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EPIDEMIOLOGY

Accuracy of screening mammography in women with a history of lobular carcinoma in situ or atypical hyperplasia of the breast

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Abstract Women with lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH), or atypical hyperplasia (AH) are at increased breast cancer (BC) risk. We investigated the accuracy and outcomes of mammography screening in women with histology-proven LCIS, ALH, ADH, or AH history who had screening through Breast Cancer Surveillance Consortium-affiliated mammography facilities. Screens from two cohorts, defined by LCIS/ALH or ADH/AH history, were compared to two cohorts without such history mammogram-matched for age-group, breast density, family history, screen-year, and mammography registry. Overall 359 BCs (277 invasive BC) occurred within 1 year from screening among 52,380 screens. In the LCIS/ALH cohort [versus comparator screens] cancer incidence rates, cancer detection rates (CDR), and interval cancer rates (ICR) were significantly higher (all $P < 0.001$); although ICR was 4.4/1,000 screens [versus 0.9/1,000; $P < 0.001$] the proportion that were interval cancers did not differ between compared cohorts ($P = 0.43$); screening sensitivity was 76.1 % [versus 82.3 %; $P = 0.43$], however, specificity was significantly lower at 85.1 % [versus 90.7 %; $P < 0.0001$]. In the ADH/AH cohort [versus comparator] cancer rates and CDR were significantly higher ($P < 0.001$); although ICR was 2.6/1,000 screens [versus 0.9/1,000; $P = 0.002$] the proportion that were interval cancers did not differ between cohorts ($P = 0.74$); screening sensitivity was 81.0 % [versus 82.6 %; $P = 0.74$] and specificity was lower at 86.2 % [versus 90.2 %; $P < 0.0001$]. Mammography screening sensitivity in LCIS/ALH and ADH/AH cohorts did not significantly differ from that of matched screens, however, specificity was lower, and ICRs were higher (reflecting underlying cancer rates). Adjunct screening may be of value in these women if it reduces ICR without substantially reducing specificity.

Keywords Mammography · High-risk screening · Interval cancer · Lobular carcinoma in situ · Atypical hyperplasia

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Background

Screening women at increased risk of breast cancer (BC) has been an area of intense research and has evolved in practice with MRI screening as an adjunct to mammography for some high-risk groups [1, 2]. Research in screening high-risk women has largely focused on women with BC gene mutations and/or those with a family history of BC [1, 2]. Women with biopsy-proven lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), or atypical ductal hyperplasia (ADH) have an increased risk of BC [3–8]. Risk in women with LCIS is approximately 2–10 times that of women without proliferative lesions on biopsy [3, 7], and for atypical hyperplasia (AH) that includes ADH or ALH the risk is 3–6 times higher than women without proliferative breast disease history [4–6, 9]. BC risk associated with LCIS or AH may be modified by factors such as family history [5] but is independent of mammographic density [4]. Despite the long-documented increased BC risk in women with a history of proliferative breast lesions, accuracy of mammography screening in women with previous LCIS or AH has received little research attention.

A few studies have examined MRI accuracy in screening women with previous LCIS [10, 11], and LCIS or AH [12]—these have focused on the incremental detection of MRI but have also indicated low mammography sensitivity [10–12]. In the largest study of screening women with LCIS (reporting 17 cancers in 14 women), mammography sensitivity approximated 30 % [10]. However, it is unknown whether this represents mammography screening accuracy in LCIS women, or whether it represents mammography accuracy in those selected to adjunct MRI due to other factors associated with reduced mammography sensitivity. For example, Port et al. [12] examined MRI screening in women with LCIS or AH history, and found that those selected to MRI screening were more likely to be younger women or to have a family history of BC.

Because of their increased risk of BC, and given the lack of evidence on the outcomes of mammography screening in women with a history of LCIS or AH as well as the interest in adjunct screening for these women, we examined the accuracy and outcomes of screening mammography in women with LCIS or AH history relative to matched women without such history.

