Adiposity Change Over the Life Course and Mammographic Breast Density in Postmenopausal Women

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ABSTRACT

Mammographic breast density is a strong risk factor for breast cancer. We comprehensively investigated the associations of body mass index (BMI) change from ages 10, 18, and 30 to age at mammogram with mammographic breast density in postmenopausal women. We used multivariable linear regression models, adjusted for confounders, to investigate the associations of BMI change with volumetric percent density, dense volume, and nondense volume, assessed using Volpara in 367 women. At the time of mammogram, the mean age was 57.9 years. Compared with women who had a BMI gain of 0.1–5 kg/m^2 from age 10, women who had a BMI gain of 5.1–10 kg/m^2 had a 24.4% decrease [95% confidence interval (CI), 6.0%–39.2%] in volumetric percent density; women who had a BMI gain of 10.1–15 kg/m^2 had a 46.1% decrease (95% CI, 33.0%–56.7%) in volumetric percent density; and women who had a BMI gain of >15 kg/m^2 had a 56.5% decrease (95% CI, 46.0%–65.0%) in volumetric percent density. Similar, but slightly attenuated associations were observed for BMI gain from ages 18 and 30 to age at mammogram and volumetric percent density. BMI gain over the life course was positively associated with nondense volume, but not dense volume. We observed strong associations between BMI change over the life course and mammographic breast density. The inverse associations between early-life adiposity change and volumetric percent density suggest that childhood adiposity may confer long-term protection against postmenopausal breast cancer via its effect of mammographic breast density.

Introduction

High-mammographic breast density is a well-established risk factor for breast cancer (1–4). Women with ≥75% mammographic breast density have a 4- to 6-fold increased risk of breast cancer than women with ≤5% mammographic breast density (5–7). The underlying mechanisms through which mammographic breast density increases breast cancer risk are, however, not well understood. Although mammographic breast density is highly heritable, it is also influenced by shared risk factors for breast cancer (8–10).

Obesity is associated with a higher risk of developing breast cancer in postmenopausal women, especially hormone receptor–positive disease (11–13). We recently showed that adiposity at age 18 was inversely associated with both premenopausal and postmenopausal breast cancer, and long-term weight gain from age 18 both during premenopause and postmenopause were associated with increased risk of postmenopausal breast cancer (14). In addition to being a risk factor, mammographic breast density is an intermediate phenotype for breast cancer (4); therefore it is possible that the associations of changes in adiposity over the life course with breast cancer risk is mediated through its associations with mammographic breast density (15). However, only a limited number of studies have investigated the association between long-term adiposity change and mammographic breast density in postmenopausal women, with conflicting results (16–18). While one study reported an inverse association between weight gain from age 18 and mammographic breast density (16), two other studies reported positive associations (17, 18), hence, new studies are needed to clarify the associations of long-term adiposity change with mammographic breast density. Furthermore, there is no data on the association of adiposity change since age 10 with mammographic breast density in postmenopausal women, in spite of the fact that weight change since age 10 is strongly associated with breast cancer risk and may partly explain the

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association of weight change since age 18 with breast cancer risk (14).

We, therefore, comprehensively investigated the associations between adiposity change [both body mass index (BMI) and weight change] from childhood (age 10), late adolescence (age 18), and early adulthood (age 30) to postmenopausal age with volumetric measures of mammographic breast density in women free from breast cancer.

Materials and Methods

Study design and populations

We recruited 400 mid-life postmenopausal women undergoing annual screening mammogram at the Joanne Knight Breast Health Center, at Siteman Cancer Center at Washington University School of Medicine (St. Louis, MO) between October 2017 and September 2018.

Women were eligible to participate in the study if they met the following inclusion criteria: (i) ages 50–64 years, (ii) postmenopausal, and (iii) able to comply with all required study procedures and schedule, including provision of blood samples at the time of enrollment. Exclusion criteria were: (i) history of any cancer, including breast cancer; (ii) history of breast augmentation, reduction, or implants; and (iii) history of selective estrogen receptor modulators or denosumab use over the previous 6 months. Postmenopause was defined using a modification of the National Comprehensive Cancer Network definition, which does not require measurement of serum hormone levels (19). A woman was considered postmenopausal if she had either a prior bilateral oophorectomy, was age 60 or older, or if under age 60, had been amenorrhoeic for at least 12 months.

