ORIGINAL RESEARCH | Annals of Internal Medicine

Short-Term Outcomes of Screening Mammography Using Computer-Aided Detection

A Population-Based Study of Medicare Enrollees

Joshua J. Fenton, MD, MPH; Guibo Xing, PhD; Joann G. Elmore, MD, MPH; Heejung Bang, PhD; Steven L. Chen, MD, MBA; Karen K. Lindfors, MD, MPH; and Laura-Mae Baldwin, MD, MPH

Background: Computer-aided detection (CAD) has rapidly diffused into screening mammography practice despite limited and conflicting data on its clinical effect.

Objective: To determine associations between CAD use during screening mammography and the incidence of ductal carcinoma in situ (DCIS) and invasive breast cancer, invasive cancer stage, and diagnostic testing.

Design: Retrospective cohort study.

Setting: Medicare program.

Participants: Women aged 67 to 89 years having screening mammography between 2001 and 2006 in U.S. SEER (Surveillance, Epidemiology and End Results) regions (409 459 mammograms from 163 099 women).

Measurements: Incident DCIS and invasive breast cancer within 1 year after mammography, invasive cancer stage, and diagnostic testing within 90 days after screening among women without breast cancer.

Results: From 2001 to 2006, CAD prevalence increased from 3.6% to 60.5%. Use of CAD was associated with greater DCIS incidence (adjusted odds ratio [OR], 1.17 [95% CI, 1.11 to 1.23]) but no difference in invasive breast cancer incidence (adjusted OR, 1.00 [CI, 0.97 to 1.03]). Among women with invasive cancer, CAD was associated with greater likelihood of stage I to II versus III to IV cancer (adjusted OR, 1.27 [CI, 1.14 to 1.41]). In women without breast cancer, CAD was associated with increased odds of diagnostic mammography (adjusted OR, 1.28 [CI, 1.27 to 1.29]), breast ultrasonography (adjusted OR, 1.07 [CI, 1.06 to 1.09]), and breast biopsy (adjusted OR, 1.10 [CI, 1.08 to 1.12]).

Limitation: Short follow-up for cancer stage, potential unmeasured confounding, and uncertain generalizability to younger women.

Conclusion: Use of CAD during screening mammography among Medicare enrollees is associated with increased DCIS incidence, the diagnosis of invasive breast cancer at earlier stages, and increased diagnostic testing among women without breast cancer.

Primary Funding Source: Center for Healthcare Policy and Research, University of California, Davis.

Ann Intern Med. 2013;158:580-587. www.annals.org
For author affiliations, see end of text.

In the past decade, 2 technologies have transformed mammography screening methods in the United States. First, digital mammography has supplanted film-screen mammography as the predominant method of image acquisition and storage. Second, most radiologists now use computer algorithms, or computer-aided detection (CAD), to mark and reassess potentially suspicious lesions that may have been missed on initial mammogram review. In 2001, Congress extended Medicare coverage to CAD, and CAD has since diffused widely into U.S. practice (1–3). In Europe, where double-reading by 2 radiologists is common, some have proposed replacing the second reader with CAD (4).

Despite broad uptake, the effectiveness and clinical utility of CAD in screening mammography remains controversial. In individual radiology practices, CAD adoption has been associated with greater rate of cancer detection, along with commensurate increases in false-positive rates (5–9), and within 3 British health system breast screening centers, outcomes were similar whether mammograms were double-read or interpreted by a single reader using CAD (10). However, in some practices, CAD adoption has been associated with little, if any, clinical effect (11, 12). The clinical effect of CAD may be heterogeneous across practices (13) or radiologists (14).

In addition, CAD may differentially facilitate detection of noninvasive breast cancer, or ductal carcinoma in situ (DCIS), rather than invasive breast cancer (6–8, 15–18). Because randomized clinical trials suggest that the effect of mammography on breast cancer mortality derives chiefly from detecting invasive cancer (19, 20), it is crucial to delineate the effect of CAD on the detection of invasive and noninvasive breast cancer. In multicenter studies, CAD has not been associated with a clear improvement in the diagnosis of invasive breast cancer (15, 16) despite greater false-positive (15, 16) and biopsy rates (15). However, because breast cancer is uncommon, studies to date may have had insufficient sample sizes of participants with cancer to precisely estimate the association of CAD with detection of invasive versus noninvasive breast cancer or its association with invasive breast cancer stage, size, or lymph node status, all of which are important predictors of breast cancer survival.

As stated in a U.S. Preventive Services Task Force evidence review, new digital technologies, such as CAD, "have become widely used in the United States without definitive studies of their effect on screening" (21). Ideally, clinical trials would compare breast cancer outcomes among women screened with CAD versus without CAD, but such trials would require long-term follow-up of very

large samples (22). To our knowledge, no such trials are planned or ongoing. However, now that CAD has diffused into clinical practice in the United States, the linked SEER (Surveillance, Epidemiology and End Results)–Medicare data enable a large-sample, population-based observational study of the clinical effect of CAD within the Medicare population. Although evaluation of CAD among both younger and older women having screening is desirable, the SEER–Medicare data offer sample sizes and analytic precision that cannot otherwise be achieved. Therefore, we assessed associations between CAD use during screening mammography received by Medicare enrollees and the incidence of invasive breast cancer and DCIS; invasive breast cancer stage, size, and lymph node status; and subsequent diagnostic testing among women without breast cancer.

Context

During the past decade, use of both computer-aided detection (CAD) in interpreting mammograms and digital mammography dramatically increased.

Contribution

Among older women, the addition of CAD interpretation to mammography resulted in more women having further diagnostic testing, including biopsy. Women were more likely to be diagnosed with ductal carcinoma in situ but not with invasive breast cancer. Cases diagnosed with use of CAD were at an earlier stage than those diagnosed without CAD.

Caution

The effect of CAD mammography on breast cancer mortality could not be assessed.

Implication

Introduction of newer technologies, such as CAD mammographic interpretation and digital mammography, will probably contribute to the current debate on the benefits and harms of screening mammography.

—The Editors

METHODS

Data

Analytic data sets were derived from SEER–Medicare data, which include detailed information about persons diagnosed with breast cancer from regional SEER registries in 15 states and their Medicare claims. SEER captures data on diagnosis dates, tumor characteristics, and initial treatment for 98% of women with breast cancer in SEER regions (23). Medicare data include claims for physician, outpatient, and hospital services. Medicare claims include service dates and Healthcare Common Procedure Coding System (HCPCS) codes, which enable identification of clinical services, and International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM), codes, which enable identification of symptoms and diagnoses. Claims data, however, do not contain information on mammogram interpretation, precluding measurement of sensitivity or specificity. We linked claims to physician data from the American Medical Association Physician Masterfile, which includes reliable data on selected physician characteristics (24). The SEER–Medicare database also includes Medicare data on a random 5% sample of women without cancer diagnoses in SEER regions. Codes for defining study variables are given in **Appendix Table 1** (available at www.annals.org).

Design, Setting, and Participants

We conducted a retrospective cohort study of Medicare enrollees who had screening mammography from 2001 to 2006 in SEER regions. Units of analyses were screening mammograms from women aged 67 to 89 years on mammography dates who were enrolled in Medicare Parts A and B for 2 previous years. We used a recently validated, claims-based algorithm to distinguish screening from diagnostic mammography (25). According to the algorithm, study mammography occurred at least 9 months apart and was done before any breast cancer diagnosis.

After screening mammography, we observed women for up to 1 year or until repeated screening mammography for breast cancer diagnoses and for 90 days for receipt of diagnostic tests. Women were excluded if they withdrew from Medicare parts A or B or died within 1 year after mammography. For analyses of cancer incidence rates, we applied probability weights of 20 to mammography derived from the 5% sample of women without breast cancer; these analyses represent the fee-for-service Medicare population that receives screening mammography within SEER regions. Analyses of diagnostic testing were unweighted and restricted to the 5% sample of women without breast cancer so analyses would represent diagnostic testing after false-positive screening mammography.

Outcomes

Breast Cancer Outcomes

We used SEER data to identify incident DCIS and invasive breast cancer diagnosed within 1 year of screening mammography. Breast cancer cases were classified by stage based on the American Joint Committee on Cancer, Seventh Edition (range, stage 0 [for DCIS] to I to IV [for invasive cancer]) (26). We classified invasive breast cancer by tumor size, using ordinal (0 to 0.49 cm, 0.5 to 0.99 cm, 1.0 to 1.99 cm, and ≥2.0 cm) and dichotomous (<1 vs. ≥1 cm and <2 vs. ≥2 cm) classifications, and lymph node status (negative or positive).

Diagnostic Testing

Among women who had no breast cancer diagnosis within 1 year of screening, we examined claims in the 90 days after mammography for HCPCS and ICD-9-CM codes for diagnostic mammography, breast ultrasonography, and breast biopsy and classified women by receipt or

nonreceipt of each test. We also classified women by receipt of either diagnostic mammography or breast ultrasonography because either test may be done on women recalled after abnormal screening results.