Methods

We identified all women with a history of histology-proven LCIS, ALH, ADH, or AH (not further specified) who participated in screening mammography in facilities affiliated with one of the seven mammography registries forming the National Cancer Institute-funded Breast Cancer Surveillance Consortium (BCSC) [13]. BCSC registries collect demographic and mammography information linked with state or Surveillance Epidemiology and End Results (SEER) cancer registries to ascertain BC diagnoses; five registries additionally collect pathology data. Each registry and BCSC Statistical Coordinating Center (SCC) received institutional review board approval for active or passive consenting processes or consent waiver to enroll women, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant and all registries and SCC received a Federal Certificate of Confidentiality and other protections for identities of women, physicians, and facilities who are subjects of this research

Screening mammograms (1996–2010) from women with LCIS, ALH, ADH, or AH based on surgery, excision biopsy, or core-needle biopsy, were included except for diagnoses with subsequent BC within 12 months. This exclusion avoids core-needle histology diagnoses of atypical lesions that represented underestimates of BC [14]. We also excluded women having mammograms for symptom evaluation, based on information from the radiologist or self-reported symptoms, and women with a personal history of BC. Definition of screening mammography was based on standard BCSC definition [15, 16], except that unilateral screens from women with LCIS/ALH or ADH/AH (and without BC history) who received mastectomy for their high-risk histology, were included (see "Sensitivity analysis" section).

Based on the above-defined eligibility criteria we assembled two cohorts of women at increased BC risk defined by histology: one cohort combined LCIS and ALH ("lobular neoplasias"), and another cohort comprising ADH and other AHs ('ADH/AH cohort') that included predominantly ADH but also mixed ADH/ALH, AH not further specified, and rare forms of AH.

Comparator cohorts

We assembled two cohorts of asymptomatic women without a history of LCIS, ALH, ADH, AH, or surgical biopsy (to ensure that comparison screens did not have a history of atypical lesions), matched at the mammogram level on a 5:1 ratio to each screen from our high-risk cohorts. Screens were matched for 5-year age-groups, breast density category, BC family history, year of screen, and mammography registry.

Demographic and mammogram characteristics

Age, self-reported race/ethnicity, first-degree family history of BC, menopausal status, time since last mammogram, and self-reported use of HRT or use of chemoprevention agents

(such as tamoxifen) were collected at time of screening. BI-RADS [17] breast density was routinely recorded.

Outcomes

A positive screening mammogram was an initial BI-RADS assessment 0, 4, 5, or 3 with recommendation for immediate follow-up. A negative mammogram was BI-RADS 1, 2, or 3 with no recommendation for immediate follow-up. For each cohort, we determined screening accuracy [sensitivity, specificity, recall rate, positive predictive value (PPV)], and screening outcomes (cancer detection and interval cancer rates). Frequency of recommendation for surgical consult/biopsy was based on final assessments and recommendations made within 90 days of initial assessment. Outcomes were ascertained at 1 year from screening or prior to the next screen (whichever occurred first) through linkage to SEER registries or regional cancer registries and also to pathology records to determine (invasive or in situ) cancer status based on clinical pathology reports. Central pathology review was not performed. LCIS was not considered a malignant outcome.

Statistical analyses

Characteristics of screening mammograms and BCs (total observed, total invasive) were summarized for each cohort. We calculated accuracy measures using BCSC definitions [15, 16], and estimated cancer incidence rates, cancer detection rate (CDR), and interval cancer rates (per 1,000 screens) at 1-year follow-up, for each cohort. Accuracy and outcome measures were compared between the LCIS/ALH and the ADH/AH cohorts with the matched comparator group. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated for each cohort relative to its comparator, using logistic regression, both unadjusted and adjusted for year of screen, age-group, BC family history, breast density, and time since last mammogram. For specificity, we accounted for potential correlation among mammograms on the same woman using GEE with an independent correlation structure and empirical standard errors.

Sensitivity analysis

For the ADH/AH cohort, sensitivity analysis for outcome measures excluded screens from women with unspecified or rare types of AH. We also examined outcomes after excluding 36 screens from women with unilateral mastectomy for atypical lesions.

