Early Detection of Breast Cancer: Is Mammography Enough?

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Breast cancer is a leading cause of cancer deaths among women in the United States, second only to lung cancer.[1] The advent of screening mammography has led to a decline in breast cancer mortality among women age 50 years or older.[2–4] For women younger than 50 years, however, the decline in mortality is less clear-cut.[5,6] Although the role of mammography in early detection of breast cancer is well recognized, mammography can miss tumors in patients with dense glandular breasts, prior surgery or radiation, and breast implants. Other modalities, such as ultrasonography and nuclear scanning, can be used in conjunction with mammography in these patients to detect tumors. This article reports the case of a woman in whom a technetium Tc 99m sestamibi scan detected an early breast cancer missed by both mammography and ultrasonography.

CASE PRESENTATION

History

A 50-year-old woman came to our clinic for a routine health maintenance visit. Medical history included a mastopexy approximately 5 years previously. She had undergone menarche at age 14 years, was nulligravid, and was currently perimenopausal. She had had annual mammograms each of the previous 3 years, all of which showed no abnormalities. She had no family history of breast cancer.

Physical Examination

Results of the general and systemic physical examination were within normal limits. Breast examination revealed the presence of scars in the inferior quadrants, bilaterally, owing to her previous breast surgery. There were no skin changes, the nipple areola complex appeared to be normal (bilaterally), and no mass was palpated in either breast.

Radiographic Studies and Other Evaluations

A current mammogram, which was reported as 0 using the Breast Imaging Reporting and Data System (BI-RADS),[7] showed a dense nodular pattern in both breasts, which was unchanged from the previous studies, but also a new asymmetric density in the left midbreast. However, a focal compression and magnification view did not show the left breast density or any other abnormalities. A subsequent sonogram showed a mass ($1.2 \times 0.75 \times 0.3$ cm) with an irregular outline in the left breast, as well as microlobulations. The patient was referred to a breast surgeon for further management. In view of the discrepancy between the focal compression and magnification mammogram and the sonogram, the surgeon ordered a technetium Tc 99m sestamibi scan, which showed increased uptake in the right midbreast; the left side showed no abnormalities. Results of needle localization and biopsy of the right breast revealed an infiltrating ductal carcinoma and ductal carcinoma in situ (DCIS).

Treatment

The patient underwent a right modified radical mastectomy. A pathology report on the resected specimen confirmed that the tumor was a poorly differentiated intraductal carcinoma, with foci of DCIS throughout the specimen. The axillary nodes were negative for any cancerous cells. The patient was subsequently scheduled to receive chemotherapy.

DISCUSSION

Epidemiology

Breast cancer is the most commonly diagnosed nondermatologic cancer in women in the United States.[1] American women have a 1:8 lifetime risk for developing breast cancer. Whereas the incidence is highest in white women, the mortality is highest in black women. Moreover, the incidence in Hispanic and Asian women

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is approximately 25% to 50% less than it is in white women, but the incidence in Hispanic women is rapidly increasing. It was estimated that approximately 182,800 women were diagnosed with breast cancer in the year 2000 and that approximately 40,800 died of the disease.[8–11] Yet, the mortality has been decreasing by approximately 2% every year since 1990, and the stage at diagnosis has been improving since 1983. More specifically, the number of stage 1 tumors has doubled, whereas the number of stage 3 and 4 tumors has decreased by almost 20%.[12–15] These improvements have been attributed to increased use of mammography and improved therapeutic options.

Risk Factors

There are several significant risk factors for developing breast cancer.[16,17] Increasing age increases a woman's risk for developing breast cancer. In addition, a family history of the disease increases a woman's risk; the risk increases 2 to 3 times when a first-degree relative is affected and is proportional to the number of relatives involved. Although a genetic predisposition for breast cancer is found in fewer than 3% of breast cancers, women carrying mutations of the *BRCA1* and *BRCA2* genes (identified as the breast cancer susceptibility genes) have a very high incidence of breast cancer, approximately 60% to 85%.[17] Women with mutations at these genes are currently offered the option of increased surveillance or prophylactic surgery and may be eligible for chemoprevention with tamoxifen.

