Supplementary Online Content

Berg WA, Zhang Z, Lehrer D, et al. Detection of Breast Cancer With Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women With Elevated Breast Cancer Risk. *JAMA*. 2012;307(13):1394-1404.

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Radiological Screening Methods for Mammography, Ultrasound, and Magnetic Resonance

Methods

Based on at least two-view screen-film (n=4351) or digital (n=3122) mammography, visually estimated breast density was recorded as < 25%; 26 to 40%; 41 to 60%; 61 to 80%; or > 80% dense. All radiologist investigators met experience requirements and had completed qualification tasks as previously detailed.[1] Computer-assisted detection was not permitted. Ultrasound scanning was physician performed within two weeks of the mammogram (and usually the same day), with standardized technique and documentation,[1] using high-resolution linear array broad bandwidth transducers with maximum frequency of at least 12 MHz. Interpretive criteria for both mammography and ultrasound were standardized as well.[2] For 1.6% of analyzable participants, the first study screen was their first-ever (baseline) mammographic examination;[1] otherwise, prior breast imaging was available at the time of interpretation for all screens.

MR Technique

To minimize background parenchymal enhancement, MR examinations were scheduled within 7 to 14 days of onset of menses in premenopausal women when possible and prior to any biopsies prompted by screening mammography or ultrasound. Simultaneous bilateral contrast-enhanced breast MRI utilized dedicated breast coils on 1.5T systems. Axial or sagittal T1 and fat-suppressed T2 or inversion recovery images were obtained prior to contrast injection. A three-dimensional spoiled gradient echo volume acquisition with fat suppression was obtained through both breasts both prior to and a minimum of three times following intravenous power injection of 0.1 mmol/kg Gd-DTPA, with entirety of both breasts imaged within 3 minutes, delayed imaging for minimum total of 6 minutes, and at least 3 post-contrast acquisitions through both breasts. In-plane voxel size was not greater than 1.0-mm x 1.0-mm x 3-mm slice thickness. Images were viewed with subtraction technique and maximum intensity projection technique. Prior to accruing MRI participants, sites submitted a deidentified sample contrast-enhanced MRI examination for review by Dr. R. Edward Hendrick for quality assurance and to adjust scanning parameters. Computer-assisted kinetic analysis could be performed.

Features and assessments of each lesion and by breast were recorded using BI-RADS.[3-5] To allow meaningful receiver operating characteristic (ROC) curve analysis, we did not allow use of BI-RADS 0, incomplete. Recommendations for routine annual imaging, short interval follow-up in 6 months, additional imaging, and/or biopsy, were recorded separately.

Additional Results

Time between Screens and Time to Perform US

Time between screening mammography rounds averaged 378 to 380 days (eTable 1) and between 24-month mammogram and protocol MRI, 25 days. Time to perform screening ultrasound decreased from an average of 19 minutes for screen 1 to less than 15 minutes for screen 3 (eTable 2).

Supplemental Yield of US after Digital Mammography

Across three years of screening, supplemental US provided significant detection benefit with both film and digital mammography, with supplemental yield of 3.7 per 1000 (95%CI 2.1 to 5.5) for film and 5.1 per 1000 (95%CI 2.7 to 7.7) for digital mammography ($p<.001$ each), and for all women less than age 50 (3.8 per 1000, 95%CI 1.4 to 6.5) or at least 50 years old (4.5 per 1000, 95%CI 2.8 to 6.1) ($p=.003$ and $p<.001$ vs. mammography alone, respectively).

References

1. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA.* May 14 2008;299(18):2151-2163.

2. http://acrin.org/Portals/0/Protocols/6666/Protocol-ACRIN%206666%20Admin%20Update%2011.30.07.pdf.

3. D'Orsi CJ, Bassett LW, Berg WA, et al. *Breast Imaging Reporting and Data System, BI-RADS: Mammography, 4th edition*. Reston: American College of Radiology; 2003.

4. Mendelson EB, Baum JK, Berg WA, Merritt CRB, Rubin E. *Breast Imaging Reporting and Data System, BI-RADS: Ultrasound, 1st Ed.* Reston: American College of Radiology; 2003.