Computer-Aided Detection

We classified mammography as using CAD if mammography claims included HCPCS codes for CAD. Codes for CAD on Medicare claims are highly accurate for both film and digital mammography (27). Because simultaneous billing for both digital mammography and CAD was not allowed until 1 April 2003, we excluded digital mammography done before that date to avoid potential misclassification by CAD status.

Patient, Mammography, and Radiologist Covariates

We classified women by age (67 to 69, 70 to 74, 75 to 79, 80 to 84, and 85 to 89 years) and race or ethnicity (White, non-Hispanic; Black; Asian or Pacific Islander; Hispanic; and other). Rurality of residence counties was classified by using Rural–Urban Continuum codes. We defined patients' neighborhood income as the median income of elderly residents within the same ZIP code according to the 2000 U.S. Census.

Because previous mammography may influence cancer prevalence and current interpretation (28), we classified patients on the basis of the timing of mammography claims before the index mammography (<18 months, 18 to 24 months, and either >24 months or no previous mammography). Previous mammography may also reflect patient attitudes toward preventive care and overall patient access to health care. We further classified mammography done within 24 months as CAD versus non-CAD.

Using outpatient and inpatient claims for the 2 years before mammography, we identified 38 comorbid conditions and classified women on the basis of both stable (0, 1, 2, or ≥3) and unstable comorbid conditions (0 or ≥1) (29). Examples of stable comorbid conditions include arthritis and diabetes, whereas unstable comorbid conditions include severe heart failure and end-stage renal disease. We also categorized mammography as digital versus film using validated procedure codes (27) and by year and SEER region.

We used the unique physician identification number on claims to link mammography to radiologists' characteristics in the American Medical Association Physician Masterfile (24) and specified the performing radiologist's age, sex, primary type of practice (direct patient care vs. teaching or other), graduation from a U.S. versus non-U.S. medical school, and years since medical school graduation.

Analyses

We compared the characteristics of CAD and non-CAD mammography and computed unadjusted incidence rates and incidence rate ratios of breast cancer diagnoses by CAD status. We compared the unadjusted stage, size, and lymph node status of invasive breast cancer diagnosed after mammography with and without CAD using chi-square tests or the Cochran–Armitage test for trend.

We used logistic regression to estimate associations between CAD use and outcomes, while adjusting for patient and physician covariates, year, and SEER region and correcting SEs for the sampling design and within-physician clustering. In analyses of tumor stage, size, and lymph node status, we estimated adjusted odds ratios (ORs) that invasive breast cancer cases had earlier stage, smaller size, and negative lymph node status after mammography with versus without CAD. Because 1 or more physician characteristics were missing for 9.8% of mammograms, we did analyses both with adjustment for physician covariates (excluding mammograms with missing physician data) and without adjustment for physician characteristics (including all mammograms). Because adjustment for physician covariates had no meaningful effect on CAD associations, we present only the latter results.

We did several sensitivity analyses. First, we did mixed-effects regression analyses to partition CAD associations into between- and within-radiologist effects (30). We also repeated analyses after excluding data from 2001 because CAD coding may have been less accurate during the initial year of Medicare coverage (31). Computer-aided detection–associated effects were not substantively different in either of these analyses, so we report only the main analyses including data from all years. Second, we did stratified regression analyses to assess differences in CAD effects within strata of women classified by previous mammography exposure, previous CAD exposure, current film versus digital mammography, and patient age (**Appendix**, available at www.annals.org). Lastly, we assessed the potential effect on study estimates of a hypothetical unmeasured confounder (32).

Analyses were done with SAS, version 9.2 (SAS Institute, Cary, North Carolina), using 2-sided hypothesis tests. The study was approved by the Institutional Review Board at the University of California, Davis.

Role of the Funding Source

This study was funded by the Center for Healthcare Policy and Research and the Department of Family and Community Medicine at University of California, Davis, and the National Cancer Institute. The funding source had no role in the study design, analysis, interpretation, or drafting of the report or the decision to submit the manuscript for publication.

RESULTS

The sample included 409 459 screening mammograms from 163 099 women. Women received an average of 2.42 screening mammographies during the study period (median, 2.0 [range, 1 to 6]). After weighting, the data represent 5 656 860 screening mammograms from

2 086 051 women, including 46 361 done within 1 year of DCIS or invasive breast cancer diagnosis.

The unweighted prevalence of CAD use during screening mammography increased during the study period from 3.6% of mammographies in 2001 to 60.5% in 2006. The prevalence of CAD use was greater among mammography done on white women, women living in metropolitan regions, and women with greater neighborhood incomes (**Table 1**). Women receiving mammography with CAD were more likely to have had previous mammography within 24 months, previous mammography with CAD, and concurrent digital rather than film mammography. Compared with radiologists who interpreted non-CAD mammography, those who interpreted mammography with CAD were slightly more likely to be female and to have graduated from U.S. rather than non-U.S. medical schools.

Breast Cancer Outcomes

After adjustment for covariates, CAD use was associated with a slightly greater overall incidence rate of breast cancer (**Table 2**). This association was explained by a greater rate of DCIS diagnosis with CAD (adjusted OR, 1.17 [95% CI, 1.11 to 1.23]; $P < 0.001$), whereas the rate of invasive breast cancer overall was similar with and without CAD. On the basis of SEER data, nearly all women diagnosed with DCIS in our sample (97.3%) received treatment with lumpectomy, mastectomy, or radiation.

Relative to mammography interpreted without CAD, the incidence rate of stage I invasive breast cancer with CAD use was greater (adjusted OR, 1.06 [CI, 1.03 to 1.10]; $P < 0.001$), whereas the incident rate of stages II to IV invasive breast cancer was lower (adjusted OR, 0.92 [CI, 0.87 to 0.96]; $P < 0.001$) (**Table 2**). In unadjusted analyses of invasive breast cancer (**Table 3**), CAD was associated with more favorable stage distribution, smaller tumor size, and a greater proportion of node-negative cancer (all $P < 0.001$).

In adjusted analyses restricted to invasive breast cancer (**Table 4**), the odds of stage I (rather than stages II to IV) breast cancer were increased relative to who received mammography with CAD than among those without CAD (adjusted OR, 1.15 [CI, 1.09 to 1.22]; $P < 0.001$). Computer-aided detection was also associated with greater adjusted odds that an invasive tumor was smaller than 1 cm in diameter and had negative lymph node status. Similar results were obtained at alternative cut points for early tumor stage and small tumor size.

Diagnostic Testing Among Women Without Breast Cancer

Among women who had no breast cancer diagnosis within 1 year of screening, women who received screening mammography with CAD had greater adjusted odds of subsequent diagnostic testing for breast cancer with diagnostic mammography, breast ultrasonography, and breast biopsy than women who received screening mammography without CAD (**Table 5**).

Secondary Analyses

We did secondary, post hoc analyses to evaluate the timing of invasive cancer diagnoses after CAD versus non-CAD mammography (**Appendix**). These analyses did not suggest that the lower incidence of late-stage cancer associated with CAD is likely to be attributable to earlier diagnosis of invasive cancer during the 1-year follow-up. To address whether CAD is associated with decreased sensitivity for late-stage cancer, we assessed the longer-term incidence of late-stage breast cancer up to 48 months after previous mammography with versus without CAD. Because longer-term incidence of late-stage cancer was similar after CAD and non-CAD mammography, these analyses do not suggest that reduced sensitivity for late-stage disease with CAD explains the lower late-stage cancer incidence with CAD during the 1-year follow-up of the primary analysis.

We also did stratified analyses to assess whether CAD associations varied by previous mammography exposure, previous exposure to CAD, current use of digital mammography, and patient age (**Appendix Tables 2** to **9**, available at www.annals.org). Although these post hoc analyses warrant cautious interpretation, CAD was consistently associated with increased DCIS incidence and increased diagnostic testing across all strata. However, the association between CAD and reduced late-stage invasive cancer stage may be stronger among women older than 75 years. In addition, the association between CAD and increased diagnostic testing may be stronger among women whose previous mammography was non-CAD rather than CAD and when used concurrently with digital rather than film mammography.

DISCUSSION

Among Medicare enrollees, CAD use during screening mammography is associated with increased incidence of DCIS and no difference in the incidence of invasive cancer. It is, however, associated with greater likelihood that incident invasive cancer will be early- rather than late-stage and rates of diagnostic testing among women without breast cancer will be greater.

