

Ultrasound Combined with Mammography for Breast Cancer Screening: Results of a Single Annual Screening Exam

Key Points

- Adding a single screening ultrasound to mammography revealed 28% more cancers that mammography alone. (Question 7)
- Neither screening modality is perfect as some participants' cancers were not discovered. In this study, 20 percent of participants' cancers were not seen with either mammography or ultrasound at the time of the initial screen, but were discovered later during the twelve month period. (Question 11)
- The combined screening strategy results in nearly four times as many false positives as mammography alone. (Question 9)
- Researchers are currently evaluating the benefits of repeat annual US screening and screening with magnetic resonance imaging (MRI). Results of these investigations will be reported in the future. (Question 20)

1. What was the purpose of this study?

This study was designed to compare the combination of mammography and physician-performed screening breast ultrasound to mammography alone for the detection of breast cancer in women with dense breasts and at increased risk for breast cancer. Eligible participants were 25 years of age or older with at least heterogeneously dense breasts, meaning 51 percent or more of the breast tissue is dense. In addition, factors that determined if participants were at increased risk for breast cancer included:

- Personal and/or moderate family history of breast cancer
- Prior abnormal (atypical) breast biopsy
- Having inherited alterations, or changes, in the genes called BRCA1 and BRCA2 (short for breast cancer 1 and breast cancer 2)
- Women who have had previous chest radiation to treat lymphoma between ages 10 and 30.

2. *Who organized this study?*

This study was conducted by the American College of Radiology Imaging Network (ACRIN) and funded by the Avon Foundation and the National Cancer Institute (NCI).

The principal investigator is Wendie A. Berg, MD, PhD, American Radiology Services, Johns Hopkins, Green Spring, Lutherville, Md. Statistical and study methods were overseen by Jeffrey D. Blume, PhD, associate professor and deputy director of the ACRIN Biostatistics and Data Management Center at Brown University in Providence, RI.

3. *How was the study conducted?*

Eligible women underwent mammography and physician-performed screening ultrasound. The order in which they had the exams was randomized, and separate radiologists interpreted each exam without knowledge of the results of the other exam. Participants continued to have annual screening with both mammography and US for two more years. We are currently reporting only the results of participant's first screening exams and 12-month breast health follow up. All three years of screening exams were recently completed, and the overall results are expected to be available in late 2009.

4. *Who enrolled in this study?*

The study enrolled 2,809 women from 21 sites (in the United States, Canada, and Argentina) between April 2004 and February 2006. (See the eligibility criteria in question 1.)

The average age of participants at enrollment was 55 years. Of the 2,637 eligible participants for whom the investigators have been able to compile a complete set of data, 1,400 (53 %) had a personal history of breast cancer and 1,812 (69 %) had a family history of breast cancer. Thirty-five percent of participants had digital mammograms and the rest had standard film-screen mammograms performed.

5. *How were the ultrasound technique and interpretation standardized?*

All investigators were required to have performed and interpreted at least 500 breast ultrasound examinations per year for at least two years prior to the study. Investigators also were required to demonstrate their ability to accurately identify, measure, and characterize breast abnormalities on ultrasound and characterize mammographic abnormalities.

6. *How many participants were diagnosed with cancer?*

Cancer was diagnosed in 1.5 % of eligible study participants (40 women) with complete data.

7. *Did the combination of mammography and ultrasound discover more cancers than mammography alone?*

Mammography alone showed 20 cancers (50 percent of all cancers detected) for a cancer detection rate of 7.6 per 1,000 women screened.

The combination of both exams revealed 31 cancers (78 percent of all cancers detected) for a cancer detection rate of 11.8 cancers per 1,000 women screened.

8. *Is the combination of mammography and ultrasound more accurate in detecting cancer than mammography alone?*

Yes. The diagnostic accuracy of the combination was 91%, compared to 78% for mammography alone.

9. *Did the combination of mammography and ultrasound increase the false positive rate over mammography alone?*

Yes. A false positive result means that something of concern was seen on the test even though no cancer was present. Mammography alone resulted in an unnecessary biopsy for 1 in every 40 women in this study. In contrast, the combination of mammography and ultrasound screening resulted in 1 in 10 women having an unnecessary biopsy.

