found to be indeterminate on mammography. Mammography was more sensitive in women over the age of 50 compared with those under the age of 50 (62.5% vs. 45.7%,  $p = 0.10$ ), while sonography was equally sensitive in women under the age of 50 and over the age of 50 (82.8% vs. 77.1%,  $p = 0.60$ ). In a subgroup analysis, the investigators found a higher sensitivity with combined mammography and breast sonography compared with mammography alone in patients of either age group.<sup>18</sup> Based on these data, breast sonography should be considered as an important part of a multimodality strategy, especially in younger patients requiring screening or diagnostic breast evaluation. When a combined mammogram and sonogram have been completed on a patient, the report should include a description of the size, shape, margin, and density of the lesion; its location and associated findings; and any changes since the previous studies.<sup>5</sup> This approach increases the power of the evaluation by taking advantage of all the data gathered in an additive manner and therefore raises the diagnostic accuracy of the combined examination.

### *Magnetic resonance imaging (MRI)*

Breast MRI has demonstrated utility in patients at a high risk of developing breast cancer, and is also useful in evaluating patients who have been newly diagnosed with breast cancer. One analysis of breast MRI among women who were high risk for developing breast cancer, was based on a personal history of breast cancer, a history of lobular carcinoma in situ, a history of atypical hyperplasia, or a family history of breast

cancer. The MRI patient cases were performed on a 1.5 Tesla (T) strength MRI unit using an imaging sequence that consisted of a localizing sequence followed by a sagittal fat-suppressed T2-weighted sequence. Subsequently, a T1-weighted three-dimensional, fat-suppressed fast spoiled gradient-echo sequence was performed before and three times after a rapid bolus intravenous (IV) injection of 0.1 mmol/L of gadopentetate dimeglumine contrast solution per kilogram of body weight. Among the 367 women screened, a biopsy for a nonpalpable lesion was recommended in 64 (17%), and 59 women ultimately underwent biopsy. Cancer that was not evident through mammography or physical examination was found in 14 (24%) of the women who underwent biopsy, which represented 4% of the original population studied. Eight of the cases identified (57%) were classified as DCIS, and the other six cases were found to be infiltrating carcinoma.<sup>19</sup> While it is difficult to determine the value of breast MRI as a screening tool in a wider population of women, these data suggest that MRI may be a useful modality in select high-risk women.

Women with newly diagnosed cancer may likewise benefit from MRI to diagnosis previously undetected cancer of the contralateral breast. One recent study evaluated 969 women with newly diagnosed breast cancer, who had no indication of abnormalities in the contralateral breast, after evaluation with clinical examination and mammography. The enrollees underwent breast MRI, and MRI-detected cancer was defined as that confirmed by biopsy within 12 months of study entry. In total, occult cancer was found in the contralateral breast in 30 (3.1%) of the women studied, and the investigators determined that the MRI modality had a sensitivity of 91%, a specificity of 88%, and a negative predictive value of 99% in detecting cancer of the contralateral

breast. Overall, 121 (12.5%) of the women evaluated had a biopsy performed, 30 who were found to have contralateral breast cancer, and 18 who were found to have invasive contralateral breast cancer. Factors such as breast density, menopausal status, and the histological findings of the primary tumor did not affect the ability to diagnose contralateral breast cancer with MRI.<sup>20</sup> Based on these findings as well as the result of other trials, the current National Comprehensive Cancer Network (NCCN) practice guidelines recommend that clinicians consider breast MRI in patients with a newly diagnosed breast cancer to evaluate the extent of ipsilateral disease and to screen for contralateral breast cancer.<sup>21</sup> It is also important to consider that MRI posts a diagnostic sensitivity for invasive breast cancer at a rate of 90%.<sup>5</sup> Unfortunately the specificity of MRI has been reported to be as low as 39% for detecting the difference between benign and malignant lesions.<sup>5</sup> This provides an opportunity to consider the utility of using MRI for suspicious breast lesions found on mammography and breast sonography to obtain an increased level of diagnostic accuracy. Contrast enhanced studies have been helpful in detecting early stage breast lesions. However, intraductal papillomas, some fibroadenomas, fat necrosis, surgical scars, and intramammary lymph nodes have all caused false positive results with MRI of the breast.<sup>5</sup> These issues highlight the need to use a multimodality approach to avoid these diagnostic pitfalls.

Breast implants have been notably difficult to image and screen for native breast disease. MRI to evaluate the implant device for potential rupture has been reportedly 71% sensitive and 91% specific.<sup>22</sup> MRI of breast implants for rupture is a highly accurate diagnostic modality and may profit from some added imaging data.

### *Computed tomography (CT)*

Breast CT may also represent another component to a multimodality breast screening paradigm. Although still in its early stages, one prototype breast CT unit, designed at the University of California, Davis, has demonstrated the ability to provide adequate anatomical images of the breast in healthy volunteers, with a radiation dose equivalent to two-view mammography. The system is now in clinical trials for women at high risk of developing breast cancer.<sup>23,24</sup> Initial reports have noted that the breast CT system provides excellent depiction of the breast anatomy, good visualization of microcalcifications, and accurate depictions of soft tissue components of any lesions found in the study.<sup>24</sup> While additional clinical studies in high-risk women are needed, breast CT may provide an additional screening or diagnostic benefit in certain patient populations. Since this imaging modality is still in clinical trials for potential diagnostic implementation, accuracy statistics are not yet available and will be critical in order to properly place this tool in the diagnostic work-up.

