

# Impact of Breast Density on Computer-Aided Detection for Breast Cancer

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**OBJECTIVE.** Our aim was to determine whether breast density affects the performance of a computer-aided detection (CAD) system for the detection of breast cancer.

**MATERIALS AND METHODS.** Nine hundred six sequential mammographically detected breast cancers and 147 normal screening mammograms from 18 facilities were classified by mammographic density. BI-RADS 1 and 2 density cases were classified as nondense breasts; BI-RADS 3 and 4 density cases were classified as dense breasts. Cancers were classified as either masses or microcalcifications. All mammograms from the cancer and normal cases were evaluated by the CAD system. The sensitivity and false-positive rates from CAD in dense and nondense breasts were evaluated and compared.

**RESULTS.** Overall, 809 (89%) of 906 cancer cases were detected by CAD; 455/505 (90%) cancers in nondense breasts and 354/401 (88%) cancers in dense breasts were detected. CAD sensitivity was not affected by breast density ( $p = 0.38$ ). Across both breast density categories, 280/296 (95%) microcalcification cases and 529/610 (87%) mass cases were detected. One hundred fourteen (93%) of the 122 microcalcifications in nondense breasts and 166 (95%) of 174 microcalcifications in dense breasts were detected, showing that CAD sensitivity to microcalcifications is not dependent on breast density ( $p = 0.46$ ). Three hundred forty-one (89%) of 383 masses in nondense breasts, and 188 (83%) of 227 masses in dense breasts were detected—that is, CAD sensitivity to masses is affected by breast density ( $p = 0.03$ ). There were more false-positive marks on dense versus nondense mammograms ( $p = 0.04$ ).

**CONCLUSION.** Breast density does not impact overall CAD detection of breast cancer. There is no statistically significant difference in breast cancer detection in dense and nondense breasts. However, the detection of breast cancer manifesting as masses is impacted by breast density. The false-positive rate is lower in nondense versus dense breasts. CAD may be particularly advantageous in patients with dense breasts, in which mammography is most challenging.

**T**he use of screening mammography has been shown to result in a reduction in mortality rates of approximately 30% [1, 2]. Mammography remains the mainstay for breast cancer screening. However, mammography is an imperfect examination with a sensitivity of 85–90% for breast cancer—that is, 10–15% of cancers are missed with mammography [3]. Therefore, additional methods to improve breast cancer detection are needed.

Computer-aided detection (CAD) has been developed to improve mammographic detection of breast cancer. Recent studies evaluating CAD have shown a greater than 20% improvement in sensitivity with the use of CAD for mammographic detection of breast cancer [4, 5].

A significant factor limiting the sensitivity of mammography is increased breast density. Analysis of characteristics of cancers missed on

screening mammography show that greater breast density is associated with missed breast cancers [6–8]. Therefore, additional methods to improve the detection of breast cancer, particularly in mammographically dense breasts, are needed. With the recent data supporting the positive impact of CAD for the mammographic detection of breast cancer, the question of the performance of the CAD in women with dense breasts was raised—that is, was the performance of CAD impacted by breast density?

The purpose of this study was to determine whether breast density affects the performance of a CAD system for the mammographic detection of breast cancer.

## Materials and Methods

A total of 906 mammographically screen-detected breast cancers and 147 normal cases from 18

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institutions were included in this study. These mammograms constituted a large multiinstitutional trial to investigate the sensitivity of CAD for the detection of breast cancer for U.S. Food and Drug Administration approval of the Second Look CAD system (version 4.0, i-CAD) [5]. Institutional review board approval was obtained for all institutions. Mammograms were evaluated for breast density and assigned a BI-RADS breast density score of 1 through 4 [9]. Images were reviewed and classified by two experienced mammographers, with any discrepancies in interpretation resolved by consensus. Mammograms with BI-RADS 1 density (entirely fatty) or BI-RADS 2 density (scattered fibroglandular tissue) were categorized as nondense. Mammograms with BI-RADS 3 density (heterogeneously dense) or BI-RADS 4 density (extremely dense) were categorized as dense. CAD performance was analyzed on the basis of the nondense and dense categories of the mammograms in this study.

The mammographic characteristics of the cancer cases were classified as microcalcifications or masses. Masses included spiculated and circumscribed masses, architectural distortions, and focal asymmetric densities. If a cancer was a mass with calcifications, the lesion was classified by the primary characteristic of the tumor. A mass with calcification was classified by the primary characteristic—that is, if the lesion was a mass with a few calcifications, it was classified as a mass. If a lesion was predominantly calcifications with an associated density, it was characterized as microcalcifications.