Weighing the potential benefits and harms of CAD use is complex, particularly because mortality benefits of screening interventions likely require many years to emerge (4). Indeed, mortality benefits in randomized trials of breast cancer screening are probably attributable to favorable shifts in invasive breast cancer stage that evolved during several rounds of screening over many years (19, 20). Thus, it is difficult to conceive that a favorable stage shift could emerge during the 1-year period after mammography in this study. Moreover, secondary analyses do not suggest that CAD was associated with earlier diagnosis of invasive breast cancer during the follow-up, as would be

Table 1. **Patient, Mammography, and Radiologist Characteristics at Screening Mammography, by CAD Use***

Characteristic	No CAD	CAD
Patient characteristics		
Total	284 501 (69.5)	124 958 (30.5)
Age		
67–69 y	57 018 (20.0)	24 811 (19.9)
70–74 y	89 510 (31.5)	38 194 (30.6)
75–79 y	76 593 (26.9)	32 932 (26.4)
80–84 y	45 254 (15.9)	21 171 (16.9)
85–89 y	16 126 (5.7)	7850 (6.3)
Race or ethnicity		
Asian or Pacific Islander	8358 (2.9)	3335 (2.7)
Black	19 137 (6.7)	5542 (4.4)
Hispanic	7284 (2.6)	2079 (1.7)
White, non-Hispanic	244 636 (86.0)	111 228 (89.0)
Other	5085 (1.8)	2774 (2.2)
Urban vs. rural residence		
Large metropolitan	156 038 (54.8)	65 182 (52.2)
Metropolitan	80 703 (28.4)	44 956 (36.0)
Nonmetropolitan	19 263 (6.8)	6783 (5.4)
Small nonmetropolitan	28 220 (9.9)	7959 (6.4)
Missing	277 (0.1)	78 (0.1)
Median annual income of elderly residents within the same ZIP code		
<$30 000	32 622 (11.5)	9928 (7.9)
$30 000–39 999	68 681 (24.1)	26 586 (21.3)
$40 000–54 999	86 975 (30.6)	42 756 (34.2)
$55 000–64 999	34 868 (12.3)	18 507 (14.8)
≥$65 000	56 750 (19.9)	24 615 (19.7)
Missing	4605 (1.6)	2566 (2.1)
Comorbid conditions†		
≥1 stable comorbid conditions	245 732 (86.4)	109 162 (87.4)
≥1 unstable comorbid conditions	46 057 (16.2)	19 908 (15.9)
Mammography characteristics		
Time since and use of CAD in previous mammography		
None or previous mammography was >24 mo earlier	79 254 (27.9)	26 277 (21.0)
CAD mammography 9–18 mo earlier	9137 (3.2)	14 668 (11.7)
Non-CAD mammography 9–18 mo earlier	174 692 (61.4)	15 246 (12.2)
CAD mammography 18–24 mo earlier	1097 (0.4)	1764 (1.4)
Non-CAD mammography 18–24 mo earlier	20 321 (7.1)	8571 (6.9)
Digital (rather than film-screen) mammography	8896 (3.1)	20 346 (16.3)
Mammography year		
2001	70 760 (24.9)	2665 (2.1)
2002	64 875 (22.8)	9307 (7.4)
2003	52 128 (18.3)	18 596 (14.9)
2004	41 634 (14.6)	27 223 (21.8)
2005	32 109 (11.3)	31 955 (25.6)
2006	22 995 (8.1)	35 212 (28.2)
Radiologist characteristics‡		
Mean age, *y*	52.7	52.2
Sex		
Female	54 094 (19.0)	28 624 (22.9)
Male	201 133 (70.7)	85 347 (68.3)
Missing or unknown	29 274 (10.3)	10 987 (8.8)
Primary type of practice		
Direct patient care	219 949 (77.3)	102 404 (82.0)
Teaching or other	35 278 (12.4)	11 567 (9.3)
Missing or unknown	29 274 (10.3)	10 987 (8.8)
Medical school location		
U.S.	229 252 (80.6)	103 875 (83.1)
Non-U.S.	38 221 (13.4)	13 751 (11.0)
Missing or unknown	17 028 (6.0)	7332 (5.9)
Mean time since medical school graduation, *y*	25.9	25.4

CAD = computer-aided detection.
* All values are numbers (percentages), unless otherwise indicated. All data are based on 409 459 mammograms from 163 099 women.
† Identified on Medicare claims for 2 y before mammography, including 38 comorbid conditions that were subclassified as stable and unstable based on severity and difficulty of control (27). Examples of stable comorbid conditions include arthritis, depression, and diabetes; examples of unstable comorbid conditions include severe heart failure, cardiac arrhythmias, and end-stage renal disease.
‡ Due to the large sample size, all variables differ significantly by CAD status ($P < 0.009$, using either chi-square or paired t tests).

Table 2. **Breast Cancer Incidence Rates by CAD Use***

Breast Cancer Diagnosis Within 1 y	Non-CAD†		CAD‡		Unadjusted IRR (95% CI)	Adjusted OR§ (95% CI)	*P* Value§
	Breast Cancer Cases, *n*	Incidence Rate‖	Breast Cancer Cases, *n*	Incidence Rate‖			
Any breast cancer	31 339	8.21	15 022	8.16	0.99 (0.97–1.01)	1.04 (1.01–1.06)	0.009
Invasive breast cancer¶	24 804	6.50	11 466	6.23	0.95 (0.93–0.98)	1.00 (0.97–1.03)	0.98
Stage I invasive	14 875	3.90	7335	3.98	1.02 (0.99–1.05)	1.06 (1.03–1.10)	<0.001
Stages II–IV invasive	8186	2.15	3441	1.87	0.87 (0.83–0.91)	0.92 (0.87–0.96)	<0.001
DCIS	6535	1.71	3556	1.93	1.13 (1.08–1.18)	1.17 (1.11–1.23)	<0.001

CAD = computer-aided detection; DCIS = ductal carcinoma in situ; IRR = incidence rate ratio; OR = odds ratio.
* Mammograms for women without breast cancer (from the SEER [Surveillance, Epidemiology and End Results]–Medicare 5% noncancer sample) are probability-weighted by a factor of 20 so that the analysis represents the entire population of fee-for-service Medicare enrollees having screening mammography (weighted: 5 656 860 screening mammograms, including 46 361 done within 1 y of breast cancer diagnosis).
† 284 501 woman-years of follow-up, unweighted.
‡ 124 958 woman-years of follow-up, unweighted.
§ Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, time since previous mammogram, use of CAD on the previous examination, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, and SEER region. Because breast cancer is uncommon, the adjusted OR closely approximates the adjusted incidence rate ratio. Owing to missing covariate or outcome data, 35 531 mammograms (8.7% of total) from 13 136 women (8.3% of total) were excluded from adjusted analyses (unweighted: 373 928 mammograms from 144 022 women).
‖ Incidence per 1000 women-years.
¶ Incidence rates for overall invasive cancer include both staged and unstaged cancer.

expected if the observed differences in early- and late-stage cancer incidence were attributable to enhanced sensitivity for earlier-stage cancer with CAD. On the other hand, secondary analyses do not suggest that the observed differences in late-stage cancer incidence are due to reduced sensitivity for late-stage cancer with CAD. Longer-term studies of the association of CAD with cancer stage are warranted to elucidate its clinical effect on invasive breast cancer stage.

Computer-aided detection was consistently associated with greater detection of DCIS in primary and secondary analyses. Treatment of DCIS detected by CAD may prevent progression to lethal invasive breast cancer and may avert more extensive treatment of subsequent invasive cancer. On the other hand, recent estimates suggest that 1 in 4 screen-detected invasive breast cancer cases are detected and treated in women who would have died of other causes without screening (33). The potential for overtreatment may be greater with DCIS (a noninvasive precursor of invasive cancer), particularly among an elderly population with more limited life expectancy than a younger screening population (34).

Among women without breast cancer, CAD use was associated with increased diagnostic testing after screening, especially with diagnostic mammography but also with

Table 3. **Unadjusted Stage, Size, and Lymph Node Status of Invasive Breast Cancer, by CAD Use**

Variable	No CAD, *n* (%)	CAD, *n* (%)	*P* Value*
Total	24 804 (100)	11 466 (100)	
Stage			<0.001
I	14 875 (60.0)	7335 (64.0)	
II	6257 (25.2)	2725 (23.8)	
III	1556 (6.3)	576 (5.0)	
IV	373 (1.5)	140 (1.2)	
Unstaged or unknown	1743 (7.0)	690 (6.0)	
Tumor size			<0.001
0–0.49 cm	1600 (6.5)	815 (7.1)	
0.50–0.99 cm	5274 (21.3)	2710 (23.6)	
1–1.99 cm	10 216 (41.2)	4752 (41.4)	
≥2 cm	6328 (25.5)	2568 (22.4)	
Unknown or missing	1386 (5.6)	621 (5.4)	
Lymph node status			<0.001
Negative	19 924 (80.3)	9441 (82.3)	
Positive	4880 (19.7)	2025 (17.7)	

CAD = computer-aided detection.
* *P* values are for the Cochran–Armitage test for trend for stage and size (excluding tumors with unknown or missing values) and for the chi-square test for lymph node status.

