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Radiology

Computer-aided Detection Output on 172 Subtle Findings on Normal Mammograms Previously Obtained in Women with Breast Cancer Detected at Follow-Up Screening Mammography[1]

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Abbreviations:
BI-RADS = Breast Imaging Reporting and Data System
CAD = computer-aided detection
DCIS = ductal carcinoma in situ

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PURPOSE: To evaluate, by using a computer-aided detection (CAD) program, the nonspecific findings on normal screening mammograms obtained in women in whom breast cancer was later detected at follow-up screening mammography.

MATERIALS AND METHODS: Four hundred ninety-three mammogram pairs—an initial negative screening mammogram and a subsequently obtained screening mammogram showing cancer—were collected. The mean interval between examinations was 14.6 months. In 169 cases, in which 172 cancers were later depicted, findings on the initial mammogram were subtle enough that either none or only one or two of five blinded radiologists recommended screening recall. On the initial negative mammograms, of the 172 areas where cancer later developed, 137 (80%) had subtle nonspecific findings and were retrospectively judged as having a benign or normal appearance. The mammograms with these subtle findings were evaluated with a commercially available CAD program, and the numbers of CAD marks on these nonspecific findings were analyzed.

RESULTS: Of the 172 cancers, 129 (75%) were invasive and 43 (25%) were ductal carcinoma in situ. The CAD program marked 72 (42%) of the 172 findings that subsequently developed into cancer: 24 (29%) of 82 findings recalled by none, 25 (49%) of 51 findings recalled by one, and 23 (59%) of 39 findings recalled by two of the five radiologists. Among the 137 areas with nonspecific normal or benign findings, 41 (30%) areas where cancer subsequently developed were marked by the CAD program.

CONCLUSION: A subset of cancers have perceptible but nonspecific mammographic findings that may be marked by a CAD program, even when the findings do not warrant recall as judged at blinded and unblinded radiologist review. The authors believe failure to act on such nonspecific but CAD-marked findings prospectively does not constitute interpretation below a reasonable standard of care.
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Computer-aided detection (CAD) of breast lesions involves the use of computer schemes to mark suspicious findings on mammograms, and the use of CAD to help improve breast cancer detection at mammographic screening has been proposed (1–3). Retrospective CAD studies of prior negative mammograms have been very sensitive in the marking of suspicious findings that were present but not prospectively recalled at screening. These studies have focused on the true-positive marks on suspicious findings that may have been missed.

We recently reported on the nonspecific findings seen on the initial normal screening

mammograms obtained in women in whom breast cancer was later detected at follow-up screening (4). In our report, we described perceptible but normal benign findings that would not be recalled for further evaluation, even in retrospect. In all cases, cancer was evident on follow-up screening mammograms obtained 9–14 months later. Thus, the purpose of our study was to evaluate, by using CAD, the nonspecific findings on normal screening mammograms obtained in women in whom breast cancer was later detected on follow-up screening mammograms.

MATERIALS AND METHODS

Case Set

The methods of mammogram collection in the case set have been previously described (1,2,4). Thirteen Mammography Quality Standards Act–certified facilities (eg, community-based hospitals, health maintenance organizations, and academic mammography centers) in the United States provided 1,083 consecutive cases of biopsy-proved cancer that was detected on screening mammograms obtained in asymptomatic women between 1994 and 1996 (1,2,4). Each institution gave institutional review board approval for use of these cases in this retrospective case-collection study, which was conducted in 1997. Informed consent was waived because any patient-identifying information was removed from all study materials. The average patient age at breast cancer detection was 62.3 years (range, 40–86 years). The 1,083 screening mammograms showing cancer were evaluated by one of the 13 facility radiologists, who, with knowledge of the biopsy-proved cancer location, marked this site on the screening mammograms by using transparent film overlays, one for each view.

The previously obtained negative screening mammograms (also referred to as prior or initial mammograms) from 493 cases were available for review. The mean time between the initial and follow-up screening examinations was 14.6 months (range, 9–24 months). Sixty-two of the 493 cases were excluded because of prior breast surgery that resulted in scars or findings marked by metallic skin markers. Four other cases were excluded because the original film hard copies were needed at the facility site before the end of the study. Thus, a total of 427 cases comprised the study cohort.

One of three board-certified radiologists, who were not among the facility radiologists, reviewed the 427 cases to determine if the cancers were visible in retrospect on the prior mammograms. One radiologist reviewed 242, one radiologist reviewed 103, and one radiologist reviewed 82 mammograms. Each radiologist used the previously created film overlays to locate the cancer on the prior mammograms. If a perceptible finding was deemed visible on the prior negative mammogram, the radiologist marked the location of the retrospectively visible finding by using a second set of transparent film overlays, thus establishing a reference-standard location of the subsequently detected cancer on the prior mammograms.

In 286 (67%) of the 427 cases, there were findings that were judged to be visible on the prior negative mammograms in locations where cancer later developed. The 286 prior negative mammograms were divided into four sets of approximately 75 mammograms each. Forty-five additional mammograms were added to each case set: five mammograms on which no abnormalities could be seen, 20 mammograms with small subtle cancers, and 20 negative mammograms, as confirmed on the basis of at least one subsequent mammographic examination with negative results during a 2-year follow-up period.