Results

Table 1 summarizes the characteristics of the 52,380 included screening mammograms and 359 cancers (277 invasive), by history of LCIS/ALH, ADH/AH, and matched cohorts. Given that we matched screens for several variables, the main notable difference in distribution of characteristics was that women in the high-risk ("atypia") cohorts were more likely to have a shorter time-interval since the last mammogram than their comparator cohort. In the LCIS/ALH group, 19 cancers (17 invasive) occurred on the same-side as the previously affected breast, 25 cancers (18 invasive) affected the contralateral breast, and 2 were bilateral invasive BC (in women with unilateral LCIS/ALH history). In the ADH/AH group, 49 cancers (33 invasive) occurred on the same-side as that previously affected, 28 cancers (19 invasive) were in the contralateral breast, and 7 were bilateral invasive BC (in women with unilateral ADH/AH history).

LCIS/ALH cohort

Table 2 reports outcomes for the 2,505 LCIS/ALH screens, and matched cohort (12,525 screens). Cancer rates and CDR were significantly higher ($P < 0.0001$) for LCIS/ALH screens than comparator screens: cancer rates indicate an approximate four-time increased risk of BC for the LCIS/ALH cohort. Interval cancer rates were 4.4/1,000 screens for LCIS/ALH cohort compared with 0.9/1,000 for matched screens ($P = 0.0003$); however, the proportion of cancers that were interval cancers did not significantly differ between the two cohorts ($P = 0.43$). Screening sensitivity of 76.1 % in the LCIS/ALH cohort was not significantly different from a sensitivity of 82.3 % in the matched cohort ($P = 0.43$) but a specificity of 85.1 % in the LCIS/ALH cohort was significantly lower than that of 90.7 % in the matched cohort ($P < 0.0001$). Recall rates, PPV, and the percentage recommended for surgical consultation were all higher for LCIS/ALH screens compared with matched screens ($P \leq 0.001$). Table 2 shows the (unadjusted or simple) ORs for the LCIS/ALH cohort relative to matched cohort, and also the adjusted ORs (see "Methods" section for variables included in adjustment). The adjusted ORs did not substantially differ from the simple ORs and did not alter the statistical associations shown in Table 2, except that the adjusted OR for DCIS detection rate showed weaker evidence of a difference compared to the matched cohort ($P = 0.10$). Other changes noted from the adjusted analysis were a slightly lower OR for interval cancer rates (adjusted OR = 4.47; $P = 0.013$) and a higher OR for sensitivity (adjusted OR = 1.10; $P = 0.90$) relative to the simple ORs. The latter reflects

Table 1 Distribution of characteristics of screening mammograms and cancers within 1 year of screen, in women with a history of LCIS/ALH, or ADH/AH, and matched screens without such history