### *Image-guided breast biopsy*

Surgical or needle biopsy is often used to rule out or confirm the presence of cancer in women who present with suspicious breast lesions, and is a critical element to patient evaluation as part of a larger multimodality imaging strategy. Percutaneous needle biopsy is particularly useful, when possible, as it is less invasive and less costly than surgical biopsy. In addition, the introduction of needle biopsy has resulted in a reduction in the total number of surgeries needed to diagnose and treat breast cancer, as an initial



needle biopsy can be used to accurately establish the presence of cancer, without the need for an initial surgical biopsy for diagnosis.

Different biopsy techniques are used and are associated with varying processing times and accuracy. Fine-needle aspiration breast biopsy (FNAB) can be performed during a diagnostic evaluation, but requires both a skilled cytopathologist and an on-site evaluation of the specimen by a qualified individual to ensure that the sampling is adequate. Processing times with FNAB are shorter, and may therefore reduce patient anxiety while waiting for results, but experts have stressed that clinicians should not sacrifice diagnostic accuracy in an effort to obtain more rapid results.<sup>25</sup> Large-core needle biopsy has demonstrated superior results to FNAB. For instance, unlike core-needle biopsies, FNAB cannot distinguish between in situ carcinoma and an invasive carcinoma. It is important to be able to diagnose invasive carcinoma prior to surgery, as invasive disease requires a lymph node dissection as well as a lumpectomy. Therefore, patients who receive a diagnosis of invasive disease before surgery can undergo both lumpectomy and lymph node dissection during the same surgical procedure, avoiding the need for a second surgery.<sup>25</sup> Based on the limitations of FNAB and the lack of complications associated with core needle biopsy, core needle biopsy is generally preferred to FNAB.<sup>25</sup>

Image-guided core needle biopsy is less expensive and less invasive than surgical excisions in breast cancer diagnosis. The introduction of large-core needles, especially with the addition of technologies such as vacuum-assisted core biopsy devices, have allowed for the removal of most of the visible signs of the lesion during the needle biopsy procedure. In these cases, the placement of a marker clip at the site of the biopsy is

sometimes warranted in case additional surgical excision or follow-up of the lesion site is necessary.<sup>25</sup> Image-guided needle biopsies are particularly useful in patients with lesions that have been detected on previous imaging studies but are not palpable.

Sonography -guided core-needle biopsy is a particularly important follow-up procedure for patients with suspicious lesions, and is associated with a false-negative rate of between 0% and 1.26%.<sup>25</sup> One validation study of 1,352 cases found that Sonography -guided core-needle biopsy was a viable alternative to surgical excision in patients with nonpalpable breast lesions.<sup>26</sup> Sonography -guided, vacuum-assisted needle biopsy may also be a viable alternative to surgery in women with non-cancerous lesions, as evidenced in a review of this technique for the management of breast papillomas.<sup>27</sup>

Stereotactic breast biopsy is another method of integrating established imaging modalities with needle biopsy to obtain additional diagnostic information without, or prior to, surgical excision. Stereotactic breast biopsy makes use of the additive accuracy of mammography, breast sonography , or sometimes MRI to guide the biopsy needle used in the procedure. With the use of stereo images, computerized coordinates can be obtained that guide the needle to the exact location of the lesion under suspicion. Like other forms of needle biopsy, stereotactic breast imaging can reduce patient pain and anxiety with shorter processing and recovery times as well as providing a cost-effective alternative to surgical excision in some women.<sup>28</sup>

## **Multimodality Breast Imaging: Sensitivity and Specificity Based on a Review of the Literature**

To determine the level of evidence that has been accumulated for using mammography, breast sonography, and MRI in the detection of early stage breast cancers, a literature review was conducted. This search was not a systematic review nor a metaanalysis, but it was conducted using specific key words (i.e., mammography + breast ultrasound + MRI + specificity) to generate a list of peer reviewed, published articles on the topic of multimodality breast imaging and the additive detection rate with this approach. The articles were sorted into levels of evidence to guide medical imaging professionals and radiologists as to the impact of using a multimodality approach to imaging the breast. The lowest level of evidence was expert opinion and the highest was a selection of cohort studies. **Table 1** provides an overview of the evidence accumulated in this literature review.

#### *Expert Opinion*

The first report provided as evidence of the effectiveness of a multimodality approach to breast imaging with mammography, breast sonography, and MRI, was based on research conducted by Kuhl et al in women at high risk for breast cancer who were carriers of the BRCA 1 or 2 gene. This preliminary report was made available to inform clinicians of the results of using MRI to refine the diagnosis of these patients who had already undergone mammography and breast sonography. Preliminary results of the study suggested that MRI was an important diagnostic tool and did not compromise the specificity of the diagnosis; MRI was 100% sensitive for breast lesions compared to only 53% for mammography paired with breast sonography.<sup>29</sup>

#### *Case Reports*

This collection of research publications were classified as case reports due to the lack of large numbers of patients and the convenient manner in which patients were recruited. Classically, case reports can be of only one or two patients; however, this classification was selected to distinguish these publications from those that had larger participant numbers and collected longitudinal data.

