Appropriate cancer screening for women with dense breasts

The data do not support mandating supplemental MRI as part of breast cancer screening for women with extremely dense breasts

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We have been interested in the quiz series focused on breast cancer screening for women with dense breasts presented in *OBG MANAGEMENT* by DenseBreast-Info.org. However, we have concerns with the answer as presented in the December 2021 issue, "Average-risk women with dense breasts—What breast screening is appropriate?" (*OBG Manag.* 2021;33(12):18-19. doi: 10.12788/obgm.0155.) The main question asks about appropriate imaging beyond mammography/tomosynthesis for women with extremely dense breasts and no other risk factors for breast cancer. The authors recommend magnetic resonance imaging (MRI), ultrasonography, or contrast-enhanced mammography (if MRI is not an option). This advice, however, does not follow current guidelines from the American College of Obstetricians and Gynecologists (ACOG) and other professional organizations.

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We can certainly understand that an advocacy group would want ObGyns to be proactive about adjunctive imaging in average-risk women with heterogeneously dense or extremely dense breasts. However, at this point in time, there are no clear data to support a recommendation for adding universal MRI in this population, for many reasons that we will discuss herein.

The concerns with breast cancer in particular

Breast cancer is not cervical cancer. It isn't one disease. It is a multitude of diseases that happen to show up in the breast. Some are relatively slow-growing—the kinds of cancers that lend themselves to screening and to early intervention. But other cancers are rapidly-growing; they show up no matter how often or what modality we use for screening. Our goal should be to find an approach to screening that can diagnose breast cancer at a stage where we can intervene and positively impact breast cancer specific and overall mortality.

Screening guidelines vary

The variety of screening guidelines published by different professional organizations reflect differing assumptions and sets of values related to the early diagnosis and treatment of breast cancer. (For a comprehensive table of current screening guidelines, see https://www.cdc.gov/cancer/breast/pdf/breast-cancer-screening-guidelines-508.pdf.)

ACOG's approach—to offer screening at age 40 but to begin by at least age 50 and, through shared decision making with the patient, screen every 1 or 2 years—is focused on capturing as many cases as we can identify, while minimizing the harms of false-positives.[1] The perspective of the US Preventive Services Task Force (USPSTF) recommendations (to screen every 2 years beginning at age 50) is at the population level, a cost-effective approach that will have the greatest benefit while minimizing harms in the population at large.[2] The American Society of Breast Surgeons recommends screening to begin by age 40.[3] Like the breast surgeons, radiologists dedicated to breast imaging are

Screening approaches reflect guidelines and individual values

We follow American College of Obstetricians and Gynecologists and US Preventive Services Task Force guidelines in discussing screening (both its hazards and benefits) with our average-risk patients beginning at age 40. We talk about risk factors for breast cancer, including breast density, but let patients know that no specific additional imaging is advised, and that density is more common in younger women (one consideration in earlier screening) and is quite common in general. Although we do not send follow-up letters to patients with dense breasts, we do educate our staff so that they can respond appropriately should patients call with questions.

Of course, we all bring to the table values that will impact the decisions that we make for ourselves and for our patients. What an ObGyn might suggest may differ from what a radiologist might suggest. Although we follow recommendations made by the radiologist at screening, an ObGyn wants to take care of the whole human being. We are concerned with bones, heart, everything about the patient, so we approach a patient in a different way. These priorities are reflected in the current varying breast cancer screening guidelines.

focused on an individual rather than a population level. They strive to identify each and every instance of possible cancer, and therefore recommend annual screening beginning at age 40.[4] However, with more aggressive screening in average-risk women many cases of ductal carcinoma in situ (DCIS) are identified—a lesion that, if not detected, may not impact the woman's health during her lifetime—representing what some might call "overdiagnosis." Yet there may be some instances in which the DCIS might affect an individual woman's health. Unfortunately, we can't prospectively distinguish between the first and the second types of cases.

Research on breast cancer screening varies by design

There has not been a randomized clinical trial conducted on screening mammography since the days of the analog mammogram. The research that has been conducted is difficult to compare due to variations in screening ages and intervals, technology sensitivity, and patient adherence with recommended screening. Treatments for breast cancer also have changed dramatically over time, so the findings of older studies may no longer be relevant to current breast cancer screening. The kind of analysis that needs to be done is an interrupted time series, where you can look at the trajectory of breast cancer survival and whether screening mammography shifts that survival in any way.

One specific study from Australia measured the impact of newer available breast cancer treatments, including tamoxifen for women with receptor-positive tumors and newer chemotherapy strategies.[5] The authors analyzed screening mammography trends in one large province where women aged 50 to 69 were offered biennial screening. Trends from the 1990s showed that more women were being screened over time. Simultaneously, however, advances in therapy were entering clinical practice. The researchers pointed to a substantial decline in mortality from breast cancer from the early 1980s until 2013. But their conclusion was that none of the decline in mortality for breast cancer could be attributed to screening mammography when they looked at time trends; from their perspective all of the important decline in breast cancer mortality resulted from better treatment. They concluded that government programs should not support screening mammography.[5]

That is a recommendation that we do not support. However, we do recognize the conundrum that mammography is less sensitive among those who have dense breasts. In order to have congruent professional guidelines, we support research funding to determine which types, starting ages, and intervals of screening would be best in various patient populations. The USPSTF cites data from studies performed in the 1980s based on outdated technology; more recent (and relevant) randomized clinical trials have not been performed, and yet this information is critical to provide sufficient evidence to develop appropriate guidelines.

