Published in final edited form as:

Ann Intern Med. 2016 February 16; 164(4): 299–300. doi:10.7326/M15-2977.

Supplemental Breast Cancer Screening in Women with Dense Breasts Should be Offered with Simultaneous Collection of Outcomes Data

Wendie A. Berg, MD, PhD, FACR

Department of Radiology, Magee-Womens Hospital of UPMC, 300 Halket St., Pittsburgh, PA 15044, wendieberg@gmail.com

While mammographic screening reduces deaths from breast cancer, all women do not share this benefit equally. Much as inadequate patient preparation for colonoscopy can hide colon cancer, dense breast tissue on mammography can hide breast cancer, especially if the cancer lacks calcifications. Women with heterogeneously or extremely dense breasts who have cancer detected soon after a normal mammogram because of clinical symptoms are said to have “interval cancers.” Interval cancers tend to be more aggressive and larger, and have worse prognosis than screen-detected cancers. Because a “negative” screening mammography result does not reliably rule out cancer in women with dense breasts, experts and advocates have promoted breast density notification laws in hopes that knowledge of having dense breasts will empower an individual woman to push for adequate screening to include supplemental tests.

Breast density, variability in breast density within a given breast, and body mass index influence breast cancer risk. In a “dose-dependent” fashion, the denser the breast tissue, the higher the risk of developing cancer (1). At the extremes of breast density, women with extremely dense breasts are at four-fold increased risk for breast cancer compared to women with fatty breasts (1). The risk of cancer presenting clinically in the interval between screens is up to 18-fold higher comparing women at density extremes (1). In the only series with sufficiently long-term follow-up to address mortality from breast cancer, Chiu et al. (2) observed a 1.9-fold risk of breast cancer death (95%CI 1.26–2.91) among women with dense breasts after adjusting for other factors. Heterogeneity of tissue density both increases risk and complicates mammographic interpretation. High body mass index after menopause increases risk of breast cancer, as does low body mass index before menopause.

Determination of which of four qualitative density categories a given patient has largely falls to the judgment of the radiologist. Computer software that provides a highly reproducible average quantitative density is not yet in widespread use and there remains need for judgment in a given patient as even small amounts of dense tissue can mask breast cancer.

In this issue of the journal, Melnikow and colleagues (3) summarize evidence about the benefits and harms of supplemental screening with ultrasound, MRI, or digital breast tomosynthesis in women with dense breasts and negative mammography. They found a few good-quality studies that showed supplemental screening finds additional breast cancers, most of which are invasive; ultrasound and MRI also increase false positives. They found no good-quality studies that reported mortality outcomes.

Supplemental screening beyond mammography is only warranted in women with dense breasts if it will improve outcomes, and important evidence indicates that it does. Across randomized trials of mammography, screening was only effective in reducing breast cancer deaths when it reduced the rate of advanced cancers (defined as stage II or higher) and increased detection of small node-negative invasive cancers (4). An excess of stage II and III disease has been observed among dense-breasted women undergoing mammographic screening in the Breast Cancer Surveillance Consortium, mostly because these cancers go undetected until they are larger.

Recently announced results from the multicenter Japan Strategic Anti-cancer Randomized Trial (J-START), too recent to be included by Melnikow, showed a reduction in interval cancers (0.05% vs. 0.10%, $p=0.034$) among 32,105 women receiving supplemental ultrasound compared to 32,812 women in the control group receiving only mammography (5). Among 202 cancers detected in the intervention group, 144 (71.3%) were stage 0 or I compared to only 79/152 (52.0%) in the control group ($p=0.019$). In the ACRIN 6666 trial, supplemental ultrasound improved detection of mostly node-negative invasive breast cancers (25/32 [78%], of women diagnosed with breast cancer seen only on ultrasound had stage I disease); detection benefits of ultrasound occurred in women whose breast density was visually estimated at only 25–40% though there was a trend for greater increase in cancer detection with increasing breast density (6).

