

Factors Associated With Rates of False-Positive and False-Negative Results From Digital Mammography Screening: An Analysis of Registry Data

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Background: Women screened with digital mammography may receive false-positive and false-negative results and subsequent imaging and biopsies. How these outcomes vary by age, time since the last screening, and individual risk factors is unclear.

Objective: To determine factors associated with false-positive and false-negative digital mammography results, additional imaging, and biopsies among a general population of women screened for breast cancer.

Design: Analysis of registry data.

Setting: Participating facilities at 5 U.S. Breast Cancer Surveillance Consortium breast imaging registries with linkages to pathology databases and tumor registries.

Patients: 405 191 women aged 40 to 89 years screened with digital mammography between 2003 and 2011. A total of 2963 were diagnosed with invasive cancer or ductal carcinoma in situ within 12 months of screening.

Measurements: Rates of false-positive and false-negative results and recommendations for additional imaging and biopsies from a single screening round; comparisons by age, time since the last screening, and risk factors.

Results: Rates of false-positive results (121.2 per 1000 women [95% CI, 105.6 to 138.7]) and recommendations for additional

imaging (124.9 per 1000 women [CI, 109.3 to 142.3]) were highest among women aged 40 to 49 years and decreased with increasing age. Rates of false-negative results (1.0 to 1.5 per 1000 women) and recommendations for biopsy (15.6 to 17.5 per 1000 women) did not differ greatly by age. Results did not differ by time since the last screening. False-positive rates were higher for women with risk factors, particularly family history of breast cancer; previous benign breast biopsy result; high breast density; and, for younger women, low body mass index.

Limitations: Confounding by variation in patient-level characteristics and outcomes across registries and regions may have been present. Some factors, such as numbers of first- and second-degree relatives with breast cancer and diagnoses associated with previous benign biopsy results, were not examined.

Conclusion: False-positive mammography results and additional imaging are common, particularly for younger women and those with risk factors, whereas biopsies occur less often. Rates of false-negative results are low.

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Clinical guidelines recommend a personalized approach to mammography screening that considers potential benefits and harms (1). Important harms include adverse effects of the screening process, such as false-positive and false-negative results and subsequent imaging and biopsies. Although procedures are often necessary to evaluate findings on screening mammography, most result in benign diagnoses. Minimizing these adverse effects could improve the balance of benefits and harms of screening for many women.

A personalized approach to screening includes identifying individual risk factors for breast cancer. Several risk factors have been associated with breast cancer in epidemiologic studies, but most relationships are modest or inconsistent (2). Factors associated with high risk for the disease include specific mutations of breast cancer susceptibility genes (3) and other hereditary genetic syndromes (4); previously diagnosed breast cancer or high-risk breast lesions (5, 6); previous high-dose radiation therapy to the chest (4, 7); and a family history of breast cancer, particularly among first-degree relatives. The degree of risk from family history varies ac-

cording to familial patterns of disease. Estimates of lifetime risk greater than 20% are considered high (8), although lower levels are also clinically important (9).

Additional factors that modestly increase risk include older age; current use of menopausal hormone therapy with combined estrogen and progestin regimens (10); current use of oral contraceptives (2); high breast density (11); and, for postmenopausal women, high body mass index (BMI) (12). How these factors influence performance outcomes of digital mammography screening has not been extensively explored.

The purpose of this study was to estimate rates of false-positive and false-negative digital mammography results and subsequent imaging and biopsies among a general population of women undergoing screening, as well as how rates vary by age, time since the last

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EDITORS' NOTES**Context**

Screening mammography can produce false-positive or false-negative results.

Contribution

This analysis of registry data describes rates of false-positive and false-negative results among women aged 40 to 89 years screened with digital mammography. False-positives and recommendations for additional imaging were highest among women aged 40 to 49 years. Rates of false-negative results were generally low. Positive family history, previous biopsy, high breast density, and low body mass index for younger women were associated with higher risk for a false-positive result.

Caution

Variation in patient characteristics and screening protocols across registries could have confounded estimates.

Implication

False-positive results and additional imaging are common, particularly for younger women and those with risk factors.

mammography screening, and individual risk factors. This analysis will be used to inform updated clinical practice recommendations in the United States (13).

METHODS**Design Overview**

This study was an analysis of data collected between 2003 and 2011 from the Breast Cancer Surveillance Consortium (BCSC), a collaborative network of mammography registries across the United States that is supported by the National Cancer Institute (14, 15). Registries collected data at the time of mammography at participating community radiology facilities. Breast cancer diagnoses were obtained by linking BCSC data to pathology databases, regional SEER (Surveillance, Epidemiology, and End Results) programs, and state tumor registries. Data were pooled at a statistical coordinating center. Registries and the coordinating center received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analysis. All procedures were compliant with the Health Insurance Portability and Accountability Act, and registries and the coordinating center received a federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

Setting and Participants

The analysis included data for 405 191 women aged 40 to 89 years who had routine screening with digital mammography between 2003 and 2011 at participating facilities in 5 BCSC breast imaging registries

(Carolina Mammography Registry, Group Health [Washington State], New Hampshire Mammography Network, San Francisco Mammography Registry, and Vermont Breast Cancer Surveillance System) (Figure). Before each mammography screening, women completed questionnaires about demographic and medical history information, including time since their last mammography screening. All women with an eligible screening mammogram who completed a questionnaire providing permission to use their information for research were included.

Mammograms were included if they were designated by the radiologist or radiology technologist as performed for screening purposes and if they were done more than 9 months after a previous imaging examination in women with no history of breast cancer, breast augmentation, or mastectomy. Each study-eligible mammogram required at least 1 examination within the previous 30 months. Initial and unilateral examinations were excluded. Mammography information included Breast Imaging Reporting and Data System (BI-RADS) breast density, assessment, and recommendations for further work-up. For women with more than 1 mammography screening during the study period, 1 observation was randomly selected to be included in the calculations to reduce potential bias, such as from preferentially choosing women with shorter or longer screening histories. These data comprise a defined subset of BCSC data intended to represent the experience of a cohort of regularly screened women with no history of breast cancer or current breast symptoms.

Outcome and Risk Factor Measures

Outcome measures included rates of false-positive and false-negative mammography results and recommendations for additional imaging and biopsies from a single screening round. False-positive and false-negative mammography results were based on follow-up data within 1 year of screening and before the next screening examination. Positive versus negative initial and final results were defined using BCSC standard definitions (16), which used standardized terminology and assessments from the fourth edition of the American College of Radiology BI-RADS Atlas (17). Each mammography screening was given an initial BI-RADS assessment based on the screening views only. Positive initial results included 4 assessment categories: needs additional imaging evaluation (category 0), probably benign (category 3) with a recommendation for immediate work-up (treated as category 0 because of the recommendation), suspicious abnormality (category 4), or highly suggestive of malignancy (category 5) (18). Negative results included assessments of negative (category 1) or benign (category 2) findings or category 3 without a recommendation for immediate work-up.

Recommendation for biopsy was defined as a positive final result after all imaging, including work-up for an abnormal screening result. Positive final results included BI-RADS assessments of category 4 or 5 or category 0 with a recommendation for biopsy (18). Negative final results included an assessment of category 1,

2, or 3 or category 0 with a recommendation for normal or short-interval follow-up or clinical examination.

We examined associations with common risk factors for breast cancer (2). These included first-degree relatives with breast cancer (none or ≥ 1), breast density (almost entirely fat, scattered fibroglandular densities, heterogeneously dense, or extremely dense), benign breast biopsy result (none or previous), race/ethnicity (white, black, Asian, Hispanic, or other), menopausal status (premenopausal, perimenopausal, or postmenopausal), menopausal hormone therapy use (none, combination [estrogen with progestin], or estrogen only), oral contraceptive use (no current use or current use), and BMI (<25, 25 to <30, or ≥ 30 kg/m²). Because the BCSC data do not include information on types of menopausal hormone therapy, we assumed that a woman with a uterus uses combination therapy and a woman without a uterus uses estrogen-only therapy, as previously described (19, 20).

The primary analysis involved 3 categories of breast density, with almost entirely fat and scattered fibroglandular densities combined into 1 group. In a sensitivity analysis, we analyzed density in 3 additional ways: 3 categories, with heterogeneously dense and extremely dense combined into 1 group; 4 separate BI-RADS categories; and 2 categories, with almost entirely fat and scattered fibroglandular densities in one group and heterogeneously dense and extremely dense in the other.