Interestingly, each of the articles in this group researched a multimodality approach to breast imaging for a different diagnostic pathology. One study evaluated 89 German patients who had been referred to the researchers for surgical biopsy of a lesion.<sup>30</sup> In this analysis, the highest sensitivity of 92% was reached with mammography and sonography of the breast. Meanwhile, combining all three modalities only provided a sensitivity of 64%. The MRI unit that was used for these patients was only a 1T magnet, and that could have hampered the resolution compared with much higher strength units that are now currently available. The authors only recommended MRI for screening and as an initial work-up technique for patients suspected of having a breast lesion.<sup>30</sup>

The second case report was another analysis by Kuhl et al in 192 patients who were carriers of BRCA 1 or 2 gene for breast cancer, including 6 symptomatic patients.<sup>31</sup> In this group of patients, mammography and breast sonography was only 44% sensitive for disease compared with MRI, which demonstrated a sensitivity of 100%.<sup>31</sup> Consequently, this study stands in stark contrast to the previously reviewed case report that placed MRI in a more subordinate role for breast cancer imaging.

Another study was conducted in 27 women with breast hamartomas who were evaluated with a combination of mammography, sonography, and computed tomography (CT) to correctly classify the lesion.<sup>32</sup> This multimodality approach has some issues

related to absorbed dose from conventional CT. A dedicated breast CT unit is in clinical trials and may prove to be of great clinical utility while providing a much lower dose than the conventional CT units.<sup>32</sup> This study provides inertia for further data that can be provided by a dedicated CT unit that has a dose appropriate for screening asymptomatic women.

In a comprehensive study of 111 women with invasive breast cancer, MRI was found to be individually more sensitive than mammography for some tumors.<sup>33</sup> In fatty composition breasts, breast sonography and MRI were superior for detection of invasive breast cancer than mammography. Overall, the data demonstrated that CBE, mammography, and MRI was the most sensitive combination for overall detection of invasive breast cancer.<sup>33</sup>

A Korean study of 132 patients with ductal breast cancer examined patients with individual imaging studies as well as the combined modalities.<sup>34</sup> Researchers found that ductal cancer was best detected when mammography and sonography were combined to detect the intraductal extension of the tumor, with 86% sensitivity compared to sensitivities of 55% and 80% with mammography and sonography alone, respectively.<sup>34</sup> For this highly prevalent form of breast cancer, the use of mammography with sonography provided an additive benefit that rivaled the separate ability of each modality to visualize the lesion and its ductal extension. Unfortunately, MRI was not included in this methodological evaluation.

An Italian study was completed in 97 women who were diagnosed with multifocal- multicentric breast cancer, which is the most difficult set of lesions to visualize.<sup>35</sup> In this group of women, combining mammography and breast sonography

only provided an overall sensitivity of 58%. In fatty breasts, the detection rate was much higher. However, younger women are more likely to have dense breasts, and this group had the lowest detection rate of 45.4%. In light of their findings, the authors called for renewed research to improve the accuracy of imaging detection for this type of breast lesion.<sup>35</sup>

Another report by Di Benedetto et al followed a group of 63 women with breast implants to determine which combination of imaging modalities provided the best detection of rupture and leakage.<sup>36</sup> Mammography, breast sonography, and MRI were used to determine the single best modality for this diagnostic dilemma. The study in this small collection of women found that MRI had a single sensitivity of 93% for implant integrity and the other modalities lagged behind, with mammography exhibiting a sensitivity of 88% and sonography with a sensitivity of only 77%.<sup>36</sup>

As discussed previously, these studies are limited in their recruitment size and the results reported are therefore only representative of the patients studied. However, these reports do spur interest in further research into a multimodality approach for breast imaging and highlight the need for a higher level of evidence.

### *Cohort Studies*

These publications were based on larger groups of patients, and the data gathered generally spans a significant span of time. These studies are important due to the longitudinal nature of the data collected and a few of the studies are very representative of larger populations. One example of this classification of research was conducted by Drew et al, which followed 285 symptomatic women from diagnostic work-up through pathologic diagnosis.<sup>37</sup> Patients underwent CBE, mammography, fine-needle aspiration,

and MRI, and the individual specificities were calculated for each individual test option as well as the combination of CBE, mammography, and fine-needle aspiration. In this large cohort of patients, the triple combination had the same specificity as MRI of the same lesion (99.2%).<sup>37</sup> The authors concluded that MRI was highly specific for diagnosis of breast lesions and could eliminate the need for other examinations.

Warner et al conducted a study in a cohort of women who were carriers of the BRCA 1 or 2 breast cancer gene.<sup>38</sup> The study provided surveillance of 236 Canadian women and detected 16 invasive and 6 ductal cancers over a period of more than 5 years. The use of CBE, mammography, breast sonography, and MRI were used and compared for their individual and combined specificity in detection of these two types of breast cancer. MRI proved to be more specific, having a detection rate of 77% compared with the other individual modalities. When all four modalities were combined, the rate jumped up to 95% specificity compared to 45% for the combination of only mammography and CBE.<sup>38</sup> Again, these data point to the pivotal role that MRI provides in detection of certain specific types of breast cancer and the powerful additive influence of MRI in the routine imaging work-up.

A comprehensive study was also published by Kuhl et al to describe results with a total of 529 women carrying the BRCA 1 or 2 breast cancer gene.<sup>39</sup> This larger cohort demonstrated that MRI provided the most sensitive diagnostic imaging criteria, posting a sensitivity of 91%, compared to a rate of 49% with the combination of mammography and breast sonography.<sup>39</sup> This final report of more than 5 years of follow-up allows for a definite statement concerning the importance of including MRI in the diagnostic work-up for patients at high risk of breast cancer due to the BRCA 1 or 2 breast cancer gene.