5. Ikeda DM, Hylton NM, Kuhl CK, et al. *Breast Imaging Reporting and Data System, BI-RADS: Magnetic Resonance Imaging*. Reston: American College of Radiology; 2003.

eTable 1. Time Between Screens (days)

	Mammography Screen 1 to Mammography Screen 2	Mammography Screen 2 to Mammography Screen 3	Mammography Screen 3 to MRI
N	2490[a]	2284[b]	612
Mean	380	378	25
SD	32	33.9	18.7
Median	371	371	22
Range	269-675	231-683	0-87

[a] Three participants not included in year 1 analysis set were included in year 2 and are not included in the time between screens 1 and 2.
[b]Thirty-seven women had analyzable results only for screen 1 and screen 3 and therefore are not included in the time between screens 2 and 3.

eTable 2. Time to Perform Screening US (minutes)

	Screen 1	Screen 2	Screen 3
N	2659	2493[a]	2321
Mean	19.2	16.7	14.7
SD	11.9	10.4	9.2
Median	17	15	13
Range	1-144	1-166	1-121

[a] Three participants not included in year 1 analysis set were included in year 2.

eTable 3A. Results of Supplemental Ultrasound Screening in Addition to Mammography for Women with and without Personal History of Breast Cancer (PHBC)

		Mammography Alone			Combined Mammography and Ultasound (Mammography Plus Ultrasound)			Difference of (Mammography Plus Ultrasound) and Mammography Alone			Ultrasound Alone		
		Est	N/Total (95% CI)		Est	N/Total	(95% CI)	Est	(95% CI)	*P* Value	Est	N/Total	95% CI
Yield, per 1000[a]	**PHBC**	8.2	33/4010	(5.7 to 11.5)	12.5	50/4010	(9.3 to 16.4)	4.2	(2.5 to6.2)	<0.001	8.7	35/4010	(6.1 to 12.1)
	No PHBC	7.5	26/3463	(4.9 to 11.0)	11.8	41/3463	(8.5 to 16.0)	4.3	(2.3 to6.6)	<0.001	6.6	23/3463	(4.2 to 9.9)
	Difference	0.7		(-3.3 to 4.4)	0.6		(-4.4 to 5.5)	-0.1	(-3.0 to2.9)	0.950	2.1		(-1.9 to 5.9)
Sensitivity, %	**PHBC**	55.9	33/59	(42.4 to 68.8)	84.7	50/59	(73.0 to 92.8)	28.8	(18.6 to40.7)	<0.001	59.3	35/59	(45.7 to 71.9)
	No PHBC	50.0	26/52	(35.8 to 64.2)	78.8	41/52	(65.3 to 88.9)	28.8	(17.3 to40.4)	<0.001	44.2	23/52	(30.5 to 58.7)
	Difference	5.9		(-12.5 to 24.6)	5.9		(-8.8 to 20.0)	-0.0	(-15.9 to15.6)	0.997	15.1		(-2.4 to 32.6)
Specificity, %	**PHBC**	91.4	3611/3951	(90.5 to 92.3)	83.1	3283/3951	(81.9 to 84.2)	-8.3	(-9.3 to-7.4)	<0.001	88.2	3485/3951	(87.2 to 89.2)
	No PHBC	89.4	3051/3411	(88.4 to 90.5)	77.8	2654/3411	(76.4 to 79.2)	-11.6	(-12.8 to-10.4)	<0.001	84.0	2865/3411	(82.7 to 85.2)
	Difference	1.9		(0.7 to 3.3)	5.3		(3.5 to 7.1)	3.3	(1.7 to4.9)	<0.001	4.2		(2.7 to 5.7)
Recall Rate, %	**PHBC**	9.3	373/4010	(8.4 to 10.2)	17.9	718/4010	(16.7 to 19.1)	8.6	(7.7 to9.5)	<0.001	12.5	501/4010	(11.5 to 13.6)
	No PHBC	11.1	386/3463	(10.1 to 12.2)	23.0	798/3463	(21.6 to 24.5)	11.9	(10.6 to13.1)	<0.001	16.4	569/3463	(15.2 to 17.7)
	Difference	-1.8		(-3.2 to -0.4)	-5.1		(-7.0 to -3.4)	-3.3	(-4.9 to-1.7)	<0.001	-3.9		(-5.6 to -2.4)
PPV1, %[b]	**PHBC**	8.8	33/373	(6.2 to 12.2)	7.0	50/718	(5.2 to 9.1)	-1.9	(-3.5 to-0.2)	0.026	7.0	35/501	(4.9 to 9.6)
	No PHBC	6.7	26/386	(4.4 to 9.7)	5.1	41/798	(3.7 to 6.9)	-1.6	(-3.2 to-0.0)	0.050	4.0	23/569	(2.6 to 6.0)
	Difference	2.1		(-1.6 to 5.8)	1.8		(-0.3 to 4.2)	-0.3	(-2.6 to2.0)	0.808	2.9		(0.8 to 6.6)