Two measures of time since the last mammography screening were evaluated to represent broad and narrow estimates of 1 versus 2 years (9 to 18 vs. 19 to 30 months and 11 to 14 vs. 23 to 26 months).

Missing data for outcomes and risk factors are summarized in **Appendix Table 1** (available at www.annals.org).

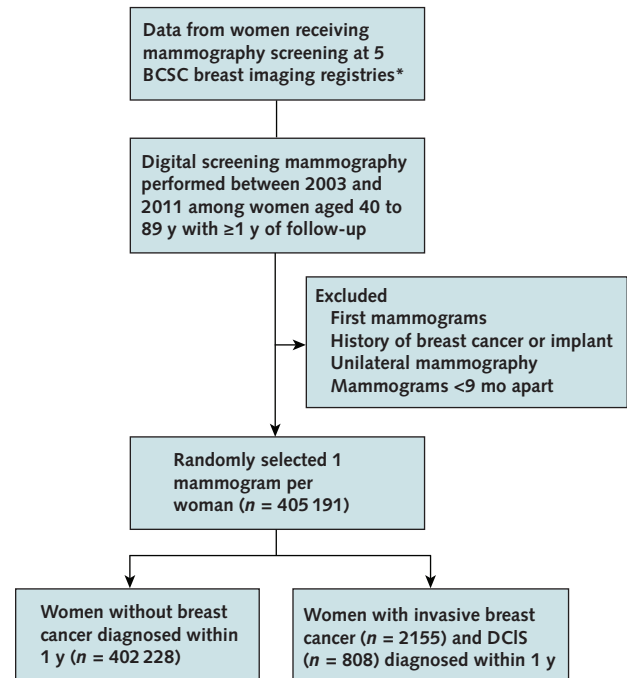
Statistical Analysis

We calculated age-specific rates (per 1000 women per single screening round) by decade for false-positive and false-negative mammography results, recommendations for additional imaging, and recommendations for biopsy and determined whether outcomes differed by age, time since the last mammography screening, and risk factors. To account for correlation among mammograms interpreted at the same radiology facility, we estimated robust SEs from logistic regression using generalized estimating equations with an independence working correlation matrix (21). We then calculated 95% CIs and, to assess differences between groups, 2-sided *P* values. This method provides population-averaged estimates of effects, which are not necessarily causal relationships. Analyses were performed using SAS, version 9.3 (SAS Institute).

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the U.S. Preventive Services Task Force. The AHRQ had no role in the analysis or the development of conclusions. The AHRQ performed a final review of the manuscript to ensure that the analy-

Figure. Description of BCSC data sources for the study.



Mammograms were included if they were designated by the radiologist or radiology technologist as performed for screening purposes and if they occurred >9 mo after a previous imaging examination in women with no history of breast cancer, breast augmentation, or mastectomy. Routine screening required ≥ 1 mammogram within the previous 30 mo. BCSC = Breast Cancer Surveillance Consortium; DCIS = ductal carcinoma in situ.

* Carolina Mammography Registry, Group Health (Washington State), New Hampshire Mammography Network, San Francisco Mammography Registry, and Vermont Breast Cancer Surveillance System.

sis met methodological standards. The investigators are solely responsible for the content and the decision to submit the manuscript for publication.

RESULTS

Outcomes by Age

Data based on results from a single screening round for women regularly receiving digital mammography indicated that false-positive results were common in all age groups (Table 1). The rate was highest among women aged 40 to 49 years (121.2 per 1000 women [95% CI, 105.6 to 138.7]) and decreased across age groups ($P < 0.001$). Rates of false-negative mammography results tended to increase with age, ranging from 1.0 to 1.5 per 1000 women, but did not statistically significantly differ across age groups.

For women with initially positive mammography results, rates of recommendations for additional imaging were highest among those aged 40 to 49 years (124.9 per 1000 women [CI, 109.3 to 142.3]) and decreased with increasing age ($P < 0.001$). Rates of recommendations for biopsy did not statistically significantly differ across age groups and ranged from 15.6 to 17.5 per 1000 women.

Table 1. Age-Specific Rates of False-Positive and False-Negative Digital Mammography Results and Recommendations for Additional Imaging and Biopsies From a Single Screening Round in the BCSC*

Variable	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y	Age 80-89 y	P Value
Women screened, <i>n</i>	113 770	127 958	94 507	50 204	18 752	-
Invasive breast cancer cases, <i>n</i>	349	574	651	427	154	-
DCIS cases, <i>n</i>	191	246	208	120	43	-
Outcomes per 1000 women screened (95% CI), <i>n</i>						
False-positive mammography result	121.2 (105.6-138.7)	93.2 (82.8-104.7)	80.8 (72.9-89.4)	69.6 (62.6-77.3)	65.2 (58.8-72.2)	<0.001
False-negative mammography result	1.0 (0.9-1.2)	1.1 (0.9-1.3)	1.2 (0.9-1.5)	1.5 (1.1-1.9)	1.3 (0.9-1.9)	0.32
Additional imaging recommended†	124.9 (109.3-142.3)	98.5 (88.0-110.1)	88.7 (80.6-97.4)	79.0 (71.9-86.9)	74.4 (67.4-82.2)	<0.001
Biopsy recommended†	16.4 (13.2-20.3)	15.9 (12.7-19.7)	16.5 (14.3-19.1)	17.5 (15.2-20.2)	15.6 (13.4-18.2)	0.120
Screen-detected invasive cancer	2.2 (1.8-2.6)	3.5 (3.1-4.0)	5.8 (5.3-6.4)	7.2 (6.4-8.1)	7.1 (5.9-8.5)	<0.001
Screen-detected DCIS	1.6 (1.3-1.9)	1.8 (1.5-2.2)	2.1 (1.7-2.5)	2.3 (1.7-3.0)	2.1 (1.5-3.0)	0.055

BCSC = Breast Cancer Surveillance Consortium; DCIS = ductal carcinoma in situ.

* 2-sided *P* values and 95% CIs were derived from a logistic regression model that used generalized estimating equations to account for clustering by radiology facility.

† After positive mammography result.

Rates of invasive breast cancer were lowest among women aged 40 to 49 years (2.2 per 1000 women [CI, 1.8 to 2.6]) and increased across age groups ($P < 0.001$). Rates of ductal carcinoma in situ also were lowest among women aged 40 to 49 years (1.6 per 1000 women [CI, 1.3 to 1.9]) and increased with age ($P = 0.055$). Women aged 70 to 79 years had the highest rates of invasive cancer (7.2 per 1000 women [CI, 6.4 to 8.1]) and ductal carcinoma in situ (2.3 per 1000 women [CI, 1.7 to 3.0]). Consequently, the yield of screening was more favorable for older women. For every case of invasive breast cancer detected by mammography screening in women aged 40 to 49 years, 464 women had mammography, 58 were recommended for additional imaging, and 10 were recommended for biopsy. In contrast, for women aged 70 to 79 years, for every case of invasive breast cancer detected by screening, 139 women had mammography, 11 were recommended for additional imaging, and 3 were recommended for biopsy.

Outcomes by Time Since the Last Mammography Screening

Rates of false-positive results, false-negative results, and recommendations for additional imaging did not differ in comparisons of time since the last mammography screening, regardless of the interval (9 to 18 vs. 19 to 30 months and 11 to 14 vs. 23 to 26 months) (Appendix Table 2, available at www.annals.org). Biopsies were recommended at a higher rate only for women aged 60 to 69 years who had their last mammogram 23 to 26 months previously compared with 11 to 14 months previously (18.8 vs. 15.2 per 1000 women; $P = 0.026$).

Outcomes by Risk Factors

False-Positive Mammography Results

Rates of false-positive mammography results were statistically significantly higher for women with specific risk factors than for those without them (Table 2). These include having a first-degree relative with breast cancer

for women aged 40 to 69 years. Women with heterogeneously dense breasts had higher false-positive rates than those with almost entirely fat and scattered fibroglandular densities or extremely dense breasts in all age groups except 80 to 89 years. Rates were also higher among women with previous benign breast biopsy results in the 40-to-79-year age group. Comparisons based on race and ethnicity indicated the lowest rates among Asian women in all age groups.

