Breast density and optimal screening for breast cancer

An expert with a personal story outlines the best imaging options for detecting cancer in dense breasts

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MY STORY  Prologue
My aunt received a breast cancer diagnosis at age 40, and she died at age 60, in 1970. Then, in 1975, my mother’s breast cancer was found at age 55, but only after she was examined for nipple retraction; on mammography, the cancer had been obscured by dense breast tissue. Mom had 2 metastatic nodes but participated in the earliest clinical trials of chemotherapy and lived free of breast cancer for another 41 years. Naturally I thought that, were I to develop this disease, I would want it found earlier. Ironically, it was, but only because I had spent my career trying to understand the optimal screening approaches for women with dense breasts—women like me.

Breast density is determined on mammography and is categorized as fatty, scattered fibroglandular, heterogeneously dense, or extremely dense. More than half of women in their 40s have dense breasts; with some fatty involution occurring around menopause, the proportion drops to 25% for women in their 60s. About half of breast cancers have calcifications, which on mammography are usually easily visible even in dense breasts. The problem is with noncalcified invasive cancers that can be hidden by dense tissue.

3D mammography improves cancer detection but is of minimal benefit in extremely dense breasts
Although 3D mammography improves cancer detection in most women, any benefit is minimal in women with extremely dense breasts, as there is no inherent soft-tissue contrast. Masked cancers are often only discovered because of a lump after a normal screening mammogram, as so-called...
“interval cancers.” Compared with screen-detected cancers, interval cancers tend to be more biologically aggressive, to have spread to lymph nodes, and to have worse prognoses. However, even some small screen-detected cancers are biologically aggressive and can spread to lymph nodes quickly, and no screening test or combination of screening tests can prevent this occurrence completely, regardless of breast density.

**MRI provides early detection across all breast densities**

In all tissue densities, contrast-enhanced magnetic resonance imaging (MRI) is far better than mammography in detecting breast cancer. Women at high risk for breast cancer caused by mutations in *BRCA1*, *BRCA2*, *p53*, and other genes have poor outcomes with screening mammography alone—up to 50% of cancers are interval cancers. Annual screening MRI reduces this percentage significantly, to 11% in women with pathogenic *BRCA1* mutations and to 4% in women with *BRCA2* mutations. Warner and colleagues found a decrease in late-stage cancers in high-risk women who underwent annual MRI screenings compared to high-risk women unable to have MRI.

The use of MRI for screening is limited by availability, patient tolerance, and high cost. Research is being conducted to further validate approaches using shortened screening MRI times (so-called “abbreviated” or “fast” MRI) and, thereby, improve access, tolerance, and reduce associated costs; several investigators already have reported promising results, and a few centers offer this modality directly to patients willing to pay $300 to $350 out of pocket. Even in normal-risk women, MRI significantly increases detection of early breast cancer after a normal mammogram and ultrasound, and the cancer detection benefit of MRI is seen across all breast densities.

Most health insurance plans cover screening MRI only for women who meet defined risk criteria, including women who have a known disease-causing mutation—or are suspected of having one, given a family history of breast cancer with higher than 20% to 25% lifetime risk by a model that predicts mutation carrier status—as well as women who had chest radiation therapy before age 30, typically for Hodgkin lymphoma, and at least 8 years earlier. In addition, MRI can be considered in women with atypical breast biopsy results or a personal history of lobular carcinoma in situ (LCIS).

Screening MRI should start by age 25 in
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women with disease-causing mutations, or at the time of atypical or LCIS biopsy results, and should be performed annually unless the woman is pregnant or has a metallic implant, renal insufficiency, or another contraindication to MRI. MRI can be beneficial in women with a personal history of cancer, although annual mammography remains the standard of care.\textsuperscript{17–19}

MRI and mammography can be performed at the same time or on an alternating 6-month basis, with mammography usually starting only after age 30 because of the small risk that radiation poses for younger women. There are a few other impediments to having breast MRI: The woman must lie on her stomach within a confined space (tunnel), the contrast that is injected may not be well tolerated, and insurance does not cover the test for women who do not meet the defined risk criteria.\textsuperscript{11}

Ultrasonography supplements mammography

Mammography supplemented with ultrasonography (US) has been studied as a “Goldilocks” or best-fit solution for the screening of women with dense breasts, as detection of invasive cancers is improved with the 2 modalities over mammography alone, and US is less invasive, better tolerated, and lower in cost than the more sensitive MRI.\textsuperscript{20} Adding US reduces the interval cancer rate in women with dense breasts to less than 10% of all cancers found—similar to results for women with fatty breasts.\textsuperscript{17,21,22}

US can be performed by a trained technologist or a physician using a small transducer, which usually provides diagnostic images (so that most callbacks would be for a true finding), or a larger transducer and an automated system can be used to create more than a thousand images for radiologist review.\textsuperscript{23,24} Use of a hybrid system, a small transducer with an automated arm, has been validated as well.\textsuperscript{25} Screening US is not available universally, and with all these approaches optimal performance requires trained personnel. Supplemental screening US usually is covered by insurance but is nearly always subject to a deductible/copay.
Reducing false-positives, callbacks, and additional testing

Mammography carries a risk of false-positives. On average, 11% to 12% of women are called back for additional testing after a screening mammogram, and in more than 95% of women brought back for extra testing, no cancer is found. Women with dense breasts are more likely than those with less dense breasts to be called back. US and MRI improve cancer detection and therefore yield additional positive, but also false-positive, findings. Notably, callbacks decrease after the first round of screening with any modality or combination of tests, as long as prior examinations are available for comparison.

