REVIEW

LAKSHMI VAIDYANATHAN, MD
Section of General Internal Medicine, Department of Medicine, University of Pittsburgh Medical Center Shadyside, Pittsburgh, PA

KAREN BARNARD, MD, MPH
Section of General Internal Medicine, Department of Medicine, University of Pittsburgh Medical Center Shadyside, Pittsburgh, PA

D. MICHAEL ELNICKI, MD
Professor of Medicine, University of Pittsburgh School of Medicine; Director, Section of General Internal Medicine, Department of Medicine, University of Pittsburgh Medical Center Shadyside, Pittsburgh, PA

Benign breast disease: When to treat, when to reassure, when to refer

ABSTRACT

Many women have breast symptoms—swelling and tenderness, nodularity, pain, palpable lumps, nipple discharge, or breast infections and inflammation. Fortunately, relatively few have breast cancer. Physicians must distinguish benign breast conditions from malignant ones, and know when to refer the patient to a specialist. We have included some of the newer diagnostic techniques and the approach to patients with nonpalpable lesions detected on a screening mammogram.

KEY POINTS

Formerly, the term "fibrocystic disease" was used to describe all benign breast conditions. However, this term caused confusion in distinguishing between normal physiologic changes and pathologic ones.

Breast pain is the second most common breast symptom for which women seek medical attention, the first being a lump in the breast. Most women with breast pain do not have cancer.

A benign mass is usually three-dimensional, mobile, and smooth, has regular borders, and is solid or cystic in consistency.

A malignant mass is usually firm in consistency, has irregular borders, and may be fixed to the underlying skin or soft tissue. There may also be skin changes or nipple retraction.

MANY WOMEN HAVE SYMPTOMS of breast disease, but few have cancer. Yet these symptoms are understandably a source of great concern for women.

The challenge for physicians is to distinguish between benign and malignant lesions, and to know when prompt referral to a surgeon or other specialist is necessary.

Making such discriminations is not easy, as the conditions are diverse and vary in presentation. They include:

- Physiologic swelling and tenderness
- Nodularity
- Breast pain
- Palpable breast lumps
- Nipple discharge
- Breast infections and inflammation.

This article presents an approach to benign breast conditions for the primary care physician, including their diagnosis, management, and appropriate referral. A systematic approach and a careful history and physical examination will simplify this seemingly complicated group of disorders.

SYMPTOMS COMMON, BUT RARELY MALIGNANT

The incidence of benign breast disease is difficult to assess clinically.[1]

A retrospective cohort study in a health maintenance organization found that 16% of women 40 to 70 years of age presented with breast symptoms,[2] but only 6% of those with symptoms had breast cancer.

In another study in Sheffield, UK, 60% of women referred to surgical outpatient or out-

TABLE 1

Pathologic classification of benign breast disease

Nonproliferative lesions
- Cysts
- Mild hyperplasia of the usual type
- Epithelial-related calcifications
- Fibroadenoma
- Papillary apocrine change

Proliferative lesions without atypia
- Sclerosing adenosis
- Radial and complexing sclerosing lesions
- Moderate and florid hyperplasia of the usual type
- Intraductal papillomas

Atypical proliferative lesions
- Atypical lobular hyperplasia
- Atypical ductal hyperplasia

BASED ON LOVE S, GELMAN RS, SILEN W. FIBROCYSTIC "DISEASE" OF THE BREAST—A NONDISEASE? N ENGL J MED 1982; 307:1010–1014.

TABLE 2

Clinical classification of benign breast disease

Physiologic swelling and tenderness
Nodularity
Breast pain
Palpable lumps
Nipple discharge
Breast infections and inflammation

BASED ON LOVE S, GELMAN RS, SILEN W. FIBROCYSTIC "DISEASE" OF THE BREAST—A NONDISEASE? N ENGL J MED 1982; 307:1010–1014.

reach clinics because of breast symptoms were diagnosed with benign breast disease.[3]

Breast nodularity and pain usually respond to conservative measures

TWO CLASSIFICATION SYSTEMS

Formerly, the term "fibrocystic disease" was used to describe all benign breast conditions. However, this term caused confusion in distinguishing between normal physiologic changes and pathologic ones.[4]

Currently, two classification systems are in use: pathologic and clinical.