Premenopausal women had higher false-positive rates than those who were perimenopausal or postmenopausal in the 40-to-59-year age group. Among women using menopausal hormone therapy, those aged 70 to 79 years had the highest rates; comparisons for the other age groups were not statistically significant. Women with lower BMI ($<30 \text{ kg/m}^2$) had higher false-positive rates in the 40-to-59-year age group.

False-Negative Mammography Results

Rates of false-negative results were higher for women aged 40 to 79 years with first-degree relatives with breast cancer, although results were of borderline statistical significance for those aged 50 to 69 years (Appendix Table 3, available at www.annals.org). Women with almost entirely fat and scattered fibroglandular densities had lower rates than those with other types of breast density in the 40-to-69-year age group. Rates were higher among women with previous benign breast biopsy results in the 50-to-89-year age group and women with lower BMI ($<30 \text{ kg/m}^2$) in the 50-to-59-year age group. Other comparisons between groups were not statistically significant.

Recommendations for Additional Imaging

Risk factors associated with differences in rates of recommendations for additional imaging were similar to those for false-positive mammography results (Appendix Table 4, available at www.annals.org). Rates were highest among women with first-degree relatives

Table 2. Rates of False-Positive Results After Screening With Digital Mammography, by Risk Factor*

Variable	Age 40-49 y	P Value	Age 50-59 y	P Value
Women screened, <i>n</i>	113 770	-	127 958	-
False-positive results, <i>n</i>	13 784	-	11 923	-
False-positive results per 1000 women screened per round (95% CI), <i>n</i>				
First-degree relatives with breast cancer				
None	118.7 (104.3-134.7)	0.028	90.4 (81.1-100.7)	0.005
≥1	139.8 (113.9-170.5)		109.0 (92.3-128.2)	
Breast density				
Almost entirely fat/scattered fibroglandular densities	108.4 (95.5-122.7)	<0.001	80.5 (71.1-90.9)	<0.001
Heterogeneously dense	142.2 (120.2-167.4)		115.8 (100.3-133.2)	
Extremely dense	112.1 (94.4-132.7)		92.7 (77.5-110.5)	
Benign results on breast biopsy				
None	114.3 (99.8-130.5)	0.001	85.9 (76.7-96.0)	<0.001
Previous	167.3 (140.6-197.9)		122.5 (106.2-140.7)	
Race/ethnicity				
White	127.0 (115.5-139.4)	0.001	97.6 (89.5-106.4)	0.012
Black	92.6 (82.0-104.5)		78.9 (65.2-95.3)	
Asian	85.2 (72.2-100.4)		67.6 (56.5-80.7)	
Hispanic	125.4 (106.8-146.7)		80.9 (69.1-94.6)	
Other	127.8 (105.8-153.6)		102.3 (88.5-117.8)	
Menopausal status				
Premenopausal	131.3 (113.3-151.8)	0.016	118.3 (107.2-130.5)	<0.001
Perimenopausal	103.9 (88.5-121.7)		97.6 (75.7-125.1)	
Postmenopausal	111.3 (100.2-123.4)		87.2 (78.8-96.4)	
Menopausal hormone therapy				
None	123.3 (107.4-141.2)	0.69	91.8 (81.6-103.2)	0.27
Combination	122.0 (78.8-184.1)		131.1 (99.5-170.7)	
Estrogen only	108.7 (84.4-138.8)		101.3 (87.1-117.6)	
Oral contraceptives				
No current use	122.9 (107.2-140.6)	0.045	93.6 (83.1-105.4)	0.63
Current use	106.2 (86.4-130.0)		97.0 (81.3-115.2)	
Body mass index				
<25 kg/m ²	129.0 (113.8-145.9)	0.009	99.5 (89.3-110.8)	0.036
25-30 kg/m ²	124.8 (110.1-141.2)		93.6 (85.0-103.0)	
≥30 kg/m ²	107.2 (96.0-119.5)		86.1 (77.7-95.2)	

NA = not applicable.

* 2-sided *P* values and 95% CIs were derived from a logistic regression model that used generalized estimating equations to account for clustering by radiology facility.

with breast cancer in all age groups, those with heterogeneously dense breasts in the 40-to-79-year age group, those with previous benign breast biopsy results in the 40-to-79-year age group, those who were premenopausal in the 40-to-49-year age group, those who were using menopausal hormone therapy in the 70-to-79-year age group, and those with lower BMI in the 40-to-49-year age group. Comparisons based on race and ethnicity indicated the lowest rates among Asian women in all age groups.

Recommendations for Biopsy

Rates of recommendations for biopsy were statistically significantly higher for women aged 40 to 69 years with first-degree relatives with breast cancer and for those aged 40 to 79 years with previous benign breast biopsy results (Table 3). Women aged 40 to 59 years with heterogeneously or extremely dense breasts had higher rates than those with less dense breasts; for women aged 60 to 79 years, rates were highest among those with heterogeneously dense breasts. Higher rates were also associated with premenopausal status for women aged 50 to 59 years, no current use of oral contraceptives for those aged 40 to 49 years, and lower BMI for those aged 40 to 49 years but higher BMI for

those aged 70 to 79 years. Other comparisons between groups were not statistically significant.

Breast Density Categories

Rates of false-positive results, false-negative results, recommendations for additional imaging, and recommendations for biopsy were lowest for women with almost entirely fat breasts in all age groups. False-negative rates were highest for women with extremely dense breasts in all age groups except 60 to 69 years (Appendix Table 5, available at www.annals.org). Rates of false-positive results, recommendations for additional imaging, and recommendations for biopsy were highest for women with heterogeneously dense breasts or those in the combined category of heterogeneously and extremely dense breasts in all age groups except 40 to 49 years, where rates of recommendations for biopsy were highest for women with extremely dense breasts.

DISCUSSION

Our analysis of BCSC data on digital mammography screening indicated that rates of false-positive results and recommendations for additional imaging

Table 2—Continued

Age 60-69 y	P Value	Age 70-79 y	P Value	Age 80-89 y	P Value
94 507	-	50 204	-	18 752	-
7633	-	3494	-	1223	-
79.4 (71.8-87.7)	0.020	68.6 (61.1-76.8)	0.108	63.3 (56.8-70.5)	0.047
87.2 (77.2-98.4)		75.0 (67.6-83.1)		73.1 (64.1-83.3)	
74.1 (66.4-82.6)	<0.001	67.3 (60.4-74.9)	0.003	60.3 (54.0-67.4)	0.001
101.8 (91.0-113.8)		88.7 (78.7-99.9)		82.4 (72.6-93.5)	
75.2 (64.7-87.1)		57.7 (43.9-75.5)		85.1 (61.7-116.2)	
74.6 (66.8-83.1)	<0.001	63.4 (56.2-71.3)	<0.001	63.0 (56.3-70.6)	0.093
98.6 (88.8-109.3)		88.6 (79.1-99.2)		71.6 (62.3-82.3)	
83.8 (77.4-90.7)	0.006	73.5 (67.7-79.8)	<0.001	68.9 (62.6-75.7)	0.039
64.5 (53.6-77.3)		58.9 (51.7-67.0)		52.4 (43.6-63.0)	
58.0 (47.9-70.2)		43.6 (36.9-51.6)		35.8 (29.6-43.4)	
72.9 (60.3-87.8)		60.7 (50.6-72.8)		55.7 (31.3-97.2)	
91.5 (76.2-109.5)		72.6 (53.3-98.2)		48.9 (29.3-80.6)	
NA		NA		NA	
-		-		-	
-		-		-	
76.2 (69.2-84.0)	0.22	67.6 (61.1-74.8)	0.012	62.2 (55.5-69.8)	0.27
122.5 (87.3-169.2)		105.9 (81.8-136.0)		94.0 (74.0-118.8)	
97.6 (77.3-122.5)		114.0 (94.8-136.5)		89.1 (68.5-115.1)	
NA		NA		NA	
-		-		-	
85.8 (77.9-94.4)	0.144	70.5 (62.0-80.0)	0.78	73.9 (60.6-89.8)	0.33
78.6 (69.5-88.9)		72.7 (64.8-81.6)		62.2 (51.4-75.1)	
81.1 (74.1-88.6)		74.2 (64.1-85.7)		73.8 (59.1-91.9)	

were highest among women aged 40 to 49 years and decreased with increasing age, whereas rates of false-negative results were low across all age groups. Rates of recommendations for biopsy did not differ across age groups. Results did not differ by time since the last mammography screening regardless of whether broad or narrow estimates of 1 versus 2 years were used.

