COMMENTARY

Should supplemental MRI be used in otherwise average-risk women with extremely dense breasts?

Recent data show that supplemental MRI screening in women with extremely dense breasts and negative screening mammograms decreases the rate of interval breast cancers. It remains unclear, however, whether supplemental MRIs will improve other outcomes, such as breast cancer mortality.

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While the frequency of dense breasts decreases with age, approximately 10% of women in the United States have extremely dense breasts (Breast Imaging, Reporting, and Data System [BI-RADS] category D), and another 40% have heterogeneously dense breasts (BI-RADS category C).[1] Women with dense breasts have both an increased risk for developing breast cancer and reduced mammographic sensitivity for breast cancer detection compared with women who have nondense breasts.[2]

These 2 observations have led the majority of states to pass legislation requiring that women with dense breasts be informed of their breast density, and most require that providers discuss these results with their patients. Thoughtful clinicians who review the available literature, however, will find sparse evidence on which to counsel patients as to next steps.

Now, a recent trial adds to our knowledge about supplemental magnetic resonance imaging (MRI) breast screening in women with extremely dense breasts.

DENSE trial offers high-quality data

Bakker and colleagues studied women aged 50 to 74 who were participating in a Netherlands population-based biennial mammography screening program.[3] They enrolled average-risk women with extremely dense breasts who had a negative screening digital mammogram into the Dense Tissue and Early Breast Neoplasm Screening (DENSE) multicenter trial. The women were randomly assigned to receive either continued biennial digital mammography or supplemental breast MRI.

The primary outcome was the between-group difference in the development of interval breast cancers—that is, breast cancers detected by women or their providers between rounds of screening mammography. Interval breast cancers were chosen as the primary outcome for 2 reasons:

- interval cancers appear to be more aggressive tumors than those cancers detected by screening mammography
- interval cancers can be identified over a shorter time interval, making them easier to study than outcomes such as breast cancer mortality, which typically require more than a decade to identify.

The DENSE trial's secondary outcomes included recall rates from

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TABLE 1 Interval cancer rates in the mammography-only group vs the supplemental MRI group[3]

	Mammography-only group	MRI-assigned group	If all had MRI[a]
Interval cancer per 1,000 screenings (95% CI)	5.0 (4.3–5.8)	2.5 (1.6–3.8)	0.8
Difference in interval cancer compared with mammography only (95% CI)	— (reference)	-2.5 (1.0–3.7)	-4.2 (2.0–6.4)

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging.

[a]Calculated using CACE (complier average causal effect) analysis estimating the effect of all women undergoing supplemental MRI.

TABLE 2 Tumor characteristics in women who had mammography only vs supplemental MRI[3]

	Breast cancers detected on MRI	Interval cancers in women who had MRI	Interval cancers in women who were assigned to but did not have MRI	Interval cancers in women who had mammography only
Median size, mm	9.5	13	15	17
Percent (N) early stage (stage 0, I)	91.1 (72)	50 (2)	50 (8)	41.6 (67)
Percent (N) late stage (stage II–IV)	9 (7)	50 (2)	50 (8)	58.4 (94)

Abbreviation: MRI, magnetic resonance imaging.

MRI, cancer detection rates on MRI, positive predictive value of MRIs requiring biopsy, and breast cancer characteristics (size, stage) diagnosed in the different groups.

Between-group difference in incidence of interval cancers

A total of 40,373 women with extremely dense breasts were screened; 8,061 of these were randomly assigned to receive breast MRI and 32,312 to continued mammography only (1:4 cluster randomization) across 12 mammography centers in the Netherlands. Among the women assigned to the MRI group, 59% actually underwent MRI (4,783 of the 8,061).

The interval cancer rate in the mammography-only group was 5.0 per 1,000 screenings (95% confidence interval [CI], 4.3–5.8), while the interval cancer rate in the MRI-assigned group was 2.5 per 1,000 screenings (95% CI, 1.6–3.8) (**TABLE 1**).[3]

Key secondary outcomes

Of the women who underwent supplemental MRI, 9.49% were recalled for additional imaging, follow-up, or biopsy. Of the 4,783 women who had an MRI, 300 (6.3%) underwent a breast biopsy, and 79 breast cancers (1.65%) were detected. Sixty-four of these cancers were invasive, and 15 were ductal carcinoma in situ (DCIS). Among women who underwent a biopsy for an MRI-detected abnormality, the positive predictive value was 26.3%.

Tumor characteristics. For women who developed breast cancer during the study, both tumor size at diagnosis and tumor stage (early vs late) were described. **TABLE 2** shows these results in the women who had their breast cancer detected on MRI, those in the MRI-assigned group who developed interval cancer, and those in the mammography-only group who had interval cancers.[3] Overall, tumor size was smaller in the interval group who underwent MRI compared with those who underwent mammography only.

Study contributes valuable data, but we need more on long-term outcomes

The trial by Bakker and colleagues employed a solid study design as women were randomly assigned to supplemental MRI screening or ongoing biennial mammography,

and nearly all cancers were identified in the short-term of follow-up. In addition, very few women were lost to follow-up, and secondary outcomes, including false-positive rates, were collected to help providers and patients better understand some of the potential downsides of supplemental screening.

The substantial reduction in interval cancers (50% in the intent-to-screen analysis and 84% in the women who actually underwent supplemental MRI) was highly statistically significant ($P<.001$). While there were substantially fewer interval cancers in the MRI-assigned group, the interval cancers that did occur were of similar stage as those in the women assigned to the mammography-only group (TABLE 2).

