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# Strategies to Identify Women at High Risk of Advanced Breast Cancer During Routine Screening for Discussion of Supplemental Imaging

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Invited Commentary

Supplemental content

**IMPORTANCE** Federal legislation proposes requiring that screening mammography reports to practitioners and women incorporate breast density information and that women with dense breasts discuss supplemental imaging with their practitioner given their increased risk of interval breast cancer. Instead of discussing supplemental imaging with all women with dense breasts, it may be more efficient to identify women at high risk of advanced breast cancer who may benefit most from supplemental imaging.

**OBJECTIVE** To identify women at high risk of advanced breast cancer to target woman-practitioner discussions about the need for supplemental imaging.

**DESIGN, SETTING, AND PARTICIPANTS** This prospective cohort study assessed 638 856 women aged 40 to 74 years who had 1 693 163 screening digital mammograms taken at Breast Cancer Surveillance Consortium (BCSC) imaging facilities from January 3, 2005, to December 31, 2014. Data analysis was performed from October 10, 2018, to March 20, 2019.

**EXPOSURES** Breast Imaging Reporting and Data System (BI-RADS) breast density and BCSC 5-year breast cancer risk.

**MAIN OUTCOMES AND MEASURES** Advanced breast cancer (stage IIB or higher) within 12 months of screening mammography; high advanced cancer rates (≥0.61 cases per 1000 mammograms) defined as the top 25th percentile of advanced cancer rates, and discussions per potential advanced cancer prevented.

**RESULTS** A total of 638 856 women (mean [SD] age, 56.5 [8.9] years) were included in the study. Women with dense breasts (heterogeneously or extremely dense) accounted for 47.0% of screened women and 60.0% of advanced cancers. Low advanced cancer rates (<0.61 per 1000 mammograms) occurred in 34.5% of screened women with dense breasts. High advanced breast cancer rates occurred in women with heterogeneously dense breasts and a 5-year risk of 2.5% or higher (6.0% of screened women) and those with extremely dense breasts and a 5-year risk of 1.0% or higher (6.5% of screened women). Density-risk subgroups at high advanced cancer risk comprised 12.5% of screened women and 27.1% of advanced cancers. Density-risk subgroups had the fewest supplemental imaging discussions per potential advanced cancer prevented compared with a strategy based on dense breasts (1097 vs 1866 discussions). Women with heterogeneously dense breasts and a 5-year risk less than 1.67% (21.7% of screened women) had high rates of false-positive short-interval follow-up recommendation without undergoing supplemental imaging.

**CONCLUSIONS AND RELEVANCE** The findings suggest that breast density notification should be combined with breast cancer risk so women at highest risk for advanced cancer are targeted for supplemental imaging discussions and women at low risk are not. BI-RADS breast density combined with BCSC 5-year risk may offer a more efficient strategy for supplemental imaging discussions than targeting all women with dense breasts.

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Recently, the US Food and Drug Administration proposed updating the Mammography Quality Standards Act of 1992 to require that mammography reports provided to health care professionals and women incorporate information regarding a woman's breast density.[1] Thirty-six states already require some level of notification on screening mammography reports of breast density,[2] a radiologic term that describes the proportion of parenchymal relative to fatty tissue in mammograms. Fifteen states advise women to discuss the possible benefits of supplemental imaging with their practitioners, which has been associated with increased supplemental ultrasonography use.[3] Supplemental screening for breast cancer may benefit women who have been notified that they have dense (heterogeneously or extremely dense) breasts and who are at increased risk of interval and advanced breast cancer.[4] The American College of Radiology suggests that supplemental ultrasonography may be useful for incremental cancer detection in women with dense breasts as the only risk factor.[5] The US Preventive Services Task Force found insufficient evidence to assess the balance of benefits and harms of supplemental screening in women with dense breasts.[6]

The American College of Radiology Imaging Network 6666 trial identified additional breast cancers using supplemental ultrasonography beyond mammography in women at elevated breast cancer risk and dense breasts, with 53% having a personal history of breast cancer.[7] The Japan Strategic Anti-cancer Randomized Trial[8] reported fewer interval breast cancers with annual supplemental ultrasonography plus mammography in average-risk women, and the Dense Tissue and Early Breast Neoplasm Screening trial[9] reported a reduction in interval breast cancers with biennial supplemental breast magnetic resonance imaging in women with extremely dense breasts. Given that supplemental imaging is associated with a decreased risk of interval cancers, of which 30% are advanced stage,[10] it seems likely that supplemental imaging may be associated with a reduced risk of advanced cancer.

We aimed to identify women undergoing routine screening at highest risk of advanced breast cancer who may benefit most from supplemental imaging and/or highest risk of false-positive results from screening who may undergo more harm from supplemental screening. We assessed advanced breast cancer (defined as stage IIB or higher),[4,11] a surrogate for breast cancer mortality,[12] and false-positive short-interval follow-up imaging or biopsy recommendation results. We identified subgroups at high risk of advanced cancer and false-positive results according to combinations of Breast Imaging Reporting and Data System (BI-RADS) breast density,[13] Breast Cancer Surveillance Consortium (BCSC) 5-year breast cancer risk,[14,15] and age. We compared strategies in these subgroups to identify the most efficient strategy to target women for supplemental imaging discussions.