Short-term	**PHBC**	2.2	90/4010	(1.8 to 2.8)	7.5	300/4010	(6.7 to 8.3)	5.2	(4.5 to5.9)	<0.001	5.5	220/4010	(4.8 to 6.2)
Follow-up Rate, %	**No PHBC**	2.0	70/3463	(1.6 to 2.5)	9.4	324/3463	(8.4 to 10.4)	7.3	(6.4 to8.2)	<0.001	7.7	266/3463	(6.8 to 8.6)
	Difference	0.2		(-0.5 to 0.9)	-1.9		(-3.1 to -0.6)	-2.1	(-3.2 to-1.0)	<0.001	-2.2		(-3.3 to -1.0)
Biopsy Rate, %	**PHBC**	2.2	87/4010	(1.7 to 2.7)	6.9	275/4010	(6.1 to 7.7)	4.7	(4.0 to5.3)	<0.001	5.4	215/4010	(4.7 to 6.1)
	No PHBC	2.2	75/3463	(1.7 to 2.7)	9.7	336/3463	(8.7 to 10.7)	7.5	(6.6 to8.4)	<0.001	8.2	284/3463	(7.3 to 9.2)
	Difference	0.0		(-0.6 to 0.7)	-2.8		(-4.2 to -1.6)	-2.8	(-4.0 to-1.8)	<0.001	-2.8		(-4.0 to -1.7)
PPV3, %[C]	**PHBC**	36.8	32/87	(26.7 to 47.8)	17.8	49/275	(13.5 to 22.9)	-19.0	(-26.7 to-11.7)	<0.001	15.3	33/215	(10.8 to 20.9)
	No PHBC	32.0	24/75	(21.7 to 43.8)	11.0	37/336	(7.9 to 14.9)	-21.0	(-29.1 to-13.1)	<0.001	6.7	19/284	(4.1 to 10.3)
	Difference	4.8		(-8.8 to 18.6)	6.8		(1.9 to 12.2)	2.0	(-8.7 to12.8)	0.714	8.7		(3.7 to 14.0)

[a] Yield is the cancer detection rate

[b] PPV1 is defined as the malignancy rate among women with a positive screening test (ie, assessment of BI-RADS 3 or higher and recalled from screening for further testing or short-interval follow-up).

[c] PPV3 is defined as the malignancy rate among women with a positive screening test who underwent biopsy of the same lesion.

eTable 3B. Results of Supplemental MRI Screening in Addition to Mammography for Women With and Without Personal History of Breast Cancer (PHBC)

