Detecting Breast Cancer Not Visible by Mammography

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Reports by Ma et al. (1) and Poon et al. (2) published in this issue of the Journal raise important issues concerning the detection of early-stage breast cancer. The study by Ma et al. of false-negative mammograms highlights an important weakness of conventional x-ray mammography, while the study by Poon et al. involving magnetic resonance breast imaging evaluates a technology that (with modification) offers a possible solution to this problem.

Ma et al. reviewed the mammograms of women with palpable breast cancer not visible by mammography and compared them with the mammograms of controls whose cancers were visible by mammography and who were matched for the same year of diagnosis. A third group was involved whose physical examination and mammograms were negative and unchanged for 4 years. The authors' analysis reinforces the well-known fact that normal, radiodense breast tissues may obscure cancers (3). This masking phenomenon is a factor in all x-ray imaging.

Insurance companies have been relatively unsuccessful in winning these cases because no universally acceptable definitions of experimental and nonexperimental exist. Payers, providers, and the courts have been unable to reach a consensus on this crucial point of contention. These terms are, therefore, functionally useless and nothing more than a source of conflict.

The development of useful definitions (i.e., ones that serve the legitimate interests of all parties) will require the active participation of medical experts like those at the NCI. These terms will never attain an independent meaning and legal significance until medical scientists from the NCI appear in court and assume an active role in developing case law. Only then will insurers be able to develop contract language that will confine coverage to patients in NCI-sponsored trials. As it now stands, insurers run the risk of having to cover the patient care costs of insureds who meet the clinical criteria for entry into the trial regardless of where or by whom the treatment is administered. In reality, this is tantamount to an uncontrolled and potentially harmful expansion of insurance coverage to unproven therapies.

Reference

Breast cancer is almost always high in its x-ray attenuation because of its cellularity and the desmoplastic response that often accompanies its growth. Small breast cancers that are surrounded by fat are easily seen because of the contrast between the high x-ray attenuation of the cancer and the relatively low attenuation of the fat. When tissues with similar x-ray attenuation are immediately adjacent to a cancer, the tumor's margins may become obscured and the lesion rendered invisible on the mammogram.

A second reason why breast cancers may be obscured on mammography is that the mammogram is a two-dimensional projection of three-dimensional tissues and the shadows of normal structures superimposed on the silhouette of the cancer can reduce its visibility. Increasing the number of mammographic images made from different projections presents the tissues to the observer from varying vantage points and will increase the detectability of breast cancers (4). Spot compression mammography is used to displace confusing, overlapping structures and also may permit improved visualization of a malignancy. Nevertheless, the radiographically dense breast remains a challenge for mammography, and the sensitivity of the technique is reduced when these normal tissues are present in sufficient quantity.

Since Ma et al. (1) reviewed only women with palpable cancers, the study was, by definition, biased against mammography. This explains why more small cancers were found on clinical examination than on mammography in this selected group of patients. The opposite is true when mammographically detected cancers are included (5) or in a screened population (6). Cancers are difficult to detect by mammography in the radiographically dense breast, but, as the authors' data confirm, many such cancers can still be seen with mammography before they become evident on clinical examination. Even early-stage cancers can be detected in women whose breasts contain high-attenuation tissue. These are usually cancers that reveal their presence by producing calcium deposition. Masses and areas of architectural distortion indicating breast cancer can be seen mammographically, despite dense breast tissue. In our own recent review of women under the age of 50 whose cancers were detected by mammography alone (Massachusetts General Hospital: unpublished data), more than 70% had radiographically dense breast tissue. Nevertheless, we were still able to detect breast cancers at an earlier stage in these women than in those who presented with palpable cancer, and their 5-year survival was significantly better (94%) than when the cancer was palpable (74%).

Ma's data also reinforce the fact that infiltrating lobular carcinoma is difficult to detect by mammography (7). This is likely because this particular cell type often occurs in radiographically dense breast tissue and its presence is masked. By the time significant architectural distortion is present, the tumor is frequently large enough to be palpable.

It is not clear if the authors included lobular carcinoma in situ in their review. This condition should probably be considered separately, since its biologic potential is uncertain and it is always found coincidentally. It is likely, if such cases were included in the "noninfiltrative" category, that they were adjacent to the palpable abnormality and not the actual lesion from which a biopsy specimen was taken. Lobular carcinoma in situ is also found serendipitously by mammography (8) and occurs more commonly in the radiographically dense breast (9). It is usually diagnosed when a biopsy is performed for calcifications seen on the mammogram that prove to be in benign tissue, but adjacent to this the pathologist finds coincident lobular carcinoma in situ.

