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Automated and Clinical Breast Imaging Reporting and Data System Density Measures Predict Risk of Screen-Detected and Interval Cancers

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Abstract

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Background: In 30 states, women who have had screening mammography are informed of their breast density on the basis of Breast Imaging Reporting and Data System (BI-RADS) density categories estimated subjectively by radiologists. Variation in these clinical categories across and within radiologists has led to discussion about whether automated BI-RADS density should be reported instead.

Objective: To determine whether breast cancer risk and detection are similar for automated and clinical BI-RADS density measures.

Design: Case-control.

Setting: San Francisco Mammography Registry and Mayo Clinic.

Participants: 1609 women with screen-detected cancer, 351 women with interval invasive cancer, and 4409 matched control participants.

Measurements: Automated and clinical BI-RADS density assessed on digital mammography at 2 time points from September 2006 to October 2014, interval and screen-detected breast cancer risk, and mammography sensitivity.

Results: Of women whose breast density was categorized by automated BI-RADS more than 6 months to 5 years before diagnosis, those with extremely dense breasts had a 5.65-fold higher interval cancer risk (95% CI, 3.33 to 9.60) and a 1.43-fold higher screen-detected risk (CI, 1.14 to 1.79) than those with scattered fibroglandular densities. Associations of interval and screen-detected cancer with clinical BI-RADS density were similar to those with automated BI-RADS density, regardless of whether density was measured more than 6 months to less than 2 years or 2 to 5 years before diagnosis. Automated and clinical BI-RADS density measures had similar discriminatory accuracy, which was higher for interval than screen-detected cancer (C-statistics: 0.70 vs. 0.62 [$P < 0.001$] and 0.72 vs. 0.62 [$P < 0.001$], respectively). Mammography sensitivity was similar for automated and clinical BI-RADS categories: fatty, 93% versus 92%; scattered fibroglandular densities, 90% versus 90%; heterogeneously dense, 82% versus 78%; and extremely dense, 63% versus 64%, respectively.

Limitation: Neither automated nor clinical BI-RADS density was assessed on tomosynthesis, an emerging breast screening method.

Conclusion: Automated and clinical BI-RADS density similarly predict interval and screen-detected cancer risk, suggesting that either measure may be used to inform women of their breast density.

Thirty states have laws requiring that women receive some level of notification of breast density (1). The Breast Imaging Reporting and Data System (BI-RADS) breast density categories (2), estimated subjectively by radiologists, is the standard for reporting breast density in the United States. Language regarding notification varies by state, with 10 states providing BI-RADS density information to all women and 20 notifying only those whose breasts are categorized as dense (heterogeneously or extremely dense). About 50% of women who have screening mammography have dense breasts (3–5), which may result in decreased cancer detection and increased cancer risk, leading several states to advise women to talk to their providers about whether supplemental screening is right for them (3).

Concern has been raised about using clinical BIRADS breast density for prevention strategies, calling into question the subjectivity and reproducibility of the measure for individual women. Recent studies of interand intrarater reliability of the BI-RADS categories have reported moderate to substantial agreement (6–9). In clinical practice, 17.2% of women with consecutive mammograms interpreted by different radiologists had discordant BI-RADS density ratings of dense versus nondense, compared with 10.0% who had consecutive mammograms interpreted by the same radiologist (10). The variation in BI-RADS density interpretations within and across radiologists has clinical implications, because breast density assessment may lead to recommendations for supplemental imaging (3), affect risk assessment (11), and guide screening frequency (12).

Automated breast density measures are available with commercial software (Quantra [Hologic], Volpara [Volpara Solutions], PowerLook Density Assessment [iCAD]) to assess automated BI-RADS and volumetric density on digital mammography. Studies have shown that automated and clinical BI-RADS density measures have similar associations with overall cancer risk (13–15). One study conducted in the Netherlands examined whether automated breast density measured with Vol para software predicts cancer detection, defining interval cancer as invasive cancer occurring within 24 months of a negative screening result (15). Wanders and colleagues (15) found that automated dense breast volume, percentage of dense volume, and BI-RADS density were more strongly associated with interval than screen-detected cancer, compared with women who did not develop breast cancer. No study has examined whether automated and clinical BI-RADS density measures similarly predict screen-detected and interval invasive breast cancer risk compared with women who do not develop breast cancer. If automated BI-RADS density measures, which are reportedly more reproducible than clinical measures on repeated examinations (16, 17), can accurately predict cancer detection, automated breast density assessment might be used more widely for breast cancer prevention strategies.

We determined screen-detected and interval invasive breast cancer risk and mammography sensitivity for clinical and automated BI-RADS density measures according to the length of time between density assessment and breast cancer diagnosis.

METHODS

Study Sample

Study participants were from 2 case-control studies nested within large prospective breast imaging cohorts. The San Francisco Mammography Registry (SFMR) participates in the National Cancer Institute-funded Breast Cancer Surveillance Consortium (BCSC) (http://www.bcsc-research.org/index.html) (18). The SFMR obtains annual institutional review board approval and passive permission for data collection and participant enrollment, as well as data linkages for research purposes, and received a federal Certificate of Confidentiality that protects the identities of research participants. For the Mayo Clinic screening cohort, the institutional review board approved a waiver of informed consent and Health Insurance Portability and Accountability Act authorization from the participants. Only persons who had not refused permission to use their medical records for research (according to Minnesota Research Authorization) were included in the Mayo Clinic cohort (19).

