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Identifying Women with Dense Breasts at Highi Risk of Interval Cancers

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Abstract

Background—Nineteen states have mandatory breast density reporting laws requiring women to be notified they have dense breasts (~50% of screened women) and be advised to discuss supplemental imaging with their provider.

Objective—To better direct supplemental imaging discussions, we determined which combinations of breast cancer risk and Breast Imaging Reporting and Data System (BI-RADS) breast density categories were associated with high interval cancer rates.

Design—Prospective cohort

Setting—Breast Cancer Surveillance Consortium (BCSC) breast-imaging facilities

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Reproducible Research Statement: Study protocol and statistical code: Available from the BCSC's statistical coordinating center (SCC@ghc.org). Data set: Available following approval by the BCSC Steering Committee (http://breastscreening.cancer.gov).

Patients—365,426 women aged 40-74 years who underwent 831,455 digital screening mammograms

Measurement(s)—BI-RADS breast density, BCSC 5-year breast cancer risk, and interval rate (invasive cancer within 12 months of a normal mammogram) per 1,000 mammograms. High interval rate was defined as >1/1,000 mammograms.

Results—High interval rates were observed for women with 5-year risk ≥1.67% and extremely dense breasts or 5-year risk >2.49% and heterogeneously dense breasts comprising 24% of all women with dense breasts. The interval rate for advanced stage disease was highest (>0.4/1,000 mammograms) among women with 5-year risk >2.49% and heterogeneously or extremely dense breasts comprising 21% of all women with dense breasts. Five-year risk was low-average (0-1.66%) for 51% of women with heterogeneously dense and 52.5% with extremely dense breasts with interval rates of 0.58-0.63 and 0.72-0.89/1,000 mammograms, respectively.

Limitations—Benefit of supplemental imaging not assessed.

Conclusions—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 of interval cancers to inform patient-provider discussions about alternative screening strategies.

Primary Funding Source—National Cancer Institute

Background

High breast density increases breast cancer risk and can mask tumors, decreasing the sensitivity of mammography (1). At least 19 US state governments now mandate notifying women if their breasts are dense, and similar bills are pending in the US Congress (2). Mandatory notification language varies by state, but in general, women whose breasts are categorized as heterogeneously dense or extremely dense according to the Breast Imaging Reporting and Data System (BI-RADS)(3) must be notified with recommendations to discuss this information with their health care provider. In states with density notification laws, about 50% of women undergoing screening mammography are notified 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 US mammography units (6), has an overall sensitivity of 81-87% to detect breast cancer in women aged 40-79 years (7). The sensitivity of mammography is low 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 mammogram may increase cancer detection among women with dense breasts, but also increases false-positive imaging tests and biopsies (8). Interval cancers, or invasive cancer diagnosed within 12 months of a normal mammogram, are associated with more aggressive tumor biology (9-11). Identifying women at high risk of interval cancers will help guide discussions of supplemental imaging, as these women are most likely to benefit if supplemental imaging can detect cancers missed or not visible on mammography.

We determined which combinations of BI-RADS breast density categories and breast cancer risk and combinations of BI-RADS density categories and age are associated with sufficiently high interval cancer rates to justify consideration of alternative screening strategies among women with dense breasts undergoing digital mammography. We used the well-calibrated Breast Cancer Surveillance Consortium (BCSC) 5-year risk model(12) to calculate breast cancer risk since the model has comparable or better discrimination as commonly used risk models (12, 13), has been validated in another screening population (14), and requires only five risk factors (age, first-degree relatives with history of breast cancer, history of breast biopsy, BI-RADS breast density, and race/ethnicity), making it is easy to use. Thus, we used breast density to stratify women by risk of interval cancer within the next year and to identify women at increased 5-year breast cancer risk.

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 >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 Health Insurance Portability and Accountability Act compliant, and registries and the Coordinating Center received a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

Participants

Digital screening mammograms performed from January 2002 through October 2011 among women aged 40-74 years who did not have a history of breast cancer or breast implants and had complete information on demographic and breast health history information were included. To minimize misclassifying diagnostic mammography as screening, we excluded mammograms that were unilateral or were preceded by a mammogram or breast ultrasound within nine months. First mammograms were excluded because sensitivity and specificity of first mammography differs from subsequent mammography (18).