	Women with LCIS/ALH history (2,505 screens in 824 women)		Matched women without LCIS/ALH or ADH/AH[a] history (12,525 screens in 12,394 women)		Women with ADH/AH[a] history (6,225 screens in 1,743 women)		Matched women without ADH/AH[a] or LCIS/ALH history (31,125 screens in 29,642 women)	
	Number of screening mammograms (%)	Number of cancers[b] [number invasive]	Number of screening mammograms (%)	Number of cancers[b] [number invasive]	Number of screening mammograms (%)	Number of cancers[b] [number invasive]	Number of screening mammograms (%)	Number of cancers[b] [number invasive]
All screening examinations	2,505	46 [37]	12,525	62 [46]	6,225	84 [59]	31,125	167 [135]
Age at mammography, years								
18–39	26 (1.0)	0 [0]	130 (1.0)	0 [0]	70 (1.1)	2 [1]	350 (1.1)	0 [0]
40–49	394 (15.7)	5 [4]	1,970 (15.7)	4 [0]	981 (15.8)	14 [6]	4,905 (15.8)	17 [13]
50–59	966 (38.6)	11 [8]	4,830 (38.6)	17 [13]	2,206 (35.4)	31 [25]	11,030 (35.4)	46 [33]
60–69	628 (25.1)	11 [8]	3,140 (25.1)	22 [18]	1,641 (26.4)	22 [13]	8,205 (26.4)	52 [43]
70–79	370 (14.8)	13 [11]	1,850 (14.8)	13 [11]	1,026 (16.5)	12 [11]	5,130 (16.5)	38 [36]
80+	121 (4.8)	6 [6]	605 (4.8)	6 [4]	301 (4.8)	3 [3]	1,505 (4.8)	14 [10]
Race/ethnicity								
White, non-Hispanic	1,875 (77.9)	39 [33]	8,897 (75.4)	45 [36]	5,057 (85.6)	69 [48]	25,430 (87.0)	146 [121]
Black, non-Hispanic	99 (4.1)	0 [0]	462 (3.9)	6 [3]	266 (4.5)	4 [2]	1,144 (3.9)	6 [4]
Hispanic	275 (11.4)	3 [1]	1,317 (11.2)	6 [3]	387 (6.5)	4 [4]	1,628 (5.6)	6 [4]
Asian	97 (4.0)	3 [2]	808 (6.9)	1 [1]	66 (1.1)	0 [0]	457 (1.6)	0 [0]
Other	62 (2.6)	1 [1]	308 (2.6)	0 [0]	135 (2.3)	3 [1]	559 (1.9)	3 [2]
Missing	97	0 [0]	733	4 [3]	314	4 [4]	1,907	6 [4]
First-degree family history of BC								
No	1,767 (79.0)	26 [19]	8,835 (79.0)	37 [28]	4,632 (77.1)	58 [39]	23,196 (77.1)	109 [87]
Yes	471 (21.0)	14 [13]	2,355 (21.0)	16 [10]	1,378 (22.9)	25 [19]	6,899 (22.9)	55 [45]
Missing	267	6 [5]	1,335	9 [8]	215	1 [1]	1,030	3 [3]
Ever given birth								
No	312 (18.4)	7 [5]	1,604 (19.1)	12 [8]	517 (12.1)	7 [4]	2,894 (13.3)	16 [13]
Yes	1,381 (81.6)	28 [22]	6,805 (80.9)	30 [23]	3,761 (87.9)	51 [36]	18,832 (86.7)	110 [90]
Missing	812	11 [10]	4,116	20 [15]	1,947	26 [19]	9,399	41 [32]
Menopausal status								
Pre/Peri	390 (18.4)	6 [4]	1,855 (17.6)	4 [2]	947 (17.8)	16 [10]	5,308 (19.4)	18 [14]
Post	1,726 (81.6)	36 [30]	8,685 (82.4)	51 [40]	4,383 (82.2)	54 [41]	22,072 (80.6)	139 [114]
Missing	389	4 [3]	1,985	7 [4]	895	14 [8]	3,745	10 [7]
BI-RADS breast density								
Almost entirely fatty	96 (5.5)	0 [0]	483 (5.5)	1 [1]	314 (5.7)	2 [2]	1,570 (5.7)	4 [3]
Scattered fibroglandular tissue	589 (33.5)	9 [5]	2,947 (33.5)	12 [7]	2,149 (38.9)	22 [16]	10,745 (38.9)	50 [44]
Heterogeneously dense	883 (50.3)	19 [17]	4,415 (50.2)	21 [14]	2,641 (47.8)	36 [23]	13,205 (47.8)	80 [61]

