Title

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Journal

Cancer Epidemiology Biomarkers & Prevention, 24(11)

ISSN

1055-9965

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Publication Date

2015-11-01

DOI

10.1158/1055-9965.epi-15-0330

Peer reviewed

HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2015 November ; 24(11): 1724–1730. doi: 10.1158/1055-9965.EPI-15-0330.

The effect of change in body mass index on volumetric measures of mammographic density

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Abstract

Background—Understanding how changes in body mass index (BMI) relate to changes in mammographic density is necessary to evaluate adjustment for BMI gain/loss in studies of change in density and breast cancer risk. Increase in BMI has been associated with a decrease in percent density, but the effect on change in absolute dense area or volume is unclear.

Methods—We examined the association between change in BMI and change in volumetric breast density among 24,556 women in the San Francisco Mammography Registry from 2007-2013. Height and weight were self-reported at the time of mammography. Breast density was assessed using single x-ray absorptiometry measurements. Cross-sectional and longitudinal associations between BMI and dense volume (DV), non-dense volume (NDV) and percent dense volume (PDV) were assessed using multivariable linear regression models, adjusted for demographics, risk factors, and reproductive history.

Results—In cross-sectional analysis, BMI was positively associated with DV (β=2.95 cm^3, 95% CI 2.69, 3.21) and inversely associated with PDV (β=-2.03%, 95% CI -2.09, -1.98). In contrast, increasing BMI was longitudinally associated with a decrease in both DV (β=-1.01 cm^3, 95% CI -1.59, -0.42) and PDV (β=-1.17%, 95% CI -1.31, -1.04). These findings were consistent for both pre- and postmenopausal women.

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Conflicts of interest: None

Conclusion—Our findings support an inverse association between change in BMI and change in PDV. The association between increasing BMI and decreasing DV requires confirmation.

Impact—Longitudinal studies of PDV and breast cancer risk, or those using PDV as an indicator of breast cancer risk, should evaluate adjustment for change in BMI.

Introduction

High mammographic density is a risk factor for primary breast cancer (1-4). Mammographic density is typically assessed by comparing the proportion of dense and non-dense area measured on a two-dimensional mammographic image. Recently, novel methods that incorporate the thickness of the breast have been proposed as enhancements to area assessment (5-8). Single X-ray absorptiometry (SXA), which calculates breast volume using a calibrated phantom included in the mammographic image, has demonstrated equivalent breast cancer risk prediction to area methods (8). Some associations between breast cancer risk factors and mammographic density differ between area and volumetric methods. In particular, higher body mass index (BMI) has been associated with lower dense area (DA) (2, 9, 10) but higher dense volume (DV) (7, 11-13) in cross-sectional analyses.

Neither mammographic density nor BMI are static values. It is understood that percent dense area (PDA) decreases during aging, and that the rate of decline is greatest during the menopausal transition (14-16). It is unclear how simultaneous change in BMI influences the decline in density. A limited number of longitudinal studies have shown an inverse relationship between change in BMI and change in PDA (17, 18), and have reported either a null (17) or positive (18) association between change in BMI and change in absolute DA. To date, no studies have evaluated the longitudinal association of change in BMI on change in mammographic density using volumetric methods, and it is unclear if the difference between area and volumetric assessment seen in cross-sectional analyses will affect this longitudinal relationship. This association must be established to understand the impact of adjusting for changing BMI in longitudinal studies of volumetric density and breast cancer risk.

We examined the cross-sectional and longitudinal associations between BMI and mammographic density using the SXA volumetric density measurement method. Our analysis was conducted in the San Francisco Mammography Registry (SFMR), a large cohort of women undergoing breast imaging in the San Francisco Bay Area. Based on prior cross-sectional analyses using volumetric methods (7, 11-13), we hypothesized that an increase in BMI over the study period would be associated with an increase in both dense volume (DV) and non-dense volume (NDV), and a decrease in percent dense volume (PDV).

Materials and methods

Study population

The SFMR was established in 1994 and participates in the NCI-funded Breast Cancer Surveillance Consortium (BCSC). The SFMR has received Institutional Review Board approval for passive permission to enroll participants, link data, and perform analyses. All procedures were Health Insurance Portability and Accountability Act compliant and the

SFMR received a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

At the time of screening mammogram at an SFMR facility, women completed a self-administered, one-page questionnaire providing basic demographic, risk factor, and reproductive history information. Women were given the option to opt out of participating in research and the opt out rate for SFMR facilities averages 1.8% (range: 0.8-3.3%). Women were eligible for the current analysis if they were age 18 and older with two or more mammograms in 2007-2013 spaced at least nine months apart. Women with a history of breast cancer, mastectomy, breast implants, or breast surgery were excluded. Mammograms that were performed within 6 months of a breast cancer diagnosis were also excluded.