The investigators are assessing the degree of anxiety and discomfort experienced by participants undergoing unnecessary biopsy and short-term follow-up. The risk of false-positive results associated with screening ultrasound remains a barrier to its increased use, however, the researchers are exploring whether this risk will decrease with repeat screening.

10. *Did any subset of participants based on factors such age, breast density, or mammogram type appear to benefit more or less from ultrasound screening than the entire group overall?*

No.

11. *Did ultrasound and mammography, either alone or in combination, identify all participants' cancers?*

No. Neither screening modality is perfect, and even in combination some cancers were not identified at screening. In this study, eight of the 40 cancers were not seen on either the initial mammography or ultrasound screening, but were discovered later during the twelve month period for a rate of 3 cancers missed per 1,000 women screened.

12. As a result of this study, should women be recommended to have a screening ultrasound? If so, in what group(s) of women?

If a woman has dense breasts, she should talk with her doctor about other breast cancer risk factors and about the benefits and risks associated with a screening ultrasound. A woman's doctor should be able to inform her, based on previous mammograms, if her breasts are dense.

13. Should a woman have only a screening ultrasound and not mammography if her tissue is dense?

No. Ultrasound is a supplement to mammography and does not replace it, as many cancers are seen only on mammography. A woman should also continue to have regular clinical breast examinations by her physician in addition to mammography.

14. What should a woman do to obtain a screening ultrasound?

Women should talk with their doctors about their breast cancer risk profile and whether a screening ultrasound exam supplemental to mammography might be beneficial, keeping in mind the potential for a false positive result and an unnecessary biopsy. At present, there is a limited supply of trained personnel and facilities who offer screening ultrasound. Women also should consult their health insurance policy regarding the coverage for breast cancer screening options.

15. How widely available is screening ultrasound? Does insurance pay for the exam?

The availability and insurance coverage for a screening ultrasound varies throughout the country. An ultrasound is referred to as *screening* when its purpose is to learn if a breast thought to be healthy has any signs of cancer. A few centers will allow a woman to pay directly for the exam, but this is not the usual practice at this time.

An ultrasound exam ordered by a physician to evaluate a specific symptom of concern or mammographic abnormality is referred to as a *diagnostic* ultrasound and is nearly always covered by insurance.

16. Is MRI recommended instead of, or in addition to, screening ultrasound?

The American Cancer Society recently recommended women at very high risk for breast cancer be screened with magnetic resonance imaging (MRI) in addition to mammography, and these results do not change that recommendation. Women who are at increased risk, who are currently undergoing mammographic screening and are not recommended for MRI, or for whom it is not available or not tolerated, may wish to consider adding screening ultrasound.

If a woman undergoes screening breast MRI, then screening ultrasound is not recommended. However, a diagnostic ultrasound is often needed after MRI to help further evaluate

abnormalities on MRI and ultrasound can often help guide a needle biopsy of suspicious areas seen on MRI.

17. When was ultrasound first used?

Ultrasound has been around a long time, having been first introduced to the medical world in the 1960s via Japan. The technology has become the second most widely used diagnostic imaging modality today. Throughout the world, breast ultrasound is being used to help make decisions on whether a mammographic finding (often referred to as a lesion or mass) or lump or other area of concern requires biopsy or follow-up.

18. What is the waiting time for results from a breast ultrasound examination?

The results from any type of breast imaging screening are usually available within a few days to a few weeks. Breast ultrasound can help shorten the overall decision-making process in breast imaging. Instead of waiting six months to see on a mammogram if a lesion grew, an US provides additional information right away because the lesion is evaluated from a completely different perspective. If there are findings on an ultrasound that are suspicious for cancer, the recommendation would likely be to go ahead with a biopsy. US also provides an efficient means to guide biopsy of suspicious areas.

19. Why are these results from the first year being reported now if the trial isn't complete?

Because there is a potential benefit from early detection of small, node-negative breast cancers seen only on ultrasound, we are announcing these results at this time so that women can consider these results when deciding whether or not to have ultrasound screening in addition to mammography.

20. When will the remaining screening rounds in the trial be completed?

Participants have completed their third annual screening ultrasound in March 2008. Some women have elected to join an additional MRI component of the study to see how well MRI discovers breast cancers above and beyond combined US and mammography. We expect to have follow-up and analysis of this further research completed by late 2009.