Using Mammographic Density to Improve Breast Cancer Screening Outcomes

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Abstract

It is possible that the performance of mammographic screening would be improved if it is targeted at women at higher risk of breast cancer or who are more likely to have their cancer missed at screening, through more intensive screening or alternative screening modalities. We conducted a case-control study within a population-based Australian mammographic screening program (1,706 invasive breast cancers and 5,637 randomly selected controls). We used logistic regression to examine the effects of breast density, age, and hormone therapy use, all known to influence both breast cancer risk and the sensitivity of mammographic screening, on the risk of small (<15 mm) and large (>15 mm) screen-detected and interval breast cancers. The risk of small screen-detected cancers was not associated with density, but the risk of large screen-detected cancers was nearly 3-fold for the second quintile and approximately 4-fold for the four highest density categories (third and fourth quintiles and the two highest deciles) compared with the lowest quintile. The risk of interval cancers increased monotonically across the density categories [highest decile odds ratio (OR), 4.65; 95% confidence interval (95% CI), 2.96-7.31]. The risk of small and large screen-detected cancers, but not interval cancers, increased with age. After adjusting for age and density, hormone therapy use was associated with a moderately elevated risk of interval cancers (OR, 1.43; 95% CI, 1.12-1.81). The effectiveness of the screening program could be improved if density were to be used to identify women most likely to have poor screening outcomes. There would be little additional benefit in targeting screening based on age and hormone therapy use. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2818–24)

Introduction

Several factors that influence the risk of breast cancer, including age, use of hormone therapy, and mammographic density (1-5), also influence the sensitivity of mammographic screening (6-13). Mammographic density is the term used to describe the appearance of radiographically dense breast tissue that appears light on a mammogram. Fat tissue appears dark, whereas the radiographically dense stroma and epithelium appear light. The proportion of the area of the breast that is mammographically dense, the percent mammographic density (hereafter described as density), is a strong predictor of breast cancer risk (3, 4). High density reduces the ability to detect cancers by mammographic screening because dense tissue may mask lesions (7, 8, 11, 13).

The sensitivity of screening programs (program sensitivity) is calculated as the number of cancers detected from screening mammograms divided by the sum of this number and the number of cancers detected in a defined interval following a negative screening mammogram. Using program sensitivity to study how age, hormone therapy use, and density impact on screening performance obscures the different contribution of each of these factors to the probability of cancer detection and to the risk of interval cancers following negative mammograms. For example, a recent study showed that high density is associated with a 3.5-fold increase in the odds of detecting a cancer from a screening mammogram and an 18-fold increase in the risk of an interval cancer within 12 months of a negative screen (13). This suggests that it is important to focus on ways to reduce interval cancers for women with high density. Despite the limitations of using program sensitivity to evaluate screening policy, it has been used for most published subgroup analyses of screening performance.

It is also important to consider whether age, hormone therapy use, and density affect the ability to detect cancers early enough to have an impact on survival. Large screen-detected cancers might have been present (as smaller, less easily detected cancers) at the time of previous screening or might have arisen in the interval since previous screening. Therefore, relatively higher detection of large cancers compared with small cancers (similar to high interval cancer risk) may indicate a need for more intensive screening.
to change policies to improve screening outcomes even when program sensitivity is high.

In this study we predict the risk of the detection of small and large screen-detected cancers and interval cancers according to age, hormone therapy use, and density. We examine the functional form of the associations between density and each cancer outcome to identify potential density cut points above which alternative approaches to screening might be considered.

Materials and Methods

Study subjects were selected from women who attended BreastScreen Victoria, a free population-based mammographic screening program for women ages $\geq 40$ y (with promotional material and direct mail invitation targeted at women ages 50-69 y). Screening is biennial and consists of two views and double reading.

The study was approved by the Human Research Ethics Committee of The Cancer Council Victoria.

Source Populations and Selection of Case Patients and Control Subjects. Cancer cases and controls without cancer were selected from two mutually exclusive source populations that were defined as women who attended:

1. First round screening between January 1, 1994 and December 31, 1995 and who reported that they had not previously had a mammogram; and
2. Subsequent (second or later round) screening between January 1, 1995 and December 31, 1996.

As the program is targeted at asymptomatic women without a personal history of breast cancer, we excluded women with a personal history of breast cancer (including ductal carcinoma in situ) and significant breast cancer symptoms (breast lump not examined by a doctor or a blood-stained or watery nipple discharge). We also excluded women $\geq 80$ y because participation in screening by this age group is extremely low.