The eligible study sample consisted of 30,000 women who contributed 75,489 mammograms. A total of 1,149 mammograms were removed due to poor placement of the SXA phantom in the mammographic image resulting in volumetric density measurement error. As a result, 368 women had only one mammogram to contribute to the analysis and were further excluded. Women were excluded if their reported height between mammograms varied by more than 3 inches (470 women, 1,197 mammograms) and if data were missing on BMI or other covariates (4,606 women, 11,122 mammograms). These exclusions resulted in a final study population of 24,556 women who contributed 61,653 mammograms.

BMI assessment

Women self-reported their current height in inches and weight in pounds at the time of their screening mammogram, and these data were used to calculate BMI (weight in kg divided by the square of the height in meters). BMI was analyzed both in its original continuous form and categorized according to World Health Organization guidelines: <18.5 kg/m^2 for underweight, 18.5-<25 kg/m^2 for normal weight, 25-<30 kg/m^2 for overweight, and >=30 kg/m^2 for obese.

Volumetric breast density assessment

DV and NDV were measured using the SXA technique and software developed by UCSF investigators (version 7.1). Total breast volume was computed by adding DV and NDV, and PDV was calculated by dividing DV by total breast volume. A complete description of the specific SXA imaging methods, development, and calibration processes has been previously published (19, 20). Briefly, a specialized SXA phantom was inserted in the corner of the x-ray field during the mammography examination. The phantom was designed to conform to the same thickness of the breast and was composed of materials mimicking known fat/glandular content. The placement of the phantom was specifically designed to not interfere with standard screening procedures and to account for tilt of the compression surfaces during the examination (8, 20). Grayscale values for the pixels in the breast image were then compared to the grayscale values in the phantom, and unique volumes of adipose (non-dense) and fibroglandular (dense) breast tissue were determined from the two-dimensional mammographic image (20).

SXA defines the total lack of dense breast tissue (i.e. 0% density) as pure fat as opposed to adipose, which contains fat and water. Therefore, in the division of breast tissue into dense and non-dense content, the SXA method includes water from adipose tissue in the fibroglandular (dense) content. This is analogous to fat saturated MRIs that have been used to measure breast density in young women (21), but in contrast to other volumetric and area techniques. However, direct comparisons demonstrate that SXA measures are highly correlated with area density measures (Shepherd 2012) and with other volumetric density techniques (Wang 2013). The mean difference in PDV measurements between repeat readings using the SXA technique has been demonstrated to be less than 2.5% (8). Further, SXA has been monitored over time using a quality control phantom to ensure stability of measurements with no systematic changes observed (13, 22).

Covariate assessment

Data on demographics, reproductive history, family history, and other breast cancer risk factors were obtained via the one-page questionnaire administered at the time of the screening mammogram. The covariates selected as potential confounders or effect modifiers were based on known predictors of mammographic density and availability within the SFMR data. Covariates assessed at the time of the first screening mammogram and considered unchanging included age at first mammogram, race, ever given birth, age at first birth, education, first-degree family history of breast cancer, and prior history of breast biopsy. Time-varying covariates included age at current mammogram, menopausal status, postmenopausal hormone therapy (HT) use, and hormonal birth control use. Consistent with previous analyses using BCSC definitions, women were considered postmenopausal if they reported that menstrual periods had stopped for more than 12 months, if they reported a bilateral oophorectomy, or if they were 55 years of age or older. Women were otherwise considered premenopausal. Current use of postmenopausal HT and hormonal birth control were assessed at the time of the screening mammogram. The questionnaire did not include specific formulations of HT or history of prior use.

Statistical analysis

There were no statistically significant differences in distributions of density, BMI, or covariates between women who were excluded from the analysis and those who were retained (data not shown). We calculated descriptive statistics for demographic and reproductive characteristics. We assessed the cross-sectional association between BMI at first mammogram and volumetric density measures at first mammogram using a generalized linear regression model adjusted for all covariates. For the longitudinal analyses we estimated the annual change in BMI and volumetric density measures as (Δ value / Δ time, days) × 365.25 days/year to account for varying time lapse between mammograms. We categorized BMI change over the study period based on change from initial BMI (at first mammogram): ≥10% loss, 5-10% loss, stable within ±5%, 5-10% gain, and ≥10% gain. We used ANOVA to compare the percent gain/loss based on initial BMI, using the underweight or normal range (<25 kg/m^2) as the reference. We summarized the annual change in each volumetric density measure over the study period and calculated adjusted means and confidence intervals using generalized linear regression.

