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Research Article

Cancer Prevention Research

Adiposity at Age 10 and Mammographic Density among Premenopausal Women

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Abstract

Although childhood adiposity is inversely associated with breast cancer risk, the association of childhood adiposity with mammographic density in premenopausal women has not been adequately studied. We analyzed data from 365 premenopausal women who came in for screening mammography at Washington University (St. Louis, MO) from 2015 to 2016. Body size at age 10 was self-reported using somatotype pictogram. Body mass index (BMI) at age 10 was imputed using data from Growing Up Today Study. Volpara software was used to evaluate volumetric percent density (VPD), dense volume (DV), and nondense volume (NDV). Adjusted multivariable linear regression models were used to evaluate the associations between adiposity at age 10 and mammographic density measures. Adiposity at age 10 was inversely associated with VPD and positively associated with NDV. A 1 kg/m^2 increase in BMI at age 10 was associated with a 6.4% decrease in VPD, and a 6.9% increase in NDV ($P < 0.001$). Compared with women whose age 10 body size was 1 or 2, women with body size 3 or 4 had a 16.8% decrease in VPD and a 26.6% increase in NDV, women with body size 5 had a 32.2% decrease in VPD and a 58.5% increase in NDV, and women with body sizes ≥6 had a 47.8% decrease in VPD and a 80.9% increase in NDV ($P < 0.05$). The associations were attenuated, but still significant after adjusting for current BMI. Mechanistic studies to understand how childhood adiposity influences breast development, mammographic density, and breast cancer in premenopausal women are needed. *Cancer Prev Res; 11(5); 1–7. ©2018 AACR.*

Introduction

Mammographic breast density is an established risk factor for breast cancer (1–3). Women with dense breasts on mammogram are 4 to 6 times more likely to develop breast cancer compared with women with almost entirely fatty breasts (1, 3). Higher breast density is also associated with more invasive tumor types (4). With 40% to 50% of women in the United States presenting with heterogeneously dense or extremely dense breasts, (5, 6), there is a need to better understand the determinants of dense breasts.

Early-life adiposity may influence breast morphology and possibly future breast density. We recently reported that body mass index (BMI) at age 18 as well as weight gain from age 18 were inversely associated with mammographic density in premenopausal women (7). Studies have also investigated the associations of childhood adiposity with mammographic density. These studies have, however, been conducted mainly among postmenopausal women, and limited data exist in premenopausal women. Although some of the studies in premenopausal women have reported inverse associations between childhood adiposity and percent density (8–10), others have not (11–13). Interestingly, although the studies by Sellers and colleagues and Lope and colleagues (11, 12) observed inverse associations between childhood adiposity and mammographic density among postmenopausal women, they reported no associations among premenopausal women, attesting to the fact that the effect of childhood adiposity on mammographic density differs by menopausal status. A good understanding of how early-life adiposity relates to mammographic density in premenopausal women may provide insight into breast cancer prevention. Furthermore, studies evaluating the associations of childhood adiposity with mammographic density in premenopausal women used body fatness between ages 7 and 16, periods with very divergent hormonal exposure. This has led to suggestions that pubertal hormone-driven increase in adiposity may be responsible for the observed associations. Only one study conducted in Mexico has evaluated associations stratified

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by age at menarche. The study did not observe associations between childhood adiposity and mammographic density in the overall analyses, as well as adiposity before and after menarche (13). Our objective in this study is to investigate the associations of adiposity at age 10 with volumetric measures of mammographic density, and to determine whether these are modified by age at menarche.

Materials and Methods

Study population and design

Between December 2015 and October 2016, we recruited 383 premenopausal women who were scheduled for annual screening mammography at the Joanne Knight Breast Health Center (BHC), at the Washington University School of Medicine (St. Louis, MO), and Siteman Cancer Center (St. Louis, MO). Annually, close to 5,000 premenopausal women undergo mammography at the BHC. Premenopausal women who were scheduled for their annual screening mammography at the BHC were mailed study flyers by research coordinators 2 weeks to one month in advance. Follow-up calls were made within 7 days of the scheduled appointments to screen interested individuals, provide further details, and answer questions on the study. Eligibility criteria included (i) premenopausal at the time of mammogram. We identified women as premenopausal if they had a regular menstrual period within the preceding 12 months, no prior history of bilateral oophorectomy, and not used menopausal hormone therapy, (ii) no serious medical condition that would prevent the participant from returning for her annual mammogram in 12 months, (iii) not pregnant, (iv) no history of any cancer, including breast cancer, (v) and no history of breast augmentation or reduction. Eligible participants were asked to fast on the day of their screening mammogram appointment. At their screening mammogram appointment, participants completed a questionnaire on demographic characteristics, reproductive factors, medication use, physical activity, family history of breast cancer, and questions on body size at age 10, weight at age 18 and 30, etc. Institutional Review Board (IRB) approval was obtained from the Washington University School of Medicine. Study approval was granted by the IRB of the Washington University School of Medicine. All study participants provided informed consent.

