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American College of Radiology ACR Appropriateness Criteria®

Clinical Condition: Breast Pain

Variant 1: Cyclical. Unilateral or bilateral. Age <40. Initial examination.

Radiologic Procedure	Rating	Comments	RRL*
US breast	2		O
Mammography diagnostic	1		☼ ☼
Digital breast tomosynthesis diagnostic	1		☼ ☼
MRI breast without and with IV contrast	1		O
MRI breast without IV contrast	1		O
FDG-PEM	1		☼ ☼ ☼ ☼
Tc-99m sestamibi MBI	1		☼ ☼ ☼
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 2: Cyclical. Unilateral or bilateral. Age ≥40. Initial examination.

Radiologic Procedure	Rating	Comments	RRL*
Mammography diagnostic	2		☼ ☼
Digital breast tomosynthesis diagnostic	2		☼ ☼
US breast	2		O
MRI breast without and with IV contrast	1		O
MRI breast without IV contrast	1		O
FDG-PEM	1		☼ ☼ ☼ ☼
Tc-99m sestamibi MBI	1		☼ ☼ ☼
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Clinical Condition: Breast Pain

Variant 3: Noncyclical. Focal. Unilateral or bilateral. Age <30. Initial examination.

Radiologic Procedure	Rating	Comments	RRL*
US breast	5	This procedure may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Although current evidence suggests that imaging is not routinely indicated due to the rarity of underlying cancer in this age group/clinical scenario, it may be used in some settings to provide reassurance and to exclude a treatable benign cause for pain.	O
Mammography diagnostic	1		☼☼
Digital breast tomosynthesis diagnostic	1		☼☼
MRI breast without and with IV contrast	1		O
MRI breast without IV contrast	1		O
FDG-PEM	1		☼☼☼☼
Tc-99m sestamibi MBI	1		☼☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Clinical Condition: Breast Pain

Variant 4: Noncyclical. Focal. Unilateral or bilateral. Age ≥30. Initial examination.

Radiologic Procedure	Rating	Comments	RRL*
Mammography diagnostic	5	This procedure may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Although current evidence suggests that imaging is not routinely indicated due to the rarity of underlying cancer in this clinical scenario, it may be used in some settings to provide reassurance and to exclude a treatable benign cause for pain.	☼☼
Digital breast tomosynthesis diagnostic	5	Although current evidence suggests that imaging is not routinely indicated due to the rarity of underlying cancer in this clinical scenario, it may be used in some settings to provide reassurance and to exclude a treatable benign cause for pain.	☼☼
US breast	5	This procedure may be appropriate, but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Although current evidence suggests that imaging is not routinely indicated due to the rarity of underlying cancer in this clinical scenario, it may be used in some settings to provide reassurance and to exclude a treatable benign cause for pain.	O
MRI breast without and with IV contrast	1		O
MRI breast without IV contrast	1		O
FDG-PEM	1		☼☼☼☼
Tc-99m sestamibi MBI	1		☼☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 5: Noncyclical. Diffuse. Unilateral or bilateral. Age <40. Initial examination.

Radiologic Procedure	Rating	Comments	RRL*
US breast	2		O
Mammography diagnostic	1		☼☼
Digital breast tomosynthesis diagnostic	1		☼☼
MRI breast without and with IV contrast	1		O
MRI breast without IV contrast	1		O
FDG-PEM	1		☼☼☼☼
Tc-99m sestamibi MBI	1		☼☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Clinical Condition: **Breast Pain**

Variant 6: **Noncyclical. Diffuse. Unilateral or bilateral. Age \geq 40. Initial examination.**

Radiologic Procedure	Rating	Comments	RRL*
Mammography diagnostic	4		☢ ☢
Digital breast tomosynthesis diagnostic	4		☢ ☢
US breast	2		O
MRI breast without and with IV contrast	1		O
MRI breast without IV contrast	1		O
FDG-PEM	1		☢ ☢ ☢ ☢
Tc-99m sestamibi MBI	1		☢ ☢ ☢
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

BREAST PAIN

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Summary of Literature Review

Introduction/Background

Breast pain (mastalgia or mastodynia) and breast tenderness are very commonly reported by patients presenting for any type of breast imaging, occurring in up to 70%–80% of women at some time in their life [1-8]. Breast pain is the second most common breast symptom (after breast lump) for which women seek medical attention, even in older age groups [7,9-17]. Although a common problem, the worldwide literature related to this topic is relatively mixed in its conclusions regarding etiology and management of this condition.