Eligible participants were mailed study flyers by research coordinators 2–4 weeks in advance of screening mammography. On the day of their mammogram, each study participant completed a blood draw and questionnaires that ascertained breast cancer risk factors and potential determinants of mammographic breast density. We excluded 32 women with error messages when their raw mammogram images were converted to volumetric measures using Volpara, and one woman due to missing information on weight at mammogram; hence, our final study population consisted of 367 women. The study was approved by the Institutional Review Boards of the Washington University School of Medicine (St. Louis, MO). All study participants provided informed consent.

Adiposity measures and adiposity change

Weight at mammogram was measured in light clothing without shoes using the OMRON full body sensor body composition monitor and scale (model HBF-514C), which also estimated percentage body fat. Height was measured using a fixed stadiometer. Waist circumference (cm) was measured as the point midway between the costal margin and iliac crest in the mid-axillary line. Hip circumference (cm) was measured at the widest point around the greater trochanter. Weight at ages 18 and 30 were obtained from questionnaires provided by study participants. We calculated BMI at different ages (ages 18, 30, and age at mammogram) by dividing weight (kg) at each age with height (m) squared (kg/m^2) at mammogram. Body size at age 10 was self-reported using the 9-level figure somatotype pictogram developed by Stunkard and colleagues (20). For this study, the Stunkard 9-level figure pictogram was categorized into four groups: (i) body size 1 or 2; (ii) body size 3 or 4; (iii) body size 5; and (iv) body size 6 or higher. We estimated BMI at age 10 using BMI and Stunkard pictograms, both provided at age 10, from the Growing Up Today Study (21, 22). Because the Stunkard 9-level figure somatotype pictogram for girls in the Growing Up Today Study ranged from 1 to only 7, we did not compute BMI at age 10 for 10 women in our study, whose body sizes at age 10 were larger than 7 (8 or 9).

We derived BMI change trajectories for three time periods, (i) between BMI at mammogram and BMI at age 10, (ii) between BMI at mammogram and BMI at age 18, and (iii) between BMI at mammogram and BMI at age 30. We defined the categories of BMI change as: (i) BMI loss, (ii) BMI gain of 0.1–5 kg/m^2, (iii) BMI gain of 5.1–10 kg/m^2, (iv) BMI gain of 10.1–15 kg/m^2, and (v) BMI gain >15 kg/m^2. We derived weight change trajectories for two time periods: (i) between weight at mammogram and weight at age 18, and (ii) between weight at mammogram and weight at age 30. We had no data on weight at age 10, hence we did not evaluate weight change from age 10. We defined the categories of weight change as: (i) weight loss, (ii) weight gain of 0.1–10 kg, (iii) weight gain of 10.1–20 kg, (iv) weight gain of 20.1–30 kg, and (v) weight gain >30 kg.

Volumetric mammographic breast density measures

We used Volpara [version 1.5, (Matakina Technology Limited)] to obtain automated, objective volumetric mammographic breast density measurements. Volpara measures volumetric percent density, dense volume, and nondense volume (23, 24). Volumetric percent density values range from 0.5% to 34.5%. Compared with Breast Imaging Reporting and Data System 5th edition, Volpara volumetric percent density translates to (i) <3.5%; (ii) ≥3.5 and <7.5%; (iii) ≥7.5 and <15.5%; and (iv) ≥15.5%. Volpara measures have been validated in many studies (25, 26), and are highly reproducible (within-breast density measurement SD is 0.99%; ref. 27).

