Clinical Pearls in Breast Disease

Sandhya Pruthi, MD; John B. Bundrick, MD; and Scott C. Litin, MD

At the 2001 Annual Conference of the American College of Physicians, a new teaching format to aid physician learning, Clinical Pearls, was introduced. Clinical Pearls is designed with the 3 qualities of physician-learners in mind. First, we physicians enjoy learning from cases. Second, we like concise, practical points that we can use in our practice. Finally, we take pleasure in problem solving.

In the Clinical Pearls format, speakers present a number of short cases in their specialty to a general internal medicine audience. Each case is followed by a multiple-choice question answered live by attendees using an audience response system. The answer distribution is shown to attendees. The correct answer is then displayed and the speaker discusses teaching points, clarifying why one answer is most appropriate. Each case presentation ends with a Clinical Pearl, defined as a practical teaching point that is supported by the literature but generally not well known to most internists.

Clinical Pearls is currently one of the most popular sessions at the American College of Physicians meeting. As a service to its readers, *Mayo Clinic Proceedings* has invited a select number of these Clinical Pearls presentations to be published in our Concise Reviews for Clinicians section. "Clinical Pearls in Breast Disease" is one of them.

CASE 1

A 68-year-old woman was diagnosed with left breast invasive ductal carcinoma 6 months ago. She underwent lumpectomy and axillary node dissection, followed by breast irradiation. The tumor measured 1 cm in greatest diameter, and 2 of 20 lymph nodes were positive for metastatic cancer. The tumor was hormone receptor positive, and an aromatase inhibitor was prescribed. The patient tells you that she wants to start exercising but is concerned about her risk of developing lymphedema. She does not report any swelling involving her left arm. Physical examination reveals a well-healed surgical scar on the lateral aspect of the left breast and a second surgical scar in the axilla. The right breast is normal. There is neither axillary adenopathy nor current edema in the left arm.

Question

At this time, which *one* of the following would you recommend?

a. Inform the patient that lymphedema is common after axillary node dissection but that observation is the best course for now
b. Examine her for peau d'orange to determine her risk
c. Refer her to a physiatrist for instruction on weight lifting
d. Tell her to avoid any further exercise because this can increase the risk of lymphedema
e. Because she did not receive chemotherapy, she is at low risk for lymphedema

Discussion

Lymphedema is a common, but often underreported, complication after breast cancer surgery with lymph node dissection. It can result in long-term adverse effects that can negatively affect overall quality of life.[1] The pathophysiology involves mechanical insufficiency of the lymphatic vessels because of either obstruction of lymphatic pathways or surgical removal of lymph nodes. In theory, exercise can enhance lymphatic drainage and improve protein resorption, and in a recent randomized controlled trial was proved to be of clinical benefit. In that study of breast cancer survivors with stable lymphedema, compared with a control group, twice weekly progressive weight lifting resulted in greater improvement in severity of symptoms of lymphedema ($P=.03$) and in both upper and lower body strength ($P<.001$) and lower incidence of lymphedema exacerbation ($P=.04$).[2]

Clinical Pearl

Patients benefit from a referral to physical medicine and rehabilitation early after axillary node dissection for instruction in a slowly progressive weight-lifting program to decrease the incidence of lymphedema and increase strength.

CASE 2

A 35-year-old woman is seen for evaluation of a 2-month history of right breast bloody discharge from the nipple. She reports intermittent spontaneous bloody discharge that seems to involve the central aspect of the nipple. She has not felt a breast mass, and denies skin changes in the nipple or areolar complex. She has no family history of breast

See end of article for correct answers to questions.

From the Division of General Internal Medicine, Mayo Clinic, Rochester, MN.

cancer, and has not undergone previous breast biopsy. Her menstrual cycles are regular. She did not experience any difficulties while breast-feeding. On examination, the breasts appear symmetric, with no skin or eczematous lesions or abnormalities. The nipples appear symmetric in size, shape, and color, without retraction. During examination of the right areolar region, you were able to reproduce the expression of bloody discharge from a single central duct. The examination was negative for a discrete mass.

Question

What is the *most likely* diagnosis with these features?

a. Fibroadenoma
b. Fibrocystic breast changes
c. Carcinoma of the breast
d. Intraductal papilloma
e. Paget disease

Discussion

The incidence of nipple discharge is 2% to 5%. Although for many women the presence of nipple discharge can be an alarming symptom, the association with breast cancer is estimated to be less than 3%.[3] Intraductal papillomas are benign and are the most common cause of bloody discharge from the nipple. In contrast, fibrocystic breast changes are associated with green, yellow, white, or black discharge. Manifestation of Paget disease most often involves an eczematous-type rash of the nipple and areola, without nipple discharge. Fibroadenomas are benign solid tumors composed of stromal tissue and breast ductules and are not associated with bloody discharge.