A prior history of breast cancer increases the risk for cancer in the opposite breast, and a history of breast biopsy increases risk for cancer in the breast on which the procedure is performed. A history of atypical ductal or lobular hyperplasia increases a woman's risk for breast cancer by approximately 5 times. Nulliparity or age greater than 30 years at first delivery similarly increases risk, as does early menarche (age < 12 years) or late menopause (age > 55 years). Other risk factors less consistently associated with breast cancer include the use of hormone replacement therapy and exposure to ionizing radiation.

Various models have been developed to assess a patient's risk for breast cancer, with the Gail and the Clauss models[18] being the two most frequently used. The Gail model predicts the cumulative risk of breast cancer according to decade of life, to age 90 years. The Claus model is based on the assumption of the prevalence of high-penetrance genes for susceptibility to breast cancer. The Clauss model is not applicable to women without a first- or second-degree relative with breast cancer.[18]

Pathologic Differentiation

Breast cancer can be classified primarily as epithelial or nonepithelial, invasive or noninvasive, and multifocal or multicentric.[19] Epithelial tumors arise from cells lining lobules or ducts (eg, infiltrating ductal carcinoma). In contrast, nonepithelial tumors arise from supporting stroma (eg, angiosarcomas, malignant cystosarcoma phylloides, primary stromal sarcomas). Nonepithelial tumors occur much less commonly. Whereas noninvasive tumors do not penetrate the basement membrane (eg, ductal/lobular carcinoma in situ), invasive tumors do cross it (eg, infiltrating ductal/lobular carcinoma, inflammatory carcinoma, Paget's disease of the nipple); of note, inflammatory carcinoma is a highly malignant tumor that grows very rapidly. Finally, multifocal disease occurs within the same quadrant as the dominant lesion, whereas multicentric disease occurs in distant quadrants within the same breast. Bilateral disease obviously occurs in both breasts.

Common Histologic Types of Breast Cancer

Ductal carcinoma in situ. DCIS is a premalignant lesion in which there is proliferation of malignant epithelial cells completely within the breast ducts. It occurs more commonly than does lobular carcinoma in situ (LCIS), and the average age at diagnosis is 55 years. Approximately 80% of DCIS lesions are nonpalpable and detected by screening mammography.[20] This type of tumor is multicentric in 35% of cases[20]; the size and extent of DCIS appears to correlate with the risk for progression to invasive carcinoma. The risk for subsequent invasive ductal carcinoma is approximately 25% to 30%, which usually occurs within 10 years of diagnosis.[20] An occult invasive carcinoma may coexist with an in situ lesion in 11% to 21% of cases.[20]

Lobular carcinoma in situ. With LCIS, there is proliferation of malignant epithelial cells completely contained within the breast lobules. This type of tumor is considered a marker for increased risk for invasive disease and is usually diagnosed in women in their mid-40s. Estrogens are hypothesized to play a central role in the pathogenesis of LCIS, and this hypothesis may explain why two thirds of women with LCIS are premenopausal at diagnosis. LCIS does not form a palpable mass and is not evident on a mammogram. It is usually discovered incidentally on biopsy performed because of another abnormality and is identified in approximately 4% of breast biopsy specimens obtained in conjunction with benign disease.[20] LCIS tends to be multicentric and bilateral and can be identified in the contralateral breast in 50% to 90% of cases.[20] The risk

for subsequent invasive carcinoma (usually ductal) is approximately 20% in either breast, usually occurring more than 15 years after diagnosis.[20]

Infiltrating ductal carcinoma. Infiltrating ductal carcinoma is the most common breast malignancy, accounting for 80% of all cases of breast cancer.[20] The average age at diagnosis is 64 years.[20] Infiltrating ductal carcinoma typically originates from ductal epithelium and infiltrates supporting stroma. Less common forms of this type of breast cancer include medullary carcinoma, colloid carcinoma, tubular carcinoma, and papillary carcinoma. The tumor is usually unilateral and forms microcalcifications that can be detected early on mammography.