Measures, Definitions, Outcomes

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

Radiologists categorized breast density at the time of clinical interpretation using BI-RADS density categories: almost entirely fat, scattered fibroglandular densities, heterogeneously dense, or extremely dense. Mammograms were classified as positive (woman recalled to undergo additional evaluation based on screening views) or negative (woman not recalled)

based on standard BI-RADS assessments and BCSC performance definitions (see Technical Appendix) (3, 18). Mammograms were linked to invasive breast cancer or ductal carcinoma *in situ* (DCIS) diagnoses within 12 months of the mammogram and before the next screening mammogram. Lobular carcinoma *in situ* was not considered breast cancer. We focused on detection of invasive cancer, because mammography sensitivity for detecting DCIS is extremely high and the rate of interval DCIS is very low (17). In addition, survival from interval DCIS is extremely high and does not differ from screen-detected DCIS (19). Thus, we calculated interval cancer rates as the number of invasive breast cancers following a negative mammogram over the total number of mammograms. Sensitivity was calculated as the number of invasive breast cancers within 12 months of a positive mammogram over the total number of invasive breast cancers. False-positive rates were calculated as the number of positive mammograms without invasive cancer or DCIS within 12 months of the examination, over the total number of mammograms. Specificity was calculated as the number of negative mammograms without invasive cancer or DCIS diagnosed within 12 months of the examination, over the total number of mammograms without an invasive cancer or DCIS diagnosis within 12 months of the examination. Invasive breast cancers were classified according to the American Joint Committee on Cancer (AJCC) staging system, 6th edition (20). We defined advanced stage disease as AJCC stages IIb, III, or IV.

BCSC 5-year risk of invasive cancer was calculated using the BCSC risk calculator (https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm) (12). Five-year risk categories are defined as low (0-<1.00%), average (1.00-1.66%), intermediate (1.67%-2.49%), high (2.5%-3.99%) and very high (>3.99%). BCSC 5-year risk (0-1.66%) is considered low-average risk as defined in the literature (12, 21).

We used published cut-points for minimally acceptable performance levels for screening mammography interpretation. Cut-points were established by expert radiologists using the Angoff method(22) as: sensitivity <75%, specificity <88% and false-positive rate >120/1000 mammograms. We considered an interval cancer rate of >1/1000 mammograms as an unacceptable performance level because sensitivity <75% for a cancer incidence of 4/1000 mammograms as routinely observed in screened populations results in a interval cancer rate of 1/1,000 mammograms (7).

Statistical Analysis

All analyses were performed using the screening mammogram as the unit of analysis; women could have more than one mammogram during the study period (Appendix, Figure). We used descriptive statistics to characterize mammograms as associated or not associated with invasive breast cancer within 12 months.

We estimated rates per 1,000 mammograms of interval cancers, false-positives, and interval cancers for advanced disease. We estimated the sensitivity and specificity of mammography for detecting invasive cancer. For a woman diagnosed with invasive breast cancer, only the mammogram within 12 months of the diagnosis was associated with breast (23) cancer for analyses. We calculated 95% confidence intervals for sensitivity and interval cancer rates using the Pearson-Klopper exact method for independent data (24). We estimated 95% confidence intervals for false-positive rate and specificity using generalized estimating

equations (GEE) with a working independence correlation structure to account for correlation among mammogram from 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 six potential scenarios for selecting women for discussion of supplemental screening including the current policy of discussion with all women with dense breasts and subgroups of women with dense breasts based on age, BCSC 5-year risk and digital mammography performance: 1) all women with dense breasts, 2) all women with extremely dense breasts, 3) women with an interval cancer rate of >1/1000 mammograms based on age and BI-RADS density category, 4) women with an interval cancer rate of >1/1000 mammograms based on BCSC 5-year risk and BI-RADS density category, 5) women with a mammography sensitivity of <75% based on age and BI-RADS density category, and 6) women with elevated interval cancer rates of advanced disease of >0.4 per 1000 mammograms with a BCSC risk >1.67% and dense breasts. We evaluated two hypothetical cohorts of 100,000 women with dense breasts: one aged 40-74 years and one aged 50-74 years. For each scenario and cohort we projected 1) the number and percentage of women with dense breasts that would be identified for discussion of supplemental imaging, 2) the number of interval cancers following digital mammography for potential detection by supplemental imaging, and 3) the ratio of women identified for discussion of supplemental imaging per interval cancer for potential detection by supplemental imaging.