Adiposity measures

Participants' attained height and weight were measured using a stadiometer and the OMRON Full Body Sensor Body Composition Monitor and Scale model HBF-514C, respectively. Body size at age 10 was self-reported using the Stunkard 9-figure somatotype pictogram (14), which has been validated and used in many studies (15). For these analyses, the Stunkard 9-figure pictogram was categorized into 4 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 further estimated BMI at age 10 by using BMI and Stunkard pictograms, both provided at age 10, from the Growing Up Today Study (GUTS; ref. 16). Because the Stunkard 9-figure somatotype pictogram for girls in GUTS ranged from 1 to only 7, we excluded three women in our study whose body sizes were 8 or 9 as GUTS did not provide BMI data in those categories. We excluded 17 women with incomplete baseline data and mammographic density measures, and 1 woman with an extreme value for attained weight (weight larger or smaller than 3 times the SD of the mean attained weight) from the final analyses; hence, these analyses included 365 women. Fifty women did not report their body size at age 10; hence, we imputed body size at age 10 for these women. To impute the missing values, we conducted linear regression analyses to determine the associations of body size at age 10 with all variables in our dataset. Weight at age 18 and BMI at age 30 were significantly and strongly predictive of body size at age 10, although other variables, such as attained BMI, were also weakly associated but not statistically significant. Thus, we used PROC MI-FCS (fully conditional specification) method using weight at age 18 and BMI at age 30 to impute missing values for body size at age 10.

Mammographic density measures

We used Volpara [version 1.5, (Matakina Technology Limited)] to determine volumetric measures of mammographic density. These include volumetric percent density (VPD), dense volume (DV), and nondense volume (NDV; refs. 17, 18). Volpara uses a computerized algorithm that calculates the X-ray attenuation at each pixel and converts the attenuation to an estimate of the tissue composition to create a density map (17, 18) and averages the cranial–caudal and mediolateral oblique views of the left and right breasts (19, 20). Volpara VPD measures range from 0.5% to 34.5%. Corresponding to the Breast Imaging Reporting and Data System categorical terms (5th edition), these percentages translate to (i) $<3.5\%$; (ii) ≥ 3.5 and $<7.5\%$; (iii) ≥ 7.5 and $<15.5\%$; and (iv) $\geq 15.5\%$ (20). Volpara density measures have been found to provide high reproducibility (17, 19, 21) and could be used in clinical practice to enhance risk assessment and prevention (22).

Statistical analysis

We calculated descriptive statistics by categories of body size at age 10. Linear trends for continuous variables and heterogeneity for categorical variables were tested across body size groups using linear regression model and χ^2 tests, respectively. We investigated age-adjusted correlations between adiposity at age 10 and mammographic density measures using Spearman

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Table 1. Characteristics of 365 premenopausal women recruited during annual screening mammography at the Joanne Knight Breast Health Center, Washington University School of Medicine