We assessed the association between annual change in BMI and annual change in DV, NDV, and PDV using a random intercept mixed effects model. The mixed effects model is appropriate for data in which each subject may contribute a varying number of observations, and the random intercept allows for individual subject variation in baseline density measures (23). The model was adjusted for all covariates listed above and time-varying factors were updated at each successive mammogram. We stratified all analyses by menopausal status because the association between BMI and breast cancer risk has been shown to vary between pre- and postmenopausal women (24, 25). Because previous analyses have shown that declines in PDA over the menopausal transition may be modified by initial BMI and postmenopausal HT use (14, 15), we tested for effect modification by BMI at the first mammogram and by HT (never user, consistent user, initiated use during the study period, discontinued use during the study period). We further considered effect modification by race/ethnicity, since BMI and the distribution of breast density have been shown to differ by race/ethnicity (26).

All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, North Carolina).

Results

A majority of the study population was Caucasian (66.3%) with 25.1% Asian or Pacific Islander (Table 1). The average age at the first mammogram was 56.4 years, and 64.1% of women were postmenopausal. Over half of the study population was classified as normal weight at the first mammogram (62.6%), while 24.2% were classified as overweight and 10.9% were classified as obese. About 12% of the study population was using postmenopausal HT at the time of the first mammogram. Women contributed an average of 2.54 mammograms, and the average time between first and last mammogram was 2.4 years (range 0.8-5.9 years).

In the fully-adjusted cross-sectional analysis, BMI at first mammogram was positively associated with both DV (β=2.95 cm^3, 95% CI 2.69, 3.21) and NDV (β=51.03 cm^3, 95% CI 49.93, 52.13) at first mammogram, and was inversely related to PDV at first mammogram (β=-2.03%, 95% CI -2.09, -1.98) (Table 2). The associations with NDV and with PDV were stronger among women who were premenopausal at first mammogram compared to those who were postmenopausal (p value for interaction by menopausal status: p=0.79 for DV, p<0.01 for NDV, p<0.01 for PDV). In cross-sectional analysis, no significant interaction by postmenopausal HT use (p value for interaction by HT use: p>0.15 for DV, NDV, and PDV) or by race (p value for interaction by race: p>0.28 for DV, NDV, and PDV) was observed

A majority of women maintained stable weight within ± 5% of their initial BMI during the study period (73.6%) (Table 3). A greater proportion of women who were initally overweight or obese lost over 5% of their initial BMI compared to those with BMI < 25 kg/m^2 (p<0.01). Among premenopausal women, a higher proportion of those who were initially overweight or obese gained over 5% of their initial BMI compared to those who initially had BMI <25 kg/m^2 (p=0.01). No difference in weight gain by initial BMI was observed among postmenopausal women (p=0.86).

The mean annual change in DV, NDV, and PDV over the study period was -0.56 cm^3/year, 6.09 cm^3/year, and -0.81 %/year, respectively. A 1 kg/m^2 annual increase in BMI was associated with a statistically significant decrease in DV (β=-1.01 cm^3/year, 95% CI -1.59, -0.42), increase in NDV (β=26.2 cm^3/year, 95% CI 23.5, 28.9), and decrease in PDV (β=-1.17%/year, 95% CI -1.31, -1.04) (Table 4). These associations remained significant after adjustment for change in total breast volume (Supplementary Table S1). When stratified by menopausal status and initial BMI, the significant annual decrease in DV with increasing BMI was observed among premenopausal women who were intitally overweight or obese, but not among those who were initially underweight or normal BMI (p value for interaction by initial BMI: $p<0.01$). Among postmenopausal women, the annual decrease in DV with increasing BMI was not statistically significant within initial BMI strata and no interaction was observed (p value for interaction by initial BMI: $p=0.67$). In longitudinal analysis, we observed no significant overall interaction by postmenopausal HT use (p value for interaction by HT use: $p>0.15$ for DV, NDV, and PDV) or race (p value for interaction by race: $p>0.19$ for DV, NDV, and PDV).

Discussion

Consistent with our expectations, we observed positive cross-sectional relationships between BMI and both DV and NDV, and an inverse cross-sectional relationship between BMI and PDV. We further observed that DV and PDV declined on average over the study period, and that a longitudinal increase in BMI was associated with an accelerated decrease in PDV. However, contrary to our expectations, we found that a longitudinal increase in BMI was also associated with an accelerated decrease in DV. This finding was consistent among pre- and postmenopausal women, and was strongest among premenopausal women who were intially overweight or obese.