Schrading et al (7) showed that MRI every one-to-three years had initial cancer detection rate of 22.6/1000 average-risk women after normal mammography and ultrasound, with similar yield across all breast densities. In that study, incidence cancer detection rate was 7.5/1000 and 93% of cancers identified on MRI were node negative, with mean size of 0.8 cm and no interval cancers. For tomosynthesis, increased cancer detection has been shown across all breast densities in the Oslo trial (8), though follow-up is incomplete at this time. Based on early results from the ASTOUND trial (in press), screening ultrasound has a similar supplemental cancer yield after tomosynthesis as for standard digital mammography.

The advantages of supplemental screening are proven in women with genetic risk factors for breast cancer. In women with a *BRCA1* or *BRCA2* mutation, surveillance MRI reduced late stage disease (9). In women with a *BRCA1* mutation or familial risk, having an annual MRI compared to matched controls produced greater metastasis-free survival (10).

In summary, while only mammography has been evaluated in studies that examined breast cancer mortality, what we know about the natural history of breast cancer suggests that supplemental screening is of benefit. The majority of cancers found with ultrasound are node-negative invasive cancers; MRI also detects some ductal carcinoma in situ. Both ultrasound and MRI have been shown to reduce interval cancers in women with dense breasts; this is a proposed endpoint in the planned TMIST trial of tomosynthesis. MRI reduces late stage disease and rates of metastatic disease. I believe that supplemental screening should be available to interested women with dense breasts, but guidance to help inform these decisions is sorely needed. Ideally, supplemental imaging should be performed clinically in settings that simultaneously collect data on molecular phenotypes, stage of detected cancers, other breast cancer risk factors, and ultimate outcomes of women who

pursue such supplemental screening. This would allow careful observational analyses comparing their outcomes to those of women with dense breasts who choose not to undergo supplemental tests.

Acknowledgments

Disclosures: In the past 12 months, I have performed data analysis and manuscript preparation for SuperSonic Imagine, Inc. My Department receives equipment and research support from Hologic, Inc. and General Electric Healthcare but I do not personally receive any compensation. I am voluntary Chief Scientific Advisor to DenseBreast-info.org which receives unrestricted educational support from General Electric Healthcare and Volpara, Inc.

References

1. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. *Breast Cancer Res.* 2011; 13(6):223. [PubMed: 22114898]
2. Chiu SY, Duffy S, Yen AM, Tabar L, Smith RA, Chen HH. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. *Cancer Epidemiol Biomarkers Prev.* 2010; 19(5):1219–1228. [PubMed: 20406961]
3. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: A systematic review for the U.S. Preventive Services Task Force. *Annals Int Med.* 2016 in press.
4. Tabar L, Yen AM, Wu WY, Chen SL, Chiu SY, Fann JC, et al. Insights from the breast cancer screening trials: how screening affects the natural history of breast cancer and implications for evaluating service screening programs. *Breast J.* 2015; 21(1):13–20. [PubMed: 25413699]
5. Ohuchi N, Suzuki A, Sobue T, Kawai M, Yamamoto S, Zheng YF, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. *Lancet.* 2015
6. Berg WA, Bandos AI, Mendelson EB, Lehrer D, Jong RA, Pisano ED. Ultrasound as the primary screening test for breast cancer: Analysis from ACRIN 6666. *J Natl Cancer Inst.* 2016; 108 (in press).
7. Schrading, S.; Strobel, K.; Kuhl, CK. MRI screening of women at average risk of breast cancer. San Antonio Breast Cancer Symposium; December 11, 2013; San Antonio, TX. 2013.
8. Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, et al. Comparison of Digital Mammography Alone and Digital Mammography Plus Tomosynthesis in a Population-based Screening Program. *Radiology.* 2013; 267(1):47–56. [PubMed: 23297332]
9. Warner E, Hill K, Causer P, Plewes D, Jong R, Yaffe M, et al. Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. *J Clin Oncol.* 2011; 29(13):1664–1669. [PubMed: 21444874]
10. Saadatmand S, Obdeijn IM, Rutgers EJ, Oosterwijk JC, Tollenaar RA, Woldringh GH, et al. Survival benefit in women with BRCA1 mutation or familial risk in the MRI screening study (MRISC). *Int J Cancer.* 2015; 137(7):1729–1738. [PubMed: 25820931]