Statistical analysis

We calculated descriptive statistics, mean and SD for continuous variables and percentages for categorical variables as appropriate. We investigated age-adjusted correlations between adiposity measures and mammographic breast density measures using Spearman partial correlation coefficients (r). Next, we used multivariable linear regression models to evaluate the associations of adiposity change over the life course with postmenopausal mammographic breast density measures. Volumetric percent density, dense volume, and nondense volume were all natural log transformed to ensure the

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normality of the residuals. The beta coefficients and 95% confidence intervals (CI) from the regression models were back-transformed to allow an easier interpretation of the results. The back-transformed beta coefficients are presented as percentage differences (Diff %), which is estimated as Diff % $= (\exp(\beta) - 1) \times 100$, and interpreted as a unit change in an adiposity measure associated with percent change in volumetric percent density, dense volume, or nondense volume. We adjusted the multivariable linear regression models for age at mammogram (continuous, years), family history of breast cancer (yes/no), age at menarche (continuous, years), parity and age at first birth (categorical), race (Non-Hispanic white/African American/Others), current alcohol consumption (yes/no), ever use of menopausal hormone therapy (yes/no), and BMI at age 10 (continuous, kg/m^2). These variables were selected as potential confounders *a priori* on the basis of their established associations with mammographic breast density and/or breast cancer risk. In addition, they were statistically significant in the final multivariable regression models. We also evaluated the associations of adiposity change at various time periods and adiposity measures at time of mammogram (e.g., percentage body fat and hip and waist circumference) with mammographic breast density in multivariable linear regression models. We further stratified our analyses by race and use of menopausal hormone therapy. Interactions between variables (race, or menopausal hormone therapy) and BMI change over the life course were assessed by including cross-product terms (i.e., race $\times$ BMI change, menopausal hormone therapy $\times$ BMI change) in multivariable-adjusted models. The statistical significance of an interaction term was based on Wald tests. We used SAS statistical software (version 9.4; SAS Institute Inc) for analyses. All *P* values were two-sided and $P < 0.05$ was considered statistically significant.

Results

The mean age at the time of screening mammogram was 57.9 years (range, 50–65 years; **Table 1**). The majority (62.1%) of participants were non-Hispanic Whites, and 35.4% were African Americans. The mean BMIs at different ages were: 17.2 kg/m^2 (age 10), 21.8 kg/m^2 (age 18), 25.1 kg/m^2 (age 30), and 31.3 kg/m^2 (age at mammogram). The mean volumetric percent density was 6.2% (range, 1.7%–35%), the mean dense volume was 121.4 cm^3 (range, 10.2 cm^3–913.8 cm^3), and the mean nondense volume was 2,136.8 cm^3 (range, 143.9 cm^3–12,708.7 cm^3).

The mean volumetric percent density by BMI change category, stratified by three time periods, is presented in **Fig. 1**. From age 10 to age at mammogram, the mean volumetric percent density decreased from 10.5% to 4.4% comparing women who had a BMI gain of 0.1–5 kg/m^2 to women who had a BMI gain >15 kg/m^2 (**Fig. 1A**). Similar decreases in the mean volumetric percent density were observed from ages 18 and 30 to age at mammogram (**Fig. 1B** and **C**).

Age-adjusted Spearman partial correlations between adiposity measures and mammographic breast density measures are summarized in **Table 2**. All adiposity measures (except for height) were significantly inversely correlated with volumetric percent density (*r* range, −0.18 to −0.59), with the strongest correlation for BMI at mammogram and weight at mammogram ($r = -0.59$) and positively correlated with nondense volume (*r* range, 0.14–0.50), with the strongest correlation for

Table 1. Characteristics of 367 postmenopausal women recruited during annual screening mammogram at the Joanne Knight Breast Health Center, Washington University School of Medicine (St. Louis, MO).