Our findings of a positive cross-sectional relationship between BMI and DV are consistent with studies using the SXA method (13) and other volumetric techniques (11, 12, 27), but in contrast with studies using area assessment (10, 28). Differences in study populations may contribute to the difference in the association of BMI and DV between area and volumetric methods; however, two studies (7, 13) compared this association using area and volumetric density measured from the same mammographic images and confirmed this contrasting result. This indicates that measurement method may be largely responsible for the difference. Unlike area methods, which rely on a dichotomous separation of dense and non-dense area, the volumetric SXA method calculates a continuous value for DV based on the comparison of each pixel on the mammographic image to a known phantom (20). Continuous assessment of DV may provide a more accurate measurement of dense tissue than dichotomous area methods. Further, the SXA method includes water in adipose tissue in its calculation of DV (8). A recent study comparing area and SXA volume measurements reported that correlations between DA and DV were stronger among lean women than among obese women as a result of this inclusion (13). The contribution of water from adipose tissue may partially account for the positive cross-sectional association between BMI and DV.

Our observed 1.17% annual decline in PDV associated with a unit annual increase in BMI is similar in magnitude to the two previous studies of change in BMI and PDA over time, which reported annual declines of 0.36% (17) and 1.44% (18). However, our observation of a decrease in DV with increasing BMI does not support their findings of no association (17) or positive association (18) between change in BMI and DA. The association between change in BMI and change in DA observed by Reeves *et al* (17) was in the same direction as our finding, but their results among 833 women were not statistically significant. Although we observed a significant annual decrease in DV, it should be noted that the magnitude, approximately 1 cm^3/year, is small compared to the initial average DV in our study population (142.3 cm^3) and compared to the difference in DV that was associated with increased breast cancer risk in a case-control analysis of 864 women using SXA (8). Women in the highest quintiles of DV (192+ cm^3) had significantly higher risk compared to those in the lowest quintile (<122 cm^3).

We observed that the longitudinal association between BMI and DV was strongest among premenopausal women who were initially overweight or obese. These women were more likely to gain more than 5% of their initial weight during the study period than their lean counterparts. It is possible that the association between change in BMI and DV was easiest to observe among women who gained more weight, since a larger change in BMI may allow us to see the associated small change in DV. Furthermore, age-related changes in breast density typically occur during early perimenopause (14-16) and a decline in DV may be more pronounced and easily observable among these women. The inverse association between BMI and DV was seen among postmenopausal women, but did not vary by initial BMI; and likewise, no difference in weight gain by initial BMI was observed among postmenopausal women.

It is understood that the number and size of breast lobules decrease with increasing age, known as breast tissue involution (29, 30), which is consistent with a decrease in DV over time. Age remained a significant factor in our multivariable models for DV that included change in BMI as well as menopausal status and parity, both of which have been associated with the rate of breast involution (29). Thus, breast involution with age may partially explain our finding of a decrease in DV. Beyond the effect of age, the biological mechanism that may link an annual increase in BMI to an annual decrease in absolute DV is unclear. Like other volumetric methods, the SXA technique calculates breast volume using the two-dimensional mammographic image. Our finding could reflect differences in capturing dense breast tissue on a mammographic image for large- versus small-breasted women as opposed to a true reduction in DV with increasing BMI. However, additional adjustment for total breast volume in the model did not change the association between change in BMI and change in DV. It is unlikely that the inclusion of adipose water in the SXA assessment of DV explains our findings of a decrease in DV with increasing BMI because this would this inclusion would tend to increase DV with increasing BMI. Further, water has been estimated to account for only 8% (21) to 20% (31) of adipose content, and therefore the impact of this measurement method on our results is likely to be minor. However, future studies using SXA are necessary to confirm our findings.

Our study is strengthened by the large number of participants and the concurrent collection of height and weight data at the time of the screening mammogram. In addition, volumetric density was assessed using a validated method that has been found to similarly predict breast cancer risk compared to area assessment (8). Our results must be interpreted in context of the study limitations, however. First, height and weight were self-reported. However, validity of self-reported height and weight measures has been assessed within a subset of the BCSC cohort (13) and the Spearman correlation coefficient between BMI from self-reported and measured values was 0.949 (95% CI 0.938, 0.957). Second, our ability to adjust for confounding variables was limited by the information collected on the SFMR questionnaire, however we adjusted for the main factors known to impact breast density including age, BMI, menopausal status, family history of breast cancer, and parity. In particular, breast tissue involution with age may partially explain our longitudinal findings, despite adjustment to the extent possible for factors associated with involution. Finally, the SXA technique has been shown to be consistent over time (22); however, placement of the breast during the mammogram examination may introduce some variability in the measurement of breast density over the course of the study.