Table 1 continued

	Women with LCIS/ALH history (2,505 screens in 824 women)		Matched women without LCIS/ALH or ADH/AH[a] history (12,525 screens in 12,394 women)		Women with ADH/AH[a] history (6,225 screens in 1,743 women)		Matched women without ADH/AH[a] or LCIS/ALH history (31,125 screens in 29,642 women)	
	Number of screening mammograms (%)	Number of cancers[b] [number invasive]	Number of screening mammograms (%)	Number of cancers[b] [number invasive]	Number of screening mammograms (%)	Number of cancers[b] [number invasive]	Number of screening mammograms (%)	Number of cancers[b] [number invasive]
Extremely dense	189 (10.8)	3 [3]	945 (10.8)	3 [2]	421 (7.6)	12 [10]	2,105 (7.6)	9 [6]
Missing	748	15 [12]	3,735	25 [22]	700	12 [8]	3,500	24 [21]
Time since last mammogram								
No prior mammogram	–	–	317 (2.8)	2 [2]	–	–	660 (2.2)	5[4]
9–18 months	2,064 (86.5)	36 [30]	7,530 (65.6)	38 [28]	5,210 (85.3)	64 [45]	20,018 (67.9)	98 [81]
19–30 months	229 (9.6)	3 [3]	2,252 (19.6)	14 [9]	642 (10.5)	15 [11]	5,659 (19.2)	25 [20]
31+ months	94 (3.9)	2 [1]	1,382 (12.0)	4 [3]	257 (4.2)	2 [1]	3,133 (10.6)	26 [19]
Missing	118	5 [3]	1,044	4 [4]	116	3 [2]	1,655	13 [11]
Current use of HRT								
No	1,698 (83.4)	29 [24]	7,810 (75.6)	30 [18]	4,739 (82.9)	68 [46]	23,260 (80.7)	126 [100]
Yes	339 (16.6)	6 [4]	2,514 (24.4)	15 [13]	978 (17.1)	8 [7]	5,580 (19.3)	29 [24]
Missing	468	11 [9]	2,201	17 [15]	508	8[6]	2,285	12 [11]
Self-reported current use of chemoprevention[c]								
No	1,658 (95.8)	26 [20]	8,459 (99.6)	37 [24]	4,691 (97.3)	68 [47]	23,891 (99.6)	129 [102]
Yes	72 (4.1)	0 [0]	37 (0.4)	0 [0]	132 (2.7)	1 [1]	105 (0.4)	0 [0]
Missing	775	20 [17]	4,029	25 [22]	1,402	15 [11]	7,129	38 [33]
Time since diagnosis of LCIS/ALH, ADH/AH[d]			NA (not applicable)	NA			NA	NA
<3 years	654 (26.1)	8 [7]			1,954 (31.4)	29 [21]		
3–5 years	864 (34.5)	17 [13]			2,344 (37.7)	27 [19]		
6–8 years	529 (21.1)	10 [9]			1,257 (20.2)	17 [10]		
9–11 years	232 (9.3)	6 [5]			550 (8.8)	8 [7]		
≥12 years	226 (9.0)	5 [3]			120 (1.9)	3 [2]		

[a] ADH/AH includes atypical ductal hyperplasia (ADH) and atypical hyperplasia (AH) comprising mixed ADH/ALH and other (or unspecified) forms of AH

[b] Total number of invasive or in situ cancers [number of invasive cancers shown in square-bracket]

[c] Current use of agents such as Tamoxifen or Raloxifene for chemoprevention (data for 'Yes' were mostly Tamoxifen or type not specified)

[d] Years since diagnosis based on first occurrence of LCIS, ALH, ADH, or AH

Table 2 Accuracy and outcomes of mammography screening in women with a history of LCIS or ALH relative to matched mammograms in women without such history

