Mammographic Density and the Risk and Detection of Breast Cancer


ABSTRACT

BACKGROUND
Extensive mammographic density is associated with an increased risk of breast cancer and makes the detection of cancer by mammography difficult, but the influence of density on risk according to method of cancer detection is unknown.

METHODS
We carried out three nested case–control studies in screened populations with 1112 matched case–control pairs. We examined the association of the measured percentage of density in the baseline mammogram with risk of breast cancer, according to method of cancer detection, time since the initiation of screening, and age.

RESULTS
As compared with women with density in less than 10% of the mammogram, women with density in 75% or more had an increased risk of breast cancer (odds ratio, 4.7; 95% confidence interval [CI], 3.0 to 7.4), whether detected by screening (odds ratio, 3.5; 95% CI, 2.0 to 6.2) or less than 12 months after a negative screening examination (odds ratio, 17.8; 95% CI, 4.8 to 65.9). Increased risk of breast cancer, whether detected by screening or other means, persisted for at least 8 years after study entry and was greater in younger than in older women. For women younger than the median age of 56 years, 26% of all breast cancers and 50% of cancers detected less than 12 months after a negative screening test were attributable to density in 50% or more of the mammogram.

CONCLUSIONS
Extensive mammographic density is strongly associated with the risk of breast cancer detected by screening or between screening tests. A substantial fraction of breast cancers can be attributed to this risk factor.
The radiographic appearance of the breast varies among women because of differences in tissue composition and differences in the radiographic attenuation properties of fat, stroma, and epithelium. Fat is radiographically lucent and appears dark on a mammogram. In contrast, epithelium and stroma are radiographically dense and look light, an appearance we refer to as mammographic density. In 1976, Wolfe described an association between a qualitative classification of mammographic densities and the risk of breast cancer, and now substantial literature shows that more extensive density is associated with an increased risk of breast cancer. Women with dense tissue in 75% or more of the breast have a risk of breast cancer four to six times as great as the risk among women with little or no dense tissue.

Extensive mammographic density may also make breast cancer more difficult to detect by mammography and thus increases the risk of the development of cancer between mammographic screening tests. Because density influences the detection of cancer, estimates of the risk of breast cancer associated with mammographic density may be distorted. Risk may be underestimated if it is based solely on cancers found at screening, because cancers masked by dense tissue will be omitted. However, risk may be overestimated if it is based only on cancers found by means other than screening, because cancers not detected by screening will be overrepresented.

Whitehead et al., using data from the 1970s, showed that a masking effect of density did exist but that it operated in addition to differences in the risk of breast cancer related to the classification of breast patterns described by Wolfe. Other studies have reached similar conclusions but have had short periods of follow-up or have not distinguished between breast cancers detected by screening and those detected by methods other than screening. There are, therefore, few data that allow an examination of the extent to which mammographic density, assessed quantitatively and using modern mammography, influences the risk of breast cancer at screening, between screening examinations, or over time.

The purpose of this study was to describe the association between mammographic density in the baseline mammogram and the subsequent risk of breast cancer. We studied the association according to the method of cancer detection and over time.

### METHODS

**SCREENED POPULATIONS**

We used data from three nested case–control studies carried out in populations that were screened with the use of mammography. The National Breast Screening Study (NBSS) was a randomized trial of screening with mammography and physical examination. The Screening Mammography Program of British Columbia (SMPBC) uses