The SFMR obtained “for-processing” digital screening examinations from Hologic Selenia machines at 4 facilities since 2006, which served as the underlying imaging cohort. Annual linkage to the California Cancer Registry identified cases of incident invasive breast cancer reported from January 2007 through May 2014. Raw digital screening examinations performed more than 6 months to 5 years before diagnosis (n = 1312) were included for case participants. Two control participants (n = 2603) without previous breast cancer or breast implants were selected from the SFMR imaging cohort and matched to each case participant by age within 5 years, race, date of screening examination within 1 year, mammography machine, and facility. For the Mayo Clinic cohort, for-processing digital images were collected from women in the tristate region of Minnesota, Iowa, and Wisconsin; the images were obtained from Hologic Selenia machines at 1 facility from March 2008 through September 2014. Annual linkage to the Mayo Clinic tumor registry identified cases of incident invasive breast cancer reported through December 2015 (n = 648). Approximately 3 control participants (n = 1806) without previous breast cancer or breast implants were selected from the Mayo imaging cohort and matched to each case participant by age within 5 years, race, state of residence, date of screening examination within 1 year, and mammography machine. We ensured that all control participants had at least 1 normal screening mammogram on or after their corresponding matched case participants’ diagnosis dates.

Interval cancer was defined as invasive breast cancer occurring within 12 months of a negative mammography result (BI-RADS 1 or 2). Screen-detected cancer was defined as invasive cancer occurring within 12 months of a positive mammography result (BI-RADS 0, 4, or 5).

Measurement of Risk Factors

Age, first-degree family history of breast cancer, race/ethnicity, breast biopsy history, height, and weight were obtained from self-report at the time of mammography for the SFMR cohort and from self-report or medical record review (height and weight) for the Mayo cohort. Body mass index was calculated by dividing weight in kilograms by height in square meters (kg/m^2). Race/ethnicity was coded by using the expanded definitions currently used in the SEER (Surveillance, Epidemiology, and End Results) program and U.S. vital statistics (non-Hispanic white, non-Hispanic black, Asian/ Pacific Islander, American Indian/Alaska Native, Hispanic, other/mixed race). We calculated the BCSC, version 1.0, 5-year risk score at the time of mammography, which estimates the probability of invasive breast cancer occurring within the next 5 years on the basis of age, race, ethnicity, family history, history of breast biopsy, and clinical BIRADS breast density (20).

Clinical and Automated BI-RADS Density

Practicing radiologists classified breast density as part of routine clinical practice at the time of mammography interpretation by using the BI-RADS density categories (2): (a), almost entirely fatty; (b), scattered fibroglandular densities; (c), heterogeneously dense; and (d), extremely dense.

Volpara, version 1.5.3, the most commonly used 3-dimensional density measure in clinical practice and research settings, is a fully automated method for assessing volumetric breast density. It uses the measured breast thickness and x-ray attenuations in the for-processing image to create estimates of dense and nondense tissue volume for each pixel. Summing the dense pixel volumes provides total dense breast volume. Volpara uses proprietary algorithms to calculate breast thickness and determine dense tissue volume by averaging measures of each breast. For this study, we used the dense breast volume output from the vendor-specific software for each woman, incorporating all 4 views (craniocaudal and mediolateral oblique of both breasts) of raw digital images, as done in the clinical setting. Dividing dense breast volume by total breast volume and multiplying by 100 defines volumetric percentage of density (VPD). Cut points are applied by Volpara to fractionate VPD into 4 categories analogous to BI002DRADS categories. The automated BIRADS categories, a to d, are defined as VPD that is (a), less than 4.5%; (b), 4.5% to 7.49%; (c), 7.5% to 15.49%; and (d), 15.5% or greater (21).

Breast density measures were assessed more than 6 months to 5 years before diagnosis. Mammograms were classified as more than 6 months to less than 2 years or 2 to 5 years before diagnosis. For stratified analysis, we selected mammograms 2 to 5 years before diagnosis for women with images available for both periods. We performed a sensitivity analysis for women who had examinations during both periods and found the results to be consistent with the main findings (Appendix Tables 1 and 2, available at Annals.org).

Statistical Analysis

We calculated frequency distributions of demographic characteristics and risk factors between case participants with screen-detected or interval cancer and control participants.

We used conditional logistic regression to assess the association of clinical and automated BI-RADS density with screen-detected and interval cancer. In these models, the mammogram furthest from the cancer diagnosis was used for each woman. These models were fit overall and stratified by length of time between density measurement and diagnosis (>6 months to <2 years [recent] vs. 2 to 5 years [distant]). Associations were summarized with odds ratios (ORs) and 95% CIs and with areas under the receiver-operating characteristic curve, or c-statistics, which accounted for the matched study design. Bootstrapping was used to test for differences in c-statistics between models. Models were adjusted for age, race/ethnicity, first-degree family history of breast cancer, history of benign results on breast biopsy, and body mass index (continuous). We used the second BI-RADS category as a reference to allow for estimations of risk at the lowest and highest categories and because it is the category with the greatest proportion of averagerisk women (3). Differences in breast cancer associations by study and timing of density measure in relation to breast cancer diagnosis were evaluated by including interaction terms in the models. Differences in risk associations between density measures and interval versus screen-detected cancer were tested by simultaneously estimating the risk for both interval and screen-detected cancer to formally compare the magnitude of associated ORs (“polytomous logistic regression”).

