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Identifying Women With Dense Breasts at High Risk for Interval Cancer

A Cohort Study

Karla Kerlikowske, MD; Weiwei Zhu, MS; Anna N.A. Tosteson, ScD; Brian L. Sprague, PhD; Jeffrey A. Tice, MD; Constance D. Lehman, MD, PhD; and Diana L. Miglioretti, PhD, for the Breast Cancer Surveillance Consortium*

Background: Twenty-one states have laws requiring that women be notified if they have dense breasts and that they be advised to discuss supplemental imaging with their provider.

Objective: To better direct discussions of supplemental imaging by determining which combinations of breast cancer risk and Breast Imaging Reporting and Data System (BI-RADS) breast density categories are associated with high interval cancer rates.

Design: Prospective cohort.

Setting: Breast Cancer Surveillance Consortium (BCSC) breast imaging facilities.

Patients: 365 426 women aged 40 to 74 years who had 831 455 digital screening mammography examinations.

Measurements: BI-RADS breast density, BCSC 5-year breast cancer risk, and interval cancer rate (invasive cancer ≤12 months after a normal mammography result) per 1000 mammography examinations. High interval cancer rate was defined as more than 1 case per 1000 examinations.

Results: High interval cancer rates were observed for women with 5-year risk of 1.67% or greater and extremely dense breasts or 5-year risk of 2.50% or greater and heterogeneously dense breasts (24% of all women with dense breasts). The interval rate of advanced-stage disease was highest (>0.4 case per 1000 examinations) among women with 5-year risk of 2.50% or greater and heterogeneously or extremely dense breasts (21% of all women with dense breasts). Five-year risk was low to average (0% to 1.66%) for 51.0% of women with heterogeneously dense breasts and 52.5% with extremely dense breasts, with interval cancer rates of 0.58 to 0.63 and 0.72 to 0.89 case per 1000 examinations, respectively.

Limitation: The benefit of supplemental imaging was not assessed.

Conclusion: Breast density should not be the sole criterion for deciding whether supplemental imaging is justified because not all women with dense breasts have high interval cancer rates. BCSC 5-year risk combined with BI-RADS breast density can identify women at high risk for interval cancer to inform patient–provider discussions about alternative screening strategies.

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For author affiliations, see end of text.
* For a list of Breast Cancer Surveillance Consortium investigators, see the Appendix (available at www.annals.org).

High breast density increases breast cancer risk and can mask tumors, decreasing the sensitivity of mammography (1). At least 21 U.S. state governments require notifying women if their breasts are dense, and similar bills are pending in Congress (2). Language on mandatory notification varies by state but, in general, women whose breasts are categorized as heterogeneously or extremely dense according to the Breast Imaging Reporting and Data System (BI-RADS) (3) must be notified and advised to discuss this information with their health care provider. In states with density notification laws, about 50% of women having screening mammography are notified that they have dense breasts; therefore, a national law would affect tens of millions of women annually (4, 5).

Digital mammography, which accounts for 95% of U.S. mammography units (6), has an overall sensitivity of 81% to 87% to detect breast cancer in women aged 40 to 79 years; however, its sensitivity is lower in women with extremely dense breasts (7). Supplemental imaging has been suggested for women with dense breasts to increase the chance that tumors masked by density will be detected before they become symptomatic. Supplemental imaging after a normal mammography result may increase cancer detection among women with dense breasts but may also increase false-positive results on imaging tests and biopsies (8). Interval cancer, or invasive cancer diagnosed within 12 months of a normal mammography result, is associated with more aggressive tumor biology (9–11). Identifying women at high risk for interval cancer will help guide discussions of supplemental imaging given that these women are most likely to benefit if supplemental imaging can detect cancer that has been missed or is not visible on mammography.

We sought to determine which combinations of BI-RADS breast density categories and breast cancer risk or age are associated with sufficiently high interval cancer rates to justify consideration of alternative screening strategies among women with dense breasts having digital mammography. We used the well-calibrated Breast Cancer Surveillance Consortium (BCSC) 5-year risk model (12) to calculate breast cancer risk because the model has discrimination similar to or better than that of commonly used risk models (12, 13); has been validated in another screening population (14); and re-

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EDITORS' NOTES

Context

Many states require health care providers to counsel women whose mammograms show dense breasts about considering supplemental imaging tests.

Contribution

Investigators analyzed screening data from the Breast Cancer Surveillance Consortium to determine the combinations of breast cancer risk and breast density categories associated with high rates of breast cancer after a normal mammography result.

Caution

Investigators were unable to assess the benefits of patient–provider discussions about supplemental breast imaging.

Implication

Breast density should not be the sole criterion for identifying women who should receive counseling about supplemental imaging. Breast cancer risk combined with breast density categories can identify women for whom supplemental imaging discussions are most appropriate.

quires only 5 risk factors (age, first-degree relatives with history of breast cancer, history of breast biopsy, BI-RADS breast density, and race/ethnicity), making it easy to use. We used breast density to stratify women by risk for interval cancer within the next year and to identify women at increased 5-year risk for breast cancer.

METHODS

Study Setting and Data Sources

Data were from the BCSC mammography registries (http://breastscreening.cancer.gov), whose populations are comparable to the U.S. population (15, 16). Registries prospectively collect data, including patient characteristics and radiology information, from community radiology facilities. Breast cancer diagnoses and tumor characteristics are obtained by linking women in the BCSC to pathology databases; regional Surveillance, Epidemiology, and End Results programs; and state tumor registries, with completeness of reporting estimated at greater than 94.3% (17). Registries and a central statistical coordinating center have received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analyses. 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.

Participants

We included digital screening mammography examinations performed from January 2002 through October 2011 among women aged 40 to 74 years who did not have a history of breast cancer or breast implants and had complete information on demographic and breast health history information. To minimize misclassification of diagnostic mammography as screening, we excluded mammography that was unilateral or that was preceded by mammography or breast ultrasonography within 9 months. First mammography examinations were excluded because their sensitivity and specificity differ from those of subsequent examinations (18).