The roles of BMI and mammographic density in breast carcinogenesis are unclear and are complicated by the dynamic nature of body and breast composition over time. Prior analyses of BMI and PDA find that these are independent breast cancer risk factors in both pre- and postmenopausal women (10, 30, 32), and that studies of either factor should control for the other to avoid negative confounding (10, 32). We observed significant associations between change in BMI and change in volumetric density measures over an average of 2.4 years of follow-up. While short-term change in BMI may not be strongly associated with breast cancer risk, adult weight gain has been consistently associated with increased risk (33, 34). Thus, change in BMI may be a confounder in long-term longitudinal studies of volumetric density and breast cancer risk; and researchers should consider adjusting for change in BMI to fully understand the independent effect of change in volumetric density on breast cancer risk. Further, longitudinal studies using change in volumetric density as an indicator of changing breast cancer risk should carefully evaluate the potential for confouding by gain or loss in BMI and consider adjustment as necessary. The inverse association we observed between change in BMI and change in DV after adjustment for factors associated with breast involution is not easily explained, and confirmation is required to ensure that our results are not due to chance or an inherent manifestation of our measurement method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: This work was supported by the National Cancer Institute-funded Breast Cancer Surveillance Consortium (P01 CA154292 (K. Kerlikowske, J. Shepherd, J.A. Tice, B.L. Sprague) and HHSN261201100031C (K. Kerlikowske, B.L. Sprague)) and U54 CA163303 (B.L. Sprague, J. Shepherd). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. A list of the BCSC investigators and procedures for requesting BCSC data for research purposes are provided at: http://breastscreening.cancer.gov/.

The collection of cancer and vital status data used in this study was supported in part by state public health departments and cancer registries throughout the US. For a full description of these sources, please see: http://breastscreening.cancer.gov/work/acknowledgement.html.

References

1. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, 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. [PubMed: 7752271]
2. Boyd NF, Lockwood GA, Martin LJ, Knight JA, Byng JW, Yaffe MJ, et al. Mammographic densities and breast cancer risk. Breast disease. 1998; 10:113–26. [PubMed: 15687568]
3. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, et al. Mammographic features and breast cancer risk: Effects with time, age, and menopause status. J Natl Cancer Inst. 1995; 87:1622–9. [PubMed: 7563205]
4. Warner E, Lockwood G, Tritchler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: A meta-analysis of the published literature to examine the effect of method of classification. Cancer Detect Prev. 1992; 16:67–72. [PubMed: 1532349]
5. Ding J, Warren R, Warsi I, Day N, Thompson D, Brady M, et al. Evaluating the effectiveness of using standard mammogram form to predict breast cancer risk: Case-control study. Cancer epidemiology, biomarkers prevention. 2008; 17:1074–81.
6. Boyd N, Martin L, Gunasekara A, Melnichouk O, Maudsley G, Peressotti C, et al. Mammographic density and breast cancer risk: Evaluation of a novel method of measuring breast tissue volumes. Cancer epidemiology, biomarkers prevention. 2009; 18:1754–62.
7. Aitken Z, McCormack V, Highnam R, Martin L, Gunasekara A, Melnichouk O, et al. Screen-film mammographic density and breast cancer risk: A comparison of the volumetric standard mammogram form and the interactive threshold measurement methods. Cancer epidemiology, biomarkers prevention. 2010; 19:418–28.
8. Shepherd J, Kerlikowske K, Ma L, Duewer F, Fan B, Wang J, et al. Volume of mammographic density and risk of breast cancer. Cancer epidemiology, biomarkers prevention. 2011; 20:1473–82.
9. Boyd N, Martin L, Bronskill M, Yaffe M, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. J Natl Cancer Inst. 2010; 102:1224–37. [PubMed: 20616353]
10. Boyd N, Martin L, Sun L, Guo H, Chiarelli A, Hislop G, et al. Body size, mammographic density, and breast cancer risk. Cancer epidemiology, biomarkers prevention. 2006; 15:2086–92.
11. Jeffreys M, Warren R, Highnam R, Davey Smith G. Breast cancer risk factors and a novel measure of volumetric breast density: Cross-sectional study. Br J Cancer. 2008; 98:210–6. [PubMed: 18087286]
12. Lokate M, Kallenberg MGJ, Karssemeijer N, Van den Bosch MA, Peeters PHM, Van Gils C. Volumetric breast density from full-field digital mammograms and its association with breast cancer risk factors: A comparison with a threshold method. Cancer epidemiology, biomarkers prevention. 2010; 19:3096–105.
13. Gierach G, Geller B, Shepherd J, Patel DA, Vacek PM, Weaver DL, et al. Comparison of mammographic density assessed as volumes and areas among women undergoing diagnostic image-guided breast biopsy. Cancer epidemiology, biomarkers & prevention. 2014
14. Kelemen L, Pankratz VS, Sellers T, Brandt KR, Wang A, Janney C, et al. Age-specific trends in mammographic density: The minnesota breast cancer family study. Am J Epidemiol. 2008; 167:1027–36. [PubMed: 18385204]
15. Maskarinec G, Pagano I, Lurie G, Kolonel L. A longitudinal investigation of mammographic density: The multiethnic cohort. Cancer epidemiology, biomarkers prevention. 2006; 15:732–9.
16. Guthrie J, Milne R, Hopper J, Cawson J, Dennerstein L, Burger H. Mammographic densities during the menopausal transition: A longitudinal study of australian-born women. Menopause. 2007; 14:208–15. [PubMed: 17091098]
17. Reeves K, Stone R, Modugno F, Ness RB, Vogel VG, Weissfeld JL, et al. Longitudinal association of anthropometry with mammographic breast density in the study of women's health across the nation. International journal of cancer. 2009; 124:1169–77.