Measure of accuracy or outcome	Women with LCIS or ALH history [2,505 screens[a] in 824 women] (95 % CI)	Matched women without LCIS/ALH/ADH/AH history [12,525 screens in 12,394 women] (95 % CI)	Odds ratio (OR) (95 % CI)	*P* value[b]	Adjusted OR[c] (95 % CI)
Number of screening mammograms	2,505	12,525			
Number of (in situ or invasive) breast cancers	46	62			
Cancer rate/1,000 mammograms	18.4 (13.5–24.4)	5.0 (3.8–6.3)	3.76 (2.55–5.51)	<.0001	3.88 (2.28–6.55)
Number of cancers detected on screening	35	51			
Cancer detection rate (CDR)/ 1,000 mammograms	14.0 (9.8–19.4)	4.1 (3.0–5.4)	3.47 (2.23–5.32)	<.0001	3.72 (2.04–6.69)
DCIS detection rate	3.6 (1.6–6.8)	1.1 (0.6–1.9)	3.22 (1.34–7.35)	0.0103	2.64 (0.81–7.62)
Invasive cancer detection rate	10.4 (6.8–15.2)	3.0 (2.1–4.1)	3.54 (2.12–5.83)	<.0001	4.30 (2.10–8.73)
Number of interval cancers	11	11			
Interval cancer rate (ICR)/ 1,000 mammograms	4.4 (2.2–7.8)	0.9 (0.4–1.6)	5.02 (2.15–11.73)	0.0003	4.47 (1.39–14.37)
Percentage of cancers that are interval cancers %	23.9 (12.6–38.8)	17.7 (9.2–29.5)	1.46 (0.56–3.77)	0.4329	0.91 (0.19–4.10)
Sensitivity %	76.1 (61.2–87.4)	82.3 (70.5–90.8)	0.69 (0.27–1.77)	0.4329	1.10 (0.24–5.28)
Specificity %	85.1 (83.6–86.5)	90.7 (90.2–91.2)	0.58 (0.51–0.67)	<.0001	0.58 (0.49–0.70)
Recall rate %	16.0 (14.6–17.5)	9.7 (9.1–10.2)	1.79 (1.58–2.02)	<.0001	1.79 (1.52–2.09)
Positive predictive value %	8.7 (6.1–11.9)	4.2 (3.2–5.5)	2.17 (1.38–3.37)	0.001	2.18 (1.16–4.01)
Percentage recommended for surgical consult %	4.0 (3.3–4.9)	1.3 (1.1–1.6)	3.13 (2.42–4.04)	<.0001	3.59 (2.60–4.95)

[a] Sensitivity analysis excluding 26 screens from women who had unilateral mastectomy (for LCIS/ALH) did not alter results

[b] *P*-values based on the likelihood ratio test comparing screens from women with LCIS/ALH history to screens from women without history of LCIS, ALH, ADH, or AH

[c] OR adjusted for variables described under "Statistical analyses" section

that there is less difference in mammography sensitivity between the LCIS/ALH and comparator cohorts after the adjustment, possibly due to allowing for differences in screening intervals (time-interval since last mammogram) between the groups.

ADH/AH cohort

Table 3 reports outcomes for the 6,225 ADH/AH screens and matched comparator (31,125 screens). Cancer rates and CDR were significantly higher ($P < 0.0001$) for the ADH/AH screens relative to matched screens: cancer rates indicate more than double the risk of BC for the ADH/AH cohort. Interval cancer rates were 2.6/1,000 screens for ADH/AH screens compared with 0.9/1,000 for matched screens ($P = 0.002$); however, the proportion of cancers that were interval cancers did not significantly differ between the two cohorts ($P = 0.74$). Screening sensitivity of 81.0 % in the ADH/AH cohort was similar to sensitivity of 82.6 % in the matched cohort ($P = 0.74$) but a specificity of 86.2 % in the ADH/AH cohort was significantly lower than that of 90.2 % in the comparator cohort ($P < 0.0001$). Recall rates, PPV, and the percentage recommended for surgical consultation were all higher for ADH/AH screens than matched screens ($P < 0.001$). A sensitivity analysis for the ADH/AH cohort that excluded 1,188 screens from women with unspecified or rare forms of AH had little to no effect on estimates of screening accuracy and outcomes. Table 3 also shows the (unadjusted/simple) ORs for the ADH/AH cohort relative to its comparator, and the adjusted ORs; the latter did not substantially differ from the (simple) ORs, and did not alter statistical associations.

Discussion

We report the first evaluation to date of the accuracy and outcomes of mammography screening in women at increased risk of BC defined by LCIS, ALH, ADH, or AH

Table 3 Accuracy and outcomes of mammography screening in women with a history of ADH or AH relative to matched mammograms in women without such history