Pathologic classification

The pathologic classification (TABLE 1), based on findings on biopsy, is useful in assessing the risk of breast cancer in women with benign breast disease. Most benign breast lesions are not associated with an increased risk of breast cancer.

Nonproliferative disease accounted for 70% of cases of benign breast lesions in a series of more than 10,000 consecutive breast biopsies performed in three hospitals in Nashville, Tenn.[5] It is not associated with an increased risk of breast cancer.

Proliferative disease without atypical hyperplasia accounted for 27% of the cases in the Nashville series. Unless the patient has a family history of breast cancer, proliferative disease without atypical hyperplasia increases the risk of breast cancer only slightly: the relative risk in the Nashville series was 1.3 without a family history and 2.4 with a family history.

Atypical hyperplasia accounted for 4% of cases in the Nashville series. It is associated with a fourfold to fivefold increase in the risk of breast cancer, and a family history in the presence of atypical hyperplasia boosts the risk of breast cancer even more.[6]

Clinical classification

The clinical classification of benign breast disease (TABLE 2) is based on signs and symptoms and is more useful for the primary care physician. The rest of this paper is based on the clinical classification.

PHYSIOLOGIC SWELLING AND TENDERNESS

Most women in their reproductive years experience varying degrees of breast swelling, fullness, or tenderness. These changes occur premenstrually and are cyclic, physiologic, and hormonally mediated.[7,8] Physical examination reveals nodularity, lumpiness, or tenderness.

If in doubt about the nature of the lumpiness, ask the patient to return after one or two menstrual cycles during midcycle when these changes regress.[9] At this point, both tenderness and lumpiness should be significantly diminished.

Patients with these physiologic changes should be reassured. Treatment, if needed, consists of analgesics and a well-fitting brassiere.[8]

NODULARITY

Nodularity is also a physiologic, hormonally mediated change characterized by lumpiness of the breast and varying degrees of pain and tenderness. The symptoms are most prominent about 1 week before menstruation and subsequently decrease.

Physical examination may reveal an area of nodularity or thickening, poorly differentiated from the surrounding tissue and often in the upper outer quadrant of the breast. If the changes are symmetric (ie, the same in both breasts), they are rarely pathologic.[9]

Follow-up of asymmetric nodularity

Follow-up of asymmetric nodularity (ie, not the same in both breasts) should be scheduled at midcycle after one or two menstrual cycles.[9] If the nodularity or thickness persists, the patient should be referred to a surgeon for evaluation and undergo bilateral mammography if older than 35 years.[9] For patients younger than 35 years, an ultrasound may be helpful. However, these patients also need a surgical referral.

Treatment of nodularity

A variety of treatments have been reported for breast nodularity. Conservative measures include mild analgesics and supportive brassieres.[8] Other treatments are described in the next section on breast pain, as most of the studies evaluating the efficacy of treatment were conducted in women with both breast nodularity and pain or tenderness.

BREAST PAIN

Breast pain, or mastalgia, is the second most common breast symptom for which women seek medical attention,[3,10] the first being a lump in the breast. Most women with breast pain do not have cancer.[11]

Common symptoms associated with mastalgia are heaviness and tenderness. The discomfort is often in the upper outer quadrant, diffuse, and may radiate to the axilla or upper arm.[8,12]

Mastalgia is broadly classified as either cyclic or noncyclic, based on its relationship to the menstrual cycle.[12]

Cyclic mastalgia usually starts 1 to 3 days before the onset of menses and subsides after menses are completed. It accounts for about two thirds of all cases of mastalgia and is more responsive to treatment than noncyclic mastalgia.[13]

Noncyclic mastalgia is unrelated to the menstrual cycle and shows a poorer response to treatment.

Follow-up of breast pain

Any palpable mass or asymmetry on clinical breast examination should be further evaluated. Diffuse nodularity, often bilateral, is not uncommon and is a benign finding.

