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In Reply

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In their letter, it is suggested that our sample size of 6081 examinations was “small” and should be considered in the context of results across 25 series encompassing more than 363 000 screens. Of the studies cited, 18 were single-institution studies, and 12 had sample sizes smaller than our study. The studies also included heterogeneous populations of women with varying distributions of breast density and underlying risk, which precludes summation of conclusive evidence across studies, as suggested. Our study of women receiving screening ultrasonography as part of routine clinical practice in the United States reported significant increases in false-positive biopsy rates without significant increase in cancer detection rates or decrease in interval cancer rates. Our conclusions apply to the observed cohort, and our study of multiple facilities with linkage to state and regional cancer registries adds high-quality evidence to the published literature.

Another comment indicated that for some women, false-positive ultrasonography results may be well tolerated compared with late-stage cancer diagnosis after a false-negative results of a screening mammogram. We agree that a woman may accept a greater likelihood of a biopsy with benign results compared with an increased risk of being diagnosed with an advanced cancer. However, many women in our cohort were at low to average risk or had nondense breasts. For these women, supplemental ultrasonography screening may not have been a good recommendation or choice. Even in high-risk women, most will not have breast cancer. Consequently, many false-positive results will be incurred in healthy women for each potential false-negative result that may be averted by supplemental screening. It is a worthy goal to increase early breast cancer detection, but we need clear selection criteria for supplemental ultrasonography use and decision aids about the likelihood of additional downstream testing.

One noted flaw in our study was lack of information regarding specifics of ultrasonography technique and documentation. We recognized this limitation in the Discussion section of our article, and it is likely that experience and quality were variable. Thus, we stated the importance of ensuring increased capacity of skilled imaging technicians so that any woman

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who may benefit from supplemental ultrasonography screening will have access to a high-quality procedure.

We appreciate the opportunity to clarify a comment about omissions in reporting of prevalent vs incident examinations, interval cancers, and stage at diagnosis. We presented this information in the Results section: “When recall rate, biopsy recommendation rate, and cancer detection rate were stratified by first vs subsequent mammography plus ultrasonography examinations (n = 2040 and n = 4041, respectively), all rates declined significantly on subsequent examinations.”^{1(p662)} In addition, interval cancer rates were presented in Table 3, and stage at diagnosis was presented in Table 4.

Referring health care providers, radiologists, and women in our care need evidence that supplemental ultrasonography outside of experimental settings can be delivered with a more favorable tradeoff of benefits (as measured by reduction in rates of interval cancers, advanced cancers, or both) vs harms than we observed in our data.

Acknowledgments

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References

1. Lee JM, Arao RF, Sprague BL, et al. Performance of screening ultrasonography as an adjunct to screening mammography in women across the spectrum of breast cancer risk. *JAMA Intern Med.* 2019;179(5):658–667. doi:10.1001/jamainternmed.2018.8372 [PubMed: 30882843]

Table 3.

Estimated Performance Measures and Results From Log Binomial Regression Analysis

Variable	Mammography Plus Ultrasonography	Mammography Alone (Matched)	Relative Risk (95% CI) ^a
BI-RADS end-of-day assessment, No. (%)			
0 (Needs additional imaging)	21 (0.3)	5159 (17.2)	NA
1 (Negative)	2689 (44.2)	23 909 (79.5)	NA
2 (Benign)	2793 (45.9)	878 (2.9)	NA
3 (Probably benign)	234 (3.8)	64 (0.2)	NA
4 (Suspicious)	342 (5.6)	49 (0.2)	NA
5 (Highly suspicious)	2 (0.0)	3 (0.0)	NA
Total	6081 (100)	30 062 (100)	NA
Performance based on end-of-day assessment			
Recall rate for additional imaging or biopsy, % (95% CI)	9.9 (9.1–10.6)	17.6 (17.1–18.0)	0.52 (0.48–0.57)
End-of-day assessment of 0, 3, 4, 5, No.	599	5275	NA
Total examinations, No.	6081	30 062	NA
Final assessment, No. (%)			
0 (Needs additional imaging)	5 (0.1)	104 (0.3)	NA
1 (Negative)	2694 (44.3)	26 848 (89.3)	NA
2 (Benign)	2798 (46.0)	1936 (6.4)	NA
3 (Probably benign)	235 (3.9)	341 (1.1)	NA
4 (Suspicious)	347 (5.7)	792 (2.6)	NA
5 (Highly suspicious)	2 (0.0)	41 (0.1)	NA
Total	6081 (100)	30 062 (100)	NA
Performance based on final assessment			
Biopsy recommendation rate per 1000 screens (95% CI)	57.4 (51.9–63.5)	27.7 (25.9–29.7)	2.05 (1.79–2.34)
Final assessment of 4, 5, No. ^b	349	833	NA
Total examinations, No.	6081	30 062	NA
Short-interval imaging follow-up rate (95% CI)	3.9 (3.4–4.4)	1.1 (1.0–1.3)	3.10 (2.60–3.70)
Final assessment of 3, No.	235	341	NA