Overall sensitivity was calculated as the number of invasive breast cancer cases within 12 months of a positive mammography result divided by the total number of invasive breast cancer cases and by BI-RADS category. Sensitivity estimates were compared for recent and distant density before diagnosis with a proportion test adjusted for several comparisons.

Analyses were performed by using SAS software, version 9.4 (SAS Institute). Statistical tests were 2-sided, and *P* values less than 0.050 were considered statistically significant. For more details, see the Supplement (available at Annals.org).

Role of the Funding Source

The National Cancer Institute had no role in the design or conduct of the study or in the reporting of results.

RESULTS

We compared 1609 case participants with screen- detected invasive cancer and 351 with interval invasive cancer with 4409 matched control participants. Of the case participants, 599 had a recent breast density measure (>6 months to <2 years before diagnosis; median, 1.2 years) and 1361 had a distant assessment (2 to 5 years before diagnosis; median, 3.4 years). Women with screen-detected or interval cancer were more likely than control participants to have a family history of breast cancer, dense breasts, high dense breast volume, and high to very high BCSC 5-year risk (Table 1). Compared with the SFMR cohort, women in the Mayo group tended to be older and white and to have a higher body mass index, and fewer had dense breasts (**Appendix Table 3,** available at Annals.org).

Screen-Detected and Interval Cancer Risk for Automated and Clinical Breast Density Measured More Than 6 Months to 5 Years Before Diagnosis

Of women whose breast density was assessed by automated BI-RADS, those with extremely dense breasts had a 5-fold greater risk for interval cancer (OR, 5.65 [95% CI, 3.33 to 9.60]) and a 1.4-fold greater risk for screen-detected cancer (OR, 1.43 [CI, 1.14 to 1.79]) than those with scattered fibroglandular densities (Table 2). This difference in ORs for density between detection modes was statistically significant (*P* for heterogeneity < 0.001). Similar statistically significant differences in the association between density and detection mode were found for clinical BI-RADS density (Table 2). Automated and clinical BI-RADS density measures had similar discriminatory accuracy, which was higher for interval than screen-detected cancer (c- statistics: 0.70 vs. 0.62, $P < 0.001$, and 0.72 vs. 0.62, $P < 0.001$, respectively). Associations between clinical and automated BI-RADS density and interval and screen-detected cancer were similar in both study cohorts (Appendix Table 4, available at Annals.org).

screen-Detected and Interval Cancer Risk by Recent and Distant Breast Density Measures Before Cancer Diagnosis

Among women who had recent automated BIRADS density measures before cancer diagnosis, those with extremely dense breasts compared with those with scattered fibroglandular densities had a 5-fold greater risk for interval cancer and a 1.4-fold greater

risk for screen-detected cancer than control participants (Table 3). Likewise, among women with distant density measures before cancer diagnosis, those with extremelydense breasts had a 6-fold greater risk for interval cancer and a 1.4-fold greater risk for screen-detected cancer than those with scattered fibroglandular densities (Table 3). The differences in density effects between detection modes were statistically significant for density measured at both time points before diagnosis: recent ($P < 0.001$) and distant ($P < 0.001$).

Similar statistically significant differences in the association between density measures and detection mode were found for recent and distant clinical BIRADS density measures before diagnosis (Table 3).

No statistically significant interactions were observed between the time point of density measure and the associations of automated and clinical BI-RADS density with interval breast cancer ($P = 0.27$ and $P = 0.84$, respectively) or screen-detected cancer ($P = 0.22$ and $P = 0.83$, respectively).

Recent and distant clinical and automated BI-RADS density measures before cancer diagnosis had greater discriminatory accuracy for interval than screen-detected cancer, but discrimination was similar across the 2 measures (Table 3 and Appendix Table 1).

Mammography Sensitivity for Clinical and Automated BI-RADS Density

Mammography sensitivity was similar between automated and clinical BI-RADS density categories: fatty, 93% versus 92%; scattered fibroglandular densities, 90% versus 90%; heterogeneously dense, 82% versus 78%; and extremely dense, 63% vs. 64%, respectively (Table 4). Sensitivity was greater for scattered fibroglandular densities, heterogeneously dense, and extremely dense categories for distant automated and clinical BI-RADS density measures than for recent measures before diagnosis (Table 4). Sensitivity was similar for women who had examinations available for both periods (Appendix Table 2).

DISCUSSION

We found automated and clinical BI-RADS breast density measures to have similar ability to predict interval and screen-detected invasive cancer, regardless of timing of density measure, recent or distant from cancer diagnosis. We also found that automated and clinical BI-RADS density more strongly predicted interval than screen-detected cancer. This finding suggests that either automated or clinical BI-RADS measures could be used to inform women of their breast density and associated interval and screen-detected cancer risk. Automated BI-RADS density is more reproducible than clinical BI-RADS density on repeated measures (16, 17) between screening assessments at different facilities, whereas clinical BI-RADS has modest interrater reproducibility if different radiologists at the same facility or different facilities assess a woman’s breast density on consecutive examinations (6–8).