18. Boyd NF, Greenberg C, Lockwood G, Little L, Martin L, Byng J, et al. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: Results from a randomized trial. canadian diet and breast cancer prevention study group. J Natl Cancer Inst. 1997; 89:488–96. [PubMed: 9086005]
19. Shepherd J, Herve L, Landau J, Fan B, Kerlikowske K, Cummings S. Novel use of single X-ray absorptiometry for measuring breast density. Technology in cancer research treatment. 2005; 4:173–82. [PubMed: 15773786]
20. Malkov S, Wang J, Kerlikowske K, Cummings S, Shepherd J. Single x-ray absorptiometry method for the quantitative mammographic measure of fibroglandular tissue volume. Med Phys. 2009; 36:5525–36. [PubMed: 20095265]
21. Boyd N, Martin L, Chavez S, Gunasekara A, Salleh A, Melnichouk O, et al. Breast-tissue composition and other risk factors for breast cancer in young women: A cross-sectional study. Lancet Oncol. 2009; 10:569–80. [PubMed: 19409844]
22. Malkov, S.; Wang, J.; Duewer, F.; Shepherd, J. Breast Imaging. Berlin Heidelberg: Springer; 2012. A calibration approach for single-energy x-ray absorptiometry method to provide absolute breast tissue composition accuracy for the long term; p. 769-774.
23. Diggle, P.; Heagerty, P.; Liang, K.; Zeger, S. Analysis of longitudinal data. 2nd. Oxford, UK: Oxford University Press; 2004.
24. Amadou A, Hainaut P, Romieu I. Role of obesity in the risk of breast cancer: Lessons from anthropometry. Journal of Oncology. 2013; 906495
25. Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A, et al. Sex hormones and risk of breast cancer in premenopausal women: A collaborative reanalysis of individual participant data from seven prospective studies. Lancet oncology. 2013; 14:1009–19. [PubMed: 23890780]
26. Razzaghi H, Troester M, Gierach G, Olshan A, Yankaskas B, Millikan R. Mammographic density and breast cancer risk in white and african american women. Breast Cancer Res Treat. 2012; 135:571–80. [PubMed: 22864770]
27. Aitken Z, McCormack V, Highnam R, Martin L, Gunasekara A, Melnichouk O, et al. Screen-film mammographic density and breast cancer risk: A comparison of the volumetric standard mammogram form and the interactive threshold measurement methods. Cancer epidemiology, biomarkers prevention. 2010; 19:418–28.
28. Haars G, van Noord PAH, van Gils C, Grobbee D, Peeters PHM. Measurements of breast density: No ratio for a ratio. Cancer epidemiology, biomarkers prevention. 2005; 14:2634–40.
29. Figueroa JD, Pfeiffer RM, Patel DA, Linville L, Brinton LA, Gierach GL, et al. Terminal duct lobular unit involution of the normal breast: Implications for breast cancer etiology. J Natl Cancer Inst. 2014; 106
30. Baglietto L, Krishnan K, Stone J, Apicella C, Southey MC, English DR, et al. Associations of mammographic dense and nondense areas and body mass index with risk of breast cancer. Am J Epidemiol. 2014; 179:475–83. [PubMed: 24169466]
31. Khazen M, Warren RML, Boggis CRM, Bryant EC, Reed S, Warsi I, et al. A pilot study of compositional analysis of the breast and estimation of breast mammographic density using three-dimensional T1-weighted magnetic resonance imaging. Cancer Epidemiol Biomarkers Prev. 2008; 17:2268–74. [PubMed: 18768492]
32. Harris H, Tamimi R, Willett W, Hankinson S, Michels K. Body size across the life course, mammographic density, and risk of breast cancer. Am J Epidemiol. 2011; 174:909–18. [PubMed: 21911827]
33. Playdon MC, Matthews SB, Thompson HJ. Weight change patterns and breast cancer risk: A brief review and analysis. Crit Rev Eukaryot Gene Expr. 2013; 23:159–69. [PubMed: 23582037]
34. Keum N, Greenwood DC, Lee DH, Kim R, Aune D, Ju W, et al. Adult weight gain and adiposity-related cancers: A dose-response meta-analysis of prospective observational studies. J Natl Cancer Inst. 2015; 10:107.