	Body size at age 10								
	1–2		3–4		5		6+		
	n	Mean ± SD/ percentage	*n*	Mean ± SD/ percentage	*n*	Mean ± SD/ percentage	*n*	Mean ± SD/ percentage	P_{trend}[a]
Attained age (years)	158	47.54 ± 4.83	129	46.72 ± 4.43	51	46.83 ± 4.71	27	45.50 ± 6.15	0.038
Menarche (years)	158	13.02 ± 1.56	129	12.71 ± 2.86	51	12.43 ± 1.63	27	12.78 ± 1.58	0.144
Age at first birth (years)	138	26.09 ± 6.12	98	26.35 ± 5.77	38	26.03 ± 6.72	19	24.84 ± 6.24	0.598
Birth index[b] (years)	158	36.61 ± 25.12	129	28.66 ± 23.79	51	26.78 ± 24.90	27	31.54 ± 32.66	0.023
Parity									0.008
Nulliparous	20	12.66%	31	24.03%	13	25.49%	8	29.63%	
One	24	15.19%	25	19.38%	13	25.49%	4	14.81%	
Two	68	43.04%	43	33.33%	15	29.41%	6	22.22%	
Three or more	46	29.11%	30	23.26%	10	19.61%	9	33.33%	
Ever breastfed	100	63.29%	73	56.59%	28	54.90%	13	48.15%	0.085
Ever used oral contraceptives	148	91.77%	113	87.60%	45	88.24%	22	77.78%	0.049
Family history of breast cancer	33	20.89%	30	23.26%	13	25.49%	10	37.04%	0.095
Race									0.265
Non-Hispanic White	109	68.99%	87	67.44%	29	56.86%	18	66.67%	
Black or African American	44	27.85%	33	25.58%	17	33.33%	9	33.33%	
Others	5	3.16%	9	6.98%	5	9.8%	0	0	
Education level									0.359
High school or less than high school	15	9.49%	10	7.75%	6	11.76%	3	11.11%	
Post high school training or some college	31	19.62%	23	17.83%	10	19.61%	10	37.04%	
College graduate	67	42.41%	46	35.66%	16	31.37%	10	37.04%	
Postgraduate	44	27.85%	50	38.76%	19	37.25%	4	14.81%	
Adiposity measures									
Attained height (cm)	158	164.62 ± 6.79	129	164.03 ± 7.09	51	164.25 ± 9.04	27	166.47 ± 5.52	0.556
Attained weight (kg)	158	77.72 ± 19.51	129	81.51 ± 21.42	51	92.68 ± 23.82	27	98.33 ± 15.21	<0.001
Attained BMI (kg/m^2)	158	28.69 ± 7.10	129	30.29 ± 7.84	51	34.49 ± 9.06	27	35.45 ± 5.00	<0.001

[a]Linear trends for continuous variables and heterogeneity for categorical variables were tested across body size groups using linear regression model and χ^2 test, respectively.
[b]Birth index (years) = attained age minus age at each given birth (the birth index is 0 for nulliparous women).

partial correlation coefficients. We used multivariable linear regression models to evaluate the associations of adiposity at age 10 with mammographic density measures. VPD, DV, and NDV were all natural log transformed to ensure the normality of the residuals in all regression models. The beta coefficients and 95% confidence intervals (95% 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% = $(\exp(\beta) - 1)^{*}100$ and interpreted as a unit change in an adiposity measure associated with 1 unit change in VPD, DV, or NDV. We adjusted the multivariable linear regression models for attained age

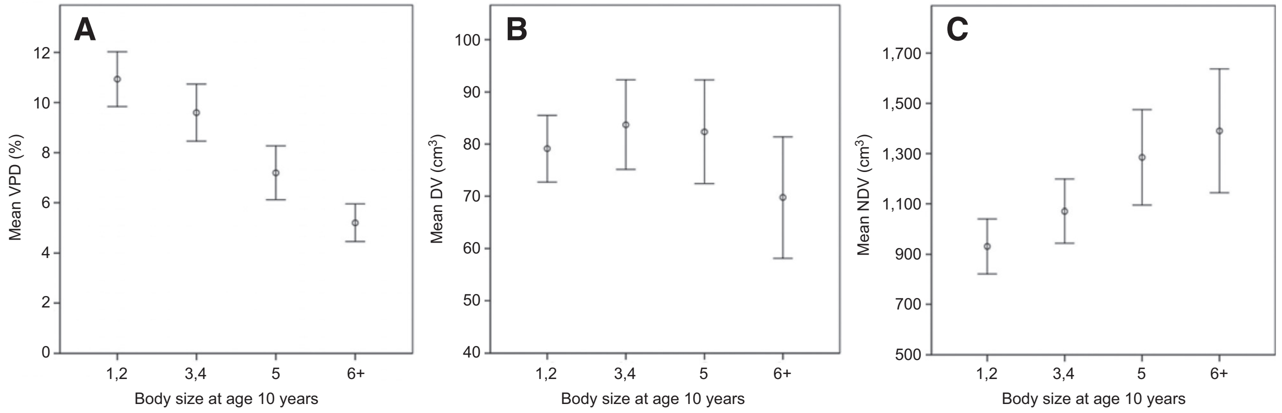

Figure 1.
Mean mammogram density measures and 95% confidence intervals by categories of body size at age 10 among 365 premenopausal women. **A–C,** Body size at age 10 was self-reported using the Stunkard 9-figure somatotype pictogram. For these analyses, the Stunkard 9-figure pictogram was categorized into 4 groups: (i) body size 1 or 2; (ii) body size 3 or 4; (iii) body size 5; and (iv) body size 6 or higher.

