Changes in mammographic density over time in breast cancer cases and women at high risk for breast cancer

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High mammographic breast density is one of the strongest intermediate markers of breast cancer risk, and decreases in density over time have been associated with decreases in breast cancer risk. Using repeated measures of mammographic density in a cohort of high-risk women, the Women at Risk (WAR) cohort at Columbia University Medical Center (N = 2670), we examined whether changes in prediagnostic mammographic density differed among 85 prospectively-ascertained breast cancer cases and 85 age-matched controls, using a nested case–control design. Median age at first mammogram was 51 years (range, 29–77 years), with a median of 4 years between first and second prediagnostic mammogram (range, 1–15 years). Using linear regression with change in percent density as the outcome, we found that in women who did not go on to be diagnosed with breast cancer, change in percent density decreased as time between first and second mammogram increased (β = −1.62% per year, p = 0.004). However, in women who did go on to be diagnosed with breast cancer, there was no overall change in percent density associated with time between first and second mammogram (β = 0.29% per year, p = 0.61); the change over time was statistically significantly different between cases versus controls (p < 0.009). If replicated in larger cohorts, these results suggest that within-individual changes in mammographic density as measured by percent density may be a useful biomarker of breast cancer risk.

Mammographic breast density is a strong and potentially modifiable risk factor for breast cancer.¹–⁶ Even though there is a strong and well-documented association between single measures of breast density and breast cancer risk, and it is well established that breast density declines with increasing age, particularly around menopause,¹⁶–⁹ and with tamoxifen use,¹⁰ few studies have examined whether declines in density over time are related to reduced breast cancer risk.¹¹–¹³ One notable study was a large cohort study of women with breast density measures based upon the American College of Radiology Breast Imaging Reporting and Data Systems (BI-RADS) classification, which found that decreases in density are associated with reduced breast cancer risk.¹¹ However, only a minority of women changed a full BI-RADS category in this study,¹¹ limiting the ability to draw conclusions about whether more modest changes in breast density may still be clinically useful to identify women at higher risk of breast cancer. A recent study that examined smaller changes in density did not find an association with decreases in breast density over time and reduced rates of breast cancer in an average risk, primarily postmenopausal population.¹³

To evaluate whether smaller changes over time using continuous measures of density were associated with reductions in breast cancer risk in a population at higher risk of breast cancer, we conducted a nested case–control study within the Women at Risk (WAR) Registry at Columbia University Medical Center. There is little information on changes in breast density in populations at higher risk for breast cancer,¹⁴–¹⁸ although the few that exist have found higher breast density in those with family history of breast cancer,¹⁶,¹⁷ and in women of Ashkenazi Jewish descent.¹⁸

Material and Methods
The details of the WAR registry have been published elsewhere (for details, see Refs. 19, 20). Briefly, from 1991 to July 2011, the WAR registry enrolled participants in the breast clinic at Columbia University Medical Center, who met at least one of...
the following criteria: one or more first-degree relative with premenopausal breast cancer; two or more first-degree relatives with postmenopausal breast cancer; known BRCA1 or BRCA2 deleterious mutation carrier; a biopsy-proven history of lobular carcinoma in situ; a biopsy-proven history of atypical ductal hyperplasia or atypical lobular hyperplasia. We extracted all patient data from medical chart reviews and a detailed epidemiological questionnaire completed at baseline enrollment, and all incident breast cancer cases were confirmed with the New York-Presbyterian Hospital Tumor Registry.

Of the 2670 women in the WAR cohort, 104 women were prospectively diagnosed with breast cancer by May, 2010 (an average of 5 years after enrollment, range 1–15 years). Of these 104 women, 85 had information from at least one prediagnostic film mammogram and 67 had information on at least two prediagnostic film mammograms (we used only film mammograms for the analysis, repeated measures were all film). We individually matched these 85 cases on year of birth with cohort members free from cancer at the time of the case’s diagnosis (the controls) in a 1:1 ratio. In addition to individual matching on year of birth and time in study, we also frequency-matched cases and controls on age at the first prediagnostic mammogram, and time (in years) between first and second mammograms. We used incidence density sampling so that per case–control pair (cases, controls) was matched on year of birth and time in study, and cases were individually matched by year of birth with controls, consistent with increasing age over time in the cohort.

Because breast density measures are known to decline around the menopause, we examined whether our pairs were concordant on menopausal status at both their first and second mammograms (i.e., both member of pair premenopausal for both mammograms, postmenopausal for both mammograms, or changed their menopausal status between first and second mammograms). We found that for 75 of 85 pairs (88%) the pairs were concordant on menopausal status. For 10 of 85 pairs (12%) the pairs were discordant. We ran sensitivity analyses excluding these 10 pairs and also additionally adjusted for menopausal status in the analysis to account for the discordance of these 10 pairs on menopausal status.