We performed statistical analyses in R, Version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria), using function “binom.confint” from package “binom” for rate and confidence interval calculations and ‘geeglm’ from package ‘geepack’ for GEE analyses.

Role of Funding Source

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

Results

We included 831,455 digital screening mammograms performed among 365,426 women, 2,696 were diagnosed with invasive breast cancers within 12 months of screening mammography (Table 1). Women with invasive cancer were more likely to be older, white, have a family history of breast cancer, have heterogeneously or extremely dense breasts, or have a BCSC 5-year breast cancer risk of ≥1.67%.

Overall, 47% of women aged 40-74 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 women with heterogeneously or extremely dense breasts. About half of women with heterogeneously dense (51.0%) and half with extremely dense (52.5%) breasts were at low-average 5-year breast cancer risk (0-1.66%).

Interval Cancer Rates by Breast Density, Age and BCSC 5-year Risk

Interval cancer rates exceeded >1/1000 mammograms among women aged 70-74 years with heterogeneously dense breasts and women aged 50-74 years with extremely dense breasts. Average interval rates were ≤1/1000 mammograms among women aged 40-49 years for all density categories (Table 3).

Interval rates of >1/1000 mammograms were observed among women with breast cancer risk ≥1.67% and extremely dense breasts (47.5% of extremely dense category, Table 2) and women with risk ≥2.50% and heterogeneously dense breasts (19.5% of heterogeneously dense category, Table 2). Together these two groups represented 24% of women aged 40-74 years with dense breasts or 12% of women undergoing screening mammography. Women with heterogeneously or extremely dense breasts and low-average BCSC 5-year risk (0-1.66%) had interval rates of 0.58-0.63 and 0.72-0.89/1,000 mammograms, respectively. The interval rate for women with scattered fibroglandular densities and 5-year risk ≥2.50% was 0.90/1,000 mammograms (Table 3). (Sensitivity results, Appendix Table 1).

False-positive Rates by Breast Density, Age and BCSC 5-year Risk

False-positive rates were below 120/1,000 mammograms among all age and density groups except among women aged 40-49 years with scattered fibroglandular densities or heterogeneously dense breasts. False-positive rates were low among women for all risk and density groups, except women with BCSC 5-year risk of 0-1.66% and heterogeneously dense breasts (Table 4). (Specificity results, Appendix Table 2).

Interval Cancer Rates for Advanced Disease by Breast Density, Age and BCSC 5-year Risk

Interval cancer rates of advanced disease were highest (>0.4 interval cancers/1,000 mammograms) among women with risk ≥2.50% and heterogeneously or extremely dense breasts (Appendix Table 3), which comprise 21% of women aged 40-74 years with dense breasts (Table 2). Using age and density, elevated interval rates of advanced stage disease were observed among women aged 60-74 years with extremely dense breasts, which comprise 3% of women aged 40-74 years with dense breasts.

Outcomes from Six Strategies for Women Aged 40-74 Considering Supplemental Imaging

Strategy 1 (current policy) and 2 are based on breast density only. Strategies 3-6 are based on breast density combined with either age or BCSC 5-year risk, reflecting groups with high interval rates or low mammography sensitivity or 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 cancers, resulting in a ratio of 1124 supplemental tests per interval cancer (Table 5) if all 100,000 women with dense breasts underwent supplemental imaging. In strategies 2 and 3, supplemental imaging would be considered in all women with extremely dense breasts (strategy 2) or based on combinations of age and density category with a high interval rate (strategy 3). These strategies would markedly reduce the number of supplemental tests considered compared to strategy 1 to 13-17% of women with dense breasts; however, the opportunity to detect interval cancers through

supplemental imaging would be reduced to 16-19/100,000 women with dense breasts, resulting in a ratio of 842-892 supplemental tests per interval cancer.