Table 4. **Adjusted Associations Between CAD Use and Nonuse and Invasive Breast Cancer Stage, Size, and Lymph Node Status***

Outcome	Adjusted OR Associated With CAD Use vs. Nonuse (95% CI)	*P* Value
Stage (*n* = 30 681)		
Stage I (vs. II, III, or IV)	1.15 (1.09–1.22)	<0.001
Stages I or II (vs. III or IV)	1.27 (1.14–1.41)	<0.001
Size (*n*= 31 071)		
Size <1 cm (vs. ≥1 cm)	1.10 (1.04–1.16)	<0.001
Size <2 cm (vs. ≥2 cm)	1.18 (1.10–1.25)	<0.001
Lymph node status (*n* = 28 237)		
Negative (vs. positive)	1.15 (1.08–1.24)	<0.001

CAD = computer-aided detection; OR = odds ratio.
* Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, time since previous mammogram, use of CAD on the previous examination, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, and SEER (Surveillance, Epidemiology and End Results) region. Sample sizes differ from the total number of invasive cancer cases (n = 36 270) because of missing or unknown stage, size, or node status or missing covariates.

Table 5. **Diagnostic Test Use After Screening Mammography Among Women Without Breast Cancer, by CAD Use***

Diagnostic Test Within 90 d of Screening Mammography	Non-CAD, *n* (%)†	CAD, *n* (%)‡	Adjusted OR Associated With CAD Use vs. Nonuse (95% CI)§	*P* Value
Diagnostic mammography	14 979 (5.8)	7939 (7.0)	1.28 (1.27–1.29)	<0.001
Breast ultrasonography	9767 (3.8)	4227 (3.8)	1.07 (1.06–1.09)	<0.001
Either diagnostic mammography or breast ultrasonography	19 136 (7.5)	9240 (8.2)	1.19 (1.18–1.20)	<0.001
Breast biopsy	3410 (1.3)	1512 (1.3)	1.10 (1.08–1.12)	<0.001

CAD = computer-aided detection; OR = odds ratio.
* Data based on 369 356 mammograms from 116 738 women.
† Data based on 256 652 mammograms.
‡ Data based on 112 704 mammograms.
§ Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, time since previous mammogram, use of CAD on the previous examination, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, and SEER (Surveillance, Epidemiology and End Results) region. Owing to missing covariate data on 8.5% of mammograms, adjusted analyses include 337 753 mammograms from 99 540 women.

breast ultrasonography and biopsy. These findings are consistent with previous research demonstrating associations between CAD use and increased false-positive rates of screening mammography (5, 6, 15–17). Diagnostic testing after false-positive mammography is associated with patient anxiety and accounts for a substantial part of the total costs of mammography screening (3, 35, 36). In post hoc, subgroup analyses, associations between CAD and increased diagnostic testing were greater among women with previous non-CAD mammography and during concurrent digital mammography. It is possible that CAD particularly reduces screening specificity during its first application on an individual woman or on a woman's first digital mammogram.

Within a study of 90 BCSC (Breast Cancer Surveillance Consortium) facilities, CAD use was not associated with more favorable stage, size, or lymph node status of invasive breast cancer (16). Differences in study samples and designs may explain the contrasting results of the BCSC analysis and the current study. First, the BCSC analysis included a smaller breast cancer sample (7722 participants vs. 46 361 in the current study), so it may have been underpowered to detect favorable associations between CAD and breast cancer stage, size, or lymph node status. Second, the BCSC analysis assessed CAD use at the facility level, potentially leading to misclassification of CAD status of individual mammography and attenuation of differences in outcomes by CAD use. On the other hand, unlike the BCSC analyses, the present study lacked measures of breast density and hormone therapy, although our adjustment for study year addresses to some extent the decline in use of hormone therapy since 2002 (37).

In the United States, the SEER–Medicare data may be unique in their ability to couple mammography data from claims with cancer outcome data for such a large sample of women with incident breast cancer. However, these data do not specifically address the effect of CAD during screening among women younger than 65 years. In addition, evidence for screening mammography effectiveness among women older than 75 years is limited (19). However, in analyses stratified by patient age 67 to 75 years versus 75 to 89 years, associations between CAD and outcomes were generally consistent with main analyses (**Appendix Tables 8** and **9**, available at www.annals.org).

Residual confounding by unmeasured factors other than CAD may influence results. However, secondary analyses suggest that previous mammography exposure, confounding by unmeasured breast density, or unmeasured radiologist characteristics are not likely to explain the observed differences (**Appendix**). Our analysis is also limited by the absence of information on mammogram interpretation, so we could not assess important performance measures, such as sensitivity or specificity. Results may not be generalizable to Medicare beneficiaries enrolled in managed care plans. Results may also reflect a transitional period when many radiologists were learning to use CAD (38). Statistically significant associations may be attributable to chance, particularly in post hoc subgroup analyses.

In conclusion, CAD use among older U.S. women having screening mammography is associated with increased diagnosis of DCIS and the diagnosis of invasive breast cancer at earlier stage. However, CAD use is also associated with increased diagnostic testing among women without breast cancer. The long-term effect of CAD on breast cancer stage, mortality, quality of life, and costs warrants investigation.

From the Center for Healthcare Policy and Research and Comprehensive Cancer Center, University of California, Davis, Sacramento, California; City of Hope Medical Center, Duarte, California; and the University of Washington, Seattle, Washington.

Grant Support: By the Clinical and Translational Science Center and Center for Healthcare Policy and Research, University of California, Davis, and the National Cancer Institute (K05 CA-104699).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-2025.

Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Fenton (e-mail, joshua.fenton@ucdmc.ucdavis.edu). *Data set:* Information about acquiring SEER–Medicare data can be found at http://healthservices.cancer.gov/seermedicare.