Invasive lobular carcinoma. Accounting for 8% to 10% of all invasive breast malignancies,[20] invasive lobular carcinoma originates from lobular epithelium and infiltrates supporting stroma. Because microcalcifications do not form, the tumor is usually not seen on mammography. This type of breast cancer is often bilateral and has a slightly better prognosis than other types.

Paget's disease of the nipple. Paget's disease of the nipple is rare, accounting for 1% to 3% of all breast malignancies.[20] The peak incidence occurs between age 50 and 60 years, with a median of 56 years, which is approximately 5 to 10 years younger than with other, more common types of breast cancer. It is usually associated with an intraductal carcinoma or an invasive carcinoma just beneath the nipple. The malignant cells invade across the epithelial-epidermal junction and enter the epidermis of the nipple. This results in eczematous change in the nipple, with crusting, scaling, erosion, or discharge—with or without an associated breast mass.

Mammography is used to detect and locate subclinical underlying tumors. The incidence of positive findings indicative of malignancy varies widely, from 24% to 97%.[21] In the presence of a palpable mass, the mammogram is positive in as many as 97% of cases.

Inflammatory breast carcinoma. The most rapidly lethal malignancy of the breast, inflammatory breast carcinoma has a reported mean age of presentation of 52 to 61 years.[22] This form of breast cancer presents as a diffuse induration with erythema, edema, warmth, and peau d'orange, with or without a palpable mass. Axillary lymphadenopathies are usually present. This tumor is poorly differentiated and is characterized by dermal lymphatic invasion on pathologic examination. Inflammatory breast carcinoma accounts for 1% to 4% of all breast malignancies and 17% to 36% of distant metastases common at the time of diagnosis.[22]

Clinical Characteristics

Since mammography was introduced as part of preventive care, breast cancer is most often diagnosed at its early asymptomatic stage as a nonpalpable suspicious lesion on a mammogram. Late presentations are typified by bloody discharge, palpable masses, skin changes, and symptoms caused by distant metastasis.

The majority of palpable masses are detected by the patient herself on routine breast self-examination. The mass is typically nontender, firm, and irregular. The mass is usually (in approximately 50% of cases) located in the upper outer quadrant of the breast. Skin changes may be present, including dimpling caused by tethering of Cooper's ligaments, peau d'orange caused by dermal lymphatic invasion, or nipple changes including retraction or ulceration (as in Paget's disease).

Metastasis occurs, in decreasing order of frequency, to the lungs, bone, liver, lymph nodes, and brain. The patient may have symptoms associated with invasion of those specific organs or may have generalized symptoms of malignancy (eg, anorexia, weight loss, cachexia).

Screening for Breast Cancer

Screening for breast cancer is accomplished through mammography, breast self-examination, and clinical breast examination. Although there is consensus on the advantages of mammography among women age 50 to 69 years, the advantages of mammography among women younger than 50 years are not as clear. Thus, various organizations (eg, American Cancer Society, National Cancer Institute, American Academy of Family Physicians, United States Preventive Services Task Force) have differing guidelines for screening women for breast cancer (**Table 1**).

Breast self-examination and clinical breast examination can detect tumors only after they become palpable. Mammography, however, can detect nonpalpable tumors. Relevant findings on mammography include soft-tissue lesions and microcalcifications.