**Key Points**

**Question** Which women with dense breasts undergoing routine screening are at high risk of advanced breast cancer?

**Findings** In this cohort study of 638 856 women, high rates of advanced breast cancer occurred in women with heterogeneously dense breasts and a 5-year risk of 2.5% or higher and those with extremely dense breasts and a 5-year risk of 1.0% or higher. Identification of density-risk subgroups at high risk of advanced cancer provided the most efficient approach for targeting women for supplemental imaging discussions (1097 discussions per potential advanced cancer prevented).

**Meaning** Assessment of 5-year risk in women with dense breasts identified subgroups at highest risk of advanced cancer and was a more efficient strategy for supplemental imaging discussions than was targeting all women with dense breasts.

## Methods

### Study Setting and Data Sources

This cohort study used data from BCSC mammography registries,[16] with population demographics comparable to the those of the US population.[17-19] Data were prospectively collected, capturing women's characteristics and radiologic information from 554 radiologists and 127 academic and community radiology facilities. Breast cancer diagnoses were obtained by linking women's risk factor and imaging data to pathology databases; regional Surveillance, Epidemiology, and End Results programs; and regional and state tumor registries with completeness of reporting estimated at greater than 94.3%.[20] Registries and a central statistical coordinating center received institutional review board approval from their respective institutions for active or passive consenting processes (3 registries) or a waiver of consent (3 registries) to enroll participants, link data, and perform analyses because the study was considered low risk. 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 to protect the identities of women, physicians, and facilities. The data housed at the statistical coordinating center that were used for analyses were deidentified.

### Participants

A cohort of women aged 40 to 74 years with no history of breast cancer, breast implants, or mastectomy who had digital screening mammography performed from January 3, 2005, through December 31, 2014, were included. A screening examination was defined according to the BCSC strict definition.[16] To reflect women routinely screened, we included only women with prior mammography performed between 9 and 30 months previously. Data analysis was performed from October 10, 2018, to March 20, 2019.

### Measures, Definitions, and Outcomes

Demographic and breast health history information were from self-administered paper or electronic questionnaires completed at each mammogram. Radiologists categorized breast density during clinical interpretation using BI-RADS density categories: almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense. Mammogram findings were classified as abnormal (BI-RADS assessment of 4 or 5) or normal (BI-RADS assessment of 1 or 2) based on standard BI-RADS definitions of final assessments after complete imaging workup.[13,21] A BI-RADS assessment of 3 was classified as abnormal because short-term follow-up imaging leads to image-detected cancers.

Mammograms were linked to invasive breast cancer or ductal carcinoma in situ (DCIS) diagnoses within 12 months after mammography. If 2 screening mammograms were taken within 12 months of a breast cancer diagnosis, we associated the cancer with the mammogram closest to diagnosis. The rates of false-positive biopsy recommendation were calculated as the number of screens with a final assessment of a BI-RADS assessment of 4 or 5 without invasive cancer or DCIS diagnosed within 12 months divided by the total number of screens. The rates of false-positive short-interval follow-up recommendation were calculated as the number of screens with a final assessment of a BI-RADS assessment of 3 without invasive cancer or DCIS diagnosed within 12 months divided by the total number of screens.

Invasive breast cancers were classified according to the American Joint Committee on Cancer *Cancer Staging Manual*, seventh edition.[22] We defined early cancer as stage I or IIA and advanced cancer as stage IIB, III, or IV.[4,11] We calculated screen-detected early cancer rates as the number of early cancers diagnosed within 12 months of a positive screen result divided by the total number of screens. We calculated advanced cancer rates as the number of advanced cancers divided by the total number of screens.

The BCSC 5-year invasive cancer risk was calculated using the BCSC risk calculator, version 2[14] and categorized as low (0 to <1.00%), average (1.00%-1.66%), intermediate (1.67%-2.49%), high (2.50%-3.99%), and very high (>3.99%).[14,23]

On the basis of benchmark levels in the literature,[19,24-26] we defined high screening outcomes as the top 25th percentile of the rates of advanced cancer and false-positive results weighted by each BCSC radiologist's sample size for each measure. With the use of this definition, high advanced cancer rates were 0.61 cases or more per 1000 mammograms, high false-positive biopsy recommendation rates were 14.0 cases or more per 1000 mammograms, and high false-positive short-interval follow-up recommendation rates were 20.0 cases or more per 1000 mammograms. We defined low screening mammography outcomes as the lowest 25th percentile of the screen-detected early cancer rates, defined as 1.6 cases or less per 1000 mammograms. We performed a sensitivity analysis defining high advanced cancer rates as the top 30th percentile of the advanced cancer rates or 0.51 cases or more per 1000 mammograms.

### Statistical Analysis

All analyses were performed using the screening mammogram as the unit of analysis; women could have more than 1 mammogram during the study period. We used descriptive statistics to characterize mammograms as associated or not associated with invasive breast cancer or DCIS.