Breast density may affect breast cancer detection by increasing the growth rate of tumors or by masking them. Masking is the phenomenon in which both tumors and dense breast tissue appear white on mammograms, limiting the discrimination of breast cancer from normal tissue. Dense tissue also increases tumor aggressiveness, resulting in a greater proportion of

advanced-stage cases of breast cancer, especially advanced-stage interval cancer (3), being diagnosed in women with dense breasts than in those with nondense breasts (22). Given these 2 mechanisms, it is not surprising that BI-RADS density has greater discriminatory accuracy in predicting interval than screen-detected cancer. Finally, on average, breast density declines about 2% per year (23), such that breast density measured several years apart shows similar associations with breast cancer risk.

The first study to report that automated BI-RADS density measured with Volpara on digital mammography is more strongly associated with interval than screened-detected cancer defined interval cancer as invasive cancer occurring within 24 months of a negative screening result (15). We extend the literature by reporting, in what we believe is the largest study to date, that automated BI-RADS density is more strongly associated with interval than screen-detected cancer when interval cancer is defined as invasive cancer occurring within 12 months of a negative screening result, which is the standard definition in the United States (2, 3). In addition, we compared automated with clinical BIRADS density, the standard for reporting breast density in the United States, and show that the 2 measures have similar predictive ability. Consistent with our results, area measures of breast density assessed on film-screen mammography in research settings have been found to be more strongly related to interval than screen-detected breast cancer risk (24, 25).

Among women who undergo mammography in the United States, 83% are screened every 12 to 35 months and 8% every 36 months or more (26). Thus, the opportunity to assess breast density on mammography for use in risk prediction models is variable. Boyd and colleagues (27) assessed percentage of mammo-graphic density on digitized film-screen mammography examinations in 3 screening programs in Canada using a continuous computer-assisted measure. Consistent with our results, the authors reported a higher percentage of breast density in women receiving a diagnosis of screen-detected or non-screen-detected cancer compared with those who did not develop breast cancer, up to 8 years after study entry. However, in contrast to our study, in which we found that associations with interval and screen-detected cancer risk were similar for recent and distant breast density measures before cancer diagnosis, Boyd and colleagues (27) reported a 17-fold higher risk for non-screen-detected cancer in the 1 to 2 years after a screening examination. Of note, the risk was 3.9-fold greater 2 to 4 years after a screening examination and 8.9-fold greater when risk was measured 4 to 8 years after screening (27). These results suggest that the ability to identify women at increased risk for interval cancer several years before diagnosis would allow improved screening strategies to be implemented to detect cancer earlier and reduce the risk for interval cancers. For example, the need for supplemental imaging could be predicted several years before cancer detection to optimize the chance to decrease interval cancer risk.

We examined mammography sensitivity to determine the absolute effect of breast density on the risk for interval and screen-detected invasive cancer. We found that automated and clinical BI-RADS density measures had similar sensitivity for each of the 4 BI-RADS categories, with slightly higher values for density measured further from the cancer diagnosis. Destounis and colleagues (28) reported that sensitivity decreased from the lowest to highest automated BI-RADS density categories (95% to 65%) but less so for clinical BI-

RADS (82% to 66%). Wanders and colleagues (29) reported lower mammography sensitivity values from the lowest to highest automated BI-RADS density categories (86% to 61%) when the median time from measurement to diagnosis was longer than 2 years. The mammography sensitivity we report for density measured 2 to 5 years before diagnosis is slightly greater than that reported by Wanders and colleagues, probably because we defined interval cancer as invasive cancer diagnosed within 12 months, as opposed to 24 months, of a negative screening result. Longer screening intervals allow more time for missed cancer to grow and become symptomatic, such that interval cancer rates are higher in women who have biennial versus annual screening (30). Also, mammography sensitivity was slightly greater for the 2- to 5-year group, because the longer the period before breast cancer diagnosis, the higher the risk for both screen-detected and interval cancer, with a disproportionately higher risk for slow-growing screen-detected cancer.

Linkage to state tumor registries to enhance the completeness of identifying interval cancer cases was a strength of our study. We examined Volpara automated density measures that are available in clinical practice. Other commercially available automated volumetric breast density software (Quantra and PowerLook Density Assessment) might be tested to verify our results. We used clinical BI-RADS density assessments when the definitions from the fourth BI-RADS edition were available in clinical practice. Breast density distributions during the available periods of the fourth and fifth BIRADS editions in the BCSC are similar, suggesting that our results are clinically applicable (Miglioretti DL. Personal communication.). California and Minnesota density laws were enacted after clinical BI-RADS measures were collected for this study. We used a case-control design for economical assessment of automated density measures from several examinations for each study participant. Our study's design did not allow us to assess the positive predictive value of mammography by breast density. Our matched control participants had a distribution of 5-year breast cancer risk similar to that of the population-based BCSC cohort (3), suggesting that our results are generalizable to women undergoing screening mammography. Our population was predominantly white and Asian. Although cancer detection has not been shown to vary by race/ethnicity (31) despite differences in breast density across racial/ethnic groups (20, 32), studies should be repeated in black and Hispanic women to ensure generalizability of results across all racial/ethnic groups. Finally, breast tomosynthesis is an emerging breast screening technique, with 30% of mammography machines in the United States producing tomosynthesis images as of 1 February 2018 (33). Volpara density measures are similar on digital and tomosynthesis C-View (Hologic) images (34), and no evidence has been published that the interval cancer rate or mammography sensitivity is different for digital mammography versus tomosynthesis (35). However, the contribution of volumetric density measures to breast cancer risk for tomosynthesis needs to be established.