We examined established breast cancer risk factors as potential confounders in our analyses (including age at first mammogram, parity, family history, body mass index (BMI), oral contraceptive use, alcohol use and menopausal status). We examined frequency statistics and univariable logistic regression to determine which risk factors were associated with case and control status and associated with breast density, to identify potential confounders. Because women were individually matched by year of birth, we did not additionally adjust for age. We then conducted a multivariable conditional logistic regression to examine the relation between breast density, change in breast density, and case/control status, adjusted for age at first mammogram (Model 1) as well as for other identified confounders (Model 2) and additionally adjusted for baseline density, (Model 3). We conducted tests of linear trend for these analyses.

Additionally, we conducted multivariable linear regression using continuous change in percent density as the dependent variable, and time between first and second mammogram (continuous) as the independent variable, adjusted for age at first mammogram and other identified confounders. We used SAS version 9.2 (Cary, NC) for all analyses.

**Results**

Table 1 describes the demographic and initial density information for cases and controls. The median age at breast cancer diagnosis was 54.5 years, and cancer diagnosis occurred a median of 1.5 years after the second mammogram (range, 6 months to 9.4 years). Cases and controls did not differ significantly on baseline factors, including median age at first mammogram used for our study (cases: 52.7-years-old, controls 51.5-years-old), median time between first and second mammogram (cases 4.7 years, controls 4.6 years), or baseline percent density (cases’ baseline percent density 29.0%, controls 29.2%). Percent density decreased from Time 1 to Time 2 in both cases and controls, consistent with increasing age over time in the cohort (mean percent density at time 2: cases 25.5%, controls 23.7%). The study population was predominantly White (90%), had an average body mass index (BMI) of 25, and about 50% of both cases and controls were postmenopausal at the time of first diagnosis.
Table 1. Distribution of demographic and density characteristics among cases and age-matched controls with mammographic data in the Women At Risk registry, Columbia University Medical Center

|                                  | Cases, $N=85$, $N$ (%) | Controls, $N=85$, $N$ (%) |
|----------------------------------|-------------------------|---------------------------|
| **Median age at diagnosis**      | 54.5 years (range 37–84) | 54.0 years (range 36–85)  |
| **Median age at first mammogram**| 52.7 years (range 32–77) | 51.5 years (range 29–76)  |
| **Median time between mammograms (years)** | 4.0 (range 1–15) | 4.0 (range 1–14)        |
| **Median time between 2nd mammogram and cancer Dx (years)** | 1.5 (range 0.5–9.4) | NA                       |
| **Density characteristics**     |                         |                           |
| Mean percent density, time 1 (%) | 29.0 (range 3–96)       | 29.2 (range 1–84)        |
| Mean percent density, time 2 (%) | 25.5 (range 5–59)       | 23.7 (range 2–77)        |
| Mean change in % density         | −2.67 (range −34–16)    | −5.35 (range −48–49)     |
| **Demographic and risk factor characteristics** | |                           |
| Race/Ethnicity                   |                         |                           |
| White                            | 70 (88)                 | 71 (91)                   |
| African American                 | 2 (3)                   | 1 (1)                     |
| Hispanic                         | 4 (5)                   | 3 (4)                     |
| Other                            | 4 (5)                   | 3 (4)                     |
| Family history of breast cancer  |                         |                           |
| Yes                              | 52 (63)                 | 60 (75)                   |
| No                               | 30 (37)                 | 20 (25)                   |
| History of benign breast disease |                         |                           |
| Yes                              | 53 (66)                 | 63 (75)                   |
| No                               | 27 (34)                 | 21 (25)                   |
| Alcohol use                      |                         |                           |
| Yes                              | 39 (62)                 | 38 (59)                   |
| No                               | 24 (38)                 | 26 (41)                   |
| BMI                              |                         |                           |
| Average                          | 24.8±5.2                | 24.8±4.0                  |
| Oral contraceptive use           |                         |                           |
| Never                            | 43 (61)                 | 45 (62)                   |
| Ever                             | 28 (39)                 | 27 (38)                   |
| Menopausal status                 |                         |                           |
| Premenopausal                    | 44 (53)                 | 42 (50)                   |
| Postmenopausal                   | 39 (47)                 | 42 (50)                   |
| Parity                           |                         |                           |
| Nulliparous                      | 23 (27)                 | 18 (22)                   |
| 1 or 2 live births               | 47 (55)                 | 47 (56)                   |
| ≥3 live births                   | 15 (18)                 | 18 (22)                   |
| Among parous women only:         |                         |                           |
| Age at first birth (mean)         | 27.2                    | 27.5                      |
| Time since last birth            |                         |                           |
| Average                          | 27.4                    | 30.0                      |
| Breastfeeding                    |                         |                           |
| Never                            | 27 (47)                 | 34 (51)                   |
| Ever                             | 31 (53)                 | 32 (49)                   |