Table 1

Selected patient characteristics measured at first mammogram (N=24,556); BCSC SFMR 2007-2013

	Study population N (%)
General characteristics	
Age at mammogram (years); Mean (SD)	56.4 (10.9)
BMI (kg/m^2); Mean (SD)	24.5 (4.6)
Underweight: <18.5	583 (2.4)
Normal weight: 18.5 - <25	15,363 (62.6)
Overweight: 25 - <30	5,938 (24.2)
Obese: 30+	2,672 (10.9)
Race	
Caucasian	16,268 (66.3)
African-American	519 (2.1)
Asian / Pacific Islander	6,184 (25.2)
Other	1,585 (6.4)
Education level	
< High school	747 (3.0)
High school diploma	1,820 (7.4)
Some college	4,970 (20.2)
College degree	17,019 (69.3)
First degree family history of breast cancer	4,787 (19.5)
Previous breast biopsy	5,785 (23.6)
Reproductive history	
Menopausal status	
Premenopausal	8,355 (34.0)
Postmenopausal	15,734 (64.1)
Ever given birth	16,315 (66.4)
Age at first birth	
Nulliparous	8,183 (33.3)
< 20 years	835 (3.4)
20 - 29 years	7,681 (31.3)
30 - 39 years	7,031 (28.6)
40+ years	826 (3.4)
Hormone therapy use (at first mammogram)	3,001 (12.2)
Birth control hormone use (at first mammogram)	1,493 (6.1)
Tamoxifen or raloxifene use (at first mammogram)	204 (< 1.0)

Percentages may not add to 100% due to unknown values (<10% for any characteristic)

Table 2

Cross-sectional association between BMI and volumetric density measures at first mammogram; BCSC SFMR 2007-2013

	N (women)	Mean (SD) at first mammogram	β (SE) [a, b]	95% CI	P value
All women	**24,556**				
Dense breast volume (cm^3)		142.3 (76.7)	2.95 (0.13)	2.69, 3.21	< 0.001
Non-dense breast volume (cm^3)		416.8 (331.0)	51.03 (0.56)	49.93, 52.13	< 0.001
Percent dense breast volume (%)		32.5 (19.5)	-2.03 (0.03)	-2.09, -1.98	< 0.001
Premenopausal at first mammogram	**8,355**				
Dense breast volume (cm^3)		166.7 (83.7)	3.05 (0.27)	2.51, 3.58	< 0.001
Non-dense breast volume (cm^3)		327.1 (303.2)	53.64 (0.98)	51.72, 55.55	< 0.001
Percent dense breast volume (%)		42.3 (21.3)	-2.88 (0.06)	-3.00, -2.77	< 0.001
Postmenopausal at first mammogram	**15,734**				
Dense breast volume (cm^3)		129.1 (69.1)	2.97 (0.16)	2.67, 3.28	< 0.001
Non-dense breast volume (cm^3)		465.6 (336.2)	49.96 (0.69)	48.61, 51.31	< 0.001
Percent dense breast volume (%)		27.3 (16.2)	-1.67 (0.03)	-1.73, -1.61	< 0.001

[a] Adjusted for age at first mammogram, race, education, first degree family history of breast cancer, history of breast biopsy, ever given birth (yes/no), menopausal status at first mammogram (all women), and hormone use at first mammogram

[b] Regression coefficient (β) represents the change in volumetric density measure associated with a 1 kg/m^2 difference in BMI, holding the covariates above constant.