Characteristics	*N*	Mean ± SD/ percentage (%)
Age at mammogram (years)	367	57.94 ± 3.82
Age at menarche (years)[a]	361	12.76 ± 1.70
Parity and age at first birth[b]		
Nulliparous	63	17.17%
1–2 children, <25 years	84	22.89%
1–2 children, 25–29 years	63	17.17%
1–2 children, ≥30 years	57	15.53%
≥3 children, <25 years	63	17.17%
≥3 children, ≥25 years	33	8.99%
Ever breastfeed	164	44.69%
Family history of breast cancer[c]	91	24.80%
Ever used menopausal hormone therapy[d]	122	33.24%
Race		
Non-Hispanic White	228	62.13%
African American	130	35.42%
Others	9	2.45%
Education[e]		
High school or less than high school	64	17.44%
Post high school training or some college	106	28.88%
College graduate	105	28.61%
Postgraduate	90	24.52%
Current alcohol consumption[f]	217	59.13%
Adiposity measures[g]		
Body fat (%)[h]	362	41.31 ± 8.64
Hip circumference (cm)[h]	365	110.09 ± 18.45
Waist circumference (cm)[h]	366	96.05 ± 18.39
Height (cm)[h]	367	163.51 ± 6.69
BMI at age 10 years (kg/m^2)[i]	357	17.21 ± 2.99
BMI at age 18 years (kg/m^2)[i]	367	21.80 ± 4.46
BMI at age 30 years (kg/m^2)[i]	367	25.08 ± 5.90
BMI at mammogram (kg/m^2)[i]	367	31.28 ± 7.70
Weight at age 18 years (kg)	367	58.05 ± 10.91
Weight at age 30 years (kg)	367	66.72 ± 14.43
Weight at mammogram (kg)	367	83.53 ± 20.55
Mammographic density		
Volumetric percent density (%)	367	6.22 ± 4.15
Dense volume (cm^3)	367	121.36 ± 125.22
Non-dense volume (cm^3)	367	2,136.76 ± 2,064.92

[a]Six women had missing information for age at menarche.
[b]Four women had missing information for parity and age at first birth.
[c]Six women had missing information for family history of breast cancer.
[d]One woman had missing information for ever use of menopausal hormone therapy.
[e]Two women had missing information for education.
[f]Two women had missing information for current alcohol consumption.
[g]Five women had missing information for body fat, two women had missing information for hip circumference, one woman had missing information for waist circumference, and 10 women had missing information for BMI at age 10.
[h]Adiposity measures at the time of mammogram.
[i]BMI was calculated as weight (kg) at each age divided by height squared (m^2).

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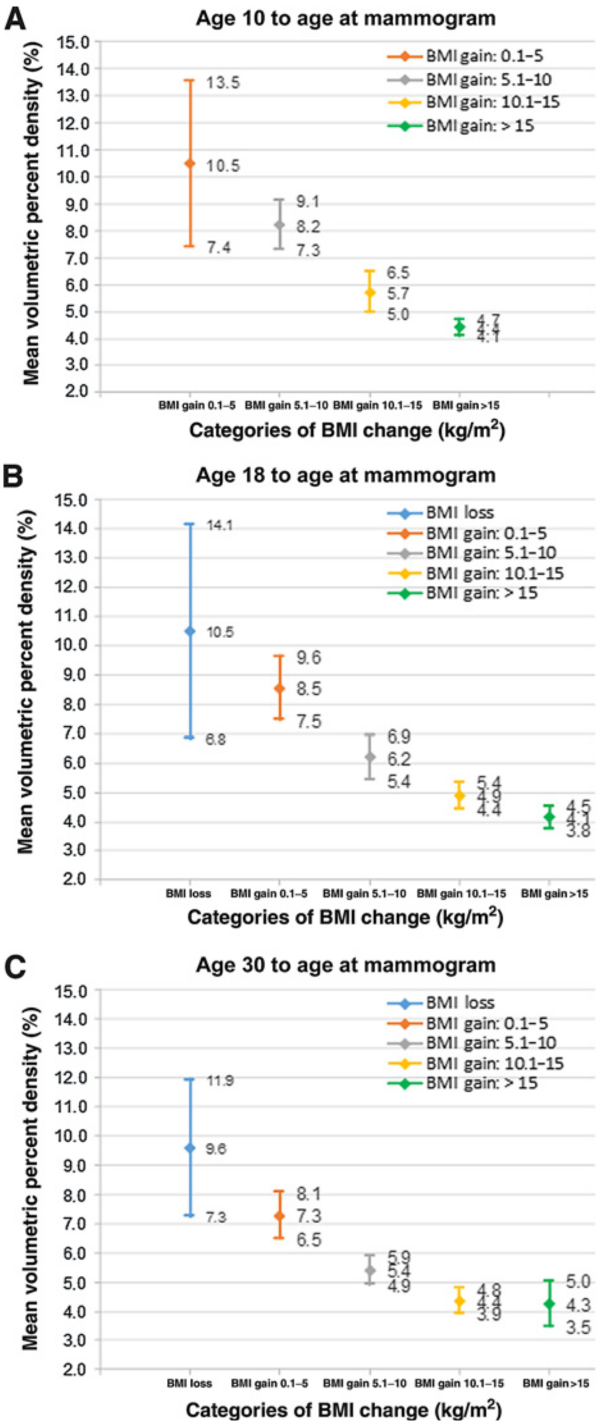

Figure 1.

