

ORIGINAL ARTICLE

Mammographic Density and the Risk and Detection of Breast Cancer

Norman F. Boyd, M.D., D.Sc., Helen Guo, M.Sc., Lisa J. Martin, Ph.D., Limei Sun, M.Sc., Jennifer Stone, M.Sc., Eve Fishell, M.D., F.R.C.P.C., Roberta A. Jong, M.D., F.R.C.P.C., Greg Hislop, M.D., F.R.C.P.C., Anna Chiarelli, Ph.D., Salomon Minkin, Ph.D., and Martin J. Yaffe, Ph.D.

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.

From the Campbell Family Institute for Breast Cancer Research (N.F.B., H.G., L.J.M., L.S.); the Ontario Cancer Institute (N.F.B., H.G., L.J.M., L.S., J.S., S.M.); the Departments of Radiology and Imaging Research, Women's College Hospital (E.F.) and Sunnybrook Health Sciences Centre (R.A.J., M.J.Y.); and the Ontario Breast Screening Program, Cancer Care Ontario (A.C.) — all in Toronto; and the British Columbia Cancer Agency, Vancouver (G.H.) — all in Canada. Address reprint requests to Dr. Boyd at Ontario Cancer Institute, 610 University Ave., Room 10-415, Toronto, ON M5G 2M9, Canada, or at boyd@uhnres.utoronto.ca.

N Engl J Med 2007;356:227-36.

Copyright © 2007 Massachusetts Medical Society.

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.¹ 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,^{2,3} 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.⁴⁻¹¹

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.¹²⁻¹⁴ 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,¹² 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.² Other studies have reached similar conclusions but have had short periods of follow-up¹³ or have not distinguished between breast cancers detected by screening and those detected by methods other than screening.¹⁴ 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.^{15,16} The Screening Mammography Program of British Columbia (SMPBC) uses

Table 1. Selected Characteristics of Mammographic-Screening Programs.

| Variable | National Breast Screening Study | Ontario Breast Screening Program | Screening Mammography Program of British Columbia |
|---|---------------------------------|---|---|
| Years of operation of the program | 1980–1985 | 1992–present | 1988–present |
| Years during which incident cancers were selected for the present study | 1981–1990 | 1993–1998 | 1993–1999 |
| No. of first examinations in the selected years | 45,000 | 166,254 | 254,082 |
| Method of recruitment | Self-referral | Letter of invitation, referral by physician, or self-referral | Letter of invitation, referral by physician, or self-referral |
| No. of centers | 15 | 8 | 19 |
| Age range for screening (yr) | 40–59 | 50–69 | 40–70 |
| Frequency of screening | Annual | Every 2 yr | Annual |
| Physical examination | Yes | Yes | No |

