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Predictors Of Breast Density In Hispanic And Latino Women Living In The Northeast Region Of The United States

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Abstract

Introduction: Breast density, the fibroglandular, non-fatty tissue in the breast, has been shown to be a significant risk factor for breast cancer. Little is currently known about the predictors of breast density among the understudied but increasing population of Hispanic and Latino women in the United States.

Objectives: The objective of this study is to identify predictors of breast density among Hispanic and Latino women in Connecticut and to determine if these differ from those described in other populations. Because the hormonal milieu is somewhat different in Hispanic/Latinas compared with White women, we are interested in how these variables impact breast density. We are primarily interested in the role of reproductive and physiological factors.

Methods: We analyzed for breast density predictors in an established cohort of 1,600 Hispanic and Latino women recruited from primary care clinics in Connecticut. Baseline interview questions provided prospective data on biological, medical care, and sociodemographic factors. Subjects provided informed consent for the retrieval of mammography reports from screening facilities during the follow-up period. These reports provided breast density information based on radiologist assigned BI-RADS classification. Associations between predictors and breast density were examined with descriptive statistics and chi square statistical tests for which p-values were reported. We additionally calculated odds ratios and 95% confidence intervals using logistic regression modeling.

Results: Breast density data were collected for 1,040 women (65.4%). 280 women (27%) were identified as having dense breasts while 760 women (73%) were classified as having nondense breasts based on screening mammogram reports. In the multivariate model, breast density predictors were generally consistent with those reported in previous studies. Additionally, we found women with diabetes to be at significantly reduced odds of breast density. There was also evidence that the relationship between age at menarche and density was modified by BMI.

Conclusion: Our findings suggest that Hispanic and Latino women differ in breast density distribution relative to the general population. Additionally, we observed the protective effect of diabetes and potential interaction

between age at menarche and BMI. This investigation enhances our understanding of breast density in Hispanic and Latino women and provides the basis for further research and inquiry within this population.

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Introduction

Breast cancer is the most common form of cancer among women in the United States and the second leading cause of cancer mortality among Americans (1, 2). In 2016, an estimated 246,660 cases and more than 40,000 deaths from breast cancer are projected in the United States (3). Among Hispanic and Latino women, breast cancer incidence is lower when compared to White and Black women, yet it is the most common cause of cancer mortality in this population (3, 4).

Breast density, referring to the fibroglandular, non-fatty tissue in the breast, is known to be one of the strongest predictors of breast cancer incidence (5, 6). Studies show a minimum three to four fold increase in breast cancer risk among women with dense breasts relative to women without dense breasts (6-8). Meta-analyses performed by McCormack and Silva show consistent findings across 42 studies of the significant association between density and breast cancer (5). Research also suggests a protective effect of fatty, nondense tissue against the development of cancer (9, 10).

Because of its association with higher risk of breast cancer and lowered sensitivity of screening mammograms, breast density is required by law in several states, including Connecticut, to be routinely disclosed on mammography reports. Density is assessed on screening mammograms through the Breast Imaging Reporting and Data System (BI-RADS) created by the American College of Radiology to categorize breast density (11). BI-RADS reflects a subjective assessment and categorization of the proportion of dense tissue relative to fatty tissue in the breast. Radiologists will classify the breast tissue into one of four categories: predominantly fatty, scattered fibrogladular densities, heterogeneously dense, and extremely dense (11).

Although numerous studies have been performed with regard to breast density in White and Black women, Hispanic and Latino women living in the United States remain understudied (12). To our knowledge, there is only one published study that has addressed breast density in Hispanic and Latino women living in the Northeast region of the United States, however the sample size of this group was small (n=81) and Hispanic and Latino women were not the primary focus of the study (13). Cross sectional studies have provided some insight regarding the association between breast density and breast cancer risk factors (such as age, menopause status, weight, and hormone replacement therapy) in this population (14). Others have included Hispanic and Latino women in their analyses but examined specific associations with dietary factors and body composition (12, 15). A number of previous studies additionally give sole focus to women of Mexican ancestry (16-19).

In the United States, the Hispanic and Latino population are the largest non-majority group, with their numbers expected to grow over the next several decades (20). Given increases in the population size of this group and cultural, demographic, and ancestral differences among Hispanic and Latino women living in the northeast, there are significant public health implications associated with the identification of the risk factors of breast density in this population, such as educational awareness and necessary access healthcare resources. In this exploratory analysis, we aim to report the distribution of breast density in Hispanic and Latino women living in four residential enclaves of Connecticut and identify significant biological, reproductive, and sociodemographic predictors of breast density in the population.