One hundred forty-seven randomly selected normal cases were included to evaluate the number of false-positive marks per mammogram. Initially, 150

normal cases were targeted to be included in this study. However, there were incomplete data for three cases; therefore, 147 cases were included. A normal case was defined as a screening mammogram for which the findings were interpreted as normal, not requiring any further workup (BI-RADS 1) and for which there had been at least 3 subsequent years of normal findings on screening mammography (BI-RADS 1 or 2) with no clinical finding to suggest malignancy. Mammograms with normal findings were obtained between 1992 and 1997.

The 906 mammograms with findings of cancer and 147 with normal findings were evaluated by the Second Look CAD system. Mammograms were digitized using a CCD digitizer with 12 bits of grayscale and 43  $\mu$  resolution. The CAD system used proprietary algorithms to detect potential areas of concern. The CAD report consists of the digitized images with ellipses and rectangles highlighting potential areas of concern. The ellipses mark potential masses (circumscribed masses, spiculated masses, architectural distortions, and asymmetric densities), and rectangles mark potential microcalcifications.

The locations of cancers on the mammogram and CAD printouts were specified with the use of a transparent grid-template overlay using 1-cm squares. The 1-cm square grid overlay was used on the mammogram to determine the precise location of the cancer. Similarly, an appropriately scaled transparent grid was overlaid on the paper CAD reports to assess the marking of the cancers by the CAD system. CAD-marked lesions were within the same 1-cm grid square on the CAD output and the mammogram, marked on at least one view by the CAD system, and correlated by lesion feature—

that is, mass or microcalcifications were considered true-positive detections.

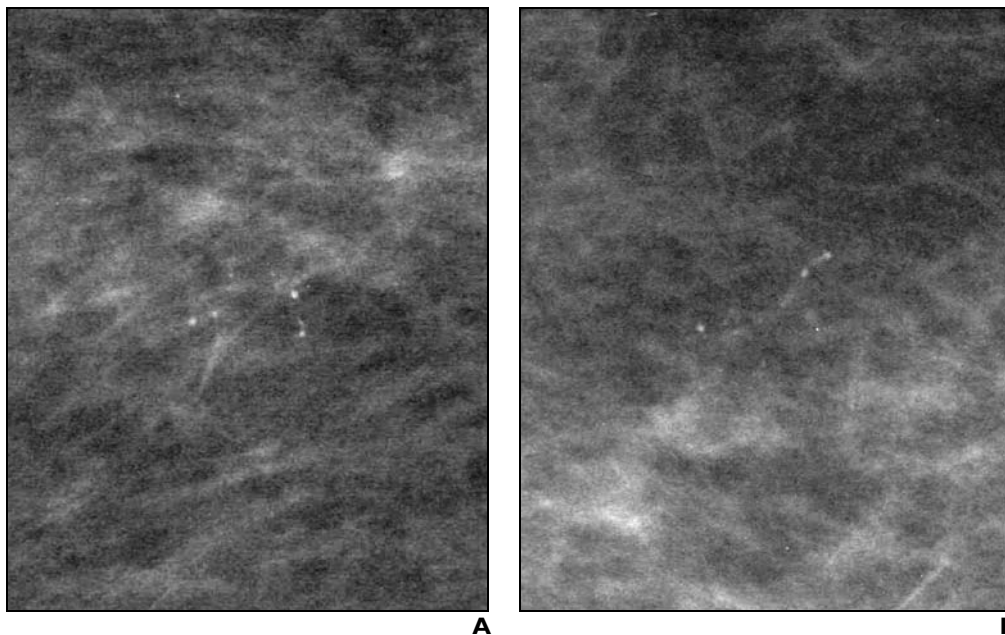
The overall sensitivity of the CAD system for the detection of breast cancer in nondense and dense breasts was evaluated for differences in performance in these two groups. In addition, CAD detection of microcalcification cancer cases and mass cancer cases in dense and nondense cases was evaluated. Differences in CAD detection rate of cancer in dense and nondense breasts were compared using chi-square analysis.

The total number of false-positive marks per case was determined by adding the number of microcalcification and mass marks in each normal case. To determine whether more false-positive marks are found in dense or nondense breasts, the number of CAD marks in normal dense and nondense mammograms were calculated and compared using chi-square analysis.