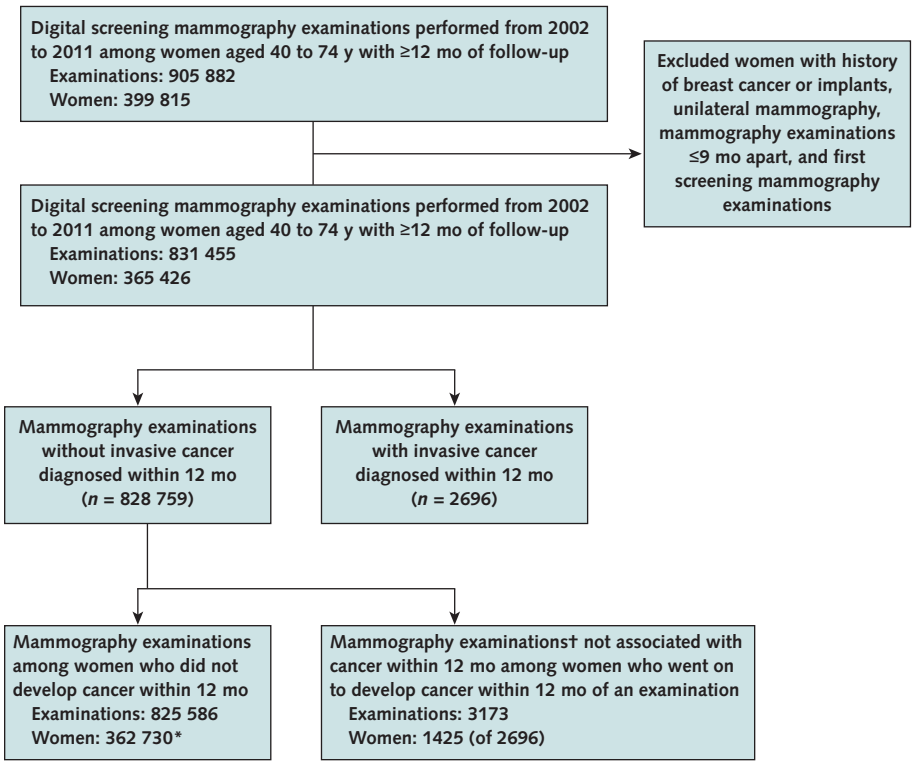
Measures, Definitions, and Outcomes

Demographic and breast health history information were obtained on a self-administered questionnaire completed at each examination.

Radiologists categorized breast density at the time of clinical interpretation by using BI-RADS density categories (almost entirely fat, scattered fibroglandular densities, heterogeneously dense, or extremely dense). Mammography results were classified as positive (woman recalled to have additional evaluation based on screening views) or negative (woman not recalled) on the basis of standard BI-RADS assessments and BCSC performance definitions (**Appendix Tables 1** and **2**, available at www.annals.org) (3, 18). Mammography examinations were linked to diagnoses of invasive breast cancer or ductal carcinoma in situ (DCIS) within 12 months of the examination and before the next screening examination. Lobular carcinoma in situ was not considered breast cancer. We focused on detection of invasive cancer because mammography sensitivity for detecting DCIS is high and the rate of interval DCIS is low (17). In addition, survival from interval DCIS is high and does not differ from that of screen-detected DCIS (19). Thus, we calculated interval cancer rates as the number of invasive breast cancer cases after a negative mammography result divided by the total number of examinations. Sensitivity was calculated as the number of invasive breast cancer cases within 12 months of a positive mammography result divided by the total number of invasive breast cancer cases. Rates of false-positive results were calculated as the number of positive mammography results without invasive cancer or DCIS within 12 months of the examination divided by the total number of examinations. Specificity was calculated as the number of negative mammography results without invasive cancer or DCIS diagnosed within 12 months of the examination divided by the total number of examinations without a diagnosis of invasive cancer or DCIS within 12 months. Invasive breast cancer was classified according to the sixth edition of the American Joint Committee on Cancer staging system (20). We defined advanced-stage disease as stage IIB, III, or IV.

Five-year risk for invasive cancer was calculated using the BCSC risk calculator (https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm) (12) and was categorized as low (0% to <1.00%), average (1.00% to 1.66%), inter-

Figure. Study flow diagram.



* Includes 1079 women with ductal carcinoma in situ.
† Mammography not associated with invasive cancer diagnosis ≤12 mo after examination and occurring >9 mo before mammography associated with invasive cancer diagnosis.

mediate (1.67% to 2.49%), high (2.50% to 3.99%), or very high (≥4.00%). Five-year risk of 0% to 1.66% was considered low to average, as defined in the literature (12, 21).

We used published cut points for minimally acceptable performance levels for interpretation of screening mammography. Cut points were established by expert radiologists using the Angoff method (22) as sensitivity less than 75%, specificity less than 88%, and a rate of false-positive results greater than 120 per 1000 mammography examinations. We considered an interval cancer rate greater than 1 case per 1000 mammography examinations as an unacceptable performance level because sensitivity less than 75% for a cancer incidence of 4 cases per 1000 examinations (as routinely observed in screened populations) results in an interval cancer rate of 1 case per 1000 examinations (7).

Statistical Analysis

All analyses were performed using the screening mammography examination as the unit of analysis; women could have more than 1 examination during the study (Figure). We used descriptive statistics to characterize examinations as associated or not associated with invasive breast cancer within 12 months.