Materials and Methods

Data Sources

Data were collected as part of a larger prospective cohort study, Cancer Screening in Hispanic/ Latinas Living in the Northeast, U.S. (RO1CA134276, Beth A. Jones, PI). The main objectives of this study were to examine predictors of mammographic screening behavior and adherence to screening guidelines during a 2.5 to 4 year follow-up period. Eligible participants were recruited from one of eleven participating primary care facilities in Waterbury, New Haven, Hartford, and Bridgeport, four of the largest enclaves for Hispanic and Latino populations in Connecticut according to U.S. Census Bureau data (21). Working within these facilities at different times and days of the week, our bilingual, bicultural research staff recruited women who self-identified as Hispanic or Latino and met the eligibility criteria for this study. Of the nearly 1,600 women (n=1,591 remained in the final data set) who provided baseline data, 98% provided written consent allowing investigators to access and review mammography reports and all relevant correspondence with regard to the mammogram results. Bilingual research staff conducted hour-long interviews with study subjects via telephone. We collected extensive information of sociodemographic, medical history, acculturation, sociocultural, and mammography screening data, as well as known predictors of breast density and established breast cancer risk factors. We accessed mammographic radiology reports and images for 1,569 women from facilities identified by the respondent as a place she had received mammography in the past, would seek a mammogram in the future, or from all mammography facilities in the city in which she was recruited. Although it is not a closed system, there is a relatively low number of large facilities that provide all mammography services in these urban areas. All activities in this study were approved by the Yale Human Investigation Committee, in addition to all research oversight committees at participating facilities.

Study Population

We targeted the four cities in Connecticut with the largest Hispanic/Latino populations (Waterbury, New Haven, Hartford, and Bridgeport). Our study sample includes Hispanic and Latino women who presented at participating primary care clinics (hospital based and Federally Qualified Health Centers [FHQCs]) in these areas and who were between the ages of 40-75 at the time of enrollment. Additional eligibility criteria included that participants have no medical history of breast cancer, breast biopsy, or cyst aspiration. Of the 2,137 eligible Hispanic/Latino women who we identified, 1,591 (74.5%) provided baseline interviews. Of the women who we were able to contact after the initial enrollment, our participation rate was 92%. Study subjects were limited to the 1,569 (98.6%) who provided signed consent to review radiology records. Mammographic data were available for 1,040 study participants who received at least one screening mammogram during the follow-up study period. Because state law mandates that breast density is recorded and shared with patients, 100% of screening mammogram reports included density information. For women who received more than one screening mammogram, breast density was recorded for each exam report retrieved.

Measures and Definitions

Dependent Variable

Based on the BI-RADS classification system, breast density, as listed on screening mammograms, was categorized as fatty, scattered fibroglandular densities, heterogeneously dense, and extremely dense. For most analyses, a dichotomized breast density variable (dense versus nondense) was utilized. Women reported as having extremely or heterogeneously dense breasts were categorized as "dense", while women in the fatty or scattered density categories were classified as "nondense". For participants for whom multiple reports were retrieved during follow-up, changes in breast density measures across tests and over time were anticipated. Previous studies show that density tends to decrease over time (i.e. with age) (22, 23). As a result, we relied on the assumption that density would not increase over the follow up period. Discrepancies in BI-RADS reported density over time may have been a result of variation in radiologist interpretation of the mammographic images. For our purposes, if earlier reports indicated a woman had nondense breasts, and a single later report indicated dense breasts, the participant was categorized as "nondense" as it is more likely and biologically plausible that density would decrease over time, not increase. As expected, some women transitioned from having dense breasts to less dense breasts over time (with age). Thus, women whose earlier mammograms were classified as dense and later transitioned to nondense were considered dense for the purpose of our analysis.

Independent Variables

Baseline characteristics

Baseline sociodemographic variables included age (<50, ≥50 years old), marital status (single, married/partnered), education level (less than high school, some college or more), income (<$10,000/year, $10,000-14,999, ≥$15,000), and employment status (yes, no). Access to care variables were insurance status (none, public only, other coverage), usual care provider (yes, no), self-rated health (fair/poor, good/very good), and mammogram in the last year (yes, no). Acculturation variables included number of years lived in the United States (U.S. born, <10 years in U.S., ≥10 years in U.S.), self-rated spoken English (no English/not well, very well), and country of origin (U.S. born, foreign born, Puerto Rican born).