The design of the CAD system limits the total number of marks per case. Therefore, theoretically, in the cancer cases, the maximum number of false-positive marks could not be achieved because of the required marks for the cancer. In practice, the maximum number of marks per case is rarely reached. Nevertheless, the design of the study used normal mammograms to assess the false-positive marks per case to allow the maximum number of false-positive marks per case. Statistical analysis showing *p* values of less than 0.05 were considered statistically significant.

## Results

Of the 906 cancer cases, 99 (11%) were classified as entirely fatty; 406 (45%) as scattered fibroglandular; 332 (37%) as heterogeneously



**Fig. 1.**—50-year-old asymptomatic woman. **A**, Right craniocaudal mammogram shows microcalcifications in nondense breast. **B**, Right mediolateral oblique mammogram shows microcalcifications in nondense breast.

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dense; and 69 (8%) as extremely dense. Of the 147 normal cases, study radiologists classified 10 (7%) as entirely fatty; 78 (53%) as scattered fibroglandular; 46 (31%) as heterogeneously dense; and 13 (9%) as extremely dense. There was no significant difference in BI-RADS breast density distribution between cancer and normal cases ( $p = 0.12$ ). Similarly, there was no significant difference in the distribution of nondense and dense categories between cancer and normal cases ( $p = 0.39$ ).

Overall, 809 (89%) of 906 cancer cases were detected by CAD. Two hundred eighty (95%) of 296 cancers that manifested mammographically as microcalcifications, and 529 (87%) of 610 cancers that manifested mammographically as masses were detected by CAD. It detected 455 (90%) of the 505 cancer cases in nondense breasts, and 354 (88%) of 401 cancer cases in dense breasts. There was no statistically significant difference in CAD of cancer in dense versus nondense breasts ( $p = 0.38$ ).

One hundred fourteen (93%) of the 122 microcalcification cancer cases in nondense breasts and 166 (95%) of 174 microcalcification cancer cases in dense breasts were detected by the CAD system. There was no statistically significant difference in detection of cancers that manifested mammographically as microcalcifications in nondense versus dense breasts ( $p = 0.46$ ). Examples of these images are seen in Figures 1 and 2.

Of the cancers that mammographically manifested as masses, 341 (89%) of 383 cases in nondense breasts and 188 (83%) of 227 cases in dense breasts were detected. There

was a statistically significant difference in the CAD performance for the detection of mass cancer cases in nondense versus dense breasts ( $p = 0.03$ ). Examples of these images are seen in Figures 3 and 4.

Of the 147 normal cases, the average number of false-positive marks per case was 2.95, with 0.65 microcalcification markers and 2.30 mass markers per case. There were 0.59 microcalcification false-positives and 2.09 mass false-positives per case in nondense normal breasts for a total of 2.68 false-positives per case in nondense normal breasts. The mean number of false-positive per case in dense normal breasts was 3.35, made up of 0.75 microcalcification false-positives and 2.60 mass false-positives per case.

Further analysis of the number of cases with no false-positive microcalcification marks revealed that 35 (58%) of 60 cases with dense breast tissue had zero microcalcification false-positives, whereas the remaining 25 (42%) had one or more. In nondense cases, 55 (63%) of 87 had no microcalcification false-positives, whereas the remaining 32 (37%) had one or more. The distribution of microcalcification false-positive marks did not differ significantly between nondense and dense breast tissue cases ( $p = 0.55$ ).