Etiology of Breast Pain

The etiology of breast pain is not well understood and is probably multifactorial. Several possible causes have been studied, particularly for cyclical mastalgia, including a disturbance of hypothalamic control, abnormal hormonal response to stimuli, abnormal end-organ sensitivity, altered local hormone receptors, and disorders of lipid metabolism/fatty acid levels (which may result in exaggerated effects of normal levels of hormones). Hormonal medications, including hormone replacement therapy, oral contraceptives and infertility treatments, can be a cause of breast pain and tenderness. Other medications are also frequently implicated, specifically the selective serotonin reuptake inhibitor form of antidepressants. Psychological factors may also be involved. Studies indicate no direct relationship between mastalgia and fibrocystic changes or total-body water retention. There is no convincing scientific evidence that eliminating or reducing caffeine intake has any significant effect on breast pain, despite widespread belief to the contrary. Breast pain can be associated with diffuse palpable nodularity, but there is no relationship between the extent of nodularity and the severity of pain [10].

Twenty-five percent of patients with noncyclical pain are reported to have duct ectasia with periductal inflammation, characterized by an exquisite continuous burning pain, usually behind the nipple, and a hypersensitive breast [14,18]. This entity is often associated with heavy smoking. Women with large breasts often have noncyclical pain simply related to the size of their breasts, which may also be associated with neck, shoulder, and back pain.

Types of Breast Pain

Breast pain is usually divided into 2 main types, cyclical and noncyclical, and should be distinguished from extramammary pain. Distribution of pain should be considered as well. We will define “diffuse” pain as involving greater than 25% of the breast and axillary tissue; “focal” as involving less than 25% of the breast and axillary tissue; and “pinpoint” as an area that is the size of a fingertip.

Cyclical Breast Pain

The cyclical form of mastalgia, which is by far the most common, is diffuse unilateral or bilateral pain and/or tenderness, often accompanied by swelling, that waxes and wanes with the menstrual cycle. This accounts for up to 70% of women with breast pain [4,7,19-22], most of whom do not meet the commonly accepted criteria for premenstrual syndrome [23], suggesting that it is a distinct entity. Patients are typically in their third decade of life. In one study, pain was unilateral in 38% (usually in the breast with more parenchyma), and 61% of those with bilateral pain had pain in one breast more than the other. Many patients had a history of low physical activity and a low rate of breastfeeding, and 87% were multiparous [24]. The pain is most pronounced in the luteal phase,

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and is most likely hormonal in origin. However, no consistent abnormalities in basal hormone levels have been found in most studies, suggesting an increased sensitivity to normal hormone levels as the etiology.

Cyclical pain is usually treated symptomatically, since the likelihood of breast cancer is extremely low in the absence of other signs or symptoms. Approximately 14%–20% of these patients have spontaneous resolution within 3 months [4,19], and most have decreasing severity of pain over time [19]. However, at least 60% of cases recur within 2 years. Some women have increasing severity of symptoms until menopause, at which time about 40% experience resolution. Women who start having cyclical pain before age 20 usually have a prolonged course [21]. Women with cyclical mastalgia tend to undergo more frequent breast investigations (consultations, mammograms, needle, and surgical biopsies) than do women without cyclical breast pain [1,3] and more commonly engage in self-treatment.

Noncyclical Breast Pain

Noncyclical breast pain accounts for up to 25% of the cases of breast pain [21]. It is predominantly inflammatory in nature, rather than hormonal in origin. It is usually unilateral, and tends to be more focal than cyclical breast pain. The site of the pain is often precisely localizable and reproducible by the patient and physician. This type of pain has no predictable chronological pattern in time but may be worse in cold weather. It is more commonly persistent and is often located in the subareolar area or nipple and in the lower inner breast. Noncyclical mastalgia is more common in women in their fourth decade of life, although 10%–15% present after the age of 50 [6]. Noncyclical mastalgia tends to be of shorter duration than cyclical mastalgia, with spontaneous resolution occurring in up to 50% of patients [6]. Most cases of noncyclic mastalgia do not respond to hormonal manipulation. This type of pain, even without additional signs or symptoms of breast disease, may need additional evaluation to exclude an underlying benign or malignant breast lesion [25]. Mammography may show duct ectasia or secretory calcifications at the site of pain. Noncyclical breast pain due to various medications is poorly understood and has various presentations.

Mastitis or breast abscess can be a cause of focal pain, which may precede induration, redness, warmth, and fever. Breast pain may also be the initial presentation of Mondor disease (thrombophlebitis, usually of the thoracoepigastric vein).

Noncyclical breast pain can be related to trauma in approximately 10% of cases. Pain related to a previous surgery is more common in patients who had postoperative infection or hematoma, or in patients in whom the surgeon cut across Langer lines of tension. Breast implants, especially those placed in a subpectoral location can be associated with pain. Postsurgical pain may be due to scar pain, nerve regeneration, or focal nerve injury due to ischemia, radiation, lymphedema, or implant capsule formation.