We estimated rates of interval cancer, false-positive results, and interval advanced-stage disease per 1000 mammography examinations. We estimated the sensitivity and specificity of mammography for detecting invasive cancer. For a woman diagnosed with invasive breast cancer, only the examination within 12 months of the diagnosis was associated with breast cancer for analyses (23). We calculated 95% CIs for sensitivity and interval cancer rates by using the Pearson–Clopper exact method for independent data (24). We estimated 95% CIs for rates of false-positive results and specificity by using generalized estimating equations, with a working independence correlation structure to account for correlation among examinations for the same woman (23). Separate performance measures were calculated by breast density and age and by breast density and BCSC 5-year risk.

We evaluated 6 scenarios for selection of women for discussion of supplemental screening: 1) all women with dense breasts (the current policy), 2) all women with extremely dense breasts, 3) women with an interval cancer rate greater than 1 case per 1000 mammography examinations based on age and BI-RADS breast density category, 4) women with an interval cancer rate greater than 1 case per 1000 examinations based on BCSC 5-year risk and BI-RADS density category, 5) women with mammography sensitivity less than 75% based on age and BI-RADS density category, and 6) women with elevated interval rates of advanced dis-

Table 1. Characteristics of 365 426 Women Undergoing 831 455 Digital Screening Mammography Examinations*

Characteristic	No Invasive Cancer	Invasive Cancer†
Screening mammography examinations‡	828 759§	2696
Age		
40–49 y	243 448 (29.4)	516 (19.1)
50–59 y	297 423 (35.9)	855 (31.7)
60–69 y	220 617 (26.6)	963 (35.7)
70–74 y	67 271 (8.1)	362 (13.4)
Race/ethnicity		
Non-Hispanic white	597 089 (72.0)	2086 (77.4)
Non-Hispanic black	45 248 (5.5)	144 (5.3)
Asian/Native Hawaiian/Pacific Islander	85 543 (10.3)	202 (7.5)
Hispanic	31 120 (3.8)	74 (2.7)
Other/mixed/unknown	69 759 (8.4)	190 (7.0)
Family history of breast cancer‖	133 542 (16.1)	662 (24.6)
History of breast biopsy	184 827 (22.3)	864 (32.0)
BI-RADS breast density		
Almost entirely fat	96 608 (11.7)	214 (7.9)
Scattered fibroglandular densities	338 882 (40.9)	1084 (40.2)
Heterogeneously dense	326 568 (39.4)	1178 (43.7)
Extremely dense	66 701 (8.0)	220 (8.2)
BCSC 5-y risk¶		
Low (0%–<1.00%)	279 385 (33.7)	472 (17.5)
Average (1.00%–1.66%)	238 893 (28.8)	698 (25.9)
Intermediate (1.67%–2.49%)	190 762 (23.0)	798 (29.6)
High (2.50%–3.99%)	90 121 (10.9)	518 (19.2)
Very high (≥4.00%)	29 598 (3.6)	210 (7.8)

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Data are numbers (percentages).
† Within 12 mo of screening mammography.
‡ After first screening mammography examination.
§ Includes 3173 not associated with invasive cancer diagnosis within 12 mo and occurring >9 mo before an examination associated with an invasive cancer diagnosis among 1425 of the 2696 women who developed invasive cancer.
‖ First-degree relative (mother, sister, or daughter) with breast cancer.
¶ Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.

ease greater than 0.4 case per 1000 examinations with a BCSC risk of 1.67% or greater and dense breasts. We evaluated 2 hypothetical cohorts of 100 000 women with dense breasts (one with women aged 40 to 74 years and the other with women aged 50 to 74 years). For each scenario and cohort, we projected the number and percentage of women with dense breasts who would be identified for discussion of supplemental imaging, the number of interval cancer cases potentially detectable by supplemental imaging, and the ratio of the number of women identified for discussion of supplemental imaging to the number of interval cancer cases potentially detectable by supplemental imaging.

We performed statistical analyses in R, version 2.15.3 (R Foundation for Statistical Computing), using the "binom.confint" function from the "binom" package for rate and CI calculations and the "geeglm" function from the "geepack" package for generalized estimating equation analyses.

Role of the Funding Source

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

RESULTS

We included 831 455 digital screening mammography examinations performed among 365 426 women, 2696 of whom were diagnosed with invasive breast cancer within 12 months of screening mammography (Table 1). Women with invasive cancer were more likely to be older and white and to have heterogeneously or extremely dense breasts, a BCSC 5-year risk of 1.67% or greater, and a family history of breast cancer.

Overall, 47% of women aged 40 to 74 years had dense breasts, and the percentage decreased with age (Table 2). The proportion of women with elevated BCSC 5-year risk was highest among those with heterogeneously or extremely dense breasts. About half of women with heterogeneously dense breasts (51.0%) and half with extremely dense breasts (52.5%) were at low to average 5-year breast cancer risk (0% to 1.66%).

Interval Cancer Rates

Interval cancer rates exceeded 1 case per 1000 mammography examinations among women aged 70 to 74 years with heterogeneously dense breasts and among those aged 50 to 74 years with extremely dense breasts. Average interval cancer rates were less than 1 case per 1000 examinations among women aged 40 to 49 years for all density categories (Table 3).

Interval cancer rates greater than 1 case per 1000 mammography examinations were observed among women with breast cancer risk of 1.67% or greater and extremely dense breasts (47.5% of women with extremely dense breasts) and those with risk of 2.50% or greater and heterogeneously dense breasts (19.5% of those with heterogeneously dense breasts) (Table 2). Together, these 2 groups represented 24% of women aged 40 to 74 years with dense breasts, or 12% of women having screening mammography. Women with heterogeneously or extremely dense breasts and low to average BCSC 5-year risk (0% to 1.66%) had interval cancer rates of 0.58 to 0.63 and 0.72 to 0.89 case per 1000 examinations, respectively. The interval cancer rate for women with scattered fibroglandular densities and 5-year risk of 2.50% or greater was 0.90 case per 1000 examinations (Table 3). Sensitivity of digital mammography is summarized in Appendix Table 3 (available at www.annals.org).