<table>
<thead>
<tr>
<th>Variable</th>
<th>National Breast Screening Study</th>
<th>Ontario Breast Screening Program</th>
<th>Screening Mammography Program of British Columbia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years during which incident cancers were selected for the present study</td>
<td>1981–1990</td>
<td>1993–1998</td>
<td>1993–1999</td>
</tr>
<tr>
<td>No. of first examinations in the selected years</td>
<td>45,000</td>
<td>166,254</td>
<td>254,082</td>
</tr>
<tr>
<td>Method of recruitment</td>
<td>Self-referral</td>
<td>Letter of invitation, referral by physician, or self-referral</td>
<td>Letter of invitation, referral by physician, or self-referral</td>
</tr>
<tr>
<td>No. of centers</td>
<td>15</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Age range for screening (yr)</td>
<td>40–59</td>
<td>50–69</td>
<td>40–70</td>
</tr>
<tr>
<td>Frequency of screening</td>
<td>Annual</td>
<td>Every 2 yr</td>
<td>Annual</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 2. Selected Characteristics of the Subjects.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>National Breast Screening Study (NBSS) (N = 330 pairs)</th>
<th>Ontario Breast Screening Program (OBSP) (N = 386 pairs)</th>
<th>Screening Mammography Program of British Columbia (SMPBC) (N = 398 pairs)</th>
<th>Combined (N = 1114 pairs)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>49.7±5.6</td>
<td>49.7±5.6</td>
<td>61.0±7.0</td>
<td>61.0±7.0</td>
<td>58.2±9.9</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>25.0±4.2</td>
<td>25.5±4.6</td>
<td>25.3±4.4</td>
<td>25.0±4.0</td>
<td>24.6±4.0</td>
</tr>
<tr>
<td>Age at menarche — yr‡</td>
<td>12.8±1.5</td>
<td>12.9±1.5</td>
<td>12.9±1.5</td>
<td>13.1±1.6</td>
<td>12.9±1.5</td>
</tr>
<tr>
<td>Age at first birth — yr§</td>
<td>25.2±4.7</td>
<td>24.7±4.4</td>
<td>24.1±4.5</td>
<td>24.1±4.2</td>
<td>25.0±4.9</td>
</tr>
<tr>
<td>Parous — %</td>
<td>77.6</td>
<td>85.8</td>
<td>85.5</td>
<td>89.9</td>
<td>88.4</td>
</tr>
<tr>
<td>No. of live births¶</td>
<td>2.3±1.9</td>
<td>2.7±2.0</td>
<td>2.8±1.9</td>
<td>2.8±1.8</td>
<td>2.3±1.4</td>
</tr>
<tr>
<td>Yr from last pregnancy to entry‖</td>
<td>NA</td>
<td>NA</td>
<td>29.7±7.9</td>
<td>30.0±6.8</td>
<td>28.3±9.5</td>
</tr>
<tr>
<td>Postmenopausal — %</td>
<td>60.0</td>
<td>61.5</td>
<td>86.5</td>
<td>89.4</td>
<td>75.4</td>
</tr>
<tr>
<td>Age at menopause — yr (95% CI)**</td>
<td>50.9 (50.5–51.7)</td>
<td>50.1 (49.5–51.3)</td>
<td>51.2 (50.8–51.7)</td>
<td>50.1 (49.4–51.0)</td>
<td>50.6</td>
</tr>
<tr>
<td>Ever used hormone-replacement therapy — %</td>
<td>30.6</td>
<td>30.6</td>
<td>40.7</td>
<td>36.3</td>
<td>35.2</td>
</tr>
<tr>
<td>Breast cancer in no. of first-degree relatives — %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>82.4</td>
<td>86.7</td>
<td>78.2</td>
<td>85.5</td>
<td>77.9</td>
</tr>
<tr>
<td>1</td>
<td>15.5</td>
<td>13.3</td>
<td>20.0</td>
<td>12.7</td>
<td>18.3</td>
</tr>
<tr>
<td>2 or more</td>
<td>2.1</td>
<td>0</td>
<td>1.8</td>
<td>1.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Percent density</td>
<td>36.4±21.7</td>
<td>28.4±21.2</td>
<td>28.8±18.3</td>
<td>24.3±17.5</td>
<td>33.3±18.7</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters. NA denotes not available.
† P values are for the comparisons between case patients and controls in the combined category. P value for age at menopause is based on the log-rank test, for symmetrically distributed variables is based on the paired t-test, for nonsymmetrically distributed variables is based on the Wilcoxon rank-sum test, and for categorical variables is based on the Mantel–Haenszel chi-square test. All tests are two-sided.
‡ There were 328 pairs in the NBSS, 369 in the OBSP, 387 case patients and 393 control subjects in the SMPBC, and 1084 case patients and 1090 controls in the combined group.
§ There were 256 case patients and 283 controls in the NBSS, 325 case patients and 343 controls in the OBSP, 351 case patients and 355 controls in the SMPBC, and 912 case patients and 981 controls in the combined group.
¶ There were 385 case patients in the OBSP, and 1113 in the combined group.
‖ There were 326 case patients and 343 controls in the OBSP, 351 case patients and 355 controls in the SMPBC, and 677 case patients and 698 controls in the combined group.
** Median age at menopause and 95% confidence interval (CI) are from Kaplan–Meier estimates. There were 318 pairs in the NBSS, 323 case patients and 336 controls in the OBSP, 351 case patients and 344 controls in the SMPBC, and 992 case patients and 998 controls in the combined group.
mammography as the only method of screening at its screening centers, and the Ontario Breast Screening Program (OBSP) uses mammography and physical examination as its methods of screening. Selected characteristics of the three screening programs included in this study are shown in Table 1. The study was approved by the ethics committees at the University of Toronto, the University Health Network (Toronto), the OBSP, and the University of British Columbia.

