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Preoperative MRI in breast cancer: effect of breast density on biopsy rate and yield

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Authors' contributions

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The National Cancer Institute had no role in the study's design; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. Likewise, the content in this manuscript is solely the responsibility of the authors and does not necessarily represent the views of PCORI, its Board of Governors or Methodology Committee.

Reproducible Research Statement

Study protocol and statistical code: Available on request, please contact kpwa.scc@kp.org with specific queries. Data set: Available after study aims of funded grants are addressed and with appropriate contracts.

ClinicalTrials.gov: NCT02980848; registered 2017

DECLARATIONS

Conflicts of interest/Competing interests Authors report no conflicts of interest or competing interests

Code availability: Not applicable

Ethics approval and Consent to Participate

The institutional review boards of the participating Breast Cancer Surveillance Consortium (BCSC) registries and Statistical Coordinating Center approved all study activities through passive consent (three registries) or waiver of written consent (two registries and the Statistical Coordinating Center). This study was Health Insurance Portability and Accountability Act compliant. Registries and the Statistical Coordinating Center received a federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities. Our study was registered on ClinicalTrials.gov (NCT02980848) and followed the Good Research Practices guidelines for comparative effectiveness research.

Consent for publication All authors consent to publication of this manuscript

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Abstract

Purpose—Preoperative breast MRI is used to evaluate for additional cancer and extent of disease for newly diagnosed breast cancer, yet benefits and harms of preoperative MRI are not well documented. We examined whether preoperative MRI yields additional biopsy and cancer detection by extent of breast density.

Methods—We followed women in the Breast Cancer Surveillance Consortium with an incident breast cancer diagnosed from 2005–2017. We quantified breast biopsies and cancers detected within 6 months of diagnosis by preoperative breast MRI receipt, overall and by breast density, accounting for MRI selection bias using inverse probability weighted logistic regression.

Results—Among 19,324 women with newly diagnosed breast cancer, 28% had preoperative MRI, 11% additional biopsy, and 5% additional cancer detected. Four times as many women with preoperative MRI underwent additional biopsy compared to women without MRI (22.6% v. 5.1%). Additional biopsy rates with preoperative MRI increased with increasing breast density (27.4% for extremely dense compared to 16.2% for almost entirely fatty breasts). Rates of additional cancer detection were almost four times higher for women with v. without MRI (9.9% v. 2.6%). Conditional on additional biopsy, age-adjusted rates of additional cancer detection were lowest among women with extremely dense breasts, regardless of imaging modality (with MRI: 35.0%; 95%CI=27.0%−43.0%; without MRI: 45.1%; 95%CI=32.6%−57.5%).

Conclusion—For women with dense breasts, preoperative MRI was associated with much higher biopsy rates, without concomitant higher cancer detection. Preoperative MRI may be considered for some women, but selecting women based on breast density is not supported by evidence.

Keywords

preoperative MRI; breast density; breast biopsy; occult cancer; Breast Cancer Surveillance Consortium; cancer detection rate

INTRODUCTION

Breast density may impact women newly diagnosed with breast cancer by underestimating extent of disease for the affected breast because of masking on mammography[1] and increased risk of mammographically occult cancer in the contralateral breast.[2] Breast MRI relies on differential contrast enhancement to better characterize cancers relative to surrounding breast tissue and is not influenced by breast density. Breast MRI use after a cancer diagnosis (i.e., ‘preoperative’ breast MRI, before first surgery) in the U.S. has increased in the past two decades, even though the evidence is not clear about the relative

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harms and benefits, particularly for subgroups of women.[3] There is some evidence breast surgeons use density as a criterion for ordering preoperative MRI based on the suggested higher cancer yield for women with dense breasts.[4]

The primary rationale for preoperative MRI is to better define extent of newly diagnosed breast cancer and to evaluate whether there is a mammographically occult tumor in the contralateral breast.[5] Better characterization of extent of the tumor(s) upon diagnosis can change surgical choice, lead to improved surgical options (fewer repeat surgeries, better identification of women for successful breast conserving surgery, wider excision when indicated, mastectomy for women with multifocal/multicentric disease) and improved patient-centered and clinical long-term outcomes. While there is evidence for additional cancer detection with MRI, its high sensitivity results in detecting benign or possibly indolent lesions, which may change women's clinical treatment choices towards more aggressive care without providing recurrence or survival benefit.[6–9] A review of more than 8 small and single-institution studies determined that preoperative MRI detected additional cancer in 10–34% of ipsilateral breasts and 3–23% of contralateral breasts.[10,11] While notable subgroup differences in occult malignancy detection were not reported, several single institution studies have found that women with high breast density or lobular histology benefited most from preoperative MRI.[11–13] No randomized controlled trials or population-based observational studies of preoperative MRI to date have studied outcomes by extent of breast density and clinical guidelines for its use are not well substantiated by breast density.[14,15]

We sought to provide population-based, generalizable evidence to inform evidence gaps in understanding the comparative effectiveness of preoperative MRI by breast density categories. We estimated rates of additional biopsies and detected cancers among women undergoing preoperative breast MRI vs. not, overall, and by breast density.