Rates of False-Positive Results

Rates of false-positive results were less than 120 per 1000 mammography examinations among all age and density groups except among women aged 40 to 49 years with scattered fibroglandular densities or heterogeneously dense breasts. Rates were low for all risk and density groups except women with BCSC 5-year risk of 0% to 1.66% and heterogeneously dense breasts

Table 2. Distributions of BI-RADS Breast Density (by Age) and BCSC 5-y Risk (by Breast Density)*

Variable	BI-RADS Breast Density				Total, *n*
	Almost Entirely Fat	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense	
Age					
40–49 y	6.5	32.0	47.7	13.9	243 964
50–59 y	11.7	40.9	39.8	7.6	298 278
60–69 y	15.7	47.5	32.8	4.0	221 580
70–74 y	16.9	50.9	29.7	2.6	67 633
BCSC 5-y risk†					
Low (0%–<1.00%)	67.1	37.6	22.7	18.7	-
Average (1.00%–1.66%)	23.0	30.0	28.3	33.8	-
Intermediate (1.67%–2.49%)	8.7	21.2	29.4	21.7	-
High (2.50%–3.99%)	1.2	9.7	13.9	16.4	-
Very high (≥4.00%)	0	1.5	5.6	9.4	-
Total, *n*	96 822	339 966	327 746	66 921	831 455

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Data are percentages unless otherwise indicated.
† Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.

(Table 4). Specificity of digital mammography is summarized in Appendix Table 4 (available at www.annals.org).

Interval Rates of Advanced-Stage Disease

Interval rates of advanced-stage disease were highest (>0.4 case per 1000 mammography examinations) among women with risk of 2.50% or greater and heterogeneously or extremely dense breasts (Appendix Table 5, available at www.annals.org), who represent 21% of women aged 40 to 74 years with dense breasts (Table 2). When age and density were considered, elevated interval rates of advanced-stage disease were observed among women aged 60 to 74 years with extremely dense breasts, who represent 3% of women aged 40 to 74 years with dense breasts.

Outcomes of Strategies to Identify Women for Discussion of Supplemental Imaging

Strategies 1 (the current policy) and 2 are based on breast density only. Strategies 3 to 6 are based on breast density combined with either age or BCSC 5-year risk, reflecting groups with high interval cancer rates, low mammography sensitivity, or an elevated interval rate of advanced disease.

In strategy 1, supplemental imaging would be considered for 100 000 women with dense breasts to potentially detect 89 interval cancer cases, resulting in a ratio of 1124 supplemental tests per interval cancer case (Table 5) if all 100 000 women with dense breasts had supplemental imaging. Supplemental imaging would be considered in all women with extremely dense breasts in strategy 2 or based on combinations of age and density category with a high interval cancer rate in strategy 3. Compared with strategy 1, these strategies would reduce the proportion of women with dense breasts considered for supplemental imaging to 13% to 17%; however, the opportunity to detect interval cancer with supplemental imaging would be reduced to 16 to 19 cases per 100 000 women with dense breasts, resulting in a ratio of 842 to 892 supplemental tests per interval cancer case.

Table 3. Interval Cancer Rates, by BI-RADS Breast Density and Age or BCSC 5-y Risk

Variable	Interval Cancer Cases (95% CI) per 1000 Mammography Examinations (by BI-RADS Breast Density), *n**			
	Almost Entirely Fat	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
Age				
40–49 y	0.19 (0.04–0.56)	0.26 (0.16–0.40)	0.76 (0.61–0.93)	0.98 (0.67–1.37)
50–59 y	0.14 (0.05–0.34)	0.33 (0.23–0.45)	0.80 (0.65–0.98)	**1.11 (0.72–1.64)**
60–69 y	0.23 (0.10–0.45)	0.49 (0.37–0.65)	0.96 (0.75–1.22)	**1.13 (0.54–2.09)**
70–74 y	0.35 (0.10–0.90)	0.55 (0.33–0.86)	**1.15 (0.73–1.72)**	**3.45 (1.27–7.50)**
BCSC 5-y risk†				
Low (0%–<1.00%)	0.14 (0.06–0.26)	0.21 (0.14–0.31)	0.63 (0.46–0.84)	0.72 (0.33–1.37)
Average (1.00%–1.66%)	0.31 (0.13–0.65)	0.38 (0.27–0.52)	0.58 (0.44–0.76)	0.89 (0.54–1.37)
Intermediate (1.67%–2.49%)	0.48 (0.13–1.22)	0.43 (0.29–0.61)	0.83 (0.66–1.03)	**1.17 (0.68–1.87)**
High or very high (≥2.50%)	-‡	0.90 (0.62–1.25)	**1.48 (1.20–1.81)**	**1.62 (1.08–2.34)**

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Boldface values are above the accepted cut point of 1 interval cancer case per 1000 examinations.
† Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.
‡ Too few cases to calculate a stable measure.

Table 4. Rates of False-Positive Results, by BI-RADS Breast Density and Age or BCSC 5-y Risk

Variable	False-Positive Results (95% CI) per 1000 Mammography Examinations (by BI-RADS Breast Density), *n**			
	Almost Entirely Fat	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
Age				
40–49 y	65 (61–69)	**123 (120–125)**	**147 (145–149)**	113 (110–117)
50–59 y	53 (51–56)	94 (93–96)	117 (115–119)	95 (91–99)
60–69 y	51 (48–53)	82 (81–84)	100 (98–102)	74 (69–80)
70–74 y	50 (46–55)	77 (74–80)	95 (91–99)	62 (51–74)
BCSC 5-y risk†				
Low (0%–<1.00%)	53 (52–55)	106 (104–108)	**131 (129–134)**	96 (91–101)
Average (1.00%–1.66%)	54 (51–57)	91 (89–92)	**125 (123–128)**	99 (95–103)
Intermediate (1.67%–2.49%)	55 (50–60)	86 (84–89)	115 (113–118)	107 (102–113)
High or very high (≥2.50%)	65 (52–81)	90 (87–93)	119 (117–122)	101 (96–106)

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Boldface values are above the accepted cut point of 120 false-positive results per 1000 examinations.
† Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.