Another study in 1,000 women with palpable breast cancers compared all combinations of mammography, breast sonography, and needle biopsy.<sup>40</sup> Needle biopsy added to an imaging modality raised the sensitivity to more than 99%. Meanwhile, when utilizing only mammography and breast sonography, the sensitivity dropped to 97.9% among this group of women.<sup>40</sup> This study provides confirmation of the value that a biopsy provides in refining the diagnosis of the lesion and helping to identify the most appropriate intervention.

A two-year study by Berg et al was conducted in 2,725 women who had a positive screening mammogram to determine whether adding breast sonography would help to further refine diagnosis.<sup>41</sup> In 40 women from the larger cohort who were diagnosed with breast cancer, the addition of sonography to mammography increased the diagnostic accuracy from 78% to 91%.<sup>41</sup> The addition of sonography did increase the number of false positives for this group, which exemplifies the need to further refine the diagnosis with a modality such as MRI, which may make the final diagnosis more precise.

Another study was conducted in a cohort of 546 women who had 259 pathology-proven breast cancers.<sup>42</sup> In this group of patients, both mammography and breast sonography were conducted and sensitivity and specificity was calculated based on both breast tissue type and age. Interestingly, the use of breast sonography in this cohort of women provided a higher specificity in younger women (88%) and those with heterogeneous breast tissue (57%).<sup>42</sup> These data reinforce the need to use breast sonography to detect breast lesions in younger women with dense breast tissue, in order to provide the most specific diagnosis possible. Increased sensitivity may also be possible with the additive information provided by MRI.



The final study reviewed involved the use of a 3T MRI unit to determine the increased accuracy in diagnosis of breast lesions compared with mammography and breast sonography.<sup>43</sup> The researchers provided this imaging technology for 434 women who were at a median age of 53 years. The study found that in this cohort of women, the specificity of MRI was slightly lower than mammography and breast sonography. However, MRI provided statistically significant better detection of malignant breast lesions than mammography and breast sonography.<sup>43</sup> The use of 3T MRI will soon become more widely available and holds the promise of providing a higher level of detection of breast cancers.

### *Summary*

This brief literature review demonstrates the importance of including MRI as part of the imaging scheme to increase the overall accuracy of breast cancer diagnostics. Many of the studies reviewed cannot be generalized to the overall population. However, the use of a 1T or 1.5T MRI has had dramatic effects on the overall diagnostic capability for the patients involved in these studies. As 3T MRI becomes more available, it may be possible to combine it with breast sonography to provide superior visualization of breast lesions among younger women with denser breast tissue. Continued research is needed and should focus on combining 3T MRI and breast sonography to combat the increase in breast cancer incidence in younger women. The table of research evidence (**Table 1**) points to the need for research designs that use a randomized selection of patients, as well as robust metaanalyses of the literature relative to a multimodality approach to breast imaging.

## **Case Study: Utilizing a Multimodality Approach to Imaging a Nodular Area in the Left Breast**

A 48-year-old patient completed her annual screening mammogram and the standard views highlighted an area in the left breast of dense consolidated breast tissue. This nodular area was asymmetrical compared to the same area within the right breast (Figure 1). The patient was recalled for additional diagnostic mammography views to further compress and magnify this nodular area in the lateral area of the left breast. The diagnostic views ordered were a mediolateral view and a magnification spot compression in the cranio-caudal view of this area (Figure 2). The diagnostic views demonstrated the same area; however, on the magnification spot compression view, the area was more compressed and minute calcifications were noted within the tissue. A BIRADS code of zero was given, which signaled the need for additional imaging. In order to raise the sensitivity and specificity of the diagnostic process, a breast sonogram was ordered of the area in question to further characterize the tissue and gain added imaging information. The area was identified as the 1 o'clock position of the outer quadrant of the left breast. The breast sonogram was conducted on the same day as the diagnostic mammography study. The targeted area was investigated with a 13MHz linear transducer to obtain both gray scale and power Doppler images of the 1 o'clock area of the outer quadrant of the left breast (Figures 3 and 4). The area in question, measuring 1.6 x 1.6 x 1.3 cm, was easily reproduced with sonography, and was further identified as existing in between zones 1 and 2 (or A & B) of the breast. The sonographic appearance of this tissue was hypoechoic and demonstrated no vascular signal. A BIRADS code of zero was again given to this study, indicating the need for further diagnostic work-up. The interpreting

physician felt that this island of fibrocystic tissue was benign; an MRI of the breast was recommended to ensure that an underlying nodule did not exist.

A breast MRI was completed 20 days later of both breasts with a 1.5 T magnet to obtain both contrast and non-contrast images. A T2 weighted axial sequence was used as well as sagittal STIR sequences of both breasts (Figures 5 and 6). Fat suppressed T1 weighted sequences were collected both before and after injection of contrast. Diffusion weighted imaging and dynamic vibrant sequences were preformed. Additionally, MR spectroscopy was performed on the area of concern in the left breast. The images and contrast kinetics were further analyzed with CAD (Figures 7 and 8). The MRI evaluation demonstrated dense glandular breast tissue that had contrast enhancement, in keeping with a fibrocystic breast condition. MR spectroscopy of that region proved that the nodular area was benign.

Although this represents a case study with a low level of evidence, it demonstrates how a complex nodule in dense breast tissue was evaluated with a multimodality approach. This multi-step diagnostic approach continued to raise the sensitivity and specificity of the diagnosis. Each imaging modality provided further information to confirm the benignity of the area in question. This case illustrates how building the imaging information and refining the patient's diagnosis can resolve certain diagnostic dilemmas common in clinical practice.