Blinded and Unblinded Radiologist Case Review

To determine if the findings on the prior negative mammograms should have been further evaluated, four panels of radiologists, each consisting of five members, performed a blinded review of the respective four case sets. The radiologists reviewed the original film hard copies and were unaware of the study purpose or the case mix. These panel radiologists (half of whom had a primary work focus in mammographic interpretation) were Mammography Quality Standards Act certified, had practiced radiology for a mean time of 17 years (range, 3–35 years), and had read a mean of 300 screening mammograms per month (range, 40–1,000 mammograms per month).

Each panel member independently assessed approximately 120 cases and categorized them according to American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) assessment codes (5). Lesions assigned BI-RADS codes 1 and 2 were considered normal or benign, and those assigned BI-RADS codes 0, 4, or 5 were considered abnormal. The use of BI-RADS code 3 was discouraged; however, the data showed that there were 16 cases with BI-RADS code 3 classifications, which for the purposes of this study were grouped with the BI-RADS codes 1 and 2 cases.

For clarity, we will refer to the cases that were assessed by the majority of five radiologists as BI-RADS codes 0, 4, or 5 as abnormal, meaning that the finding required immediate action. We will refer to mammograms showing findings that led the majority of radiologists to judge the case as BI-RADS code 1, 2, or 3 as normal, meaning that the finding was negative, benign, or not requiring immediate action. The panel radiologists were given the patients' ages, they were shown only the prior negative mammograms (ie, mammograms obtained 9–24 months before the cancer was diagnosed at screening mammography), and no earlier obtained mammograms were presented. The panel radiologists had a mean sensitivity of 84% (mean of 16.8 of 20 cases) for cancer detection in the 20 cases of subtle cancer findings added to each case set and a mean specificity of 81% (mean of 16.2 of 20 cases) for diagnosing the 20 normal cases added to the case set.

Mammograms that were judged by three or more of the five blinded panel radiologists to show abnormal findings at the reference location were considered missed cancers, the rationale being that if the majority of radiologists at blinded review interpreted the mammogram as requiring immediate work-up, then the finding had been prospectively missed (1,2). One hundred twelve cases were judged to be abnormal by using these criteria (ie, by the majority of the panel) and thus were excluded from this study.

Three or more of the five blinded panel radiologists judged the remaining 174 cases to be negative, benign, or requiring no immediate work-up. We classified these cases as having nonspecific findings by using the rationale that if the majority of radiologists at blinded review interpreted a mammogram as normal, then the finding was very subtle, normal, or benign in appearance. Five of the 174 nonspecific finding cases were excluded: four cases in which the cancer location indicated on the mammogram was judged to be inconsistent with the pathologic diagnosis or the cancer location and one symptomatic case that should have been excluded in the original study. The remaining 169 cases, in which 172 cancers were depicted at subsequent follow-up screening, comprised our final study group or case set.

All mammograms were digitized at 50-μm spatial resolution capability by us-

TABLE 1
CAD Results for 172 Findings, Stratified according to Number of Blinded Radiologists Who Recommended Recall and BI-RADS Rating

No. of Recall Radiologists*	No. of Findings Marked by CAD/Total No. of Findings†	BI-RADS Rating‡			
		0	1	2	4
0	24/82 (29)	7/9	4/31	13/42	0
1	25/51 (49)	9/10	3/14	13/27	0
2	23/39 (59)	14/15	1/5	7/18	1/1
Total	72/172 (42)	30/34	8/50	33/87	1/1

* Numbers of radiologists, out of a total of five blinded radiologists, who recommended recall of cases for further evaluation.

† "Number of findings marked by CAD" refers to the number of findings marked by CAD system where cancer later developed. Numbers in parentheses are percentages.

‡ Data are numbers of findings (in cases assigned the given BI-RADS rating) marked by the CAD system where cancer later developed/number of findings. BI-RADS ratings were assigned by two nonblinded breast imaging specialists.

ing a Lumisys LS85 digitizer (Lumisys, Sunnyvale, Calif) and downloaded to an Imation HQ969 laser printer (Imation Enterprises, St Paul, Minn) at 12 bits per pixel and 100-μm spatial resolution at the time of the initial study. These digitized images were then available on screen and printed to film hard copies for subsequent case review for this study. The digitized images were also archived for later CAD analysis.

The purpose of the unblinded review was to have the findings independently assessed by breast imaging specialists who knew the reference location of the subsequently detected cancer, to retrospectively reconfirm the assigned BI-RADS categories, to categorize each finding appearance, and to determine the reasons why the findings were nonspecific to the extent that they were categorized prospectively as BI-RADS category 1, 2, or 3 by the majority of five blinded radiologists. Two radiologists who specialize in breast imaging and have 14 (D.M.I.) and 19 (R.L.B.) years of experience in interpreting mammograms jointly reviewed the 169 cases in an unblinded review to categorize the findings and assess the possible reasons for the nondetection of and/or the nonaction on these findings. The digital-copy mammograms printed on film were used for this part of the study.

To ensure that the digital-copy mammograms were of sufficient quality for analysis, 20 original mammograms that included both masses (n = 12) and calcifications (n = 8) were recalled from the sites and compared side by side with the corresponding digital copies on dedicated mammography alternators. The two radiologists rated the image quality of the original and digital-copy mammograms by using a scale from 1 to 5—with 1 meaning unable to read, 3 meaning acceptable quality, and 5 meaning good quality—and a narrative description of mass or calcification visibility. The average quality ratings for the original (4.5) and digital-copy (4.4) mammograms were similar. The narrative descriptions revealed no cases in which the quality of the digital copy compromised the detection or characterization of a mass or calcification, further supporting the acceptability of using digital-copy mammograms for our study.