Several risk factors (family history of breast cancer, high breast density, and previous benign breast biopsy result) were statistically significantly associated with higher rates of false-positive and false-negative results and recommendations for additional imaging and biopsy across most age groups. Premenopausal status, use of menopausal hormone therapy, and lower BMI were associated with some outcomes for specific age groups only. Comparisons based on race and ethnicity indicated the lowest rates of false-positive results and additional imaging among Asian women. Although some risk factors (such as premenopausal status and use of menopausal hormone therapy) reflect higher exposure to estrogen and related changes in breast tissue, others (such as family history and previous benign biopsy result) may serve primarily as markers of increased breast cancer risk.

Our analysis comparing different combinations of breast density categories indicated that rates for all outcomes were lowest for women with almost entirely fat breasts and highest for those with heterogeneously

dense breasts or those in the combined category of heterogeneous and extreme density. Women with extremely dense breasts had the highest rates of false-negative results. This is probably related to this group's particularly complex mammography images, which are more difficult to interpret and thus limit discrimination between breast cancer and normal tissue and lead to more callbacks and biopsies and higher false-negative rates in clinical practice (22-24).

This analysis indicated higher rates of false-positive results and recommendations for additional imaging and lower rates of recommendations for biopsy than our previous analysis of BCSC data, which included 600 830 women screened between 2000 and 2005 using predominantly film mammography (25). The lower rates of recommendations for biopsy may be due to more selective use of procedures by radiologists because of improvements in image quality and interpretation for digital mammography and ultrasonography over time.

Our finding that results did not differ by time since the last mammography screening differs from previous analyses by the BCSC that indicated higher rates for annual versus biennial screening (19, 26-30). However, our rates were based on digital mammography only and on a single round of screening that did not capture the longitudinal screening experiences of individual women, which more accurately reflect clinical practice.

Table 3. Rates of Recommendations for Biopsy After Screening With Digital Mammography, by Risk Factor*

Variable	Age 40-49 y	P Value	Age 50-59 y	P Value
Women screened, <i>n</i>	113 770	-	127 958	-
Biopsy recommended, <i>n</i>	1863	-	2030	-
Recommendations per 1000 women screened per round (95% CI), <i>n</i>				
First-degree relatives with breast cancer				
None	15.7 (12.6-19.4)	0.002	14.8 (11.8-18.4)	<0.001
≥1	21.1 (16.9-26.3)		21.9 (17.5-27.3)	
Breast density				
Almost entirely fat/scattered fibroglandular densities	12.2 (9.9-15.0)	<0.001	11.8 (9.6-14.5)	<0.001
Heterogeneously dense	18.9 (15.8-22.5)		20.2 (17.3-23.7)	
Extremely dense	20.2 (16.8-24.3)		19.2 (14.3-25.7)	
Benign results on breast biopsy				
None	14.8 (11.8-18.7)	<0.001	13.9 (11.1-17.3)	<0.002
Previous	27.8 (22.8-33.7)		25.1 (20.1-31.2)	
Race/ethnicity				
White	16.7 (13.7-20.3)	0.21	16.6 (13.6-20.2)	0.39
Black	13.6 (10.4-17.8)		14.7 (10.4-20.6)	
Asian	16.2 (10.6-24.5)		14.8 (9.5-22.9)	
Hispanic	16.3 (10.3-25.6)		11.9 (8.1-17.5)	
Other	19.8 (14.4-27.3)		17.4 (10.5-28.6)	
Menopausal status				
Premenopausal	17.6 (14.0-22.1)	0.49	19.8 (15.7-24.9)	0.023
Perimenopausal	17.8 (14.4-22.0)		16.4 (10.6-25.4)	
Postmenopausal	15.8 (12.5-20.0)		15.4 (12.1-19.4)	
Menopausal hormone therapy				
None	16.3 (13.2-20.2)	0.34	15.6 (12.6-19.2)	0.50
Combination	15.2 (8.2-28.2)		18.3 (12.7-26.3)	
Estrogen only	26.4 (14.7-47.2)		18.3 (12.3-27.2)	
Oral contraceptives				
No current use	16.7 (13.6-20.6)	0.007	16.0 (13.1-19.5)	0.32
Current use	12.5 (9.5-16.3)		13.0 (7.0-24.3)	
Body mass index				
<25 kg/m ²	21.4 (17.0-26.8)	0.016	19.3 (14.7-25.1)	0.40
25-30 kg/m ²	17.6 (13.7-22.6)		18.0 (13.3-24.4)	
≥30 kg/m ²	15.3 (12.3-19.2)		18.4 (14.5-23.4)	

NA = not applicable.

* 2-sided *P* values and 95% CIs were derived from a logistic regression model that used generalized estimating equations to account for clustering by radiology facility.

A previous analysis of BCSC data that provided results of screening over a 10-year period indicated that when screening began at age 40 years, cumulative rates of false-positive mammography and benign biopsy results were higher for annual than biennial screening (mammography, 61% vs. 42%; biopsy, 7% vs. 5%) (29).

The results of our analysis of associations with risk factors are generally consistent with previous BCSC analyses indicating that 10-year cumulative risks for false-positive results and benign biopsy results were higher for women with heterogeneously or extremely dense breasts, those with a family history of breast cancer, and those who used combination menopausal hormone therapy (29, 31). Although our analysis identified associations with additional risk factors, it differed from the study of 10-year cumulative risks because it was based on a single round of screening, did not adjust for other covariates, and included only digital mammography.

Strengths of this study include its use of digital mammography data and patient information from a large national collaborative database of women screened in the United States, which provided a comprehensive data source representing current clinical practice. This study used the methods of the BCSC, which have been standardized across the participating

registries, allowing our analysis to build on prior work in this area (22, 23, 32).

To estimate screening outcomes applicable to clinical practice in the United States, data sources must include information from U.S. practices because rates of false-positive and false-negative results and additional imaging and biopsies differ substantially elsewhere (33-35). These differences relate to the variability in how mammography screening and diagnostic services are delivered and practiced.

This study has several limitations. The BCSC data reflect opportunistic screening in a fluctuating population of women in the United States whose information was collected by the participating registries. Findings may not be applicable to other populations. Other limitations include the use of registry data based on pre-defined elements and the inherent biases of observational data. Some outcomes, such as the effectiveness and harms of different screening intervals, would be more accurately determined by comparing outcomes between women who were randomly assigned to comparison groups. However, this question has not been resolved by randomized trials of screening that used intervals ranging from 12 to 33 months (13).

Our goal was to provide overall rates of the outcome measures by time since the last mammography

Table 3—Continued

Age 60-69 y	P Value	Age 70-79 y	P Value	Age 80-89 y	P Value
94 507	-	50 204	-	18 752	-
1562	-	880	-	293	-
15.8 (13.7-18.3)	0.002	17.0 (14.7-19.6)	0.086	15.2 (12.8-18.0)	0.24
20.1 (17.0-23.7)		20.3 (16.7-24.6)		17.6 (14.1-22.1)	
15.6 (13.7-17.7)	0.008	16.2 (14.2-18.4)	0.007	14.2 (12.0-16.8)	0.072
19.3 (16.9-22.2)		21.0 (18.0-24.5)		19.0 (15.5-23.2)	
13.8 (10.5-18.2)		13.0 (7.2-23.3)		16.1 (8.0-32.1)	
15.0 (12.7-17.8)	<0.001	15.3 (13.1-17.7)	<0.001	15.8 (13.4-18.7)	0.54
21.8 (19.1-24.9)		25.2 (21.4-29.7)		17.1 (13.7-21.5)	
17.6 (15.6-20.0)	0.049	18.7 (16.6-21.2)	0.23	16.2 (13.5-19.4)	0.119
13.9 (10.6-18.0)		14.9 (11.4-19.5)		8.9 (4.4-18.0)	
12.0 (6.9-20.6)		11.8 (6.8-20.3)		9.2 (5.6-15.3)	
14.2 (11.4-17.6)		15.9 (10.1-25.1)		16.4 (8.5-31.5)	
16.4 (10.8-24.8)		16.6 (10.0-27.6)		5.4 (0.7-39.2)	
NA		NA		NA	
-		-		-	
-		-		-	
15.9 (13.9-18.3)	0.37	17.2 (15.1-19.4)	0.138	15.2 (12.8-17.9)	0.130
16.9 (12.6-22.6)		33.0 (23.7-45.9)		21.9 (14.0-34.2)	
21.0 (14.5-30.2)		25.3 (17.7-36.1)		32.2 (22.2-46.4)	
NA		NA		NA	
-		-		-	
17.4 (14.4-21.0)	0.123	16.5 (13.5-20.1)	0.021	17.1 (13.8-21.2)	0.26
18.9 (15.3-23.4)		21.9 (18.2-26.3)		16.6 (12.5-21.9)	
22.2 (18.1-27.2)		26.7 (21.9-32.4)		26.6 (18.5-38.1)	