## **Conclusions**

While mammography has long been considered the gold standard for breast screening, the introduction and advancement of new technologies have made a

multimodality approach to breast imaging possible in clinical practice. Breast MRI and breast sonography have both gained wide acceptance, particularly in high-risk women and those who are less likely to have definitive results with mammography, such as younger women and those with dense breasts. Breast CT may also provide an additional imaging benefit. While the expense of new technologies is an important consideration, it is possible that an improved, multimodality screening paradigm could prevent unnecessary biopsies and reduce patient anxiety stemming from inconclusive findings. Additional research will be needed to determine the exact role and characteristics of multimodality breast screening in future practice.

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**Table 1. Literature review of multimodality breast imaging**

Levels of evidence (Lowest to highest)	Author/Year	Participants (n)	Notes
Anecdotal	Kuhl 2002		Radiology practice experience
Case reports	Muller-Schimplfle et al 1997	N=89	Mam, US, and MRI
	Kuhl, et al 2000	N=192	Mam, US, and MRI
	Berna et al 2001	N=27	CT for breast hamartoma
	Berg et al 2004	N=111	CBE, Mam, US, and MRI
	Kang et al 2007	N=132	Mam & US in IDC
	Bozzini et al 2008	N=97	Mam, US, and 2 <sup>nd</sup> reading Mam
	Benedetto et al 2008	N=63	Mam, US, and MRI for breast implants
	Cross-sectional study	None	
Case control studies	None		
Cohort	Drew et al 1999	N=285	CBE, Mam, US, Needle asp. and MRI
	Warner et al 2004	N=236	CBE, Mam, US, and MRI (BRCA 1 & 2)
	Kuhl et al 2005	N=529	Mam, US, and MRI
	Ciatto et al 2007	N=1000	Mam, US, and Needle bx
	Berg et al 2008	N=2637	Mam and US
	Devolli-Disha et al 2009	N=546	CBE, Mam, and US
	Elsamaloty et al 2009	N=434	Mam, US and MRI
	RCT	None	
Meta-analysis	None		

Mam=mammography; US=breast sonography ; MRI=magnetic resonance imaging; CT=computed tomography; CBE=clinical breast examination; Asp=aspiration; BRCA=breast cancer gene; Bx=biopsy

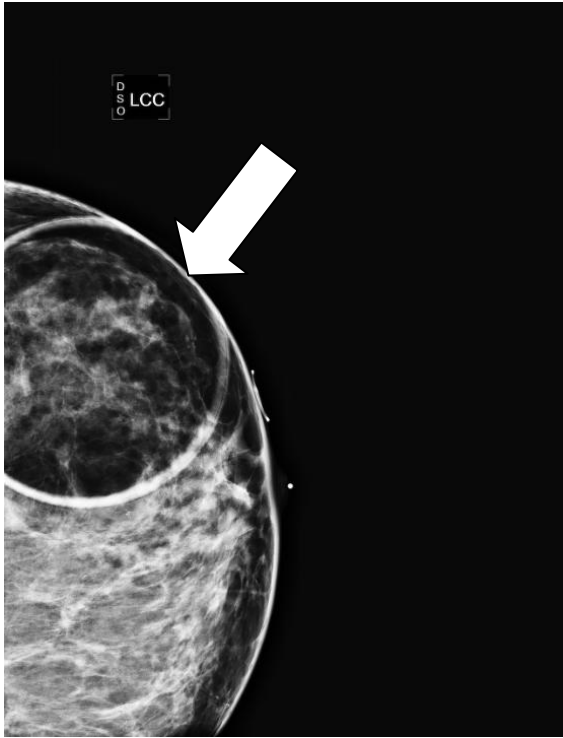
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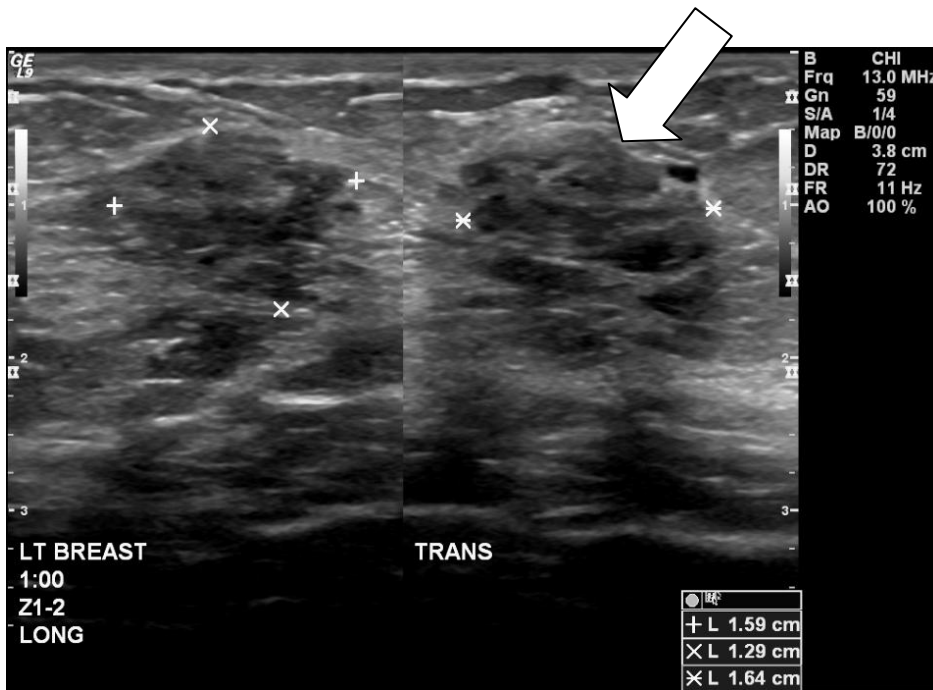
**Figure 1. Left CC view of the dense glandular tissue on the screening digital mammogram**