Our recommendations for gathering new data

The kind of data we would find most valuable would assess how different screening strategies impact overall mortality and breast cancer-specific mortality. It would require decades of follow-up—which of course means that screening technology will change over that time. A surrogate for evalu-

Inequities in breast cancer screening and outcomes

The importance of health equity is receiving more attention. When examining equity according to breast cancer mortality, ethnic minority populations have worse cancer survival outcomes than White women; the mortality rate is 40% higher among Black women than among White women.[1] Lower survival rates are also noted among lower socioeconomic groups and among women who live in rural areas. Lower survival rates among ethnic minority women are also noted for cervical and colorectal cancers.[2]

In the past, these disparities in mortality were attributed to the historically lower breast cancer screening rates among Black women compared with White women. However, decades of efforts to increase mammography rates have effectively addressed much of the racial/ethnic gap in screening rates.[1] In fact, a 2021 study showed Black and Hispanic women to have 6% to 10% higher rates of breast, cervical, and colorectal cancer screening than White women according to US Preventive Services Task Force guidelines.[2] The study authors point out that other national data have demonstrated similar results and conclude that "higher cancer mortality among racial/ethnic minority groups will not be reduced solely by increasing rates of cancer screening. Although preventive screenings and timely diagnosis are important elements of prognosis, they are just 2 elements of many along the cancer care continuum that need to be addressed to eliminate disparities in cancer mortality."

Unfortunately, the randomized trials that have been conducted on mammography have been conducted overwhelmingly in White populations. National registry studies from the Netherlands and Sweden are not representative patient populations for the United States. Recently, the US government proposed an ambitious plan to cut cancer mortality rates and has promised vast amounts of research funding to achieve that goal.[3] Hopefully, this funding will support studies which enroll diverse patient populations. We hope to gain knowledge on what elements along the cancer care continuum can be addressed to better reduce or eliminate cancer mortality inequities.

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ating overall survival is to look at interval cancers, which are all breast cancers diagnosed following negative mammograms and prior to the next screening. These cancers may or may not be biologically active, again focusing us on the need to look at overall survival of the patient. In addition, reducing breast cancer mortality may not reduce overall mortality, because the treatment for breast cancer may cause heart disease, or osteoporosis, or something else that impacts overall survival. These are important considerations for women and physicians who are making choices on treatment. What matters to a patient are 2 overlapping questions:

- Do I have a life-threatening condition or do I not?
- Has screening identified a condition that might lead to treatment that's unnecessary?

The problem is that with breast cancer we can't tell the difference. We do not understand the biological potential of a lesion when we evaluate an image on MRI, or computed tomography (CT), or mammography.

A re-look at presented data

A trial conducted by Bakker and colleagues[6] was discussed by the authors of the DenseBreast-info.org quiz in which they recommended breast MRI for all women with extremely dense breasts (but no other risk factors for breast cancer) detected on screening mammograms.[7] The Bakker study was large and conducted in the Netherlands. The primary outcome of the trial was to compare the incidence of interval breast cancers of women aged 50 to 75 randomly assigned to MRI versus those assigned to continued screening mammography every 2 years. Importantly, **among the more than 8,000 women who were assigned to MRI, 59%, or fewer than two-thirds, chose to actually undergo MRI**.

Among women randomized to MRI, 20 interval cancers were found—4 were diagnosed in those who actually had MRIs, and 16 were diagnosed among women who were randomized to MRI but didn't

undergo the study. Among women assigned to screening mammography only, 161 interval cancers were diagnosed among more than 32,000 women screened. The primary outcome findings were 2.5 interval cancers per 1,000 screenings among women randomly assigned to MRI, and 5 interval cancers per 1,000 screenings among those randomly assigned to mammography only.[6]

Because the trial included women aged 50 and older, we can't apply these results to younger women, who often undergo screening mammography in the United States. In addition, the majority of the population in the Netherlands are of Western European ethnicity, a less-diverse population of women than in the United States. Furthermore, among the tumors that were detected in the MRI group, a larger proportion were DCIS, early-stage tumors, well differentiated, and hormone receptor-positive. This observation supports that many of the MRI-detected tumors were cases of overdiagnosis, or the detection of tumors destined not to cause clinical problems for the patient during her lifetime, or for which earlier diagnosis would impact survival.

We also know that treatment of these small ER-positive tumors carries risks for patients, as we may treat them by depriving a patient of estrogen for the rest of her life, with potential consequences of sexual dysfunction, osteoporosis, and perhaps cardiovascular disease depending on her age at the time of that diagnosis. Weighing the risks and benefits of not only treatment but also use of more sensitive screening techniques such as MRI is extremely important. Although Bakker and colleagues' study results are interesting, we do not feel they support routinely recommending MRI for women found to have extremely dense breasts with mammography.