In strategy 4, supplemental screening would be considered for women based on combinations of BCSC 5-year risk and density category associated with a high interval rate. Under this strategy, the number of supplemental imaging tests considered would be reduced compared to strategy 1 to 24% of women with dense breasts with a more favorable ratio of 694 supplemental tests per interval cancer. However, the opportunity to detect interval cancers with supplemental imaging was lower (35/100,000 women with dense breasts) for strategy 4 than 1. In strategy 5, supplemental imaging would be considered based on 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 strategy 4 with a similar opportunity to detect interval cancers (41/100,000 women with dense breasts).

In strategy 6, the number of supplemental imaging tests would increase to 49% of all women with dense breasts with a more favorable ratio of 870 supplemental imaging tests per interval cancer than strategy 1. In strategy 6, the opportunity to detect interval cancers increased compared to strategies 2-5 to 56/100,000 women with dense breasts. For all strategies, results were similar for women aged 50-74 years (Appendix Table 4).

Discussion

We identified women aged 40-74 years who could be considered for supplemental breast imaging or alternative imaging strategies because they have high rates of interval cancer following a normal digital screening mammogram 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 risk of ≥1.67% and women with heterogeneously dense breasts and 5-year breast cancer risk of ≥2.5%; supplemental imaging discussions with these two groups (strategy 4) results in the lowest ratio of discussions per interval cancer. Using combinations of breast cancer risk and BI-RADS density identified twice as many women with dense breasts and a high rate of interval cancer following a normal digital mammogram as using combinations of age and breast density.

For the vast majority of women undergoing digital mammography—including women with dense breasts but low breast cancer risk—the rate of interval cancer was low. The false-positive rate was also low for most women except low-risk women with heterogeneously dense breasts. The higher false-positive rate in this group may be due to difficulty in discerning 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 of advanced disease, discussions of supplemental imaging or alternative

screening modalities can be directed to women who are more likely to benefit. For example, breast magnetic resonance imaging (MRI) has very high sensitivity to detect early stage breast cancer in BRCA1 and 2 mutation carriers. Breast MRI might be beneficial for women at very high breast cancer risk with dense breasts because these women are at increased risk of advanced disease (25-28). There are no data on screening ultrasound performance according to breast density and breast cancer risk. The addition of screening ultrasound following a normal mammography examination for women with dense breasts has been shown to increase cancer detection rates compared to mammography alone (8, 27, 29-31).

The purpose of screening mammography is to detect cancers at an early stage before they become symptomatic; thus, the number of interval cancers should be as low as possible, especially interval cancers associated with advanced stage disease. With increasing age, the rates of both screen-detected and interval cancers increase (32), but rates increase more rapidly for screen-detected cancers because of high mammography sensitivity in older women (4, 7). Therefore, we identified women with high interval cancer rates regardless of age. We found identifying women with a low mammography sensitivity could lead to discussions of supplemental imaging among women with extremely dense breasts but low rates of interval cancers and advanced stage disease. In fact, we found 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 of breast cancer could facilitate prioritizing 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 of large tumors and advanced cancer (26, 33-35). We elected to estimate 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-risk and low-risk groups to determine which subgroups of women would benefit from discussions of supplemental and/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 false-positive rate (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 at low breast cancer risk and high risk of a false-positive result could lower the false-positive rate in these subgroups.

Our results cannot determine if women with a high rate of interval cancer or false-positive mammograms would benefit from supplemental screening tests, imaging alternatives to mammography, 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 breast imaging alternatives to digital mammography. We specifically identified women at high risk for interval cancers or false-positive mammograms who are more likely to benefit from alternative screening strategies.