Measure of accuracy or outcome	Women with ADH/AH history [6,225 screens[a] in 1,743 women] (95 % CI)	Matched women without ADH/AH/LCIS/ALH history [31,125 screens in 29,642 women] (95 % CI)	Odds ratio (OR) (95 % CI)	*P* value[b]	Adjusted OR[c] (95 % CI)
Number of screening mammograms	6,225	31,125			
Number of (in situ or invasive) breast cancers	84	167			
Cancer rate/1,000 mammograms	13.5 (10.8–16.7)	5.4 (4.6–6.2)	2.54 (1.94–3.29)	<.0001	2.58 (1.90–3.46)
Number of cancers detected on screening	68	138			
Cancer detection rate (CDR)/ 1,000 mammograms	10.9 (8.5–13.8)	4.4 (3.7–5.2)	2.48 (1.84–3.31)	<.0001	2.49 (1.77–3.46)
DCIS detection rate	3.5 (2.2–5.3)	1.0 (0.7–1.4)	3.56 (2.03–6.12)	<.0001	3.37 (1.78–6.22)
Invasive cancer detection rate	7.4 (5.4–9.8)	3.4 (2.8–4.2)	2.16 (1.51–3.03)	<.0001	2.20 (1.47–3.25)
Number of interval cancers	16	29			
Interval cancer rate (ICR)/ 1,000 mammograms	2.6 (1.5–4.2)	0.9 (0.6–1.3)	2.76 (1.47–5.02)	0.0022	2.97 (1.51–5.69)
Percentage of cancers that are interval cancers %	19.0 (11.3–29.1)	17.4 (11.9–24.0)	1.12 (0.56–2.18)	0.744	1.11 (0.50–2.43)
Sensitivity %	81.0 (70.9–88.7)	82.6 (76.0–88.1)	0.89 (0.46–1.79)	0.744	0.90 (0.41–2.01)
Specificity %	86.2 (85.3–87.0)	90.2 (89.9–90.6)	0.68 (0.62–0.74)	<.0001	0.65 (0.59–0.71)
Recall rate %	14.7 (13.8–15.6)	10.2 (9.8–10.5)	1.53 (1.41–1.65)	<.0001	1.59 (1.46–1.74)
Positive predictive value %	7.4 (5.8–9.3)	4.4 (3.7–5.1)	1.76 (1.29–2.36)	0.0004	1.70 (1.20–2.39)
Percentage recommended for surgical consult %	3.2 (2.8–3.7)	1.2 (1.1–1.4)	2.64 (2.21–3.14)	<.0001	2.79 (2.29–3.39)

[a] Sensitivity analysis excluding 10 screens from women who had unilateral mastectomy (for ADH/AH) did not alter results

[b] *P*-values based on the likelihood ratio test comparing screens from women with ADH/AH history to screens from women without history of LCIS, ALH, ADH, or AH

[c] OR adjusted for variables described under "Statistical analyses" section

history. Our findings from screening these women are presented in comparison to screens from women without such history, matched for variables known to affect mammography screening accuracy. Our work confirms that women with a history of these atypical lesions are at substantially increased risk of BC (relative to matched cohorts) even though risk was estimated only for 1-year follow-up from screening given that the study focused on screening accuracy. Our findings also highlight that these atypical lesions are markers of generalized (bilateral) BC risk, particularly in the LCIS/ALH cohort, as evidenced by our data on BC laterality (see "Results" section) and in keeping with the findings from other researchers [5]. The bilaterality of the observed cancers also reinforces the potential value of considering chemoprevention for management of these women, particularly the LCIS/ALH cohort, as recommended in guidelines [18]. We noted that although women in our high-risk cohorts were much more likely to report current use of chemoprevention agents (including tamoxifen, Table 1) than those in the matched cohorts, overall only a minority reported receiving chemo-prevention.

In the LCIS/ALH cohort, cancer rates, CDR, and interval cancer rates indicate approximately four-times increased risk of BC relative to the matched cohort. Despite the higher cancer rates, mammography screening did not have significantly lower sensitivity in these women relative to matched screens. Our estimated screening sensitivity of 76.1 % is inconsistent with the low mammography sensitivity (<50 %) from small studies restricted to subjects selected to adjunct screening (described in our "Background" section) [10–12]. High interval cancer rates in the LCIS/ALH cohort reflect the higher underlying cancer rates in these women, and raise the possibility that some interval cancers (conventionally defined as cancers arising after a negative mammographic screen and before the next routine screen) may have been identified through adjunct (MRI or ultrasound) screening. Whereas most interval cancers emerge as symptomatic or clinically-detected cancers, if these women are being referred for adjunct screening on the basis of their history of atypical lesions, then some cancers may have been detected through more intensive screening and would be identified as