Requests for Single Reprints: Joshua J. Fenton, MD, MPH, University of California, Davis, Department of Family and Community Medicine, 4860 Y Street, Suite 2300, Sacramento, CA 95817; e-mail, joshua.fenton@ucdmc.ucdavis.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Fenton JJ, Foote SB, Green P, Baldwin LM.** Diffusion of computer-aided mammography after mandated Medicare coverage. Arch Intern Med. 2010;170:987-9. [PMID: 20548013]
2. **Rao VM, Levin DC, Parker L, Cavanaugh B, Frangos AJ, Sunshine JH.** How widely is computer-aided detection used in screening and diagnostic mammography? J Am Coll Radiol. 2010;7:802-5. [PMID: 20889111]
3. **Gross CP, Long JB, Ross JS, Abu-Khalaf MM, Wang R, Killelea BK, et al.** The cost of breast cancer screening in the Medicare population. JAMA Intern Med. 2013;173:220-6. [PMID: 23303200]
4. **Bazzocchi M, Mazzarella F, Del Frate C, Girometti R, Zuiani C.** CAD systems for mammography: a real opportunity? A review of the literature. Radiol Med. 2007;112:329-53. [PMID: 17440698]
5. **Cupples TE, Cunningham JE, Reynolds JC.** Impact of computer-aided detection in a regional screening mammography program. AJR Am J Roentgenol. 2005;185:944-50. [PMID: 16177413]
6. **Freer TW, Ulissey MJ.** Screening mammography with computer-aided detection: prospective study of 12,860 patients in a community breast center. Radiology. 2001;220:781-6. [PMID: 11526282]
7. **Morton MJ, Whaley DH, Brandt KR, Amrami KK.** Screening mammograms: interpretation with computer-aided detection—prospective evaluation. Radiology. 2006;239:375-83. [PMID: 16569779]
8. **Romero C, Varela C, Muñoz E, Almenar A, Pinto JM, Botella M.** Impact on breast cancer diagnosis in a multidisciplinary unit after the incorporation of mammography digitalization and computer-aided detection systems. AJR Am J Roentgenol. 2011;197:1492-7. [PMID: 22109307]
9. **Brancato B, Houssami N, Francesca D, Bianchi S, Risso G, Catarzi S, et al.** Does computer-aided detection (CAD) contribute to the performance of digital mammography in a self-referred population? Breast Cancer Res Treat. 2008;111:373-6. [PMID: 17939035]
10. **Gilbert FJ, Astley SM, Gillan MG, Agbaje OF, Wallis MG, James J, et al; CADET II Group.** Single reading with computer-aided detection for screening mammography. N Engl J Med. 2008;359:1675-84. [PMID: 18832239]
11. **van den Biggelaar FJ, Kessels AG, van Engelshoven JM, Boetes C, Flobbe K.** Computer-aided detection in full-field digital mammography in a clinical population: performance of radiologist and technologists. Breast Cancer Res Treat. 2010;120:499-506. [PMID: 19418215]
12. **Gur D, Sumkin JH, Rockette HE, Ganott M, Hakim C, Hardesty L, et al.** Changes in breast cancer detection and mammography recall rates after the introduction of a computer-aided detection system. J Natl Cancer Inst. 2004;96:185-90. [PMID: 14759985]
13. **Taylor P, Potts HW.** Computer aids and human second reading as interventions in screening mammography: two systematic reviews to compare effects on cancer detection and recall rate. Eur J Cancer. 2008;44:798-807. [PMID: 18353630]
14. **Povyakalo AA, Alberdi E, Strigini L, Ayton P.** How to Discriminate between Computer-Aided and Computer-Hindered Decisions: A Case Study in Mammography. Med Decis Making. 2013;33:98-107. [PMID: 23300205]
15. **Fenton JJ, Taplin SH, Carney PA, Abraham L, Sickles EA, D'Orsi C, et al.** Influence of computer-aided detection on performance of screening mammography. N Engl J Med. 2007;356:1399-409. [PMID: 17409321]
16. **Fenton JJ, Abraham L, Taplin SH, Geller BM, Carney PA, D'Orsi C, et al; Breast Cancer Surveillance Consortium.** Effectiveness of computer-aided detection in community mammography practice. J Natl Cancer Inst. 2011;103:1152-61. [PMID: 21795668]
17. **Gromet M.** Comparison of computer-aided detection to double reading of screening mammograms: review of 231,221 mammograms. AJR Am J Roentgenol. 2008;190:854-9. [PMID: 18356428]
18. **Karssemeijer N, Bluekens AM, Beijerinck D, Deurenberg JJ, Beekman M, Visser R, et al.** Breast cancer screening results 5 years after introduction of digital mammography in a population-based screening program. Radiology. 2009;253:353-8. [PMID: 19703851]
19. **Autier P, Héry C, Haukka J, Boniol M, Byrnes G.** Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening. J Clin Oncol. 2009;27:5919-23. [PMID: 19884547]
20. **Duffy SW, Tabar L, Vitak B, Day NE, Smith RA, Chen HH, et al.** The relative contributions of screen-detected in situ and invasive breast carcinomas in reducing mortality from the disease. Eur J Cancer. 2003;39:1755-60. [PMID: 12888371]
21. **Nelson HD, Tyne K, Naik A, Bougatsos C, Chan B, Nygren P, et al.** Screening for Breast Cancer: Systematic Evidence Review Update for the U.S. Preventive Services Task Force. Evidence Review Update No. 74. AHRQ Publication No. 10-05142-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2009.
22. **Jiang Y, Miglioretti DL, Metz CE, Schmidt RA.** Breast cancer detection rate: designing imaging trials to demonstrate improvements. Radiology. 2007;243:360-7. [PMID: 17456866]
23. **Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF.** Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care. 2002;40:IV-3-18. [PMID: 12187163]
24. **Baldwin LM, Adamache W, Klabunde CN, Kenward K, Dahlman C, L Warren J.** Linking physician characteristics and Medicare claims data: issues in data availability, quality, and measurement. Med Care. 2002;40:IV-82-95. [PMID: 12187173]
25. **Fenton JJ, Zhu W, Balch S, Smith-Bindman R, Fishman P, Hubbard RA.** Distinguishing screening from diagnostic mammograms using Medicare claims data. Med Care. 2012. Aug 23. [Epub ahead of print] [PMID: 22922433]
26. **Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds.** AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
27. **Fenton JJ, Zhu W, Balch S, Smith-Bindman R, Lindfors KK, Hubbard RA.** External validation of Medicare claims codes for digital mammography and computer-aided detection. Cancer Epidemiol Biomarkers Prev. 2012;21:1344-7. [PMID: 22695737]
28. **Yankaskas BC, Taplin SH, Ichikawa L, Geller BM, Rosenberg RD, Carney PA, et al.** Association between mammography timing and measures of screening performance in the United States. Radiology. 2005;234:363-73. [PMID: 15670994]
29. **Yasmeen S, Xing G, Morris C, Chlebowski RT, Romano PS.** Comorbidities and mammography use interact to explain racial/ethnic disparities in breast cancer stage at diagnosis. Cancer. 2011;117:3252-61. [PMID: 21246529]
30. **Neuhaus JM.** Assessing change with longitudinal and clustered binary data. Annu Rev Public Health. 2001;22:115-28. [PMID: 11274514]
31. **Fenton JJ, Green P, Baldwin LM.** Internal validation of procedure codes on Medicare claims for digital mammograms and computer-aided detection. Cancer Epidemiol Biomarkers Prev. 2009;18:2186-9. [PMID: 19661075]
32. **Lin DY, Psaty BM, Kronmal RA.** Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics. 1998;54:948-63. [PMID: 9750244]
33. **Kalager M, Adami HO, Bretthauer M, Tamimi RM.** Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian screening program. Ann Intern Med. 2012;156:491-9. [PMID: 22473436]
34. **Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, et al; Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network.** Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med. 2009;151:738-47. [PMID: 19920274]
35. **Kerlikowske K, Salzmann P, Phillips KA, Cauley JA, Cummings SR.** Continuing screening mammography in women aged 70 to 79 years: impact on life expectancy and cost-effectiveness. JAMA. 1999;282:2156-63. [PMID: 10591338]
36. **Brewer NT, Salz T, Lillie SE.** Systematic review: the long-term effects of false-positive mammograms. Ann Intern Med. 2007;146:502-10. [PMID: 17404352]
37. **Hersh AL, Stefanick ML, Stafford RS.** National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004;291:47-53. [PMID: 14709575]
38. **Miglioretti DL, Gard CC, Carney PA, Onega TL, Buist DS, Sickles EA, et al.** When radiologists perform best: the learning curve in screening mammogram interpretation. Radiology. 2009;253:632-40. [PMID: 19789234]

Current Author Addresses: Dr. Fenton: University of California, Davis, Department of Family and Community Medicine, 4860 Y Street, Suite 2300, Sacramento, CA 95817.
Dr. Xing: University of California, Davis, Center for Healthcare Policy & Research, 2103 Stockton Boulevard, Suite 2224, Sacramento, CA 95817.
Dr. Elmore: University of Washington, Division of General Internal Medicine, Harborview Medical Center, Box 359780 10EH15, 325 9th Avenue, Seattle, WA 98104.
Dr. Bang: University of California, Davis, Division of Biostatistics, Med Sci 1-C, One Shields Avenue, Davis, CA 95616.
Dr. Chen: City of Hope Medical Center, 1500 Duarte Road, Duarte, CA 91010.
Dr. Lindfors: University of California, Davis, Department of Radiology, Lawrence J. Ellison Ambulatory Care Center, 4860 Y Street, Suite 3100, Sacramento, CA 95817.
Dr. Baldwin: University of Washington, Department of Family Medicine, Box 354982, Seattle, WA 98195-4982.

Author Contributions: Conception and design: J.J. Fenton, J.G. Elmore, S.L. Chen, K.K. Lindfors.
Analysis and interpretation of the data: J.J. Fenton, G. Xing, H. Bang, S.L. Chen, K.K. Lindfors, L.M. Baldwin.
Drafting of the article: J.J. Fenton, J.G. Elmore, H. Bang, K.K. Lindfors.
Critical revision of the article for important intellectual content: J.J. Fenton, J.G. Elmore, S.L. Chen, K.K. Lindfors, L.M. Baldwin.
Final approval of the article: J.J. Fenton, J.G. Elmore, H. Bang, S.L. Chen, K.K. Lindfors, L.M. Baldwin.
Statistical expertise: G. Xing, H. Bang.
Obtaining of funding: J.J. Fenton.
Administrative, technical, or logistic support: J.J. Fenton, S.L. Chen.
Collection and assembly of data: S.L. Chen.

Appendix: Timing of Invasive Breast Cancer Diagnosis by CAD

In primary analyses, CAD use during screening mammography was associated with significantly reduced adjusted odds of diagnosis of stage II to IV invasive breast cancer (adjusted OR, 0.92 [CI, 0.87 to 0.96]; $P < 0.001$). We conducted secondary analyses to provide further information about potential biological mechanisms for this association.

First, if CAD increases sensitivity for early-stage tumors, we reasoned that it may be possible that some early-stage tumors detected by CAD may be prevented from progressing to late-stage, invasive cancer during the 1-year follow-up. In this case, one would expect the time from the screening mammography to the diagnosis of invasive breast cancer to be longer after non-CAD mammography than CAD mammography. One may also expect that late-stage (that is, stages II to IV) cancer with a delayed diagnosis (that is, >90 days after mammography) would comprise a larger proportion of all invasive breast cancer diagnosed during the 1-year period after non-CAD than with CAD mammography.

However, the mean number of months from the mammography date to invasive breast cancer diagnosis was similar among CAD and non-CAD mammography (2.4 vs. 2.3 months). In addition, of all invasive breast cancer diagnosed within 1 year after mammography, a similar proportion both were late-stage (stages II to IV) and were diagnosed more than 90 days after mammography (7.7% with CAD vs. 8.1% with non-CAD; $P = 0.26$).

Second, we considered the possibility that CAD may lead to reduced sensitivity for late-stage cancer. Some research suggests that CAD output may focus attention on subsets of mammographic lesions with the potential for enhancing detection of marked lesions but decreasing the detection of unmarked (potentially later-stage) lesions (39, 40). If CAD causes radiologists to miss late-stage cancer, then CAD may be associated with reduced incidence of late-stage cancer during a 1-year follow-up, but increased late-stage incidence in later years as late-stage cancer cases come to clinical attention.