Overdiagnosis: A difficult concept

One reason overdiagnosis is so challenging to understand is that it can't be directly measured, which makes comprehending it that much more problematic for clinicians and our patients.

One way to help grasp the overall issue is to compare screening mammography with cervical and colon cancer screening.

We are well aware that cervical cancer screening has reduced the incidence of mortality from invasive cervical cancer.[8] We can argue very validly that the biggest success in any cancer screening program in history and globally has been cervical cancer screening. Our specialty, in particular, should feel proud about this. Screening colonoscopy also has repeatedly been found to reduce colon cancer mortality.[9] For breast cancer, decades of media messaging have emphasized the benefits of screening mammograms; however, in contrast with cervical cancer screening and colonoscopy, **screening mammography has not reduced the incidence of breast cancer presenting with metastatic or advanced disease.** Danish authors pointed out in 2017 that screening mammography has not achieved the hoped for or the promised reduction in breast cancer mortality.[10]

A report published in the March 2022, issue of *Annals of Internal Medicine* used modeling techniques to estimate the incidence of overdiagnosis and concluded that, among women aged 50-74 years receiving biennial screening mammograms (consistent with USPSTF recommendations), more than 15% of screen-detected breast cancers would represent cases of overdiagnosis. Of note, the study authors found that, among screen-detected cancers, the proportion representing overdiagnosis among women in their 60s (16.7%) and early 70s (23.6%) was higher than among women in their 50s-60s (11.5%-11.6%).[11]

The former Chief Medical and Scientific Officer for the American Cancer Society Otis Brawley, MD, has stated that, at the same time that breast cancer screening should not be abandoned, "We must acknowledge that overdiagnosis is common. The benefits of screening have been overstated, and some patients considered as 'cured' from breast cancer have, in fact, been harmed by unneeded treatment."[12]

"Everybody loves early detection," said Donald Berry, PhD, from MD Anderson Cancer Center, "but it comes with harms." He points out that mortality rates have improved for breast cancer, but he attributes it to improved treatment. "The harms [of screening] we know, but the benefits of screening are very uncertain."[13]

Limitations of breast MRI

Overall, MRI is a diagnostic and monitoring test. It is costlier than mammography, and because it is not recommended in guidelines as a screening modality for most women, it is not typically covered by insurance. Abbreviated (rapid) MRI is a non-standardized imaging strategy being used at a few health centers. It has a shorter protocol overall than MRI, so it takes less time than current MRI and is less expensive, but there are few data on sensitivity and specificity. It is yet to be determined which populations could benefit from this newer technology.

As mentioned, 41% of women in the Bakker et al trial who were

randomly assigned to breast MRI chose not to proceed with that exam even though it would have been at no cost to them.[6] Anecdotally, some patients who have undergone MRI say they would forgo it a second time as a screening modality because it was a very unpleasant, stressful experience. It's not a perfect test, although it is more sensitive than mammography.

Other options for following up dense-breast screening. Besides MRI and abbreviated MRI, the following modalities can be used to evaluate women found to have dense breasts with screening mammograms: CT mammography with contrast, molecular breast imaging, and ultrasonography.

Screening and treatment advances

3D mammography. In the US, the great majority of screening mammography now is performed with tomosynthesis, or what our patients sometimes call 3D mammography. In fact, it is approaching standard of care. Women whose screening mammography includes tomosynthesis are less likely to experience a so-called callback for additional imaging with diagnostic mammography or breast ultrasonography.[14]

Liquid biopsy. A potential major advancement for making decisions about when to treat cancers in general involves determining the biological behavior of a tumor, based on analysis of either circulating tumor DNA or proteins in the blood. As more experience with this new technology accumulates, the role of liquid biopsies for breast cancer will expand.[15] Liquid biopsies for screening remain investigational for now, but they hold tremendous potential.

Noninvasive proteomics. With the development of noninvasive proteomic biomarkers obtained from blood, saliva, or nipple aspiration fluid, there exists the possibility of not just evaluating an image of a tumor seen on a mammogram, but actually studying the biological characteristics of that lesion.[16] The cost of this technology is far less in terms of resources than MRI or molecular-based imaging, and actually reveals the flaws with using image-based screening. With proteomics, we can tell whether or not a lump is generating proteins that are going to make that disease biologically meaningful, and treatment decisions can be based on that information. This idea has the potential to disrupt our current breast cancer screening paradigm.

Advocacy's role in mandating legislation

Many advocacy groups lobby on Capitol Hill for legislation related to health care, but we don't feel that is the best way to make scientific decisions, and it's not the way to do medicine. Passionate people, who truly believe that their outcome would have been different had something else been done, have every right to advocate, and should. However, without longer-term data focusing on breast cancer and overall mortality, rather than surrogate outcomes like interval cancers, it is not clear that routinely recommending supplemental MRI will improve survival for women with extremely dense breasts. Unfortunately, overall, earlier diagnosis of highly aggressive breast cancer tumors does not result in better outcomes for patients. ●

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