Soft-tissue lesions can present as a mass, a density, or an architectural distortion. A mass is defined as a region of increased density with a distinct edge, making it distinguishable from the surrounding breast tissue on both mediolateral and craniocaudal mammographic views. Masses should always be seen in 2 views. They are suggestive of malignancy if they have irregular margins and if there is distortion of the adjacent stroma. A density, on the other hand, has no distinct edge and can usually be seen with only a single view. In patients with only a soft-tissue lesion evident on mammography, biopsy is positive for malignancy in 22% of cases; however, if the lesion is associated with microcalcification,

Table 1. Recommendations for Breast Cancer Screening

Age of Patient	ACS*	NCI†	AAFP	USPSTF‡
20 to 39 years	Clinical breast examination every 3 years, monthly breast self-examination	§	NP‖	NP
40 to 49 years	Clinical breast examination every year, monthly breast self-examination, mammography every year	Mammography every 1 to 2 years	Counseling about risks versus benefits of mammography¶	Mammography every 1 to 2 years, with or without clinical breast examination
50 to 69 years	Clinical breast examination every year, monthly breast self-examination, mammography every year	Mammography every 1 to 2 years	Clinical breast examination every 1 to 2 years, mammography every 1 to 2 years#	Mammography every 1 to 2 years, with or without clinical breast examination
Older than 69 years	Clinical breast examination every year, monthly breast self-examination, mammography every year	Mammography every 1 to 2 years	NP	Mammography every 1 to 2 years, with or without clinical breast examination

AAFP = American Academy of Family Practice; ACS = American Cancer Society; NCI = National Cancer Institute; USPSTF = United States Preventive Services Task Force.

*Data from Leitch et al.[9]

†Data from NCI statement on mammography screening. Available at http://newscenter.cancer.gov/pressreleases/mammstatement31jan02.html. Accessed 8 Aug 2002.

‡Data from Screening for breast cancer. Available at http://www.ahrq.gov/clinic/3rduspstf/breastcancer. Accessed 8 Aug 2002.

§Women younger than 40 years who are at higher-than-normal risk for breast cancer should seek expert medical advice about whether and how often to have screening mammography.

‖NP indicates that a guideline for this patient population is not provided.

¶Data from Periodic health examination. Recommend: general population. Available at http://www.aafp.org/x10598.xml. Accessed 8 Aug 2002.

#Data from Periodic health examination. Strongly recommend: general population. Available at http://www.aafp.org/x10600.xml. Accessed 8 Aug 2002.

biopsy is positive in 42% of cases.[23] Architectural distortion in the absence of a density or a mass is usually benign and is defined as a discontinuity or a tenting of the surrounding tissue.[23,24]

Microcalcifications are better predictors of malignancy if they are fine (eg, < 0.5 mm), linear, branching, clustered, or pleomorphic. In case of clustered microcalcifications, biopsy is positive for malignancy in 13% of cases.[23] Benign microcalcifications are usually larger, coarser, and rounder and have smooth margins; they occur in patients with arteriosclerosis, fibroadenoma, and fat necrosis.

The sensitivity of mammography is approximately 85% and increases with age, whereas the specificity is approximately 90% and is unchanged with age.[4,5] To standardize the reporting of mammography results, BI-RADS categories are used.[7] Mammography is limited by the fact that radiologic resolution is less than optimal in patients with dense breasts.[25] The radiologist's experience is vital in interpreting mammograms correctly.

Further Diagnostic Imaging

Our case highlights some of the problems with mammography. Although an initial mammogram detected an asymmetric soft-tissue density in the left breast and sonography heightened the suspicion, magnification views as well as technetium Tc 99m sestamibi scanning did not find any abnormality in the left breast. Thus, an abnormality seen on a mammogram may not represent breast cancer and may require more intensive and expensive investigations to rule out breast cancer. A false-positive mammogram also causes considerable anxiety in the patient.

To improve the detection of breast cancer, various other modalities are being used as adjuncts when a

mammogram has abnormal or inconclusive results. These modalities include ultrasonography, nuclear scanning, magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning.[25]

Ultrasonography is useful for evaluation of the internal matrix of the circumscribed masses found on mammography or for evaluation of palpable masses obscured by radiographically dense parenchyma on mammography.[25] Ultrasonography is very sensitive in detecting cystic lesions but is not as useful in detecting lesions that are less than 1 cm in diameter.[26] Moreover, Doppler ultrasonography is being used to identify the increased vascularity of malignant tumors, as compared to benign lesions. However it is only an investigational technique and has no role in the clinical management of breast masses at present.[25] In our patient, results of ultrasonography were false-positive; this lack of specificity is a major problem of this technique.

