EDITORIAL

An Abbreviated MRI Protocol for Breast Cancer Screening in Women With Dense Breasts

Promising Results, but Further Evaluation Required Prior to Widespread Implementation

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Few areas of medicine have been as controversial and emotionally charged as breast cancer screening. Although mammography screening is a mainstay of preventive health care for women in the United States, the limitations of mammography for detecting breast cancer among women with mammographically dense breasts have received increasing attention from both advocacy groups and the medical community. Currently, legislation addressing communication regarding breast density is in place for a majority of states (38 states and the District of Columbia), and a federal law mandates that the US Food and Drug Administration advance minimum national standards for breast density reporting to women undergoing mammography screening through changes to Mammography Quality Standards Act regulations.[1]

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Legislative efforts to improve communication have raised women's awareness about breast density nationally[2] but have outpaced research on how best to screen women with dense breasts. When the US Preventive Services Task Force last reviewed breast cancer screening in 2016, the evidence for supplemental screening among women with dense breasts was found to be insufficient for making recommendations.[3,4] Since then, studies have been reported addressing supplemental ultrasound screening among women with dense breasts and previously negative digital mammograms (ASTOUND-2)[5] and supplemental breast magnetic resonance imaging (MRI) screening among women with extremely dense breasts and negative mammograms (DENSE trial).[6] These studies have focused on near-term screening outcomes and either cancer detection rates or interval cancer rates.

A primary limitation of ultrasound screening is the relatively high false-positive examination rate for the additional cancer yield, and simulation studies have suggested that ultrasound screening is of limited value for women with dense breasts.[7] In contrast, breast MRI, which is currently only recommended for screening women at high risk of breast cancer (lifetime risk >20%),[8] remains costly and has limited availability and accessibility for use in widespread screening.[9] With population estimates for dense breast prevalence in screening-aged women exceeding 40% in the United States (36% heterogeneously dense and 7% extremely dense),[10] the use of breast MRI for screening women with dense breasts is widely viewed as impractical. In the recent Dutch study of supplemental MRI screening among 40 373 women with extremely dense breasts and a negative mammogram result in which 8061 women were assigned to receive supplemental full-protocol MRI,[6] the interval cancer detection rate was reduced to 2.5 per 1000 women screened among women who received MRI compared with 5.0 per 1000 among those who did not have MRI.

For these reasons, the study reported in this issue of *JAMA* by Comstock et al[11] evaluating an abbreviated protocol for breast MRI acquisition among women with dense breasts has been highly anticipated. The promise of abbreviated breast MRI is that it may improve cancer detection without the lengthy examination time and high costs of conventional breast MRI. Abbreviated breast MRI acquisition requires less than 10 minutes. However, abbreviated breast MRI still requires the contrast-enhancing agent used in full-protocol breast MRI and thus carries the same gadolinium-associated risks.[12]

Comstock et al report on a study in which 1444 women were randomized to receive abbreviated breast MRI followed by digital breast tomosynthesis (DBT, also referred to as 3-dimensional mammography) or DBT followed by abbreviated breast MRI, with examination interpretations conducted independently.[11] The reference standard (verification by core biopsy or surgical excision) was positive for invasive cancer with or without ductal carcinoma in situ (DCIS) in 17 women and for DCIS alone in another 6 women. The main finding was that 7 additional invasive cancers per 1000 women with dense breasts were detected by screening with abbreviated breast MRI vs DBT (11.8 vs 4.8 per 1000 women, respectively). These results compare favorably with results from a recent trial of supplemental ultrasound vs DBT among women with dense breasts that found only 2 additional cancers per 1000 screens with ultrasound over DBT after negative digital mammography screening results.[5] Recognizing that prevalent screens have higher cancer detection rates than incident screens, the abbreviated breast MRI trial, which compared prevalent MRI screens with incident DBT screens, is still notable.

The primary study end point was invasive breast cancer rather than DCIS, which could represent findings that would not subsequently cause women harm in their lifetimes if left undiagnosed (ie, overdiagnosis).[13] Of note, in addition to detecting invasive cancers in 10 women whose cancer was undetected by DBT (including 3 high-grade invasive cancers), abbreviated breast MRI also detected DCIS in an

additional 4 women. Although DCIS remains controversial in the absence of definitive prognostic information, 2 of these DCIS diagnoses were high grade.

Apart from cancer detection, women's breast cancer screening experience must be considered. Although it is reassuring that the authors indicate that a future publication will address the acceptability of abbreviated breast MRI to women, it is evident from the results in the current report by Comstock et al that there are limitations to abbreviated breast MRI screening for women with dense breasts. Abbreviated breast MRI had significantly lower specificity and more benign biopsies than DBT. The abbreviated breast MRI protocol has no additional imaging callbacks. Instead, all abbreviated breast MRI callbacks entailed biopsy. Thus, abbreviated breast MRI was associated with a high number of biopsies (107 vs 29 for DBT), with somewhat lower positive predictive value (although not statistically significantly lower after correction for multiple comparisons). Overall, the cascade of care ensuing from an abbreviated breast MRI callback would likely also be more costly because of the more involved and expensive types of additional imaging and procedures (eg, follow-up MRI or MRI-guided biopsy after abbreviated breast MRI vs diagnostic mammography and/or ultrasound for DBT). Further study of the longitudinal care cascade and ensuing health outcomes is warranted.