Intraductal papilloma is composed of ductal epithelial proliferation with a fibrovascular stalk that is attached to the duct wall. Papillomas can arise as solitary or multiple lesions along the duct. Management includes diagnostic breast imaging using mammography and retroareolar breast ultrasonography to assess for an intraductal lesion and exclude a malignant lesion. If an intraductal lesion is detected on ultrasonography, percutaneous, vacuum-assisted, core needle biopsy can be performed at the radiologist's discretion.[4] However, results of these tests are frequently negative in women with nipple discharge. Diagnostic subareolar duct excision is performed to both provide symptom relief and obtain tissue to assess for malignancy.

Clinical Pearl

The most common cause of bloody discharge from the nipple is an intraductal papilloma, which is a benign finding.

CASE 3

A 46-year-old woman has just learned that her 48-year-old sister has been diagnosed with breast cancer. The family history also includes breast cancer in their mother at age 50 years. The patient is concerned about her risk of breast cancer, and comes to your office to ask about undergoing breast magnetic resonance imaging (MRI) to screen for breast cancer. She has had 4 children, and her first parity was at age 26 years. She underwent transabdominal hysterectomy with bilateral salpingo-oophorectomy 2 years previously because of menorrhagia. She has undergone no previous breast biopsies. She used estrogen therapy for management of hot flashes shortly after the transabdominal hysterectomy with bilateral salpingo-oophorectomy and recently discontinued it because the hot flashes have subsided. You decide to use a breast cancer risk calculation model called the IBIS (International Breast Cancer Intervention Study; also known as the Tyrer Cuzick model) to assess her risk of developing breast cancer, and the lifetime breast cancer risk is estimated at 23%. Breast examination yields normal findings. A screening mammogram is normal except for the presence of heterogeneously dense breast tissue.

Question

Which *one* of the following would you recommend next?

a. Order the *BRCA1/2* genetic blood test
b. Order annual digital screening mammograms starting at age 50 years
c. Order breast MRI
d. Order screening whole-breast ultrasonography
e. Order molecular breast imaging

Discussion

An accurate and individualized risk assessment of women with a family history can guide screening options for early detection of breast cancer. Risk calculation models are available to assist clinicians in estimating breast cancer risk. The models are limited by the level of specificity of the input data and vary in ability to estimate breast cancer risk. The IBIS model includes the combination of reproductive risk factors, age at cancer onset, number of affected first- and second-degree relatives, and previous breast biopsies. Other models include the Claus model (includes only family history) and the Gail model (includes only first-degree relatives and does not take into account paternal relatives or age at onset of affected relatives). Criteria published by the American Cancer Society

Mayo Clin Proc. ■ October 2012;87(10):1015-1020 ■ http://dx.doi.org/10.1016/j.mayocp.2012.07.003
www.mayoclinicproceedings.org

for annual screening breast MRI in conjunction with mammography includes a lifetime risk of invasive breast cancer of greater than 20% to 25% based on family history–based risk calculation models.[5] The Gail model may underestimate or overestimate lifetime risk given the limited input on family history, and would not be an ideal model to more accurately estimate lifetime risk.

Compared with film mammography, digital mammography as a screening study is more accurate in women with radiographically dense breast tissue. Factors associated with breast cancer risk in this patient include dense breast tissue and first-degree relatives with breast cancer, and mammographic screening beginning at age 40 years would be appropriate given an at least 2-fold increased risk of breast cancer.[6] Whole-breast ultrasonography has not been reported to decrease breast cancer mortality and results in higher false-positive findings. Compared with mammography and ultrasonography alone, breast MRI is more sensitive and improves detection of breast cancer in women at high risk. Molecular breast imaging has not been reported to decrease breast cancer mortality and is still under investigation as a screening tool in women with dense breast tissue and familial or genetic breast cancer risk.

Predisposition to hereditary breast cancer is associated with a family history that includes multiple relatives with breast, ovarian, or colon cancer diagnosed at an early age (<50 years). Women with a family history who have features suggestive of hereditary breast cancer benefit from referral to a genetic counselor. Genetic counselors can use risk models specific for estimating the likelihood that a *BRCA* sequence variation is present and can also provide counseling about the risks, benefits, and limitations of genetic testing before the *BRCA* genetic test results are obtained.[7]

Clinical Pearl

The American Cancer Society has published criteria for annual screening breast MRI in conjunction with mammography (based on evidence), and these include (1) *BRCA* sequence variation carriers, (2) untested first-degree relative of a *BRCA* carrier, or (3) lifetime risk of greater than 20% to 25% of developing invasive breast cancer on the basis of family history–based risk calculation models such as the IBIS.