Reproductive and Physiological Variables

Women who reported having completed menopause (no menses for previous 12 months) or whose periods had ceased due to hormone replacement therapy, hysterectomy, or oophorectomy were categorized as postmenopausal. Those who had a period in the previous 12 months were categorized as premenopausal. Women who reported that they were in the process of going through menopause were categorized as perimenopausal. Women were also classified (yes, no) based on hormone replacement therapy use, hysterectomy/oophorectomy status, regular exercise (at least one time per week), diabetes status (ever been told by a doctor that they had diabetes; of note, 94% of women who self-reported diabetes diagnosis also reported insulin use and/or oral medication), history of infertility (trying for one year or more without getting pregnant), family history of breast cancer (among primary relatives), and alcohol consumption in the last year. BMI categories (normal/underweight, obese, and overweight) were created from continuous, height and weight data. Although these data were self-reported by participants, in general the information was read from a card that was filled out at the time of the primary care appointment and reflected current, measured height and weight at the time of the appointment. The mean number of live births in this sample was 4 births, and as such, parity was categorized as nulliparous, <4, and ≥4 live births. Age at first birth was also collected as a continuous variable (mean age being 19 years old) and later stratified into three groups, nulliparous, <19, and, ≥19. Breastfeeding was assessed through the cumulative number of months that a woman breastfed. The strata included never breastfed, <12 months, and ≥12 months. Women with no children were included in the "never breastfed" strata. Additional variables in the analysis were consumption of traditional Hispanic/Latino diet (less than weekly, 1-3 times per week, 4-6 times per week, everyday), sum of comorbidities (0-1, 2,3,>3), bra size (A, B, C, D, DD or larger), and oral contraceptive use (never used, ≤4 years, >4 years).

Statistical Analysis

Bivariate analyses were conducted using chi square, for which p-values were reported, and logistic regression. Baseline characteristics were adjusted for age while reproductive and physiological variables were adjusted for age and BMI. Total number of comorbidities and diabetes were adjusted with age, a continuous variable for BMI, and bra size, in order to control for residual confounding. Multivariate logistic regression was performed to calculate odds ratios and 95% confidence intervals to determine associations between significant baseline characteristics and all reproductive and physiological factors and breast density. We used stepwise elimination and set significance levels for which variables entered and exited the model to 0.1 and 0.15 respectively. Additionally, education was forced into this multivariate model in order to control for socioeconomic factors that were not included in the analysis. Possible interactions with age and BMI were tested among significant variables using stratified analyses and the Breslow-Day test for homogeneity. For these analyses, BMI was dichotomized (normal/underweight, obese/overweight). A categorical variable for age at menarche was created based on the average age at menarche reported by women in the cohort (>12, ≤12 years old). Interaction terms were also tested in the multivariate model. All analyses and data management were conducted using SAS version 9.4.

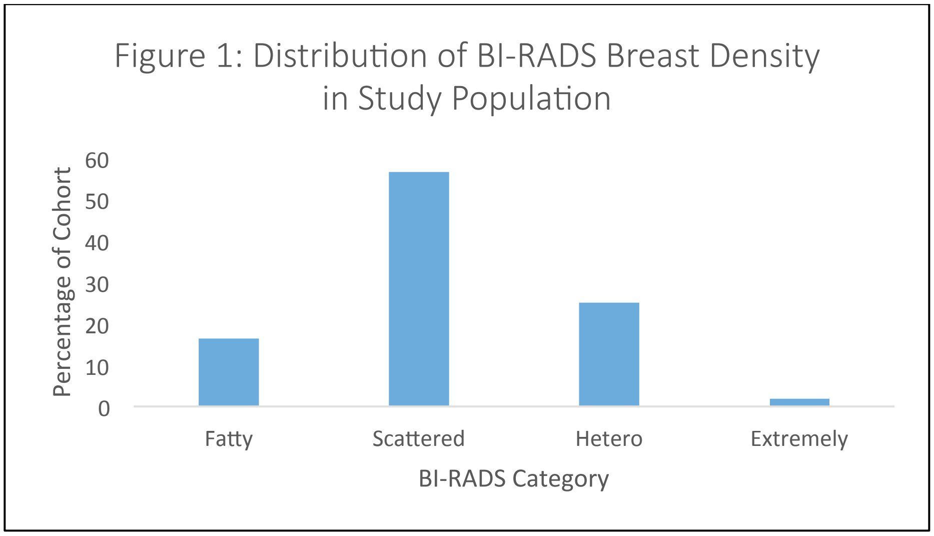
Results

Of the women who received screening mammograms during the follow-up period (n=1,040), 16.4% were reported as having fatty breasts, 56.6% with scattered fibroglandular densities, 25% with heterogeneously dense breasts, and 2% with extremely dense breasts (Table 1, Figure 1). With categorization of the breast density variable into "dense" and "nondense", we report that 280 (27%) had dense breasts and 760 (73%) had nondense breasts.