PATIENTS AND METHODS

Data Sources

Data from six Breast Cancer Surveillance Consortium (BCSC)[16] breast imaging registries (Carolina Mammography Registry, New Hampshire Mammography Network, Vermont Breast Cancer Surveillance System, San Francisco Mammography Registry, Metropolitan Chicago Breast Cancer Registry, and Kaiser Permanente Washington) prospectively collected information related to women's breast imaging use and assessments, benign and malignant breast pathology, breast cancer outcomes, and other clinical and sociodemographic characteristics. Registries collect data through a combination of women's self-report (socio-demographics, first-degree family history), radiology imaging systems, pathology records, electronic health records, and North American Association of Central Cancer Registries (NAACCR)-affiliated cancer registries. Data from the registries were pooled and analyzed at the Statistical Coordinating Center.

The institutional review boards of the participating BCSC[16] registries and Statistical Coordinating Center approved all study activities through passive consent (three registries) or waiver of written consent (two registries and the Statistical Coordinating Center). This

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study was Health Insurance Portability and Accountability Act compliant. Registries and the Statistical Coordinating Center received a federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities. Our study was registered on ClinicalTrials.gov (NCT02980848) and followed the Good Research Practices guidelines for comparative effectiveness research.[17]

Study Population

We studied women ages 18–89 years with a biopsy-determined incident invasive breast cancer or ductal carcinoma *in situ* (DCIS) (index biopsy) diagnosed between 2005 and 2017, identified in the BCSC pathology records. Women were required to have evidence of surgery (lumpectomy or uni- or bilateral mastectomy) within 6 months of the index biopsy in either the pathology or cancer registry records. Women were excluded if the index biopsy was missing laterality, if they had no mammogram within one month before the index biopsy, and if there was no measure of breast density within 10 years before the index biopsy. For 98.2% of the study population, the breast density measure was determined within the 18 months prior to the index biopsy

Study Variables

Main Exposure—We compared women who received preoperative MRI (completed between index biopsy and surgery) (Figure 1) to women who did not receive preoperative MRI. Breast MRI with contrast and dedicated breast coils was performed for women in the study population based on clinical recommendation of the treating physicians. We evaluated breast density as a potential effect modifier of preoperative breast MRI associated with additional biopsies/biopsy yield. Breast density was classified based on mammographic assessment using BI-RADS density categories: a=almost entirely fatty, b=scattered fibroglandular densities, c=heterogeneously dense, and d=extremely dense.[18] Non-dense breasts includes categories a and b; Dense breasts includes categories c and d.

Main Outcomes—The primary outcomes were rates of additional biopsies and additional cancer detected. Additional biopsy rate was defined as the number of individuals with at least one additional biopsy performed after the date of diagnosis and before surgery over the total number of women in that subgroup. Rates of additional cancers detected were defined as the number of individuals with an additional breast cancer diagnosed (i.e., biopsy positive for DCIS or invasive carcinoma *after* index biopsy before surgery) over the total number of women in that subgroup, calculated separately for ipsilateral and contralateral cancers. Secondary outcomes included definitive surgery type (mastectomy or lumpectomy, with laterality noted) and rate by biopsy type (core vs. surgical). Pathology information was collected on all breast biopsies and breast surgeries performed on women with a breast cancer diagnosis. These data include type of biopsy (fine needle aspiration, core biopsy, surgical biopsy) or surgery (lumpectomy, mastectomy including laterality), up to five Systematized Nomenclature of Medicine-Clinical Terms codes describing biopsy results, and cancer characteristics (e.g., stage, tumor size).

Other Key Variables—We included covariates measured prior to diagnosis: women's age, race/ethnicity, educational attainment for ZIP code of residence based on the 2010 Census

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percentage of individuals with a high school degree (in quartiles), first-degree family history of breast cancer, initial cancer laterality, previous biopsies/aspirations, menopausal status, index biopsy year, DCIS v. invasive index biopsy result, mode of detection (screen-detected, interval detected following a negative screening mammogram, clinically detected with no mammogram in prior 27 months)[19], and invasive cancer histology (lobular, ductal including mixed ductal/lobular, DCIS, other).

Statistical Analysis

We computed frequency distributions overall and subdivided by breast density and compared them for individuals with and without preoperative MRI. Cross-tabulations were performed by breast density to examine the relation of MRI use to additional biopsies, overall and by biopsy type, and additional cancer detected. We calculated propensity scores using generalized boosted regression modeling to obtain the probability of MRI receipt given age, race/ethnicity, diagnosis year, density, BCSC registry site, biopsy history, education, menopausal status, index cancer type (invasive v. DCIS), and mode of detection. Stabilized inverse probability weights were calculated from the estimated propensity scores and used as weights and applied to the logistic regression models for each outcome by preoperative breast MRI receipt, overall and by breast density categories. We estimated the standardized predictive margins for each outcome by averaging the predicted rates over the age distribution, and estimated 95% Wald confidence intervals using the delta method.[20] If negative CI limits were observed, we alternatively computed confidence intervals by applying inverse link transform to the confidence limits on the logit scale. Analyses were conducted on the full denominator of the study population to estimate rates for all individuals with a breast cancer diagnosis, and separately in sub-analyses using the denominator of individuals who had an additional biopsy. We used Stata Statistical Software, Release 15 (College Station, TX: StataCorp LP.), R version 3.6.2 for all analyses.

RESULTS

Among 19,324 women diagnosed with breast cancer during the study period, 5,455 (28%) underwent preoperative MRI. Women with MRI were younger, with 28% <50 years of age, compared to 18% of women without MRI (Table 1). We found no differences in race/ethnicity or first-degree family history of breast cancer by preoperative breast MRI. However, women with MRI lived in a ZIP code with higher level of educational attainment, were more likely to have a previous breast biopsy, more likely to have an interval rather than screen-detected index breast cancer, and more likely to have invasive lobular histology (Table 1). A higher proportion of women with MRI compared to no MRI had heterogeneously dense (48% v. 39%) or extremely dense breasts (15% v. 8%). When stratifying by breast density, we found that for women with extremely dense breasts, those with an MRI had a slightly higher percentage of invasive cancer (MRI: 78%, without MRI: 72%) (Appendix 1).