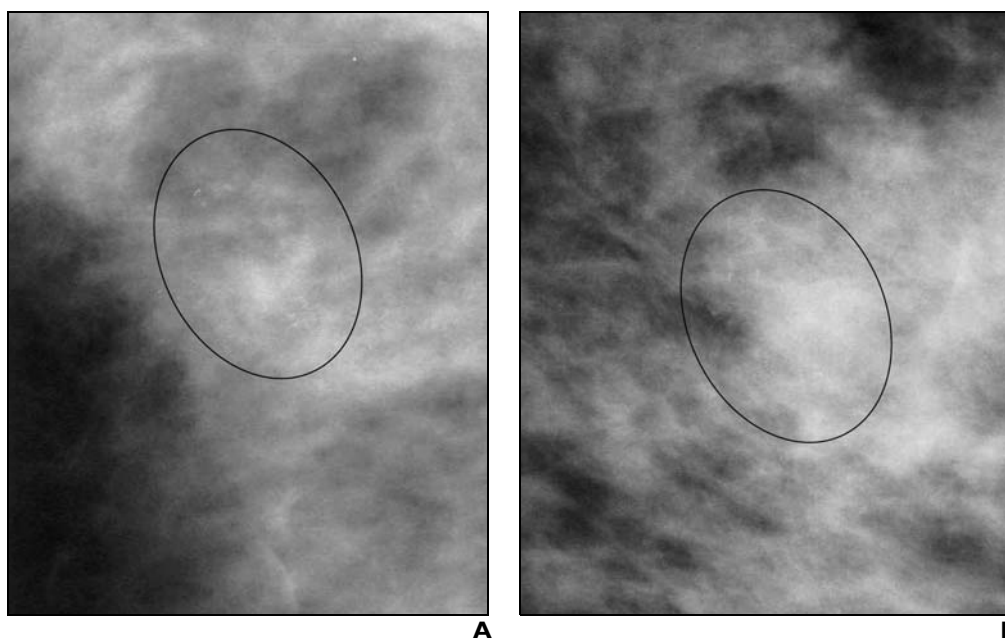
Regarding mass false-positives, 25 (42%) of 60 cases with dense breasts had two or fewer mass false-positives, whereas the remaining 35 (58%) had three or more false-positives. In nondense breasts, 52 (60%) of 87 cases had two or fewer mass false-positives, whereas the remaining 35 (40%) had three or

more. There were statistically significantly fewer mass false-positive marks in nondense than in dense breast cases ( $p = 0.03$ ).

In 18 (30%) of 60 cases with dense tissue there were two or fewer total false-positive marks, whereas the remaining 42 (70%) had three or more. Of the 87 nondense cases, 41 (47%) had two or fewer total false-positives, whereas 46 (53%) had three or more. There were significantly more total false-positive marks in dense breasts than in nondense breasts ( $p = 0.04$ ).

## Discussion

Breast density is affected by age, use of hormone replacement therapy, body mass index, and family history [10]. Kolb et al. [8] conducted a study that found breast density to be the single most important predictor of mammographic sensitivity. In women with fatty breasts, mammography failed to show only 2% of breast cancer. However, in women with markedly dense breasts, mammography failed to show over 52% of all cancers. Decreased mammographic sensitivity in dense breasts was also shown in a report of women participating in a screening program through an HMO. Mammographic sensitivity was found to be 80% in women with predominantly fatty breasts and 30% in women with mammographically dense breasts [7]. Finally, a recent report by Birdwell et al. [11] evaluating causes of missed breast cancers found that breast density was the second most common reason for missed cancers, second only to a distracting lesion.



**Fig. 2.**—51-year-old asymptomatic woman. **A**, Right craniocaudal mammogram shows microcalcifications in dense breast. **B**, Right mediolateral oblique mammogram shows microcalcifications in dense breast.

Multiple studies have shown the improvement in breast cancer detection with the implementation of CAD [4, 5, 12]. Evaluations of CAD in both the academic [4, 5] and private [12] practice settings have shown a similar improvement in breast cancer detection. Warren Burhenne et al. [4] found that the radiologists' false-negative rate of 21% potentially could have been reduced by 77% with CAD prompting. A study by Brem et al. [5] showed similar results with a false-negative rate decrease of 65% with CAD.

Our study shows that overall CAD performance for the detection of breast cancer was not impacted by breast density. Similarly, no statistically significant difference in CAD detection of cancers manifesting as microcalcifications was found. However, a statistically significant difference in CAD detection of malignant masses occurred in nondense versus dense breasts. CAD detection of masses is lower in dense breasts because of the greater "background noise" and similar density of masses to the surrounding parenchymal density. This difference, however, is still a smaller impact of breast density on mammographic sensitivity of breast cancer detection than has been reported for mammographic detection when CAD is not used. Few studies have evaluated the sensitivity of CAD in breasts of different densities. Ho and Lam [13] showed a decrease in sensitivity of CAD from 93.9% in women with nondense breasts