Table 2. Selected Characteristics of the Subjects.*

| Characteristic | National Breast Screening Study (NBSS) (N=330 pairs) | | Ontario Breast Screening Program (OBSP) (N=386 pairs) | | Screening Mammography Program of British Columbia (SMPBC) (N=398 pairs) | | Combined (N=1114 pairs) | | P Value† |
|--|--|------------------|---|------------------|---|------------------|-------------------------|------------------|----------|
| | Case | Control | Case | Control | Case | Control | Case | Control | |
| Age — yr | 49.7±5.6 | 49.7±5.6 | 61.0±7.0 | 61.0±7.0 | 58.2±9.9 | 58.3±9.9 | 56.7±9.1 | 56.7±9.1 | |
| Body-mass index | 25.0±4.2 | 25.5±4.6 | 25.3±4.4 | 25.0±4.0 | 24.6±4.0 | 24.5±4.1 | 25.0±4.2 | 24.9±4.2 | 0.91 |
| Age at menarche — yr‡ | 12.8±1.5 | 12.9±1.5 | 12.9±1.5 | 13.1±1.6 | 12.9±1.5 | 13.0±1.5 | 12.9±1.5 | 13.0±1.5 | 0.05 |
| Age at first birth — yr§ | 25.2±4.7 | 24.7±4.4 | 24.1±4.5 | 24.1±4.2 | 25.0±4.9 | 24.2±4.7 | 24.8±4.7 | 24.3±4.4 | 0.05 |
| Parous — % | 77.6 | 85.8 | 85.5 | 89.9 | 88.4 | 89.2 | 84.2 | 88.4 | 0.004 |
| No. of live births¶ | 2.3±1.9 | 2.7±2.0 | 2.8±1.9 | 2.8±1.8 | 2.3±1.4 | 2.6±1.5 | 2.5±1.8 | 2.7±1.8 | <0.001 |
| Yr from last pregnancy to entry | NA | NA | 29.7±7.9 | 30.0±6.8 | 28.3±9.5 | 28.3±9.6 | 29.0±8.8 | 29.1±8.4 | 0.72 |
| Postmenopausal — % | 60.0 | 61.5 | 86.5 | 89.4 | 75.4 | 75.1 | 74.7 | 76.0 | 0.46 |
| Age at menopause — yr (95% CI)** | 50.9 (50.5–51.7) | 50.1 (49.5–51.3) | 51.2 (50.8–51.7) | 50.1 (49.4–51.0) | 50.6 (50.1–51.2) | 50.7 (49.7–51.8) | 51.0 (50.9–51.0) | 50.9 (50.8–51.0) | 0.03 |
| Ever used hormone-replacement therapy — % | 30.6 | 30.6 | 40.7 | 36.3 | 35.2 | 30.4 | 35.7 | 32.5 | 0.11 |
| Breast cancer in no. of first-degree relatives — % | | | | | | | | | <0.001 |
| 0 | 82.4 | 86.7 | 78.2 | 85.5 | 77.9 | 81.4 | 79.4 | 84.4 | |
| 1 | 15.5 | 13.3 | 20.0 | 12.7 | 18.3 | 16.8 | 18.0 | 14.4 | |
| 2 or more | 2.1 | 0 | 1.8 | 1.8 | 3.8 | 1.8 | 2.6 | 1.3 | |
| Percent density | 36.4±21.7 | 28.4±21.2 | 28.8±18.3 | 24.3±17.5 | 33.3±18.7 | 28.1±18.5 | 32.7±19.7 | 26.9±19.1 | <0.001 |

* 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 932 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.

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

| Mammographic Density | All Methods of Detection† | | | | Detection by Screening | | | | Detection <12 Mo after Negative Screening | | | | Detection ≥12 Mo after Negative Screening | | | |
|----------------------|---------------------------|------------------|---------------------|----------|------------------------|-----------------|---------------------|----------|---|-----------------|---------------------|----------|---|-----------------|---------------------|----------|
| | Case (N=1112) | Control (N=1112) | Odds Ratio (95% CI) | P value‡ | Case (N=717) | Control (N=717) | Odds Ratio (95% CI) | P value‡ | Case (N=124) | Control (N=124) | Odds Ratio (95% CI) | P value‡ | Case (N=262) | Control (N=262) | Odds Ratio (95% CI) | P value‡ |
| <10% | 230 | 362 | 1.0 | | 173 | 242 | 1.0 | | 12 | 35 | 1.0 | | 43 | 82 | 1.0 | |
| 10 to <25% | 272 | 270 | 1.8 (1.4-2.2) | | 171 | 162 | 1.6 (1.2-2.2) | | 22 | 29 | 2.1 (0.9-5.2) | | 79 | 79 | 2.0 (1.2-3.4) | |
| 25 to <50% | 336 | 290 | 2.1 (1.6-2.6) | | 219 | 196 | 1.8 (1.3-2.4) | | 33 | 29 | 3.6 (1.5-8.7) | | 80 | 62 | 2.6 (1.5-4.6) | |
| 50 to <75% | 178 | 144 | 2.4 (1.8-3.3) | | 102 | 88 | 2.0 (1.3-2.9) | | 32 | 23 | 5.6 (2.1-15.3) | | 42 | 30 | 3.1 (1.6-6.2) | |
| ≥75% | 96 | 46 | 4.7 (3.0-7.4) | <0.001 | 52 | 29 | 3.5 (2.0-6.2) | <0.001 | 25 | 8 | 17.8 (4.8-65.9) | <0.001 | 18 | 9 | 5.7 (2.1-15.5) | <0.001 |
| P value‡: | | | | | | | | | | | | | | | | |

* 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.