Four times as many women with pre-operative MRI underwent ≥1 additional biopsy compared to women without MRI (22.6% v. 5.1%) (Table 2). Crude biopsy rates increased with increasing breast density, with 27.4/100 of women with extremely dense breasts having

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additional biopsy compared to 16.2/100 of women with almost entirely fatty breasts. Crude additional cancer detection rates for the entire study population were approximately three times higher for women with MRI (9.9/100 v. 2.6/100 without MRI). There were no notable differences in additional cancer detection by density for women with or without MRI, including by laterality. Additional ipsilateral cancers were detected at about a 3-fold higher rate than contralateral (7.6/100 v. 2.5/100), with most being detected by MRI.

Weighted logistic regression models showed rates (per 100 women) for additional biopsy were several-fold higher across all density categories in women with MRI v. without ($p<0.05$ for across all density groups), with the highest rates among women with extremely dense breasts (with MRI: 25.6; 95% CI:21.7–29.6; without MRI: 5.2 (3.9, 6.6)) and the lowest in women with almost entirely fatty breasts (with MRI: 16.8% CI:11.3–22.2; without MRI: 3.3 (2.3–4.3) (Table 3). Both core biopsy and surgical biopsy rates mirrored the results for overall additional biopsy rates; they were very low and did not notably differ between the MRI and no MRI groups, but did increase with increasing density (Appendix Table 2). Additional contralateral cancer on MRI decreased with breast density, while the ipsilateral pattern not monotone. We also observed higher mastectomy rates with MRI across all density groups (almost entirely fatty: with MRI: 39.7 (95% CI:32.1–47.3); without MRI: 26.9 (95% CI: 24.5–29.4); extremely dense: with MRI:47.1 (95% CI:42.7–51.5); without MRI: 42.3 (95%CI: 38.9–45.7p-value = 0.087. Mastectomy rates were higher among women with MRI and across all density groups, and higher among women with denser breasts, regardless of preoperative MRI. (Table 3, $p<0.05$ for all comparisons except for extremely dense group)

In sub-analyses including only the women with additional biopsy (N=1,943), we calculated adjusted rate of additional cancer detection overall and by laterality. For women with additional biopsy(ies), the lowest additional cancer detection rates were among women with extremely dense breasts, regardless of imaging modality (with MRI: 35.0 (95% CI: 27.0–43.0); without MRI: 45.1 (95%CI: 32.6–57.5) (Table 4). For all density categories, women with MRI consistently had lower additional ipsilateral cancer rates than women without MRI who presumably had alternative breast imaging biopsy guidance. The trend was the opposite for contralateral cancers for women without dense breasts; MRI was associated with higher rates of contralateral cancers for the two lowest density categories (Table 4).

DISCUSSION

This study provides the largest, generalizable study to date of the effects of preoperative MRI on additional biopsies and additional cancer detection for women with breast cancer when explicitly considering extent of breast density. Overall, we found more than a 4-fold increase in additional breast biopsies in women who received preoperative MRI compared to women without MRI. Among individuals receiving preoperative MRI, those with dense breasts had twice the rates of additional biopsies compared to those with non-dense breasts. Finding additional lesions that lead to biopsy must be placed in the context of biopsy yield. Additional cancer detection was higher following preoperative MRI compared to without MRI, but density did not play a notable role; this was shown for both ipsilateral and contralateral biopsies. Thus, for women with heterogeneously or extremely dense breasts

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(categories c and d), preoperative MRI was associated with much higher biopsy rates, without concomitant higher cancer detection, compared to women with non-dense breasts.

Our study helps to address the clinical issue of whether breast density is an appropriate clinical factor to consider when determining who may benefit from preoperative MRI among individuals with newly diagnosed breast cancer. As in the recent study of preoperative MRI in 1,396 women from a regional breast imaging center,[3] breast density did not result in significant benefit. Similarly, in two other single-institution studies, density was found to be unrelated to detecting occult cancer with preoperative MRI.[21,22] Our findings mirror those results in a large national sample including all four BI-RADS breast density categories and evaluated biopsy type and yield. Thus, our results provide substantive evidence that MRI's ability to detect additional occult cancer is not modified preferentially by breast density for any of the four density categories. However, density does impact likelihood of undergoing additional biopsies for women with preoperative MRI, with higher rates for women with dense breasts and thus higher benign (false negative) biopsy rates in women with dense breasts.

Among women with preoperative MRI, we found additional biopsy rates were twice as high for women with dense vs. non-dense breasts. Taking the two-fold higher biopsy rates together with similar rates of additional cancer detection across density categories, our analysis demonstrated a lower biopsy yield for women with dense breasts. This shift in the benefit-to-harm ratio may be salient to women's workup and management choices. Systematic reviews have identified the diagnostic work-up period following an initial breast cancer diagnosis as one of heightened psychological distress for women, with short- and long-term implications for mental health, treatment decision-making, and future screening participation.[23,24] Decreasing cancer worry and satisfaction with treatment decisions may be of particular concern to women with dense breasts and for those whose cancers were not identified or detected by mammography. However, since breast MRI has a high negative predictive value, women may feel reassured by a negative MRI examination, potentially reducing cancer worry, and unnecessary surgery. At the same time, undergoing additional biopsy delays treatment, which may produce anxiety for women, or may identify risk-associated epithelial hyperplasia that may inappropriately bias surgical treatment decisions.