'interval cancers' even though they may not have emerged as true interval cases in the absence of adjunct screening. Because we did not have the data on adjunct screening we cannot determine whether or not some of these interval cancers were detected through adjunct screening. We found that mammography specificity was significantly lower in the LCIS/ALH cohort than comparator cohort; other measures of screening accuracy (recalls, PPV, recommendation for surgical assessment) were also significantly higher in the LCIS/ALH cohort due in part to lower specificity but also due to higher cancer rates. We cannot compare our findings to those from other studies because we did not identify any studies investigating the accuracy of mammography screening in unselected women with a history of these atypical lesions. Of note, a recent study of 776 women with a history of LCIS reported that there were no differences in crude CDRs among women who had annual mammography with clinical examination for screening and the subgroup that also had adjunct MRI screening [19].

The pattern of findings for the ADH/AH cohort relative to its matched comparator was generally similar to that outlined above for the LCIS/ALH cohort, except that the underlying risk of BC in the ADH/AH cohort was approximately 2.5-times that of its comparator cohort. CDR and interval cancer rates were significantly higher in the ADH/AH cohort relative to its comparator, reflecting higher underlying BC rates in the ADH/AH cohort and again raising the possibility that adjunct screening may have contributed to higher interval cancer rates. Mammography screening in the ADH/AH cohort had similar sensitivity to that estimated for the matched cohort; here our findings again contradict the low mammography sensitivity suggested in studies of subjects selected to adjunct screening [10–12, 19]. Mammography specificity was significantly lower in the ADH/AH cohort (relative to comparator) and recall rates, PPV, and recommendation for surgical review were also higher in the ADH/AH cohort, due to the combination of lower specificity and higher underlying cancer rates.

The lower mammography screening specificity in the LCIS/ALH and ADH/AH cohorts relative to matched screens may be partly due to the vast majority of women with these atypical lesions having had surgical biopsy, whereas the comparator group included women without a biopsy history. A history of surgical biopsy is associated with lower mammography specificity [20], hence a limitation of our study is that we cannot differentiate the effect from these histological markers, as opposed to that from surgical biopsy history, in contributing to relatively lower screening specificity in the cohorts with a history of atypical lesions. It is also possible that knowledge of the woman's history of an atypical lesion leads radiologists to adopt a lower threshold for recommending further (potentially unnecessary) testing and biopsy hence leading to lower specificity. Another study limitation (outlined above) is that we did not have information on whether some interval cancers were detected through adjunct screening of women with history of atypical lesions. Some might argue that 1-year follow-up from screening could lead to relatively modest risk estimates in our LCIS/ALH and ADH/AH women; however, we emphasize that our study focused on screening outcomes (not risk calculation) hence 1-year follow-up was appropriate for the aim of our research.

Although the relatively high interval cancer rates in the LCIS/ALH and ADH/AH cohorts raise concern, our findings should not be taken as inference of recommendation for or against adjunct screening of women with a history of these lesions. Our study primarily establishes mammography screening accuracy in women with a history of LCIS/ALH or ADH/AH using methods that avoid selection bias, and reports these estimates in the context of matched screening participants. The high interval cancer rates in both LCIS/ALH and ADH/AH cohorts appear to be predominantly due to higher underlying cancer rates, because the proportion of cancers that were interval BC did not statistically differ from that in the matched cohorts, and screening sensitivity was not significantly lower in our high-risk cohorts. Importantly, our results suggest that incremental BC detection from adjunct screening for other high-risk cohorts (for example gene mutation carriers) where mammography sensitivity is very low [1, 2] cannot be extrapolated to LCIS/ALH or ADH/AH women in whom mammography screening has adequate sensitivity evidenced by our study findings. Given the high interval cancer rates, we suggest that adjunct screening may be of value in women with LCIS/ALH or ADH/AH history if it can be shown to reduce interval cancer rates. Because of the relatively lower specificity and higher recall rates in the LCIS/ALH and the ADH/AH cohorts, it will be particularly important to examine the impact on specificity and on recall and biopsy rates of introducing adjunct screening in these women.

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Conflicts of interest None.

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