We assessed this possibility by comparing incidence rates of stage II to IV invasive breast cancer 9 to 24 months and 24 to 48 months after previous CAD versus non-CAD mammography. (To assess the latter subgroup, we identified the subsample of mammography done on women aged 69 to 89 years who had 4 years of previous continuous Medicare Part A and B enrollment.) Among mammography interpreted with CAD, the unadjusted incident rates of late-stage cancer were similar both 9 to 24 months after CAD versus non-CAD mammography (1.50 vs. 1.52 cases per 1000 woman-years) and 24 to 48 months after CAD versus non-CAD mammography (2.44 vs. 2.39 cases per 1000 woman-years). Thus, these results do not suggest that the association between CAD and reduced late-stage cancer incidence during the 1-year follow-up arises as a result of missed late-stage cancer cases that become incident at a greater rate with longer follow-up.

Secondary Stratified Analyses

In secondary, post hoc analyses, we assessed whether main effects of CAD use may be modified by differences in the timing of previous mammography, use versus nonuse of CAD during previous mammography, use of digital rather than film-screen during the index study mammography, and patient age. We also conducted sensitivity analyses among the subgroup of women aged 69 to 89 years on the screening mammography date who had continuous Medicare Parts A and B coverage for the 4 previous years, allowing for longer-term assessment for previous mammography. These analyses used stratified logistic regression with covariate adjustment and probability weighting as in the main analysis. Standard errors are corrected for clustering within physicians and the sampling design. We did not conduct formal tests of interaction between CAD and stratified variables. The number of study events among women who had obtained previous digital (rather than film-screen) mammography was too small to allow stratified analyses within these subgroups. Notably, CAD was associated with increased incidence of DCIS and increased odds of 1 or more diagnostic tests in every stratum (**Appendix Tables 2** to **9**).

As shown in **Appendix Tables 2** to **5**, stratified analyses of breast cancer incidence and diagnostic testing by previous mammography status were largely consistent with the primary analyses. Computer-aided detection was associated with increased adjusted incidence of DCIS and increased adjusted odds of diagnostic mammography in all strata. In addition, point esti-

mates and CIs for the CAD-associated OR for the incidence of early- versus late-stage invasive breast cancer are all consistent with the main analysis.

In stratified analyses by current film versus digital mammography (**Appendix Tables 6** and 7), CIs for cancer incidence outcomes were wide within the stratum of digital mammography. Nevertheless, the OR for DCIS diagnosis associated with CAD among digital mammography was greater (adjusted OR, 1.40 [CI, 1.17 to 1.68]) than the OR within the stratum of film mammography (adjusted OR, 1.13 [CI, 1.07 to 1.19]). Meanwhile, CAD-associated ORs for diagnostic testing among women without breast cancer were greater among the stratum of digital mammography than among film mammography.

In stratified analyses by patient age (**Appendix Tables 8** and **9**), the association between CAD and decreased stage II to IV invasive cancer was statistically significant only among women aged 75 to 89 years. In addition, the ORs for diagnostic mammography and breast biopsy associated with CAD were greater among women aged 67 to 75 years than among women aged 75 to 89 years.

Sensitivity Analysis of Unmeasured Confounding

Using the method of Lin and colleagues (32), we assessed the potential effect of imbalance in the CAD and non-CAD groups of an unmeasured confounder with as strong an effect on study outcomes as increased breast density (defined as either heterogeneously dense or extremely dense breasts). Unmeasured in our study, increased breast density is associated with increased risk for breast cancer, decreased sensitivity, and reduced specificity of screening mammography (41). Although we can see no reason why women with increased breast density would be differentially allocated to CAD and non-CAD mammography facilities, we conducted sensitivity analyses under the assumption that the relative prevalence of increased breast density is 10% greater among women who received screening mammography with versus without CAD. Because the overall prevalence of increased breast density in the population is 46.6% (4), if the relative prevalence were 10% greater in CAD facilities, then it would be 51.3% in this group. We further assumed that the relative risk for breast cancer associated with the greater density is 1.75 (42). We also assumed that this relative risk affects both invasive breast cancer incidence and DCIS. In sensitivity analyses (**Appendix Table 10**), ORs are mostly attenuated toward the null. However, most ORs that were significantly different from 1.0 in the primary analysis remain so in the sensitivity analyses.

39. **Zheng B, Ganott MA, Britton CA, Hakim CM, Hardesty LA, Chang TS, et al.** Soft-copy mammographic readings with different computer-assisted detection cuing environments: preliminary findings. Radiology. 2001;221:633-40. [PMID: 11719657]

40. **Taplin SH, Rutter CM, Lehman CD.** Testing the effect of computer-assisted detection on interpretive performance in screening mammography. AJR Am J Roentgenol. 2006;187:1475-82. [PMID: 17114540]

41. **Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM, et al.** Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med. 2003;138:168-75. [PMID: 12558355]

42. **Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K.** Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. Ann Intern Med. 2008;148:337-47. [PMID: 18316752]

Appendix Table 1. Codes Used to Define Study Variables

Variable	Codes Used to Define Variable	Coding System
CAD	G0203, G0205, G0236, 76082, 76083, 76085	HCPCS
Diagnostic tests		
Diagnostic mammography	76090, 76091, G0204, G0206	HCPCS
Breast ultrasonography	76645	HCPCS
Breast biopsy	19100–19103, 19120, 19125, 10021-2	HCPCS
	85.11, 85.12, 85.20, 85.21	ICD-9-CM
Rurality of residence counties	Large metropolitan (code 1: counties in metropolitan areas with population ≥1 000 000) Metropolitan (codes 2–3: counties in metropolitan areas with population <1 000 000) Nonmetropolitan (codes 4–5: counties with urban population ≥20 000) Small nonmetropolitan (codes 6–9: counties with urban population <20 000)]	Rural–Urban Continuum codes

CAD = computer-aided detection; HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Appendix Table 2. Breast Cancer Incidence Rates by CAD Use, Stratified by Mammography Use in the Previous 24 Months and Whether Previous Mammography Was CAD or Non-CAD*

Breast Cancer Diagnosis Within 1 y, by Previous Mammography Stratum	Non-CAD		CAD		Adjusted OR (95% CI)†	*P* Value
	Breast Cancer Cases, *n*	Incidence Rate‡	Breast Cancer Cases, *n*	Incidence Rate‡		
Non-CAD mammography 9–24 mo previous (*n* = 243 604)						
Any breast cancer	18 978	6.86	4411	7.45	1.10 (1.06–1.14)	<0.001
Invasive breast cancer§	14 708	5.32	3347	5.65	1.08 (1.04–1.13)	<0.001
Stage I invasive	9280	3.36	2254	3.81	1.15 (1.09–1.21)	<0.001
Stages II–IV invasive	4518	1.63	902	1.52	0.97 (0.90–1.05)	0.47
DCIS	4270	1.54	1064	1.80	1.16 (1.08–1.25)	<0.001
CAD mammography 9–24 mo previous (*n* = 61 537)						
Any breast cancer	367	6.70	6084	6.77	0.99 (0.88–1.12)	0.85
Invasive breast cancer§	288	5.26	4606	5.13	0.94 (0.82–1.08)	0.39
Stage I invasive	167	3.05	3030	3.37	1.03 (0.87–1.22)	0.72
Stages II–IV invasive	100	1.83	1345	1.50	0.84 (0.67–1.05)	0.118
DCIS	79	1.44	1478	1.64	1.16 (0.91–1.48)	0.24
No mammography in previous 24 mo (*n* = 104 318)						
Any breast cancer	12 372	11.90	4723	12.58	1.00 (0.96–1.05)	0.96
Invasive breast cancer§	10 093	9.71	3656	9.74	0.95 (0.90–0.99)	0.029
Stage I invasive	5606	5.39	2144	5.71	1.01 (0.95–1.08)	0.73
Stages II–IV invasive	3653	3.51	1241	3.31	0.86 (0.80–0.93)	<0.001
DCIS	2279	2.19	1067	2.84	1.25 (1.14–1.37)	<0.001

CAD = computer-aided detection; DCIS = ductal carcinoma in situ; OR = odds ratio.

* Mammograms for women without breast cancer (from the SEER [Surveillance, Epidemiology and End Results]–Medicare 5% noncancer sample) are weighted by a factor of 20 so that the analysis represents the entire population of fee-for-service Medicare enrollees having screening mammography (weighted: 5 656 860 screening mammograms, including 46 361 done within 1 y of breast cancer diagnosis).

† Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, and SEER region. Owing to missing covariate or outcome data, 35 531 mammograms (8.7% of total) from 13 136 women (8.3% of total) were excluded from adjusted analyses (unweighted: 373 928 mammograms from 144 022 women).

‡ Incidence per 1000 women-years.

§ Incidence rates for overall invasive cancer include both staged and unstaged cancer.