To assess the mammographic characteristics of the visible findings, the 169 prior negative digital-copy mammograms, the subsequently obtained follow-up mammograms on which cancer was detected, and the corresponding reference-location clear overlays were reviewed on a two-tiered dedicated motorized mammography alternator (RADX MS-604A; S&S X-Ray Products, Houston, Tex), with bright lights and magnifying lenses available for use. The four-view prior negative mammogram and its corresponding reference-location overlay were displayed on the top row, and the mammogram obtained 9–24 months later showing the cancer and its corresponding overlay were displayed on the bottom row. At the time of case review, although the locations of the subsequent cancers were evident from the follow-up mammograms, no patient information, examination date, or pathologic data were available to the unblinded reviewers.

The perceptible finding identified by using the reference-location overlay on the prior negative mammogram (reviewed on digital copies of the films) was analyzed according to finding type, size, location, and depth in the breast. The visibility of the lesion on each appropriate view, as well as the breast density, was also recorded. Each finding that was visible in retrospect was categorized by using the BI-RADS lexicon for masses and calcifications and BI-RADS categories 0–5, with category 3 excluded (5). Because we endeavored to fully describe all findings, we used several non–BI-RADS terms to describe the normal and benign findings that are not included in the lexicon. Nonspecific finding terms included focal islands of normal-appearing tissue, benign-appearing calcifications, few benign calcifications, and densities. Otherwise, the findings were characterized by using the BI-RADS lexicon. The term that best described the major characteristic of the perceived finding was considered the finding type.

After mammogram analysis, the pathology reports were reviewed (by D.M.I.) for each cancer that was subsequently detected on the follow-up screening mammograms and each finding on the prior negative mammogram was compared with the subsequently detected cancer according to type and grade.

The patient population associated with and the cancer types and descriptors of the findings in this study have been fully described previously (4). The following is a summary of these data: The average age of the 169 patients in whom the 169 mammograms were obtained was 62.3 years. Sixteen (10%) patients were aged 40–49 years; 50 (30%) patients, 50–59 years; 58 (34%) patients, 60–69 years; 40 (24%) patients, 70–79 years; and five (3%) patients, 80 years or older. The breast tissue was judged to be fatty in 16 (10%) of the 169 cases, was of scattered fibroglandular density in 78 (46%) cases, was heterogeneously dense in 54 (32%) cases, and was extremely dense in 21 (12%) cases.

One hundred seventy-two cancers were detected at follow-up screening mammography performed in the 169 patients. At the time of diagnosis, 43 (25%) of the 172 cancers were ductal carcinoma in situ (DCIS) and the remaining 129 (75%) were invasive cancers. The median DCIS lesion size was 10 mm (range, 2–75 mm). The sizes of 24 (56%) of the 43 DCIS lesions were determined from the pathology report, and the sizes of the remaining DCIS lesions were based on the maximal diameter measurements of abnormal calcifications on the mammogram. The median lesion size of the invasive cancers was 10 mm (range, 1–55 mm). The sizes of 119 (92%) of the 129 invasive cancers were determined from the pathology report, and the sizes of the remaining invasive cancers were based on measure-