Variable	Mammography Plus Ultrasonography	Mammography Alone (Matched)	Relative Risk (95% CI) ^a
Total examinations, No.	6081	30 062	NA
Sensitivity (95% CI)	78.6 (67.1–92.0)	73.8 (68.1–80.0)	1.08 (0.92–1.27)
Final assessment of 4, 5 and cancer, No.	33	155	NA
Total cancers, No.	42	210	NA
Specificity (95% CI)	94.8 (94.2–95.3)	97.7 (97.6–97.9)	0.97 (0.97–0.98)
Final assessment of 0, 1, 2, 3 and no cancer, No.	5719	29 169	NA
Noncancers, No.	6035	29 843	NA
PPV ₂ (95% CI)	9.5 (6.8–13.1)	21.4 (19.6–23.5)	0.50 (0.35–0.71)
Final assessment of 4, 5 and cancer	33	367	NA
Biopsy recommended (final assessment of 4, 5)	349	1713	NA
Cancer detection rate per 1000 screens (95% CI)	5.4 (3.9–7.6)	5.5 (4.7–6.4)	1.14 (0.76–1.68)
Final assessment of 4, 5 and cancer	33	165	NA
Total examinations	6081	30 062	NA
False-negative rate per 1000 screens (95% CI) ^c	1.5 (0.8–2.8)	1.9 (1.4–2.4)	0.67 (0.33–1.37)
Final assessment of 0, 1, 2, 3 and cancer, No.	9	56	NA
Total examinations, No.	6081	30 062	
Cancer rate per 1000 screens (95% CI)	6.9 (5.1–9.3)	7.4 (6.4–8.4)	0.99 (0.70–1.42)
All cancers, No.	42	221	NA
Total examinations, No.	6081	30 062	NA
False-positive biopsy recommendation rate per 1000 (95% CI)	52.0 (46.7–57.8)	22.2 (20.6–24.0)	2.23 (1.93–2.58)
Final assessment of 4, 5 and no cancer, No.	316	668	NA
Total examinations, No.	6081	30 062	NA

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; DCIS, ductal carcinoma in situ; NA, not applicable; PPV₂, positive predictive value of biopsy recommendation.

^aRelative risk is from log binomial model adjusted for site, age, menopausal status, first-degree family history of breast cancer, year of examination, prior benign biopsy result, and correlation among women within the same matched set using generalized estimated equations. Sensitivity was adjusted for site and first-degree family history of breast biopsy.

^bFinal assessment of 4, 5 considered a positive examination result and was used to calculate performance measures.

^cFalse-negative rate includes both invasive and DCIS.

Characteristics of Breast Cancers Occurring Within 1 Year of the Screening Examination Among the Study Groups

Table 4.

Variable	No./Total No. (%)	Mammography Plus Ultrasonography	Mammography Alone (Matched)	Mammography Alone (Overall)
Total	249	470	719	
Cancer histology				
Noninvasive (DCIS)	20/42 (47.6)	77/221 (34.8)	249/719 (34.6)	
Invasive	22/42 (52.4)	144/221 (65.2)	470/719 (65.4)	
Ductal	19/20 (95.0)	113/141 (80.1)	384/458 (83.8)	
Lobular	1/20 (5.0)	20/141 (14.2)	50/458 (10.9)	
Mixed	0/20	8/141 (5.7)	24/458 (5.2)	
Other/unknown	2	3	12	
Invasive tumor size, mm				
1–5	2/20 (10.0)	8/140 (5.7)	48/454 (10.6)	
6–10	5/20 (25.0)	37/140 (26.4)	116/454 (25.6)	
11–15	3/20 (15.0)	25/140 (17.9)	87/454 (19.2)	
16–20	3/20 (15.0)	26/140 (18.6)	74/454 (16.3)	
>20	7/20 (35.0)	44/140 (31.4)	129/454 (28.4)	
Unknown	2	4	16	
Minimal cancer				
No	13/41 (31.7)	95/210 (45.2)	290/691 (42.0)	
Yes	28/41 (68.3)	115/210 (54.8)	401/691 (58.0)	
Unknown	1	11	28	
Axillary lymph node status				
Negative	35/41 (85.4)	183/219 (83.6)	620/708 (87.6)	
Positive	6/41 (14.6)	36/219 (16.4)	88/708 (12.4)	
Unknown	1	2	11	
AJCC stage				
0	20/41 (48.8)	77/219 (35.2)	249/706 (35.3)	
I	11/41 (26.8)	85/219 (38.8)	297/706 (42.1)	

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No./Total No. (%)			
Variable	Mammography Plus Ultrasonography	Mammography Alone (Matched)	Mammography Alone (Overall)
II	8/41 (19.5)	43/219 (19.6)	131/706 (18.6)
III	2/41 (4.9)	13/219 (5.9)	24/706 (3.4)
IV	0/41	1/219 (0.5)	5/706 (0.7)
Unknown	1	2	13
Grade of invasive cancer			
1	8/19 (42.1)	48/138 (34.8)	173/448 (38.6)
2	8/19 (42.1)	62/138 (44.9)	191/448 (42.6)
3	3/19 (15.8)	28/138 (20.3)	84/448 (18.8)
Unknown	3	6	22
Hormone receptor status of invasive cancer			
ER ⁺ or PR ⁺	17/21 (81.0)	134/142 (94.4)	426/457 (93.2)
ER ⁻ and PR ⁻	4/21 (19.0)	8/142 (5.6)	31/457 (6.8)
Unknown	1	2	13

Abbreviation: AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor.