Longitudinal Trends in Mammographic Percent Density and Breast Cancer Risk

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Abstract

Background: Mammographic density is a strong risk factor for breast cancer. However, whether changes in mammographic density are associated with risk remains unclear.

Materials and Methods: A study of 372 incident breast cancer cases and 713 matched controls was conducted within the Mayo Clinic mammography screening practice. Controls were matched on age, exam date, residence, menopause, interval between, and number of mammograms. All serial craniocaudal mammograms 10 years before ascertainment were digitized, and quantitative measures of percent density (PD) were estimated using a thresholding method. Data on potential confounders were abstracted from medical records. Logistic regression models with generalized estimating equations were used to evaluate the interactions among PD and time from earliest to each serial mammogram, and absolute change in PD between the earliest mammogram and subsequent mammograms. Analyses were done separately for PD measures from the ipsilateral and contralateral breast. Results: Subjects had an average of five mammograms available, were primarily postmenopausal (83%), and averaged 61 years at the earliest mammogram. Mean PD at earliest mammogram was higher for cases (31%) than controls (27%; ipsilateral). There was no evidence of an association between change in PD and breast cancer risk by time. Compared with no change, an overall reduction of 10% PD (lowest quartile of change) was associated with an odds ratio of 0.9997 and an increase of 6.5% PD (highest quartile of change) with an odds ratio of 1.002. The same results held within the group of 220 cases and 340 controls never using HT. Among the 124 cases and 337 controls known to use HT during the interval, there was a statistically significant interaction between change in PD and time since the earliest mammogram (P = 0.01). However, in all groups, the risk associated with the earliest mammogram remained a stronger predictor of risk than change in PD.

Conclusion: We observed no association between change in PD with breast cancer risk among all women and those never using HT. However, the interaction between change in PD and time should be evaluated in other populations.

Introduction

Mammographic breast density is a major risk factor for breast cancer. Dense regions comprising >50% of the breast are associated with a 2-fold to 5-fold increase in risk (1, 2). Most studies of breast density and breast cancer are based on a single time point, typically between 1 and 16 years before diagnosis (2). However, breast density is not a static characteristic unlike risk factors, such as age at menarche and adult height.

There is emerging evidence that mammographic density has a heritable component (3-5). We reported results of a segregation analysis of families that provided statistical evidence for the existence of a major gene that could account for up to 30% of the variability in the trait (6). Careful inspection of the model variables suggested that the genetic influence could be through an effect on the rate of dense tissue involution. From studies on hormonal interventions and mammographic density, we know that combination hormone therapy (HT) is associated with increased densities (7) and tamoxifen with decreased densities (8-10). Mammographic densities decline with increasing age (11, 12) with some of the greatest decreases occurring with menopause (11). This raises the hypothesis that the rate of change in breast density may be more relevant to risk than breast density measured at a point in time.

To date, three studies have examined changes in breast density or parenchymal pattern with breast cancer risk. Two small studies of 100 or fewer cases (13, 14) and limited statistical power provided suggestive evidence that decreases in categorical measures of breast density across time were associated with reductions in risk. This contrasts the results from a larger case-control study (607 cases), with serial mammograms spanning an average of 5 years for cases (and 4 years for controls), that found no association between changes in quantitative estimates of percent density (PD) or dense area by case and control status. Adjusting for several relevant risk factors, a nonsignificant decrease of 1.4% per decade in cases relative to controls was observed (12).

These previous studies had several limitations, including self-reported covariate data, older mammograms, broad categories of density, low participation rates, and lack of body mass index (BMI) and other relevant confounders at each mammogram. Furthermore, none of these studies examined changes in density in the ipsilateral breast or comprehensively examined the influence of changes by time on risk. Although breast density has been shown to be symmetrical (15, 16), changes in the breast on the same side of the cancer may reflect the disease process more appropriately than those in the contralateral breast.

The current report is based on a well-matched case-control study with high participation rates and with potential confounders (including BMI) abstracted from medical records

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at each mammogram (17). Using serial mammograms over a period of 7 years on average before the cancer, we attempt to corroborate the findings of Maskarinec et al. (12) and extend them to the breast with eventual cancer.