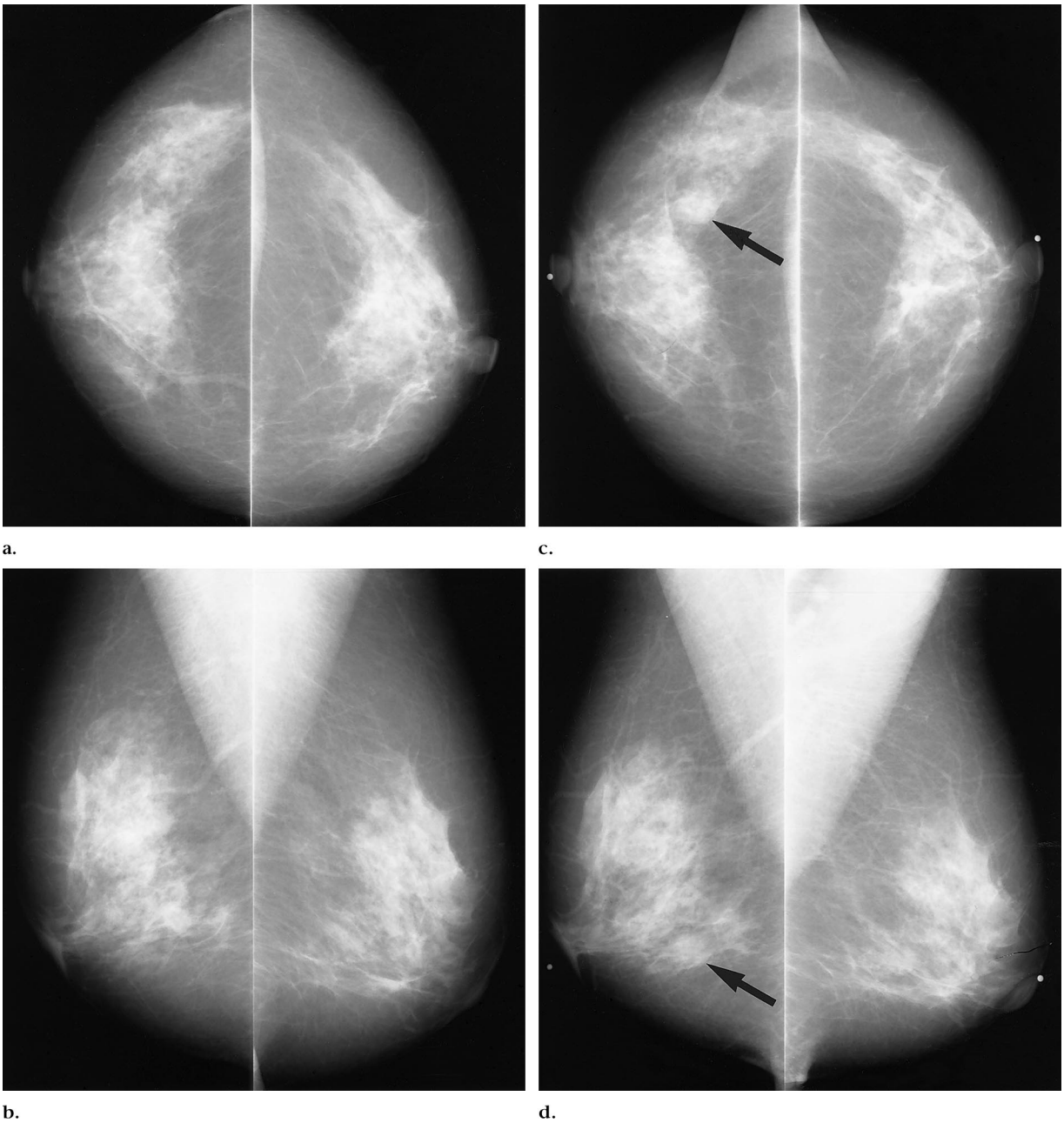
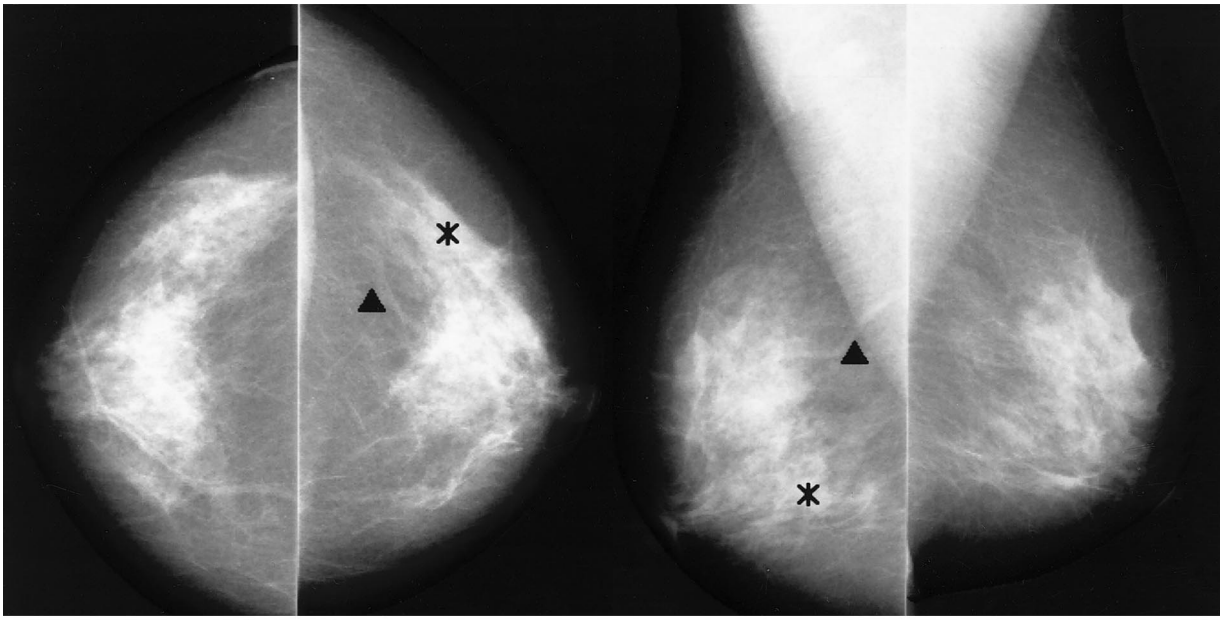


Figure 1. Mammograms obtained in 61-year-old woman show a BI-RADS 1 lesion seen at unblinded rereview with CAD output. Normal-appearing **(a)** craniocaudal and **(b)** mediolateral-oblique screening mammograms obtained 13 months prior to diagnosis of a 1.2-cm, grade II invasive ductal carcinoma are shown. When the location of the subsequently developing cancer is noted, in retrospect, there is a focal island of normal tissue in the lower part of the right breast that was interpreted as normal by the two breast imaging specialists at unblinded review. **(c)** Craniocaudal view subsequently obtained at the time of cancer diagnosis shows an oval obscured mass (arrow) in the outer part of the right breast that is denser than the tissue seen in **a**. **(d)** Mediolateral oblique view obtained at the time of cancer diagnosis shows the same mass (arrow) in the lower part of the right breast *(Fig 1 continues)*.

ments of the abnormal findings on the mammograms. Of the invasive cancers, 112 were T1 tumors and 17 were T2 or higher-stage tumors. Of the 104 women with invasive cancer and known axillary node status, 22 (21%) had lymph nodes that were positive for metastatic disease.