Selection of subjects

For the OBSP and the SMPBC, lists were prepared of subjects with histologically verified invasive breast cancer that was diagnosed from 1993 through 1998 for the OBSP and from 1993 through 1999 for the SMPBC. Subjects who had a diagnosis of breast cancer less than 12 months after their first screening examination were excluded. For each case of breast cancer, the method of detection (screening or other means) was determined by each program, independent of this study, and was based on the active follow-up of women in whom abnormalities had been found. In addition, each program periodically carried out linkage with provincial and national cancer registries to identify breast cancers that were diagnosed in subjects in whom breast cancer had not been detected at screening.

Written informed consent for research applications using the data collected at entry to the NBSS had been obtained at entry to the NBSS. All 354 patients in whom invasive breast cancer was diagnosed between 1981 and 1990 and their matched controls were included.

Table 3. Mammographic Density and Risk of Breast Cancer According to Method of Detection.*

<table>
<thead>
<tr>
<th>Mammographic Density</th>
<th>All Methods of Detection†</th>
<th>Detection by Screening</th>
<th>Detection &lt;12 Mo after Negative Screening</th>
<th>Detection ≥12 Mo after Negative Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case (N = 1112)</td>
<td>Control (N = 1112)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>230</td>
<td>362</td>
<td>1.0</td>
<td>173</td>
</tr>
<tr>
<td>10 to &lt;25%</td>
<td>272</td>
<td>270</td>
<td>1.8 (1.4–2.2)</td>
<td>171</td>
</tr>
<tr>
<td>25 to ≤50%</td>
<td>236</td>
<td>290</td>
<td>2.1 (1.6–2.6)</td>
<td>219</td>
</tr>
<tr>
<td>50 to &lt;75%</td>
<td>178</td>
<td>144</td>
<td>2.4 (1.8–3.3)</td>
<td>102</td>
</tr>
<tr>
<td>≥75%</td>
<td>96</td>
<td>46</td>
<td>4.7 (3.0–7.4)</td>
<td>52</td>
</tr>
<tr>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Odds ratios are adjusted for age, body-mass index, age at menarche, parity, number of live births, age at first birth, menopausal status, age at menopause, hormone-replacement therapy (ever or never), breast cancer in first-degree relatives (0, 1, or 2 or more), study (NBSS, OBSP, or SMPBC), and observation time (1 to ≤2 years, >2 to ≤4 years, or >4 years). CI denotes confidence interval.
† Nine pairs were excluded from the group analysis because of missing information on detection (one subject) or on the date of the last mammogram (eight subjects).
‡ P values are for the Cochran–Armitage test for trend.
Data Collection
In the NBSS, information about risk factors for breast cancer was obtained by self-administered questionnaire at the time of study entry. For the other two programs, information was collected by self-administered questionnaire at the time of recruitment into the present study. Information about demographic characteristics, use (including the date started and duration of use) or nonuse of hormone therapy, and menstrual and reproductive risk factors was collected with reference to the time of the first screening mammogram.

Assessment of Mammographic Density
Mammographic density was assessed independently by radiologists and by a computer-assisted method. Two radiologists who had previously classified density each read approximately half the mammograms. The craniocaudal view of the unaffected breast of case patients and the corresponding image of matched control subjects were read in sets of 100 images on a multiviewer, in random order, without knowledge of case or control status. Each image was placed into one of six categories of density (0%, <10%, 10 to <25%, 25 to <50%, 50 to <75%, and ≥75%) that have been used in previous work. Ten percent of each set was reread by each radiologist, and both radiologists read a further 10%. The reliability of each reader was 0.73 to 0.89, and reliability between readers was 0.68.

The same craniocaudal images that were read by the radiologists were digitized with the use of a Lumisys 85 digitizer (Lumisys) and measured by one observer using a computer-assisted technique described elsewhere. The mammograms were read in sets of approximately 120, including equal numbers of randomly ordered case patients and control subjects, by the same observer, who was unaware of case or control status or of the classifications made by the radiologists. A random sample of 10% of the images was reread, within and between each set, and reproducibility was 0.94 both within sets and between sets.