Materials and Methods

Study Population. Subjects were selected from the Mayo Clinic mammography screening practice in Rochester, MN. Patients who did not provide research authorization for medical record studies (3.6%) were not eligible. Breast cancer cases (n = 372) were women at the Mayo Clinic who were diagnosed with primary invasive cancer (n = 301) or ductal carcinoma in situ (n = 71) between 1997 and 2001, were 50 years or older at diagnosis, had at least two prior screening mammograms done 2 years before diagnosis, and lived within a 120-mile radius of the clinic. Cases were either asymptomatic and diagnosed through a routine screening mammogram (72%) or symptomatic and found through a palpable lesion (28%). Women with bilateral cancers, bilateral mastectomies, or breast implants before diagnosis were excluded. The requirement for multiple mammograms established a population of women having routine screening mammograms, and the age requirement provided the opportunity for women to have a 10-year experience of routine screening mammography before cancer.

Two controls with no prior history of breast cancer from the screening practice were matched to each case on age (within 5 years), final mammogram date (screening or diagnostic; within 4 months), menopausal status at final exam date (pre or post), time between baseline and final mammogram (within 8 months), number of prior screening mammograms (within one mammogram), and county of residence. Some controls were deemed ineligible (n = 29) due to inability to obtain prior mammograms or a history of prior breast cancer. Otherwise, mammogram and risk factor information was available on all participants. Weight, height, and HT were abstracted from the medical record for the dates closest to all mammogram dates. Weight was available within a week of all mammogram dates for 67% of all participants (60% of cases and 68% controls). For the remaining, the median was 13 months after mammogram date. Height and weight were used to construct BMI in kilograms per meters squared. Complete HT information (ever or never) at all mammogram dates was available on 77% of cases and 88% of controls. For the majority of those remaining, we could not identify the start or stop date of HT use using the medical record information but knew that they were current users of HT sometime during the mammogram interval. Thus, we used broad categorizations to classify the participant as either a never user of HT, ever use but not within the mammogram interval, or use within the mammogram interval. All remaining patient information was obtained from a clinical database of self-reported information gathered at each visit. Serial mammograms were available on all cases and controls. All mammograms available up until 2 years before the breast cancer (or corresponding matching index date for the controls) were used for this analysis. The time interval between the initial mammogram and the diagnosis of cancer or exam date in controls was 7.0 ± 1.5 years on average (range, 2.1-10.4).

This study was approved by the Mayo Clinic Institutional Review Board.

Breast Density Estimation. The left and right craniocaudal views for all serial mammograms were digitized on a Lumiscan 75 scanner with 12-bit grayscale depth. The pixel size was 0.130 × 0.130 mm² for both the 18 × 24 cm² and 24 × 30 cm² films. Batch files were created, composed of both cases and controls, with randomly assigned dates and sides within a woman to maximize precision of estimates. A 5% repeat set of images was included within each batch file for assessment of reliability. Percent breast density (dense area divided by total area × 100) was estimated for each view using a computer-assisted thresholding program (18-21). Briefly, two thresholds are set by a trained programmer; one separates the breast from the background and the other separates dense from nondense tissues. In the batch files examined for this study, we consistently showed high reliability (r > 0.90), while reading duplicate images on 5% of the total used in the study.

Statistical Methods. Summaries of the distributions of risk factors, matching factors, and breast density are presented as means and SDs or counts and percentages. T tests or χ² tests were used to compare differences between cases and controls. Risk factors used for adjustment in the analyses of all women combined were BMI, menopausal status, breast cancer in a first degree relative, age at first birth, number of births, and HT status. The overall trends in percent breast density were graphically summarized as a function of the number of years preceding the index date of cancer diagnosis or corresponding exam date for the matched controls. BMI was treated as a time-dependent covariate obtained at the time of each mammogram. HT was categorized as use within the mammogram interval, never use, or outside the mammogram interval, and other risk factors corresponded to dates of the earliest mammogram.

Logistic regression models were used to analyze the association between longitudinal change in PD and breast cancer risk (case-control status). Generalized estimating equations were used to account for the longitudinal nature of the mammography data (22). To examine associations between changes in PD and breast cancer risk, we evaluated the interaction among density at earliest mammogram, the time from earliest mammogram to each subsequent mammogram in the series, and absolute change in density from earliest to each subsequent mammogram. In this manner, we accounted for the level of baseline PD in our analyses while also assessing associations between the changes in density and breast cancer. All two-way interactions between these three factors were also examined. Data at each time point were used in these logistic regression analyses. The generalized linear model routines implemented in the Genmod SAS were used to fit these models, and the generalized estimating equations models implemented in that procedure were used to correct for the repeated measurements taken per subject. Significance levels were obtained using score statistics from the generalized estimating equations analysis, and estimates of odds ratios (OR) were likewise estimated via generalized estimating equations approaches. When appropriate, we illustrated the presence or absence of interactions using ORs estimated for median values within quartiles of the control distribution for the variable of interest. For example, ORs for absolute change in PD were estimated at the median value within the quartiles of change in PD among the respective control group (all women combined, HT only or no HT).

Analyses were done on PD from both the ipsilateral and contralateral breasts. Also, analyses were done among women who used HT sometime during the mammogram interval and never HT users separately. The number of HT users not within the mammogram interval was minimal and was not used in these secondary analyses.

We also evaluated whether a measure of excess exposure to PD over the mammogram interval was a risk factor for breast cancer. The excess PD exposure attempts to measure how a woman compares to the age-specific mean PD across the entire mammogram interval. A measure of the mean excess PD was computed by calculating the difference between each individual PD estimate in the mammogram series and the age-specific mean PD for all women combined. Within each woman, these
per-mammogram differences were summed across all mammo-
grams in the interval, and the sum was standardized by the
number of mammograms per woman. Large positive values for
this measurement reflect a woman whose PD was consistently
higher than the mean; and large negative values reflect a
woman whose PD was consistently lower than average. This
excess PD measure then does not examine changes in breast
density with age but instead treats age as a fixed effect. Mean
excess PD was examined in association with breast cancer risk
while adjusting for the variables above. The \( c \) statistic or the
area under the receiver-operator characteristics curve for a
logistic regression model was calculated and compared with
models with PD alone. This statistic measures how often the
model correctly identifies the case in a random case-control pair
as having a higher risk. Values range from 0.5 (random chance)
to 1.0 (perfect prediction).

**Results**

Table 1 presents descriptive information on the 372 cases and
713 controls included in this report. The matching algorithm
was quite effective, as evidenced by the similarity of cases and
controls with regard to the design variables, including age,
menopausal status at exam date, residence, interval between
mammograms, and number of mammograms. On average,
there were five mammograms spanning the 7 years before
breast cancer (or corresponding exam date for controls).
Approximately 84% of the cases and controls were postmen-
opausal at baseline. Case-control differences were evident for
HT (<0.001) and suggestive for BMI (0.09) and family history
(0.14). No difference was apparent for parity (0.47) in this
matched case-control study. In this population, we previously
reported a strong positive association between PD from the
earliest available mammogram and breast cancer risk; results
were similar for PD estimated from the ipsilateral and
contralateral breast (17).

Cross-sectional trends illustrated little evidence for differ-
ences between cases and controls across time until the
diagnosis of cancer (Fig. 1). At all time points, the cases had
higher average PD than the matched controls, and this
difference decreased with time until the cancer in both the
ipsilateral and contralateral breast. The difference in PD in
the contralateral breast between cases and controls was 5.5% at
9 years before the cancer, 5.3%, at 5 years, and only 4.0% at
3 years. The corresponding values for the ipsilateral side were
4.9%, 4.9%, and 4.1%, respectively.

Among all women combined, the primary analysis which
examined the association of PD change and breast cancer risk
resulted in no evidence that changes in PD over time influence
breast cancer risk. The best-fitting model for both the
ipsilateral and contralateral sides included no variables in