A–C, Mean volumetric percent density and 95% CI of BMI changes over the life course among 367 postmenopausal women. There were 356 women who had BMI gain from age 10 to age at mammogram, we did not show data on one woman who had BMI loss from age 10 to age at mammogram; 10 women had missing information for BMI from age 10 to age at mammogram.

weight at mammogram and hip circumference at mammogram ($r = 0.50$). We observed weaker positive correlations between adiposity measures and dense volume.

BMI at age 10 was inversely associated with volumetric percent density. A 1 kg/m^2 increase in BMI at age 10 was associated with a 2.3% lower (95% CI, 0.5%–4.0%) volumetric percent density ($P = 0.01$; **Table 3**). There were strong inverse associations between BMI changes during the life course and volumetric percent density (**Table 3**). The largest decreases in volumetric percent density were observed for BMI gain from age 10 to age at mammogram. Compared with women who had a BMI gain of 0.1–5 kg/m^2 from age 10, women who had a BMI gain of 5.1–10 kg/m^2 had a 24.4% decrease (95% CI, 6.0%–39.2%) in volumetric percent density; women who had a BMI gain of 10.1–15 kg/m^2 had a 46.1% (95% CI, 33.0%–56.7%) decrease in volumetric percent density; and women who had a BMI gain of >15 kg/m^2 had a 56.5% decrease (95% CI, 46.0%–65.0%) in volumetric percent density. A 1 kg/m^2 increase in BMI from age 10 to age at mammogram was associated with a 3.5% decrease (95% CI, 2.8%–4.2%) in volumetric percent density (Supplementary Table S1). Similar, but slightly attenuated associations were observed for BMI changes from ages 18 and 30 and volumetric percent density (**Table 3**). Compared with women who had a BMI gain of 0.1–5 kg/m^2, women who had a BMI gain >15 kg/m^2 from age 18 had a 46.2% decrease (95% CI, 37.2%–53.9%), and those who had a BMI gain of >15 kg/m^2 from age 30 had a 34.0% decrease (95% CI, 18.6%–46.4%) in volumetric percent density. Women who had a reduction in BMI from age 30 had a 23.4% increase (95% CI, 3.6%–47.1%) in volumetric percent density, compared with women who had a BMI gain of 0.1–5 kg/m^2. BMI reduction from age 18 was associated with a 6.4% increase in volumetric percent density, but it was not statistically significant.

BMI gain over the life course was positively associated with nondense volume, but not dense volume (**Table 3**). Compared with women who had a BMI gain of 0.1–5 kg/m^2 from age 10, women who had a BMI gain of 5.1–10 kg/m^2 had a statistically nonsignificant 17.0% increase in nondense volume; women who had a BMI gain of 10.1–15 kg/m^2 had a 124.4% increase (95% CI, 48.4%–239.5%) in nondense volume; and women who had a BMI gain of >15 kg/m^2 had a 174.6% increase (95% CI, 82.6%–313.1%) in nondense volume. The associations of BMI changes from ages 18 and 30 to age at mammogram with nondense volume were similar to those of BMI change from age 10. There were no consistent associations between BMI change over the life course and dense volume, although women who gained >15 BMI units after age 18 had a significant increase in dense volume.

The associations of weight change over the life course and mammographic breast density were very similar to what we observed for BMI change (**Table 4**).

We further examined the associations between adiposity change over the life course and volumetric percent density stratified by race (Supplementary Table S2) and menopausal hormone therapy (Supplementary Table S3). We observed no interaction by race or by menopausal hormone therapy.

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Table 2. Partial spearman correlation coefficients between adiposity measures and mammographic breast density[a].