Table 1: Distribution of BI-RADS breast density in Hispanic/Latino women in Connecticut (n=1,040)

BI-RADS Category	Frequency	%
Fatty (0 - <25%)[a]	171	16.4
Scattered with fibroglandular densities (25-50%)	589	56.6
Heterogeneous (51-75%)	260	25.0
Extremely (>75%)	20	2.0

[a]Percentage of breast density.



Descriptive data by breast density are shown in Table 2. The distribution of breast density in the cohort differed significantly by age group, marital status, income, employment, insurance status, whether or not a mammogram was received in the last year, and by country of origin. Women younger than 50 years old were more likely to have dense breasts relative to women aged 50 years or older. Participants who reported being unemployed, single, receiving public insurance, having a mammogram in the last year, and earning a low income (particularly women who earned less than $10,000 per year) were found to be at significantly reduced odds of having dense breasts. Women born outside the continental United States but living in the United States for over ten years were at 1.59 times the odds of having dense breasts relative to women who were born within the United States. Women born outside the continental United States but living in the United States for less than 10 years were also at 1.59 times the odds of having dense breasts however this association was not significant. Puerto Rican born (OR = 1.33, 95% CI 0.87 – 2.04) and foreign born (OR = 2.11 95% CI 1.34 – 3.31) participants were at increased odds of density relative to those born in the United States. Once adjusted for age, marital status, income, and insurance status were not significantly associated with density. After adjusting for age, breast density was still significantly lower among women who received a mammogram in the last year and women who were unemployed. Women living in the United States for over 10 years were at significantly increased odds of having dense breasts adjusting for age (OR = 1.96, 95% CI, 1.28 – 3.00) while living in the United States for less than 10 years showed only a marginally significant association with breast density (OR = 1.74, 95% CI, 1.00 – 3.02). Foreign born women were at 2.32 (95% CI 1.46 – 3.69) times the odds of having dense breasts, while women born in Puerto Rico were at 1.68 (95% CI 1.08 – 2.60) times the odds of dense breasts compared to women born in the United States. No significant associations were found between density and English language skill, self-rated health, having a usual care provider, and level of education.

Table 2: Descriptive characteristics of cohort by breast density

Characteristic	n (%)[a]	Dense[b] Breasts (n = 280)	Non-Dense Breasts (n = 760)	OR (95% CI)	p-value[c]	Age Adjusted OR (95%CI)
Sociodemographic						
Age (years)						
<50	443 (42.6)	171 (61.1)	272 (35.8)	2.81 (2.12 – 3.73)	<.0001	--
≥50	597 (57.4)	109 (38.9)	488 (64.2)	1.00		
Marital status						
Single	686 (66.0)	166 (59.3)	520 (68.4)	0.67 (0.51 – 0.89)	0.0058	0.77 (0.58 – 1.03)
Married/Partnered	354 (34.0)	114 (40.7)	240 (31.6)	1.00		1.00
Education Level						
<12 years	568 (54.8)	143 (51.2)	425 (56.1)	0.82 (0.62 – 1.08)	0.1608	1.01 (0.76 – 1.35)
≥12 years	468 (45.2)	136 (48.8)	332 (43.9)	1.00		1.00
Income						
<$10, 000	495 (50.2)	115 (43.1)	380 (52.8)	0.57 (0.41 – 0.80)	0.0043[d]	0.73 (0.52 – 1.05)
$10,000-$14,999	247 (25.0)	67 (25.1)	180 (25.0)	0.70 (0.48 – 1.03)		0.78 (0.52 – 1.15)
$15,000+	245 (24.8)	85 (31.8)	160 (22.2)	1.00		1.00
Employment						
No	762 (73.3)	177 (63.2)	585 (77.0)	0.51 (0.38 – 0.69)	<0.0001	0.63 (0.47 – 0.86)
Yes	278 (26.7)	103 (36.8)	175 (23.0)	1.00		1.00
Access to Care						
Insurance Status						
None	169 (16.3)	59 (21.1)	110 (14.5)	1.03 (0.62 – 1.72)	0.0037	1.03 (0.61 – 1.74)
Public only	764 (73.6)	185 (66.0)	579 (76.4)	0.61 (0.40 – 0.95)		0.64 (0.41 – 1.00)
Other Coverage	105 (10.2)	36 (12.9)	69 (9.1)	1.00		1.00
Usual Care Provider						
No	487 (47.1)	134 (48.0)	353 (46.8)	1.05 (0.79 – 1.38)	0.7290	1.05 (0.80 – 1.39)
Yes	546 (52.9)	145 (52.0)	401 (53.2)	1.00		1.00
Self-rated Health						
Fair/Poor	570 (56.4)	151 (55.5)	419 (56.8)	0.95 (0.72 – 1.26)	0.7201	0.93 (0.70 – 1.24)
Good/Excellent	440 (43.6)	121 (44.5)	319 (43.2)	1.00		1.00
Mammogram in Last Year						
No	336 (32.5)	77 (27.7)	259 (34.3)	0.73 (0.54 – 0.99)	0.0444	0.67 (0.49 – 0.91)
Yes	697 (67.5)	201 (72.3)	496 (65.7)	1.00		1.00
Acculturation						
Acculturation						
≥10 years in U.S.	736 (71.4)	209 (74.9)	527 (70.1)	1.59 (1.05 – 2.40)	0.0836	1.96 (1.28 – 3.00)
<10 years in U.S.	130 (12.6)	37 (13.3)	93 (12.4)	1.59 (0.93 – 2.73)		1.74 (1.00 – 3.02)
U.S. Born	165 (16.0)	33 (11.8)	132 (17.5)	1.00		1.00