This study included a large, diverse population-based sample of women undergoing digital mammography. The cut-points we used for defining low performance were developed for identifying minimally acceptable performance levels for screening mammography interpretation for invasive and DCIS outcomes combined (22). We do not know if these performance cut-points are related to long-term outcomes such as breast cancer mortality. For some subgroups with an average interval cancer rate <1/1,000 mammograms, we cannot rule out a higher interval cancer rate because the upper 95% confidence limit exceeds one. A 24-month interval was not evaluated since women may return early for screening and/or have mammograms 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 false-positive rates who may benefit from supplemental screening tests or alternative screening strategies.

Conclusion

Digital mammography has sufficiently high breast cancer detection and reasonably low false-positive rates for routine use even among women with dense breasts. We found that not all women with dense breasts are at sufficiently high risk of interval cancers to justify consideration of supplemental or alternative screening modalities. 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 modalities in women with dense breasts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of 365,426 women undergoing 831,455 digital screening mammograms by invasive breast cancer status

	No invasive cancer N (%)	Invasive Cancer* N (%)
Screening mammograms†	N = 828,759§	N = 2,696
Age, years		
40-49	243,448 (29.4)	516 (19.1)
50-59	297,423 (35.9)	855 (31.7)
60-69	220,617 (26.6)	963 (35.7)
70-74	67,271 (8.1)	362 (13.4)
Race/ethnicity		
White, non-Hispanic	597,089 (72.0)	2,086 (77.4)
Black, non-Hispanic	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-year risk¶		
0 - <1.00%	279,385 (33.7)	472 (17.5)
1.00-1.66%	238,893 (28.8)	698 (25.9)
1.67-2.49%	190,762 (23.0)	798 (29.6)
2.50-3.99%	90,121 (10.9)	518 (19.2)
≥4.00%	29,598 (3.6)	210 (7.8)

*Invasive cancer cases within 12 months of screening mammography

†Subsequent screening examinations after first screening mammography

§Includes 3173 mammograms not associated with invasive cancer diagnosis within 12 months and occurring >9 months prior to a mammogram associated with invasive cancer diagnosis among 1,425 of the 2,696 women who develop invasive cancer

‡Defined as first degree relative (mother, sister or daughter) with breast cancer

//Breast Imaging Reporting and Data System (BI-RADS)

¶Breast Cancer Surveillance Consortium (BCSC) 5-year risk calculated using age, race, first degree family history of breast cancer, history of breast biopsy, BI-RADS density. Risk categories are defined as low (0-<1.00%), average (1.00-1.66%), intermediate (1.67%-2.49%), high (2.5%-3.99%) and very high (>3.99%).

Table 2

Distribution (row percentages) of breast density by age, and distribution (column percentages) of BCSC 5-year risk by breast density

	BI-RADS BREAST DENSITY*				
	Almost entirely fat	**Scattered fibroglandular densities**	**Heterogeneously dense**	**Extremely dense**	
Age (years)		Row Percentages			Total
40-49	6.5	32.0	47.7	13.9	243,964
50-59	11.7	40.9	39.8	7.6	298,278
60-69	15.7	47.5	32.8	4.0	221,580
70-74	16.9	50.9	29.7	2.6	67,633
BCSC 5-year risk†		Column Percentages			
0-<1.00%	67.1	37.6	22.7	18.7	
1.00-1.66%	23.0	30.0	28.3	33.8	
1.67-2.49%	8.7	21.2	29.4	21.7	
2.50-3.99%	1.2	9.7	13.9	16.4	
≥4.00%	0	1.5	5.6	9.4	
Total	96,822	339,966	327,746	66,921	**831,455**

*Breast Imaging Reporting and Data System (BI-RADS)

†Breast Cancer Surveillance Consortium (BCSC) 5-year risk calculated using age, race, first degree family history of breast cancer, history of breast biopsy, BI-RADS density. Risk categories are defined as low (0-<1.00%), average (1.00-1.66%), intermediate (1.67%-2.49%), high (2.5%-3.99%) and very high (>3.99%).