This study looked at the timing of automated and clinical BI-RADS density measures and found that measures close to breast cancer diagnosis and those up to 5 years before were similar in predicting interval and screen-detected cancer risk. These findings suggest that automated or clinical BI-RADS measures may be used to inform women of their breast density and predict their risk for interval and screen-detected cancer, even as long as 5 years before cancer diagnosis. Because automated BI-RADS breast density is more reproducible than clinical density (16, 17) and is being used increasingly in the clinical setting, our results

suggest that automated density measures may be used to predict risk and help identify women most in need of supplemental screening. Future research should focus on developing prediction models comparing automated with clinical BI-RADS density to determine whether repeated automated or clinical measures more accurately predict the 5-year cumulative risk for interval cancer.

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Appendix

Appendix Table 1.

Risk for Screen-Detected and Interval Cancer for Recent and Distant BI-RADS Breast Density Measures Before Cancer Diagnosis, Among Women With Mammograms in Both Time Periods

Variable	Screen-Detected Cancer			Interval Cancer			*P* Value for Interval vs. Screen-Detected Cancer
	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	
Recent breast density measure†							
Clinical BI-RADS density			0.63(0.60–0.66)			0.75 (0.69–0.80)	0.003
Almost entirely fatty	54/218	0.44 (0.30–0.63)		5/43	0.40(0.14–1.17)		
Scattered fibroglandular densities	244/509	1.00 (reference)		27/86	1.00 (reference)		
Heterogeneously dense	190/359	1.26(0.98–1.64)		60/99	1.83(0.97–3.47)		
Extremely dense	40/70	1.54(0.94–2.52)		26/20	4.31 (1.64–11.3)		
Automated BI-RADS density‡			0.63 (0.60–0.66)			0.75 (0.69–0.80)	<0.001
Almost entirely fatty	131/354	0.71 (0.53–0.95)		8/58	0.87 (0.31–2.42)		
Scattered fibroglandular densities	191/394	1.00 (reference)		23/91	1.00 (reference)		
Heterogeneously dense	153/289	1.23(0.92–1.66)		48/60	5.85 (2.56–13.3)		
Extremely dense	53/119	1.10(0.70–1.72)		39/39	9.79(3.51–27.3)		
Distant breast density measure§							
Clinical BI-RADS density			0.63(0.60–0.66)			0.75 (0.69–0.80)	<0.001
Almost entirely fatty	65/238	0.49 (0.34–0.70)		4/44	0.49(0.15–1.59)		
Scattered fibroglandular densities	225/482	1.00 (reference)		23/89	1.00 (reference)		
Heterogeneously dense	188/365	1.26(0.96–1.65)		62/87	2.83(1.45–5.51)		
Extremely dense	50/71	2.09(1.30–3.34)		29/28	4.40(1.75–11.1)		
Automated BI-RADS density‡			0.63 (0.60–0.66)			0.75 (0.69–0.80)	<0.001
Almost entirely fatty	118/302	0.80(0.59–1.07)		6/50	0.52 (0.18–1.53)		
Scattered fibroglandular densities	192/410	1.00 (reference)		26/86	1.00 (reference)		
Heterogeneously dense	151/317	1.19(0.88–1.60)		39/66	2.72 (1.28–5.77)		
Extremely dense	67/127	1.41 (0.92–2.16)		47/46	6.20(2.39–16.1)		

BI-RADS = Breast Imaging Reporting and Data System; OR = odds ratio.

*Adjusted for age, body mass index, family history of breast cancer, history of breast biopsy, and race/ethnicity.

[/] Defined as >6 mo to <2 y before cancer diagnosis.

[≠] Measured with Volpara software (Volpara Solutions).

[§] Defined as 2–5 y before cancer diagnosis.

Appendix Table 2.

Mammography Sensitivity by Clinical and Automated BI-RADS Breast Density, by Timing of Density Measure Before Cancer Diagnosis, Among Women With Mammograms in Both Time Periods

Variable	Almost Entirely Fatty	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense	Overall
Recent breast density measure *					
Clinical BI-RADS density					
Interval cancer cases	5	27	60	26	118
Screen-detected cancer cases	54	244	190	40	528
Sensitivity (95% CI), *%*	92 (84–99)	90(86–94)	76(71–81)	61 (49–72)	82 (79–85)
Automated BI-RADS density †					
Interval cancer cases	8	23	48	39	118
Screen-detected cancer cases	131	191	153	53	528
Sensitivity (95% CI), *%*	94 (90–98)	89 (85–93)	76 (70–82)	58 (48–68)	82 (79–85)
Distant breast density measure ‡					
Clinical BI-RADS density					
Interval cancer cases	4	23	62	29	118
Screen-detected cancer cases	65	225	188	50	528
Sensitivity (95% CI), *%*	94(89–100)	91 (87–94)	75(70–81)	63 (53–74)	82 (79–85)
Automated BI-RADS density †					
Interval cancer cases	6	26	39	47	118
Screen-detected cancer cases	118	192	151	67	528
Sensitivity (95% CI), *%*	95 (91–99)	88 (84–92)	79 (74–85)	59 (50–68)	82 (79–85)

BI-RADS = Breast Imaging Reporting and Data System.