Self-rated Spoken English						
None/not well	784 (86.9)	215 (84.3)	569 (87.9)	0.74 (0.49 – 1.11)	0.1453	1.01 (0.66 – 1.55)
Very well	118 (13.1)	40 (15.7)	78 (12.1)	1.00		1.00
Country of Origin						
Puerto Rico	584 (56.2)	146 (52.3)	438 (57.6)	1.33 (0.87 -2.04)	0.0011[d]	1.68 (1.08 – 2.60)
Foreign born	290 (27.9)	100 (35.9)	190 (25.0)	2.11 (1.34 – 3.31)		2.32 (1.46 – 3.69)
US Born	165 (15.9)	33 (11.8)	132 (17.4)	1.00		1.00

[a]As a result of missing data, numbers may not sum to totals.
[b]Dense defined as having heterogeneously or extremely dense breasts according to BI-RADS (>50% dense).
[c]p-values from chi-square tests.
[d]Significant trend p-value.

Reproductive and physiological variables are listed in Table 3 by breast density. Perimenopausal (OR = 1.89, 95% CI 1.06 – 3.36) and premenopausal women (OR = 3.04, 95% CI 2.23 – 4.08) were at significantly increased odds of having dense breasts relative to postmenopausal women. After adjusting for age and BMI, only premenopausal status was significantly associated with density. Relative to nulliparous women, women with higher parity (≥4 births) had reduced odds while women with lower parity (<4 births) were at increased odds of having dense breasts. In the unadjusted and adjusted bivariate models, the effect of parity was not significant. Hormone replacement therapy and receipt of a bilateral oophorectomy were significantly inversely associated with having dense breasts. Women who reported having a history of infertility were at significantly higher odds of having dense breasts relative to women with no history of infertility. Adjusting for age and BMI, neither hormone replacement therapy, oophorectomy status, nor history of infertility were associated with density. We observed a significant trend in increasing number of comorbidities and increased bra size with lower breast density ($p<0.0001$). Higher BMI and having diabetes were also significantly protective ($p<0.0001$). After adjustment, diabetes and increasing bra size remained protective while total number of comorbidities was no longer associated with density. Age at menarche, oral contraceptive use, age at first birth, duration of breastfeeding, family history of breast cancer, exercise, alcohol use, and consuming a traditional Hispanic or Latino diet were additionally not found to be significantly predictive of breast density.

Table 3: Bivariate associations of reproductive and physiological variables with breast density