Some degree of noncyclic breast pain and tenderness associated with pregnancy and breastfeeding is common and is usually of short duration, resolving spontaneously. Rarely, breast pain is one of the first symptoms of pregnancy. Breast pain can also occur physiologically at thelarche. Breast pain during exercise may occur in many women due to movement of breast tissues.

Various other causes of pain that are perceived to be within the breast, or referred to the breast, have been described, accounting for 10%–15% of the cases of “breast pain.” The nerve supply to the breast is from the anterolateral and anteromedial branches of the intercostal nerves from T3-T5, and irritation anywhere along their course can lead to breast or nipple pain. The extramammary (nonbreast) causes of pain include Tietze syndrome (costochondritis); other musculoskeletal or chest-wall conditions, such as pectoral muscle strains or spasms, entrapment of the lateral cutaneous branch of the third intercostal nerve, fibromyositis, fibromyalgia, myalgia, and rib fracture; spinal (cervical or thoracic) nerve root syndrome; coronary ischemia; esophageal disease (ie, achalasia, hiatal hernia); pulmonary disease (ie, pleurisy, pulmonary embolus, TB); gallbladder pathology; peptic ulcer disease; gastroesophageal reflux; shingles; and sickle cell anemia. Even infected teeth have been reported as a cause of breast pain.

Association of Breast Pain with Breast Cancer and Benign Breast Disease

Although pain is not a common symptom of breast cancer, some studies have suggested that cyclical mastalgia may represent an independent and useful clinical marker of increased breast cancer risk [26,27], especially in premenopausal women. One study [28] reports a 2.1–3.6 increase in relative risk for breast cancer, and a 5-fold increase in breast cancer in women with symptoms persisting for more than 97 months. Another study [26] reports a 5-fold increase in breast cancer after 37 months of pain. These authors suggest increased tissue

sensitivity to estrogen as the cause. However, other authors imply a protective effect of breast pain by causing patients to seek medical attention early [29] and report no overall increase in breast cancer risk [27,30-32]. Several studies have reported that premenopausal women with severe pain of long duration during their menstrual cycles more commonly had very dense breasts mammographically [5], which has recently been cited as a risk factor for breast cancer.

Advanced cancers may present with breast pain as the only symptom [33], especially if they are present deep in a large breast or have chest-wall invasion. Invasive lobular carcinoma [34] and anaplastic carcinoma [35] are disproportionately associated with mastalgia as compared to other cancer types. Pain has also been described with adenoid cystic carcinoma [36].

Imaging

For all types of breast pain, breast imaging may be helpful in determining whether there is an underlying, and potentially treatable, cause. It is not used simply to exclude breast cancer. Even if negative, imaging is useful to alleviate patient anxiety and guide referring physicians in considering possible treatment options. Reassurance is often cited as the main reason for imaging of these patients [30,37]. Many women with mastalgia do not seek further medical attention after reassurance that their pain is not due to breast cancer [14,21]. However, there is some evidence to suggest that imaging does not always provide such reassurance. Howard et al [38] showed that embarking on imaging evaluation of breast pain in the situation of a negative clinical examination does not lead to an increase in cancer detection over those without breast pain, but more importantly increases the odds of additional clinical and imaging utilization above the initial imaging.

There is very little literature related specifically to breast pain and breast imaging, even though a “persistent or focal area of pain or tenderness” is one of the indications for diagnostic mammography listed in the ACR Practice Guideline for the Performance of Screening and Diagnostic Mammography [39].

Mammography is often used to evaluate breast pain. However, the yield is low when the clinical examination is normal. The risk of malignancy after normal clinical and mammographic workup for breast pain is approximately 0.5% [15,18,40]. In a case-controlled study, there was no significant difference in the incidence of breast cancer in women referred for mammography with a painful breast (0.5%) as compared to the contralateral nonpainful breast (0.5%) and as compared to women without breast pain referred for mammographic screening (0.7%) [30].

A prospective observational follow-up study of 987 patients (1992–1996, with 2 years of follow-up) by Duijm et al [30] evaluated breast imaging in women (age range 10–86) with breast pain alone (either diffuse or localized). The control group consisted of 987 asymptomatic women presenting for a screening mammogram. Patients with breast cancer history or implants were excluded. Pain was unilateral in 76% and bilateral in 24%. Mammography was the main imaging technique. Ultrasound (US) was only performed to evaluate an inconclusive mammographic finding, or in dense breasts. US only was performed in women younger than 25 years with pain limited to one quadrant. The cancer rate was reported as 0.4% in the painful breast. A total of 0.8% of patients in the breast pain group had breast cancer, as compared to 0.7% of the asymptomatic control group. In the study group, 86.5% of imaging was negative; 8.6% had benign abnormalities; 3.6% had probably benign abnormalities; 0.8% had suspicious findings; and 0.4% had cancer in the symptomatic breast.

