EDITORIAL AND COMMENT

Supplemental Breast Cancer Screening: A Density Conundrum

Jeffrey A. Tice, MD[1] and Karla Kerlikowske, MD[2]

[1]Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA; [2]General Internal Medicine Section, Department of Veteran Affairs and Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA.

J Gen Intern Med 32(6):593–4
DOI: 10.1007/s11606-017-3989-y

Mammography is widely accepted as an effective tool for reducing death from breast cancer, but also leads to overdiagnosis and overtreatment of breast cancer.[1] Overtreatment means surgery, radiation therapy, and/or chemotherapy for breast cancer that is unnecessary because the cancer would not have affected the woman's health during her lifetime. Investigators using data from the Surveillance Epidemiology and End Results Program (SEER) registry estimated that widespread use of mammography in the United States (US) increased the incidence of small (<2 cm) invasive breast cancers by 162 per 100,000 women, but the incidence of larger tumors decreased by only 30 per 100,000 women.[2] Thus, approximately 81% (132/162) of the additional breast cancers detected with screening mammography represent cancers that may not have impacted women's breast cancer mortality. Supplemental screening in women with dense breasts may add to this unintended consequence of screening, without improving outcomes for women.

New evidence published in this issue of *JGIM* suggests that the availability of supplemental screening covered by insurance in women with dense breasts has not reduced the incidence of late-stage disease. Richman et al.[3] used SEER data to assess the impact of the availability of supplemental screening for breast cancer in Connecticut, which in 2009 was the first state to require both breast density notification and coverage of supplemental screening by private insurers. Prior studies in Connecticut demonstrated that the use of supplemental ultrasound increased breast cancer detection and that approximately 25% of women with dense breasts used supplemental imaging.[4,5] In their primary analysis, Richman et al. looked for evidence of a stage shift for breast cancer following implementation of the legislation in more than 500,000 women diagnosed with breast cancer from 2005 to 2013. The investigators found a modest but significant increase in the proportion of women diagnosed with early-stage invasive breast cancer (+1.4%, 95% CI 0.1–2.6). However, they did not find a corresponding reduction in the proportion of women diagnosed with advanced-stage disease. They also evaluated changes in stage-specific breast cancer incidence in counties in Connecticut and in control counties in states without breast density legislation, and found no significant differences in the incidence of localized or advanced-stage disease. Richman et al. did not measure the prevalence of supplemental screening, so the absence of an effect could be because the prevalence of supplemental screening was too low to cause a detectable stage shift effect. Also, as the investigators highlight, this increase in early-stage invasive cancer may represent overdiagnosis, or it may be that there has not been sufficient time for the increase in early detection to translate into a reduction in the incidence of late-stage disease. In either case, the evidence supporting the effectiveness of supplemental screening in reducing morbidity and mortality remains incomplete.

Most states in the US now require that mammography reports sent to women with dense breasts describe the implications of breast density,[6] specifically that dense breast tissue increases the risk of breast cancer and can mask invasive breast cancer, leading to a decrease in the sensitivity of mammography.[3] Digital mammography improves the sensitivity of mammography in dense breast tissue, but cancers are still missed.[7] Supplemental screening techniques such as whole breast ultrasound, tomosynthesis, and breast magnetic resonance imaging (MRI) have been proposed as supplemental screening tests that can detect cancers in dense breast tissue that are not identified with digital mammography.[4] Supplemental screening ultrasound increases the detection of breast cancer by 1–2 cancers per 1000 screened, but also markedly increases the rate of false-positive breast biopsy, with few additional deaths averted beyond screening mammography, making it a costly strategy for women with dense breasts.[8] Screening tomosynthesis also increases cancer detection among women with dense breasts, and false-positive screening examinations are reduced, making it a more cost-effective strategy than screening ultrasound for women with dense breasts.[9]

Since 43% of women ages 40–74 years have dense breasts,[10] breast density legislation has the potential to substantially increase the use of supplemental imaging tests for breast cancer with no definitive evidence of the effectiveness of such screening in reducing breast cancer morbidity and mortality for women. Women with high breast density are more likely to be diagnosed with interval cancers prior to their

Published online February 27, 2017

next mammogram; however, not all women with dense breasts are at increased risk of a missed cancer.[3] Only 21% of women with dense breasts are at elevated risk of an interval cancer with advanced disease.[3] Studies have not demonstrated that supplemental imaging can identify interval cancers missed by digital mammography in women with dense breasts at high risk of an interval cancer.