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 diagnosed in subjects in whom breast cancer had not been detected at screening.

Eligible case patients in the OBSP and the SMPBC were sent a letter, followed by a telephone call, and were asked to provide informed consent for the release of their mammogram and to complete a self-administered questionnaire. For each case patient who provided consent, we selected up to 10 control subjects, individually matched by age (within 1 year), by year of entry to the screening program, and by screening center, and who had a duration of follow-up that was at least as long as the time the corresponding case subject had been in the program before the diagnosis of breast cancer. Potential control subjects were approached in random order, and we selected the first to provide consent who had an available mammogram. Fifty percent of case patients and 54% of control subjects selected from the OBSP and the SMPBC agreed to take part.

Written informed consent for research applications using the data collected 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.⁶

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 density¹⁷ 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.^{6,17} 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.¹⁸ 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 4. Risk of Breast Cancer Associated with the Percentage of Mammographic Density According to Time since Study Entry.

| Method of Detection | Yr after Entry | No. of Matched Pairs | Beta Coefficient* <i>estimate ± SE</i> | Odds Ratio (95% CI)† | P Value‡ |
|---------------------|----------------|----------------------|---|-------------------------|----------|
| Screening | 1 to ≤2 | 144 | 0.2374±0.1423 | 2.6 (0.8–7.9) | 0.10 |
| | >2 to ≤4 | 362 | 0.1789±0.0796 | 2.0 (1.1–3.8) | 0.02 |
| | >4 to ≤8 | 211 | 0.3260±0.1185 | 3.7 (1.5–9.3) | 0.006 |
| Other | 1 to ≤2 | 122 | 0.7133±0.1817 | 17.3 (4.2–72.1) | <0.001 |
| | >2 to ≤4 | 128 | 0.3378±0.1411 | 3.9 (1.3–11.7) | 0.02 |
| | >4 to ≤8 | 144 | 0.5465±0.1488 | 8.9 (2.8–28.6) | <0.001 |
| All§ | 1 to ≤2 | 266 | 0.4311±0.1065 | 5.6 (2.4–12.9) | <0.001 |
| | >2 to ≤4 | 491 | 0.2248±0.0677 | 2.5 (1.4–4.2) | <0.001 |
| | >4 to ≤8 | 355 | 0.4276±0.0903 | 5.5 (2.7–11.2) | <0.001 |

* 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 = $e^{(\beta) / (n-1)}$, 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 $\beta=0$.

§ One pair was excluded from the group analysis because of missing information on detection.

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.¹⁹ 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 = $(RR - 1)P_c \div RR$, where RR denotes relative risk of greater than 50%, and P_c prevalence of density of greater than 50% in case patients.²⁰

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.