Appendix Table 3. **CAD Use and Breast Cancer Diagnostic Testing Among Women Without Breast Cancer, Stratified by Mammography Use in the Previous 24 Months and Whether Previous Mammography Was CAD or Non-CAD***

Diagnostic Test, by Previous Mammography Stratum	Non-CAD, *n* (unadjusted %)	CAD, *n* (unadjusted %)	Adjusted OR (95% CI)†	*P* Value
Non-CAD mammography in previous 9–24 mo (*n* = 222 861)				
Diagnostic mammography	10 122 (5.39)	2720 (7.19)	1.32 (1.31–1.34)	<0.001
Breast ultrasonography	6476 (3.45)	1446 (3.82)	1.14 (1.12–1.16)	<0.001
Either diagnostic mammography or breast ultrasonography	12 906 (6.88)	3202 (8.47)	1.25 (1.24–1.27)	<0.001
Breast biopsy	2259 (1.20)	533 (1.41)	1.22 (1.18–1.25)	<0.001
CAD mammography in previous 9–24 mo (*n* = 56 700)				
Diagnostic mammography	197 (5.89)	3412 (6.32)	1.13 (1.08–1.18)	<0.001
Breast ultrasonography	124 (3.71)	1711 (3.17)	0.85 (0.81–0.90)	<0.001
Either diagnostic mammography or breast ultrasonography	250 (7.47)	3899 (7.22)	1.01 (0.97–1.04)	0.80
Breast biopsy	45 (1.34)	601 (1.11)	0.82 (0.76–0.90)	<0.001
No previous mammography in the past 24 mo or previous mammography >24 mo (*n* = 89 795)				
Diagnostic mammography	4834 (7.06)	1889 (8.44)	1.20 (1.18–1.22)	<0.001
Breast ultrasonography	3290 (4.81)	1124 (5.02)	1.02 (1.00–1.04)	0.093
Either diagnostic mammography or breast ultrasonography	6202 (9.06)	2240 (10.01)	1.12 (1.10–1.13)	<0.001
Breast biopsy	4834 (7.06)	1889 (8.44)	1.07 (1.03–1.11)	<0.001

CAD = computer-aided detection; OR = odds ratio.
* Based on 369 356 mammograms from 116 738 women.
† Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, SEER (Surveillance, Epidemiology and End Results) region, and a radiologist-level random effect. Owing to missing covariate data, adjusted analyses include 337 753 mammograms from 99 540 women.

Appendix Table 4. **Breast Cancer Incident Rates by CAD Use, Stratified by Mammography Use in the Previous 48 Months***

Breast Cancer Diagnosis Within 1 y, by Previous Mammography Stratum	Non-CAD		CAD		Adjusted OR (95% CI)†	*P* Value
	Breast Cancer Cases, *n*	Incidence Rate‡	Breast Cancer Cases, *n*	Incidence Rate‡		
Previous mammography 9–24 mo earlier (*n* = 268 306)						
Any breast cancer	16 999	26.94	9218	7.12	1.05 (1.01–1.08)	0.005
Invasive breast cancer§	13 234	5.40	7017	5.42	1.02 (0.99–1.02)	0.22
Stage I invasive	8374	3.42	4693	3.62	1.08 (1.03–1.13)	<0.001
Stages II–IV invasive	4018	1.64	1947	1.50	0.95 (0.89–1.01)	0.116
DCIS	3765	1.54	2201	1.70	1.14 (1.07–1.22)	<0.001
Previous mammography 24–48 mo earlier (*n* = 26 122)						
Any breast cancer	2436	10.51	1626	10.92	0.99 (0.92–1.07)	0.85
Invasive breast cancer§	1922	8.29	1250	8.39	0.96 (0.88–1.05)	0.39
Stage I invasive	1117	4.82	805	5.40	1.05 (0.94–1.17)	0.36
Stages II–IV invasive	672	2.90	358	2.40	0.78 (0.67–0.91)	0.001
DCIS	514	2.22	376	2.52	1.11 (0.95–1.29)	0.20
No mammography in previous 48 mo (*n* = 59 992)						
Any breast cancer	8171	13.27	2310	15.67	1.01 (0.95–1.08)	0.66
Invasive breast cancer§	6777	11.00	1819	12.34	0.95 (0.88–1.02)	0.123
Stage I invasive	3695	6.00	1004	6.81	1.02 (0.93–1.11)	0.73
Stages II–IV invasive	2470	4.01	659	4.47	0.88 (0.79–0.98)	0.023
DCIS	1394	2.26	491	3.33	1.37 (1.20–1.57)	<0.001

CAD = computer-aided detection; DCIS = ductal carcinoma in situ; OR = odds ratio.
* All women were aged 69–89 y on mammography dates and had 4 previous y of continuous Medicare Parts A and B. Mammograms for women without breast cancer (from the SEER [Surveillance, Epidemiology and End Results]–Medicare 5% noncancer sample) are probability-weighted by a factor of 20 so that the analysis represents the entire population of fee-for-service Medicare enrollees having screening mammography (weighted: 4 888 409 screening mammograms, including 40 760 done within 1 y of breast cancer diagnosis).
† Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, and SEER region. Owing to missing covariate or outcome data, adjusted analyses include unweighted mammograms (*n* = 323 771) from 126 564 women.
‡ Incidence per 1000 women-years.
§ Incidence rates for overall invasive cancer include both staged and unstaged cancer.

Appendix Table 5. **CAD Use and Breast Cancer Diagnostic Testing Among Women Without Breast Cancer, Stratified by Mammography in the Previous 48 Months***

Diagnostic Test, by Previous Mammography Stratum	Non-CAD, *n* (unadjusted %)	CAD, *n* (unadjusted %)	Adjusted OR (95% CI)†	*P* Value
Previous mammography between 9–24 mo (*n* = 245 512)				
Diagnostic mammography	8819 (5.32)	5242 (6.57)	1.28 (1.26–1.29)	<0.001
Breast ultrasonography	5621 (3.39)	2695 (3.38)	1.06 (1.05–1.08)	<0.001
Either diagnostic mammography or breast ultrasonography	11 238 (6.78)	6073 (7.61)	1.20 (1.18–1.21)	<0.001
Breast biopsy	1950 (1.18)	971 (1.22)	1.11 (1.09–1.14)	<0.001
Previous mammography between 24–48 mo (*n* = 22 705)				
Diagnostic mammography	907 (6.45)	619 (7.17)	1.16 (1.13–1.20)	<0.001
Breast ultrasonography	603 (4.29)	365 (4.23)	0.97 (0.93–1.01)	0.090
Either diagnostic mammography or breast ultrasonography	1153 (8.19)	736 (8.52)	1.07 (1.04–1.10)	<0.001
Breast biopsy	185 (1.31)	117 (1.36)	1.03 (0.96–1.11)	0.34
No mammography in previous 48 mo (*n* = 50 809)				
Diagnostic mammography	3028 (7.24)	869 (9.65)	1.20 (1.17–1.23)	<0.001
Breast ultrasonography	2068 (4.95)	517 (5.74)	1.01 (0.98–1.04)	0.47
Either diagnostic mammography or breast ultrasonography	3885 (9.29)	1028 (11.41)	1.13 (1.10–1.15)	<0.001
Breast biopsy	756 (1.81)	193 (2.14)	1.05 (1.00–1.11)	0.066

CAD = computer-aided detection; OR = odds ratio.
* Data based on 319 026 mammograms from 97 336 women. All women were aged 69–89 y on mammography dates and had 4 previous y of continuous Medicare Parts A and B.
† Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, SEER (Surveillance, Epidemiology and End Results) region, and a radiologist-level random effect. Owing to missing covariate data on 10.1% of mammograms, adjusted analyses include 286 829 mammograms from 89 622 women.

Appendix Table 6. **Breast Cancer Incidence Rates by CAD Use, Stratified by Mammography Use in the Previous 24 Months and Whether Mammography Was CAD or Non-CAD***

Breast Cancer Diagnosis Within 1 y, by Mammography Type	Non-CAD		CAD		Adjusted OR (95% CI)†	*P* Value
	Breast Cancer Cases, *n*	Incidence Rate‡	Breast Cancer Cases, *n*	Incidence Rate‡		
Current film-screen mammography (*n* = 380 217)						
Any breast cancer	30 314	8.23	12 378	8.12	1.01 (0.98–1.04)	0.55
Invasive breast cancer§	23 999	6.51	9518	6.24	0.98 (0.95–1.01)	0.126
Stage I invasive	14 379	3.90	6109	4.01	1.05 (1.01–1.09)	0.019
Stages II–IV invasive	7944	2.16	2844	1.86	0.88 (0.84–0.93)	<0.001
DCIS	6315	1.71	2860	1.88	1.13 (1.07–1.19)	<0.001
Current digital mammography (*n* = 29 242)						
Any breast cancer	1025	7.77	2644	8.38	1.07 (0.97–1.17)	0.170
Invasive breast cancer§	805	6.11	1948	6.17	0.98 (0.88–1.08)	0.69
Stage I invasive	496	3.76	1226	3.88	0.98 (0.87–1.11)	0.78
Stages II–IV invasive	242	1.84	597	1.89	1.02 (0.86–1.22)	0.78
DCIS	220	1.67	696	2.21	1.40 (1.17–1.68)	<0.001

CAD = computer-aided detection; DCIS = ductal carcinoma in situ; OR = odds ratio.
* Mammograms for women without breast cancer (from the SEER [Surveillance, Epidemiology and End Results]–Medicare 5% noncancer sample) are probability-weighted by a factor of 20 so that the analysis represents the entire population of fee-for-service Medicare enrollees having screening mammography (weighted: 5 656 860 screening mammograms, including 46 361 done within 1 y of breast cancer diagnosis).
† Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, time since previous mammogram, use of CAD on the previous examination, presence of stable and unstable comorbid conditions, digital vs. film mammography, year of examination, and SEER region. Because breast cancer is uncommon, the adjusted OR closely approximates the adjusted incidence rate ratio. Owing to missing covariate or outcome data, 35 531 mammograms (8.7% of total) from 13 136 women (8.3% of total) were excluded from adjusted analyses (unweighted: 373 928 mammograms from 144 022 women).
‡ Incidence per 1000 women-years.
§ Incidence rates for overall invasive cancer include both staged and unstaged cancer.