One advantage of 3D over 2D mammography is a decrease in extra testing for areas of asymmetry, which are often recognizable on 3D mammography as representing normal superimposed tissue. Architectural distortion, which is better seen on 3D mammography and usually represents either cancer or a benign radial scar, can lead to false-positive biopsies, although the average biopsy rate is no higher for 3D than for 2D alone. Typically, the 3D and 2D examinations are performed together (slightly more than doubling the radiation dose), or synthetic 2D images

![Figure 2: Four-category visual description of breast density](image)

According to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS), mammography reports categorize breast density on the basis of appearance: (A) almost entirely fatty; (B) scattered areas of fibroglandular density; (C) heterogeneously dense, which could obscure detection of small masses; and (D) extremely dense, which lowers the sensitivity of mammography. Breasts in category C or D are considered dense; about half of cancers in such breasts may go undetected on mammography. Thirty states require that the mammography results given to patients include some information about breast density (legislation and regulations: http://densebreast-info.org/legislation.aspx).

![Figure 3: Cancer detection in fatty vs dense breasts](image)

In fatty breasts (A), small cancers (yellow arrow) are usually easily seen on mammography. In dense breasts (B), cancers (red circle) are often hidden by dense tissue, are often larger on detection, and are more likely to require more extensive treatment.

Figure courtesy of www.DenseBreast-info.org and Wendie A. Berg, MD, PhD.
Some aggressive high-grade breast cancers go undetected even when mammography is supplemented with US. MRI is particularly effective in depicting high-grade cancers, even small ones.

Fast Track

The table summarizes the relative rates of cancer detection and additional testing by various breast screening tests or combinations of tests. Neither clinical breast examination by a physician or other health care professional nor routine breast self-examination reduces the number of deaths caused by breast cancer. Nevertheless, women should monitor any changes in their breasts and report these changes to their clinician. A new lump, skin or nipple retraction, or a spontaneous clear or bloody nipple discharge merits diagnostic breast imaging even if a recent screening mammogram was normal.

Figure 4 is an updated decision support tool that suggests strategies for optimizing cancer detection with widely available screening methods.

My Story Epilogue

My annual 3D mammograms were normal, even the year my cancer was present. In 2014, I entered my family history into the IBIS Breast Cancer Risk Evaluation Tool (Tyrer-Cuzick model of breast cancer risk) (http://www.ems-trials.org/riskevaluator/) and calculated my lifetime risk at 19.7%. That is when I decided to have a screening MRI. My invasive breast cancer was easily seen on MRI and then on US. The cancer was node-negative, easily confirmed with needle biopsy, and treated with lumpectomy and radiation. There was no need for chemotherapy.

My personal experience prompted me to join JoAnn Pushkin and Cindy Henke-Sarmento, RT(R)(M), BA, in developing a website, www.DenseBreast-info.org, to give women and their physicians easy access to information on making decisions about screening in dense breasts.

My colleagues and I are often asked what is the best way to order supplemental imaging for a patient who may have dense breasts. Even in cases in which a mammogram does not exist or is unavailable, the following prescription can be implemented easily at centers that offer US: “2D plus 3D mammogram if available; if dense, perform ultrasound as needed.”
FIGURE 4 Breast cancer screening strategy flowchart

Developed by members of the medical advisory board of DenseBreast-info, this flowchart depicts a breast cancer screening strategy that optimizes detection by supplementing mammography with either annual magnetic resonance imaging (MRI), in women at high risk starting at age 25, or annual ultrasonography, in women age 40 or older with dense breasts or high-risk women unable to have MRI.

Figure courtesy of www.DenseBreast-info.org.

*While breast self examination and clinical breast examination have not been proven to reduce deaths from breast cancer, women should be familiar with their breasts and promptly report changes to their health provider. For information about cancer detection by modality, see DenseBreast-info.org (Technology tab Table: Summary of Cancer Detection Rates for Commonly Available Breast Screening Tests).

**See DenseBreast-info.org (Health Professional tab/Risk Models).

***Contrast-enhanced MRI is not recommended in women who are pregnant, have a pacemaker, have a non-MRI compatible metallic implant near vital structures, or who have decreased renal function. If you have a screening MRI, there is no added benefit from screening ultrasound.

**In women with dense breasts, several studies have shown that ultrasound significantly improved cancer detection even after 2D and 3D (tomonithesis) mammography, though further research is ongoing.

Note: This flow chart was developed as an educational tool and reflects the consensus opinion of our medical reviewers based on the best available scientific evidence. The proposed strategy is relatively aggressive, designed to optimize cancer detection. Every technology may not be available at every site. Other guidelines may recommend a later start or different screening frequency. This is not intended to be a substitute for medical advice from a physician or to create a standard of care for health care providers.

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Breast density screening: Take advantage of today’s technology

Breast screening and diagnostic imaging have improved significantly since the 1970s, when many of the randomized trials of mammography were conducted. Breast density is one of the most common and important risk factors for development of breast cancer and is now incorporated into the Breast Cancer Surveillance Consortium model (https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm) and the Tyrer-Cuzick model (see also http://densebreast-info.org/explanation-of-dense-breast-risk-models.aspx). Although we continue to validate newer approaches, women should take advantage of the improved methods of early cancer detection, particularly if they have dense breasts or are at high risk for breast cancer.

References