<table>
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<th>Table 1. Distribution of matching variables, mammographic density and potential confounders by case-control status</th>
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<td><strong>Characteristic</strong></td>
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<tr>
<td><strong>Matching variables</strong></td>
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<td>Number of screening mammograms</td>
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<td><strong>Density variables</strong></td>
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<td>Percent density from earliest mammogram</td>
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<td>Ipsilateral side</td>
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<td>Age, 40-49 y</td>
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<td>Age, 50-59 y</td>
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<td>Age, 60-69 y</td>
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<td>Age, 70+ y</td>
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<td>Contralateral side</td>
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<td>Changes in BMI from earliest mammogram to latest mammogram</td>
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<td>First degree family history of breast cancer</td>
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<td>Yes</td>
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<tr>
<td>Menopausal status at earliest mammogram</td>
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<tr>
<td>Postmenopausal</td>
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<td><strong>HT use</strong></td>
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<tr>
<td>During mammogram interval</td>
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<tr>
<td>Not during interval</td>
</tr>
<tr>
<td>Unknown time period</td>
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<tr>
<td>AFB and parity combined</td>
</tr>
<tr>
<td>Nulliparous</td>
</tr>
<tr>
<td>AFB ≤ 20, 1 or 2 children</td>
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<tr>
<td>AFB &gt; 20, 1 or 2 children</td>
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<tr>
<td>AFB ≤ 20, 3+ children</td>
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<td>AFB &gt; 20, 3+ children</td>
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Abbreviation: AFB, age at first birth.
which effects changed with follow-up (all $P$ values testing for time-varying effects of mammographic density were 0.10 or higher). The same result held when examining among women who had never used HT.

Figure 2 illustrates the effect of absolute change in PD, independent of time and baseline PD, for all women combined and women not on HT. The estimated ORs are shown for four selected values of change in PD that correspond to the median value within the four quartiles of change in PD among the controls for each group. The reference group is a change of zero or constant PD across follow-up. This figure illustrates the very small observed association for change in PD with breast cancer across the follow-up period. For contralateral PD, the ORs range from 1.0043 (for change in PD of $-10$ or quartile 1) to 0.9972 (for change in PD of $+6.5$ or quartile 4) and the confidence intervals exclude all values smaller than 0.99 and $>1.02$ ($P = 0.42$). These results were similar for the ipsilateral side (for change in PD of $-10$ or quartile 1) to 1.0002 (for change in PD of $+6.5$ or quartile 4) and invasive cancers only (data not shown). Results were similar for the group of women who never used HT; however, a nonstatistically significant inverse trend with increased change in PD was noted in the contralateral breast.

When examining the association of PD change and breast cancer risk among the subset of 124 cases and 288 controls who used HT during the mammogram interval, there was statistically significant evidence of a two-way interaction between absolute change between initial and follow-up mammogram and time between these mammograms (see Fig. 3A) which was not present among women not on HT (Fig. 3B). Positive trends were observed between increased PD and risk of breast cancer closer to the baseline mammogram, but the trends were inverse farther from the baseline mammogram and consequently, closer to the time of breast cancer. This was true for both the ipsilateral and contralateral PD analyses of HT users (ipsilateral not pictured).

Even with the somewhat discrepant results between HT and non-HT users, the PD and breast cancer association was dominated by the baseline measurement of PD. To illustrate this, we included a term for the two-way interaction between

**Figure 1.** Cross-sectional trends in PD across time until cancer by case and control status. A. Contralateral side. B. Ipsilateral side.
baseline PD and absolute change that was not significant for any of the models. Using the contralateral view, baseline PD and PD change values were again selected as the median value within corresponding quartiles. Measurements with baseline PD at the median (27.6%) and with no change in PD from baseline (constant PD) were used as the reference values. Figure 4A shows similar ORs across levels of PD change within all categories of baseline PD. This illustrates the lack of association between change in PD and breast cancer as well as the absence of an interaction between baseline PD and change in PD in association with breast cancer risk. Among HT users and never users, these figures were similar (Fig. 4B and C).

Finally, we estimated the mean excess PD exposure for each woman and found a strong correlation between this measurement and the baseline PD measure (r = 0.88; Fig. 5). For contralateral PD, 41% of cases and 33% of controls were above the age-specific mean density at all mammograms (ipsilateral, 48% of cases and 36% of controls). Median excess PD exposure in cases was 2.6 and ranged from −4.8 to 10.7 [ipsilateral, 4.5 (−4.3, 11.5)]. In controls, this was lower, −0.9 (−9.3 to 8.0) [ipsilateral, 0.5 (−9.6, 8.7)]. The adjusted ORs for the excess PD exposure quartiles were 1.0 (ref), 1.6, 2.7, 3.2 [P < 0.01; ipsilateral: 1.0 (ref), 2.0, 3.4, 3.5]. This result is similar to those for baseline PD in this population [ORs = 1.0 (ref), 2.0, 2.5, 4.3; ipsilateral, 1.0 (ref), 1.9, 3.4, 3.7].