An important result of this review confirms another well-known phenomenon, namely, the failure of even expert observers to perceive all abnormalities. The radiologists reviewing the mammograms detected abnormalities that were apparently missed at the primary interpretation. One or both of the reviewers suggested a biopsy for 34 (54%) of 63 women whose mammograms were originally read as negative. This figure is inflated, since the reviewers knew they were reviewing selected cases with a much higher than average probability of a breast cancer. Nevertheless, the occasional initial failure to perceive a retrospectively visible abnormality has been shown in other observational specialties, and for other radiologic procedures as well, and is virtually guaranteed regardless of the expertise of the observer. Review of imaging studies by more than one observer is, therefore, always desirable. "Double reading" will reduce false-negative observations, but it only can be done where practical. If not done efficiently, it will increase cost, which will limit the availability of screening for segments of the population.

Radiographically dense or highly attenuating breast tissue cannot be predicted by clinical examination (10,11). Poone et al. (2) have shown in their study that the pattern of breast tissue seen with magnetic resonance imaging (MRI) does correlate directly with that seen with mammography. In other words, many of the signal intensities produced by various tissue elements correlate well with the tissue characteristics revealed by mammography. Unfortunately, this was one of the reasons why MRI without the intravenous infusion of a contrast agent did not, in the early development of the technology, prove successful in detecting and diagnosing early breast cancers. Although the cross-sectional technique reduced the interference of the normal structures, the similarity of benign and malignant tissue signal characteristics reduced the effectiveness of MRI (12). Improvements in technology and the use of contrast enhancement have once again raised the potential of MRI for breast cancer detection (13,14). The increased x-ray attenuation of breast cancer following the intravenous administration of contrast in computed tomography of the breast (15) and digital subtraction angiography (16) suggests that the neovascularity of a cancer increases the tissue concentration of the contrast material above normal tissue concentrations, either through diffusion and the increased concentration of vessels associated with the cancer (17) or through increased leakage or permeability of tumor vessels. This same phenomenon has been seen using magnetic resonance to image the breast with tissue enhancement provided by the intravenous administration of gadolinium diethylenetriamine pentaacetic acid (18). Preliminary data suggest that gadolinium enhancement using MRI can reveal foci of breast cancer not discernible by mammography and can better delineate the extent of a breast cancer. This is particularly true in the radiographically dense breast. If the cost can be reduced and the technology improved to shorten the time required for scanning, MRI may offer an opportunity to improve the detection of early breast cancers in the radiographically dense breast. At the present time, however, although sensitivity in detecting breast cancer using MRI is very high, specificity may be low.
As with x-ray mammography, the trade-off for earlier detection with MRI may be an increase in the number of biopsies with benign results. Nevertheless, detecting breast cancer earlier in the radiographically dense breast is important. Depending on the criteria used, 10%-35% of a population of women will have breast tissues containing a high percentage of attenuating and confusing structures. Mammography and physical examination are currently the only tests with any proven screening effectiveness. The fact that there are a significant number of interval cancers (cancers diagnosed within a year of a negative screen), however, is clear evidence that cancers are present in the breast at a given moment that are neither palpable nor visible by mammography. MRI with contrast enhancement may offer earlier detection.

Considerable debate prevailed in the 1970s concerning the relationship of radiographically dense breast tissue and risk of subsequent breast cancer. Numerous studies suggested increased risk, and equally as many suggested no increased risk. There have been many methodological problems associated with virtually all such studies involved in looking at this relationship. Since no investigation has suggested that these women are at diminished risk and the possibility remains that they may be at some increased risk, it is reasonable to continue to investigate the question. Even if women with radiographically dense breasts are at some increased risk, the fact remains that a greater number of cancers occur in women whose breasts contain large percentages of fat. This is simply because, at least among women who undergo mammography, there are many more in the latter group than in the former (19). Deciding screening policy on the basis of density of breast patterns is, therefore, not reasonable.

Other technologies are being explored for the detection of cancers in breast tissue that is difficult to assess mammographically. Positron emission tomography has demonstrated early success (20). This technology is likely to be most helpful for staging or as a technique to determine the presence of residual or recurrent breast cancer. Positron emission tomography scanning requires administration of radioactive material, however, and this will preclude its general application in screening. Unfortunately, most potentially useful evolving technologies require the intravenous administration of an agent to enhance tissue differentiation. This requirement will likely limit their application as well.

Women and physicians alike must understand that, although mammography is the single best method of detecting early-stage breast cancer and thus reducing mortality, it is far from perfect. It should be considered primarily as a screening technique. Although the term “diagnostic” mammography is frequently used, mammography is only occasionally diagnostic. Intervention (obtaining cells or tissue) is required to diagnose a clinically evident abnormality. Mammography has some value in such a situation, but its primary role should be to screen the remainder of the ipsilateral breast and the contralateral breast for clinically occult malignancy (21).

The patient who has had a negative screening mammogram and her physician should remain vigilant between screenings. Should a woman’s self-examination reveal a change, she should bring it immediately to her doctor’s attention, and appropriate action should be taken. Unwarranted trust in a negative mammogram can lead to unreasonable delay in diagnosis.

As yet, no test or group of tests can guarantee that a woman does not have breast cancer. Until preventative measures can be devised or curative treatment discovered, periodic screening with mammography and clinical examination augmented by breast self-examination between screenings remains the best approach to reducing the mortality from breast cancer.

References