If the breast examination is normal, most women younger than 35 years do not need any further diagnostic evaluation, as the risk of breast cancer is low.[11,14] On the other hand, women older than 35 years should have a mammogram even if the physical examination is normal to detect the rare presence of malignancy.[14,15]

Symmetric breast nodularity is rarely cancer

A patient with mild pain of less than 6 months' duration who is started on conservative treatment should be followed up after 3 to 6 months unless the pain gets worse.[14] If the pain persists or is severe despite initial treatment, or if the patient has concerns, referral to a breast specialist is indicated for possible initiation of medical therapy.[15]

Treatment of breast pain

Up to 85% of patients respond to nonmedical treatment and reassurance that breast cancer is a rare cause of breast pain. Therefore, the first-line approach to all patients with mastalgia should include education and recommending the use of a well-fitting brassiere.

Dietary modifications such as caffeine reduction or avoidance, a diet low in saturated fat, and vitamin E supplementation are often recommended, even though they have not shown benefit in clinical trials.[16,17] Nevertheless, they can't hurt.

Evening primrose oil, an herbal supplement, can be used as a first-line agent since it

has a low side-effect profile.[15] One placebo-controlled trial demonstrated a clinically significant improvement in breast pain at a dose of 1,500 mg twice daily. The drug is available in US health food stores and by prescription in the United Kingdom.[9]

Various drugs have been studied for treating mastalgia and nodularity but are rarely prescribed for these conditions because of their side effects. They are mentioned for completeness:

Danazol, an antigonadotropin, has been shown in randomized studies to relieve pain in 97% of patients and to decrease premenstrual nodularity in 73% to 93%.[18] It is approved by the US Food and Drug Administration (FDA) for treating mastalgia. Common side effects include acne, weight gain, hirsutism, and menstrual dysfunction, including amenorrhea. Women in their reproductive years should use barrier contraception in view of this drug's teratogenicity and interaction with birth control pills.

Tamoxifen, a synthetic antiestrogen, relieved pain in 75% to 96% of patients in different randomized trials.[15] The drug is not approved by the FDA for treating mastalgia. Patients should be evaluated every 3 months while taking tamoxifen to monitor for irregular menstrual bleeding or menopausal symptoms. The relapse rate is as high as 39% to 48% after tamoxifen is stopped.[15]

Any discrete solid masses should prompt a surgical referral for tissue diagnosis

The long-term effects of tamoxifen in women of reproductive age are uncertain, and it is not considered to be a first-line drug. Tamoxifen may induce ovulation, so birth control measures need to be addressed carefully.

Bromocriptine, a dopamine receptor agonist, inhibits prolactin release. Many patients (29%) stop taking bromocriptine because of its side effects, such as headache and dizziness.[19] In addition, bromocriptine is teratogenic and can interfere with birth control pills. Its use is restricted to patients who do not respond to danazol or tamoxifen.

Hormonal agents. Estrogen-progesterone combinations have been shown to alleviate breast nodularity associated with breast pain in 70% to 90% of women.[20] Medroxyprogesterone improved these symptoms in 85% of women.[8] Reducing the dosage of estrogen or stopping hormone replacement therapy in postmenopausal women alleviates mastalgia.

Diuretics have been tried for the treatment of nodularity and breast tenderness, but there is very little evidence to support their use.[21]

PALPABLE BREAST LUMP

Most breast lumps are benign.[22,23] Nevertheless, they are a considerable source of anxiety to patients.

Key points in the history are the onset, duration, and progress of the lump, any past history of breast problems, and any surgical procedures of the breast. Any risk factors for breast cancer should be noted, eg, age, family history of breast cancer, personal history of breast cancer, or biopsy showing atypical hyperplasia, but most women with breast cancer have no identifiable risk factors.

A careful examination of the breast and the axillary and supraclavicular lymph nodes is essential. A benign mass is usually three-dimensional, mobile, and smooth, has regular borders, and is solid or cystic in consistency. A malignant mass is usually firm in consistency, has irregular borders, and may be fixed to the underlying skin or soft tissue. There may also be skin changes or nipple retraction.

Follow-up of breast lumps

Women older than 35 years with a discrete breast mass (solid or cystic) should undergo bilateral diagnostic mammography to look for evidence of malignancy.[9] In contrast, breast cancer is rare in women younger than 35 years, and the diagnostic yield of a mammogram is low due to dense breast tissue.[22] Therefore, in young women a mammogram should be obtained only if the mass is suspicious for malignancy on clinical examination or if there is a strong family history of breast cancer.