screening and risk factors. Thus, our estimates were derived from population-averaged models, which provided variance estimates adjusted for correlation within facilities but did not decompose within- versus between-facility effects or adjust for potential confounders. For example, compared with women without risk factors, those with risk factors may tend to seek care at facilities with different performance characteristics (for example, academic medical centers); present for screening more often; or have other characteristics that explain the higher rates of screening harms, such as more complex breast tissue or increased risk for benign breast disease. Understanding the mechanisms through which risk factors affect performance or variation across facilities and radiologists is beyond the scope of this study.

Our estimates are based on digital mammography performed without supplemental imaging. Digital breast tomosynthesis (36-41) and supplemental tests, such as screening ultrasonography (42), are becoming more widely used in the United States. A similar analysis of screening outcomes of these newer technologies using a large generalizable cohort, such as the BCSC, is needed.

In conclusion, our analysis of outcomes from a single round of digital mammography screening in 405 191 women indicated that false-positive results and additional imaging are common, particularly for

younger women and those with risk factors, whereas biopsies occur less often. Rates of false-negative results are low. The results of this study may be useful for women and clinicians considering the individual benefits and harms of screening as well as for health service administrators and planners determining the implications of screening for populations.

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Reproducible Research Statement: *Study protocol and statistical code:* Available from the statistical coordinating center of the BCSC (e-mail, SCC@ghc.org). *Data set:* Available with approval of the BCSC Steering Committee (<http://breastscreening.cancer.gov>).

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Appendix Table 1. Rates of Missing Data for Outcome and Risk Factor Measures for 405 191 Women Screened*

Variable	Women With Missing Data	
	Number	Percentage
Outcome		
Invasive breast cancer cases	0	0
DCIS cases	0	0
False-positive mammography result	0	0
False-negative mammography result	0	0
Additional imaging recommended	0	0
Biopsy recommended	9633	2.4
Screen-detected invasive cancer	0	0
Screen-detected DCIS	0	0
Risk factor		
First-degree relatives with breast cancer	3943	1.0
Breast density	65 919	16.3
Benign breast biopsy	23 588	5.8
Race/ethnicity	31 061	7.7
Menopausal status	41 288	17.1†
Menopausal hormone therapy	65 717	16.2
Oral contraceptives	37 098	15.3†
Body mass index‡	190 560	47.0
Months since last examination§	0	0

DCIS = ductal carcinoma in situ.

* Women with missing data were excluded from the specific analysis only.

† Percentage of 241 728 screened women aged 40–59 y; women aged ≥60 y are postmenopausal.

‡ Most missing values were from facilities that do not collect this information.

§ No missing data for broad categories (9–18 vs. 19–30 mo).

Appendix Table 2. Rates of False-Positive and False-Negative Digital Mammography Results and Recommendations for Additional Imaging and Biopsies Based on Time Since Last Mammography Examination*

Outcome	Time Since Last Examination, mo	Age 40-49 y	P Value	Age 50-59 y	P Value	Age 60-69 y	P Value	Age 70-79 y	P Value	Age 80-89 y	P Value
Comparing 9-18 vs. 19-30 mo											
Women screened, n	9-18	79 637	-	91 864	-	71 324	-	39 474	-	14 865	-
	19-30	34 133	-	36 094	-	23 183	-	10 730	-	3887	-
Invasive breast cancer cases, n	9-18	240	-	391	-	474	-	322	-	119	-
	19-30	109	-	183	-	177	-	105	-	35	-
DCIS cases, n	9-18	126	-	185	-	156	-	94	-	32	-
	19-30	65	-	61	-	52	-	26	-	11	-
Outcomes per 1000 women screened (95% CI), n											
False-positive mammography result	9-18	122.1 (105.4-141.0)	0.65	94.2 (83.3-106.5)	0.37	80.6 (72.8-89.2)	0.89	69.1 (61.9-77.0)	0.55	66.5 (60.8-72.8)	0.22
	19-30	119.0 (103.0-137.1)		90.5 (80.4-101.8)		81.1 (71.4-92.1)		71.6 (62.2-82.2)		60.2 (49.3-73.3)	
False-negative mammography result	9-18	1.1 (0.9-1.3)	0.14	1.2 (1.0-1.4)	0.06	1.3 (1.0-1.6)	0.26	1.6 (1.2-2.1)	0.17	1.4 (0.9-2.2)	0.27
	19-30	0.8 (0.6-1.1)		0.9 (0.6-1.2)		0.9 (0.6-1.5)		1.0 (0.5-2.0)		0.8 (0.3-2.3)	
Additional imaging recommended†	9-18	125.6 (109.0-144.3)	0.74	99.3 (88.2-111.7)	0.47	88.2 (80.2-96.9)	0.59	78.0 (70.7-86.1)	0.30	75.3 (68.6-82.6)	0.46
	19-30	123.3 (107.0-141.7)		96.4 (85.9-108.0)		90.1 (80.1-101.2)		82.8 (72.5-94.3)		71.3 (59.8-84.8)	
Biopsy recommended†	9-18	15.6 (12.8-19.0)	0.11	15.7 (12.7-19.3)	0.50	15.9 (14.0-18.2)	0.10	17.3 (15.2-19.6)	0.44	14.9 (12.4-17.9)	0.25
	19-30	18.2 (13.7-24.1)		16.4 (12.5-21.4)		18.4 (14.7-23.0)		18.5 (14.6-23.5)		18.3 (13.9-24.0)	
Screen-detected invasive cancer	9-18	2.0 (1.6-2.5)	0.12	3.2 (2.7-3.7)	0.009	5.5 (4.9-6.2)	0.07	6.7 (5.8-7.7)	0.04	6.8 (5.4-8.5)	0.39
	19-30	2.5 (2.1-3.0)		4.3 (3.7-5.1)		6.8 (5.7-8.1)		8.9 (7.4-10.8)		8.2 (5.8-11.6)	
Screen-detected DCIS	9-18	1.5 (1.2-1.8)	0.18	1.9 (1.5-2.4)	0.13	2.0 (1.8-2.4)	0.79	2.3 (1.7-3.0)	0.97	2.0 (1.2-3.1)	0.42
	19-30	1.8 (1.4-2.3)		1.6 (1.2-2.0)		2.2 (1.4-3.3)		2.2 (1.4-3.6)		2.8 (1.5-5.3)	
Comparing 11-14 vs. 23-26 mo											
Women screened, n	11-14	55 278	-	65 219	-	53 419	-	30 497	-	11 299	-
	23-26	13 584	-	14 407	-	9907	-	4291	-	1504	-
Invasive breast cancer cases, n	11-14	163	-	274	-	348	-	247	-	78	-
	23-26	42	-	70	-	76	-	41	-	15	-
DCIS cases, n	11-14	83	-	127	-	111	-	71	-	20	-
	23-26	26	-	22	-	23	-	12	-	3	-
Outcomes per 1000 women screened (95% CI), n											
False-positive mammography result	11-14	119.1 (103.5-136.8)	0.69	93.3 (82.8-105.0)	0.46	79.2 (72.2-86.8)	0.91	67.6 (60.7-75.2)	0.70	63.8 (58.2-69.9)	0.71
	23-26	115.8 (98.7-135.4)		89.9 (78.8-102.4)		79.6 (70.3-90.2)		65.7 (56.7-76.0)		61.2 (47.3-78.7)	
False-negative mammography result	11-14	1.2 (1.0-1.5)	0.20	1.2 (1.0-1.5)	0.11	1.2 (0.9-1.6)	0.32	1.4 (1.1-2.0)	0.95	1.2 (0.7-1.8)	0.44
	23-26	0.9 (0.5-1.5)		0.8 (0.4-1.4)		0.8 (0.4-1.8)		1.4 (0.6-3.4)		2.0 (0.7-6.0)	
Additional imaging recommended†	11-14	122.4 (106.7-139.9)	0.77	98.3 (87.7-109.9)	0.57	86.6 (79.5-94.3)	0.55	76.6 (69.3-84.5)	0.98	71.3 (65.4-77.7)	0.98
	23-26	119.9 (102.6-139.7)		95.5 (83.9-108.5)		88.8 (79.2-99.5)		76.7 (66.5-88.2)		71.1 (57.1-88.3)	
Biopsy recommended†	11-14	14.7 (12.2-17.8)	0.31	15.1 (12.2-18.6)	0.66	15.2 (13.5-17.2)	0.03	16.6 (14.5-18.9)	0.85	13.2 (10.8-16.0)	0.33
	23-26	16.9 (11.9-24.0)		15.8 (11.7-21.3)		18.8 (15.2-23.2)		17.0 (12.6-23.0)		16.6 (11.2-24.7)	
Screen-detected invasive cancer	11-14	1.8 (1.5-2.3)	0.31	3.1 (2.6-3.7)	0.05	5.5 (4.9-6.2)	0.07	6.8 (5.8-7.9)	0.35	5.9 (4.5-7.8)	0.33
	23-26	2.3 (1.6-3.2)		4.2 (3.3-5.4)		7.0 (5.7-8.5)		8.4 (5.7-12.4)		8.0 (4.9-13.1)	
Screen-detected DCIS	11-14	1.4 (1.1-1.8)	0.20	1.9 (1.4-2.4)	0.22	1.9 (1.6-2.3)	0.59	2.2 (1.6-3.0)	0.69	1.6 (0.9-2.8)	0.75
	23-26	1.8 (1.3-2.7)		1.4 (0.9-2.1)		2.2 (1.3-3.7)		2.6 (1.3-5.1)		2.0 (0.6-6.1)	