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Table 2. Spearman correlations between BMI at age 10 and mammographic density measures in 365 premenopausal women

	BMI at age 10	
	r	*P*
VPD (%)	−0.274	<0.001
DV (cm^3)	0.004	0.940
NDV (cm^3)	0.257	<0.001

(years), birth index, race (non-Hispanic White/African American/others), and family history of breast cancer (yes/no); because of the breast cancer risk factors selected *a priori*, these were the ones that were significant in our final multivariable regression models. Birth index was estimated as attained age minus age at each given birth (the birth index is 0 for nulliparous women). Birth index has shown a stronger influence on cumulative incidence of breast cancer compared with age at the first birth (23). Next, we investigated the associations between adiposity at age 10 and mammographic density measures stratified by age at menarche. The mean age at menarche was 12.81 years; thus, we categorized the study population into two groups: (i) age at menarche < 12.81 years and (ii) age at menarche ≥ 12.81 years. We also performed sensitivity analyses limited to women ($N = 315$) who had no missing data on body size at age 10. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). 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 47.1 years (range, 31–58 years). The mean age at menarche was 12.8 years (range, 9–18 years). The mean BMI at enrollement was 30.6 kg/m^2. The majority of the women (43.8%) reported having body size 1 or 2 at age 10, followed by body size 3 or 4 (34.9%), body size 5 (13.8%), and body size 6 (7.6%). The baseline characteristics of participants according to body size group are presented in Table 1. There were significant differences in age, birth index, parity, oral contraceptive use, attained weight, attained BMI, VPD, and NDV across the body size categories. Attained weight and BMI in adulthood increased with greater age 10 body size (for each, $P < 0.0001$). VPD decreased, whereas NDV increased with the greater body size (for each, $P < 0.0001$). The mean mammographic density measures by categories of body size are presented in Fig. 1A–C. The mean VPDs were 11.0%, 9.6%, 7.2%, and 5.3% for women whose body sizes at age 10 were: (i) 1 or 2; (ii) 3 or 4; (iii) 5; and (iv) ≥6, respectively. The mean NDVs were 930.3, 1,071.1, 1,284.8, and 1,396, for women whose body sizes at age 10 were (i) 1 or 2; (ii) 3 or 4; (iii) 5; and (iv) ≥6, respectively.

Age-adjusted Spearman partial correlations between BMI at age 10 and mammographic density measures are summarized in Table 2. We observed a negative correlation between BMI at age 10 ($r = -0.28$, $P < 0.001$) and VPD and a positive correlation with NDV ($r = 0.26$, $P < 0.001$). No significant correlation was found with DV ($r = 0.004$, $P = 0.940$).

In multivariable adjusted regression models, adiposity at age 10 was significantly inversely associated with VPD and positively associated with NDV (Table 3). A 1 kg/m^2 increase in BMI at age 10 was associated with a 6.4% decrease in VPD ($P < 0.001$) and a 6.9% increase in NDV ($P < 0.001$). Compared with women whose body sizes were 1 or 2 at age 10, women with body size 3 or 4 had a 16.8% decrease in VPD, and a 26.6% increase in NDV; women with body size 5 had a 32.2% decrease in VPD, and a 58.5% increase in NDV, and women with body sizes ≥6 had a 47.8% decrease in VPD and a 80.9% increase in NDV (all $P < 0.05$). The associations of body size at age 10 and VPD were attenuated, but still statistically significant when we adjusted for current BMI. No statistically significant associations were found between adiposity at age 10 and DV. Findings were identical in sensitivity analyses limited to women who had no missing data on body size at age 10.

We observed similar associations between women who achieved menarche before 12.8 years and those who achieved after 12.8 years, except for DV among women with body sizes 3 and 4, for whom the estimates are in the opposite direction, but still nonsignificant (Table 4).