If the mass is cystic on examination, the next step is needle aspiration. If the aspirate is nonbloody and the mass disappears completely, all the patient needs is a follow-up clinical breast examination after 4 to 6 weeks. If the fluid is bloody or if there is a residual mass on clinical breast examination, the aspirate should be sent to the laboratory for cytologic study and the patient should be referred to a surgeon. Recurrent cyst formation is another

indication for surgical referral.

Any discrete solid masses should prompt a surgical referral for tissue diagnosis even if the mammogram is negative.[7,9,14] In women younger than 35 years such a mass is usually a fibroadenoma. A tissue diagnosis can be obtained by fine needle aspiration, core needle biopsy, or excisional biopsy.

According to Van Dam and associates,[24] the sensitivity of mammography alone for the diagnosis of breast cancer in women with breast masses is 94% and its specificity is 55%. Therefore, a normal mammogram cannot exclude a cancer suspected on clinical grounds.

Some centers advocate a combination of physical examination, fine needle aspiration cytology, and mammography or ultrasonography.[25] If all three are positive for cancer, the diagnosis is confirmed on open biopsy in more than 99% of cases; when all three are benign, cancer is found in fewer than 0.5% of cases.[26]

If it is unclear on clinical examination whether the mass is solid or cystic, needle aspiration can be performed in the office as a first step. Alternatively, the patient can be directly referred to a breast specialist.

If the clinical breast examination and mammogram are normal but the patient says she can feel a lump, a follow-up clinical breast examination should be scheduled after 3 months.[5] Diffuse nodularity without a discrete lump should be followed clinically at midcycle after one or two menstrual cycles.[9]

NIPPLE DISCHARGE

In a prospective study, Urban[27] found that 11.8% of women with nonlactational nipple discharge had carcinoma of the breast; the number was 32% in patients older than 60 years who had spontaneous bloody nipple discharge.

Physiologic nipple discharge

Physiologic nipple discharge is usually seen only with nipple manipulation. It is usually bilateral and involves multiple ducts. The discharge may be milky, yellow, green, brown, or black, and is generally nonbloody and nonwatery. A spontaneous nonmalignant bloody discharge is seen occasionally in the third trimester of pregnancy. It usually resolves spontaneously and needs a full workup only if it persists after delivery.

Common causes of physiologic nipple discharge are extensive nipple manipulation, vigorous aerobic exercise, stress, pregnancy, and Montgomery tubercles in adolescents.[9,28]

Follow-up. If the discharge is determined to be physiologic, the patient should be reassured, and surgical referral is not needed. A follow-up visit should be scheduled to ensure that no new symptoms develop and that the problem resolves.

Persistent nonlactational galactorrhea

Galactorrhea is a spontaneous, milky, nonlactational discharge, usually bilateral and from multiple ducts, resulting from elevated prolactin levels. If it persists, it suggests an underlying medical condition and should be evaluated, especially if there are certain concurrent symptoms. For example, amenorrhea and visual symptoms should raise the possibility of a pituitary tumor. Other causes of galactorrhea include chest wall trauma, cirrhosis, spinal cord lesions, hypothyroidism, anovulatory syndromes, and drugs such as estrogens, tricyclic antidepressants, and cimetidine.

Follow-up. A medical evaluation should be started, including the serum prolactin level, the thyroid-stimulating hormone level, magnetic resonance imaging (MRI) of the brain to evaluate the pituitary gland, and a funduscopic examination to look for papilledema.

Medications that cause galactorrhea should be discontinued. Patients with galactorrhea can be treated with bromocriptine.[29] A patient on bromocriptine should be initially followed at intervals of 3 months. The drug may be discontinued in 3 months if the symptoms subside. Bromocriptine can restore fertility in patients with amenorrhea; therefore, patients should be warned about the possibility of getting pregnant.

Persistent galactorrhea, amenorrhea, and visual symptoms raise the possibility of a pituitary tumor

Pathologic nipple discharge

Pathologic nipple discharge is usually unilateral, confined to one duct, spontaneous, commonly bloody or watery, purulent, cloudy, serous, milky, and sometimes associated with a mass.

Intraductal papilloma is the most common cause of pathologic nipple discharge, followed by mammary duct ectasia.[27] Other causes include cancer and mastitis.