Discussion

Results of the present study confirm that PD is a strong risk factor for breast cancer. However, we find no consistent evidence that changes in density over an average 7-year interval is a strong risk factor for breast cancer, at least in postmenopausal women. Nor does an excess exposure to increased PD over this period add information beyond PD at one point in time. These findings were similar for both the ipsilateral and contralateral breast and within the subgroup of women never having used HT. Among women using HT during the interval, there was evidence for a differential association between absolute change and risk of breast cancer by time from baseline mammogram. However, these risk estimates were miniscule and the baseline measure of breast density remained the stronger risk factor for breast cancer.

Whether longitudinal change in PD influences breast cancer risk remains a clinically and biologically important, yet understudied, question. Only one prior study to date (12) had a sufficient sample size and appropriate quantitative PD assessment to address this question. Maskarinec et al. examined the contralateral PD among 607 cases and controls from three ethnic groups and found results similar to ours. Because the prior studies (12-14) had been done using the contralateral breast, we also examined changes on the ipsilateral side, where change in PD could be more biologically relevant as the cancer progresses. However, there was little evidence of an association of change in density from either breast with breast cancer risk.

The results from Maskarinec et al. (12) coupled with our findings do not rule out the influence of mammographic density change on risk but instead provide important insight for future studies. Both our study and Maskarinec et al. (12) were composed of a large proportion of postmenopausal women (~80%). One of the earlier studies examining change in breast density (assessed as the parenchymal pattern) at two time points was mostly composed of premenopausal women (13); although a small study with low power, they did find a 2-fold elevation in risk for women who persisted at the highest categories of density (P2 or D2) over the time period compared with those who were N1 or P1 at both time points (13). Thus, it is possible that the time interval of our study did not contain the relevant time period in which there might be an association between change in density and risk. Reductions in breast density that occur at a young age, potentially even earlier than the recommended mammogram ages, may be the critical period for association of change with risk. Additionally, an effect on breast cancer risk may only be seen with large reductions in density, as would more often occur among premenopausal women, especially around the menopause. In fact, the study described above dichotomized density into low (N1 and P1) and high risk (P2 and D2) parenchymal patterns to examine large mammographic changes between two screening mammograms. Corresponding changes in quantitative PD could range anywhere from 15% to 41% on average (23), much larger than the average reduction of 2.5% for cases and controls combined (contralateral side) over a decade seen in our study or the 5% seen by Maskarinec et al. (12). Similarly, van Gils et al. (14) used an automated method trained to classify density into four broad categories, <5%, 5% to 25%, 26% to 75%, >75%, and collapsed the last two categories for

Figure 2. Odds ratios for breast cancer by average change in PD for all women combined and never HT users. Model with no interactions. Ipsilateral and contralateral PD results.

Figure 3. A. Evidence of an interaction between time from earliest mammogram and change in PD among HT users (contralateral side). B. No evidence of an interaction between time from earliest mammogram and change in PD among never HT users.
assessing change (>25%) due to sparse data. Interestingly, even with the assessment of large mammographic changes, results from both of these studies were only suggestive, and in the case of van Gils et al. (14), trends were consistent among women who were 5% to 25% at baseline and reduced to <5%.

It is possible that the changes in breast density that may be necessary to influence risk are substantial and not frequent in the general population.

Finally, the somewhat discrepant results found between HT and non-HT subgroups should be investigated further. Unfortunately, our results for women on HT sometime during the mammogram interval are difficult to interpret without the knowledge of exact date of HT initiation, which was absent for a portion of cases and controls. One hypothesis to draw from our data could be that the majority of HT use was early in the mammogram interval and the positive trend between PD change and risk seen at 1 and 3 years after baseline density may indicate that those experiencing positive PD changes due to HT are at a greater risk. At a later interval, the inverse trend of absolute change and risk looks similar to that seen among the never HT users.