DCIS = ductal carcinoma in situ.
 * 2-sided P values and 95% CIs were derived from a logistic regression model that used generalized estimating equations to account for clustering by radiology facility.
 † After positive mammography result.

Appendix Table 3. Rates of False-Negative Results After Screening With Digital Mammography, by Risk Factors*

Variable	Age 40-49 y	P Value	Age 50-59 y	P Value	Age 60-69 y	P Value	Age 70-79 y	P Value	Age 80-89 y	P Value
Women screened, n	113 770	-	127 958	-	94 507	-	50 204	-	18 752	-
False-negative mammography result, n	115	-	139	-	112	-	73	-	24	-
False-negative results per 1000 women screened per round (95% CI), n										
First-degree relatives with breast cancer										
None	0.9 (0.8-1.1)	0.02	1.0 (0.8-1.2)	0.09	1.1 (0.8-1.4)	0.10	1.2 (0.9-1.6)	0.01	1.2 (0.8-1.9)	0.49
≥1	1.8 (1.3-2.5)		1.6 (1.1-2.4)		1.7 (1.1-2.7)		2.4 (1.6-3.7)		1.6 (0.8-3.1)	
Breast density										
Almost entirely fat/scattered fibroglandular densities	0.4 (0.3-0.6)	<0.001	0.6 (0.4-0.8)	0.002	0.8 (0.5-1.1)	0.006	1.0 (0.6-1.5)	0.01	0.9 (0.5-1.6)	0.25
Heterogeneously dense	1.3 (1.0-1.7)		1.4 (1.0-2.0)		1.7 (1.3-2.3)		2.3 (1.6-3.4)		1.1 (0.5-2.4)	
Extremely dense	1.7 (1.2-2.5)		1.6 (0.9-2.8)		1.2 (0.6-2.7)		5.6 (2.4-12.9)		6.9 (2.5-18.5)	
Benign breast biopsy result										
None	0.9 (0.8-1.1)	0.53	0.8 (0.7-1.1)	0.002	0.8 (0.6-1.1)	0.001	0.9 (0.6-1.3)	0.004	0.9 (0.5-1.6)	0.02
Previous	1.1 (0.7-1.7)		1.7 (1.3-2.3)		2.1 (1.6-2.8)		2.6 (1.8-3.9)		2.6 (1.6-4.2)	
Race/ethnicity										
White	1.2 (1.0-1.4)	0.31	1.2 (0.9-1.4)	0.04	1.3 (1.0-1.6)	0.36	1.7 (1.2-2.4)	0.29	1.4 (0.9-2.3)	0.77
Black	0.7 (0.3-1.4)		1.2 (0.6-2.2)		1.5 (0.8-2.9)		0.9 (0.3-2.3)		1.0 (0.2-6.4)	
Asian	0.8 (0.5-1.3)		1.1 (0.7-1.7)		0.6 (0.3-1.2)		0.8 (0.4-1.6)		0†	
Hispanic	0.5 (0.2-1.6)		0.2 (0.0-1.1)		0.7 (0.2-2.4)		0.8 (0.1-4.6)		3.3 (0.4-23.9)	
Other	1.1 (0.4-3.2)		1.6 (0.6-4.1)		1.2 (0.2-7.1)		1.5 (0.3-8.5)		5.4 (1.0-27.8)	
Menopausal status										
Premenopausal	1.2 (1.0-1.4)	0.17	1.3 (0.9-1.9)	0.53	NA		NA		NA	
Perimenopausal	0.8 (0.2-2.5)		1.0 (0.5-2.1)							
Postmenopausal	0.7 (0.4-1.3)		1.0 (0.8-1.3)							
Menopausal hormone therapy										
None	1.0 (0.9-1.2)	0.76	1.0 (0.8-1.2)	0.37	1.0 (0.8-1.3)	0.33	1.3 (0.9-1.8)	0.58	1.2 (0.8-2.0)	0.62
Combination	0†		1.9 (0.9-3.7)		2.3 (1.0-5.6)		0†		3.1 (1.5-6.6)	
Estrogen only	1.5 (0.2-10.1)		0.4 (0.1-2.6)		1.2 (0.4-3.1)		0.8 (0.1-5.6)		2.5 (0.4-13.7)	
Oral contraceptives										
No current use	1.0 (0.8-1.2)	0.77	1.1 (0.9-1.3)	0.54	NA		NA		NA	
Current use	1.1 (0.6-2.1)		1.4 (0.6-3.5)							
Body mass index										
<25 kg/m ²	1.4 (1.2-1.7)	0.06	1.3 (1.0-1.6)	0.008	1.3 (0.9-1.8)	0.66	2.4 (1.6-3.6)	0.09	1.7 (0.7-3.8)	0.96
25-<30 kg/m ²	0.8 (0.6-1.3)		1.0 (0.7-1.6)		1.2 (0.7-2.1)		1.0 (0.5-1.8)		1.6 (0.7-3.7)	
≥30 kg/m ²	0.7 (0.3-1.4)		0.4 (0.2-0.8)		1.0 (0.6-1.8)		1.0 (0.4-2.4)		0†	

NA = not applicable.

* 2-sided P values and 95% CIs were derived from a logistic regression model that used generalized estimating equations to account for clustering by radiology facility.

† No false-negative outcomes. Category omitted from model used to obtain CI and P value.