Follow-up. A pathologic discharge warrants immediate surgical referral and bilateral mammograms (specifying the patient's symptoms so that optimal views are obtained).[22] If the discharge is not bloody but shows signs of a pathologic process, it should be tested for occult blood. The role of nipple fluid cytology and galactography is controversial and will depend on local practice style.[27] Most patients with pathologic discharge will need terminal duct excision, which is diagnostic and, in the case of benign causes such as papillomatosis and duct ectasia, therapeutic.

BREAST INFECTIONS AND INFLAMMATION

Mastitis or inflammation of the breast can be broadly classified as lactational or nonlactational.[30] The diagnosis of lactational mastitis is generally straightforward, but it is important for the general internist to be able to differentiate nonlactational breast infections from inflammatory breast cancer.

If mastitis does not resolve in 1 month on antibiotics, referral is warranted

Lactational mastitis

Lactational mastitis occurs when breast ducts are blocked with engorged milk, and bacteria enter from cracks in the nipple skin. A wedge-shaped abscess in the peripheral part of the breast tissue subsequently develops. There may be associated breast engorgement and axillary lymphadenopathy.

Treatment includes symptom-relieving measures such as warm compresses and acetaminophen for pain and fever. Encourage the patient to continue breast-feeding with the unaffected breast, and once letdown occurs in the affected breast, feed with the affected breast until it is completely empty. A 10-day course of a penicillinase-resistant antibiotic such as dicloxacillin or nafcillin should be started. A localized abscess will require incision and drainage, and the material should be sent for culture.

Nonlactational mastitis

Nonlactational mastitis is characterized by periareolar abscesses, typically resulting from duct ectasia, in which lactiferous ducts become obstructed with cellular debris and lipid-laden material. This is followed by retrograde entry of bacteria from the skin, producing periductal inflammation and abscess formation.

This disease has a chronic recurrent course. The patient presents with noncyclic mastalgia, nipple discharge or retraction, periareolar abscess, subareolar mass, or cellulitis of overlying skin. Spontaneous peripheral abscesses in nonlactating women are generally associated with conditions such as diabetes and immunosuppressive diseases such as human immunodeficiency virus infection.

Follow-up. Subareolar and periareolar nonlactational abscesses require surgical referral, as these need prolonged antibiotic treatment and duct excision. Nonlactational peripheral duct abscesses should be drained, and the underlying cause (eg, diabetes) should also be treated. Patients with sporadic, infectious, nonlactational mastitis and Mondor disease should undergo mammography.[7,15]

Mondor disease is an uncommon self-limiting condition of the breast characterized by superficial thrombophlebitis.[31] Clinical features include sudden-onset breast pain and visible, palpable, tender, cord-like, branching cutaneous grooves. These findings usually resolve spontaneously over 6 weeks to 6 months. The treatment is mainly symptomatic, with analgesics and warm compresses.

Inflammatory breast cancer causes pain, redness, and induration of the skin, usually affecting the dependent portion of the breast. The progression of symptoms is very rapid, and within 1 month the breast may have the *peau d'orange* appearance (dimpled, like the skin of an orange). Any patient in whom presumed mastitis does not resolve completely after 1 month of treatment with antibiotics warrants surgical referral to rule out inflammatory breast cancer.

NONPALPABLE ABNORMALITIES DETECTED ON SCREENING MAMMOGRAPHY

The American College of Radiology recommends standardized terminology for reporting mammography results:

- Category 0—incomplete assessment; additional imaging evaluation is needed
- Category 1—negative
- Category 2—benign
- Category 3—probably benign
- Category 4—suspicious
- Category 5—highly suggestive of malignancy.

Patients in categories 1 and 2 need routine, age-appropriate breast cancer screening; those in categories 4 and 5 warrant surgical referral for breast biopsy.

The further workup of patients with category 3—"probably benign"—lesions is less clear. We believe they should have a follow-up clinical breast examination and a follow-up mammogram at 6 months, as suggested by Sickles[32] in an analysis of a series of 7,484 category 3 cases. In this series, 36 cancers developed in 3 years of follow-up; of these, 6 were detected by mammography at 6 months and 2 more were detected by palpation between 6 months and 1 year. Although mammographic screening at 6 months would therefore appear to have a low yield, 4 (80%) of the 5 aggressive tumors that occurred in this series were detected before 1 year.