All five of the blinded panel radiologists rated nearly half (n = 80 [47%]) of the 169 mammograms as normal at review. Fifty-one (30%) of the 169 mammograms were rated as normal by four of the five blinded panel radiologists, and 38 (22%) were rated as normal by three of these radiologists.

At unblinded review, with knowledge of the subsequent cancer location, the two breast imaging specialists would have recalled 35 (20%) of the 172 findings, rating them as BI-RADS 0 or 4 tumors. At unblinded review, the remaining 137 (80%) of the 172 findings were considered to be nonspecific, even in retrospect, by the two unblinded radiolo-



e.

Figure 1 *(continued).* **(e)** CAD output shows low-spatial-resolution mammograms (from left to right: right craniocaudal, left craniocaudal, right mediolateral-oblique, left mediolateral-oblique views) and marked findings. The CAD system marked the focal island of tissue (*) on only the right mediolateral-oblique view (left image on right side) of the prior normal mammograms in **a** and **b**. The CAD system also marked benign-appearing calcifications (▲) in the upper part of the right breast on the right mediolateral-oblique view (left image on right side). The CAD system marked skin calcifications (▲) and a region of glandular tissue (*) in the outer part of the left breast on the left craniocaudal view (right image on left side). Note that the finding where cancer later developed is seen on only one view (right mediolateral-oblique) and looks like normal tissue.

gists, and all of these findings were judged to be BI-RADS 1 and 2 tumors with the radiologists having knowledge of the subsequent cancer location.

CAD Evaluation

The 169 original mammograms (ie, the high-spatial-resolution digital images copied from the original mammograms) showing the 172 findings were processed through a CAD system, and the number of CAD marks on each image was recorded. The CAD system (V2.3; R2 Technology, Los Altos, Calif) that was used consists of a laser digitizer, a computer that uses proprietary signal-processing algorithms, and a customized motorized viewer with video display monitors. The CAD algorithm involves the use of a neural network that identifies features of microcalcifications (ie, clusters of bright spots) and marks them with triangles. The program identifies masses or architectural distortions as regions of high density with or without radiating lines and marks them with asterisks. This software version has been found to make an average of two marks per four-film normal case. In this study, there were an average of 3.9 (range, 0–12) CAD marks per case.

In general, cases with findings have more marks per case owing to the necessary addition of one or two marks per finding, depending on whether the finding is marked on one or on both standard mammographic views. A low-spatial-resolution (640 × 480 pixels) version of the marked digital mammogram is displayed on a small monitor on a motorized viewer directly below the digital mammograms when the unit is prompted. In normal clinical use, the marked images would be displayed only after the original film hard-copy images had been reviewed.

The 169 original mammograms were digitized and analyzed by the CAD program, and the resulting low-spatial-resolution images with marked areas were reviewed (by D.M.I., R.L.B., K.F.O.). The CAD-marked areas were directly compared with the findings on the digital-copy prior negative mammograms, and the corresponding reference-location overlays, described by the two unblinded breast imaging specialists. Each finding was judged to be either unmarked or marked by the CAD system. Marked findings included marks of the correct type on any part of the finding on either view, marks of either type on calcified masses, and calcification marks on any part of a calcification cluster. Unmarked findings were marks of the incorrect type on the finding or no marks on the findings. All other marks were recorded and counted as marks that were unrelated to the findings in this study.

Marks were recorded as "marks" or as "marks unrelated to the findings under study" and were compared with the pathology results, with each finding, and with the ratings assigned the findings at review by the five blinded panel radiologists and the two unblinded radiologists.

RESULTS

The numbers of cases and findings recalled by the five blinded radiologists as compared with the numbers of cases recalled by the two unblinded breast imaging specialists—data that indicate the number of times the CAD system correctly marked each finding—are summarized in Table 1. None of the five blinded panel radiologists recalled the cases associated with 82 (48%) of the 172 findings; CAD marked 24 (29%) of these 82 findings. The CAD system marked increasingly higher percentages of findings when one