Technetium Tc 99m sestamibi scanning is now being used as an adjunct to mammography in detecting breast cancer. The technetium-sestamibi complex is injected into the arm contralateral to the one in which breast cancer is suspected, and images are taken using different views. The uptake of the radiotracer is then checked; it concentrates 9 times more in cancer cells because of the increased metabolic activity and binds to mitochondrial membrane. This technique is useful in patients in whom mammography is less sensitive because of other factors (eg, dense breasts, prior surgery, radiation, breast implants). The sensitivity of a technetium Tc 99m sestamibi scan is approximately 75% and specificity is 82%. The sensitivity decreases with lesions that are less than 1 cm in diameter.[27] Our case clearly demonstrates the advantages of technetium Tc 99m sestamibi scanning, particularly in patients who have undergone prior breast surgery, as was the case with our patient. Whereas both mammography and sonography had false-positive results for the left breast, they were falsely negative for the cancer in the right breast cancer; only technetium Tc 99m sestamibi scanning detected the tumor in this patient on the right side.

MRI is able to differentiate between cancerous and noncancerous tissue because of differing water content and blood flow and can detect tumors missed by other modalities. MRI also may play an key role in surveillance of patients at high risk for breast cancer (particularly those with mutations of *BRCA1* and *BRCA2*) and those who are difficult to evaluate because of prior breast surgery or implants. The role of MRI is also being evaluated in treatment planning after a breast cancer is diagnosed. Patients with breast cancer may have multifocal lesions that make them unfit candidates for lumpectomy, because of the high incidence of local recurrence in these patients. MRI detection of these lesions can determine whether a patient should have lumpectomy or mastectomy. In addition, because MRI uses radio waves and magnetic fields to diagnose disease, it avoids the damage potentially caused by modalities using radiation (eg, mammography). However, MRI cannot detect calcifications that may be markers for early breast cancer. Another significant disadvantage of MRI is its high cost.[28]

PET scanning is another modality being investigated as a tool for detection of breast cancer. In this technique, fluorodeoxyglucose is injected into a patient, and images are taken approximately 45 minutes later. Because glucose is utilized more by cancerous than by healthy tissue, areas with cancer appear as high-uptake areas. PET scanning may be useful in assessing patients with difficult-to-evaluate breasts (eg, women with dense breasts, previous surgery or radiation, breast implants). Moreover, PET scanning can determine the presence of metastasis even before other modalities do so because it detects biochemical abnormalities that might precede structural changes. Finally, PET scanning might be helpful in determining response to therapy.

However, the role of newer modalities is still being investigated, and mammography remains the primary screening modality for detection of breast cancer. Ultrasonography and MRI avoid radiation and may have a role in screening in the future; technetium Tc 99m sestamibi and PET scanning are not yet mature enough to use as screening tools and may never have such a role.[29]

SUMMARY

Early detection of breast cancer is vital to decrease the mortality and morbidity caused by the disease. Mammography is the best screening modality available currently, although it is, unfortunately, both underused and overrated. Only 40% of high-risk women undergo regular screening mammography, despite the fact that it reduces mortality by 30% in women 50 years and older.[2–4,6] Moreover, despite a high sensitivity and specificity, mammography can miss deadly tumors. Our patient's tumor was missed, even though she had infiltrating ductal carcinoma—the most common type of breast cancer and one that forms detectable microcalcification early. Many of the missed tumors occur in younger women and those with dense breasts, prior surgery, previous radiation, or breast implants. Even if they have normal results on mammography (and despite the increased cost), patients in this group may need to have their screening mammogram complemented by other studies (eg, ultrasonography, MRI,

technetium Tc 99m sestamibi scanning) to improve rates of early detection of breast cancer. In particular, technetium Tc 99m sestamibi scanning is a promising adjunctive modality for early detection of breast cancer in these women.[27] **HP**

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