We estimated rates per 1000 mammograms of advanced and early cancer and false-positive biopsy recommendation and short-interval follow-up recommendation. We calculated 95% CIs for screening outcomes using generalized estimating equations with a working independence correlation structure to account for correlation among mammograms from the same woman, radiologist, or facility.[27,28] Separate screening outcomes were calculated by each breast density category and BCSC 5-year risk or age. Thus, breast density was used to stratify women's risk of masking within the next year and to estimate their breast cancer risk in the next 5 years. For each density-risk and density-age subgroup, we calculated the expected number and percentage of screen-detected early and advanced cancers per 100 000 screened women by multiplying the prevalence of women in each subgroup by the corresponding rate in that subgroup. We used 5-fold cross-validation to calculate the area under the receiver operating characteristic curve to evaluate the discriminatory accuracy of using breast density, breast density plus BCSC 5-year risk, and breast density plus age to estimate the risk of advanced breast cancer in an independent sample.

We evaluated the relative efficiency of 4 alternative strategies for selecting women for supplemental imaging discussion using a hypothetical cohort of 100 000 women aged 40 to 74 years: (1) women with advanced cancer rates of 0.61 cases or more per 1000 mammograms based on BI-RADS density and BCSC 5-year risk, (2) women with advanced cancer rates of 0.61 cases or more per 1000 mammograms based on BI-RADS density and age, (3) women with advanced cancer rates of 0.51 cases or more per 1000 mammograms based on BI-RADS density and BCSC 5-year risk, and (4) women with dense breasts. For each strategy, we projected (1) number and percentage of women who would be identified for supplemental imaging, (2) advanced cancer rate and proportion of all advanced breast cancers in the total population, (3) mean ratio of women identified for supplemental imaging per potential advanced cancer prevented, (4) incremental increase in number of women and advanced cancer prevented, and (5) incremental ratio of additional women considered for supplemental imaging per additional potential advanced cancer prevented. The latter incremental ratio was used to evaluate the relative efficiency of alternative approaches to identifying women for targeted discussions of supplemental imaging.

Statistical analyses used SAS statistical software, version 9.4 (SAS Institute Inc) and a macro for generalized estimating equation analysis.[28]

## Results

A total of 638 856 women (mean [SD] age, 56.5 [8.9] years) were included in the study. Women with invasive cancer or DCIS were more likely to be older, to be white, and to have a first-degree family history of breast cancer, history of breast biopsy, dense breasts, and a BCSC 5-year risk of 1.67% or greater (**Table 1**).

### Advanced and Early Cancer Rates by Breast Density and BCSC 5-Year Risk or Age

Women with dense breasts accounted for 47.0% of screened women and 60.0% of advanced cancers (**Table 2**). Low advanced cancer rates (<0.61 per 1000 mammograms) occurred

Table 1. Characteristics of 638 856 Women Undergoing 1 693 163 Subsequent Digital Screening Mammograms Overall and by Invasive Breast Cancer and DCIS Status Within 1 Year of Follow-up[a]

| Characteristic | Screening Mammograms, % | | |
|---|---|---|---|
| | No Invasive Cancer or DCIS (n = 1 685 648) | Invasive Cancer (n = 5326)[b] | DCIS (n = 2189)[b] |
| Age, y | | | |
| 40-49 | 26.1 | 16.4 | 22.5 |
| 50-59 | 35.6 | 30.7 | 32.3 |
| 60-69 | 29.2 | 38.5 | 34.7 |
| 70-74 | 9.0 | 14.4 | 12.6 |
| Race/ethnicity | | | |
| White, non-Hispanic | 67.0 | 73.3 | 66.2 |
| Black, non-Hispanic | 7.5 | 7.1 | 6.8 |
| Asian, Native Hawaiian, or Pacific Islander | 13.7 | 12.2 | 18.0 |
| Hispanic | 4.8 | 3.1 | 3.4 |
| Other, mixed, or unknown | 7.1 | 4.2 | 5.7 |
| Menopausal status | | | |
| Premenopausal or perimenopausal | 29.8 | 20.7 | 26.2 |
| Postmenopausal | | | |
| Current HT use | 7.3 | 9.9 | 7.7 |
| No current HT use | 53.6 | 58.1 | 55.9 |
| Current HT use unknown | 6.8 | 9.2 | 8.3 |
| Surgical menopausal | 2.5 | 2.1 | 1.9 |
| Family history of breast cancer[c] | 16.5 | 25.1 | 23.0 |
| History of breast biopsy | 19.9 | 37.4 | 35.9 |
| BI-RADS breast density | | | |
| Almost entirely fatty | 10.9 | 7.1 | 5.7 |
| Scattered areas of fibroglandular densities | 42.1 | 41.3 | 38.6 |
| Heterogeneously dense | 38.9 | 43.4 | 45.2 |
| Extremely dense | 8.1 | 8.3 | 10.4 |
| BI-RADS final assessment | | | |
| Normal (1) | 69.1 | 12.1 | 4.2 |
| Normal, benign finding (2) | 28.2 | 7.4 | 2.6 |
| Probably benign (3) | 1.7 | 4.2 | 5.5 |
| Suspicious (4) | 1.0 | 56.4 | 83.6 |
| Malignant (5) | 0 | 20.0 | 4.2 |
| BCSC 5-y risk[d] | | | |
| 0 to <1.00%, low | 29.6 | 14.1 | 18.2 |
| 1.00%-1.66%, average | 40.1 | 34.8 | 36.6 |
| 1.67%-2.49%, intermediate | 20.7 | 29.0 | 24.5 |
| 2.50%-3.99%, high | 8.4 | 18.2 | 17.2 |
| ≥4.00%, very high | 1.2 | 4.0 | 3.4 |

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; BI-RADS, Breast Imaging Reporting and Data System; DCIS, ductal carcinoma in situ; HT, hormone therapy.