* Defined as >6 mo to <2 y before cancer diagnosis.

† Measured with Volpara software.

‡ Defined as 2–5 y before cancer diagnosis.

Appendix Table 3.

Characteristics of Study Population, by Study Cohort

Variable	San Francisco Mammography Registry Control Participants (*n* = 2603)	Mayo Clinic Control Participants (*n* = 1806)
Mean age (SD), *y*	58.3(11.9)	61.3(11.4)
Mean body mass index (SD), kg/m^2	24.9 (5.1)	28.6 (6.5)
Median dense breast volume (IQR), mL *	50.7 (36.3–71.9)	52.5 (39.7–70.6)
Family history of breast cancer, *n (%)* †	453 (17.4)	384(21.4)
History of breast biopsy, *n (%)*	315 (12.1)	473 (26.2)
Race/ethnicity, *n (%)*		
White	1768 (67.9)	1758 (97.3)
Asian	549 (21.1)	21 (1.2)
Black	87 (3.3)	2 (0.1)
Hispanic	101 (3.9)	9 (0.5)
Other	98 (3.8)	16 (0.9)
Clinical BI-RADS density, *n (%)*		
Almost entirely fatty	369 (14.2)	432 (23.9)
Scattered fibroglandular densities	1018 (39.1)	746 (41.3)
Heterogeneously dense	939 (36.1)	530 (29.3)
Extremely dense	277 (10.6)	98 (5.4)
Automated BI-RADS density, *n (%)* *		
Almost entirely fatty	448 (17.2)	519 (28.7)
Scattered fibroglandular densities	760 (29.2)	635 (35.2)
Heterogeneously dense	876 (33.7)	477 (26.4)
Extremely dense	519 (19.9)	175 (9.7)
BCSC 5–y risk, *n (%)*		
Low (G%-G.99%)	952 (36.6)	421 (23.3)
Average (1.GG%–1.66%)	756 (29)	454(25.1)
Intermediate (1.67%–2.49%)	583 (22.4)	527 (29.2)
High (2.5G%–3.99%)	239 (9.2)	289 (16)
Very high (≥4.GG%)	73 (2.8)	115(6.4)

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System; IQR = interquartile range.

Measured with Volpara software (Volpara Solutions).

†Mother, sister, or daughter with breast cancer.

Appendix Table 4

Risk for Screen-Detected and Interval Cancer for BI-RADS Breast Density Measured More Than 6 Months to 5 Years Before Cancer Diagnosis, by Study Cohort

Variable	Screen-Detected Cancer			Interval Cancer			*P* Value for Interval vs. Screen-Detected Cancer
	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	
San Francisco Mammography Registry							
Clinical BI-RADS density			0.63(0.61–0.65)			0.72 (0.68–0.75)	<0.001
Almost entirely fatty	114/303	0.66(0.50–0.86)		13/66	0.63(0.29–1.40)		
Scattered fibroglandular densities	407/834	1.00 (reference)		54/184	1.00 (reference)		
Heterogeneously dense	394/745	1.26(1.05–1.52)		107/194	2.25(1.44–3.51)		
Extremely dense	139/208	1.80 (1.36–2.38)		84/69	5.23(2.97–9.21)		
Automated BI-RADS densityt			0.62 (0.60–0.64)			0.71 (0.67–0.75)	<0.001
Almost entirely fatty	158/371	0.75 (0.59–0.96)		16/77	0.96(0.47–1.96)		
Scattered fibroglandular densities	314/628	1.00 (reference)		39/132	1.00 (reference)		
Heterogeneously dense	385/704	1.36(1.11–1.67)		85/172	2.36(1.36–4.10)		
Extremely dense	197/387	1.48 (1.13–1.94)		118/132	5.58(2.93–10.6)		
Mayo Clinic							
Clinical BI-RADS density			0.64(0.62–0.67)			0.73 (0.68–0.79)	0.001
Almost entirely fatty	93/388	0.57 (0.42–0.76)		6/44	0.78(0.26–2.31)		
Scattered fibroglandular densities	243/647	1.00 (reference)		20/99	1.00 (reference)		
Heterogeneously dense	184/450	1.27 (0.99–1.64)		53/80	3.70(1.83–7.48)		
Extremely dense	35/75	1.91 (1.17–3.10)		14/23	4.10(1.34–12.6)		
Automated BI-RADS density†			0.66 (0.63–0.68)			0.71 (0.65–0.76)	<0.001
Almost entirely fatty	138/457	0.69 (0.53–0.90)		7/62	0.41 (0.15–1.10)		
Scattered fibroglandular densities	222/554	1.00 (reference)		22/81	1.00 (reference)		
Heterogeneously dense	137/408	0.97 (0.73–1.28)		31/69	2.06 (0.98–4.30)		
Extremely dense	58/141	1.53(1.01–2.33)		33/34	7.45 (2.65–20.9)		

BI-RADS = Breast Imaging Reporting and Data System; OR = odds ratio.