CASE 4

A 60-year-old woman is seen for a routine physical examination. She informs you that her mother was diagnosed with breast cancer at age 65 years. She recently heard on the news about medications that can be used to prevent breast cancer and wants your advice about these medications. Her medical history is significant for hypercholesterolemia, type 2 diabetes mellitus, and hypertension. She is a smoker with a 10-pack-year history. Her current medications include lisinopril, aspirin, simvastatin, and metformin. She continues to have annual screening mammograms, and findings on the most recent one, this year, were normal. You perform the computerized Gail model (accessible on the National Cancer Institute Web site at www.brca.nci.nih.gov/brc/), and the patient's 5-year risk of developing invasive breast cancer is 2.5%.

Question

Which *one* of the following should you advise?

a. Take raloxifene, 60 mg/d, for 5 years
b. Take tamoxifen, 20 mg/d, for 5 years
c. That according to the Gail model, the 5-year risk is not high enough to justify chemoprophylaxis
d. That the Gail model accurately predicts development of breast cancer
e. Take exemestane, 25 mg/d, for 5 years

Discussion

Large randomized breast cancer prevention clinical trials have been conducted in the United States during the past decade. The largest randomized double-blind prevention trial was the National Surgical Adjuvant Breast and Bowel Project Study on Tamoxifen and Raloxifene, which compared tamoxifen vs raloxifene in 19,747 postmenopausal women. Both medications were found to decrease breast cancer risk by about 50%.[8] The eligibility criterion for this study was a Gail model 5-year predicted breast cancer risk of at least 1.66%. The Gail model takes into account age, age at menarche, number of first-degree family members (maternal side only) diagnosed with breast cancer, number of breast biopsies, age at first live birth, and history of atypical hyperplasia. The model is validated from a population perspective and predicts absolute risk of breast cancer but has limited usefulness in providing an individual risk prediction. The discriminatory power (C statistic) of this model is 0.5 to 0.6 and is slightly better than chance in generating a higher risk estimate in women with vs without breast cancer.

On the basis of data from the Study on Tamoxifen and Raloxifene trial, both tamoxifen and raloxifene have been approved by the US Food and Drug Administration for breast cancer prevention when given for 5 years in women with a Gail model 5-year risk of at least 1.66%. Subsequently, the RUTH (Raloxifene Use for The Heart) trial was performed,

which evaluated the effects of raloxifene on the incidence of coronary events and invasive breast cancer in 10,101 postmenopausal women. In that study, although raloxifene was beneficial in decreasing breast cancer risk, it did not significantly affect the risk of coronary heart disease (CHD). Although the overall all-cause mortality (cardiovascular and noncardiovascular causes) was not increased with raloxifene, the absolute annual rate of fatal stroke was 0.22% in patients on raloxifene compared to 0.15% in patients on placebo. This represents a 49% increase in the relative risk of fatal stroke on raloxifene in women with multiple risk factors for CHD or with known CHD.[9]

Aromatase inhibitors are another class of antiestrogen therapies and have recently been found beneficial for breast cancer prevention. Aromatase inhibitors markedly decrease estrogen synthesis by blocking the conversion of androgens to estrogen, leading to a profound reduction in estrogen concentration in postmenopausal women. A large randomized trial that compared exemestane vs placebo in postmenopausal women at moderately increased risk of breast cancer found that exemestane decreased breast cancer risk by 65%. The drug was administered for 5 years and was well tolerated by study participants.[10] Adverse effects and risks commonly associated with aromatase inhibitors include osteoporosis, fatigue, exacerbation of vasomotor symptoms, and vaginal dryness. In contrast to raloxifene and tamoxifen, there does not seem to be any evidence of increased vascular or thrombotic risk associated with aromatase inhibitors.[10] It is essential that the decision to initiate chemopreventive therapy be individualized, taking into account comorbid conditions and breast cancer risk.

Clinical Pearl

In postmenopausal women with multiple cardiac risk factors or a history of coronary artery disease, raloxifene use is associated with an increased incidence of fatal stroke.

