

The "Coming of Age" of Nonmammographic Screening for Breast Cancer

Christiane K. Kuhl, MD

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The study by Berg and colleagues¹ published in this issue of JAMA addresses important clinical questions: What is the additional cancer diagnosis yield of screening ultrasound in women at increased risk of breast cancer, and what are the "costs" of such strategies in terms of false-positive diagnoses. The design of this American College of Radiology Imaging Network (ACRIN) trial, from the multi-institutional setting to source documentation and independent data analysis, is excellent from every aspect. This study and several other previously published trials²⁻⁴ demonstrate how important it is to have institutions like ACRIN sponsor and help organize prospective clinical trials that follow good clinical practice in the world of diagnostic imaging, which, unlike clinical research in the therapeutic sector, has to proceed without the financial support and scientific infrastructure usually provided by the pharmaceutical and medical device industries.

The results of this study are impressive. Ultrasound was associated with a 55% increase in diagnosing breast cancer compared with mammography alone: a 7.6 per 1000 to 11.8 per 1000. The sensitivity with which breast cancer was detected was 77.5% (32 of 41) for the combined use of ultrasound and mammography vs 49% (20 of 41) for mammography alone.

Given that mammography is the standard of care, one could argue that a main finding of this study is the apparently limited sensitivity of screening mammography. However, this finding is in keeping with recent results of several mammographic screening studies. Depending on the composition of the screening cohort, the sensitivity can be as low as 25% for *BRCA1* mutation carriers,⁵⁻¹⁰ but even in women at average risk, for instance in almost 50 000 women who participated in the Digital Mammographic Imaging Screening trial,² the overall sensitivity of screening mammography was only 55%.

It is well established that mammography and ultrasound are complementary for diagnosing breast cancer. Ultrasound performs best in cases for which mammography performs weakest, ie, in breast areas with of dense fibroglandular tissue.¹¹⁻¹⁵ Yet, breast ultrasound is seldom used for screening in the United States, and to date, none of the worldwide screening programs offers ultrasound. Reservations against the use of ultrasound include costs, frequency of false-positive findings, and lack of evidence from randomized trials on mortality end points.

The results from this study by Berg and colleagues confirm that the positive predictive value of screening ultrasound is indeed low. Of 233 women for whom biopsy was recommended based on a suspicious ultrasound finding, only 20 (8.6%) were diagnosed with breast cancer. Stated otherwise, 91.4% of all suspicious ultrasound findings identified by expert breast radiologists were due to benign changes. Although this seems to be a key argument against the use of breast ultrasound, one should consider that mammography, the accepted standard of care

for screening, had a positive predictive value of 14.7% (20 of 136) in the same cohort.

In the cohort of 2712 women, the number of false-positive diagnoses increased from 116 (for mammography alone) to 275 (for the combined use of mammography and ultrasound). This might be considered far too many. But this has to be weighted against the benefit of the additional cancer diagnosis yield of ultrasound. Twelve cancers, ie, 29% of the total 41 cancers, were only detected by ultrasound. Whether this is sufficient to justify the many false-positive ultrasound diagnoses is something every individual woman may have to decide for herself.

Of note, comparing only numbers of false-positive diagnoses may not be fair because a suspicious finding made by mammography usually requires stereotactic, mostly vacuum-assisted biopsy, an expensive and time-consuming procedure. In comparison, a positive ultrasound finding can be investigated by ultrasound-guided core biopsy (or even fine-needle aspiration), a simple, fast, and inexpensive procedure that often may be performed immediately. Accordingly, the average false-positive ultrasound may not have the same implications as the average false-positive mammographic diagnosis.

This statement should not downplay the problem. False-positive diagnoses should be avoided not only because they add to the overall costs of a screening program but also because they may stimulate unnecessary anxieties. However, a recent study on the psychological impact of false-positive screening diagnoses¹⁶ concluded that "women who are recalled for additional tests do not appear to be harmed by screening: these women's positive views about mammography suggest that they view any distress caused by recall as an acceptable part of screening." In the study by Berg et al,¹ half of the study population were women who had been treated for breast cancer; the other half consisted mainly of women who had more than 1 family member diagnosed with breast cancer. What these women probably fear most is a late diagnosis of breast cancer. If these women were told that screening mammography detects only half of the cancers, they may perceive that fact as the real threat they want to be protected against, not false-positive diagnoses.

Women have trusted in mammography for many years; they have learned to believe that mammographic screening is the key to an early diagnosis of breast cancer. Radiologists are reluctant to educate women on the actual diagnostic performance of screening mammography for fear of reduced participation rates in mammographic screening and because of a perceived lack of alternatives. Yet once women understand that possibly only 1 in 2 breast cancers will be diagnosed by regular screening, they will likely request an approach that helps cover the limitations of mammography. Candidate technologies are ultrasound and magnetic resonance imaging (MRI).