Appendix Table 7. **CAD Use and Breast Cancer Diagnostic Testing Among Women Without Breast Cancer, Stratified by Current Film-Screen Versus Digital Mammography***

Diagnostic Test, by Mammography Type	Non-CAD, *n* (unadjusted %)	CAD, *n* (unadjusted %)	Adjusted OR (95% CI)†	*P* Value
Current film-screen mammography (*n* = 343 032)				
Diagnostic mammography	14 626 (5.88)	6731 (7.13)	1.24 (1.23–1.25)	<0.001
Breast ultrasonography	9520 (3.83)	3623 (3.84)	1.05 (1.04–1.06)	<0.001
Either diagnostic mammography or breast ultrasonography	18 674 (7.51)	7862 (8.33)	1.16 (1.15–1.17)	<0.001
Breast biopsy	3326 (1.34)	1291 (1.37)	1.07 (1.04–1.09)	<0.001
Current digital mammography (*n* = 26 324)				
Diagnostic mammography	353 (4.39)	1208 (6.61)	1.67 (1.61–1.73)	<0.001
Breast ultrasonography	247 (3.07)	604 (3.30)	1.17 (1.12–1.22)	<0.001
Either diagnostic mammography or breast ultrasonography	462 (5.74)	1378 (7.54)	1.43 (1.38–1.48)	<0.001
Breast biopsy	84 (1.04)	221 (1.21)	1.32 (1.22–1.42)	<0.001

CAD = computer-aided detection; OR = odds ratio.
* Data based on 369 356 mammograms from 116 738 women.
† Adjusted for age, race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, presence of stable and unstable comorbid conditions, time since previous mammogram, use of CAD on the previous examination, year of examination, SEER (Surveillance, Epidemiology and End Results) region, and a radiologist-level random effect. Owing to missing covariate data on 8.5% of mammograms, adjusted analyses include 337 753 mammograms from 99 540 women.

Appendix Table 8. **Breast Cancer Incidence Rates by CAD Use, Stratified by Patient Age***

Breast Cancer Diagnosis Within 1 y, by Patient Age on Mammography Date	Non-CAD		CAD		Adjusted OR (95% CI)†	*P* Value
	Breast Cancer Cases, *n*	Incidence Rate‡	Breast Cancer Cases, *n*	Incidence Rate‡		
Age 67–75 y (*n* = 233 874)						
Any breast cancer	16 557	7.55	7917	7.62	1.05 (1.01–1.09)	0.009
Invasive breast cancer§	12 940	5.90	5910	5.69	1.00 (0.96–1.04)	0.97
Stage I invasive	7741	3.53	3670	3.53	1.02 (0.97–1.07)	0.37
Stages II–IV invasive	4441	2.03	1938	1.86	0.99 (0.92–1.05)	0.68
DCIS	3617	1.65	2007	1.93	1.23 (1.14–1.31)	<0.001
Age 75–89 y (*n* = 175 585)						
Any breast cancer	14 782	9.11	7105	8.87	1.02 (0.98–1.06)	0.25
Invasive breast cancer§	11 864	7.31	5556	6.93	1.00 (0.96–1.04)	0.96
Stage I invasive	7134	4.40	3665	4.57	1.11 (1.05–1.16)	<0.001
Stages II–IV invasive	3745	2.31	1503	1.88	0.84 (0.78–0.91)	<0.001
DCIS	2918	1.80	1549	1.93	1.11 (1.03–1.20)	0.008

CAD = computer-aided detection; DCIS = ductal carcinoma in situ; OR = odds ratio.
* Mammograms for women without breast cancer (from the SEER [Surveillance, Epidemiology and End Results]–Medicare 5% noncancer sample) are probability-weighted by a factor of 20 so that the analysis represents the entire population of fee-for-service Medicare enrollees having screening mammography (weighted: 5 656 860 screening mammograms, including 46 361 done within 1 y of breast cancer diagnosis).
† Adjusted for race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, time since previous mammogram, use of CAD on the previous examination, presence of stable and unstable comorbid conditions, year of examination, and SEER region. Owing to missing covariate or outcome data, 35 531 mammograms (8.7% of total) from 13 136 women (8.3% of total) were excluded from adjusted analyses (unweighted: 373 928 mammograms from 144 022 women).
‡ Incidence per 1000 women-years.
§ Incidence rates for overall invasive cancer include both staged and unstaged cancer.

Appendix Table 9. CAD Use and Breast Cancer Diagnostic Testing Among Women Without Breast Cancer, Stratified by Patient Age*

Diagnostic Test, by Patient Age on Mammography Date	Non-CAD, *n* (unadjusted %)	CAD, *n* (unadjusted %)	Adjusted OR (95% CI)†	*P* Value
Age 67–75 y (*n* = 212 900)				
Diagnostic mammography	8966 (6.02)	4706 (7.35)	1.32 (1.30–1.33)	<0.001
Breast ultrasonography	6022 (4.04)	2537 (3.96)	1.07 (1.05–1.09)	<0.001
Either diagnostic mammography or breast ultrasonography	11 531 (7.74)	5460 (8.53)	1.21 (1.20–1.22)	<0.001
Breast biopsy	2049 (1.38)	912 (1.42)	1.15 (1.12–1.18)	<0.001
Age 75–89 y (*n* = 156 456)				
Diagnostic mammography	6013 (5.58)	3233 (6.64)	1.23 (1.21–1.24)	<0.001
Breast ultrasonography	3745 (3.48)	1690 (3.47)	1.08 (1.06–1.10)	<0.001
Either diagnostic mammography or breast ultrasonography	7605 (7.06)	3780 (7.76)	1.17 (1.16–1.19)	<0.001
Breast biopsy	1361 (1.26)	600 (1.23)	1.03 (1.01–1.05)	0.011

CAD = computer-aided detection; OR = odds ratio.
* Data based on 369 356 mammograms from 116 738 women.
† Adjusted for race or ethnicity, rural vs. urban residence, median income of elderly residents within the same ZIP code, presence of stable and unstable comorbid conditions, time since previous mammography, use of CAD on the previous examination, year of examination, SEER (Surveillance, Epidemiology and End Results) region, and a radiologist-level random effect. Owing to missing covariate data on 8.5% of mammograms, adjusted analyses include 337 753 mammograms from 99 540 women.

Appendix Table 10. Effect on Primary Analyses of a Potentially Unmeasured Confounder*

Outcome by Table	OR Associated With CAD (95% CI)	
	Original Analysis With Potential Unmeasured Confounding	Sensitivity Analysis Accounting for Unmeasured Confounder
Table 1		
Any breast cancer	1.04 (1.01–1.06)	1.00 (0.98–1.03)
Invasive breast cancer	1.00 (0.97–1.03)	0.96 (0.95–0.99)
Stage I invasive	1.06 (1.03–1.10)	1.03 (1.00–1.07)
Stages II–IV invasive	0.92 (0.87–0.96)	0.89 (0.85–0.93)
DCIS	1.17 (1.11–1.23)	1.15 (1.09–1.21)
Table 4		
Smallest OR: Invasive size <1 cm (vs. ≥1 cm)	1.10 (1.04–1.16)	1.08 (1.02–1.14)
Largest OR: Invasive stage I or II (vs. III or IV)	1.27 (1.14–1.41)	1.25 (1.13–1.38)
Table 5		
Smallest OR: Breast ultrasonography	1.08 (1.06–1.09)	1.05 (1.03–1.06)
Largest OR: Diagnostic mammography	1.28 (1.27–1.29)	1.25 (1.24–1.26)

CAD = computer-aided detection; DCIS = ductal carcinoma in situ; OR = odds ratio.
* Sensitivity analyses assume a 10% relative imbalance in the prevalence of unmeasured increased breast density among women who receive screening mammography with CAD compared with women who receive screening without CAD.