CASE 5

A 68-year-old woman recently underwent screening mammography and was called back to the radiology department for further evaluation using magnification views to assess new right breast microcalcifications that measured about 5 mm in greatest diameter. The microcalcifications were reported as indeterminate, and the radiologist recommended a stereotactic core needle biopsy, which revealed lobular carcinoma in situ (LCIS). The patient has no family history of breast cancer. She comes to you for a second opinion about management options.

Question

Which of the following statements is *correct* about LCIS?

a. It is one of the more common types of breast cancer, and surgical management includes either lumpectomy with radiation therapy or simple mastectomy
b. Medical management is not indicated to reduce the risk of developing invasive breast cancer
c. Sentinel node biopsy is indicated at the time of surgery
d. This lesion is a marker for breast cancer risk and is associated with a 20% lifetime risk of developing invasive breast cancer
e. It is more likely than ductal carcinoma in situ to be observed on a mammogram

Discussion

Lobular carcinoma in situ is defined as a neoplastic or precancerous lesion and is, therefore, a marker of future risk of developing invasive breast cancer in either breast. It is confined to the milk lobules and terminal ducts, and the estimated lifetime breast cancer risk is 20%.[11,12] It is often detected as an incidental lesion during the work-up of a mammographic abnormality or biopsy of a palpable breast lump. There are no clinical or radiologic features that are specifically associated with LCIS. This is in contrast to ductal carcinoma in situ, in which the mammographic features often include pleomorphic microcalcifications with a segmental distribution.

The diagnostic management of LCIS has evolved over the past decade, with more emphasis on chemopreventive therapy rather than prophylactic mastectomy. The selective estrogen receptor modulators tamoxifen and raloxifene have both been found effective in reducing the risk of breast cancer development by up to 50%. A large, randomized, placebo-controlled study with the aromatase inhibitor exemestane found a 65% reduction in the risk of invasive breast cancer in postmenopausal women who were at moderately increased risk for breast cancer. In that study, exemestane was superior to placebo in women with previous atypical hyperplasia and LCIS.[10]

Prophylactic mastectomy is associated with a 90% reduction in breast cancer and is considered in selected individuals with a strong family history or genetic predisposition to develop breast cancer.

Clinical Pearl

Lobular carcinoma in situ is not a true malignant lesion; rather, it is a marker of increased risk for which chemopreventive therapy is the first line of management.

Mayo Clin Proc. ■ October 2012;87(10):1015-1020 ■ http://dx.doi.org/10.1016/j.mayocp.2012.07.003
www.mayoclinicproceedings.org

CASE 6

A 56-year-old woman was diagnosed with left breast invasive ductal carcinoma 6 years ago. She underwent lumpectomy followed by breast irradiation. The tumor measured 1.5 cm in greatest diameter and was estrogen and progesterone receptor positive and *HER 2/neu* negative, and the sentinel lymph node was negative for metastasis. The patient completed 5 years of adjuvant hormone therapy. About 3 months ago, she began to experience vaginal itching and dryness, dyspareunia, and postcoital spotting. She has no urinary tract symptoms and is otherwise well. The vaginal speculum examination revealed atrophy of the labia majora and vaginal introitus, and the vulvar and vaginal mucosae were pale, with petechiae. She has been using over-the-counter vaginal lubricants, which have not been effective.

Question

Which *one* of the following would you advise?

a. Continue using over-the-counter vaginal lubricants
b. Take short-term systemic estrogen therapy
c. Use a low-dose vaginal tablet or ring
d. Use a transdermal estrogen patch
e. Discontinue having intercourse

Discussion

With improved breast cancer treatment, the number of women living with breast cancer has increased. However, cancer treatment–related menopausal symptoms have become more prevalent and can negatively affect the quality of life for many survivors. A survey of breast cancer survivors reported that, compared with premenopausal or perimenopausal women, postmenopausal women had more severe vaginal dryness and dyspareunia.[13] Breast cancer survivors are not only affected with urogenital atrophy as a result of estrogen deficiency during their menopausal years, but their symptoms are exacerbated secondary to antiestrogen therapies. Specifically, aromatase inhibitors, compared with tamoxifen, are associated with a greater incidence of urogenital atrophy.