From each source population we identified all invasive screen-detected and interval cancers. For the first round, this included 920 screen-detected and 195 interval cancers, and in the subsequent round there were 370 screen-detected and 221 interval cancers. We then randomly selected a set of controls from each source population (2,143 at first and 3,494 at subsequent rounds, equivalent to a sampling fraction of 1 in 64.65 and 1 in 30.80 for the first and the subsequent rounds, respectively).

Although cancers detected at the first round screening are prevalent cancers, for simplicity we use the term "risk" to describe the proportion of women undergoing screening who had screen-detected cancers or interval cancers, regardless of screening round.

Classification of Cancer Case Patients. We categorized invasive cancers into three groups: interval cancers and small ($\leq 15$ mm) and large (>15 mm) screen-detected cancers, in accordance with the BreastScreen Australia’s National Accreditation Standards (14). Interval cancers were defined as those that were diagnosed after a mammogram but before the next recommended screening attendance (usually 24 mo; ref. 15). They were identified by matching the BreastScreen Victoria registry with the population-based Victorian Cancer Registry using processes described previously (16). Cancer size was defined as the largest cross-sectional diameter of the dominant lesion as indicated in the pathology report.

Self-Reported Questionnaire Data. We used data from a self-administered questionnaire completed at the time of screening to categorize family history (any, none); symptoms (no symptoms or ‘other’ symptoms, defined as any breast symptom other than a breast lump and/or blood-stained or watery nipple discharge); and current hormone therapy use (yes, no). Age at the time of screening was categorized into the following age groups (40-49, 50-54, 55-59, 60-64, 65-69, and 70-79 y). Five-year age groups were used for the 50- to 69-y-old women as this is the target age group for screening and there were sufficient numbers of cases and controls for analysis.

Measurement of Density. Density was measured using a computer-assisted method described in detail elsewhere (8) using four observers, previously shown to have good inter-rater reliability (8). Density measures from the cancer-affected breast were used for case subjects except for the 9% of cases where there was no image of the affected breast and for whom the image of the contralateral breast was used instead. For control subjects, one breast image was randomly selected for measurement.

Statistical Analysis. We limited statistical analyses to cases and controls for whom the following information was complete: density, histologic size, hormone therapy use, family history, and symptoms.

We tested for differences between the distributions of density according to hormone therapy use and case status (using the Wilcoxon rank-sum test) and according to age group (using Stata’s nptrend test for trend across ordered groups, which is an extension of the Wilcoxon rank-sum test for comparison across ordered groups; ref. 17).

Density was analyzed as both a categorical and a continuous variable. For the categorical variable, density was partitioned into six categories defined by the four lowest quintiles and the upper two deciles. The upper quintile was divided into two deciles because Boyd et al. (13) found that associations with density were strongest at very high levels of density. The lowest quintile was used as the reference category. We used unconditional logistic regression to estimate associations with age, categorical density, and hormone therapy use for small and large screen-detected cancers and for interval cancers. We tested for interactions between screening round (first or subsequent) and each of the variables in the regression models (density, age, hormone therapy use, family history, and symptoms) to determine whether analyses should be stratified by screening round. There were no statistically significant interactions (likelihood-ratio tests: $P$ values ranging from 0.15 to 0.99), so we combined first and subsequent round data in a single regression model and included a covariate for round.

We analyzed the continuous density variable using a nonparametric smoothing method (cubic splines) to explore the functional form of the dose-response relationships between density and cancer detection. We used multivariable cubic regression splines (miros command in Stata) and followed the procedures outlined by Royston and Sauerbrei (2007; ref. 18); that is, we fitted density as...
both a linear and a log term, and assessed the goodness of fit using the Akaike’s information criterion. The goodness of fit was similar for untransformed density and the natural logarithm of density, so linear models are reported. As the splines were used as a descriptive tool, we set α at 0.2 (P = 0.2) to privilege description over hypothesis testing. Age was fitted as a continuous linear term in these models.

To predict the risk of small and large screen-detected cancers and interval cancers according to density, age, and hormone use, we adjusted the regression estimates according to the sampling fraction of the control set. We used the predicted values to calculate the risk differences between subgroups (based on age group, hormone therapy use, and density percentiles) for each outcome. When calculating risk differences between the subgroups of age, hormone therapy use, and density, we held constant the other key variables as: 60 to 64 y of age, non–hormone therapy users, and in the 3rd quintile of density. For example, the risk difference for small screen-detected cancers at first round between ages 60-64 y and 40-49 y is for women not using hormone therapy with density in the 3rd quintile of the density distribution.