If density does reflect the exposure of the breast to factors, such as hormones and growth factors that stimulate growth of breast cells (24, 25), women who persist at higher density over time may be at a greater risk than those persisting at lower densities. However, the mean excess PD measure was strongly correlated with baseline PD and the associations between mean excess PD and breast cancer and their corresponding area under the receiver-operator characteristics curves, were essentially identical. Taken together, our findings imply that a single measure of mammographic density remains the most relevant predictor of risk in the postmenopausal time period, overshadowing longitudinal change or cumulative PD exposure during post menopause.

The biological basis for why lower levels of mammographic density are associated with decreased breast cancer risk is unknown. The age-associated decrease in mammographic density mirrors the reductions in endogenous estrogen levels that occur around the menopause (1, 26, 27), and endogenous hormones are associated with breast cancer risk in postmenopausal women (28, 29). However, recent reports show weak (30), if any (31, 32), cross-sectional associations between serum estrogen levels and mammographic density and a large cohort study with both endogenous estrogen levels, and PD measures illustrates that the PD and breast cancer association does not seem to be mediated through endogenous estrogens (33). Age-related involution involves the reduction in size and number of acini per lobule as well as the replacement of the extralobular stroma by fat (34-37) and can be characterized through careful pathologic scoring of representative breast tissue slides. The rate and extent of involution is variable across the population, is similar to mammographic density, and is influenced by factors including reproductive and lactational history. Also, age-related lobular involution has been associated with a decreased risk of breast cancer (38). Additional research is needed to understand the relationship, if any, between mammographic breast density and involution of breast lobules.

It is important to emphasize that the absence of detectable differences between cases and controls for longitudinal change in breast density does not address whether modifying breast density via hormonal therapies (such as Tamoxifen; ref. 8 or HT, refs. 39-41), or lifestyle interventions (such as diet, ref. 42, or physical activity, ref. 43) will lower breast cancer risk. Both our study and Maskarinec et al. (12) addressed the age-associated changes that occur over a limited window of a woman’s lifetime and not those which were purposely induced by interventions. The timing of the intervention to change density must be carefully considered, as prior data on changes with interventions have been seen either stronger or weaker.
present only among premenopausal women (8, 42). Thus our findings do not rule out breast density as an appropriate biomarker in prevention trials. The inclusion of this biomarker as the only end point for these trials may be premature because there are no data to illustrate whether modification of breast density influences risk. However, the results from these trials may actually provide the necessary data to determine whether the modification of breast density does influence risk.

Our study had several strengths, including the close matching on pertinent factors, high participation rates, medical record–abstracted weight, height, and risk factor data on all cases and controls corresponding to time of mammogram, and the quantitative estimate of density by an experienced reader. Further, our findings add to the limited literature on changes in mammographic density with breast cancer and confirm previous findings seen in postmenopausal women (12). Limitations include the primarily postmenopausal population and the minimal ethnic diversity of this Midwest population. Although this was not a population-based study, by restricting to the 120-mile radius and requiring serial mammograms on all women, the study population was closer to a community-based than a referral or high-risk population. The quantitative estimate is reproducible and has consistently shown association with breast cancer; however, it is subjective (18) and might not be ideal for assessing serial changes. An automated estimate would reduce reader variability and potential noise; but unfortunately, this is currently unavailable. Also, clinical mammograms could differ in positioning, compression, and thickness of the imaged breast which also could affect the evaluation of serial changes of PD. The increased variability in the PD estimate would likely result in nondifferential misclassification of change and could have attenuated our findings. Also, the weight information abstracted from the medical records coincided with the date of the mammogram in 67% of the participants. Of the 33%, half of these had weights abstracted over a year after their mammogram and could have resulted in inaccurate adjustment for weight change in the mammogram interval.

Finally, our assessment of the effect of differential use of HT on the association of change in density with risk was less than optimal. This was directly a result of incomplete data on HT status and type of therapy at each mammogram date. Although this does not affect our findings among women who never used HT, it precludes the ability to precisely adjust for HT in the combined analyses and the HT only analyses. The discrepant findings among the never HT and HT group underscore the need for future studies that have detailed information on HT at serial mammograms.

Conclusion

The current study found no evidence for strong associations between change in PD and breast cancer risk.

Acknowledgments

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References


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