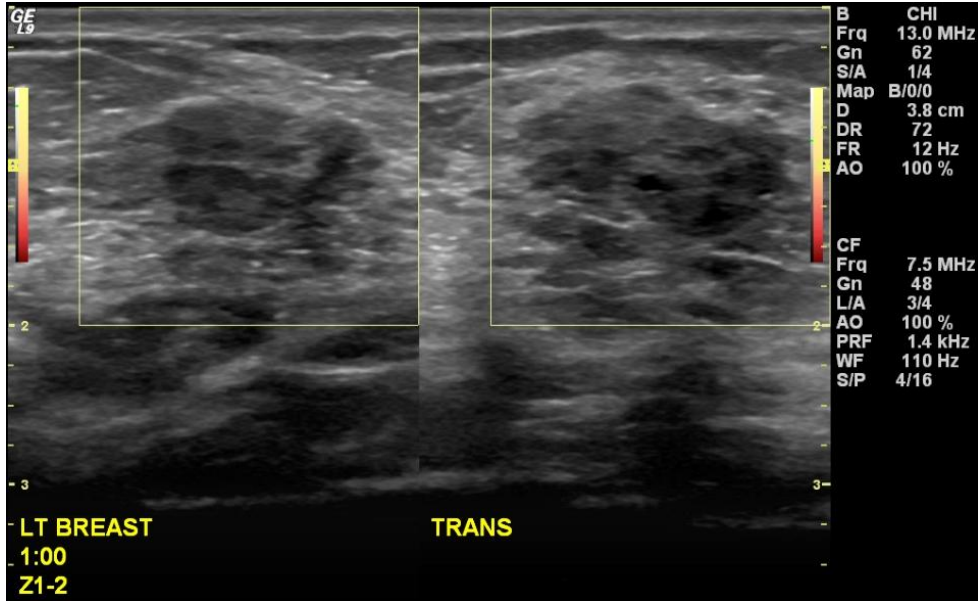
**Figure 2. Spot compression magnification of the 1 o'clock nodular area**



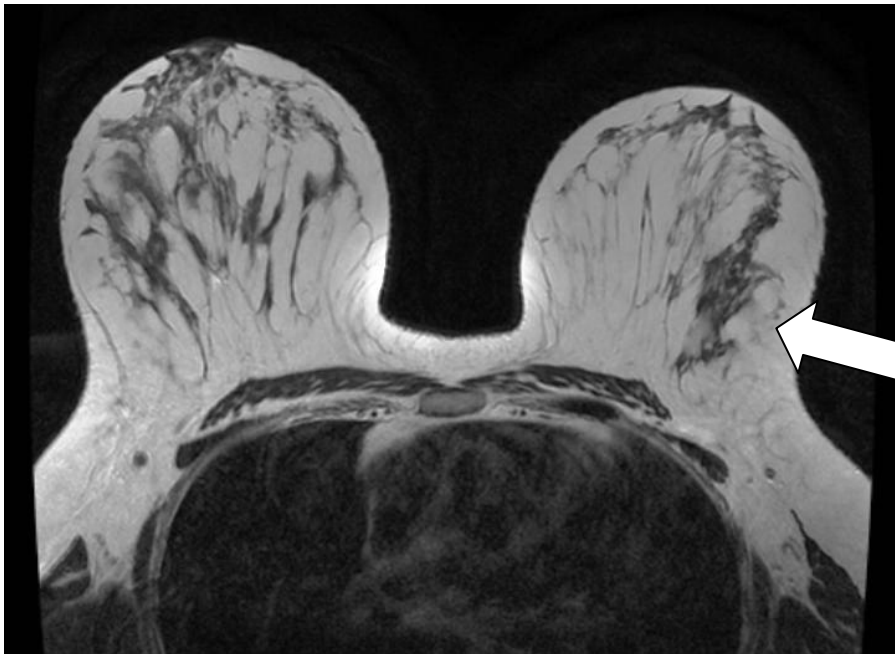
**Figure 3. Gray-scale breast sonogram that further defines the dimensions of the 1 o'clock nodular area within the left breast**



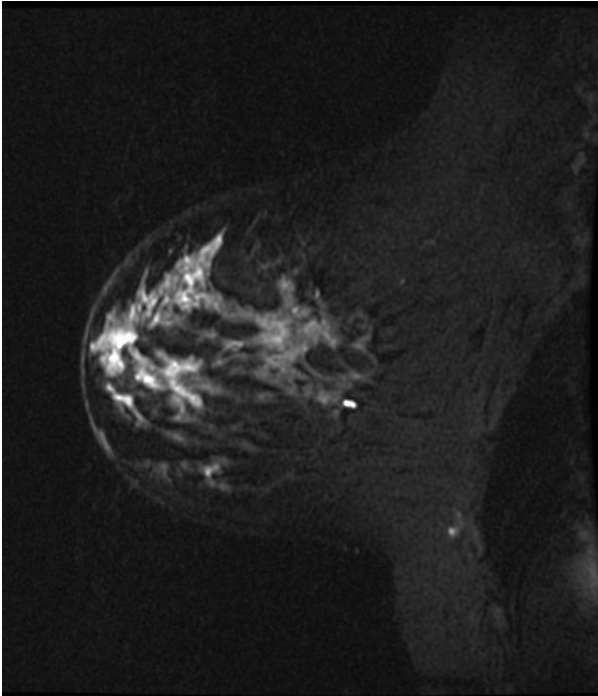
**Figure 4. Power Doppler region of interest overlaid to detect the presence of vascular flow**