Although our study was the largest to date in the U.S. to examine intermediate outcomes of preoperative MRI overall and by breast density categories, there were limitations. First, we were not able to quantify the exact sequences of additional imaging and biopsy within the preoperative window, so cannot definitively attribute an additional biopsy to the preoperative MRI. However, this presumption of a preoperative MRI contributing to an additional biopsy in that same preoperative window corresponds to typical clinical practice. Secondly, we were not able to report on the effect of MRI on additional cancer detection by breast density in conjunction with other clinical characteristics, such as histology and subtype due to small numbers. Further, we were not able to assess whether the cancer was upgraded based on additional biopsies. As with most prior studies, we did not have information on whether women and their doctors modified treatment plans following preoperative MRI findings and did not examine re-operation rates. Other outcomes should also be considered, such as high negative predictive value that may be useful for decisions regarding surgical management.

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Despite these limitations, the results when considered in conjunction with clinician and individual perspectives, could inform decisions for women newly diagnosed with breast cancer.

This study contributes new, generalizable evidence on preoperative breast MRI effectiveness compared to mammography alone by extent of breast density. Specifically, women with dense breasts are suspected to benefit through additional cancer yield from preoperative breast MRI similar to women without dense breasts; however, we observed they were more likely to experience additional biopsy without an increase in cancer detection. Thus, while preoperative MRI may be important for some women for additional cancer detection, selecting women based on breast density is not supported by evidence.

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The ideas and opinions expressed herein are those of the authors and endorsement by the State of California, the California Department of Public Health; Illinois Department of Public Health; New Hampshire Department of Health and Human Services; the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

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Availability of data and material:

Publicly-available data and instructions for requesting additional data are available at: Breast Cancer Surveillance Consortium (BCSC) Data :: BCSC (bcsc-research.org)

APPENDIX

Appendix

Appendix Table 1.a.

Study population characteristics for women with breast cancer (13,869) without preoperative MRI[1,2] overall and by breast density from 2005–2017.

	a: Almost entirely fatty		b: Scattered fibroglandular		c: Heterogeneously dense		d: Extremely dense	
	N	%	N	%	N	%	N	%
Total N = 13,869	1442	10.4	5996	43.2	5347	38.6	1084	7.8
Age At Exam								
<50	54	3.8	555	9.2	1401	26.2	519	47.9
50–59	182	12.6	1467	24.5	1437	26.9	315	29.1
60–69	541	37.5	1879	31.3	1362	25.5	148	13.7
70–79	440	30.5	1445	24.1	810	15.2	76	7.0
80–89	225	15.6	650	10.8	337	6.3	26	2.4
Race (NCI Reporting Standard)								
White, non Hispanic	1112	78.6	4597	77.9	3914	74.6	743	69.9
Black, non Hispanic	164	11.6	639	10.8	530	10.1	49	4.6
Asian	63	4.5	423	7.2	554	10.6	220	20.7
Non-Hispanic Pacific Islander, Alaska Native, American Indian	10	0.7	24	0.4	29	0.6	5	0.5
Hispanic	66	4.7	221	3.7	217	4.1	46	4.3
Other, Mixed, Unknown	27	1.9	92	1.5	103	1.9	21	1.9
Family History of Breast Cancer								
No	1053	77.1	4273	76.2	3869	76.9	779	75.5
Yes	313	22.9	1332	23.8	1164	23.1	253	24.5
Unknown	76	5.3	391	6.5	314	5.9	52	4.8
Previous biopsy/ aspiration								

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	a: Almost entirely fatty		b: Scattered fibroglandular		c: Heterogeneously dense		d: Extremely dense	
	N	%	N	%	N	%	N	%
None	1002	74.0	3683	66.1	3169	64.5	609	61.3
Biopsy Only	240	17.7	1238	22.2	1151	23.4	227	22.8
Aspiration Only	37	2.7	264	4.7	248	5.0	66	6.6
Biopsy and Aspiration	75	5.5	391	7.0	346	7.0	92	9.3
Unknown	88	6.1	420	7.0	433	8.1	90	8.3
Menopause								
Pre	60	4.4	745	13.8	1490	32.2	552	59.3
Post	1302	95.6	4645	86.2	3134	67.8	379	40.7
Unknown	80	5.6	606	10.1	723	13.5	153	14.1
Current HRT Use								
No	980	97.5	3762	95.3	3590	95.0	814	95.7
Yes	25	2.5	185	4.7	189	5.0	37	4.3
Unknown	437	30.3	2049	34.2	1568	29.3	233	21.5
Laterality								
Left	707	49.0	2912	48.6	2611	48.8	540	49.8
Right	722	50.1	3004	50.1	2676	50.1	534	49.3
Both	13	0.9	80	1.3	60	1.1	10	0.9
Index biopsy year								
2005–2008	423	29.3	1829	30.5	1906	35.7	374	34.5
2009–2011	372	25.8	1399	23.3	1331	24.9	293	27.0
2012–2014	380	26.3	1609	26.8	1213	22.7	245	22.6
2015–2017	267	18.5	1159	19.3	897	16.8	172	15.9
Geo coding education								
<=Q1	404	29.9	1452	26.6	1241	25.3	227	22.1
Q1 – Q2	392	29.1	1551	28.5	1301	26.5	271	26.4
Q2 – Q3	291	21.6	1429	26.2	1305	26.6	271	26.4
> Q3	262	19.4	1017	18.7	1058	21.6	256	25.0
Unknown	93	6.5	547	9.1	442	8.3	59	5.4
Index biopsy[2]								
DCIS	219	15.2	1311	21.9	1267	23.7	306	28.2
Invasive[3]	1223	84.8	4685	78.1	4080	76.3	778	71.8
Mode of Detection[4]								
Screen Detected	851	60.3	4151	70.3	3248	61.9	504	48.1
Interval Detected	213	15.1	1000	16.9	1216	23.2	330	31.5
Clinically Detected	348	24.6	754	12.8	787	15.0	213	20.3
Unknown Mode	30	2.1	91	1.5	96	1.8	37	3.4
Histology Type								