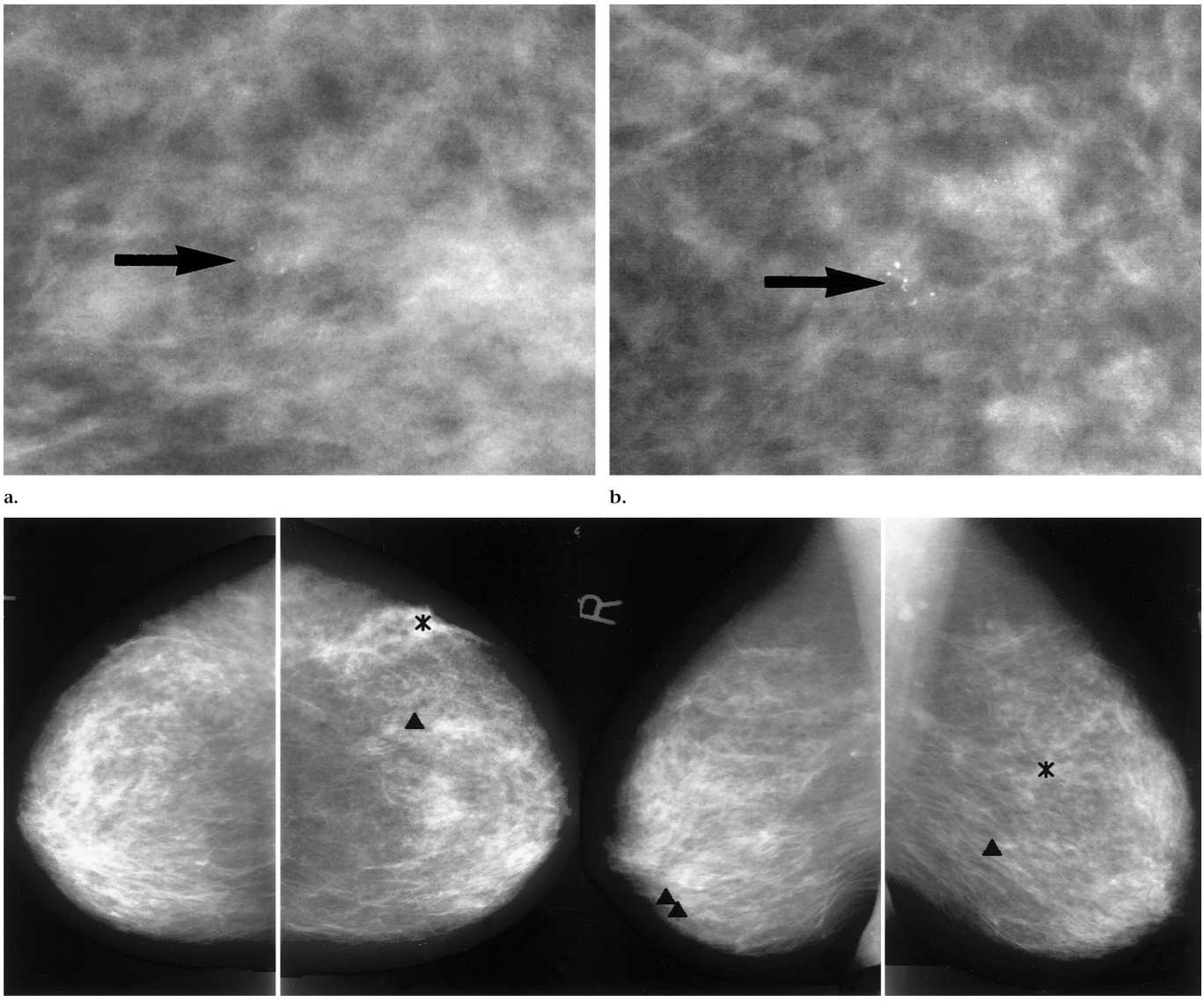


Figure 2. **(a)** Prior negative and **(b)** subsequently obtained follow-up screening mammograms obtained in 69-year-old woman. **(a)** Photographically magnified left craniocaudal view of prior mammogram shows four benign-appearing calcifications (arrow) that were rated as BI-RADS 2 lesions by the unblinded radiologists and recalled by none of the five blinded panel radiologists. **(b)** Photographically magnified left craniocaudal view obtained 11 months later shows a 4-mm cluster of pleomorphic calcifications (arrow) that developed at the site of the normal-appearing calcifications in **a**. Biopsy revealed intermediate-grade DCIS. **(c)** CAD output shows low-spatial-resolution mammograms (from left to right: right craniocaudal, left craniocaudal, right mediolateral-oblique, left mediolateral-oblique views) and marked findings. On the prior normal mammogram, the CAD system marked the benign-appearing calcifications (▲) and a focal island of normal tissue (*) in the left breast on the craniocaudal (right image on left side) and mediolateral-oblique (right image on right side) views of the left mammogram. The CAD system also marked a few possible calcifications (two triangles) in the lower part of the right breast on the right mediolateral-oblique view (left image on right side).

or more of the five blinded radiologists recalled the case—specifically, it marked 25 (49%) of 51 findings recalled by one and 23 (59%) of 39 findings recalled by two of the five radiologists.

The data in Table 1 also show that of the 137 findings rated as normal or benign (ie, BI-RADS 1 or 2) by the two radiologists at unblinded retrospective review, 41 (30%) were marked by the CAD system. Specifically, CAD marked 41 findings that were judged to be not worthy of immediate action by both the majority of five blinded radiologists and the two unblinded radiologists (Figs 1, 2). CAD also marked the majority of findings (31 [89%] of 35) that were judged to be abnormal (BI-RADS 0 or 4) by the two radiologists at unblinded review.