[a] Subsequent screening examinations after recent prior mammogram within 9 to 30 months.

[b] Invasive cancer cases and DCIS within 12 months of screening mammography.

[c] Defined as first-degree relative (mother, sister, or daughter) with breast cancer.

[d] The BCSC 5-year risk was calculated using age, race/ethnicity, first-degree family history of breast cancer, history of breast biopsy, and BI-RADS density.

in 34.5% of screened women with dense breasts. High advanced cancer rates (≥0.61 cases per 1000 mammograms) occurred in women with heterogeneously dense breasts and 5-year risk of 2.5% or higher (6.0% of screened women) and those with extremely dense breasts and 5-year risk of 1.0% or higher (6.5% of screened women). These density-risk subgroups at high advanced cancer risk comprised 12.5% of screened women and 27.1% of advanced cancers. Advanced cancer rates of 0.51 cases or more per 1000 mammograms occurred in density-risk subgroups of scattered fibroglandular densities or heterogeneously dense breasts and 5-year risk of 1.67% or higher and extremely dense breasts and 5-year risk of 1.00% or higher, accounting for 32.7% of screened women and 54.7% of advanced cancers. Women with any BI-RADS density and 5-year risk less than 1.0% (29.5% of screened women) had the lowest advanced cancer rates and screen-detected early cancer rates.

High advanced cancer rates were observed in density-age groups of heterogeneously dense breasts and age of 60 to 74 years and extremely dense breasts and age of 50 to 69 years, accounting for 16.4% of screened women and 27.6% of advanced cancers (**Table 3**).

Breast density plus BCSC 5-year risk had the highest area under the receiver operating characteristic curve (0.642) for identifying women at risk of advanced breast cancer (eTable in the Supplement).

Table 2. Rates of Early and Advanced Cancer by Breast Density and BCSC Risk

| BCSC 5-Year Risk by Breast Density Category[a] | Prevalence in Population, % | Early Cancer (n = 3665): Rate of Stage I or IIA Screen-Detected Invasive Cancer per 1000 Examinations (95% CI) | Early Cancer (n = 3665): Expected Stage I or IIA Screen-Detected Invasive Cancers in 100 000 Screened Women, No. (%) | Advanced Cancer (n = 741): Rate of Stage IIB or Higher Invasive Cancer per 1000 Examinations (95% CI) | Advanced Cancer (n = 741): Expected Stage IIB or Higher Invasive Cancers in 100 000 Screened Women, No. (%) |
|---|---|---|---|---|---|
| Almost Entirely Fatty | | | | | |
| 0 to <1.00% | 7.2 | 1.0 (0.9-1.2) | 7.2 (3.4) | 0.13 (0.08-0.21) | 0.94 (2.2) |
| 1.00%-1.66% | 3.1 | 2.4 (2.0-3.0) | 7.4 (3.5) | 0.17 (0.08-0.37) | 0.53 (1.3) |
| 1.67%-2.49% | 0.5 | 4.8 (3.6-6.3) | 2.4 (1.1) | 0.41 (0.16-1.01) | 0.21 (0.5) |
| ≥2.50% | 0.07 | 6.4 (3.3-12.1) | 0.47 (0.2) | NE | 0.091 (0.2) |
| Scattered Areas of Fibroglandular Densities | | | | | |
| 0 to <1.00% | 13.1 | 1.1 (0.9-1.3) | 14.4 (6.8) | 0.26 (0.18-0.36) | 3.4 (8.1) |
| 1.00%-1.66% | 20.1 | 2.2 (1.9-2.6) | 44.3 (20.8) | 0.31 (0.24-0.40) | 6.2 (14.8) |
| 1.67%-2.49% | 6.7 | 3.8 (3.3-4.3) | 25.4 (11.9) | 0.60 (0.46-0.79) | 4.0 (9.5) |
| ≥2.50% | 2.3 | 5.9 (4.8-7.2) | 13.3 (6.3) | 0.60 (0.37-0.95) | 1.4 (3.3) |
| Heterogeneously Dense | | | | | |
| 0 to <1.00% | 7.7 | 0.8 (0.6-1.0) | 6.2 (2.9) | 0.31 (0.20-0.46) | 2.4 (5.7) |
| 1.00%-1.66% | 14.0 | 1.5 (1.3-1.7) | 21.0 (9.9) | 0.35 (0.26-0.47) | 4.9 (11.7) |
| 1.67%-2.49% | 11.2 | 2.8 (2.4-3.2) | 31.5 (14.8) | 0.56 (0.42-0.73) | 6.2 (14.8) |
| ≥2.50% | 6.0 | 4.5 (3.9-5.2) | 27.1 (12.7) | 1.08 (0.87-1.35) | 6.5 (15.5) |
| Extremely Dense | | | | | |
| 0 to <1.00% | 1.6 | 0.7 (0.4-1.3) | 1.1 (0.52) | 0.17 (0.08-0.37) | 0.28 (0.67) |
| 1.00%-1.66% | 2.9 | 0.9 (0.6-1.3) | 2.6 (1.2) | 0.61 (0.43-0.86) | 1.7 (4.0) |
| 1.67%-2.49% | 2.3 | 1.8 (1.4-2.4) | 4.1 (1.9) | 0.68 (0.51-0.91) | 1.6 (3.8) |
| ≥2.50% | 1.3 | 3.2 (2.4-4.1) | 4.3 (2.0) | 1.25 (0.87-1.82) | 1.6 (3.8) |