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	a: Almost entirely fatty		b: Scattered fibroglandular		c: Heterogeneously dense		d: Extremely dense	
	N	%	N	%	N	%	N	%
DCIS	219	18.6	1311	28.3	1267	30.4	306	37.5
Invasive, Ductal	847	72.1	2934	63.4	2516	60.4	444	54.4
Invasive, Lobular	89	7.6	302	6.5	297	7.1	45	5.5
Invasive, Ductal & Lobular	20	1.7	83	1.8	86	2.1	21	2.6
Unknown	267	18.5	1366	22.8	1181	22.1	268	24.7
Surgery type								
Lumpectomy	1092	75.7	4510	75.2	3563	66.6	622	57.4
Mastectomy	350	24.3	1486	24.8	1784	33.4	462	42.6
All	1442		5996		5347		1084	

Appendix Table 1.b.

Study population characteristics for women with breast cancer (13,869) with preoperative MRI[1,2] overall and by breast density from 2005–2017.

	a: Almost entirely fatty		b: Scattered fibroglandular		c: Heterogeneously dense		d: Extremely dense	
	N	%	N	%	N	%	N	%
Total N = 5,455	284	5.2	1745	32.0	2622	48.1	804	14.7
Age At Exam								
<50	14	4.9	227	13.0	847	32.3	433	53.9
50–59	34	12.0	566	32.4	775	29.6	224	27.9
60–69	147	51.8	589	33.8	635	24.2	101	12.6
70–79	75	26.4	297	17.0	302	11.5	40	5.0
80–89	14	4.9	66	3.8	63	2.4	6	0.8
Race (NCI Reporting Standard)								
White, non Hispanic	219	78.5	1313	76.1	1949	75.7	576	72.6
Black, non Hispanic	41	14.7	239	13.8	264	10.2	50	6.3
Asian	6	2.2	77	4.5	213	8.3	108	13.6
Non-Hispanic Pacific Islander, Alaska Native, American Indian	.	.	11	0.6	14	0.5	2	0.3
Hispanic	13	4.7	86	5.0	136	5.3	57	7.2
Other, Mixed, Unknown	5	1.8	19	1.1	46	1.8	11	1.4
Family History of Breast Cancer								
No	207	76.7	1225	73.9	1878	76.4	580	77.7
Yes	63	23.3	433	26.1	580	23.6	166	22.3
Unknown	14	4.9	87	5.0	164	6.3	58	7.2

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	a: Almost entirely fatty		b: Scattered fibroglandular		c: Heterogeneously dense		d: Extremely dense	
	N	%	N	%	N	%	N	%
Previous biopsy/ aspiration								
None	181	72.4	948	63.3	1386	60.3	410	60.1
Biopsy Only	62	24.8	413	27.6	659	28.7	186	27.3
Aspiration Only	4	1.6	53	3.5	124	5.4	43	6.3
Biopsy and Aspiration	3	1.2	83	5.5	130	5.7	43	6.3
Unknown	34	12.0	248	14.2	323	12.3	122	15.2
Menopause								
Pre	17	6.4	291	19.3	914	40.5	438	65.1
Post	250	93.6	1219	80.7	1343	59.5	235	34.9
Unknown	17	6.0	235	13.5	365	13.9	131	16.3
Current HRT Use								
No	197	99.0	1043	96.0	1727	95.9	599	96.6
Yes	2	1.0	44	4.0	74	4.1	21	3.4
Unknown	85	29.9	658	37.7	821	31.3	184	22.9
Laterality								
Left	135	47.5	858	49.2	1278	48.7	412	51.2
Right	144	50.7	869	49.8	1323	50.5	388	48.3
Both	5	1.8	18	1.0	21	0.8	4	0.5
Index biopsy year								
2005–2008	23	8.1	177	10.1	317	12.1	74	9.2
2009–2011	66	23.2	473	27.1	658	25.1	228	28.4
2012–2014	104	36.6	587	33.6	844	32.2	277	34.5
2015–2017	91	32.0	508	29.1	803	30.6	225	28.0
Geo coding education								
<=Q1	93	35.0	437	27.6	584	24.4	174	23.5
Q1 – Q2	69	25.9	390	24.7	583	24.3	186	25.2
Q2 – Q3	49	18.4	445	28.1	709	29.6	190	25.7
> Q3	55	20.7	309	19.5	522	21.8	189	25.6
Unknown	18	6.3	164	9.4	224	8.5	65	8.1
Index biopsy[2]								
DCIS	38	13.4	317	18.2	516	19.7	178	22.1
Invasive[3]	246	86.6	1428	81.8	2106	80.3	626	77.9
Mode of Detection[4]								
Screen Detected	141	51.3	1197	69.5	1512	58.5	328	41.5
Interval Detected	58	21.1	291	16.9	687	26.6	267	33.8
Clinically Detected	76	27.6	235	13.6	385	14.9	196	24.8
Unknown Mode	9	3.2	22	1.3	38	1.5	13	1.6