*Adjusted for age, body mass index, family history of breast cancer, history of breast biopsy, and race/ethnicity.

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Table 1.

Characteristics of Study Population *

Characteristic	Women With Screen-Detected Invasive Cancer (*n* = 1609)	Women With Interval Invasive Cancer (*n* = 351)	Matched Control Participants (*n* = 4409)
Mean age (SD), *y*	60.2 (11.8)	56.6(12.2)	59.6 (11.8)
Mean body mass index (SD), kg/m^2 †	26.9 (5.9)	24.1 (4.6)	26.4 (6)
Median dense breast volume (IQR), *ml*‡	57.6 (41.4–80.5)	67.0(45.9–97.8)	51.5 (37.7–71.4)
Family history of breast cancer, *n (%)*§	448 (28.2)	110(31.3)	837 (19)
History of breast biopsy, *n (%)*‖	358 (22.4)	99 (28.4)	788 (17.9)
Race/ethnicity, *n (%)*			
White	1248 (77.6)	263 (74.9)	3526 (80)
Asian	225 (14)	61 (17.4)	570 (12.9)
Black	45 (2.8)	4(1.1)	89 (2)
Hispanic	36 (2.2)	8 (2.3)	110(2.5)
Other	55 (3.4)	15 (4.3)	114(2.6)
Clinical BI-RADS density, *n (%)*			
Almost entirely fatty	207 (12.9)	19 (5.4)	801 (18.2)
Scattered fibroglandular densities	650 (40.4)	74(21.1)	1764(40)
Heterogeneously dense	578 (35.9)	160 (45.6)	1469 (33.3)
Extremely dense	174(10.8)	98 (27.9)	375 (8.5)
Automated BI-RADS density, *n (%)*‡			
Almost entirely fatty	296 (18.4)	23 (6.6)	967 (21.9)
Scattered fibroglandular densities	536 (33.3)	61 (17.4)	1395 (31.6)
Heterogeneously dense	522 (32.4)	116(33)	1353 (30.7)
Extremely dense	255 (15.8)	151 (43)	694(15.7)
BCSC 5-y risk, *n (%)*			
Low (0%−0.99%)	387 (24.1)	79 (22.5)	1373 (31.1)
Average (1.00%−1.66%)	446 (27.7)	84 (23.9)	1210 (27.4)
Intermediate (1.67%−2.49%)	399 (24.8)	93 (26.5)	1110(25.2)

Characteristic	Women With Screen-Detected Invasive Cancer (*n* = 1609)	Women With Interval Invasive Cancer (*n* = 351)	Matched Control Participants (*n* = 4409)
High (2.50%−3.99%)	282 (17.5)	68 (19.4)	528 (12)
Very high (≥4.00%)	95 (5.9)	27 (7.7)	188 (4.3)

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System; IQR = interquartile range.

[*] Percentages may not sum to 100 due to rounding.

[†] Data missing for 73 participants (1.1%).

[‡] Measured with Volpara software (Volpara Solutions).

[§] Defined as having a mother, sister, or daughter with breast cancer. Data missing for 35 participants (0.6%).

[‖] Data missing for 17 participants (0.3%).

Table 2.

Risk for Screen-Detected and Interval Cancer for BI-RADS Breast Density Measured More Than 6 Months to 5 Years Before Cancer Diagnosis

Variable	Screen-Detected Cancer			Interval Cancer			*P* Value for Interval vs. Screen-Detected Cancer
	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	
Clinical BI-RADS density	-	-	0.62 (0.61–0.64)	-	-	0.72 (0.69–0.75)	<0.001
Almost entirely fatty	207/691	0.62 (0.51–0.75)	-	19/110	0.74(0.41–1.36)	-	
Scattered fibroglandular densities	650/1481	1.00 (reference)	-	74/283	1.00 (reference)	-	
Heterogeneously dense	578/1195	1.26 (1.09–1.46)	-	160/274	2.51 (1.74–3.61)	-	
Extremely dense	174/283	1.83(1.44–2.32)	-	98/92	5.09(3.11–8.35)	-	
Automated BI-RADS densityt†	-	-	0.62 (0.60–0.63)	-	-	0.70 (0.66–0.73)	<0.001
Almost entirely fatty	296/828	0.73 (0.61–0.87)	-	23/139	0.73(0.42–1.29)	-	
Scattered fibroglandular densities	536/1182	1.00 (reference)	-	61/213	1.00 (reference)	-	
Heterogeneously dense	522/1112	1.20 (1.02–1.41)	-	116/241	2.22(1.44–3.43)	-	
Extremely dense	255/528	1.43 (1.14–1.79)	-	151/166	5.65 (3.33–9.60)	-	

BI-RADS = Breast Imaging Reporting and Data System; OR = odds ratio.

*Adjusted for age, body mass index, family history of breast cancer, history of breast biopsy, and race/ethnicity.

†Measured with Volpara software (Volpara Solutions).

Table 3.