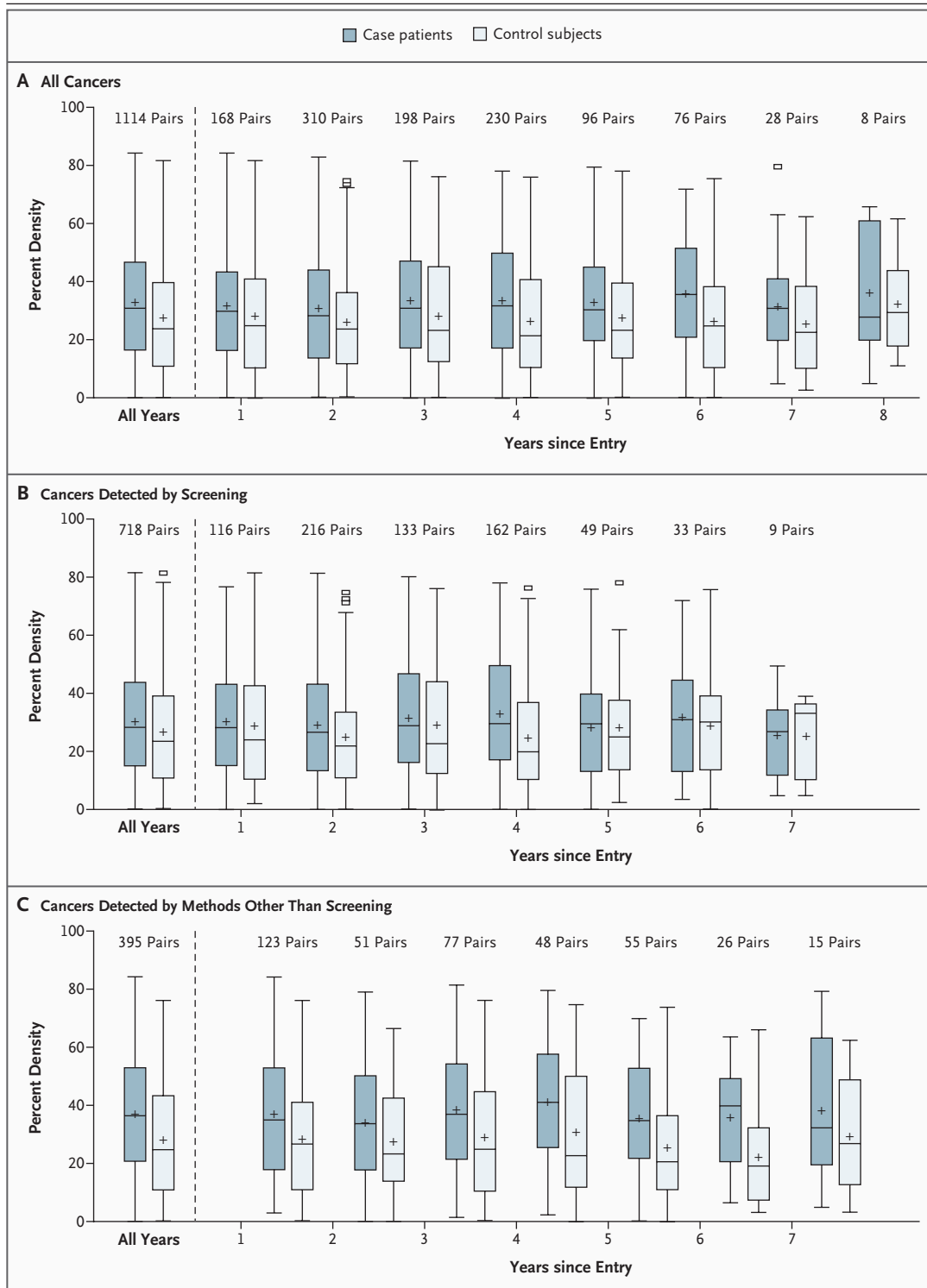
Figure 1 (facing page). Box Plots Showing Percent Density in the Baseline Mammograms of Matched Pairs of Case Patients and Control Subjects.

Panel A shows the percentage of mammographic density, determined by the computer-assisted method, in the baseline mammogram of women in whom breast cancer later developed and of controls, regardless of the method of detection. Panel B shows the percentage of density in women in whom cancers were detected by screening. Panel C shows the percentage of density in women in whom cancers were detected by methods other than screening. Boxes show interquartile ranges, and I bars represent the highest and lowest observed values within 1.5 times the length of the box. Data points outside this range are shown individually. Plus signs denote mean values, and horizontal lines median values.

PERCENTAGE OF MAMMOGRAPHIC DENSITY AND THE RISK AND DETECTION OF BREAST CANCER

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 4.7 (95% confidence interval [CI], 3.0 to 7.4) for all cancers. In the 717 cases of breast cancer detected at screening, the odds ratio was 3.5 (95% CI, 2.0 to 6.2). In the 124 cases of breast cancer detected less than 12 months after the last screening examination, the odds ratio for the risk of breast cancer in those with density of 75% or more was 17.8 (95% CI, 4.8 to 65.9). For cancers detected 12 months or more after the last screening examination, the odds ratio for those with density of 75% or more was 5.7 (95% CI, 2.1 to 15.5). Within each category of detection, there was a monotonic increase in risk with each category of density, and the tests for trend were all significant ($P < 0.001$).