Characteristic	n (%)	Dense Breasts (n = 280)	Non-Dense Breasts (n = 760)	OR (95% CI)	p-value[b]	Adjusted OR[c]	p-value[c]
Age at Menarche (Mean, SD)	12.4 (2.03)			1.02 (0.96 – 1.09)	0.5400	1.00 (0.93 – 1.08)	0.9861
Menopause Status[a]							
Perimenopausal	63 (6.2)	19	44	1.89 (1.06 – 3.36)	<.0001[e]	1.37 (0.73 – 2.58)	0.0519
Premenopausal	344 (33.6)	141	203	3.04 (2.23 – 4.08)		1.66 (1.10 – 2.51)	
Postmenopausal	618 (60.3)	115	503	1.00		1.00	
HRT Use[d]							
Yes	120 (11.8)	22	98	0.58 (0.36 – 0.94)	0.0259	0.77 (0.46 – 1.30)	0.3336
No	899 (88.2)	251	648	1.00		1.00	
Oral Contraceptive Use							
>4 years	147 (14.5)	32	112	0.85 (0.55 – 1.31)	0.7298	0.77 (0.48 – 1.24)	0.4774
≤4 years	442 (43.7)	119	323	0.99 (0.74 – 1.35)		0.86 (0.61 – 1.19)	
Never used	423 (41.8)	114	309	1.00		1.00	
Oophorectomy							
Yes	146 (14.4)	29	117	0.64 (0.41 – 0.98)	0.0416	0.86 (0.53 – 1.39)	0.5405
No	868 (85.6)	243	625	1.00		1.00	
Parity							
≥4	419 (40.8)	76	343	0.47 (0.20 – 1.13)	<0.0001[e]	0.49 (0.19 – 1.29)	0.0004
<4	582 (56.7)	191	391	1.04 (0.44 – 2.45)		0.96 (0.37 – 2.46)	
Nulliparous	25 (2.5)	8	17	1.00		1.00	
Age at first birth							
≥19	544 (53.1)	178	366	0.97 (0.46 – 2.05)	<0.0001[e]	1.00 (0.44 – 2.23)	0.0007
<19	448 (43.7)	86	362	0.48 (0.22 – 1.02)		0.54 (0.24 – 1.22)	
Nulliparous	33 (3.2)	11	22	1.00		1.00	
Months of Breastfeeding							
≥12 months	274 (27.2)	78	196	1.12 (0.80 – 1.57)	0.7533	1.00 (0.69 – 1.45)	0.8598
<12 months	289 (28.6)	75	214	0.99 (0.70 – 1.38)		0.91 (0.36 – 1.31)	
Never	446 (44.2)	117	329	1.00		1.00	
History of Infertility							
Yes	140 (13.7)	52	88	1.76 (1.21 – 2.57)	0.0031	1.32 (0.87 – 1.98)	0.1881
No	884 (86.3)	222	662	1.00		1.00	
Family History of Breast cancer							
Yes	110 (12.2)	25	85	0.73 (0.46 – 1.17)	0.1938	0.89 (0.54 – 1.49)	0.6627
No	795 (87.9)	228	567	1.00			
BMI							
Overweight	308 (31.0)	102	206	0.47 (0.31 – 0.71)	<0.0001[e]	--	--
Obese	551 (55.5)	94	457	0.19 (0.13 – 0.29)			
Normal/underweight	134 (13.5)	69	65	1.00			
Sum of comorbidities[f]							
>3	290 (28.8)	45	245	0.32 (0.21 – 0.46)	<0.0001[e]	0.59 (0.38 – 0.90)[f]	0.0917 [f]
3	182 (18.1)	47	135	0.59 (0.40 – 0.88)		0.71 (0.45 – 1.11)	
2	210 (20.9)	60	150	0.68 (0.47 – 0.99)		0.76 (0.50 – 1.14)	
0-1	324 (32.2)	120	204	1.00		1.00	
Diabetic[f]							
Yes	522 (33.8)	58	297	0.40 (0.29 – 0.55)	<0.0001	0.62 (0.43 – 0.90)[f]	0.0113 [f]
No	1023 (66.2)	213	435	1.00		1.00	

Bra Size							
DD or larger	53 (5.2)	6	47	0.11 (0.40 – 0.31)	<0.0001[e]	0.21 (0.22 – 0.41)	0.0267
D	223 (22.0)	47	176	0.23 (0.12 – 0.46)		0.36 (0.17 – 0.74)	
C	343 (3.8)	87	256	0.30 (0.16 – 0.56)		0.42 (0.21 – 0.85)	
B	350 (34.5)	110	240	0.40 (0.21 – 0.75)		0.49 (0.25 – 0.99)	
A	45 (4.4)	24	21	1.00		1.00	
Exercise Once per week							
Yes	430 (44.4)	122	308	1.09 (0.82 – 1.45)	0.5344	1.05 (0.77 – 1.43)	0.7623
No	538 (55.6)	143	395	1.00		1.00	
Traditional Hispanic/Latino Diet							
Everyday	549 (61.9)	162	387	1.84 (0.67 – 4.95)	0.0754[e]	1.12 (0.39 – 3.25)	0.3215
4-6 times/week	129 (14.6)	42	87	2.12 (0.75 – 6.00)		1.28 (0.42 – 3.93)	
1-3 times/week	181 (20.4)	39	142	1.21 (0.43 – 3.40)		0.78 (0.26 -2.38)	
Less than weekly	27 (3.1)	5	22	1.00		1.00	
Alcohol Consumption							
Yes	230 (24.0)	68	162	1.15 (0.83 – 1.59)	0.4169	0.95 (0.67 – 1.37)	0.8059
No	727 (76.0)	195	532	1.00		1.00	

[a]Postmenopausal group includes women with induced menopause.
[b]p-values from chi-square tests.
[c]Adjusted for BMI and age.
[d]HRT, hormone replacement therapy.
[e]Significant trend p-value.
[f]Adjusted with age, continuous BMI variable, and bra size.