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; NE, not estimable (only 1 advanced cancer in group).

[a] The BCSC 5-year risk was calculated using age, race/ethnicity, first-degree family history of breast cancer, history of breast biopsy, and Breast Imaging Reporting and Data System breast density.

### Screening False-Positive Rates by Breast Density and BCSC 5-Year Risk or Age

High rates of false-positive short-interval follow-up recommendation (≥20.0 cases per 1000 mammograms) occurred in density-risk subgroups of heterogeneously dense breasts and 5-year risk less than 1.67% (21.7% of screened women) and in density-age subgroups of heterogeneously or extremely dense breasts and age of 40 to 49 years (**Table 4**). High rates of false-positive biopsy recommendation rates (≥14.0 cases per 1000 mammograms) occurred in density-risk subgroups with any breast density category and 5-year risk of 2.5% or higher and extremely dense breasts and 5-year risk of 1.0% to 1.66%, and in density-age subgroups of heterogeneously dense breasts and age of 40 to 49 years and extremely dense breasts and age of 40 to 59 years (Table 4).

### Evaluation of Strategies for Identifying Women for Supplemental Imaging Discussions

In a hypothetical cohort of 100 000 women, supplemental imaging in all 47 012 women with dense breasts would result in a ratio of 1866 supplemental imaging discussions per potential advanced breast cancer prevented (**Table 5**). If supplemental imaging was considered based on combinations of density category and BCSC 5-year risk associated with a high advanced cancer rate of 0.61 cases or more per 1000 mammograms, the number of women considered for supplemental imaging would be reduced to 12 506, for a mean ratio of 1097 supplemental imaging discussions per potential advanced cancer prevented.

Examining the increase in the number of women identified for supplemental imaging compared with the increase in potential advanced cancer prevented (Table 5) revealed that counseling strategies that identified women for supplemental imaging based on breast density and BCSC 5-year risk were more efficient compared with strategies based on age and density or density alone. Identifying women based on breast density and BCSC 5-year risk and an advanced cancer rate of 0.51 cases or more per 1000 mammograms resulted in 1740 additional supplemental imaging examinations per potential advanced cancer prevented compared with density-risk subgroup with an advanced cancer rate of 0.61 cases or more per 1000 mammograms.

## Discussion

Current breast density state and federal notification laws encourage health care professionals to counsel women about how dense breasts can mask or hide breast cancers and increase risk and about the possible need for supplemental or alternative screening options. However, studies[29-32] consistently report that women can experience