In strategy 4, supplemental screening would be considered for women on the basis of combinations of BCSC 5-year risk and density category associated with a high interval cancer rate. Compared with strategy 1, this strategy would reduce the proportion of women with dense breasts considered for supplemental imaging to 24%, with a more favorable ratio of 694 supplemental tests per interval cancer case. However, the opportunity to detect interval cancer with supplemental imaging would be lower (35 cases per 100 000 women with dense breasts) for strategy 4 than strategy 1. In strategy 5, supplemental imaging would be considered on the basis of combinations of age and density category and low mammography sensitivity. In this strategy, the number of women considered for supplemental imaging would be almost 2-fold higher than for strategy 4, with a similar opportunity to detect interval cancer (41 cases per 100 000 women with dense breasts).

In strategy 6, the proportion of women with dense breasts considered for supplemental imaging would increase to 49%, with a more favorable ratio of 870 supplemental imaging tests per interval cancer case compared with strategy 1. Compared with strategies 2 to 5, the opportunity to detect interval cancer with strategy 6 would increase to 56 cases per 100 000 women with dense breasts. For all strategies, results were similar for women aged 50 to 74 years (Appendix Table 6, available at www.annals.org).

DISCUSSION

We identified women aged 40 to 74 years who could be considered for supplemental breast imaging or alternative imaging strategies because they have high rates of interval cancer after a normal digital screening mammography result based on combinations of BCSC 5-year breast cancer risk and BI-RADS breast density categories. Interval cancer rates were highest among women with extremely dense breasts and BCSC 5-year breast cancer risk of 1.67% or greater and women with heterogeneously dense breasts and 5-year risk of 2.50% or greater; supplemental imaging discussions with women in these 2 groups (strategy 4) resulted in the lowest ratio of discussions to interval cancer cases. Use of combinations of breast cancer risk and BI-RADS density identified twice as many women

Table 5. Projected Outcomes (per 100 000 Women With Dense Breasts) of Strategies to Identify Women Aged 40 to 74 y for Discussion of Supplemental Imaging

Strategy	Women Considered for Discussion of Supplemental Imaging, *n (%)*	Interval Cancer Cases for Potential Detection by Supplemental Imaging (95% CI), *n*	Ratio of Women Considered for Discussion of Supplemental Imaging to Interval Cancer Cases for Potential Detection
1. All women with heterogeneously or extremely dense breasts	100 000 (100)	89 (80–98)	1124
2. All women with extremely dense breasts	16 956 (17)	19 (15–24)	892
3. Women aged 50–74 y with extremely dense breasts or aged 70–74 y with heterogeneously dense breasts*	13 470 (13)	16 (13–21)	842
4. Women with risk ≥1.67% and extremely dense breasts or risk ≥2.50% and heterogeneously dense breasts*	24 294 (24)	35 (30–42)	694
5. Women aged 40–74 y with extremely dense breasts or aged 40–49 y with heterogeneously dense breasts†	46 412 (46)	41 (35–49)	1132
6. Women with risk ≥1.67% and heterogeneously or extremely dense breasts‡	48 722 (49)	56 (49–64)	870

* Interval cancer rate >1 case per 1000 examinations.
† Sensitivity <75%.
‡ Interval rate of advanced-stage disease >0.4 case per 1000 examinations.

with dense breasts and a high rate of interval cancer after a normal digital mammography result compared with combinations of age and breast density.

For the vast majority of women undergoing digital mammography—including those with dense breasts but low breast cancer risk—the rate of interval cancer was low. The rate of false-positive results was also low for most women except those with low risk and heterogeneously dense breasts. This may be due to difficulty in distinguishing suspicious from benign lesions in heterogeneously dense breasts.

Current notification laws encourage women with dense breasts to discuss supplemental or alternative screening options with their provider. Our findings provide important information to inform this discussion. We show that not all women with dense breasts have high interval cancer rates, but women in groups with high interval cancer rates are at higher breast cancer risk. By identifying women with a high likelihood of interval cancer who are also at higher risk for advanced disease, discussions of supplemental imaging or alternative screening methods can be directed to women who are more likely to benefit. For example, breast magnetic resonance imaging has high sensitivity to detect early-stage breast cancer in *BRCA1* and *BRCA2* mutation carriers. Breast magnetic resonance imaging might be beneficial for women with dense breasts who are at very high breast cancer risk because these women are at increased risk for advanced disease (25–28). There are no data on performance of screening ultrasonography according to breast density and breast cancer risk. The addition of screening ultrasonography after a normal mammography result for women with dense breasts has been shown to increase cancer detection rates compared with mammography alone (8, 27, 29–31).

The purpose of screening mammography is to detect cancer at an early stage before it becomes symptomatic; thus, the number of interval cancer cases should be as low as possible, especially those associated with advanced-stage disease. With increasing age, the rates of both screen-detected and interval cancer increase (32), but rates increase more rapidly for screen-detected cancer because of high mammography sensitivity in older women (4, 7). Therefore, we identified women with high interval cancer rates regardless of age. We found that identifying women with low mammography sensitivity could lead to discussions of supplemental imaging among those with extremely dense breasts but low rates of interval cancer and advanced-stage disease. In fact, we found that the number of women who might be considered for supplemental imaging was about 2-fold higher when low sensitivity was used to identify women instead of a combination of interval cancer rate, breast cancer risk, and density categories. Targeting women with high interval cancer rates and high risk for breast cancer could facilitate prioritization of discussions for women who could benefit from supplemental screening.