Adjusting for education, history of infertility, receipt of a mammogram in the last year, bra cup size, and parity, breast density was significantly associated with age at menarche, age, premenopausal status, diabetes, and BMI (Table 4). We observed a strong negative association between density, age, and BMI. Compared to women of normal weight, overweight and obese women were less likely to have dense breasts. Additionally, women over the age of 50 years old were at significantly reduced odds of dense breasts relative to women younger than 50 years old (OR = 0.48, 95% CI 0.30 – 0.78). We also observed an inverse relationship between age at menarche and breast density (OR = 0.89, 95% CI 0.81 – 0.98). In our multivariate model, premenopausal women were at 1.82 times the odds of having dense breasts (95% CI 1.13 – 2.92) compared to women who were postmenopausal. Perimenopausal women were also at increased odds of density (OR = 1.36, 95% CI 0.65 – 2.83), however this association was not significant. Interestingly, the protective effect of diabetes persisted in the multivariate model. Our findings showed that women with diabetes had significantly reduced odds of dense breasts relative to women without diabetes (OR=0.62, 95% CI 0.41 – 0.90). Although having children before or after the age of 19 years old appeared protective from breast density compared to being nulliparous, these associations were not statistically significant.

Table 4: Multivariate associations of participant characteristics with breast density[a]

Characteristic	OR	95% CI
Age at Menarche	0.89	0.81 – 0.98
Age		
≥50	0.48	0.30 – 0.78
<50	1.00	--
Age at first birth		
≥19	0.46	0.06 – 3.42
<19	0.29	0.04 – 2.18
Nulliparous	1.00	--
Menopause Status		
Premenopausal	1.82	1.13 – 2.92
Perimenopausal	1.36	0.65 – 2.83
Postmenopausal	1.00	--
Diabetes		
Yes	0.62	0.41 – 0.95
No	1.00	--
BMI		
Overweight	0.53	0.31 – 0.90
Obese	0.23	0.13 – 0.38
Normal/underweight	1.00	--

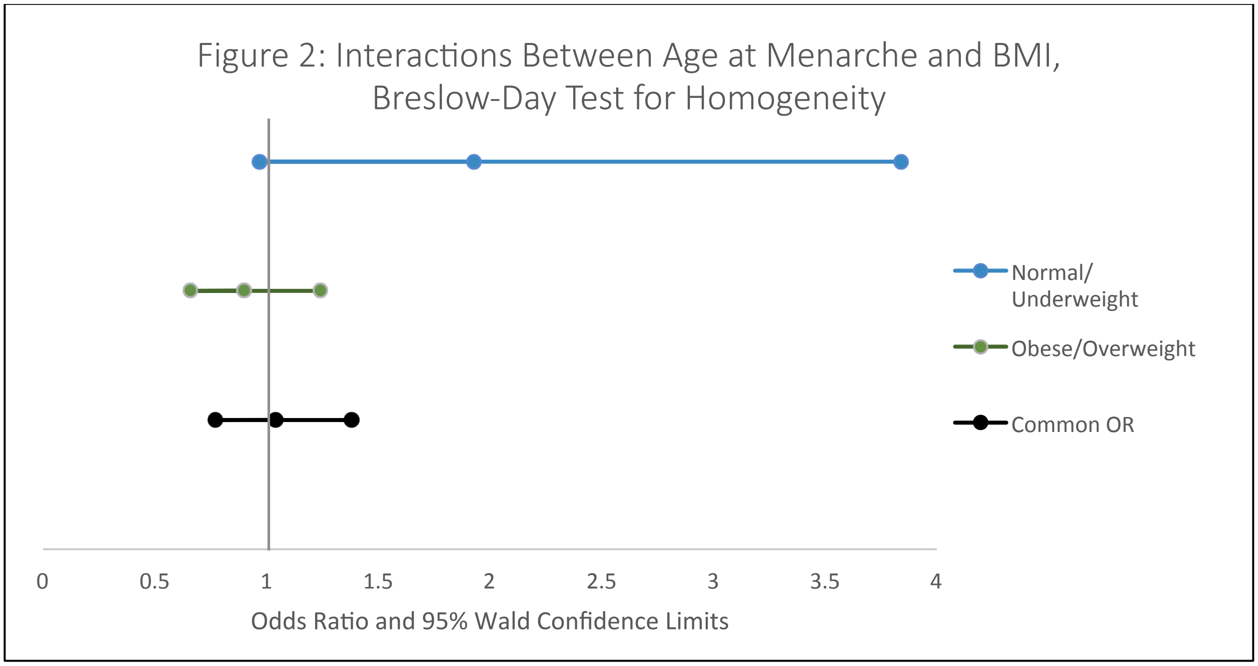
[a]Adjusted for education, history of infertility, receipt of mammogram in the last year, bra cup size, and parity.