For a screening test to be effective, not only must it detect disease at an early stage, but treatment at this early stage must improve outcomes compared to treatment at a later stage. In the case of supplemental screening, this means cancer detection at the time of supplemental screening must lead to better outcomes than detection of the cancer at the next screening mammogram or when it becomes clinically palpable. Many studies have shown that supplemental screening with ultrasound or tomosynthesis detects additional cancers, and that they are usually early-stage breast cancers.[4] However, no study to date has shown that early detection with supplemental screening improves outcomes for women with dense breasts. Studies would need to demonstrate either a reduction in interval cancers, advanced-stage disease, or breast cancer-specific mortality, or equivalent mortality with less aggressive treatment. A randomized controlled trial is under way to evaluate whether breast MRI can reduce interval cancer rates among women with dense breasts. The Dense Tissue and Early Breast Neoplasm Screening, or DENSE, trial is a multicenter randomized controlled trial performed in the Dutch biennial population-based screening program (subject age range, 50–75 years). Participants with extremely dense breasts (American College of Radiology breast density category d) and a negative result at digital mammography (Breast Imaging Recording and Data System category 1 or 2) are randomly assigned to undergo additional MRI imaging or to be treated according to current practice. The primary outcome is the difference in the proportion of interval cancers between the two study arms; the study should be completed by December 2019.[11]

Supplemental screening of women with dense breasts makes intuitive sense, given that 64% of all interval cancers occur among women with dense breasts.[3] However, the study by Richman et al.,[3] which found that the availability of supplemental screening ultrasound through mandated coverage in Connecticut did not improve cancer outcomes, calls into question the routine use of supplemental screening ultrasound in all women with dense breasts. Given the current incomplete evidence of benefit, it is premature to routinely recommend supplemental screening to all women with dense breasts, since not all women with dense breasts are at increased risk of a missed cancer. Comprehensive risk assessment with a risk model that incorporates breast density, such as the Breast Cancer Surveillance Consortium risk model (https://tools.bcsc-scc.org/BC5yearRisk/), may better inform the level of risk that is needed for recommending supplemental screening in women with dense breasts, and which supplemental screening test is associated with detection of interval cancers. Clinicians can use the calculator to estimate a woman's risk for breast cancer based on her risk factors and can compare her risk to that of an average woman of the same age to help put her risk in perspective. However, routine supplemental screening should not be recommended. Scientific evidence from a pragmatic comparative effectiveness study or randomized trial of supplemental screening of women at high risk of a missed cancer is needed to determine whether supplemental imaging improves the detection of interval cancers.

Corresponding Author: *Jeffrey A. Tice, MD; Division of General Internal Medicine, Department of MedicineUniversity of California, San Francisco, San Francisco, CA, USA (e-mail: jeff.tice@ucsf.edu).*

Compliance with Ethical Standards:

Conflict of Interest: *Drs. Tice and Kerlikoske have no conflicts to report.*

REFERENCES

1. **Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L.** Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive services task force recommendation. Ann Intern Med. 2016;164(4):256–267.
2. **Welch HG, Prorok PC, O'Malley AJ, Kramer BS.** Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med. 2016;375(15):1438–1447.
3. **Richman I, Asch SM, Bendavid E, Bhattacharya J, Owens DK.** Breast density notification legislation and breast cancer stage at diagnosis: early evidence from the SEER registry. J Gen Intern Med doi:10.1007/s11606-016-3904-y.
4. **Tice JA, Ollendorf DA, Lee JM, Pearson SD.** California technology assessment forum. The comparative clinical effectiveness and value of supplemental screening test following negative mammography in women with dense breast tissue. San Francisco, CA: California Technology Assessment Forum; 2013: http://www.ctaf.org/sites/default/files/assessments/ctaf-final-report-dense-breast-imaging-11.04.2013-b.pdf. Accessed 24 Jan 2014.
5. **Weigert JM**. The Connecticut experiment; The third installment: 4 Years of screening women with dense breasts with bilateral ultrasound. Breast J. 2016.
6. Are You Dense: Oklahoma Governor Ushers in the 26th State to Report Dense Breast Tissue to Patients. 2016.
7. **Kerlikowske K, Hubbard RA, Miglioretti DL, et al.** Comparative effectiveness of digital versus film-screen mammography in community practice in the United States: a cohort study. Ann Intern Med. 2011;155(8):493–502.
8. **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.
9. **Lee CI, Cevik M, Alagoz O, et al.** Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. Radiology. 2015;274(3):772–780.
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).
11. **Emaus MJ, Bakker MF, Peeters PH, et al.** MR imaging as an additional screening modality for the detection of breast cancer in women aged 50–75 years with extremely dense breasts: the DENSE trial study design. Radiology. 2015;277(2):527–537.