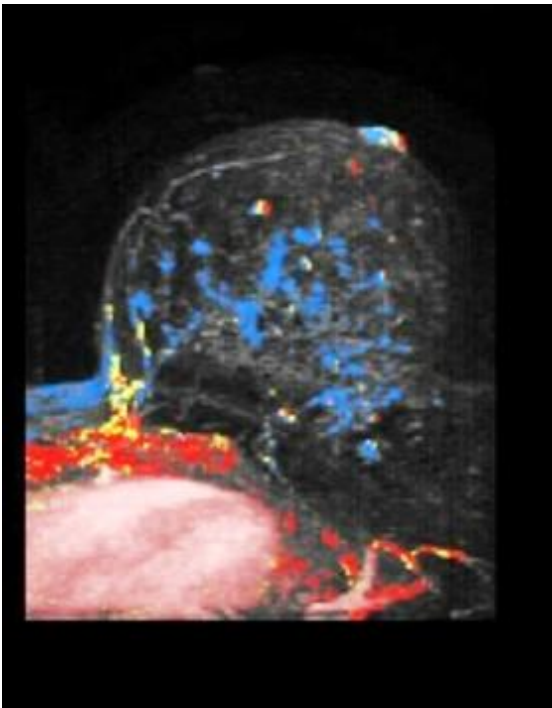
**Figure 5. Bilateral T2 weighted MRI breast image**



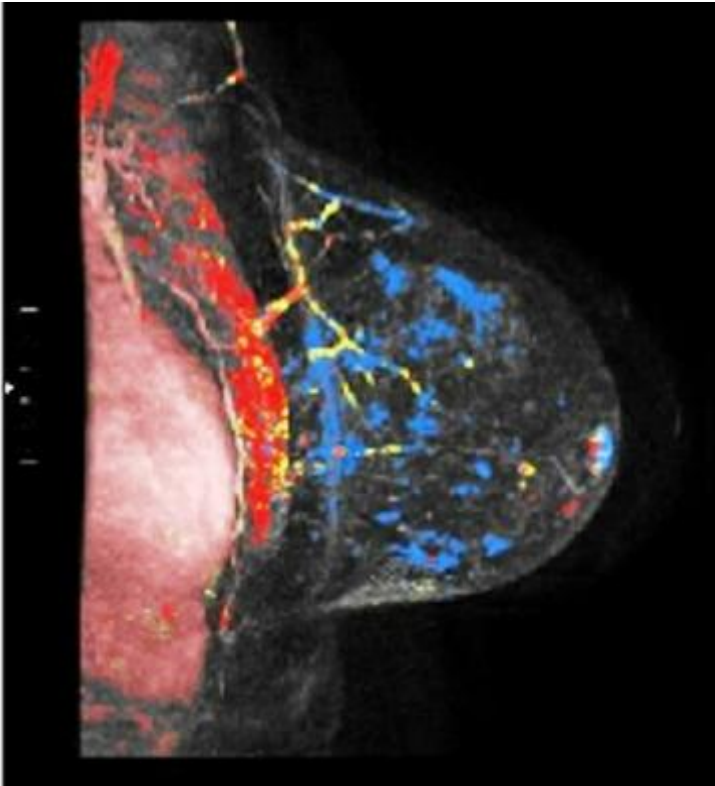
**Figure 6. Sagittal T1 weighted MRI breast image on the 1 o'clock outer breast tissue**



**Figure 7. CAD assistance with interpretation of the axial left breast MRI image**



**Figure 8. CAD assistance with interpretation of the sagittal left breast MRI image**



**CE Posttest**

1. Most benign and malignant disorders of the breast stem from \_\_\_\_\_.

- A. the breast's network of ducts and lobules.
- B. connective tissue.
- C. fat tissue.
- D. Cooper's ligaments.

**Answer: A; Breast Anatomy and Physiology**

2. Breast abnormalities are more difficult to detect with clinical breast examination (CBE) or mammography in women with a higher percentage of \_\_\_\_\_.

- A. fat tissue.
- B. muscle tissue.
- C. ductal or glandular breast tissue.
- D. none of the above.

**Answer: C; Breast Anatomy and Physiology**



3. Most neoplastic breast pathologies originate in the \_\_\_\_\_ of the breast.
- A. fatty tissue
  - B. terminal ductal lobular units (TDLUs)
  - C. fibrous tissue
  - D. Cooper's ligaments

**Answer: B; Breast Anatomy and Physiology**

4. Which of the following is true about fibrocystic changes in the breast?
- A. Fibrocystic changes have been found in 60% of North American women.
  - B. An increased number of cysts or fibrous tissue do not necessarily signal the presence of fibrocystic disease.
  - C. Fibrocystic changes are only considered a disease state if they are accompanied by pain, nipple discharge, or fibrocystic lumps that are suspicious of cancer.
  - D. All of the above.