Table 3

Interval cancer rate of digital mammography for detecting invasive breast cancer by breast density and age and breast density and BCSC 5-year risk

	BI-RADS BREAST DENSITY*			
	Almost entirely fat	**Scattered fibroglandular**	**Heterogeneously**	**Extremely dense**
Age (years)	Interval cancer rate per 1000 mammograms (95% CI)			
40 – 49	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	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	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	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-year risk†				
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)
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)
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)
≥2.50%	NA	0.90 (0.62, 1.25)	**1.48** (1.20, 1.81)	**1.62** (1.08, 2.34)

*Breast Imaging Reporting and Data System (BI-RADS); CI, confidence interval

†Breast Cancer Surveillance Consortium (BCSC) 5-year risk calculated using age, race, first degree family history of breast cancer, history of breast biopsy, BI-RADS density. Risk categories are defined as low (0-<1.00%), average (1.00-1.66%), intermediate (1.67%-2.49%), high (2.5%-3.99%) and very high (>3.99%).

Bold numbers outside minimally accepted cut-points: interval cancer rate >1/1000 mammograms

NA: too few breast cancers in this category to calculate a stable measure

Table 4

False-positive rate of digital mammography for detecting invasive cancer by breast density and age and breast density and BCSC 5-year risk

	BI-RADS Breast Density*			
	Almost entirely fat	**Scattered fibroglandular densities**	**Heterogeneously dense**	**Extremely dense**
Age (years)	False-positive rate per 1000 mammograms (95% CI)			
40 – 49	65 (61, 69)	**123** (120, 125)	**147** (145, 149)	113 (110, 117)
50 – 59	53 (51, 56)	94 (93, 96)	117 (115, 119)	95 (91, 99)
60 – 69	51 (48, 53)	82 (81, 84)	100 (98, 102)	74 (69, 80)
70 – 74	50 (46, 55)	77 (74, 80)	95 (91, 99)	62 (51, 74)
BCSC 5-year risk†				
0 - <1.00%	53 (52, 55)	106 (104, 108)	**131** (129, 134)	96 (91, 101)
1.00-1.66%	54 (51, 57)	91 (89, 92)	**125** (123, 128)	99 (95, 103)
1.67-2.49%	55 (50, 60)	86 (84, 89)	115 (113, 118)	107 (102, 113)
≥2.50%	65 (52, 81)	90 (87, 93)	119 (117, 122)	101 (96, 106)

*Breast Imaging Reporting and Data System (BI-RADS); CI, confidence interval

†Breast Cancer Surveillance Consortium (BCSC) 5-year risk calculated using age, race, first degree family history of breast cancer, history of breast biopsy, BI-RADS density. Risk categories are defined as low (0-<1.00%), average (1.00-1.66%), intermediate (1.67%-2.49%), high (2.5%-3.99%) and very high (>3.99%).

Bold numbers outside minimally accepted cut-points: false-positive rate >120/1000 mammograms.

Table 5

Projected outcomes from six strategies to identify women for discussion of supplemental imaging among 100,000 women with dense breasts aged 40-74 years undergoing digital screening mammography

	Projected Outcomes of Discussion of Supplemental Imaging		
Six strategies to identify women for discussion of supplemental imaging	**No. (%) of women for discussion of supplemental imaging**	**Interval cancers following digital mammography for potential detection by supplemental imaging (95% CI)***	**Ratio of No. of women for discussion of supplemental imaging per interval cancer for potential detection by supplemental imaging**
All women with heterogeneously or extremely dense breasts (1)	100,000 (100%)	89 (80,98)	1124
All women with extremely dense breasts (2)	16,956 (17%)	19 (15,24)	892
Ages 50-74 and extremely dense breasts or ages 70-74 and heterogeneously dense breasts† (3)	13,470 (13%)	16 (13,21)	842
Risk ≥1.67% and extremely dense breasts or risk ≥2.5% and heterogeneously dense breasts† (4)	24,294 (24%)	35 (30,42)	694
Ages 40-74 and extremely dense breasts or ages 40-49 and heterogeneously dense breasts§ (5)	46,412 (46%)	41 (35,49)	1132
Risk ≥1.67% and heterogeneously or extremely dense breasts‡ (6)	48,722 (49%)	56 (49,64)	870

*CI, confidence interval

†Interval cancer rate >1/1,000 mammograms for group

§Sensitivity less than 75% for group

‡Interval cancer rate for advanced stage disease >0.4 per 1000 mammograms