Data demonstrate that interval cancers appear to be more aggressive than screen-detected cancers.[4] While reducing interval cancers should be a good thing overall, it remains unproven that using supplemental MRI in all women with dense breasts would reduce breast cancer specific mortality, all-cause mortality, or the risk of more invasive treatments (for example, the need for chemotherapy or requirement for mastectomy).

On the other hand, using routine supplemental breast MRI in women with extremely dense breasts would result in very substantial use of resources, including cost, radiologist time, provider time, and machine time. In the United States, approximately 49 million women are aged 50 to 74.[5] Breast MRI charges commonly range from $1,000 to $4,000. If the 4.9 million women with extremely dense breasts underwent supplemental MRI this year, the approximate cost would be somewhere between $4.9 and $19.5 billion for imaging alone. This does not include callbacks, biopsies, or provider time for ordering, interpreting, and arranging for follow-up.

While the reduction in interval cancers seen in this study is promising, more assurance of improvement in important outcomes—such as reduced mortality or reduced need for more invasive breast cancer treatments—should precede any routine change in practice.

Unanswered questions

This study did not address a number of other important questions, including:

Should MRI be done with every round of breast cancer screening given the possibility of prevalence bias? Prevalence bias can be defined as more cancers detected in the first round of MRI screening with possible reduced benefit in future rounds of screening. The study authors indicated that they will continue to analyze the study results to see what occurs in the next round of screening.

Is there a similar impact on decreased interval cancers in women undergoing annual mammography or in women screened between ages 40 and 49? This study was conducted in women aged 50 to 74 undergoing mammography every 2 years. In the United States, annual mammography in women aged 40 to 49 is frequently recommended.

What effect does supplemental MRI screening have in women with heterogeneously dense breasts, which represents 40% of the population? The US Food and Drug Administration recommends that all women with dense breasts be counseled regarding options for management.[6]

Do these results translate to the more racially and ethnically diverse populations of the United States? In the Netherlands, where this study was conducted, 85% to 90% of women are either Dutch or of western European origin. Women of different racial and ancestral backgrounds have biologically different breast cancers and cancer risk (for example, higher rates of triple-negative breast cancers in African American women; 10-fold higher rates of *BRCA* pathogenic variants in Ashkenazi Jewish women).

Use validated tools to assess risk comprehensively

Women aged 50 to 74 with extremely dense breasts have reduced interval cancers following a normal biennial mammogram if supplemental MRI is offered, but the long-term benefit of identifying these cancers earlier is unclear. Until more data are available on important long-term outcomes (such as breast cancer mortality and need for more invasive treatments), providers should consider breast density in the context of a more comprehensive assessment of breast cancer risk using a validated breast cancer risk assessment tool.

I prefer the modified version of the International Breast Cancer Intervention Study (IBIS) tool, which is readily available online (https://ibis.ikonopedia.com/).[7] This tool incorporates several breast cancer risk factors, including reproductive risk factors, body mass index, *BRCA* gene status, breast density, and family history. The tool takes 1 to 2 minutes to complete and provides an estimate of a woman's 10-year risk and lifetime risk of breast cancer.

If the lifetime risk exceeds 20%, I offer the patient supplemental MRI screening, consistent with current recommendations of the National Comprehensive Cancer Network and the American Cancer Society.[8,9] I generally recommend starting breast

imaging screening 7 to 10 years prior to the youngest breast cancer occurrence in the family, with mammography starting no earlier than age 30 and MRI no earlier than age 25. Other validated tools also can be used.[10-13]

Incorporating breast density and other important risk factors allows a more comprehensive analysis upon which to counsel women about the value (benefits and harms) of breast imaging.[8]

References

1. Sprague BL, Gagnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst.* 2014;106:dju255. doi: 10.1093/jcni/dju255.
2. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med.* 2007;356:227-236.
3. Bakker MF, de Lange SV, Pijnappel RM, et al; for the DENSE Trial Study Group. Supplemental MRI screening for women with extremely dense breast tissue. *N Engl J Med.* 2019;381:2091-2102.
4. Drukker CA, Schmidt MK, Rutgers EJT, et al. Mammographic screening detects low-risk tumor biology breast cancers. *Breast Cancer Res Treat.* 2014;144:103-111.
5. Statista website. Resident population of the United States by sex and age as of July 1, 2018. https://www.statista.com/statistics/241488/population-of-the-us-by-sex-and-age. Accessed January 6, 2020.
6. US Food and Drug Administration website. Mammography: what you need to know. https://www.fda.gov/consumers/consumer-updates/mammography-what-you-need-know. Accessed January 13, 2020.
7. IBIS (International Breast Cancer Intervention Study) website. Online Tyrer-Cuzick Model Breast Cancer Risk Evaluation Tool. ibis.ikonopedia.com. Accessed January 13, 2020.
8. Bevers TB, Anderson BO, Bonaccio E, et al; National Comprehensive Cancer Network. Breast cancer screening and diagnosis: NCCN practice guidelines in oncology. *JNCCN.* 2009;7:1060-1096.
9. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin.* 2007;57:75-89.
10. Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br J Cancer.* 2008;98:1457-1466.
11. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer: implications for risk prediction. *Cancer.* 1994;73:643-651.
12. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet.* 1998;62:145-158.
13. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med.* 2004;23:1111-1130.