Table 3. Multivariable adjusted associations between BMI at age 10, body size at age 10, and mammographic density measures among 365 premenopausal women[a]

		VPD (%)			DV (cm^3)			NDV (cm^3)		
Variable	***n***	**Diff%**[b]	**95% CI**	***P***[c]	**Diff%**	**95% CI**	***P***[b]	**Diff%**	**95% CI**	***P***[b]
BMI at age 10 years (kg/m^2)	365	−6.44	−8.36 to −4.48	<0.001	−0.89	−2.46–0.70	0.268	6.88	4.27–9.55	<0.001
Body size at age 10 years										
1–2	162	Ref			Ref			Ref		
3–4	129	−16.80	−27.37 to −4.68	0.008	1.80	−8.26–12.96	0.737	26.55	8.05–49.22	0.004
5	51	−32.21	−43.66 to −18.42	<0.001	1.13	−12.22–16.52	0.876	58.54	27.26–97.50	<0.001
6+	28	−47.81	−58.88 to −33.76	<0.001	−13.11	−27.60–4.28	0.131	80.90	36.31–140.08	<0.001

[a]BMI at age 10 and body size at age 10, as independent variables in separate models. All models are adjusted for attained age, birth index, family history of breast cancer, and race.

[b]Percentage differences (%Diff) represents one unit change in an adiposity measure associated with one unit change in VPD, DV, or NDV.

[c]Multivariable linear regression models were used to evaluate the associations of adiposity at age 10 with mammographic density measures. The *P* values for body size compare each category with the reference category. The *P* values for BMI test for trends.

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Table 4. Multivariable adjusted associations between adiposity at age 10 and mammographic density measures stratified by age at menarche[a]

		VPD (%)			DV (cm^3)			NDV (cm^3)		
	n	Diff%[b]	95% CI	*P*[c]	Diff%	95% CI	*P*[c]	Diff%	95% CI	*P*[c]
Age at menarche < 12.81 years										
BMI at age 10		−6.37	−9.17, −3.50	<0.001	−1.63	−4.03, −0.83	0.190	6.26	2.61, −10.04	<0.001
Age at menarche ≥ 12.81 years										
BMI at age 10		−6.37	−8.99, −3.67	<0.001	−0.32	−2.40, −1.81	0.765	7.19	3.57, −10.95	<0.001
Age at menarche < 12.81 years										
Body size at age 10										
1–2	65	Ref			Ref			Ref		
3–4	66	−24.36	−38.06, −7.63	0.007	−12.83	−25.88, −2.52	0.096	24.13	−1.44, −56.33	0.066
5	27	−35.65	−50.32, −16.67	0.001	−6.90	−24.53, −14.85	0.502	56.96	16.45, −111.57	0.003
6+	12	−44.19	−60.69, −20.77	0.001	−17.93	−38.25, −9.09	0.172	63.03	8.78, −144.33	0.018
Age at menarche ≥ 12.81 years										
Body size at age 10										
1–2	93	Ref			Ref			Ref		
3–4	63	−5.64	−21.91, −14.01	0.546	12.12	−2.44, −28.86	0.106	19.46	−5.02, −50.24	0.128
5	24	−30.61	−47.11, −8.97	0.009	6.04	−13.15, −29.48	0.563	60.26	15.33, −122.70	0.005
6+	15	−48.55	−62.85, −28.75	<0.001	−9.63	−28.87, −14.82	0.405	87.56	26.42, −178.28	0.002

[a]All models are adjusted for attained age, birth index, family history of breast cancer, and race.
[b]Percentage differences (%Diff) represents one unit change in an adiposity measure associated with one unit change in VPD, DV, or NDV.
[c]Multivariable linear regression models were used to evaluate the associations of adiposity at age 10 with mammographic density measures. The *P* values for body size compare each category to the reference category. The *P* values for BMI test for trends.

Discussion

We observed that adiposity at age 10 was strongly inversely associated with VPD and positively associated with NDV among premenopausal women. No significant association was observed for adiposity at age 10 and DV. Associations did not materially differ by age at menarche.