Adiposity measures	N	Volumetric percent density (%)	Dense volume (cm^3)	Nondense volume (cm^3)
Body fat (%)[b]	362	−0.54*	0.21*	0.44*
Hip circumference (cm)[b]	365	−0.52*	0.26*	0.50*
Waist circumference (cm)[b]	366	−0.57*	0.22*	0.49*
Height (cm)[b]	367	0.00	0.01	0.03
BMI at age 10 years (kg/m^2)	357	−0.18*	0.12*	0.19*
BMI at age 18 years (kg/m^2)	367	−0.20*	0.08	0.14*
BMI at age 30 years (kg/m^2)	367	−0.35*	0.16*	0.30*
BMI at mammogram (kg/m^2)	367	−0.59*	0.23*	0.49*
BMI change from age 10 to age at mammogram (kg/m^2)	357	−0.53*	0.21*	0.44*
BMI change from age 18 to age at mammogram (kg/m^2)	367	−0.52*	0.20*	0.44*
BMI change from age 30 to age at mammogram (kg/m^2)	367	−0.47*	0.15*	0.37*
Weight at age 18 years (kg)	367	−0.21*	0.09	0.18*
Weight at age 30 years (kg)	367	−0.37*	0.19*	0.35*
Weight at mammogram (kg)	367	−0.59*	0.24*	0.50*
Weight change from age 18 to age at mammogram (kg)	367	−0.54*	0.22*	0.47*
Weight change from age 30 to age at mammogram (kg)	367	−0.48*	0.16*	0.39*

*Correlation is statistical significant at the *P*-value < 0.05 level.
[a]All Spearman partial correlation models were adjusted for age at mammogram (continuous, years); Spearman partial correlation coefficient statistically significant at $P < 0.05$.
[b]Adiposity measures at the time of mammogram.

Discussion

BMI (and weight) gains after ages 10, 18, and 30 were inversely associated with volumetric percent density, while BMI (and weight) loss after age 30 was positively associated with volumetric percent density in postmenopausal women. Associations did not differ by race or menopausal hormone therapy use. To the best of our knowledge, our study is the first to comprehensively investigate the associations of

Table 3. Multivariable-adjusted associations between changes in BMI over the life course and mammographic breast density.

BMI[a]	N (%)	Volumetric percent density (%) Diff % (95% CI)[b]	Dense volume (cm^3) Diff % (95% CI)[b]	Nondense volume (cm^3) Diff % (95% CI)[b]
BMI at age 10 years (kg/m^2)[c]	357 (97.3%)	**−2.3 (−4.0** to **−0.5)**	1.4 (−1.6–4.4)	**3.4 (0.2–6.7)**
BMI change from age 10 to age at mammogram (kg/m^2)[d]				
BMI gain: 0.1–5	19 (5.2%)	Reference	Reference	Reference
BMI gain: 5.1–10	99 (27.0%)	**−24.4 (−39.2** to **−6.0)**	−17.5 (−46.2–26.3)	17.0 (−22.6–76.7)
BMI gain: 10.1–15	102 (27.8%)	**−46.1 (−56.7** to **−33.0)**	6.2 (−30.7–62.9)	**124.4 (48.4–239.5)**
BMI gain: >15	136 (37.1%)	**−56.5 (−65.0** to **−46.0)**	10.7 (−27.4–68.7)	**174.6 (82.6–313.1)**
BMI change from age 18 to age at mammogram (kg/m^2)[d]				
BMI loss	18 (4.9%)	6.4 (−16.3–35.2)	−8.9 (−41.6–41.9)	−16.4 (−46.1–29.8)
BMI gain: 0.1–5	81 (22.1%)	Reference	Reference	Reference
BMI gain: 5.1–10	108 (29.4%)	**−24.8 (−34.3** to **−14.0)**	15.4 (−10.1–48.1	**64.2 (28.3–110.3)**
BMI gain: 10.1–15	96 (26.2%)	**−38.3 (−46.2** to **−29.3)**	11.5 (−13.5–43.7)	**89.3 (47.2–143.5)**
BMI gain: >15	64 (17.4%)	**−46.2 (−53.9** to **−37.2)**	**53.3 (15.2–104.1)**	**179.8 (110.7–271.5)**
BMI change from age 30 to age at mammogram (kg/m^2)[d]				
BMI loss	36 (9.8%)	**23.4 (3.6–47.1)**	26.0 (−8.4–73.3)	−12.5 (−36.8–21.1)
BMI gain: 0.1–5	129 (35.2%)	Reference	Reference	Reference
BMI gain: 5.1–10	119 (32.4%)	**−23.0 (−31.6** to **−13.3)**	11.0 (−10.4–37.6)	**43.6 (15.4–78.7)**
BMI gain: 10.1–15	58 (15.8%)	**−32.5 (−41.7** to **−21.8)**	25.2 (−4.1–63.3)	**79.6 (36.9–135.6)**
BMI gain: >15	25 (6.8%)	**−34.0 (−46.4** to **−18.6)**	43.8 (−1.6–109.9)	**118.5 (48.4–221.7)**