Risk for Screen-Detected and Interval Cancer for Recent and Distant BI-RADS Breast Density Measures Before Cancer Diagnosis

Variable	Screen-Detected Cancer			Interval Cancer			*P* Value for Interval vs. Screen-Detected Cancer
	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	Case Participants/ Control Participants, *n/N*	OR (95% CI)*	C-Statistic (95% CI)	
Recent breast density measure†							
Clinical BI-RADS density	-	-	0.62 (0.59–0.65)	-	-	0.72 (0.68–0.77)	0.023
Almost entirely fatty	53/167	0.64 (0.44–0.94)	-	7/47	0.61 (0.23–1.62)	-	
Scattered fibroglandular densities	171/403	1.00 (reference)	-	34/122	1.00 (reference)	-	
Heterogeneously dense	164/320	1.36(1.02–1.81)	-	61/104	2.67 (1.50–4.77)	-	
Extremely dense	62/87	2.06(1.35–3.15)	-	47/36	5.98(2.81–12.7)	-	
Automated BI-RADS density‡	-	-	0.62 (0.59–0.65)	-	-	0.70 (0.65–0.75)	<0.001
Almost entirely fatty	64/209	0.56(0.38–0.81)	-	6/63	0.37(0.14–1.01)	-	
Scattered fibroglandular densities	144/298	1.00 (reference)	-	26/77	1.00 (reference)	-	
Heterogeneously dense	162/306	1.31 (0.96–1.78)	-	51/99	2.44(1.20–4.97)	-	
Extremely dense	80/164	1.38 (0.92–2.07)	-	66/70	5.39(2.30–12.6)	-	
Distant breast density measure§							
Clinical BI-RADS density	-	-	0.62 (0.60–0.64)	-	-	0.71 (0.67–0.76)	<0.001
Almost entirely fatty	154/524	0.61 (0.49–0.77)	-	12/63	0.84(0.38–1.84)	-	
Scattered fibroglandular densities	479/1078	1.00 (reference)	-	40/161	1.00 (reference)	-	
Heterogeneously dense	414/875	1.22(1.02–1.45)	-	99/170	2.57 (1.57–4.19)	-	
Extremely dense	112/196	1.72 (1.29–2.31)	-	51/56	4.62 (2.38–8.98)	-	
Automated BI-RADS density‡	-	-	0.62 (0.60–0.64)	-	-	0.69 (0.65–0.74)	<0.001
Almost entirely fatty	232/619	0.79 (0.64–0.97)	-	17/76	1.07 (0.53–2.17)	-	
Scattered fibroglandular densities	392/884	1.00 (reference)	-	35/136	1.00 (reference)	-	
Heterogeneously dense	360/806	1.15(0.95–1.40)	-	65/142	2.11 (1.20–3.69)	-	
Extremely dense	175/364	1.44(1.10–1.89)	-	85/96	6.11 (3.07–12.2)	-	

BI-RADS = Breast Imaging Reporting and Data System; OR = odds ratio.

*Adjusted for age, body mass index, family history of breast cancer, history of breast biopsy, and race/ethnicity.

† Defined as >6 mo to <2 y before cancer diagnosis.

‡ Measured with Volpara software (Volpara Solutions).

§ Defined as 2–5 y before cancer diagnosis.

Table 4.

Mammography Sensitivity by Clinical and Automated BI-RADS Breast Density, by Timing of Density Measure Before Cancer Diagnosis

Variable	Almost Entirely Fatty	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense	Overall
Density measure >6 mo to 5 y before cancer diagnosis					
Clinical BI-RADS density					
Interval cancer cases	19	74	160	98	351
Screen-detected cancer cases	207	650	578	174	1609
Sensitivity (95% CI), %	92(88–95)	90 (88–92)	78(75–81)	64 (58–70)	82 (80–84)
Automated BI-RADS density *					
Interval cancer cases	23	61	116	151	351
Screen-detected cancer cases	296	536	522	255	1609
Sensitivity (95% CI), %	93 (90–96)	90 (87–92)	82 (79–85)	63 (58–68)	82 (80–84)
Recent breast density measure †					
Clinical BI-RADS density					
Interval cancer cases	7	34	61	47	149
Screen-detected cancer cases	53	171	164	62	450
Sensitivity (95% CI), %	89(81–97)	84(79–89)‡	73 (67–79)§	57 (48–66)‖	75 (72–79)
Automated BI-RADS density *					
Interval cancer cases	23	61	116	151	149
Screen-detected cancer cases	296	536	522	255	450
Sensitivity (95% CI), %	92 (85–98)	85(79–90)¶	76(70–82)¶	55 (47–63)¶	75 (72–79)
**Distant breast density measure ** **					
Clinical BI-RADS density					
Interval cancer cases	12	40	99	51	202
Screen-detected cancer cases	154	479	414	112	1159
Sensitivity (95% CI), %	93(89–97)	92 (90–95)‡	81 (77–84)§	69 (62–76)‖	85 (83–87)
Automated BI-RADS density *					
Interval cancer cases	17	35	65	85	202

Variable	Almost Entirely Fatty	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense	Overall
Screen-detected cancer cases	232	392	360	175	1159
Sensitivity (95% CI), %	93 (90–96)	92 (89–94)¶	85(81–88)¶	67 (62–73)¶	85 (83–87)

BI-RADS = Breast Imaging Reporting and Data System.

* Measured with Volpara software (Volpara Solutions).

† Defined as >6 mo to <2 y before cancer diagnosis.

‡ $P = 0.002$.

§ $P = 0.039$.

‖ $P = 0.046$.

¶ $P = 0.039$.

** Defined as 2–5 y before cancer diagnosis.