Table 3. Rates of Early and Advanced Cancer by Breast Density and Age

| Breast Density by Decade of Age | Prevalence in Population, % | Early Cancer (n = 3665): Rate of Stage I or IIA Screen-Detected Invasive Cancer per 1000 Examinations (95% CI) | Early Cancer (n = 3665): Expected Stage I or IIA Screen-Detected Invasive Cancers in 100 000 Screened Women, No. (%) | Advanced Cancer (n = 741): Rate of Stage IIB or Higher Invasive Cancer per 1000 Examinations (95% CI) | Advanced Cancer (n = 741): Expected Stage IIB or Higher Invasive Cancer in 100 000 Screened Women, No. (%) |
|---|---|---|---|---|---|
| **40-49 Years of Age** | | | | | |
| Almost entirely fatty | 1.5 | 0.5 (0.3-0.9) | 0.74 (0.35) | 0.09 (0.02-0.45) | 0.14 (0.33) |
| Scattered areas of fibroglandular densities | 8.1 | 1.1 (0.9-1.4) | 9.0 (4.3) | 0.21 (0.14-0.31) | 1.70 (4.0) |
| Heterogeneously dense | 12.5 | 1.2 (1.0-1.4) | 15.0 (7.1) | 0.42 (0.30-0.57) | 5.3 (12.6) |
| Extremely dense | 3.8 | 1.0 (0.8-1.3) | 3.8 (1.8) | 0.56 (0.42-0.74) | 2.1 (5.0) |
| **50-59 Years of Age** | | | | | |
| Almost entirely fatty | 3.7 | 0.9 (0.7-1.1) | 3.3 (1.6) | 0.11 (0.06-0.21) | 0.41 (1.0) |
| Scattered areas of fibroglandular densities | 14.8 | 1.7 (1.5-2.0) | 25.2 (11.9) | 0.36 (0.28-0.47) | 5.3 (12.6) |
| Heterogeneously dense | 14.1 | 2.0 (1.8-2.2) | 28.3 (13.4) | 0.44 (0.35-0.55) | 6.2 (14.8) |
| Extremely dense | 2.8 | 1.8 (1.4-2.2) | 5.1 (2.4) | 0.77 (0.58-1.02) | 2.2 (5.2) |
| **60-69 Years of Age** | | | | | |
| Almost entirely fatty | 4.3 | 2.2 (1.8-2.7) | 9.4 (4.4) | 0.20 (0.13-0.32) | 0.86 (2.0) |
| Scattered areas of fibroglandular densities | 14.3 | 3.2 (2.9-3.6) | 45.9 (21.7) | 0.39 (0.32-0.49) | 5.6 (13.3) |
| Heterogeneously dense | 9.6 | 3.2 (2.8-3.6) | 30.9 (14.6) | 0.67 (0.53-0.85) | 6.4 (15.2) |
| Extremely dense | 1.2 | 1.9 (1.2-3.0) | 2.4 (1.1) | 0.70 (0.46-1.08) | 0.84 (2.0) |
| **70-74 Years of Age** | | | | | |
| Almost entirely fatty | 1.4 | 2.9 (2.4-3.4) | 4.2 (2.0) | 0.23 (0.12-0.46) | 0.32 (0.76) |
| Scattered areas of fibroglandular densities | 4.8 | 3.3 (2.8-3.9) | 15.8 (7.5) | 0.48 (0.32-0.71) | 2.3 (5.5) |
| Heterogeneously dense | 2.7 | 4.2 (3.5-4.9) | 11.4 (5.4) | 0.82 (0.60-1.12) | 2.2 (5.2) |
| Extremely dense | 0.3 | 3.5 (2.2-5.6) | 0.93 (0.44) | 0.51 (0.15-1.67) | 0.15 (0.36) |

anxiety or concern in response to breast density notification, and most practitioners are not prepared to counsel women about breast density and are uncertain about offering supplemental imaging. Our findings provide important information to guide women and practitioners about when supplemental imaging may be most beneficial and when it would not. The most efficient strategies identified women at high risk of advanced breast cancer based on breast density and BCSC 5-year risk. The strategies targeted 12.5% of screened women for supplemental imaging discussions because they have the highest risk of advanced cancer, with heterogeneously dense breasts and a BCSC 5-year risk of 2.5% or higher or extremely dense breasts and a 5-year risk of 1.0% or higher. The next best strategy for possible supplemental imaging discussions also targeted women with scattered fibroglandular densities (ie, nondense breasts) with a BCSC 5-year risk of 1.67% or higher and women with heterogeneously dense breasts and a 5-year risk of 1.67% to 2.49%. Supplemental imaging based on density alone or density plus age was less efficient compared with density-risk strategies. This finding suggests that breast density notification should be provided but not as a stand-alone risk factor.[33] Breast density notification should incorporate breast cancer risk estimations so women at highest risk of advanced cancer can be appropriately targeted for supplemental imaging and/or considered for primary preventions to reduce risk. Moreover, women at low risk of advanced cancer would be reassured that supplemental imaging is not indicated, thereby avoiding potential harms.

We previously reported on interval invasive cancer risk according to BCSC 5-year risk and BI-RADS breast density categories.[4] However, a large proportion of women with interval cancers are diagnosed with early disease and thus have good survival.[10] In this study, we defined advanced breast cancer as stage IIB or higher irrespective of whether screen or clinically detected because all advanced cancer is associated with increased breast cancer mortality.[12] A recent study[34] similarly defined poor screening outcomes as stage IIB or higher diagnosed after a screening episode with negative results or at the next subsequent screening examination, with women in the highest quartile of volumetric breast density having the highest risk of advanced cancer. Consistent with the findings of Puliti et al,[34] we found that advanced breast cancer rates were highest in women with dense breasts.

Table 4. Rate of False-Positive Screening Results by Breast Density and BCSC Risk and Breast Density and Age