On the other hand, the utility of the 6-month follow-up mammogram for category 3 findings has been debated. Alternatives have been suggested, such as only following up women with nonpalpable, noncalcified solitary nodules or using fine needle aspiration cytology.[33] The general internist faced with this predicament should refer the patient to a breast specialist, especially if the patient is not satisfied with mammography as the only follow-up.

THE FUTURE: NEW TUMOR MARKERS AND IMAGING

Many new diagnostic tests such as tumor markers and imaging techniques are currently being studied for the screening of breast cancer, its diagnosis, and its differentiation from benign breast disease.

Ductal lavage. For women at high risk of breast cancer (eg, with either a strong family history, personal history of breast cancer, or personal history of atypical proliferative breast lesions), potential risk-stratifying strategies include ductal lavage or ductoscopy to obtain specimens for cytologic study.[34]

Tumor markers. Expression of P53 in immunohistochemical staining of fine needle aspiration specimens of breast lesions may help identify the subgroup of patients with benign breast lesions who are at a higher risk of malignant transformation.[35]

Women with benign proliferative breast lesions who demonstrate overexpression of HER-2/neu amplification may be at a substantially higher risk of developing subsequent breast cancer.[36]

MRI. A number of studies found MRI to have a high sensitivity (88% to 100%) in diagnosing breast cancer. However, the specificity is variable (37% to 97%).[37] The role of MRI in differentiating benign from malignant lesions needs to be better defined, as MRI could potentially decrease the number of invasive biopsies that need to be performed. In a study by Daniel et al,[38] dynamic spiral MRI of the breast could not differentiate ductal carcinoma in situ from other benign lesions.

Nuclear imaging. Technetium-99m methoxyisobutylisonitrile (MIBI) scintimammography may have a role in the diagnosis of palpable breast lesions that cannot be clearly defined by conventional mammography. In theory, this imaging study might decrease the number of biopsies.[39]

The workup of 'probably benign' mammogram lesions is not clear

REFERENCES

1. **Johnson C.** Benign breast disease. Nurse Pract Forum 1999; 10(3):137–144.
2. **Barton MB, Elmore JG, Fletcher SW.** Breast symptoms among women enrolled in a health maintenance organization: frequency, evaluation, and outcome. Ann Intern Med 1999; 130:651–657.
3. **Laver RC, Reed MW, Harrison BJ, Newton PD.** The management of women with breast symptoms referred to secondary care clinics in Sheffield: implications for improving local services. Ann R Coll Surg Engl 1999; 81:242–247.
4. **Love S, Gelman RS, Silen W.** Fibrocystic "disease" of the breast—a nondisease? N Engl J Med 1982; 307:1010–1014.
5. **Dupont W, Page D.** Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985; 312:146–151.
6. **Dupont W, Parl F, Hartmann W, et al.** Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer 1993; 71:1258–1265.
7. **Zylstra S.** Office management of benign breast disease. Clin Obstet Gynecol 1999; 42:234–248.