To identify subgroups with a high interval cancer rate, we accounted for both masking of tumors by breast density and breast cancer risk. High breast density is associated with decreased cancer detection on mammography and increased risk for large tumors and advanced cancer (26, 33–35). We estimated 5-year risk because it is more clinically relevant for determining near-term screening and prevention strategies. Although breast cancer risk models may not be as accurate at predicting individual risk as population risk, our purpose was to place women into high- and low-risk groups to determine which subgroups would benefit from discussions of supplemental or alternative imaging. Therefore, using a well-calibrated risk model was appropriate.

Discussions of alternative screening strategies among women with dense breasts could consider the effect of breast density on the rate of false-positive results (33, 36). Thus, density information combined with breast cancer risk could be used to prioritize women who could benefit from breast imaging tests with better specificity than digital mammography, such as tomosynthesis (37–41). Considering tomosynthesis in women with heterogeneously dense breasts, low breast cancer risk, and high risk for a false-positive result could decrease the rate of false-positive results in these subgroups.

We could not determine whether women with a high rate of interval cancer or false-positive mammography results would benefit from supplemental screening tests, alternative imaging strategies, or more frequent screening mammography. Rather, our findings provide a starting point for identifying women who may have the most to gain from supplemental imaging or alternative imaging strategies. We specifically identified women at high risk for interval cancer or false-positive mammography results who are more likely to benefit from alternative screening strategies.

This study included a large, diverse, population-based sample of women having digital mammography. The cut points we used to define low performance were developed to identify minimally acceptable levels for screening mammography interpretation for invasive and DCIS outcomes combined (22). We do not know whether these performance cut points are related to long-term outcomes, such as breast cancer death. For some subgroups with an average interval cancer rate less than 1 case per 1000 mammography examinations, we cannot rule out a higher interval cancer rate because the upper 95% confidence limit exceeds 1. A 24-month interval was not evaluated because women may return early for screening or have mammography outside the BCSC.

Our results suggest that breast density should not be the sole criterion for deciding whether women with dense breasts should be considered for supplemental breast imaging. Age and breast cancer risk influence screening performance, cancer incidence, and tumor stage at diagnosis (7, 26, 35, 42). These factors should be considered along with breast density to optimize identification of women with high interval cancer rates or high rates of false-positive results who may benefit

from supplemental screening tests or alternative screening strategies.

In conclusion, digital mammography has sufficiently high breast cancer detection and reasonably low rates of false-positive results for routine use, even among women with dense breasts. We found that not all women with dense breasts are at sufficiently high risk for interval cancer to justify consideration of supplemental or alternative screening methods. Primary care providers can calculate 5-year breast cancer risk using the BCSC risk calculator and use this information in their discussions about supplemental or alternative screening methods in women with dense breasts.

From the University of California, San Francisco, San Francisco, California; Group Health Cooperative and University of Washington School of Medicine, Seattle, Washington; Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire; University of Vermont, Burlington, Vermont; and University of California, Davis, Davis, California.

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Requests for Single Reprints: Karla Kerlikowske, MD, San Francisco Veterans Affairs Medical Center, General Internal Medicine Section, 111A1, 4150 Clement Street, San Francisco, CA 94121.

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

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Current Author Addresses: Dr. Kerlikowske: San Francisco Veterans Affairs Medical Center, General Internal Medicine Section, 111A1, 4150 Clement Street, San Francisco, CA 94121.
Ms. Zhu: Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101.
Dr. Tosteson: Geisel School of Medicine at Dartmouth, One Medical Center Drive (HB7505), Lebanon, NH 03756.
Dr. Sprague: Office of Health Promotion Research, 1 South Prospect Street, Burlington, VT 05446.
Dr. Tice: Associate Professor of Medicine, University of California, San Francisco, 1545 Divisadero, 309, San Francisco, CA 94143-0320.
Dr. Lehman: University of Washington, Seattle Cancer Care Alliance, 825 Eastlake Avenue East, G2-600, Seattle, WA 98109.
Dr. Miglioretti: UC Davis School of Medicine, Department of Public Health Sciences, One Shields Avenue, Med Sci 1C, Room 145, Davis, CA 95616.

Author Contributions: Conception and design: K. Kerlikowske, B.L. Sprague, D.L. Miglioretti.
Analysis and interpretation of the data: K. Kerlikowske, W. Zhu, A.N.A. Tosteson, B.L. Sprague, J.A. Tice, C.D. Lehman, D.L. Miglioretti.
Drafting of the article: K. Kerlikowske.
Critical revision of the article for important intellectual content: K. Kerlikowske, A.N.A. Tosteson, B.L. Sprague, J.A. Tice, C.D. Lehman, D.L. Miglioretti.
Final approval of the article: K. Kerlikowske, W. Zhu, A.N.A. Tosteson, B.L. Sprague, J.A. Tice, C.D. Lehman, D.L. Miglioretti.
Provision of study materials or patients: K. Kerlikowske.
Statistical expertise: K. Kerlikowske, W. Zhu, D.L. Miglioretti.
Obtaining of funding: K. Kerlikowske, A.N.A. Tosteson, B.L. Sprague, D.L. Miglioretti.
Administrative, technical, or logistic support: K. Kerlikowske.
Collection and assembly of data: K. Kerlikowske, W. Zhu, B.L. Sprague, D.L. Miglioretti.