Statistical Analysis
Of the 1209 case–control pairs we recruited, 95 were excluded because of missing data (NBSS, 24; OBSP, 34; SMPBC, 37), leaving a total of 1114 matched case–control pairs for analysis. The radiologists did not classify 2 case patients, so their results have 1112 case–control pairs.

We compared selected characteristics of the

<table>
<thead>
<tr>
<th>Table 4. Risk of Breast Cancer Associated with the Percentage of Mammographic Density According to Time since Study Entry.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of Detection</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Screening</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Other</td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>All§</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* The beta coefficient refers to the increase in risk for each of the five categories of density in the radiologists’ classification (<10%, 10 to <25%, 25 to <50%, 50 to <75%, and ≥75%).
† The odds ratios compare the highest percentage of density (≥75%) with the lowest percentage of density (<10%) and are calculated by the following formula: odds ratio = e^β, where e is the mathematical constant that is the base of natural logarithms, and n the number of categories. Analysis was carried out on a matched-pair data set and adjusted for body-mass index, age at menarche, parity, number of live births, age at first birth, menopausal status, age at menopause, hormone-replacement therapy (ever or never), and breast cancer in first-degree relatives (0, 1, or 2 or more).
‡ P values are for the test for β = 0.
§ One pair was excluded from the group analysis because of missing information on detection.

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case and control subjects, using paired t-tests for symmetrically distributed continuous variables, Wilcoxon rank-sum tests for continuous variables with skewed distributions, and Mantel–Haenszel chi-square tests for categorical variables. All P values were calculated from two-tailed tests of statistical significance.

We examined the association of mammographic density with the risk of breast cancer, using logistic regression. We used logistic regression to analyze unmatched data and conditional logistic regression to analyze matched data. The categories of density of 0% and less than 10% were combined because of small numbers in some categories after the data were divided according to method of cancer detection. An increase in risk associated with greater density was tested by the Cochran–Armitage test for trend. For the computer-assisted method, the percentage of mammographic density was modeled as a continuous variable. All analyses were adjusted for other risk factors for breast cancer. Attributable risk was calculated with the use of the following formula: attributable risk = \( (RR - 1)P_c(\frac{e^{RR}}{RR}) \), where RR denotes relative risk of greater than 50%, and \( P_c \) prevalence of density of greater than 50% in case patients.

RESULTS

The results shown are for the classifications by the radiologists. Matched and unmatched results for the two readers were very similar to the unmatched results, and most results shown are unmatched, since these are easier to display. Matched results for both radiologists and the computer-assisted measure are shown in the tables in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

CHARACTERISTICS OF THE SUBJECTS

Table 2 shows selected characteristics of case patients and control subjects for the three screening programs. Earlier age at menarche, later age at first birth, nulliparity, a smaller number of live births, later age at menopause, a family history of breast cancer, and use of hormone therapy were all more frequent among patients with breast cancer than among control subjects. The average percentage of mammographic density in the baseline mammogram was 5.8 percentage points greater in case patients than in controls.

Table 3 shows the distribution of case patients and control subjects in the combined studies according to the percentage of mammographic density and the method of detection. Odds ratios from unmatched analyses were adjusted for age, body-mass index, age at menarche, parity, number of live births, age at first birth, menopausal status, age at menopause, hormone-replacement therapy (ever or never), breast cancer in first-degree relatives (0, 1, or 2 or more), study (NBSS, OBSP, or SMPBC), and observation time (1 to ≤2 years, >2 to ≤4 years, or >4 years). When those who had less than 10% mammographic density were compared with those who had 75% or more, the odds ratio was 17.8 (95% confidence interval [CI], 10.7 to 29.7) for cancers detected by screening, the odds ratio was 17.8 (95% CI, 10.7 to 29.7) for cancers detected by screening 12 months or more after the last screening examination, and the odds ratio for the risk of breast cancer in those with density of 75% or more was 17.8 (95% CI, 10.7 to 29.7) for cancers detected 12 months or more after the last screening examination, and the odds ratio for the risk of breast cancer in those with density of 75% or more was 17.8 (95% CI, 10.7 to 29.7).