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	a: Almost entirely fatty		b: Scattered fibroglandular		c: Heterogeneously dense		d: Extremely dense	
	N	%	N	%	N	%	N	%
Histology Type								
DCIS	38	14.3	317	22.0	516	24.3	178	28.5
Invasive, Ductal	195	73.3	935	64.8	1299	61.2	384	61.4
Invasive, Lobular	29	10.9	168	11.6	269	12.7	55	8.8
Invasive, Ductal & Lobular	4	1.5	23	1.6	38	1.8	8	1.3
Unknown	18	6.3	302	17.3	500	19.1	179	22.3
Surgery type								
Lumpectomy	180	63.4	1190	68.2	1485	56.6	395	49.1
Mastectomy	104	36.6	555	31.8	1137	43.4	409	50.9
All	284		1745		2622		804	

Appendix Table 2.

Adjusted rates[*] (per 100 women) of for biopsy type in relation to pre-operative imaging modality using inverse weighted probability regression methods among women who had an additional biopsy (N=1,943) stratified by BIRADS breast density categories.

	BIRADS Density			
Outcome	**a: Almost entirely fatty**	**b: Scattered fibroglandular**	**c: Hetero-genously dense**	**d: Extremely dense**
Additional	**Adjusted Rate (95% Confidence Interval)**			
Core Biopsy				
No MRI	75.7 (62.6,88.9)	75.6 (70.3,80.9)	88.5 (84.9,92.1)	82.5 (73.7,91.4)
MRI	100	95.4 (92.7,98.0)	94.2 (91.8,96.5)	90.1 (81.8,98.4)
Surgical Biopsy				
No MRI	9.6 (1.1,18.1)	12.2 (8.4,16)	7.9 (4.8,10.9)	19.7 (8.1,31.4)
MRI	1.3 (0.2,8.7)	2.6 (0.3,4.9)	2.4 (0.8,4.0)	5.9 (1.3,23.9)

[*] Rates are from weighted logistic regression model adjusting by age and propensity score model weights that include registry, age, race/ethnicity, education, previous breast biopsy, breast density, menopausal status, index cancer type, mode of detection of index cancer and year of diagnosis.

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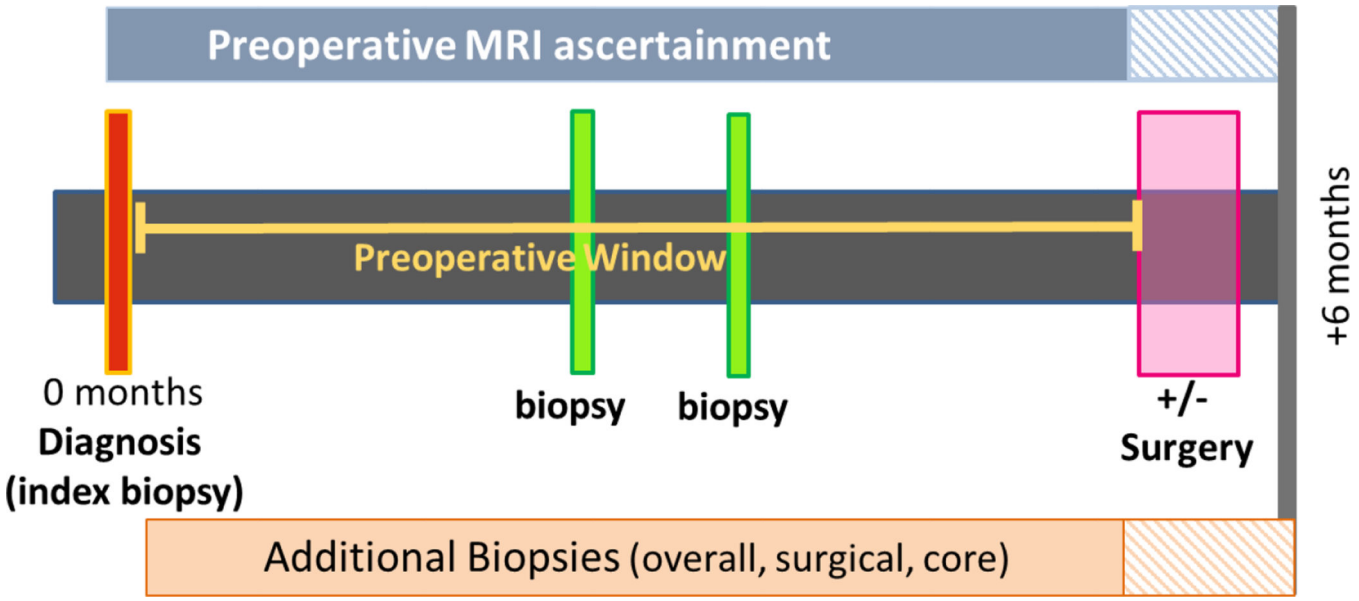

Figure 1.