Appendix: Breast Cancer Surveillance Consortium Investigators

Rob Arao, MS*, Andrew Avins, MD (Kaiser Permanente Division of Research), Steve Balch, MS, MBA*, Erin Aiello Bowles, MPH*, Susan Brandzel, MPH*, Diana Buist, PhD, MPH*, Tammy Dodd*, Pete Frawley*, Hongyuan Gao, MS*, Erika Holden*, Laura Ichikawa, MS*, Doug Kane, MS*, Jane Lange, PhD*, Casey Luce, MSPH*, Ellen O'Meara, PhD*, Julie Reardon*, KatieRose Richmire*, Deborah Seger*, Rod Walker, MS*, Rob Wellman, MS*, Karen Wernli, PhD*, Heidi Whiting, MS*, Yue Zhang, PhD*, and Weiwei Zhu, MS† (Group Health Cooperative, Seattle, Washington); Thad Benefield, MS*, Mikael Anne Greenwood-Hickman, MPH*, Louise Henderson, PhD, MSPH*, Tiffany Hoots*, Gabe Knop, MS*, Katie Marsh, MPH*, Susan Maygarden, MD*, and Bonnie Yankaskas, PhD* (University of North Carolina at Chapel Hill, Chapel Hill, North Carolina); Mark Bowman*, Rachael Chicoine, BS*, Berta Geller, PhD*, Cindy Groseclose*, Kathleen Howe, AA*, John Mace, PhD*, Tiffany Pelkey, BA*, Dusty Quick*, and Brian Sprague, PhD† (University of Vermont, Burlington, Vermont); David Burian, BA*, Elyse Chiapello, BASc*, Michael Hofmann, MS*, Karla Kerlikowske, MD†, Lin Ma, MS*, Kathy Malvin, BA*, John Shepherd, PhD*, Jennette Sison, MPH*, Jeffrey Tice, MD†, and Elad Ziv, MD* (University of California, San Francisco, San Francisco, California); Steven Cummings, MD* (California Pacific Medical Center Research Institute and the University of California Department of Epidemiology and Biostatistics, San Francisco, California); Firas Dabbous, MS*, Therese Dolecek, PhD, MS*, Jenna Khan, MPH*, Garth Rauscher, PhD*, and Katherine Tossas-Milligan, MS* (University of Illinois at Chicago, Chicago, Illinois); Scottie Eliassen, MS*, Martha Goodrich, MS*, Tracy Onega, PhD, MA, MS*, Scott Savioli, MA*, Anna Tosteson, ScD†, and Julie Weiss, MS* (Dartmouth College, Hanover, New Hampshire); Sarah Friedewald, MD*, Terry Macarol*, and William Thomas Summerfelt, PhD* (Advocate Health Care, Downers Grove, Illinois); Charlotte Gard, PhD, MS* (consultant); Deirdre Hill, PhD* (University of New Mexico, Albuquerque, New Mexico); Constance Lehman, MD, PhD†, and Jennifer Maeser, MS* (University of Washington, Seattle, Washington); Diana Miglioretti, PhD† (University of California, Davis, Davis, California); and Anne Marie Murphy, PhD* (Metropolitan Chicago Breast Cancer Task Force, Chicago, Illinois).

* Investigator who contributed to this work but did not author it.

† Investigator who authored this work.

Appendix Table 1. Definitions of Terms to Calculate Performance Measures

Term	BCSC Definitions
BI-RADS assessments	
1 (normal)	Negative mammogram
2 (benign finding)	Negative mammogram
3 (probably benign)	Positive mammogram if associated with recommendation for immediate additional imaging, biopsy, or surgical evaluation; negative mammogram if associated with recommendation for short-interval or routine follow-up
0 (needs additional imaging)	Positive mammogram
4 (suspicious for malignancy)	Positive mammogram
5 (malignant)	Positive mammogram
Performance terms	
FN	Invasive breast cancer within 12 mo of negative mammogram
TP	Invasive breast cancer within 12 mo of positive mammogram
FP	No invasive breast cancer or DCIS within 12 mo of positive mammogram
TN	No invasive breast cancer or DCIS within 12 mo of negative mammogram
Sensitivity	Number of invasive breast cancer cases within 12 mo of positive mammogram divided by total number of invasive breast cancer cases (TP/[TP + FN])
Specificity	Number of negative mammograms without invasive cancer or DCIS diagnosed within 12 mo of examination divided by total number of mammograms without invasive cancer or DCIS diagnosis within 12 mo of examination (TN/[TN + FP])
Interval cancer rate	Number of invasive breast cancer cases after negative mammogram divided by total number of mammograms (FN/total number of mammograms)
False-positive rate	Number of positive mammograms without invasive cancer or DCIS within 12 mo of examination divided by total number of mammograms (FP/total number of mammograms)

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System; DCIS = ductal carcinoma in situ; FN = false-negative; FP = false-positive; TN = true-negative; TP = true-positive.

Appendix Table 2. Illustration of Definitions of Terms to Calculate Performance Measures

Mammography Result	Disease Status 12 mo After Mammography Result			
	Invasive Cancer	DCIS	No Invasive Cancer or DCIS	Total
Positive	a (TP)	b	c (FP)	a + b + c
Negative	d (FN)	e	f (TN)	d + e + f
Total	a + d	b + e	c + f	Total number of mammograms

DCIS = ductal carcinoma in situ; FN = false-negative; FP = false-positive; TN = true-negative; TP = true-positive.

Appendix Table 3. Sensitivity of Digital Mammography for Detection of Invasive Breast Cancer, by BI-RADS Breast Density and Age or BCSC 5-y Risk

Variable	Sensitivity (95% CI) (by BI-RADS Breast Density), %*			
	Almost Entirely Fat	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
Age				
40–49 y	81.2 (54.4–96.0)	84.3 (76.7–90.1)	**68.9 (63.2–74.3)**	**63.3 (52.5–73.2)**
50–59 y	89.6 (77.3–96.5)	87.2 (83.0–90.7)	76.7 (72.2–80.7)	**71.3 (60.6–80.5)**
60–69 y	92.7 (86.2–96.8)	88.6 (85.3–91.4)	80.9 (76.5–84.8)	**65.5 (45.7–82.1)**
70–74 y	90.0 (76.3–97.2)	89.8 (84.6–93.8)	81.0 (72.9–87.6)	**57.1 (28.9–82.3)**
BCSC 5-y risk†				
Low (0%–<1.00%)	90.7 (83.1–95.7)	87.4 (82.3–91.6)	**67.6 (59.3–75.1)**	**40.0 (16.3–67.7)**
Average (1.00%–1.66%)	90.4 (81.2–96.1)	87.5 (83.3–90.9)	78.0 (72.2–83.0)	**71.0 (58.8–81.3)**
Intermediate (1.67%–2.49%)	89.7 (75.8–97.1)	90.1 (86.3–93.2)	80.0 (75.8–83.9)	**61.4 (45.5–75.6)**
High or very high (≥2.50%)	100 (47.8–100)	86.1 (81.1–90.2)	75.5 (70.8–79.7)	**69.6 (59.1–78.7)**

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Boldface values are below the accepted cut point of 75%.
† Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.