Similar results were seen in each of the three screening programs. The odds ratios for 75% or more density as compared with 10% or less for all cancers were 5.7 (95% CI, 2.8 to 11.3) for the NBSS, 3.4 (95% CI, 1.1 to 10.3) for the OBSP, and 4.5 (95% CI, 1.9 to 11.0) for the SMPBC (data not
Matched analyses for both the radiologists and the computer-assisted measure of density gave similar results (see Tables 1 and 2 in the Supplementary Appendix).

Table 4 shows the risk of breast cancer in the combined data according to mammographic density (as shown).
classified by radiologists), method of detection of breast cancer, and number of years after entry into the screening programs, grouped into three time periods. Percentage of density was associated with an increased risk of breast cancer in all categories of detection and at all time periods, up to 8 years after entry. However, for breast cancers detected by methods other than screening, risk was notably higher in the first 2 years after the first screening examination. The continuous computer-assisted measure showed a higher percentage of density in the baseline mammograms of women in whom breast cancer later developed, as compared with women in whom no breast cancer developed, regardless of whether the cancer was detected by screening or by methods other than screening, up to 8 years after entry (Fig. 1).

MAMMOGRAPHIC DENSITY AND ATTRIBUTABLE RISKS OF BREAST CANCER

Table 5 shows the prevalence of a mammographic density of 50% or more and the associated relative and attributable risks of breast cancer for each category of cancer detection. The attributable risks of breast cancer, which assume causality, for a mammographic density of 50% or more were 16% for all cancers, 12% for cancers detected by screening, 40% for cancers detected less than 12 months after a negative screening test, and 16% for cancers detected 12 months or more after a screening examination.

For women below the median age of 56 years, the prevalence of mammographic density of 50% or more was about three times as great as the prevalence in older women in each category of detection, and the attributable risks of breast cancer were 26% for all cancers, 21% for cancers detected by screening, 50% for cancers detected less than 12 months after a negative screening examination, and 28% for cancers detected 12 months or more after a screening examination.

**DISCUSSION**

Our results showed that after adjustment for other risk factors, extensive mammographic density was strongly and reproducibly associated with an increased risk of breast cancer, regardless of whether the cancer was detected by screening or other means. We also found that this increased risk persisted for an extended period of time. Calculations of attributable risk showed that mammographic density accounted for a substantial proportion of cases of breast cancer, particularly in younger women, in whom 26% of all breast cancers and 50% of cancers detected less than 12 months after a negative screening examination were associated with density in 50% or more of the mammogram.

The marked increase in the risk of breast cancer associated with extensive mammographic density up to 12 months after screening is probably due to cancers that were present at the time of screening but were not detected because of masking by dense breast tissue. Calculation of the risk of breast cancer associated with mammographic density that includes only screen-detected cancers will thus underestimate the true risk, because cancers that are masked by density are omitted. However, risk estimates based on cancers detected up to 12 months after screening will overestimate risk, because cancers that were present but not detected at screening (because of masking by density) will be overrepresented. The annual incidence of breast cancer associated with mammographic density is thus best estimated with these data by combining cancers that were detected by screening with those that were diagnosed up to 12 months after a screening examination. The risk of breast cancer associated with mammographic density 12 months or more after a screening examination was similar to the overall risk.

It is unlikely that bias, confounding, or chance can explain these results. Measurement of mammographic density was made by two independent methods, without knowledge of the status of case patients or control subjects, and similar results were obtained in each of three separate populations. In the NBSS, all eligible case patients had mammograms and other data available, but not all eligible case patients in the OBSP and the SMPBC participated. However, differences in the percentage of density between case patients and controls, and the associated risks of breast cancer, were similar in each of the three populations and similar to risk estimates found by others who used quantitative methods to classify density. It is unlikely that bias, confounding, or chance can explain these results.

Recall bias might influence information about nonmammographic risk factors obtained after the diagnosis of breast cancer in the OBSP and the SMPBC. However, in the NBSS, data collection occurred before the diagnosis of breast cancer. The distribution of nonmammographic risk factors...
was similar in each of the three populations. We also observed the expected effects on risk of breast cancer of most known risk factors. Recall bias affecting risk factors in the OBSP and the SMPBC is thus unlikely.