Bold terms denote statistical significance at the *P*-value < 0.05 level.
[a]There were 357 women who had BMI at age 10, 10 women had missing information for BMI at age 10; there were 356 women who had BMI gain from age 10 to age at mammogram, we did not show data on one woman who had BMI loss from age 10 to age at mammogram; and 10 women had missing information for BMI from age 10 to age at mammogram.
[b]Diff % represents one unit change in BMI associated with percent change in volumetric percent density, dense volume, and nondense volume.
[c]All models were adjusted for age at mammogram (continuous, years), family history of breast cancer (yes/no), age at menarche (continuous, years), parity and age at first birth (categorical), race (Non-Hispanic white/African American/Others), current alcohol consumption (yes/no), and menopausal hormone therapy use (yes/no).
[d]All models were adjusted for age at mammogram (continuous, years), family history of breast cancer (yes/no), age at menarche (continuous, years), parity and age at first birth (categorical), race (Non-Hispanic white/African American/Others), current alcohol consumption (yes/no), menopausal hormone therapy use (yes/no), and BMI at age 10 (continuous, kg/m^2).

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Table 4. Multivariable-adjusted associations between change in weight over the life course and mammographic breast density.

Weight change[a]	*N* (%)	Volumetric percent density (%) Diff % (95% CI)[b]	Dense volume (cm³) Diff % (95% CI)[b]	Nondense volume (cm³) Diff % (95% CI)[b]
Weight change from age 18 to age at mammogram (kg)				
Weight loss	15 (4.1%)	19.4 (−8.3–55.4)	−0.4 (−39.7–64.3)	−18.6 (−50.1–32.9)
Weight gain: 0.1–10	55 (15.0%)	Reference	Reference	Reference
Weight gain: 10.1–20	75 (20.4%)	**−17.1** (**−29.0** to **−3.1**)	21.2 (−9.8–62.9)	**50.4 (12.6–100.8**)
Weight gain: 20.1–30	89 (24.3%)	**−33.9** (**−43.4** to **−22.8**)	19.4 (−11.1–60.4)	**96.5 (47.3–162.3**)
Weight gain: >30	133 (36.2%)	**−46.1** (**−53.4** to **−37.6**)	**41.8 (7.4–87.2**)	**169.9 (105.6–254.2**)
Weight change from age 30 to age at mammogram (kg)				
Weight loss	30 (8.2%)	**23.7 (2.2–49.7**)	42.0 (−0.5–102.6)	−0.6 (−30.3–41.8)
Weight gain: 0.1–10	91 (24.8%)	Reference	Reference	Reference
Weight gain: 10.1–20	112 (30.5%)	**−24.4** (**−33.4** to **−14.2**)	18.8 (−6.2–50.4)	**67.6 (32.4–112.1**)
Weight gain: 20.1–30	77 (21.0%)	**−33.5** (**−42.3** to **−23.3**)	**33.1 (2.1–73.4**)	**106.4 (58.5–168.9**)
Weight gain: >30	57 (15.5%)	**−41.9** (**−50.2** to **−32.2**)	**38.6 (4.1–84.7**)	**140.9 (80.9–220.7**)

[a]All models were adjusted for age at mammogram (continuous, years), family history of breast cancer (yes/no), age at menarche (continuous, years), parity and age at first birth (categorical), race (Non-Hispanic white/African American/Others), current alcohol consumption (yes/no), menopausal hormone therapy use (yes/no), and for BMI at age 10 (continuous, kg/m^2).

[b]Diff % represents one unit change in weight associated with percent change in volumetric percent density, dense volume, and nondense volume.

adiposity change over the life course with volumetric measures of mammographic breast density in postmenopausal women.

