Supplemental Breast Cancer Screening in Women With Dense Breasts Should Be Offered With Simultaneous Collection of Outcomes Data

Although mammographic screening reduces breast cancer mortality, all women do not share this benefit equally. Just 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 cancer.” Interval cancers tend to be more aggressive and larger and have a worse prognosis than screen-detected cancers. Because a negative screening mammography result cannot reliably rule out cancer in women with dense breasts, experts and advocates have promoted breast density notification laws in the hopes that knowledge of having dense breasts will empower women to push for adequate screening that includes supplemental tests.

Breast density, variable density within a breast, and body mass index influence breast cancer risk. In a “dose-dependent” relationship, the denser the breast tissue, the higher the risk for cancer (1). Women with extremely dense breasts have a 4-fold increased risk for breast cancer and up to an 18-fold increased risk for interval cancer compared with women with fatty breasts (1). In the only series with sufficient follow-up to address breast cancer mortality, Chiu and colleagues (2) observed a 1.9-fold increased risk for breast cancer death (95% CI, 1.26 to 2.91) among women with dense breasts after adjusting for other factors. Heterogeneity of tissue density not only increases risk but also complicates mammographic interpretation. High body mass index after menopause increases risk as does low body mass index before menopause. Determination of which of 4 qualitative density categories a patient falls into largely depends on the judgment of the radiologist. Computer software that provides a highly reproducible average quantitative density is not yet widely used, and a need remains for judgment in a given patient because even small amounts of dense tissue can mask breast cancer.

In this issue, Melnikow and colleagues (3) summarize evidence about the benefits and harms of supplemental screening with ultrasonography, magnetic resonance imaging (MRI), or digital breast tomosynthesis in women with dense breasts and negative mammography results. They found a few good-quality studies showing that supplemental screening finds additional breast cancer, most of which is invasive. Ultrasonography and MRI also increase false-positive results. The researchers found no good-quality studies that reported mortality outcomes.

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

Results from the multicenter J-START (Japan Strategic Anti-cancer Randomized Trial), which were published too recently to be included by Melnikow and colleagues, showed a reduction in interval cancer (0.05% vs. 0.10%; P = 0.034) among 32 105 women receiving supplemental ultrasonography compared with 32 812 women in the control group receiving mammography only (5). Among 202 cancer cases detected in the intervention group, 144 (71.3%) were stage 0 or I compared with only 79 of 152 (52.0%) in the control group (P = 0.019). In the ACRIN (American College of Radiology Imaging Network) 6666 trial, supplemental ultrasonography improved detection of mostly node-negative invasive breast cancer (25 of 32 [78%] women diagnosed with breast cancer seen only on an ultrasonogram had stage I disease); detection benefits of ultrasonography occurred in women whose breast density was visually estimated at only 25% to 40%, although there was a trend toward a greater increase in cancer detection with increasing breast density (6).

Schrading and colleagues (7) showed that MRI every 1 to 3 years had an initial cancer detection rate of 22.6 cases per 1000 average-risk women after normal results on mammography and ultrasonography, with a similar yield across all breast densities. In that study, the cancer detection rate on incidence screening was 7.5 cases per 1000 women, and 93% of cancer cases identified on MRI were node-negative, with a mean tumor size of 0.8 cm and no interval cancer. For tomosynthesis, increased cancer detection has been shown across all breast densities in the Oslo trial (8), although follow-up is incomplete. Based on early results from the ASTOUND (Adjunct Screening with Tomosynthesis or Ultrasound in Mammography-Negative Women With Dense Breasts) trial (Houssami N. Personal communication), screening ultrasonography after adjunct tomosynthesis has a supplemental cancer yield similar to that of screening ultrasonography after standard digital mammography.

Supplemental screening has proven advantages 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...
**Editorial**

**Breast Cancer Screening and Simultaneous Collection of Outcomes Data**

**References**


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**BRCA1 mutation or familial risk, annual MRI resulted in greater metastasis-free survival compared with matched control women (10).**

In summary, although only mammography has been evaluated in studies that examined breast cancer mortality, what we know about the natural history of the disease suggests that supplemental screening is beneficial. Most cancers found with ultrasonography are node-negative invasive cancers, and MRI also detects some ductal carcinoma in situ. Both ultrasonography and MRI have been shown to reduce interval cancer in women with dense breasts; this is a proposed end point in the planned TMIST (Tomosynthesis Mammography Imaging Screening Trial). Magnetic resonance imaging reduces rates of late-stage and metastatic disease. I believe that supplemental screening should be available to interested women with dense breasts, but guidance to help inform the choice to have supplemental screening is sorely needed. Ideally, supplemental imaging should be performed in clinical settings that simultaneously collect data on molecular phenotypes, stage of detected cancer, other breast cancer risk factors, and outcomes of women who pursue supplemental screening. This would allow careful observational analyses comparing their outcomes to those of women with dense breasts who choose not to have supplemental tests.

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