From the analysis of the continuous measure of density, we plotted the predicted risk according to density, round, and outcome for women ages 60 y, not using hormone therapy, with no symptoms, and with no family history. The X-axis in these graphs is the percentile of density rather than the actual density measurement to show variation in risk according to density as it is distributed in the screened population.

Analyses were conducted in Stata 8.2 (17).

### Results

We excluded all 623 subjects with missing data for any of the variables in the regression models, leaving 2,918 first round subjects (426 small and 260 large screen-detected cancers, 180 interval cancers, and 2,052 control subjects) and 3,802 subsequent round subjects (257 small and 91 large screen-detected cancers, 190 interval cancers, and 3,264 control subjects).

### Description of Sample

Table 1 shows the distribution of density for each of the variables in the regression model.

Density decreased with age (P < 0.001) and was higher for hormone therapy users (P < 0.001) and for women who had interval or screen-detected cancers (P < 0.001 at first round and P = 0.02 at subsequent rounds). Supplementary Table S1 provides a more detailed cross-tabulation of the primary predictor variables of interest: density, age, and use of hormone therapy.

### Logistic Regression Analysis of Categorical Variables

Table 2 shows the results of logistic regression modeling. Density was associated with large cancers and interval cancers, but not small cancers. We found no evidence of association between small screen-detected cancers and density, the odds ratios (OR) being close to 1 for all categories of density. The risk of large screen-detected cancers was elevated for all density categories compared with the lowest quintile but the ORs were similar (3.5-4.2) for the highest four categories (3rd quintile and above). The risk of interval cancers increased monotonically from the lowest quintile to the highest decile of density, with women in the highest decile having nearly five times the risk of interval cancer.

### Table 1. Distribution of density according to age, use of hormone therapy, family history, symptom status, screening round, and case or control status

<table>
<thead>
<tr>
<th>Density group*</th>
<th>Q1 (≤2.1%)</th>
<th>Q2 (2.1%, 6.3%)</th>
<th>Q3 (6.3%, 14.0%)</th>
<th>Q4 (14.0%, 26.5%)</th>
<th>D9 (26.5%, 37.0%)</th>
<th>D10 (&gt;37.0%)</th>
<th>Total 0-100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent density values†</td>
<td>1,228 (18.3)</td>
<td>1,345 (20.0)</td>
<td>1,380 (20.5)</td>
<td>1,406 (20.9)</td>
<td>676 (10.1)</td>
<td>685 (10.2)</td>
<td>6,720 (100.0)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>(n = 599)</td>
<td>7.5</td>
<td>8.9</td>
<td>15.7</td>
<td>19.5</td>
<td>20.5</td>
<td>27.9</td>
</tr>
<tr>
<td>50-54</td>
<td>(n = 1,265)</td>
<td>11.1</td>
<td>14.9</td>
<td>19.6</td>
<td>25.2</td>
<td>13.0</td>
<td>16.3</td>
</tr>
<tr>
<td>55-59</td>
<td>(n = 1,369)</td>
<td>17.0</td>
<td>18.2</td>
<td>21.0</td>
<td>22.5</td>
<td>10.6</td>
<td>10.7</td>
</tr>
<tr>
<td>60-64</td>
<td>(n = 1,285)</td>
<td>20.2</td>
<td>22.9</td>
<td>22.4</td>
<td>20.9</td>
<td>8.1</td>
<td>5.5</td>
</tr>
<tr>
<td>65-69</td>
<td>(n = 1,289)</td>
<td>25.1</td>
<td>25.5</td>
<td>20.0</td>
<td>18.2</td>
<td>6.6</td>
<td>4.6</td>
</tr>
<tr>
<td>70-79</td>
<td>(n = 913)</td>
<td>24.9</td>
<td>25.5</td>
<td>22.3</td>
<td>17.3</td>
<td>6.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Hormone therapy use (current)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>(n = 5,149)</td>
<td>20.7</td>
<td>21.5</td>
<td>21.3</td>
<td>19.7</td>
<td>8.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Yes</td>
<td>(n = 1,571)</td>
<td>10.4</td>
<td>15.2</td>
<td>18.2</td>
<td>25.0</td>
<td>14.8</td>
<td>16.5</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>(n = 6,130)</td>
<td>18.5</td>
<td>20.0</td>
<td>20.6</td>
<td>20.7</td>
<td>10.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Any</td>
<td>(n = 590)</td>
<td>15.8</td>
<td>20.0</td>
<td>19.7</td>
<td>23.2</td>
<td>9.7</td>
<td>11.7</td>
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<tr>
<td>Symptoms</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>(n = 6,349)</td>
<td>18.7</td>
<td>20.0</td>
<td>20.6</td>
<td>20.7</td>
<td>10.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Yes</td>
<td>(n = 371)</td>
<td>11.6</td>
<td>19.7</td>
<td>20.0</td>
<td>25.6</td>
<td>10.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Screening round</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalent</td>
<td>(n = 2,918)</td>
<td>19.4</td>
<td>19.5</td>
<td>20.2</td>
<td>20.8</td>
<td>10.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Subsequent</td>
<td>(n = 3,802)</td>
<td>17.4</td>
<td>20.4</td>
<td>20.8</td>
<td>21.0</td>
<td>10.1</td>
<td>10.3</td>
</tr>
<tr>
<td>Case/control status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>(n = 1,394)</td>
<td>14.1</td>
<td>19.2</td>
<td>22.2</td>
<td>23.5</td>
<td>10.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Controls</td>
<td>(n = 5,316)</td>
<td>19.4</td>
<td>20.2</td>
<td>20.1</td>
<td>20.2</td>
<td>10.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*Q1-Q4 represent quintile groups 1 to 4, and D9 and D10 represent decile groups 9 and 10.
†Distribution of density groups is weighted by control sampling fraction—this means, as expected, there is an over-representation of denser breasts in the actual sample available for analysis.
than women in the lowest quintile [OR 4.65; 95% confidence interval (95% CI), 2.96-7.31].