Our study will be one of the few studies that have investigated the associations of childhood adiposity with mammographic density in premenopausal women. The inverse association between childhood adiposity and VPD seen in our study is similar to what has been reported in some studies (8–10), although other studies have also reported no associations (11–13). Dorgan and colleagues found significant inverse associations between BMI at ages 8 to 10 and percentage dense breast volume measured using semiautomatic 3D segmentation in 173 healthy young U.S. women (8), whereas Hopper and colleagues reported that girls with higher BMI from ages 7 to 15 years had a lower percent density (10). Similar to our findings, the associations were attenuated but still significant after adjusting for current BMI. The studies are, however, different in terms of study population, breast cancer risk factor distribution, mammographic density measures. Dorgan and colleagues evaluated associations among young women aged 25 to 29 years (mean age of 27 years). Our study population was older, with a mean age of 47 years. As many as 80% of our study participants were parouns compared with 27% in their study. Furthermore, African Americans constitute 29% of our study population as against 10% in Dorgan and colleagues' study, whereas participants in the Hooper and colleagues' study were all recruited from Tasmania, an island in Australia. In addition, we stratified our analyses by age at menarche, which the two studies did not. This is important because there are suggestions that pubertal hormone-driven increase in adiposity is responsible for the observed associations. We observed that the effect of adiposity is consistent regardeless of age at menarche, suggesting that adiposity is important. The only other study that stratified analyses by age at menarche, conducted in Mexico, did not observe any associations between adiposity, before and after menarche, with mammographic density in premenopausal women (13); hence, our study provides additional important new information. Furthermore, we used Volpara, an automated software to determine volumetric measures of density, whereas Hooper and colleagues used CUMULUS.

Childhood adiposity is inversely associated with breast cancer risk in both premenopausal women and postmenopausal women, whereas adult adiposity is positively associated with breast cancer risk in postmenopausal women (24–27). Our findings support the hypothesis, as demonstrated in a mediation analyses (28) showing that mammographic density may mediate some of the associations of childhood BMI with breast cancer risk in premenopausal women. The mechanisms underlying this are not well understood but could be related to metabolic and hormonal changes taking place in the breasts during late childhood and adolescence when the breasts develop rapidly. It is important to understand how these changes, occurring at such a critical time lead to long-term changes in breast morphology, breast density, and breast cancer development. In a previous study, we observed that childhood body fatness was associated with slower peak height velocity, which is a measure of adolescent growth, and it is also associated with lower breast cancer risk (29). In addition, childhood adiposity is inversely associated with

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insulin-like growth factor 1 level (30, 31), and it is a possible pathway to reduced breast cancer risk.

Limitations of our study include the following. It is observational; hence, it cannot establish causality. Body size at age 10 was retrospectively reported by participants; thus, it is possible that participants may be less likely to identify themselves as being heavier at age 10. However, a validation study from a Boston-area longitudinal study of school children reported a high correlation between participants' adult-recalled body size at age 10 and their measured BMI at age 10 ($r = 0.65$; ref. 32). Thus, the recalled body size at age 10 should be reliable for this analysis. Also, caution should be used when assessing adiposity with BMI, as it may not be the most accurate method to depict body fatness (33).

In spite of the limitations, our study has the following strengths. Study participants were recruited among all women attending annual routine screening mammography at the Joanne Knight Breast Health Center, Washington University School of Medicine, which enhances generalizability. We conducted our study among premenopausal women only. Some studies have shown that although childhood adiposity is associated with mammographic density in overall analyses, these findings are only evident among postmenopausal, and not premenopausal women (11, 12). It is well established that mammographic density is higher in premenopausal, compared with postmenopausal women and menopausal transition is associated with a decrease in mammographic density. We assessed mammographic density using Volpara, which provides volumetric measures of density and has been found to be highly reproducible compared with some other mammographic density softwares (17, 18, 21, 34). Volumetric density measures may also be more accurate predictors of breast cancer risk than area-based measures because different areas on one view (e.g., CC) can appear similar on another view (e.g., MLO) in area-based measures, which could influence density calculations, a scenario mitigated by volumetric density measures like Volpara (35, 36).

Conclusion

Our findings of an inverse association between adiposity at age 10 and VPD suggest that adiposity at age 10 could impact breast cancer development via its effect on mammographic density. Mechanistic studies to understand how childhood adiposity influences breast development, mammographic density, and breast cancer in premenopausal women are needed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funders had no role in study design, data collection, analysis, interpretation of data, preparation of the report, 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

Conception and design: A. Alimujiang, G.A. Colditz, A.T. Toriola
Development of methodology: A. Alimujiang, G.A. Colditz, A.T. Toriola
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.R. Imm, C.M. Appleton, A.T. Toriola
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Alimujiang, K.R. Imm, C. M. Appleton, G.A. Colditz, C.S. Berkey, A.T. Toriola
Writing, review, and/or revision of the manuscript: A. Alimujiang, K. R. Imm, C.M. Appleton, G.A. Colditz, C.S. Berkey, A.T. Toriola
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.R. Imm, A.T. Toriola
Study supervision: K.R. Imm, A.T. Toriola

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