Appendix Table 4. Rates of Recommendations for Additional Imaging After Screening With Digital Mammography, by Risk Factors*

Variable	Age 40-49 y	P Value	Age 50-59 y	P Value	Age 60-69 y	P Value	Age 70-79 y	P Value	Age 80-89 y	P Value
Women screened, <i>n</i>	113 770	-	127 958	-	94 507	-	50 204	-	18 752	-
Additional imaging recommended, <i>n</i>	14 209	-	12 604	-	8380	-	3968	-	1396	-
Recommendations per 1000 women screened per round (95% CI), <i>n</i>										
First-degree relatives with breast cancer										
None	122.1 (107.7-138.1)	0.02	95.2 (85.8-105.6)	0.003	86.7 (79.0-95.1)	0.002	77.5 (69.9-85.7)	0.02	71.7 (64.6-79.5)	0.01
≥1	145.6 (119.6-176.2)		117.1 (99.7-137.0)		98.3 (87.9-109.8)		86.9 (79.1-95.4)		86.0 (75.5-97.7)	
Breast density										
Almost entirely fat/scattered fibroglandular densities	110.8 (97.9-125.2)	0.001	84.4 (74.8-95.1)	<0.001	81.0 (73.1-89.6)	<0.001	75.6 (68.5-83.4)	0.003	68.9 (61.7-76.9)	0.002
Heterogeneously dense	146.0 (123.9-171.3)		121.6 (105.8-139.3)		110.6 (99.7-122.6)		99.0 (87.9-111.4)		93.6 (82.4-106.2)	
Extremely dense	116.5 (98.4-137.4)		98.4 (83.1-116.2)		81.0 (70.3-93.2)		63.3 (49.7-80.1)		92.0 (66.6-125.7)	
Benign breast biopsy result										
None	117.8 (103.4-134.0)	0.001	90.9 (81.7-101.0)	<0.001	81.9 (74.1-90.6)	<0.001	72.2 (65.1-79.9)	<0.001	72.1 (64.3-80.7)	0.07
Previous	172.5 (145.9-202.8)		129.3 (112.8-147.8)		108.2 (98.2-118.9)		100.5 (90.0-112.1)		82.7 (72.9-93.7)	
Race/ethnicity										
White	131.1 (119.4-143.8)	0.001	103.2 (94.8-112.3)	0.01	92.4 (85.7-99.4)	0.005	83.3 (77.1-90.1)	0.004	78.0 (71.1-85.5)	0.11
Black	95.9 (85.0-108.0)		82.6 (68.4-99.4)		70.8 (59.3-84.3)		66.3 (59.1-74.4)		60.3 (49.1-74.0)	
Asian	89.1 (76.0-104.2)		73.5 (62.1-86.8)		64.6 (54.0-77.0)		52.6 (44.9-61.4)		40.5 (33.4-48.9)	
Hispanic	127.8 (109.2-149.0)		84.6 (71.9-99.3)		76.9 (64.1-92.0)		72.1 (61.6-84.3)		62.3 (38.7-98.9)	
Other	131.6 (109.8-157.1)		109.8 (97.1-123.8)		98.8 (82.5-117.8)		84.7 (64.0-111.3)		65.2 (39.4-106.2)	
Menopausal status										
Premenopausal	135.4 (117.4-155.6)	0.01	124.6 (113.6-136.4)	<0.001	NA	NA	NA	NA	NA	NA
Perimenopausal	109.0 (92.8-127.7)		101.4 (78.7-129.8)							
Postmenopausal	114.2 (103.1-126.4)		92.7 (84.0-102.1)							
Menopausal hormone therapy										
None	127.0 (111.2-144.8)	0.63	97.0 (86.7-108.5)	0.28	83.8 (76.5-91.7)	0.18	76.5 (69.8-83.9)	0.01	71.5 (64.2-79.6)	0.20
Combination	125.8 (83.6-185.0)		137.4 (105.5-177.1)		129.5 (96.3-172.0)		120.7 (94.9-152.4)		106.6 (79.4-141.6)	
Estrogen only	110.1 (85.6-140.7)		105.4 (90.9-121.8)		106.1 (86.0-130.3)		125.1 (106.4-146.6)		106.4 (82.6-136.1)	
Oral contraceptives										
No current use	126.6 (110.9-144.2)	0.05	99.0 (88.3-110.7)	0.85	NA	NA	NA	NA	NA	NA
Current use	110.4 (90.9-133.6)		100.3 (84.4-118.9)							
Body mass index										
<25 kg/m ²	133.9 (118.1-151.3)	0.006	105.9 (95.6-117.2)	0.05	93.4 (85.4-102.1)	0.31	79.5 (70.5-89.5)	0.28	83.4 (69.8-99.5)	0.20
25-30 kg/m ²	129.2 (114.7-145.2)		99.3 (90.4-108.9)		88.7 (79.1-99.4)		84.1 (75.5-93.6)		69.5 (58.5-82.3)	
≥30 kg/m ²	110.7 (99.4-123.2)		93.1 (84.2-102.8)		89.2 (82.1-96.8)		89.3 (78.5-101.5)		88.4 (71.5-108.8)	

NA = not applicable.
* 2-sided *P* values and 95% CIs were derived from a logistic regression model that used generalized estimating equations to account for clustering by radiology facility.

Appendix Table 5. Rates of False-Positive and False-Negative Digital Mammography Results and Recommendations for Additional Imaging and Biopsies, by Different Breast Density Categories*

Variable	Age 40-49 y	P Value	Age 50-59 y	P Value	Age 60-69 y	P Value	Age 70-79 y	P Value	Age 80-89 y	P Value
Women screened, n	113 770	-	127 958	-	94 507	-	50 204	-	18 752	-
False-positive mammography results per 1000 women screened per round (95% CI), n										
A: Almost entirely fat/scattered fibroglandular densities	108.4 (95.5-122.7)	<0.001	80.5 (71.1-90.9)	<0.001	74.1 (66.4-82.6)	<0.001	67.3 (60.4-74.9)	0.003	60.3 (54.0-67.4)	0.001
Heterogeneously dense	142.2 (120.2-167.4)		115.8 (100.3-133.2)		101.8 (91.0-113.8)		88.7 (78.7-99.9)		82.4 (72.6-93.5)	
Extremely dense	112.1 (94.4-132.7)		92.7 (77.5-110.5)		75.2 (64.7-87.1)		57.7 (43.9-75.5)		85.1 (61.7-116.2)	
B: Almost entirely fat	63.0 (51.2-77.4)	<0.001	52.1 (44.9-60.3)	<0.001	48.5 (43.1-54.4)	<0.001	45.4 (39.7-51.9)	<0.001	39.5 (32.1-48.5)	<0.001
Scattered fibroglandular densities	116.8 (102.9-132.3)		87.7 (77.1-99.6)		81.6 (72.7-91.4)		73.4 (65.4-82.2)		65.8 (58.4-73.9)	
Heterogeneously/extremely dense	135.3 (113.9-160.0)		112.0 (96.9-129.2)		98.9 (88.4-110.4)		86.2 (76.4-97.1)		82.7 (72.6-93.9)	
C: Almost entirely fat	63.0 (51.2-77.4)	<0.001	52.1 (44.9-60.3)	<0.001	48.5 (43.1-54.4)	<0.001	45.4 (39.7-51.9)	<0.001	39.5 (32.1-48.5)	<0.001
Scattered fibroglandular densities	116.8 (102.9-132.3)		87.7 (77.1-99.6)		81.6 (72.7-91.4)		73.4 (65.4-82.2)		65.8 (58.4-73.9)	
Heterogeneously dense	142.2 (120.2-167.4)		115.8 (100.3-133.2)		101.8 (91.0-113.8)		88.7 (78.7-99.9)		82.4 (72.6-93.5)	
Extremely dense	112.1 (94.4-132.7)	0.003	92.7 (77.5-110.5)	<0.001	75.2 (64.7-87.1)	<0.001	57.7 (43.9-75.5)	<0.001	85.1 (61.7-116.2)	<0.001
D: Almost entirely fat/scattered fibroglandular densities	108.4 (95.5-122.7)		80.5 (71.1-90.9)		74.1 (66.4-82.6)		67.3 (60.4-74.9)		60.3 (54.0-67.4)	
Heterogeneously/extremely dense	135.3 (113.9-160.0)		112.0 (96.9-129.2)		98.9 (88.4-110.4)		86.2 (76.4-97.1)		82.7 (72.6-93.9)	
False-negative mammography results per 1000 women screened per round (95% CI), n										
A: Almost entirely fat/scattered fibroglandular densities	0.4 (0.3-0.6)	<0.001	0.6 (0.4-0.8)	0.002	0.8 (0.5-1.1)	0.006	1.0 (0.6-1.5)	0.01	0.9 (0.5-1.6)	0.25
Heterogeneously dense	1.3 (1.0-1.7)		1.4 (1.0-2.0)		1.7 (1.3-2.3)		2.3 (1.6-3.4)		1.1 (0.5-2.4)	
Extremely dense	1.7 (1.2-2.5)		1.6 (0.9-2.8)		1.2 (0.6-2.7)		5.6 (2.4-12.9)		6.9 (2.5-18.5)	
B: Almost entirely fat	0.2 (0.0-0.9)	<0.001	0.3 (0.1-0.7)	<0.001	0.6 (0.2-1.5)	0.007	0.3 (0.1-1.1)	0.001	0.4 (0.1-3.1)	0.14
Scattered fibroglandular densities	0.5 (0.3-0.7)		0.7 (0.5-0.9)		0.8 (0.6-1.2)		1.2 (0.7-1.9)		1.0 (0.6-1.7)	
Heterogeneously/extremely dense	1.4 (1.2-1.8)		1.5 (1.1-1.9)		1.6 (1.2-2.2)		2.6 (1.8-3.7)		1.7 (0.8-3.3)	
C: Almost entirely fat	0.2 (0.0-0.9)	<0.001	0.3 (0.1-0.7)	<0.001	0.6 (0.2-1.5)	0.02	0.3 (0.1-1.1)	0.002	0.4 (0.1-3.1)	0.17
Scattered fibroglandular densities	0.5 (0.3-0.7)		0.7 (0.5-0.9)		0.8 (0.6-1.2)		1.2 (0.7-1.9)		1.0 (0.6-1.7)	
Heterogeneously dense	1.3 (1.0-1.7)		1.4 (1.0-2.0)		1.7 (1.3-2.3)		2.3 (1.6-3.4)		1.1 (0.5-2.4)	
Extremely dense	1.7 (1.2-2.5)	<0.001	1.6 (0.9-2.8)	<0.001	1.2 (0.6-2.7)	0.002	5.6 (2.4-12.9)	0.003	6.9 (2.5-18.5)	0.18
D: Almost entirely fat/scattered fibroglandular densities	0.4 (0.3-0.6)		0.6 (0.4-0.8)		0.8 (0.5-1.1)		1.0 (0.6-1.5)		0.9 (0.5-1.6)	
Heterogeneously/extremely dense	1.4 (1.2-1.8)		1.5 (1.1-1.9)		1.6 (1.2-2.2)		2.6 (1.8-3.7)		1.7 (0.8-3.3)	