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



shown). 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).

RISK ACCORDING TO METHOD OF DETECTION AND YEARS SINCE ENTRY

Table 4 shows the risk of breast cancer in the combined data according to mammographic density (as

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.^{4,5,7,21,22} Bias in selection affecting percentage of density is thus unlikely.

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

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

| Age | Method of Cancer Detection | Mammographic Density $\geq 50\%$ | | | | |
|--------------|---|----------------------------------|-------------------------|------------------|-------------------------------------|-------------------------------------|
| | | No. of Case Patients | No. of Control Subjects | Prevalence* % | Relative Risk (95% CI) [†] | Attributable Risk [‡] % |
| All ages | All | 1112 | 1112 | 24.6 | 2.8 (2.1–3.8) | 16.0 |
| | Screening | 717 | 717 | 21.5 | 2.3 (1.6–3.3) | 12.1 |
| | Detection <12 mo after negative screening | 124 | 124 | 46.0 | 7.2 (2.7–19.1) | 39.6 |
| | Detection ≥ 12 mo after negative screening | 262 | 262 | 22.9 | 3.6 (1.9–6.9) | 16.5 |
| ≤ 56 yr | All | 561 | 561 | 37.2 | 3.3 (2.2–5.1) | 26.1 |
| | Screening | 351 | 351 | 32.5 | 2.8 (1.6–4.7) | 20.8 |
| | Detection <12 mo after negative screening | 84 | 85 | 58.3 | 7.0 (2.1–23.5) | 50.0 |
| | Detection ≥ 12 mo after negative screening | 119 | 118 | 36.1 | 4.7 (1.7–13.2) | 28.4 |
| >56 yr | All | 551 | 551 | 11.8 | 2.5 (1.6–4.1) | 7.2 |
| | Screening | 366 | 366 | 10.9 | 2.2 (1.2–4.0) | 6.0 |
| | Detection <12 mo after negative screening | 40 | 39 | 20.0 | 8.2 (0.8–81.9) | 17.6 |
| | Detection ≥ 12 mo after negative screening | 143 | 144 | 11.9 | 2.9 (1.1–7.7) | 7.8 |

* 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 = $(RR - 1)P_C \div RR$, where RR denotes relative risk of greater than 50%, and P_C prevalence of density of greater than 50% in case patients.

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.^{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.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.²³⁻²⁸ Density may mask non-palpable 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.^{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.³¹ In the NBSS, 75% of cancers were detected by mammography alone or in combination with physical examination.^{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

rate of detection of cancers; attention should be directed to the development and evaluation of alternative imaging techniques for such women. Digital mammography,³² ultrasonography,³³ and magnetic resonance imaging³⁴ 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.

Supported by grants from the National Cancer Institute of Canada and the Canadian Breast Cancer Research Alliance. Dr. Boyd is supported by the Lee K. and Margaret Lau Chair in Breast Cancer Research.