Age was associated with small and large cancers but not interval cancers. The risk of small and large screen-detected cancers increased monotonically with age. In particular, women ages 70 to 79 years had substantially increased risk of both small and large screen-detected cancers (small: OR, 4.45; 95% CI, 2.92-6.80; and large: OR, 3.08-4.97). We found no evidence of association with density (approximately 6% percent density; Table 1) and a 4-fold increase of large cancer detection. The lack of association between density and small cancer detection, but the risk of large cancer detection rose until approximately the 40th percentile of density (approximately 6% percent density; Table 1) and then leveled off. Interval cancers increased with increasing density but they seemed to increase more dramatically after the 40th percentile.

Discussion

Principal Findings

Increasing density was associated with an increased risk of cancers associated with relatively poor prognosis (large screen-detected and interval cancers) whereas the risk of cancers with a better prognosis (small screen-detected cancers) was unrelated to density. Women in the highest decile of density had a nearly 5-fold increased risk of interval cancer when compared with those in the lowest quintile, and a 4-fold increase of large cancer detection. The lack of association between density and small cancer detection at screening is likely to be a consequence of the “masking” of small tumors in dense breasts (19).

These findings imply that strategies that reduce the risk of interval cancers for women with higher density are likely to achieve considerable improvements in the effectiveness of the mammographic screening program. Because the risk of interval cancer increases monotonically with density (even women in the 3rd quintile of density but they seemed to increase more dramatically after the 40th percentile).
density have double the risk of those in the 1st quintile), there is no obvious cutoff point at which to target additional screening strategies according to density. Therefore, decisions regarding the optimal threshold for targeting should be made in the context of available resources and the relative costs of the various screening strategies.

The other critical findings from these analyses relate to age. After adjusting for density and hormone therapy use, increasing age was associated with an increased risk of both small and large screen-detected cancers, but was not associated with the risk of interval cancers. This suggests that more intensive screening or alternative screening modalities for women ages 40 to 49 years to improve screening may not be justified once density and hormone therapy use are taken into account. We also found that women ages 70 to 79 years are at considerably increased risk of screen-detected cancers; for example, we estimate that for women of this age group in the 3rd quintile of density and not taking hormone therapy, there are an additional 23 small screen-detected cancers per 10,000 compared with 40- to 49-year-olds at subsequent rounds’ screening. If these high levels of detection for women ages 70 to 79 years translated into improved survival, population-based screening for these older women may be beneficial.

After adjusting for density and age, hormone therapy use was associated with only a moderately increased risk of interval cancers, leading to an additional 7 cancers per 10,000 women at first round and 4 at the subsequent round for women ages 60 to 64 years and in the 3rd quintile of density. As these differences are small, there are unlikely to be large population benefits from targeting women using hormone therapy, over and above a focus on density and age.