Preoperative MRI and additional biopsy and cancer outcome windows

Definitions: 1) Preoperative window = index biopsy (the biopsy associated with the diagnosis) date to surgery; 2) Preoperative MRI = from index biopsy to surgery) 3) Index biopsy = biopsy associated with the diagnosis; 4) Additional biopsies = biopsy after index biopsy and before surgery; 5) Positive biopsy = invasive or DCIS = additional cancer detected; 6) Surgery type = lumpectomy or mastectomy.

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Table 1.

Study population characteristics for women with breast cancer with or without preoperative MRI[1,2].

	No MRI (N, %)		MRI (N, %)	
	Overall		Overall	
Total N = 19,324	13,869 (72.0 %)		5,455 (28.0%)	
Age At Exam (years)				
<50	2529	18.2	1521	27.9
50–59	3401	24.5	1599	29.3
60–69	3930	28.3	1472	27.0
70–79	2771	20.0	714	13.1
80–89	1238	8.9	149	2.7
Race (NCI Reporting Standard)				
White, non Hispanic	10366	76.1	4057	75.5
Black, non Hispanic	1382	10.1	594	11.1
Asian	1260	9.2	404	7.5
Non-Hispanic Pacific Islander, Alaska Native, American Indian	68	0.5	27	0.5
Hispanic	550	4.0	292	5.4
Other, Mixed, Unknown	243	1.8	81	1.5
First Degree Family History of Breast Cancer				
No	9974	76.5	3890	75.8
Yes	3062	23.5	1242	24.2
Unknown	833	6.0	323	5.9
Previous biopsy/aspiration				
None	8463	65.9	2925	61.9
Biopsy Only	2856	22.2	1320	27.9
Aspiration Only	615	4.8	224	4.7
Biopsy and Aspiration	904	7.0	259	5.5
Unknown	1031	7.4	727	13.3
Menopause				
Pre	2847	23.1	1660	35.3
Post	9460	76.9	3047	64.7
Unknown	1562	11.3	748	13.7
Current hormone therapy use				
No	9146	95.4	3566	96.2
Yes	436	4.6	141	3.8
Unknown	4287	30.9	1748	32.0
Laterality of index biopsy[2]				
Left	6770	48.8	2683	49.2

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	No MRI (N, %)		MRI (N, %)	
	Overall		Overall	
Right	6936	50.0	2724	49.9
Bilateral	163	1.2	48	0.9
Index biopsy[2] year				
2005–2008	4532	32.7	591	10.8
2009–2011	3395	24.5	1425	26.1
2012–2014	3447	24.9	1812	33.2
2015–2017	2495	18.0	1627	29.8
Geo coding education				
<=Q1	3324	26.1	1288	25.8
Q1 – Q2	3515	27.6	1228	24.6
Q2 – Q3	3296	25.9	1393	27.9
> Q3	2593	20.4	1075	21.6
Unknown	1141	8.2	471	8.6
Index biopsy[2]				
DCIS	3103	22.4	1049	19.2
Invasive[3]	10766	77.6	4406	80.8
Mode of Detection[4]				
Screen Detected	8754	64.3	3178	59.1
Interval Detected	2759	20.3	1303	24.3
Clinically Detected	2102	15.4	892	16.6
Unknown Mode	254	1.8	82	1.5
Breast Density				
Almost entirely fat	1442	10.4	284	5.2
Scattered fibroglandular	5996	43.2	1745	32.0
Heterogeneously dense	5347	38.6	2622	48.1
Extremely dense	1084	7.8	804	14.7
Histology Type				
DCIS	3103	28.8	1049	23.5
Invasive, Ductal	6741	62.5	2813	63.1
Invasive, Lobular	733	6.8	521	11.7
Invasive, Ductal & Lobular	210	1.9	73	1.6
Unknown	3082	22.2	999	18.3
Surgery Type				
Lumpectomy	9787	70.6	3250	59.6
Mastectomy	4082	29.4	2205	40.4
All	13869		5455	

[1] Preoperative MRI was defined as any MRI completed between index biopsy and the definitive surgery

[2]Index biopsy was defined as the biopsy associated with the pathologically-determined breast cancer diagnosis of invasive breast cancer or ductal carcinoma in situ.

[3]Invasive cancer includes lobular invasive, ductal invasive, and other invasive.

[4]Mode of detection is as follows: Screen detected: cancer detected within 12 months of a positive screening mammogram; Interval detected: cancer detected cancer within 27 months of a prior negative screening exam; Clinically detected: Cancer detected on a diagnostic exam with no mammogram in prior 27 months.

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Table 2.

Summary of additional biopsies and biopsy outcomes in relation to pre-operative imaging modality overall and by breast density among a cohort of women with a recent breast cancer diagnosis (N=19,324).

	BIRADS Density				
	Overall	**a: Almost entirely fatty**	**b: Scattered fibroglandular**	**c: Hetero-genously dense**	**d: Extremely dense**
No MRI	13869	1442	5996	5347	1084
MRI	5455	284	1745	2622	804
Additional Biopsy (N, %)					
Any laterality					
No MRI	711 (5.1)	44 (3.1)	286 (4.8)	310 (5.8)	71 (6.5)
MRI	1232 (22.6)	46 (16.2)	318 (18.2)	648 (24.7)	220 (27.4)
Additional Cancer (N, %)					
Any laterality					
No MRI	356 (2.6)	22 (1.5)	158 (2.6)	141 (2.6)	35 (3.2)
MRI	540 (9.9)	25 (8.8)	158 (9.1)	274 (10.5)	83 (10.3)
Ipsilateral					
No MRI	303 (2.2)	19 (1.3)	140 (2.3)	114 (2.1)	30 (2.8)
MRI	414 (7.6)	13 (4.6)	119 (6.8)	214 (8.2)	68 (8.5)
Contralateral					
No MRI	51 (0.4)	3 (0.2)	15 (0.3)	28 (0.5)	5 (0.5)
MRI	136 (2.5)	13 (4.6)	45 (2.6)	66 (2.5)	12 (1.5)
Surgery (N, %)					
Mastectomy as definitive surgery					
No MRI	4082 (29.4)	350 (24.3)	1486 (24.8)	1784 (33.4)	462 (42.6)
MRI	2205 (40.4)	104 (36.6)	555 (31.8)	1137 (43.4)	409 (50.9)

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Table 3.