		Mammography Alone			Combined Mammography Plus MRI			Difference of (Mammography Plus MRI) and Mammography Alone			MRI Alone		
		Est	N/ Total	(95% CI)	Est	N/ Total	(95% CI)	Est	(95% CI)	*P* Value	Est	N/ Total	(95% CI)
Yield per 1000 [a]	**PHBC**	7.3	2/275	(0.9 to 26.0)	14.5	4/275	(4.0 to 36.8)	7.3	(-6.4 to 21.0)	0.500	10.9	3/275	(2.3 to 31.5)
	No PHBC	8.9	3/337	(1.8 to 25.8)	35.6	12/337	(18.5 to 61.4)	26.7	(6.5 to 46.9)	0.004	32.6	11/337	(16.4 to 57.7)
	Difference	-1.6		(-15.7 to 12.4)	-21.1		(-45.7 to 3.5)	-19.4	(-40.0 to 1.1)	0.063	-21.7		(-44.4 to 0.9)
Sensitivity (%)	**PHBC**	50.0	2/4	(6.8 to 93.2)	100.0	4/4	(39.8 to 100.0)	50.0	(-24.0 to 124.0)	0.500	75.0	3/4	(19.4 to 99.4)
	No PHBC	25.0	3/12	(5.5 to 57.2)	100.0	12/12	(73.5 to 100.0)	75.0	(42.2 to 107.8)	0.004	91.7	11/12	(61.5 to 99.8)
	Difference	25.0		(-28.4 to 78.4)	0.0			-25.0	(-78.4 to 28.4)	0.359	-16.7		(-63.3 to 29.9)
Specificity (%)	**PHBC**	95.2	258/271	(91.9 to 97.4)	78.6	213/271	(73.2 to 83.3)	-16.6	(-21.4 to -11.8)	<.001	81.5	221/271	(76.4 to 86.0)
	No PHBC	89.5	291/325	(85.7 to 92.6)	64.0	208/325	(58.5 to 69.2)	-25.5	(-30.6 to -20.5)	<.001	70.8	230/325	(65.5 to 75.7)
	Difference	5.7		(1.5 to 9.8)	14.6		(7.4 to 21.8)	8.9	(2.4 to 15.5)	0.008	10.8		(3.9 to 17.6)
PPV1 (%) [b]	**PHBC**	13.3	2/15	(1.7 to 40.5)	6.5	4/62	(1.8 to 15.7)	-6.9	(-22.0 to 4.8)	0.337	5.7	3/53	(1.2 to 15.7)
	No PHBC	8.1	3/37	(1.7 to 21.9)	9.3	12/129	(4.9 to 15.7)	1.2	(-6.1 to 8.3)	0.750	10.4	11/106	(5.3 to 17.8)
	Difference	5.2		(-14.3 to 24.8)	-2.9		(-10.7 to 5.0)	-8.1	(-24.2 to 8.1)	0.327	-4.7		(-13.1 to 3.7)
Recall (%)	**PHBC**	5.5	15/275	(3.1 to 8.8)	22.5	62/275	(17.7 to 27.9)	17.1	(12.3 to 21.9)	<.001	19.3	53/275	(14.8 to 24.4)
	No PHBC	11.0	37/337	(7.8 to 14.8)	38.3	129/337	(33.1 to 43.7)	27.3	(22.2 to 32.4)	<.001	31.5	106/337	(26.5 to 36.7)
	Difference	-5.5		(-9.7 to -1.4)	-15.7		(-22.9 to -8.5)	-10.2	(-16.8 to -3.7)	0.002	-12.2		(-19.2 to -5.2)

Short-term Follow-up Rate (%)	**PHBC**	0.4	1/275	(0.0 to 2.0)	14.2	39/275	(10.3 to 18.9)	13.8	(9.4 to 18.3)	<.001	13.8	38/275	(10.0 to 18.5)
	No PHBC	0.6	2/337	(0.1 to 2.1)	18.1	61/337	(14.1 to 22.6)	17.5	(13.2 to 21.9)	<.001	17.5	59/337	(13.6 to 22.0)
	Difference	-0.2		(-1.3 to 0.9)	-3.9		(-9.9 to 2.0)	-3.7	(-9.6 to 2.2)	0.219	-3.7		(-9.6 to 2.2)
Biopsy Rate (%)	**PHBC**	1.5	4/275	(0.4 to 3.7)	5.5	15/275	(3.1 to 8.8)	4.0	(1.3 to 6.7)	<.001	4.0	11/275	(2.0 to 7.0)
	No PHBC	1.8	6/337	(0.7 to 3.8)	13.1	44/337	(9.6 to 17.1)	11.3	(7.6 to 14.9)	<.001	12.2	41/337	(8.9 to 16.1)
	Difference	-0.3		(-2.3 to 1.6)	-7.6		(-12.2 to -3.0)	-7.3	(-11.4 to -3.1)	<.001	-8.2		(-12.4 to -3.9)
PPV3 (%)[c]	**PHBC**	50.0	2/4	(6.8 to 93.2)	26.7	4/15	(7.8 to 55.1)	-23.3	(-66.7 to 20.0)	0.251	18.2	2/11	(2.3 to 51.8)
	No PHBC	50.0	3/6	(11.8 to 88.2)	25.0	11/44	(13.2 to 40.3)	-25.0	(-58.3 to 10.6)	0.166	24.4	10/41	(12.4 to 40.3)
	Difference	0.0		(-63.4 to 63.4)	1.7		(-22.5 to 25.8)	1.7	(-51.9 to 55.2)	0.951	-6.2		(-31.5 to 19.1)

[a] Yield is the cancer detection rate

[b] PPV1 is defined as the malignancy rate among women with a positive screening test (ie, assessment of BI-RADS 3 or higher and recalled from screening for further testing or short-interval follow-up).

[c] PPV3 is defined as the malignancy rate among women with a positive screening test who underwent biopsy of the same lesion.