| BCSC 5-Year Risk by Breast Density Category and Age[a] | False-Positive Screening Result: Prevalence in Population, % | Rate of False-Positive Short-Interval Follow-up Recommendation per 1000 Examinations (95% CI) | Rate of False-Positive Biopsy Recommendation per 1000 Examinations (95% CI) |
|---|---|---|---|
| **Almost Entirely Fatty** | | | |
| 0 to <1.00% | 7.2 | 9.9 (7.9-12.4) | 5.8 (4.8-7.0) |
| 1.00%-1.66% | 3.1 | 10.0 (8.2-12.1) | 7.6 (6.4-9.0) |
| 1.67%-2.49% | 0.5 | 10.6 (7.8-14.3) | 9.0 (6.4-12.5) |
| ≥2.50% | 0.1 | 11.8 (6.7-20.7) | 15.5 (9.5-25.1) |
| **Scattered Areas of Fibroglandular Densities** | | | |
| 0 to <1.00% | 13.1 | 17.5 (13.5-22.7) | 8.3 (6.8-10.2) |
| 1.00%-1.66% | 20.1 | 15.0 (12.0-18.7) | 8.1 (6.9-9.4) |
| 1.67%-2.49% | 6.7 | 15.4 (12.1-19.6) | 11.1 (9.5-12.9) |
| ≥2.50% | 2.3 | 16.6 (12.2-22.5) | 15.4 (12.6-18.7) |
| **Heterogeneously Dense** | | | |
| 0 to <1.00% | 7.7 | 21.7 (17.0-27.5) | 11.6 (9.4-14.3) |
| 1.00%-1.66% | 14.0 | 20.5 (16.8-25.0) | 11.9 (10.2-14.0) |
| 1.67%-2.49% | 11.2 | 18.4 (15.7-21.5) | 12.1 (10.2-14.4) |
| ≥2.50% | 6.0 | 19.6 (16.3-23.5) | 15.8 (12.9-19.3) |
| **Extremely Dense** | | | |
| 0 to <1.00% | 1.6 | 18.4 (13.6-24.8) | 11.8 (9.0-15.5) |
| 1.00%-1.66% | 2.9 | 19.5 (15.5-24.6) | 14.0 (12.1-16.3) |
| 1.67%-2.49% | 2.3 | 17.0 (13.6-21.2) | 12.9 (10.7-15.6) |
| ≥2.50% | 1.3 | 17.0 (13.6-21.0) | 15.7 (12.2-20.1) |
| **40-49 Years of Age** | | | |
| Almost entirely fatty | 1.5 | 11.8 (8.9-15.5) | 5.9 (4.5-7.7) |
| Scattered areas of fibroglandular densities | 8.1 | 19.6 (15.2-25.3) | 10.0 (8.4-11.8) |
| Heterogeneously dense | 12.5 | 24.2 (19.7-29.8) | 14.6 (12.5-17.0) |
| Extremely dense | 3.8 | 21.2 (16.7-26.9) | 15.5 (13.4-17.8) |
| **50-59 Years of Age** | | | |
| Almost entirely fatty | 3.7 | 10.0 (8.3-12.1) | 6.4 (5.2-7.7) |
| Scattered areas of fibroglandular densities | 14.8 | 16.4 (12.8-21.0) | 9.0 (7.7-10.6) |
| Heterogeneously dense | 14.1 | 19.4 (16.1-23.3) | 13.0 (11.2-15.1) |
| Extremely dense | 2.8 | 17.3 (13.7-21.9) | 14.4 (12.2-17.0) |
| **60-69 Years of Age** | | | |
| Almost entirely fatty | 4.3 | 9.5 (7.6-11.9) | 6.8 (5.8-8.0) |
| Scattered areas of fibroglandular densities | 14.3 | 14.1 (11.3-17.5) | 8.8 (7.8-10.0) |
| Heterogeneously dense | 9.6 | 16.4 (13.9-19.3) | 9.9 (8.3-11.8) |
| Extremely dense | 1.2 | 12.5 (10.3-15.1) | 8.0 (6.8-9.4) |
| **70-74 Years of Age** | | | |
| Almost entirely fatty | 1.4 | 9.4 (7.4-12.0) | 6.6 (5.3-8.1) |
| Scattered areas of fibroglandular densities | 4.8 | 13.7 (10.7-17.5) | 7.9 (6.7-9.3) |
| Heterogeneously dense | 2.7 | 16.7 (14.0-20.0) | 9.9 (8.4-11.7) |
| Extremely dense | 0.3 | 11.4 (8.4-15.5) | 4.3 (2.4-7.6) |

Abbreviation: BCSC, Breast Cancer Surveillance Consortium.

[a] The BCSC 5-year risk was calculated using age, race/ethnicity, first-degree family history of breast cancer, history of breast biopsy, and Breast Imaging Reporting and Data System breast density.

Women are concerned about being diagnosed with advanced breast cancer,[35-37] which can result in more aggressive treatment and decreased survival from breast cancer.[12] Identifying women with a high likelihood of advanced cancer can direct supplemental imaging discussions to women who are more likely to benefit.[7] For example, women with extremely dense breasts and average 5-year breast cancer risk (1.00%-1.66%) have low rates of early breast cancer but high rates of advanced cancer; supplemental imaging may decrease the likelihood of advanced cancer diagnosis in these women. By comparison, the 29.5% of screened women with low 5-year breast cancer risk (<1.0%), regardless of breast density, had low early and advanced cancer rates and should not be considered for