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Johns PC, Yaffe MJ. X-ray characterization of normal and neoplastic breast tissues. *Phys Med Biol* 1987;32:675-95.
2. Wolfe JN. Breast patterns as an index of risk for developing breast cancer. *AJR Am J Roentgenol* 1976;126:1130-7.
3. *Idem*. Risk for breast cancer development determined by mammographic parenchymal pattern. *Cancer* 1976;37:2486-92.
4. Ursin G, Ma H, Wu AH, et al. Mammographic density and breast cancer in three ethnic groups. *Cancer Epidemiol Biomarkers Prev* 2003;12:332-8.
5. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst* 1995;87:1622-9.
6. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst* 1995;87:670-5.
7. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. *AJR Am J Roentgenol* 1987;148:1087-92.
8. Byrne C, Schairer C, Brinton LA, et al. Effects of mammographic density and benign breast disease on breast cancer risk (United States). *Cancer Causes Control* 2001;12:103-10.
9. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology* 2004;230:29-41.
10. Boyd NF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol* 2005;6:798-808.
11. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;15:1159-69.
12. Whitehead J, Carlile T, Kopecky KJ, et al. Wolfe mammographic parenchymal patterns: a study of the masking hypothesis of Egan and Mosteller. *Cancer* 1985;56:1280-6.
13. Sala E, Warren R, McCann J, Duffy S, Day N, Luben R. Mammographic parenchymal patterns and mode of detection: implications for the breast screening programme. *J Med Screen* 1998;5:207-12.
14. van Gils CH, Otten JD, Verbeek AL, Hendriks JH. Mammographic breast density and risk of breast cancer: masking bias or causality? *Eur J Epidemiol* 1998;14:315-20.
15. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *CMAJ* 1992;147:1459-76. [Erratum, *CMAJ* 1993;148:718.]
16. *Idem*. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ* 1992;147:1477-88. [Erratum, *CMAJ* 1993;148:718.]
17. Jong R, Fishell E, Little L, Lockwood G, Boyd NF. Mammographic signs of potential relevance to breast cancer risk: the agreement of radiologists' classification. *Eur J Cancer Prev* 1996;5:281-6.
18. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. *Phys Med Biol* 1994;39:1629-38.
19. Breslow NE, Day NE. *Statistical methods in cancer research. Vol. 1. The analysis of case-control studies.* Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publications no. 32.)
20. Rothman KJ, Greenland S. *Modern epidemiology.* 2nd ed. Philadelphia: Lippincott-Raven, 1998.
21. Boyd NF, O'Sullivan B, Campbell JE, et al. Mammographic signs as risk factors for breast cancer. *Br J Cancer* 1982;45:185-93.
22. Saftlas AF, Hoover RN, Brinton LA, et al. Mammographic densities and risk of breast cancer. *Cancer* 1991;67:2833-8.
23. Ma L, Fishell E, Wright B, Hanna W, Allan S, Boyd NF. Case-control study of factors associated with failure to detect breast cancer by mammography. *J Natl Cancer Inst* 1992;84:781-5.
24. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 2000;92:1081-7.
25. Buist DS, Porter PL, Lehman C, Taplin SH, White E. Factors contributing to mammography failure in women aged 40-49 years. *J Natl Cancer Inst* 2004;96:1432-40.
26. Porter PL, El-Bastawissi AY, Mandelson MT, et al. Breast tumor characteristics as predictors of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 1999;91:2020-8.
27. Roubidoux MA, Bailey JE, Wray LA, Helvie MA. Invasive cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. *Radiology* 2004;230:42-8.
28. Gilliland FD, Joste N, Stauber P, et al. Biologic characteristics of interval and screen-detected breast cancers. *J Natl Cancer Inst* 2000;92:743-9.
29. Sickles EA. Mammographic features of 300 consecutive nonpalpable breast cancers. *AJR Am J Roentgenol* 1986;146:661-3.
30. Meyer JE, Kopans DB, Stomper PC, Lindfors KK. Occult breast abnormalities: percutaneous preoperative needle localization. *Radiology* 1984;150:335-7.
31. Knight JA, Libstug AR, Moraven V, Boyd NF. An assessment of the influence of clinical breast examination reports on the interpretation of mammograms in a breast screening program. *Breast Cancer Res Treat* 1998;48:65-71.
32. Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med* 2005;353:1773-83.
33. Crystal P, Strano SD, Shcharynski S, Koretz MJ. Using sonography to screen women with mammographically dense breasts. *AJR Am J Roentgenol* 2003;181:177-82.
34. Wright H, Listinsky J, Rim A, et al. Magnetic resonance imaging as a diagnostic tool for breast cancer in premenopausal women. *Am J Surg* 2005;190:572-5.

Copyright © 2007 Massachusetts Medical Society.