1The age at diagnosis for the controls refers to the age of the controls when their matched case was diagnosed with cancer.
2Age at first mammogram is age at the first mammogram used for density readings in this analysis, NOT the age of the woman at her first ever mammogram.
3Indicates menopausal status at first mammogram used for density readings.
4For cases, time since last birth is time between last birth and cancer diagnosis. For controls, time since last birth is time between last birth and the cancer diagnosis of their matched case.
mammogram used for analysis. Greater than 60% of both cases and controls had a personal history of BBD, and greater than 60% had a family history of breast cancer.

Table 2 describes the findings of the logistic regression for percent density and change in percent density, using a conditional logistic regression to create three models: a model adjusted for age at first mammogram, a model additionally adjusted for age at first mammogram, parity, family history and menopausal status, and a model adjusted for those factors and additionally adjusted for baseline density reading. A $>5\%$ decrease in percent density was inversely associated with breast cancer (OR = 0.56, 95%CI 0.15–2.17), while a $>5\%$ increase in percent density was positively associated with breast cancer (OR = 2.55, 95%CI 0.63–10.26); however, these associations were not statistically significant, and a test for trend did not demonstrate significance.

Figure 1 illustrates the association between time between first and second mammograms and change in percent density, adjusted for age at first mammogram, parity, family history and baseline density. For the controls, as time between first and second mammograms increased, breast density decreased significantly ($\beta = -1.62\%$ per year in percent density $p = 0.004$). For the cases, as time between first and second mammograms increased, breast density did not decrease ($\beta = 0.29\%$ per year in percent density, $p = 0.63$); in an ANCOVA comparing the slopes of the regression lines, the slopes were significantly different for cases as compared with controls ($p = 0.009$).

**Discussion**

We found that, as calendar time between mammograms increased, mammographic density decreased, on average, for women that did not go on to be diagnosed with breast cancer (controls), but not for...
high-risk women who developed breast cancer. Few studies have prospectively examined changes in continuous measures of density.\textsuperscript{11–13,22} Although larger decreases (20–25%) in percent density reduced breast cancer risk in several studies\textsuperscript{11,22}; another study found no association between change in percent density with breast cancer risk when examining changes in percent density by quartiles\textsuperscript{12}; the range of percent density changes was relatively small in the study (−10% to +6.5%). In a more recent study, where changes in density were examined prospectively, a decrease in density was not associated with a change in breast cancer risk.\textsuperscript{13} We prospectively assessed breast cancer risk in relation to density on mammograms that occurred between 6 months and 9.5 years before diagnosis, in a population at higher risk of breast cancer, and found that there was, overall, an association with change in breast density in cases versus controls.

Although we observed an approximate two-fold association between higher breast density and breast cancer risk, our cohort is limited by the overall sample size, which decreased the statistical power to evaluate this association. We were also limited by incomplete data on exogenous hormone use from the statistical power to evaluate this association. We were also limited by incomplete data on exogenous hormone use from the medical record. Tamoxifen, a chemopreventive agent, has been shown to decrease breast density,\textsuperscript{10,23} and a previous limited by incomplete data on exogenous hormone use from the medical record. Tamoxifen, a chemopreventive agent, has been shown to decrease breast density,\textsuperscript{10,23} and a previous study indicated that a 10% or greater decrease in density was associated with a 63% reduction in breast cancer risk.\textsuperscript{22} However, the use of tamoxifen as a preventive agent was likely more limited given that the cohort was established in the mid-1990s. If controls, however, were more likely to use tamoxifen as compared to the cases this might explain the decrease in breast density over time relative to the cases. Given that all women were part of a high risk registry, at a single institution follow-up care and prevention recommendations were likely more homogenous.

If replicated in larger studies, our findings suggest that high-risk women who go on to develop breast cancer may have slower declines in breast density over time as compared to women who are not diagnosed with breast cancer. Tracking of changes in mammographic density within individuals may be clinically possible, as automated calculations of mammographic density now exist for digital mammography.\textsuperscript{24} However, it is important to note that the declines observed in the women who did not go on to be diagnosed with cancer were modest, and therefore larger studies that replicate our findings are needed before clinical guidelines on breast density changes are used for risk monitoring. The promise, however, could mean that following women over time to observe within-individual changes in density may help target women at higher future risk, and allow them to engage in preventive measures, including chemoprevention, if they do not experience decreases in breast density over time.

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