Table 5. Projected Outcomes per 100 000 Women of Strategies to Target Women for Discussion of Supplemental Imaging

| Stategy[a] | Women Identified for Supplemental Imaging Discussions, No. (%) | Advanced Breast Cancers per 1000 Women, No. (%) | Mean Ratio of Women Considered for Supplemental Imaging Discussions per Potential Advanced Breast Cancer Prevented | Incremental Increase in No. of Women Identified for Supplemental Imaging Discussions[b] | Incremental Increase in Advanced Breast Cancers for Potential Detection[b] | Incremental Value of Strategies[b] |
|---|---|---|---|---|---|---|
| Women with advanced breast threshold ≥0.61 per 1000 examinations based on breast density and BCSC 5-y risk[c,d] | 12 506 (12.5) | 11.4 (27.1) | 1097 | NE | NE | NE |
| Women with advanced breast cancer threshold ≥0.61 per 1000 examinations based on breast density and age[e] | 16 301 (16.3) | 11.6 (27.6) | 1405 | 3795 | 0.2 | Inefficient[f] |
| Women with advanced breast cancer threshold ≥0.51 per 1000 examinations based on breast density BCSC 5-y risk[c,g] | 32 695 (32.7) | 23 (54.7) | 1422 | 16 394 | 11.4 | 1740 |
| Women with heterogeneously or extremely dense breasts | 47 012 (47.0) | 25.2 (60.0) | 1866 | 14 317 | 2.2 | Inefficient[f] |
| All women | 100 000 (100) | 42 (100) | 2380 | 52 988 | 16.8 | 3542 |

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; NE, not estimable.

[a] Strategies were ranked based on number of women identified for supplemental imaging discussions (lowest to highest).

[b] Incremental ratio of increase in number of women targeted per increase in potential advanced breast cancers prevented when strategies are ranked by increasing number of women identified for supplemental imaging discussions.

[c] The BCSC 5-year risk was calculated using age, race, first degree family history of breast cancer, history of breast biopsy, and Breast Imaging Reporting and Data System breast density.

[d] Heterogeneously dense breasts and 5-year risk of 2.5% or higher and extremely dense breasts and 5-year risk of 1.0% or higher.

[e] Age of 60 to 74 years and heterogeneously dense breasts or age of 50 to 69 years and extremely dense breasts.

[f] Because of the relatively small increase in advanced cancers, for potential prevention, this strategy is weakly dominated or inefficient.

[g] Scattered fibroglandular densities or heterogeneously dense breasts and 5-year risk of 1.67% or higher or extremely dense breasts and 5-year risk of 1.0% or higher.

supplemental imaging, given the low likelihood of benefit relative to the high risk of false-positive test results. Of note, we found that the 21.7% of screened women with heterogeneously dense breasts and low 5-year breast cancer risk (<1.67%) were at high risk of a false-positive short-interval follow-up recommendation. Supplemental imaging with ultrasonography or magnetic resonance imaging in this low-risk, high-density subgroup could further increase the number of false-positive test results.[38]

Although state and federal breast density notification laws require radiology facilities to recommend supplemental imaging discussions for women notified of dense breasts, our study found that targeted discussions based on BCSC 5-year risk and breast density are a more efficient strategy. Strategies based on risk and breast density are appropriate because advanced cancer rates are highest among women with dense breasts[4,39,40] and high 5-year risk. The most efficient strategy would offer supplemental imaging discussions to the 12.5% of women at highest risk of advanced cancer based on breast density and 5-year risk, but this strategy potentially averts only 27.1% of advanced cases occurring in a screened population. The next most efficient strategy was also based on breast density and 5-year risk and would offer supplemental imaging to almost 3 times as many screened women (32.7%), potentially preventing 54.7% of advanced cancers. Identifying women at highest risk of advanced cancer requires assessing BCSC 5-year risk in women with dense breasts. This risk assessment can be repeated every 3 to 5 years to determine whether breast density and risk have decreased, eliminating eligibility for supplemental imaging.[41,42]

Women are concerned about false-positive mammography results and associated anxiety.[43] We found that the risk of false-positive biopsy recommendation increased with increasing 5-year breast cancer risk and breast density. Thus, women at greatest risk of advanced cancer would be at greatest risk of a false-positive biopsy recommendation. Performance of supplemental imaging among all women with dense breasts could increase the number of false-positive test results, particularly among women aged 40 to 49 years who experience high rates of false-positive results with digital mammography. Limiting supplemental imaging to women at highest risk of advanced cancer may minimize the number of additional false-positive test results.

## Strengths and Limitations

This study included a large, diverse, population-based sample of women undergoing digital mammography. We could not determine whether women at high risk of advanced cancer would benefit from supplemental screening tests. Our study also did not address individual preferences about screening outcomes or women's and practitioners' preferences for advanced cancer thresholds. Only 0.59% of study participants with dense breasts underwent supplemental imaging within a year of mammography because most data (93.9%) were collected from states before having density laws. We were unable to evaluate digital breast tomosynthesis outcomes. However, to our knowledge, no published evidence indicates that advanced cancer rates differ for digital mammography vs tomosynthesis according to breast density.[44,45] In addition, breast density distributions are similar for digital mammography and tomosynthesis and the fourth and fifth editions of BI-RADS.[46]

## Conclusions

The findings suggest that targeting women for supplemental imaging discussions because of high risk of advanced breast cancer based on breast density and BCSC 5-year risk is a more efficient strategy than targeting all women with dense breasts or targeting women within density and age groups. Women and practitioners may use this information to determine the need to discuss and perform supplemental imaging.

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