The data in Table 2 are the two unblinded radiologists' BI-RADS ratings of the findings, the pathologic diagnoses categorized by mammographic finding type, and the numbers of times the CAD system marked the findings. The CAD system frequently but not invariably marked nonspecific findings in locations where both invasive and noninvasive cancers later developed. Specifically, the system marked findings where 47 (36%) of the 129 invasive cancers and 25 (58%) of the 43 DCIS lesions later developed. The data in Table 2 also show the types of

TABLE 2
Findings Marked by CAD System Categorized by Finding Type, BI-RADS Rating, and Diagnosis at Follow-up Screening

Finding Type	No. of Findings	Diagnosis at Follow-up*†		BI-RADS Rating*‡	
		Invasive Cancer	DCIS	0 or 4	1 or 2
Focal island of normal tissue	65	13/63	1/2	0	14/65
Benign-appearing calcifications	44	17/21	18/23	20/21	15/23
Few benign calcifications	24	4/9	3/15	0	7/24
Mass	11	6/11	0	5/7	1/4
Density (only on one view)	9	3/8	1/1	3/4	1/5
Mass with calcifications	3	2/2	1/1	3/3	0
Other	16	2/15	1/1	0	3/16
Total	172	47/129	25/43	31/35	41/137

* Data are numbers of findings marked by the CAD system and subsequently determined to be cancer/total number of findings.
† Diagnoses determined at follow-up screening mammography.
‡ BI-RADS rating assigned to findings seen on initial negative screening mammograms by two nonblinded breast imaging specialists.

TABLE 3
Number of Mammographic Views on Which a Finding Was Seen and CAD Results, Stratified according to BI-RADS Ratings

No. of Views and CAD Results*	No. of Findings	BI-RADS 0 or 4†	BI-RADS 1 or 2†
No view, none marked	6	0	6
One view			
Marked	18	4	14
Not marked	46	2	44
Two views			
Both marked	23	15	8
One marked	31	12	19
None marked	48	2	46
All marked views‡	72	31	41
Total	172	35	137

* Numbers of views on which findings were seen and marked by the CAD system.
† Data are numbers of findings with the given BI-RADS classification, as assigned by two nonblinded breast imaging specialists.
‡ Total numbers of findings seen on marked views.

findings in the 137 cases that were considered normal or benign by the two radiologists at unblinded review and what types of findings were marked by the CAD system. Specifically, the CAD system marked 14 (22%) of the 65 focal islands of glandular tissue, 15 (65%) of the 23 benign-appearing calcifications, seven (29%) of the 24 benign calcifications, one (25%) of the four benign-appearing masses, one (20%) of the five benign-appearing densities, and three (19%) of the 16 other findings.

Thirty-five findings were rated as BI-RADS 0 or 4 tumors by the two radiologists at unblinded review. Of these 35 findings, 31 (89%) were marked by the CAD system and 22 (63%) subsequently became invasive cancers in the same area. Of the 137 findings rated as BI-RADS 1 or 2 tumors at unblinded review, 41 (30%) were marked by the CAD system and 107 (78%) subsequently became invasive cancers in the same area.

The data in Table 3 show the numbers of views on which a finding was seen and the numbers of views on which the finding was marked, with both groups of data stratified according to the BI-RADS categories assigned by the two unblinded radiologists. Six findings were judged to have the appearance of normal fibroglandular tissue, which was essentially undetectable on both views. None of these six findings were marked by the CAD system. Of the 64 findings that were seen on only one mammographic view, 18 (28%) were marked by the CAD system on that view. Of the 102 findings that were seen on two views, 23 were marked by the CAD system on both views (22%). The CAD system marked 31 (30%) of the 102 findings on only one of the two views.

DISCUSSION

In most retrospective mammographic CAD studies, emphasis is placed on research of the true-positive marks on suspicious mammographic findings that require immediate action. Our study was focused on CAD marks on nonspecific findings that are perceptible on initial negative screening mammograms and subsequently develop into cancer. In the present study, a subset of 137 such nonspecific findings were not considered suspicious and did not warrant recall, even in retrospect. The CAD system marked 41 (30%) of these nonspecific findings, including 22 (47%) of 47 benign and benign-appearing calcifications and up to one-fifth (19 [21%] of 90) of other findings such as nonspecific islands of normal-appearing fibroglandular tissue. The CAD system marked nonspecific findings in locations where invasive cancer and DCIS subsequently developed.

Our finding that the CAD system marks normal or benign findings in locations where cancer later develops prompts several questions: When CAD is used on screening mammograms in a normal clinical setting, what is the clinical importance of CAD marks on nonspecific mammographic findings? Do all CAD marks on nonspecific findings warrant recall? Do all CAD marks on areas where cancer later develops warrant recall prospectively, even when the finding is nonspecific and cannot be distinguished from other nonspecific findings?

The CAD system marks a percentage of suspicious findings that might represent cancer—usually spiculated or irregular masses or pleomorphic calcifications. The benefit of CAD manifests when the radiologist's attention is drawn to a find-

ing that is interpreted as abnormal, the patient is recalled at the screening, and the work-up results in a diagnosis of breast cancer that is treated adequately, and, thus, an improved prognosis for the woman is expected. With this scenario, one assumes that the radiologist interprets the marked finding correctly. However, mammographic interpretation is based on the mammographic features of the finding and the experience of the radiologist and not specifically on the CAD marks.

In clinical practice, nonspecific findings are often seen on mammograms. We have shown in prior work (4) that these nonspecific findings do not necessarily warrant recall, and it is our opinion that failure to act on these findings does not deviate from the appropriate standard of care. On the basis of standard medical practice, nonspecific findings do not require recall at screening (6,7) because these findings are ordinarily not reported. Thus, the CAD system may mark nonspecific findings, but these marks should be subordinated to standard interpretation. If nonspecific findings are correctly interpreted as benign and returned to screening in routine clinical practice, then it is reasonable that these findings will be returned to screening even when they are marked by a CAD system.