**Answer: D; Breast Anatomy and Physiology**

5. Progressive, atypical hyperplasia of the breast is diagnosed as \_\_\_\_\_.
- A. fibrocystic breast disease
  - B. diffuse papillomatosis
  - C. carcinoma in situ
  - D. complex fibroadenoma

**Answer: C; Breast Anatomy and Physiology**

6. Women are encouraged to receive a baseline mammogram at the age of \_\_\_\_\_, followed by a regular schedule of follow-up examinations.
- A. 30 years
  - B. 35 years
  - C. 40 years
  - D. 45 years

**Answer: B; Breast Anatomy and Physiology**

7. Digital mammography may offer a particular advantage to film screen mammography in which of the following populations?
- A. Pre- and perimenopausal women
  - B. Women under the age of 50 years
  - C. Women with dense breasts
  - D. All of the above

**Answer: D; Conventional Breast Imaging and a Multimodality Approach**

8. A major limitation of CAD-assisted digital mammography is:

- A. Increased false negatives
- B. Increased false positives
- C. Decreased sensitivity in screening applications
- D. Decreased sensitivity in diagnostic applications

**Answer: B; Conventional Breast Imaging and a Multimodality Approach**

9. Breast ultrasound can be used as an alternative to mammography in \_\_\_\_\_.

- A. younger women with dense breast tissue
- B. older women
- C. women with diffuse papillomatosis
- D. women with complex fibroadenoma

**Answer: A; Conventional Breast Imaging and a Multimodality Approach**

10. The addition of adjunctive ultrasound to mammography may be \_\_\_\_\_ than mammography alone.

- A. more specific
- B. more sensitive
- C. less conclusive
- D. less accurate

**Answer: B; Conventional Breast Imaging and a Multimodality Approach**

11. One study found that \_\_\_\_\_ was more sensitive in women over the age of 50 compared with those under the age of 50, while \_\_\_\_\_ was equally sensitive in women under the age of 50 and over the age of 50.

- A. ultrasound; magnetic resonance imaging (MRI)
- B. ultrasound; mammography
- C. mammography; ultrasound
- D. Age has no bearing on the sensitivity of different modalities.

**Answer: C; Conventional Breast Imaging and a Multimodality Approach**

12. \_\_\_\_\_ has demonstrated utility in detecting cancer of the contralateral breast in patients newly diagnosed with breast cancer.

- A. MRI

- B. Ultrasound
- C. Mammography
- D. Computed tomography (CT)

**Answer: A; Conventional Breast Imaging and a Multimodality Approach**

13. While still in its early stages, breast imaging with \_\_\_\_\_ has been shown to provide excellent depictions of the breast anatomy, good visualization of microcalcifications, and accurate depictions of soft tissue components of any lesions found in the study.

- A. MRI
- B. Ultrasound
- C. Mammography
- D. Computed tomography (CT)

**Answer: D; Conventional Breast Imaging and a Multimodality Approach**

14. Which of the following statements is true about needle biopsies?

- A. Core-needle biopsies cannot distinguish between in situ carcinoma and an invasive carcinoma.
- B. Fine-needle aspiration breast biopsy (FNAB) cannot distinguish between in situ carcinoma and an invasive carcinoma.
- C. Neither core-needle biopsies nor FNAB can distinguish between in situ carcinoma and an invasive carcinoma.
- D. None of the above

**Answer: B; Conventional Breast Imaging and a Multimodality Approach; Breast Biopsy**

15. In a study evaluating 89 German patients who had been referred to the researchers for surgical biopsy of a suspicious breast lesion, the combined sensitivity of a multimodality approach declined from 92% with mammography and sonography to 64% with the addition of MRI, possibly due to:

- A. reader error.
- B. the use of an MRI with a 3 Tesla (T) magnet strength.
- C. the use of an MRI with a 1T magnet strength.
- D. the patient population studied.

**Answer: C; Multimodality Breast Imaging: Sensitivity and Specificity Based on a Review of the Literature**

16. A case report by Kuhl et al in 192 patients who were carriers of BRCA 1 or 2 gene for breast cancer reported a sensitivity of 100% with the use of which modality?

- A. Mammography
- B. MRI
- C. CT
- D. Breast sonography

**Answer: B; Multimodality Breast Imaging: Sensitivity and Specificity Based on a Review of the Literature**

17. A Korean study of 132 patients found that in patients with ductal cancer, \_\_\_\_\_ was most effective in visualizing the lesion and its ductal extension.

- A. mammography
- B. sonography
- C. MRI
- D. mammography and sonography combined

**Answer: D; Multimodality Breast Imaging: Sensitivity and Specificity Based on a Review of the Literature**

18. A study by Drew et al followed 285 symptomatic women from diagnostic work-up through pathologic diagnosis, finding that the combination of CBE, mammography, and fine-needle aspiration resulted in the same diagnostic specificity as \_\_\_\_\_ alone.

- A. CBE
- B. mammography
- C. fine-needle aspiration
- D. MRI

**Answer: D; Multimodality Breast Imaging: Sensitivity and Specificity Based on a Review of the Literature**

19. In a study by Warner et al of a cohort of women who were carriers of the BRCA 1 or 2 breast cancer gene, the diagnostic strategy resulting in the highest detection rate was:

- A. MRI alone
- B. CBE, mammography, breast sonography, and MRI combined
- C. mammography and CBE combined
- D. mammography alone

**Answer: B; Multimodality Breast Imaging: Sensitivity and Specificity Based on a Review of the Literature**

20. In younger women and in those with heterogeneous breast tissue, \_\_\_\_\_ may provide a higher diagnostic specificity; increased sensitivity may also be possible with the addition of \_\_\_\_\_ in a multimodality approach.

- A. mammography; breast sonography
- B. MRI; breast sonography
- C. breast sonography; MRI
- D. mammography; MRI

**Answer: C; Multimodality Breast Imaging: Sensitivity and Specificity Based on a Review of the Literature**