The study by Berg et al¹ shows that despite the combined use of ultrasound and mammography, almost a quarter of breast cancers were not diagnosed by screening. It is well established that MRI is superior to both, mammography and ultrasound.³⁻^{10,17-19} Based on a recent MRI-screening study,³ MRI has a negative predictive value of close to 100%, and a positive predictive value that is much higher than that obtained with ultrasound. In addition, and unlike screening ultrasound, MRI allows the detection of biologically aggressive (high grade) ductal carcinoma in situ with an even higher sensitivity than mammography.¹⁷ So why not use MRI for screening? Berg et

al argue that "Ultrasound may be more appropriate than MRI for screening women of intermediate risk due to its reduced cost relative to MRI." However, this is debatable.

Ultrasound may be about as expensive as MRI because with modern high-frequency ultrasound probes, screening both entire breasts is a time-consuming endeavor. As Berg et al point out, a breast screening ultrasound takes an average of 19 minutes of physician time. The actual costs of screening ultrasound will therefore be substantially higher than what is reflected by the respective billing codes. Due to the amount of physician time screening ultrasound requires, it may be the most expensive of all breast imaging modalities. A breast radiologist will complete less than 3 screening ultrasound studies per hour by comparison. However a breast radiologist, if involved in batch reading of screening mammograms, will read about 50 studies per hour. Similar numbers are conceivable for reading screening MRI studies. Although diagnostic MRI may be time consuming to interpret, a negative MRI requires only a rapid reading, and in a screening setting, the vast majority of studies will be negative. In addition, a negative MRI yields more definite answers than a negative ultrasound.

Because screening ultrasound is so time consuming, offering it to all eligible women is probably impractical and would require a much larger number of breast radiologists than currently available. Sonographers may reduce the demand for radiologists, but it is questionable whether the diagnostic accuracy achieved in the study by Berg and colleagues would have been the same if nonradiologists had performed screening ultrasound. Because ultrasound is not available population-wide, it would be desirable to identify subgroups of women who benefit most from an additional ultrasound. The authors had already made such a selection by including women with some elevated risk and with at least "heterogeneously dense tissue in at least one quadrant." This latter definition was relatively loose.

As a result, the authors included women with a broad range of breast densities. However, the additional cancer diagnosis yield achieved with ultrasound proved to be independent of the mammographic breast density; it was fairly stable across all breast density categories (as long as no complete involution had occurred). This finding is congruent with other recent results obtained for MRI screening^{3-4,17, 19} and provides more evidence that breast density is not the only factor that determines the likelihood with which the mammographic diagnosis of breast cancer fails. Accordingly, mammographic breast density may not be a suitable criterion to stratify women for additional (nonmammographic) screening tests. Individual lifetime risk may be more appropriate, but this leads to the question of where to draw the line. Which risk level would justify additional screening tests? With an average lifetime risk as high as 12% to 14% for women, one could argue that "female sex" is already sufficient to call for screening methods that help compensate the limitations of mammography.

Cost-effectiveness was not addressed in the study by Berg and associates. Limited resources mandate a diligent investment of private and public money for health care. However, irrespective of cost-effectiveness for a society, a screening test can still be medically effective or even life saving for an individual. With the ever-increasing pace with which progress is made in contemporary clinical medicine, it will be less likely that any society will be able to afford the best possible care for every medical condition population-wide. Individuals, however, may choose to prioritize their personal health care. This should not be discouraged as long as the society is given accurate information on the possible advantages—and disadvantages—of screening.

Mammography will probably remain the basis for breast cancer screening for the foreseeable future. However, increasing evidence suggests that for many women (indeed, for the majority of women, ie, those with noninvoluted breasts), mammography does not provide the best possible accuracy. Early diagnosis is important and has been the single major reason for improved breast cancer survival rates. Notwithstanding this success, a success mainly credited to mammographic screening, there is good reason to move on. As long as breast cancer remains the most common cause of cancer death in women, the search for techniques that can help cover the limitations of screening mammography must continue.

Nonmammographic screening techniques have been discredited for the alleged lack of evidence from randomized clinical trials. Berg and colleagues elegantly note:

Such trials are costly, require extensive infrastructure and resources, and are not practical under all contexts. Surrogate aims and end points . . . have been correlated with mortality outcomes and can be used to project the mortality reduction if the screening modality were implemented.

The concept of mammographic screening has been in use for more than 40 years. It may now be time to carefully reconsider. Individualized screening schemes tailored to the individual risk and to the personal preferences of a woman may be the way to consider how to screen for breast cancer. Whether in the long run, ultrasound or breast MRI will be more appropriate for this purpose remains to be seen.

AUTHOR INFORMATION

Corresponding Author: Christiane K. Kuhl, MD, Department of Radiology, University of Bonn, Sigmund-Freud Strasse 25, Bonn, D-53105 Germany (kuhl@uni-bonn.de ).

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Author Affiliation: Department of Radiology, University of Bonn, Bonn, Germany.

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