CAD algorithms are specifically designed to have a high stand-alone sensitivity for cancer detection, with a corresponding high number of false marks per case. Radiologists who purchase CAD systems are informed of the average number of marks per negative case and that the majority of marks do not indicate breast cancer. It is neither necessary nor reasonable for a radiologist to call back all findings marked by a CAD system. The CAD system used in this study made approximately two false-positive marks per mammographic examination. To calculate how many benign findings might be marked in this scenario, let us assume that there was a prevalence of six cancers per 1,000 screening mammograms and a (high) rate of possible missed cancer of one cancer per 1,000 screenings and that the CAD system marked the missed cancer on two views. If we also assume that there were five radiologist-detected cancers per 1,000 screenings and that the CAD system marked these cancers on two views, then there would be 10 marks on the radiologist-detected cancers. This would result in 1,988 marks on the benign findings, 10 marks on the five radiologist-detected cancers, and two marks on the missed cancer. With these assumptions, the CAD system would mark more than 1,000 benign findings for every cancer that would otherwise be missed by a single radiologist reader.

In clinical practice, it is expected and recognized that many benign and normal findings will be marked by the CAD system and that the threshold to mark findings emphasizes the system's increased sensitivity. The radiologist interprets CAD-marked findings on the basis of the finding's mammographic features and the radiologist's experience and knowledge of mammographic appearances of breast cancer. Thus, the most important element of image interpretation in the setting of CAD marks is how the radiologist uses his or her knowledge of mammography and breast cancer. Recalling all findings marked by a CAD system is neither prudent nor reasonable, especially given the known programming thresholds of this tool. Ultimately, it is the radiologist's knowledge of breast cancer imaging and diagnostic acumen that influences the choice to recall a finding, not the marking of a finding by a CAD system.

Our study findings are relevant not only to prospective medical management outcomes but also to medicolegal issues. Medicolegal issues are not trivial: According to the results of a recent national study (8), delayed diagnoses of breast cancer remain the most common reason that physicians are sued, and radiologists remain the most commonly named defendants. In a Physicians Insurers Association of America study (9,10), follow-up mammography depicted a nonpalpable lesion in 48 patients, with an average delay in diagnosis of 20.1 months after the initial mammographic examination.

The presence of subthreshold or nonspecific features seen retrospectively on mammograms obtained in patients who developed breast cancer has been previously reported (4,10–13). What effect, then, should CAD marks have on the potential legal liability of the radiologist who decides not to recall the patient for immediate evaluation? The law has repeatedly held physicians to the standard of care of a reasonable and prudent physician under similar circumstances (14). The CAD mark is intended to draw the radiologist's attention to a given area and is used to mitigate the possibility of detection error in case the anatomic site of concern has not been sufficiently evaluated (15). Once an area is identified, either with or without a CAD mark, the decision to recall the patient is based on the radiologist's training, familiarity with signs of breast cancer, and experience. This decision is subject to the legal test of reasonableness—not of accuracy or certainty—so that a mistake is not tantamount to breaching the requisite standard of care (16).

Our study results indicate that CAD systems mark a finite percentage of nonspecific mammographic findings in areas where cancer subsequently develops. However, that percentage is neither sufficiently high nor designed for specificity to the extent that it can be an independent variable in deciding the reasonableness of recall. Similarly, if a finding that would be reasonable to recall is not recalled, then the presence (or absence) of a CAD mark is subordinate to the analysis of the specific mammographic features of that area. Although research of ways to reduce the variability of diagnoses by using CAD is underway (17), CAD technology has not been advocated with respect to recall rates, the determinants of which have been reported in other studies (18,19). Our study results indicate that when a nonspecific area is identified by using CAD in a detection setting, the clinical importance—and especially the legal importance—of the mark with respect to the decision to recall are moot.

There were several limitations in our study. The first limitation was our use of digital-copy mammograms, which never have the spatial resolution or lesion conspicuity that completely matches those of the original films. Standard parameters were used to print the digital-copy films. However, we performed a matched evaluation of a subset of original and digital-copy mammograms, which revealed no substantial difference between the two images, validating our results.

A second possible limitation was our use of digitized mammograms from analog films. The fact that most commercially available CAD systems are used on digitized film, however, justifies the technique used in this study despite the noise and image degradation produced by the digitization process. In the future, other studies might be performed by using CAD on directly acquired digital mammograms.

Another limitation was the use of the five-radiologist panel that performed experimental blinded readings, as compared with truly prospective blinded readings, to define the set of nonspecific findings. It is well known that retrospective readings may yield more positive findings than prospective readings (13). The unblinded two-radiologist readings used to characterize and assess the nonspecific findings were another potential

but unavoidable limitation of our study, because complete case knowledge was necessary to truly know whether a finding was located where the cancer later developed. Also, since this was a retrospective study, whether the CAD marks would have prompted a change in prospective assessments was not evaluated, because CAD was not available at the time of the original interpretations. Although determining radiologists' responses to CAD marks would have been interesting from a psychological aspect, it was beyond the scope of this study.

Our study results show that a subset of cancers have perceptible but nonspecific mammographic findings that do not warrant recall, as judged by a majority of blinded radiologists and by two unblinded radiologists, and that these findings may be marked by a CAD program. We believe failure to act on the nonspecific findings marked by a CAD program does not necessarily constitute mammographic interpretation below a reasonable standard of care.

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