The study population was intended to exclude high-risk women eligible for full-protocol breast MRI but was not necessarily composed of average-risk women. In fact, the study did not exclude women with a personal history of breast cancer, prior breast biopsy with atypia, or family history of breast cancer. Based on the Breast Cancer Surveillance Consortium 5-year risk scores[14] available for 16 of the 17 women with invasive cancer detected by abbreviated breast MRI, 10 (62.5%) were found among women with at least intermediate risk, and 5 (31.2%) were found among women with high risk. This suggests that risk stratification and more targeted use of abbreviated breast MRI for women with dense breasts and other additional risk factors may be helpful.

Before widespread adoption, further evidence is needed to demonstrate that abbreviated breast MRI will address the limitations of conventional breast MRI in terms of practicality and cost-effectiveness for the larger screening population of women with dense breasts. Importantly, the reductions in image acquisition and interpretation time will not overcome the need for better patient access to MRI,[9] the requirement for intravenous gadolinium contrast administration, and the associated patient preparation time. Furthermore, full breast MRI protocols are becoming faster and more efficient, with times lowering to 15 to 20 minutes; thus, the time advantage of abbreviated breast MRI may not be as great as initially envisioned.

Currently, abbreviated breast MRI requires hundreds of dollars in out-of-pocket costs for women who desire this new screening modality. From a woman's perspective, abbreviated breast MRI may initially cost more out of pocket than the co-payment associated with a full-protocol MRI among women with insurance coverage. Whether abbreviated breast MRI is worth this added cost relative to full breast MRI or other supplemental imaging modalities is uncertain. Dissemination of abbreviated breast MRI into clinical practice could well exacerbate breast cancer screening inequities unless issues of cost and access are addressed. In addition, notwithstanding the promising short-term screening outcomes for abbreviated breast MRI, the question of whether it will lead to any gains in life expectancy for women with dense breasts requires longer-term studies.

Despite increased attention to tailored breast cancer screening that considers women's breast density and breast cancer risk, firm evidence regarding the best approaches to supplemental screening for women with dense breasts remains elusive and is much needed.[15] Given the large number of women with dense breasts and the lengthy time horizon required to fully understand the potential benefits of emerging breast cancer screening technologies, it is imperative that systems be designed to track long-term screening outcomes. This need is underscored by the fact that emerging breast cancer screening modalities, including DBT, against which abbreviated breast MRI was compared, have disseminated into clinical practice without definitive clinical trial evidence regarding long-term outcomes. Meanwhile, women with dense breasts and their clinicians must make breast cancer screening decisions based on the screening modalities available and the evidence at hand. Trade-offs in cancer detection rates, cost, time, anxiety, and discomfort associated with callbacks and ensuing care will need to be considered in view of uncertain long-term health benefits.

ARTICLE INFORMATION

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REFERENCES

1. Mammography Quality Standards Act: a proposed rule by the Food and Drug Administration. *Federal Register*. https://www.federalregister.gov/documents/2019/03/28/2019-05803/mammography-quality-standards-act. Published March 28, 2019. Accessed January 30, 2020.

2. Cappello NM, Richetelli D, Lee CI. The impact of breast density reporting laws on women's awareness of density-associated risks and conversations regarding supplemental screening with providers. *J Am Coll Radiol*. 2019;16(2):139-146. doi:10.1016/j.jacr.2018.08.009

3. Melnikow J, Fenton JJ, Whitlock EP, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the US Preventive Services Task Force. *Ann Intern Med*. 2016;164(4):268-278. doi:10.7326/M15-1789

4. Siu AL; US Preventive Services Task Force. Screening for breast cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2016;164(4):279-296. doi:10.7326/M15-2886

5. Tagliafico AS, Mariscotti G, Valdora F, et al. A prospective comparative trial of adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts (ASTOUND-2). *Eur J Cancer*. 2018;104:39-46. doi:10.1016/j.ejca.2018.08.029

6. Bakker MF, de Lange SV, Pijnappel RM, et al; DENSE Trial Study Group. Supplemental MRI screening for women with extremely dense breast tissue. *N Engl J Med*. 2019;381(22):2091-2102. doi:10.1056/NEJMoa1903986

7. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med*. 2015;162(3):157-166. doi:10.7326/M14-0692

8. Saslow D, Boetes C, Burke W, et al; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57(2):75-89. doi:10.3322/canjclin.57.2.75

9. Onega T, Lee CI, Benkeser D, et al. Travel burden to breast MRI and utilization: are risk and sociodemographics related? *J Am Coll Radiol*. 2016;13(6):611-619. doi:10.1016/j.jacr.2016.01.022

10. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst*. 2014;106(10):dju255. doi:10.1093/jnci/dju255

11. Comstock CE, Gatsonis C, Newstead G, et al. Comparison of abbreviated breast MRI vs digital breast tomosynthesis for breast cancer detection among women with dense breasts undergoing screening [published February 25, 2020]. *JAMA*. doi:10.1001/jama.2020.0572

12. FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings. US Food and Drug Administration website. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body. Updated May 16, 2018. Accessed January 30, 2020.

13. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst*. 2010;102(9):605-613. doi:10.1093/jnci/djq099

14. Breast Cancer Surveillance Consortium. Breast Cancer Surveillance Consortium risk calculator. http://tools.bcsc-scc.org/BC5yearRisk/intro.htm. Accessed January 19, 2020.

15. Kerlikowske K, Sprague BL, Tosteson ANA, et al. Strategies to identify women at high risk of advanced breast cancer during routine screening for discussion of supplemental imaging [published online July 1, 2019]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.1758