Other studies have shown that mammographic density is associated with an increased risk of breast cancer at screening and in the intervals after a negative mammographic examination.\textsuperscript{23,24} However, some of these studies have been based on older methods of mammography than those we used, have used qualitative classifications of density, or have not adjusted risk estimates for covariates.\textsuperscript{12-14}

Among women with extensive mammographic density, the extent to which the markedly increased risk of breast cancer up to 12 months after a negative screening examination is due to masking or to the rapid growth of tumors in dense breasts is unknown.\textsuperscript{23-28} Density may mask nonpalpable cancers presenting on mammography as a mass or architectural distortion but is less likely to mask calcification, which is present in about 40% of cancers.\textsuperscript{29,30} Mammography was the only screening method in the SMPBC and the method by which 88% of cancers were detected at screening in the OBSP.\textsuperscript{31} In the NBSS, 75% of cancers were detected by mammography alone or in combination with physical examination.\textsuperscript{15,16}

Because the increase, by a factor of 17, in the risk of breast cancer associated with extensive mammographic density is apparently limited to the 12 months after a screening examination, masking — rather than rapid growth — seems likely to be the principal mechanism at work. These results further suggest that annual screening examinations in women with extensive mammographic density are not likely to increase the

### Table 5. Mammographic Density and Attributable Risks of Breast Cancer.

<table>
<thead>
<tr>
<th>Age</th>
<th>Method of Cancer Detection</th>
<th>No. of Case Patients</th>
<th>No. of Control Subjects</th>
<th>Prevalence*</th>
<th>Relative Risk (95% CI)†</th>
<th>Attributable Risk‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>1112</td>
<td>1112</td>
<td>24.6</td>
<td>2.8 (2.1–3.8)</td>
<td>16.0</td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>717</td>
<td>717</td>
<td>21.5</td>
<td>2.3 (1.6–3.3)</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>Detection &lt;12 mo after negative screening</td>
<td>124</td>
<td>124</td>
<td>46.0</td>
<td>7.2 (2.7–19.1)</td>
<td>39.6</td>
</tr>
<tr>
<td></td>
<td>Detection ≥12 mo after negative screening</td>
<td>262</td>
<td>262</td>
<td>22.9</td>
<td>3.6 (1.9–6.9)</td>
<td>16.5</td>
</tr>
<tr>
<td>≤56 yr</td>
<td>All</td>
<td>561</td>
<td>561</td>
<td>37.2</td>
<td>3.3 (2.2–5.1)</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>351</td>
<td>351</td>
<td>32.5</td>
<td>2.8 (1.6–4.7)</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>Detection &lt;12 mo after negative screening</td>
<td>84</td>
<td>85</td>
<td>58.3</td>
<td>7.0 (2.1–23.5)</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>Detection ≥12 mo after negative screening</td>
<td>119</td>
<td>118</td>
<td>36.1</td>
<td>4.7 (1.7–13.2)</td>
<td>28.4</td>
</tr>
<tr>
<td>&gt;56 yr</td>
<td>All</td>
<td>551</td>
<td>551</td>
<td>11.8</td>
<td>2.5 (1.6–4.1)</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Screening</td>
<td>366</td>
<td>366</td>
<td>10.9</td>
<td>2.2 (1.2–4.0)</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>Detection &lt;12 mo after negative screening</td>
<td>40</td>
<td>39</td>
<td>20.0</td>
<td>8.2 (0.8–81.9)</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>Detection ≥12 mo after negative screening</td>
<td>143</td>
<td>144</td>
<td>11.9</td>
<td>2.9 (1.1–7.7)</td>
<td>7.8</td>
</tr>
</tbody>
</table>

* Prevalence was the prevalence of mammographic density of 50% or more in case patients.
† The relative risk refers to the relative risk of breast cancer associated with density of 50% or more as compared with the reference category (density of <10%), adjusted for age, body-mass index, age at menarche, parity, number of live births, age at first birth, menopausal status, age at menopause, hormone-replacement therapy (ever or never), breast cancer in first-degree relatives (0, 1, or 2 or more), study (NBSS, OBSP, or SMPBC), and observation time (1 to ≤2 years, >2 to ≤4 years, or >4 years). CI denotes confidence interval.
‡ We used the following formula: attributable risk = (RR−1)Pc/RR, where RR denotes relative risk of greater than 50%, and Pc prevalence of density of greater than 50% in case patients.
rate of detection of cancers; attention should be
directed to the development and evaluation of alter-
native imaging techniques for such women. Digital mammography, ultrasonography, and
magnetic resonance imaging may increase the
detection of cancer in women who have extensive
mammographic density and in whom the risk of
breast cancer, detected at screening and between
screening examinations, is greatest.

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