Table 3. Estimates of differences in predicted rates of small (≤15 mm) and large (>15 mm) screen-detected (SD) and interval cancers per 10,000 women by screening round according to density, age group, and hormone therapy use

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Small SD</th>
<th>Large SD</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First round</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 vs Q1</td>
<td>10.9</td>
<td>28.9</td>
<td>7.9</td>
</tr>
<tr>
<td>D10 vs Q1</td>
<td>−1.1</td>
<td>25.8</td>
<td>29.0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79 y vs 40-49 y</td>
<td>66.1</td>
<td>54.5</td>
<td>0.7</td>
</tr>
<tr>
<td>60-64 y vs 40-49 y</td>
<td>39.9</td>
<td>25.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Hormone therapy (HT) use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT user vs nonuser</td>
<td>−7.2</td>
<td>−5.7</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Subsequent rounds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 vs Q1</td>
<td>3.8</td>
<td>5.7</td>
<td>4.8</td>
</tr>
<tr>
<td>D10 vs Q1</td>
<td>−0.4</td>
<td>5.1</td>
<td>17.8</td>
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<td>Age</td>
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<td></td>
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</tr>
<tr>
<td>70-79 y vs 40-49 y</td>
<td>22.7</td>
<td>10.8</td>
<td>0.5</td>
</tr>
<tr>
<td>60-64 y vs 40-49 y</td>
<td>13.7</td>
<td>5.1</td>
<td>0.4</td>
</tr>
<tr>
<td>HT use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT user vs nonuser</td>
<td>−2.7</td>
<td>−1.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

NOTE: Except where otherwise specified (i.e., for the subgroups being compared), these results pertain to women ages 60-64 y, non–hormone therapy users, in 3rd quintile of density (Q3), with no family history, and with no symptoms.

**Strengths and Weaknesses.** This study has three important strengths. First, rather than using screening program sensitivity to measure screening program performance, we considered the risk of screen-detected and interval cancers separately. Second, we examined the risk of screen-detected cancers by size. Hence, we provide a unique picture of the prognosis of screen-detected cancers by age, hormone therapy, and density. Our approach enabled us to identify the groups of women for whom improved screening performance might produce the greatest absolute benefit (i.e., women with higher density). Further, because our study is large and density was estimated using a continuous, reliable, and well-validated measure (3), we were able to explore the functional form of the association between density and the related risk of screen-detected and interval cancers, which minimized our a priori assumption about what constitutes ‘high density.’ This revealed that there is no clear ‘high density’ group, and that many effects increase incrementally with increasing density.

The study has a number of limitations, including the lack of information on menopausal status (because this is associated with age, density, and hormone therapy use) and the use of only one tumor prognostic indicator, namely size, as a proxy for prognosis. Other indicators of tumor aggressiveness such as grade should be investigated.

**Unanswered Questions and Future Research.** The most cost-effective approach to screening women with higher density is yet to be determined. Possibilities include more frequent screening or the introduction of alternative or additional screening modalities (such as ultrasound, magnetic resonance imaging, or digital mammography). Small studies on ultrasound and mammography together suggest that the addition of ultrasound improves sensitivity for women with dense breasts (20, 21) but specificity is lower (22). The American College of Radiology Imaging Network study is conducting a randomized controlled trial of combined ultrasound and mammography for women classified by the Breast Imaging-Reporting and Data System classification as having heterogeneously dense or extremely dense breasts (approximately 40% of women ages ≥40 years; ref. 7, 23); the results of this study will be extremely important in informing future policy for screening women with higher density.

Digital mammography seems to have higher sensitivity for women with high density (24), but this also requires further investigation. Magnetic resonance imaging improves the sensitivity of screening for women who have a high familial or genetic risk of breast cancer (25), and it is possible that it may be a better screening modality for women with higher density; its drawback is that it is expensive, uncomfortable, and has a high false-positive rate (25).

Increases in the cost of screening can be anticipated from more intensive screening of women with high density. These costs relate to increased requirements for equipment and workforce, as well as the costs of managing the expected increase in false-positive screens. If the efficacy of alternative screening approaches is established, then cost-effectiveness analyses will be required to assess whether they should be introduced.
Figure 1. Predicted rates of small (≤15 mm) and large (>15 mm) screen-detected cancers and interval cancers according to screening round, for women aged 60 y, not using hormone therapy, with no symptoms, and no family history of breast cancer.
for population-based screening programs. To offset any increases in cost, less frequent screening of women with lower density (perhaps the 30th percentile or lower) should also be tested in a clinical trial.

Summary. Our study shows that although increasing density is associated with the increased risk of large and interval cancers, density is unrelated to the risk of small screen-detected cancers. These findings suggest that considerable improvements in the effectiveness of the screening program could be achieved if density is used to identify women most likely to have poor screening outcomes. Although age and hormone therapy use are predictors of program sensitivity and breast cancer risk, our regression analyses which adjusted for density suggest that there would be little additional benefit from targeting screening programs based on these variables.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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