Stratified results exclude 467 women with unknown menopausal status at first mammogram
P value for interaction by menopausal status: p=0.79 for DV, p<0.01 for NDV, p<0.01 for PDV

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Table 3

Change in BMI from first mammogram to last mammogram, stratified by menopausal status and by BMI at first mammogram (kg/m^2) (N=24,556); BCSC SFMR 2007-2013

	N (women)	> 10% loss N (%)	5-10% loss N (%)	Stable ± 5% N (%)	5-10% gain N (%)	> 10% gain N (%)
All women	**24,556**	**839 (3.4)**	**2,177 (8.9)**	**18,059 (73.6)**	**2,584 (10.5)**	**897 (3.6)**
Premenopausal (all exams)	**7,266**					
Underweight or normal: <25	5,203	45 (0.9)	271 (5.2)	4,163 (80.0)	558 (10.7)	166 (3.2)
Overweight: 25 - <30	1,487	71 (4.8)	172 (11.6)	983 (66.0)	185 (12.4)	78 (5.2)
Obese: 30+	576	57 (9.9)	65 (11.3)	356 (61.8)	78 (13.5)	20 (3.5)
Postmenopausal (all exams)	**15,715**					
Underweight or normal: <25	9,682	168 (1.7)	735 (7.6)	7,489 (77.4)	956 (9.9)	331 (3.4)
Overweight: 25 - <30	4,093	239 (5.8)	513 (12.5)	2,787 (68.1)	417 (10.2)	137 (3.4)
Obese: 30+	1,940	191 (9.9)	272 (14.0)	1,224 (63.1)	181 (9.3)	72 (3.7)

Stratified results exclude 486 women with unknown menopausal status at one or more mammogram(s) and 1,089 women who transitioned from pre- to postmenopausal during the study period.

Table 4

Association between annual increase in BMI and annual change in volumetric mammographic breast density, stratified by menopausal status and BMI at first mammogram (kg/m^2): BCSC SFMR 2007-2013

		Annual change in dense breast volume (cm^3 per year)			Annual change in non-dense breast volume (cm^3 per year)			Annual change in percent dense breast volume (% per year)		
	N (women)	β (SE) [a]	95% CI	p value	β (SE) [a]	95% CI	p value	β (SE) [a]	95% CI	p value
All women	**24,556**	**-1.01 (0.30)**	**-1.59, -0.42**	**0.001**	**26.2 (1.38)**	**23.45, 28.87**	**< 0.001**	**-1.17 (0.07)**	**-1.31, -1.04**	**< 0.001**
Premenopausal (all exams)	**7,266**	**-1.73 (0.73)**	**-3.17, -0.30**	**0.02**	**32.64 (2.63)**	**27.47, 37.80**	**< 0.001**	**-1.83 (0.14)**	**-2.10, -1.56**	**< 0.001**
Underweight or normal: <25	5,203	0.92 (0.74)	-0.52, 2.37	0.21	31.17 (2.65)	25.97, 36.37	< 0.001	-2.84 (0.23)	-3.30, -2.38	< 0.001
Overweight: 25 - <30	1,487	-2.71 (0.98)	-4.63, -0.80	0.01	33.56 (4.50)	24.74, 42.37	< 0.001	-1.47 (0.21)	-1.87, -1.07	< 0.001
Obese: 30+	576	-3.29 (1.90)	-7.01, 0.44	0.08	32.63 (6.48)	19.93, 45.32	< 0.001	-0.86 (0.17)	-1.18, -0.53	< 0.001
Postmenopausal (all exams)	**15,715**	**-0.74 (0.32)**	**-1.36, -0.12**	**0.02**	**24.08 (1.63)**	**20.89, 27.27**	**< 0.001**	**-0.95 (0.08)**	**-1.10, -0.80**	**< 0.001**
Underweight or normal: <25	9,682	-0.32 (0.32)	-0.95, 0.31	0.32	22.93 (2.95)	17.15, 28.70	< 0.001	-1.51 (0.20)	-1.91, -1.11	< 0.001
Overweight: 25 - <30	4,093	-0.94 (0.66)	-2.23, 0.36	0.16	31.09 (1.73)	27.70, 34.47	< 0.001	-1.08 (0.11)	-1.29, -0.87	< 0.001
Obese: 30+	1,940	-0.53 (0.61)	-1.73, 0.67	0.39	20.57 (2.56)	15.55, 25.58	< 0.001	-0.35 (0.09)	-0.52, -0.17	< 0.001

[a] Adjusted for age at first mammogram, age at first birth, history of breast biopsy, education, ever given birth (yes/no), first degree family history of breast cancer, hormone use during study period, menopausal status (all women), and race

Stratified results exclude 486 women with unknown menopausal status at one or more mammogram(s) and 1,089 women who transitioned from pre- to postmenopausal during the study period.

P value for interaction by menopausal status: DV p=0.43, NDV p=0.01, PDV p<0.01
P value for interaction by BMI at first mammogram among:
premenopausal women: DV p<0.01, NDV p=0.87, PDV p<0.01
postmenopausal women: DV p=0.67, NDV p<0.01, PDV p<0.01