Treatment of symptomatic urogenital atrophy can be challenging in breast cancer survivors who worry about breast cancer recurrence but struggle with symptoms that affect the quality of their life. Nonhormonal options include not using scented hygiene products, maintaining regular coital activity, and using vaginal lubricants and moisturizers on a regular basis, all of which are helpful in decreasing symptoms of dyspareunia and dryness. If symptoms persist, local vaginal estrogen in the form of cream, tablets, or ring would be the next treatment option and is effective in relieving urogenital atrophy.[14]

In breast cancer survivors, there is concern about use of estrogen therapy, in particular in women who had a hormone-responsive malignant lesion. The concern is primarily about systemic (including transdermal) estrogen preparations, which have been associated with an increase in risk of breast cancer recurrence.[15] An assessment of the maximum annual dose delivered provides a theoretical maximum of estradiol for the first year of therapy. A review of various vaginal and oral estrogen agents demonstrated that when they were administered vaginally either as a tablet or ring, the serum estradiol concentration was substantially less than with oral or transdermal estrogen medications.[16] Compared with oral estrogen therapy, consideration of local low-dose vaginal estrogen (eg, vaginal tablet once a week) is reasonable for treatment of severe symptoms, given the potential for much lower serum estradiol concentrations. A clinical trial evaluating the safety of vaginal estrogen preparations is under way (http://clinicaltrials.gov/ct2/show/NCT00984399).

Clinical Pearl

Low-dose vaginal estrogen therapy is effective in the management of genitourinary atrophy, and systemic absorption is minimal, with a consequent low risk of recurrent breast cancer.

ACKNOWLEDGMENT

We thank Ms Gladdie Hebl of the Mayo Clinic Grant and Publication Support Services for assistance with manuscript preparation.

Correspondence: Address to Sandhya Pruthi, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (pruthi.sandhya@mayo.edu).

REFERENCES

1. Shih YC, Xu Y, Cormier JN, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. *J Clin Oncol*. 2009;27(12):2007-2014.
2. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. *N Engl J Med*. 2009;361(7):664-673.
3. Gray RJ, Pockaj BA, Karstaedt PJ. Navigating murky waters: a modern treatment algorithm for nipple discharge. *Am J Surg*. 2007;194(6):850-854; discussion 854-855.
4. Dennis MA, Parker S, Kaske TI, Stavros AT, Camp J. Incidental treatment of nipple discharge caused by benign intraductal papilloma through diagnostic Mammotome biopsy. *AJR Am J Roentgenol*. 2000;174(5):1263-1268.
5. Saslow D, Boetes C, Burke W, et al; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to

mammography [published correction appears in *CA Cancer J Clin*. 2007;57(3):185]. *CA Cancer J Clin*. 2007;57(2):75-89.

6. Nelson HD, Zakher B, Cantor A, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156(9):635-648.
7. Pruthi S, Gostout BS, Lindor NM. Identification and management of women with *BRCA* mutations or hereditary predisposition for breast and ovarian cancer. *Mayo Clin Proc*. 2010; 85(12):1111-1120.
8. Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial [published corrections appear in *JAMA*. 2008;296(24):2926 and *JAMA*. 2007; 298(9):973]. *JAMA*. 2006;295(23):2727-2741.
9. Barrett-Connor E, Mosca L, Collins P, et al; Raloxifene Use for the Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355(2):125-137.
10. Goss PE, Ingle JN, Alés-Martinez JE, et al; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women [published correction appears in *N Engl J Med*. 2011;365(14):1361]. *N Engl J Med*. 2011; 364(25):2381-2391.
11. Hanby AM, Hughes TA. In situ and invasive lobular neoplasia of the breast. *Histopathology*. 2008;52(1):58-66.
12. Simpson PT, Gale T, Fulford LG, Reis-Filho JS, Lakhani SR. The diagnosis and management of pre-invasive breast disease: pathology of atypical lobular hyperplasia and lobular carcinoma in situ. *Breast Cancer Res*. 2003;5(5):258-262.
13. Crandall C, Petersen L, Ganz PA, Greendale GA. Association of breast cancer and its therapy with menopause-related symptoms. *Menopause*. 2004;11(5):519-530.
14. Trinkaus M, Chin S, Wolfman W, Simmons C, Clemons M. Should urogenital atrophy in breast cancer survivors be treated with topical estrogens? *Oncologist*. 2008;13(3):222-231.
15. Holmberg L, Anderson H; HABITS Steering and Data Monitoring committees. HABITS (hormonal replacement therapy after breast cancer: is it safe?), a randomised comparison: trial stopped. *Lancet*. 2004;363(9407):453-455.
16. Pruthi S, Simon JA, Early AP. Current overview of the management of urogenital atrophy in women with breast cancer. *Breast J*. 2011;17(4):403-408.

CORRECT ANSWERS: Case 1: c. Case 2: d. Case 3: c. Case 4: e. Case 5: d. Case 6: c.