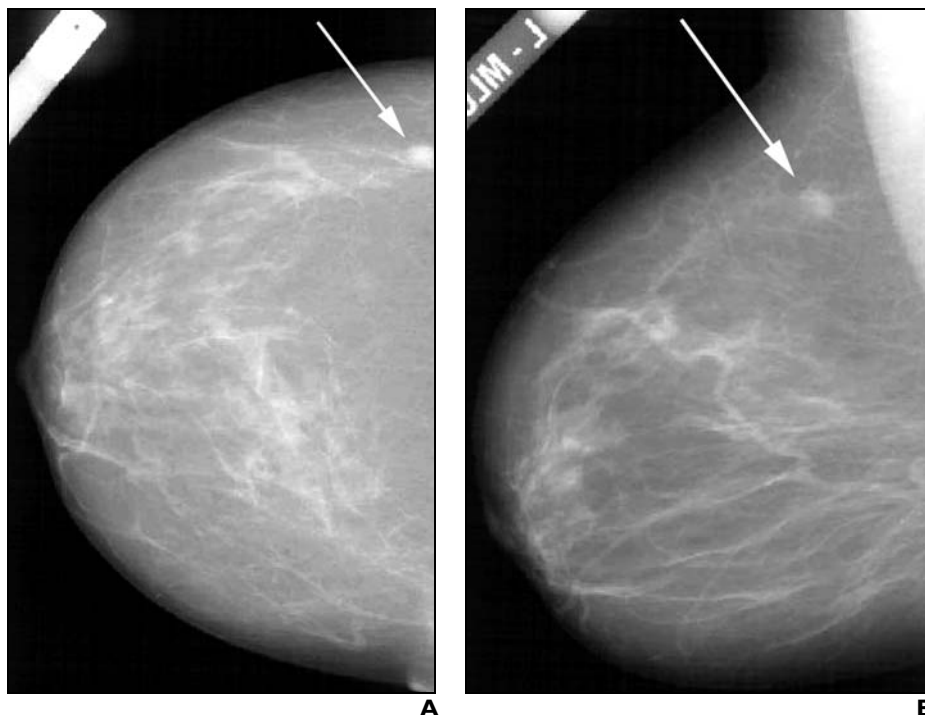
to 64.3% in women with markedly dense breasts. This study included a total of 264 mammograms with 108 cancer and 156 normal cases. Although Ho and Lam's findings are in contrast to ours, the difference may be due to the variance in the size of the study population in the two studies, with our study containing a nearly ninefold larger sample size of cancer cases. Another possible explanation for the difference in findings may be the proportion of mass versus microcalcification cases included in the study populations. Our study showed a statistically greater detection of mass cancer cases in nondense breasts. Therefore, it is possible that the proportion of mass versus microcalcification cases included could impact the statistical analysis. However, this study, which included 33% microcalcification cases, reflects the proportion of cancer cases that manifest as microcalcifications in clinical practice.

Similar to our findings, a recent study by Birdwell et al. [11], which included 110 positive cancer-screening mammograms, showed no significant difference in CAD performance in dense and nondense breasts. During screening mammography without the use of a CAD system, Birdwell et al. found that the second most frequently suggested reason for a missed cancer was greater breast density, second only to another distracting lesion. The dense breast was cited as a factor for lesion misses more often in cases of missed calcifications (34%) than

for masses (14%), a finding that is different from that reported in our study. Birdwell et al. showed that CAD performed similarly in the detection of calcifications (83%) and masses (82%) in dense breasts and in nondense breasts. The results of our study, in conjunction Birdwell et al.'s findings, show that CAD has a high sensitivity for the detection of microcalcifications equally throughout all breast densities. Although our study shows a difference in the sensitivity of CAD of masses in nondense (89%) and dense (83%) breasts, the sensitivity remains high in mammograms depicting both nondense and dense breast parenchyma.

Our study again confirmed multiple prior studies reporting significantly higher sensitivity of CAD in detecting microcalcifications versus masses [4, 5, 12]. Our results indicate that CAD may be particularly helpful in patients with dense breasts. Overall CAD sensitivity for the detection of breast cancer in dense breasts is 88%, with a 95% sensitivity for microcalcifications. When compared with other detection techniques such as sonography, physical examination, and mammography alone, mammography with CAD showed superior sensitivity at breast cancer detection in BI-RADS 3 and 4 density breasts [8].