8. **Neinstein LS.** Breast disease in adolescents and young women. Pediatr Clin North Am 1999; 46:607–629.
9. **Smith BL, Souba WW.** Clinical problems: breast disease. In: Wilmore DW, Brennan MF, editors. Scientific American Surgery. New York: Scientific American, Inc, 1999.
10. **The BRIDGE Study Group.** The presentation and management of breast symptoms in general practice in South Wales. Br J Gen Pract 1999; 49:811–812.
11. **Dujim LE, Guit GL, Hendriks JH, Zaat JO, Mali WP.** Value of breast imaging in women with painful breasts: observational follow-up study. BMJ 1998; 317:1492–1495.
12. **Ashley B.** Mastalgia. Lippincotts Prim Care Pract 1998; 2:189–193.
13. **Davies EL, Gateley CA, Miers M, Mansel RE.** The long-term course of mastalgia. J R Soc Med 1998; 91:462–464.
14. **Morrow M.** The evaluation of common breast problems. Am Fam Physician 2000; 61:2371–2378.
15. **Faiz O, Fentiman IS.** Management of breast pain. Int J Clin Pract 2000; 54:228–232.
16. **Allen SS, Froberg DG.** The effect of decreased caffeine consumption on benign breast disease: a randomized clinical trial. Surgery 1987; 101:720–730.
17. **Ernster VL, Goodson WH 3rd, Hunt TK, Petrakis NL, Sickles EA, Miike R.** Vitamin E and benign breast "disease": a double-blind, randomized clinical trial. Surgery 1985; 97:490–494.
18. **London RS, Sundaram GS, Goldstein PJ.** Medical management of mammary dysplasia. Obstet Gynecol 1982; 59:519–523.
19. **Mansel RE, Dogliotti L.** European multicentre trial of bromocriptine in cyclical mastalgia. Lancet 1990; 335:190–193.
20. **Vorherr H.** Fibrocystic breast disease: pathophysiology, pathomorphology. Am J Obstet Gynecol 1986; 154:161–179.
21. **Preece PE, Richards AR, Owen GM, Hughes LE.** Mastalgia and total body water. BMJ 1975; 4:498–500.
22. **Ligon RE, Stevenson DR, Diner W, Westbrook KC, Lang NP.** Breast masses in young women. Am J Surg 1980; 140:779–782.
23. **The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer.** The palpable breast lump: information and recommendations to assist decision-making when a breast lump is detected. Can Med Assoc J 1998; 158:S3–S8.
24. **Van Dam P, Van Goethem M, Kersschot E, et al.** Palpable solid breast masses: retrospective single and multimodality evaluation of 201 lesions. Radiology 1988; 166:435–439.
25. **Roche NA, Ray SA, Layer GT.** Immediate cytodiagnosis and imaging in the clinical management of discrete benign breast lesions. Ann R Coll Surg Engl 1997; 79:268–271.
26. **Donegan WL.** Evaluation of a palpable breast mass. N Engl J Med 1992; 327:937–942.
27. **Urban J.** Non-lactational nipple discharge. CA Cancer J Clin 1978; 28:130–140.
28. **Morrison C.** The significance of nipple discharge: diagnosis and treatment regimes. Lippincotts Prim Care Pract 1998; 2:129–140.
29. **Kleinberg DL, Gordon MD, Noel L, Frantz AG.** Galactorrhea: a study of 235 cases, including 48 with pituitary tumors. N Engl J Med 1977; 296:589–600.
30. **Appling SE.** Mastitis. Lippincott's Prim Care Pract 1998, 2:184–188.
31. **Hou MF, Huang CJ, Huang YS, et al.** Mondor's disease in the breast. Kaohsiung J Med Sci 1999; 15:632–639.
32. **Sickles EA.** Probably benign breast lesions: when should follow-up be recommended and what is the optimal follow-up protocol? Radiology 1999; 213:11–14.
33. **Apesteguia L, Pina L, Inchusta M, et al.** Nonpalpable, well-defined, probably benign breast nodule: management by fine-needle aspiration biopsy and long-interval follow-up mammography. Eur Radiol 1997; 7:1235–1239.
34. **Evron E, Dooley WC, Umbricht CB, et al.** Detection of breast cancer cells in ductal lavage fluid by methylation-specific PCR. Lancet 2001; 357:1335–1336.
35. **Kalogeraki A, Panayiotides J, Tamiolakis D, et al.** P53 expression in patients with malignant and benign breast diseases. Anticancer Res 2000; 20:1801–1806.
36. **Stark A, Hulka BS, Joens S, et al.** Her-2/neu amplification in benign breast disease and the risk of subsequent breast cancer. J Clin Oncol 2000; 18:267–274.
37. **Gilbert F.** New screening techniques for breast cancer (MRI). Dis Markers 1999; 15:115–116.
38. **Daniel BL, Yen YF, Glover GH, et al.** Breast disease: dynamic spiral MR imaging. Radiology 1998; 209:499–509.
39. **Sun SS, Hsieh JF, Tsai SC, Ho YJ, Lee JK, Kao CH.** The role of Tc-99m methoxyisobutylisonitrile scintimammography as compared to mammography in evaluating palpable breast masses of Taiwanese women. Anticancer Research 2000; 20(3B):2133–2136.

ADDRESS: *D. Michael Elnicki, MD, University of Pittsburgh Medical Center Shadyside, 5230 Centre Avenue, Pittsburgh, PA 15232, e-mail elnickim@msx.upmc.edu.*