The biological mechanisms through which adiposity change over the life course influences mammographic breast density in postmenopausal women are not well known, and the relation between adiposity and breast density features is complex, which is also complicated by dynamic changes in the body and breast composition over time (28). Adipose tissue is the largest endocrine organ in the body and the main source of peripheral estrogens, especially in postmenopausal women (29), thus adiposity change could play a role in hormone homeostasis throughout life (30). Increased childhood or adolescent adiposity modulate hormonal exposure (e.g., estrogen) and growth factor levels, thus influence breast cellular proliferation and breast density tissue development later in life (31–34). Progesterone signaling and, more recently, stem cell biology have also been shown to be associated with mammographic breast density. Progesterone increases breast density, and breast cancer incidence, independent of estrogen (35, 36). A recent study showed that the expression of stem cell markers was increased in dense breast tissue as compared with nondense breast tissue within the same woman (37).

The inverse associations we observed suggest that childhood adiposity may confer long-term protection on breast cancer risk, probably, via its effect on breast density. Childhood adiposity is inversely associated with the risk of both pre- and postmenopausal breast cancer, suggesting a long-term protective effect of adiposity at young ages on breast cancer risk later in life (38). This is in contrast with the higher risk of breast cancer in postmenopausal women who have greater body adiposity in adulthood (11–13). Early life, including childhood and adolescence, is a critical window for breast development (14). The rapid growth of breast tissue during this period, together with changing hormonal milieu, may influence mammographic breast density later in life and future breast cancer development (39, 40).

Our results are similar to those from the Nurses' Health Study where the authors reported an inverse association between weight gain after age 18 and percent density after adjusting for BMI at age 18 (beta coefficient range, −0.029 to −0.032, for the difference in percent mammographic breast density for every unit weight; ref. 16). They did not, however, report on the associations of BMI change since age 10 and mammographic breast density, hence, we provide novel data on adiposity change since age 10 and mammographic breast density. Another longitudinal study demonstrated that a short-term increase in BMI over a 2 year period was associated with a decrease in percent dense volume (28). In contrast, two other studies reported that weight gain since age 18 was positively associated with percent breast density in postmenopausal women (17, 18).These two studies, did not, however, adjust their analyses for early-life weight, but adjusted for current weight, which likely accounts for the differences in results. We previously observed that adiposity measures at mammogram were correlated with adult weight gain in premenopausal women, thus, including the adiposity measure at mammogram in the regression models could lead to multicollinearity (41). We adjusted for BMI at age 10 instead of BMI at mammogram to take into consideration an individual's initial body size, which likely explains why our findings are consistent with those of Nurses' Health Study, that also adjusted for BMI at age 18 (16).

Our study has several strengths. Study participants were recruited among women attending annual routine screening mammogram, which enhances generalizability. We assessed mammographic breast density using Volpara, which provides robust volumetric measures of density, and is highly reproducible (42, 43). Furthermore, our analytic approach is

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strengthened by controlling for important confounders, including adiposity at age 10.

Our study has limitations. This is a cross-sectional study, and body size at age 10 and weight at ages 18 and 30 were collected retrospectively. However, studies have demonstrated that there is a high correlation between individuals' adult-recalled body size at earlier life and their measured BMI at earlier life (44, 45).

In conclusion, changes in BMI and weight from childhood, late adolescence, and early adulthood were associated with mammographic breast density in postmenopausal women. The inverse associations between early-life adiposity change and volumetric percent density suggest that childhood adiposity may confer long-term protection against breast cancer via its effect of mammographic breast density. There is a need to better understand how long-term adiposity changes, especially since age 10 is associated with mammographic breast density, as this could have utility in breast cancer prevention.

Disclosure of Potential Conflicts of Interest

C.M. Appleton reports personal fees and other from WhiteRabbit, Inc. outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The funders had no role in study design, data collection, analysis, interpretation of data, preparation of the article, or decision to publish. All authors had full access to all the data and analyses and had final responsibility for the decision to submit for publication.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.R. Herman, C.M. Appleton, A.T. Toriola
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Han, C.S. Berkey, A. Alimujiang, G.A. Colditz, A.T. Toriola
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