The need for improved diagnosis of breast cancer in women with increased breast density is further emphasized by the greater risk of breast cancer in this population. Boyd et al. [14] showed that women with mammographi-



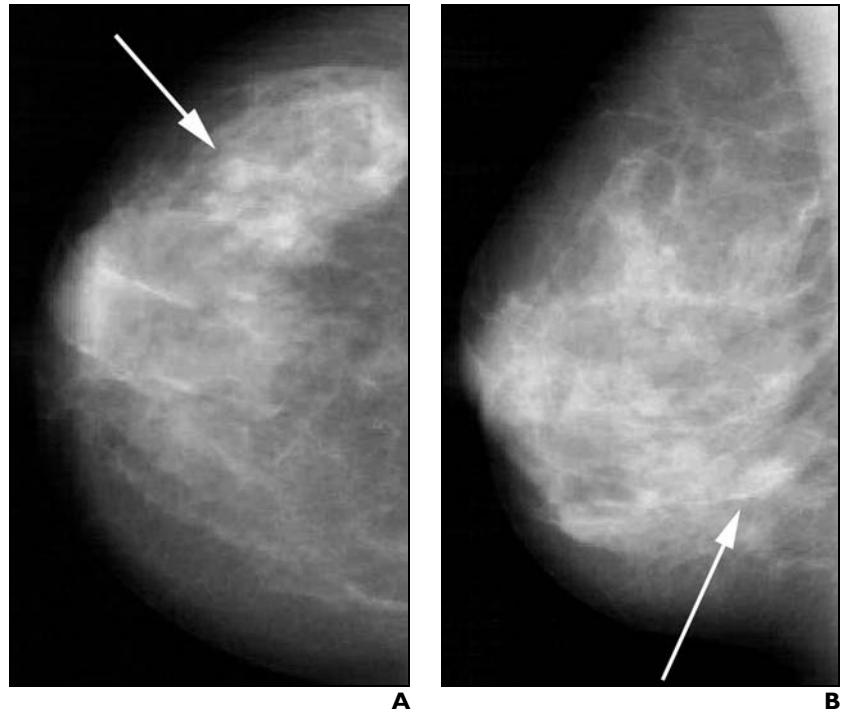
**Fig. 3.**—59-year-old asymptomatic woman.  
**A.** On left craniocaudal mammogram, arrow indicates mass in nondense breast.  
**B.** In left mediolateral oblique mammogram, arrow indicates mass in nondense breast.

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**Fig. 4.**—45-year-old asymptomatic woman.

**A.** In left craniocaudal mammogram, arrow indicates mass in dense breast.

**B.** In left mediolateral oblique mammogram, arrow indicates mass in dense breast.



cally dense breasts have a 1.8- to sixfold increased risk of breast cancer. A possible explanation for this finding is that the increased glandular tissue in a dense breast may result in greater propensity for malignant transformation by virtue of the increased amount of tissue. However, it is unclear what mechanism or genetic predisposition results in increased breast density or the resultant increased risk for breast cancer [15]. Regardless, the impact of using CAD for the detection of breast cancer may lead to a reduction in breast cancer mortality rates in these higher risk women. Additional studies are needed to further investigate the impact of CAD in women with dense breast tissue and breast cancer mortality.

Baum et al. [16] have shown that CAD can be used without significantly increasing workup rate or radiologist interpretation time, resulting in improved breast cancer detection without decreased radiologist productivity. Although our study shows additional false-positives in patients with dense breasts, this finding should not impact workup rate. The increased false-positives without additional workup rate can be explained by the fact that not all false-positives result in patient recall. The function of CAD is to point out potential areas of concern to the radiologist. The radiologist makes the final decision. The results of the findings by Baum et al. imply that the false-positives are

noted not to be of clinical concern and therefore do not result in patient recall. Furthermore, a recent study by Freer and Ulissey [12] showed that the use of CAD does not decrease the positive predictive value for biopsy. These studies show that CAD does not result in a negative impact on recall rate or positive predictive rate for breast biopsy.

In conclusion, our data suggest that increased breast density does not affect the performance of a CAD system for the detection of breast cancer. The use of CAD can improve breast cancer detection, regardless of breast density. The importance of this finding becomes more significant when considering the intrinsic increased risk of women with dense breasts. In addition, dense breast tissue is generally found in predominantly young and premenopausal women [14]. CAD proved to be particularly adept at marking microcalcifications in dense breasts but was nevertheless effective in detecting mass lesions in dense breast tissue. The decreased performance of CAD for detecting mass lesions in women with dense breasts supports further development of CAD algorithms to enhance the detection of malignant masses in patients with dense breast tissue.

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