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Appendix Table 5—Continued

Variable	Age 40–49 y	P Value	Age 50–59 y	P Value	Age 60–69 y	P Value	Age 70–79 y	P Value	Age 80–89 y	P Value
Recommendations for additional imaging per 1000 women screened per round (95% CI), n										
A: Almost entirely fat/scattered fibroglandular densities	110.8 (97.9–125.2)	0.001	84.4 (74.8–95.1)	<0.001	81.0 (73.1–89.6)	<0.001	75.6 (68.5–83.4)	0.003	68.9 (61.7–76.9)	0.002
Heterogeneously dense	146.0 (123.9–171.3)		121.6 (105.8–139.3)		110.6 (99.7–122.6)		99.0 (87.9–111.4)		93.6 (82.4–106.2)	
Extremely dense	116.5 (98.4–137.4)		98.4 (83.1–116.2)		81.0 (70.3–93.2)		63.3 (49.7–80.1)		92.0 (66.6–125.7)	
B: Almost entirely fat	64.4 (52.3–79.1)	<0.001	54.1 (46.5–62.8)	<0.001	53.4 (47.9–59.4)	<0.001	52.0 (46.5–58.2)	<0.001	44.8 (36.6–54.6)	<0.001
Scattered fibroglandular densities	119.4 (105.5–135.0)		92.1 (81.2–104.3)		89.0 (79.9–99.1)		82.1 (73.9–91.2)		75.2 (66.5–84.8)	
Heterogeneously/extremely dense	139.3 (117.7–164.1)		117.8 (102.4–135.3)		107.3 (96.7–118.9)		96.1 (85.5–107.9)		93.5 (82.1–106.3)	
C: Almost entirely fat	64.4 (52.3–79.1)	<0.001	54.1 (46.5–62.8)	<0.001	53.4 (47.9–59.4)	<0.001	52.0 (46.5–58.2)	<0.001	44.8 (36.6–54.6)	0.001
Scattered fibroglandular densities	119.4 (105.5–135.0)		92.1 (81.2–104.3)		89.0 (79.9–99.1)		82.1 (73.9–91.2)		75.2 (66.5–84.8)	
Heterogeneously dense	146.0 (123.9–171.3)		121.6 (105.8–139.3)		110.6 (99.7–122.6)		99.0 (87.9–111.4)		93.6 (82.4–106.2)	
Extremely dense	116.5 (98.4–137.4)		98.4 (83.1–116.2)		81.0 (70.3–93.2)		63.3 (49.7–80.1)		92.0 (66.6–125.7)	
D: Almost entirely fat/scattered fibroglandular densities	110.8 (97.9–125.2)	0.003	84.4 (74.8–95.1)	<0.001	81.0 (73.1–89.6)	<0.001	75.6 (68.5–83.4)	0.001	68.9 (61.7–76.9)	<0.001
Heterogeneously/extremely dense	139.3 (117.7–164.1)		117.8 (102.4–135.3)		107.3 (96.7–118.9)		96.1 (85.5–107.9)		93.5 (82.1–106.3)	
Recommendations for biopsy per 1000 women screened per round (95% CI), n										
A: Almost entirely fat/scattered fibroglandular densities	12.2 (9.9–15.0)	<0.001	11.8 (9.6–14.5)	<0.001	15.6 (13.7–17.7)	0.008	16.2 (14.2–18.4)	0.007	14.2 (12.0–16.8)	0.07
Heterogeneously dense	18.9 (15.8–22.5)		20.2 (17.3–23.7)		19.3 (16.9–22.2)		21.0 (18.0–24.5)		19.0 (15.5–23.2)	
Extremely dense	20.2 (16.8–24.3)		19.2 (14.3–25.7)		13.8 (10.5–18.2)		13.0 (7.2–23.3)		16.1 (8.0–32.1)	
B: Almost entirely fat	7.5 (5.5–10.1)	<0.001	8.4 (6.0–11.7)	<0.001	11.7 (9.5–14.6)	<0.001	12.8 (10.2–16.1)	0.003	9.7 (5.8–16.0)	0.04
Scattered fibroglandular densities	13.1 (10.6–16.1)		12.7 (10.3–15.6)		16.7 (14.7–19.0)		17.1 (14.9–19.6)		15.4 (12.5–18.8)	
Heterogeneously/extremely dense	19.2 (16.2–22.7)		20.1 (16.9–23.7)		18.7 (16.6–21.2)		20.4 (17.4–23.8)		18.7 (15.2–23.0)	
C: Almost entirely fat	7.5 (5.5–10.1)	<0.001	8.4 (6.0–11.7)	<0.001	11.7 (9.5–14.6)	<0.001	12.8 (10.2–16.1)	0.003	9.7 (5.8–16.0)	0.06
Scattered fibroglandular densities	13.1 (10.6–16.1)		12.7 (10.3–15.6)		16.7 (14.7–19.0)		17.1 (14.9–19.6)		15.4 (12.5–18.8)	
Heterogeneously dense	18.9 (15.8–22.5)		20.2 (17.3–23.7)		19.3 (16.9–22.2)		21.0 (18.0–24.5)		19.0 (15.5–23.2)	
Extremely dense	20.2 (16.8–24.3)		19.2 (14.3–25.7)		13.8 (10.5–18.2)		13.0 (7.2–23.3)		16.1 (8.0–32.1)	
D: Almost entirely fat/scattered fibroglandular densities	12.2 (9.9–15.0)	<0.001	11.8 (9.6–14.5)	<0.001	15.6 (13.7–17.7)	0.002	16.2 (14.2–18.4)	0.008	14.2 (12.0–16.8)	0.03
Heterogeneously/extremely dense	19.2 (16.2–22.7)		20.1 (16.9–23.7)		18.7 (16.6–21.2)		20.4 (17.4–23.8)		18.7 (15.2–23.0)	

* 2-sided P values and 95% CIs were derived from a logistic regression model that used generalized estimating equations to account for clustering by radiology facility.