Appendix Table 4. Specificity of Digital Mammography for Detection of Invasive Breast Cancer, by BI-RADS Breast Density and Age or BCSC 5-y Risk

Variable	Specificity (95% CI) (by BI-RADS Breast Density), %*			
	Almost Entirely Fat	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
Age				
40–49 y	93.5 (93.1–93.9)	87.7 (87.5–87.9)	**85.2 (85.0–85.5)**	88.7 (88.3–89.0)
50–59 y	94.7 (94.4–94.9)	90.6 (90.4–90.7)	88.2 (88.0–88.4)	90.5 (90.1–91.9)
60–69 y	94.9 (94.7–95.2)	91.7 (91.6–91.9)	90.0 (89.7–90.2)	92.5 (92.0–93.1)
70–74 y	95.0 (94.5–95.3)	92.3 (92.0–92.5)	90.5 (90.1–91.9)	93.8 (92.5–94.8)
BCSC 5-y risk†				
Low (0%–<1.00%)	94.7 (94.5–94.8)	89.4 (89.2–89.6)	**86.9 (86.6–87.1)**	90.4 (89.9–90.9)
Average (1.00%–1.66%)	94.6 (94.3–94.9)	90.9 (90.7–91.1)	**87.4 (87.2–87.6)**	90.1 (89.7–90.5)
Intermediate (1.67%–2.49%)	94.5 (94.0–95.0)	91.3 (91.1–91.5)	88.4 (88.2–88.6)	89.2 (88.7–89.7)
High or very high (≥2.50%)	93.5 (91.8–94.8)	91.0 (90.7–91.3)	88.2 (87.7–88.3)	89.9 (89.4–90.3)

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Boldface values are below the accepted cut point of 88%.
† Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.

Appendix Table 5. Rates of Interval Stage IIB or Higher Invasive Breast Cancer, by BI-RADS Breast Density and Age or BCSC 5-y Risk

Variable	Cases of Interval Stage IIB or Higher Invasive Breast Cancer (95% CI) per 1000 Mammography Examinations (by BI-RADS Breast Density), *n*			
	Almost Entirely Fat	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
Age				
40–49 y	0.13 (0.02–0.46)	0.04 (0.01–0.11)	0.20 (0.13–0.30)	0.18 (0.07–0.39)
50–59 y	0.03 (0.00–0.16)	0.11 (0.06–0.18)	0.27 (0.18–0.38)	0.31 (0.12–0.64)
60–69 y	–*	0.12 (0.07–0.21)	0.29 (0.18–0.44)	0.57 (0.18–1.32)
70–74 y	0.18 (0.02–0.63)	0.15 (0.05–0.34)	0.35 (0.14–0.72)	1.73 (0.36–5.04)
BCSC 5-y risk†				
Low (0%–<1.00%)	0.05 (0.01–0.13)	0.03 (0.01–0.08)	0.12 (0.06–0.23)	0.16 (0.02–0.58)
Average (1.00%–1.66%)	0.04 (0.0–0.25)	0.12 (0.06–0.21)	0.22 (0.13–0.33)	0.22 (0.07–0.52)
Intermediate (1.67%–2.49%)	0.12 (0.0–0.66)	0.14 (0.07–0.25)	0.28 (0.18–0.41)	0.28 (0.07–0.70)
High or very high (≥2.50%)	–*	0.21 (0.09–0.42)	0.42 (0.28–0.61)	0.58 (0.28–1.06)

BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging Reporting and Data System.
* Too few cases to calculate a stable measure.
† Model includes age, race, family history of breast cancer, history of breast biopsy, and BI-RADS breast density.

Appendix Table 6. Projected Outcomes (per 100 000 Women With Dense Breasts) of Strategies to Identify Women Aged 50 to 74 y for Discussion of Supplemental Imaging

Strategy	Women Considered for Discussion of Supplemental Imaging, *n (%)*	Interval Cancer Cases for Potential Detection by Supplemental Imaging (95% CI), *n*	Ratio of Women Considered for Discussion of Supplemental Imaging to Interval Cancer Cases for Potential Detection
1. All women with heterogeneously or extremely dense breasts	100 000 (100)	94 (82–107)	1064
2. All women with extremely dense breasts	13 531 (14)	17 (12–23)	796
3. Women aged 50–74 y with extremely dense breasts or aged 70–74 y with heterogeneously dense breasts*	21 735 (22)	26 (20–33)	836
4. Women with risk ≥1.67% and extremely dense breasts or risk ≥2.50% and heterogeneously dense breasts*	36 074 (36)	52 (43–62)	694
5. Women aged 40–74 y with extremely dense breasts or aged 40–49 y with heterogeneously dense breasts†	NA	NA	NA
6. Women with risk ≥1.67% and heterogeneously or extremely dense breasts‡	71 648 (71)	81 (70–93)	885

NA = not applicable.
* Interval cancer rate >1 case per 1000 examinations for group.
† Sensitivity <75% for group.
‡ Interval rate of advanced-stage disease >0.4 case per 1000 examinations.