Adjusted rates* (per 100 women) for additional biopsies and biopsy outcomes (per 100 women) in relation to pre-operative imaging modality using inverse weighted probability regression methods among a cohort of women with breast cancer (N=19,324) stratified by BIRADS breast density categories.

	BIRADS Density			
	a: Almost entirely fatty	**b: Scattered fibroglandular**	**c: Heterogenously dense**	**d: Extremely dense**
	Adjusted Rate (95% Confidence Interval)			
Additional Biopsies				
No MRI	3.3 (2.3,4.3)	4.9 (4.3,5.5)	5.4 (4.8,6)	5.2 (3.9,6.6)
MRI	16.8 (11.3,22.2)	20.6 (17.9,23.3)	23.6 (21.4,25.9)	25.6 (21.7,29.6)
Additional Cancer Detected				
No MRI	1.5 (0.9,2.2)	2.6 (2.2,3.0)	2.4 (2.0,2.9)	2.4 (1.6,3.3)
MRI	8.4 (4.4,12.4)	9.5 (7.7,11.4)	10.5 (8.9,12.2)	8.8 (6.5,11.1)
Additional Cancer (Ipsilateral)				
No MRI	1.4 (0.8,2.0)	2.4 (2.0,2.8)	1.9 (1.5,2.2)	2.0 (1.3,2.8)
MRI	4.7 (1.5,8.0)	6.8 (5.4,8.3)	8.1 (6.6,9.6)	6.7 (4.7,8.6)
Additional Cancer (Contralateral)				
No MRI	0.2 (0,0.5)	0.2 (0.1,0.3)	0.6 (0.4,0.8)	0.4 (0,0.8)
MRI	3.9 (1.5,6.3)	2.5 (1.5,3.4)	2.7 (1.9,3.5)	1.4 (0.6,2.2)
Mastectomy				
No MRI	26.9 (24.5,29.4)	26.6 (25.4,27.9)	33.7 (32.3,35.1)	42.3 (38.9,45.7)
MRI	39.7 (32.1,47.3)	33.1 (29.9,36.3)	41.7 (39.1,44.3)	47.1 (42.7,51.5)
Core Biopsy				
No MRI	2.5 (1.6,3.4)	3.7 (3.2,4.3)	4.8 (4.2,5.4)	4.3 (3.1,5.6)
MRI	16.8 (11.3,22.2)	19.6 (16.9,22.3)	22.3 (20.1,24.4)	23.1 (19.5,26.7)
Surgical Biopsy				
No MRI	0.3 (0,0.6)	0.6 (0.4,0.8)	0.4 (0.3,0.6)	1.1 (0.3,2.0)
MRI	0.2 (0,1.6)	0.6 (0.1,1.0)	0.6 (0.2,1.0)	1.6 (0.3,6.8)

*Rates are from weighted logistic regression model adjusting by age and propensity score model weights that include registry, age, race/ethnicity, education, previous breast biopsy, breast density, menopausal status, index cancer type, mode of detection of index cancer and year of diagnosis.

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Table 4.

Adjusted rates[*] (per 100 women) for biopsy outcomes in relation to pre-operative imaging modality using inverse weighted probability regression methods among women who had an additional biopsy (N=1,943) stratified by BIRADS breast density categories.

	BIRADS Density			
	a: Almost entirely fatty	**b: Scattered fibroglandular**	**c: Hetero-genously dense**	**d: Extremely dense**
	Adjusted Rate (95% Confidence Interval)			
Additional Cancer Detected				
No MRI	45.0 (30.1,59.8)	53.7 (47.4,59.9)	45.3 (39.4,51.3)	45.1 (32.6,57.5)
MRI	50.6 (32.8,68.4)	46.3 (39,53.6)	44.2 (39.1,49.3)	35.0 (27.0,43.0)
Additional Cancer (Ipsilateral)				
No MRI	42.0 (26.9,57.1)	48.6 (42.3,54.9)	34.8 (29.3,40.4)	38.1 (26.1,50.0)
MRI	28.2 (11.5,44.9)	33.3 (26.8,39.8)	34.3 (29.3,39.4)	26.2 (19.1,33.4)
Additional Cancer (Contralateral)				
No MRI	3.9 (1.2,12.2)	4.6 (2.3,6.9)	11.2 (7.1,15.4)	6.9 (1,12.9)
MRI	20.7 (8.1,33.3)	11.6 (7.6,15.6)	10.8 (7.6,13.9)	5.3 (2.2,8.4)

[*] Rates are from weighted logistic regression model adjusting by age and propensity score model weights that include registry, age, race/ethnicity, education, previous breast biopsy, breast density, menopausal status, index cancer type, mode of detection of index cancer and year of diagnosis.