Only 2 studies in the United States have evaluated the role of imaging in focal breast pain. In the retrospective study by Leung et al [41], 110 targeted US examinations were performed on 99 patients who presented with focal breast pain without an associated palpable mass (65% of patients also had mammography). The mean age was 41 (range of 23–77 years old), with half of the patients younger than 40. Focal breast pain was defined as “pain that the patient could localize to one specific area.” No cancers were detected at the site of pain in any of the 110 examinations. The authors concluded that imaging, particularly targeted US, in patients with focal breast pain was useful primarily for patient reassurance. However, their patient population was low risk, mostly young patients, with no family history of breast cancer. Approximately 20% of patients had cysts or benign masses as the root cause of the focal pain.

In a retrospective study by Tumyan et al [42], 86 consecutive patients with a complaint of focal breast pain without a palpable mass underwent diagnostic mammography and US evaluation. Four cancers were detected (4.6%): 2 at the site of pain (2.3%) and 2 incidental cancers presenting as microcalcifications in an area unrelated to the area of pain. Both of the cancers at the site of pain were seen on both mammography and US. The negative predictive value of mammography and US for cancer at the site of focal breast pain was 100%.

Digital breast tomosynthesis (DBT) addresses some of the limitations encountered with standard mammographic views. In addition to planar images, DBT allows for creation and viewing of thin-section reconstructed images that may decrease the lesion-masking effect of overlapping normal tissue, and reveal the true nature of potential false positive findings. DBT can be useful in the diagnostic setting, improving lesion characterization [43-46] in noncalcified lesions, when compared to conventional mammographic workup. Interpretation time for DBT images is greater than for standard mammography [47,48]. Additionally, dose is increased if standard 2-D images are obtained in addition to DBT images. However, synthesized reconstructed images (a virtual planar image created from the tomographic data set) may replace the need for a 2-D correlative view; and current data suggests that these synthetic images perform as well as standard full-field digital images [49,50].

US is preferable to mammography in younger women. Loving et al [51] showed that in women under age 30 with focal breast signs and symptoms, breast US had 100% sensitivity with a negative predictive value of 100%.

Summary of Recommendations

- The imaging recommendations for women presenting with various types of breast pain as their only symptom are focused on ‘non–high-risk’ women and assume that all women, with or without breast symptoms, will have routine mammography according to ACR guidelines based on their risk status and personal history.
- Women with cyclical and/or bilateral nonfocal breast pain or tenderness usually do not require nonroutine imaging due to the low yield of finding a specific cause.
- In patients with noncyclical, unilateral, or focal breast pain that is not extramammary in origin (such as chest-wall pain), imaging can be pursued to exclude the unlikely presence of breast cancer as the cause of pain, to determine a benign but treatable etiology, or to offer reassurance that there is no anatomic abnormality present.
 - In symptomatic women less than 30 years of age, US is more accurate in making a diagnosis than mammography [52].
 - In the 30–39 year old age group, adding unilateral or bilateral mammography may be appropriate, since some of the small cancers found at the site of pain as reported in several studies were only visible mammographically. Mammography may also be indicated in patients under the age of 30 if a suspicious lesion is found on the initial US examination, or if the patient’s history or risk status justifies the radiation exposure.
 - Mammography should be performed with US in patients age 40 and older, or in a patient of any age who would normally qualify for a mammogram based on risk factors and the date of the last mammogram.
- There are no data to suggest that breast magnetic resonance imaging (MRI) or nuclear imaging (molecular breast imaging [MBI], or positron emission mammography [PEM]) meet the risk/benefit or cost-effectiveness criteria to be considered useful in the workup of breast pain.

Summary of Evidence

Of the 52 references cited in the *ACR Appropriateness Criteria® Breast Pain* document, 1 is categorized as a therapeutic reference. Additionally, 51 references are categorized as diagnostic references including 1 well designed study, 4 good quality studies, and 15 quality studies that may have design limitations. There are 32 references that may not be useful as primary evidence.

The 52 references cited in the *ACR Appropriateness Criteria® Breast Pain* document were published between 1976-2014.

While there are references that report on studies with design limitations, 5 well designed or good quality studies provide good evidence.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional

information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document.

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
⊛	<0.1 mSv	<0.03 mSv
⊛ ⊛	0.1-1 mSv	0.03-0.3 mSv
⊛ ⊛ ⊛	1-10 mSv	0.3-3 mSv
⊛ ⊛ ⊛ ⊛	10-30 mSv	3-10 mSv
⊛ ⊛ ⊛ ⊛ ⊛	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies”.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.