We tested for interactions between age, BMI, and significant variables in the multivariate model. There was evidence of an interaction between age at menarche and BMI (Table 5, Figure 2). Normal and underweight women who experienced menarche before the age of 12, were at 1.92 times the odds of having dense breasts relative to women who experienced menarche after age 12. Conversely, obese and overweight women who experienced menarche earlier were at reduced odds of dense breasts relative to obese and overweight women who began menstruating at an older age. We analyzed this interaction term within the final multivariate model, however, adding the term worsened the overall model fit. Consequently, we reported the results from the stratified analysis and Breslow-Day test for homogeneity (p-value = 0.049).

Table 5: Results from stratified analysis of age at menarche and breast density by BMI

BMI Category	OR	95% CI	p-value[a]
Normal/Underweight	1.93	0.97 - 3.84	0.049
Overweight/Obese	0.9	0.65 - 1.24	
Common	1.03	0.77 - 1.38	

[a]p-value from Breslow-Day test for homogeneity.



Discussion

In this study we aimed to identify predictors of breast density, an important risk factor for breast cancer, in Hispanic and Latino women living in Connecticut. Unlike other studies in which cross sectional study designs were utilized to examine breast density in Hispanic and Latino women, we followed participants prospectively in order to uncover potential factors that give rise to density. Additionally, this study focused primarily on women living in the Northeast region of the United States. Considering the limited data on this particular population, we comprehensively examined a number of breast cancer risk factors, known predictors of breast density, and sociodemographic variables. Our multivariate analyses showed associations of breast density with age, BMI, age at menarche, diabetes, and premenopausal status adjusting for education, history of infertility, receipt of mammogram in the last year, bra cup size, and parity. We also observed a potential interaction between age at menarche and BMI.

Breast density predictors in Hispanic and Latino women identified in this study including age, BMI, menopause status, and age at menarche are consistent with previously reported studies (14, 22-24). Although risk factors across populations appear comparable, we note that the overall distribution of breast density among our study population differs from that of the general population. Our results showed that of women for whom density data were collected, only 25% had dense breasts (2% extremely dense and 25% heterogeneously dense). The American College of Radiology, however, report that in the general population, 50% of women have dense breasts (10% extremely and 40% heterogeneous) (25). This variation in breast density distribution may, in part, explain lower breast cancer incidence among Hispanic and Latino women compared to White and Black women. Further investigation is required to understand contributing factors to these distributional differences and determine if lower breast density is a potential driver of reduced breast cancer risk in this population.

Despite its association with increased breast cancer risk, BMI is significantly inversely associated with dense breasts (12, 14, 26). Obese and overweight women have a lower ratio of dense to fatty tissue in the breast relative to normal weight women (26). Studies indicate that fatty breasts may be protective against breast cancer, possibly as a result of fewer epithelial and stromal cells in the breast that could give rise to cancerous tumors (5, 9). Obese and overweight women may also have larger breasts relative to women of normal weight. We've shown that increasing bra size is associated with decreased odds of dense breasts and studies suggest that the effect of density on breast cancer risk is lower among women with larger breasts relative to women with smaller breasts (27). Controlling for bra size however, we've shown an independent protective effect of higher BMI on breast density. BMI and breast size may be related, but they appear to operate independently of one another as predictors of breast density.

Our findings also suggest an interaction between age at menarche and BMI. Among normal weight women, experiencing menarche before the age of 12 is associated with a two fold increase in the odds of having dense breasts relative to women who began menses over the age of 12. Among obese women however, the effect of early age at menarche is truncated by the effect of obesity. These women are protected against dense breasts even if they experience menarche earlier. This finding has implications for the relative importance of each of these breast density predictors as it appears the effect of BMI is stronger than that of age at menarche.

Among other variables included in the analysis is diabetes, which is suggested to be a weak risk factor for breast cancer, although the biological mechanism of disease has yet to be identified (28-30). In contrast, in our population, diabetes was associated with a decrease in odds of dense breasts. Previous studies examining the relationship between diabetes and breast density yielded conflicting results. Among Native American women, diabetes was similarly shown to have a negative relationship with dense breasts, however this was only significant among premenopausal women (31). Other studies report no association between density and diabetes (28, 32). Discrepancies between studies could be a result of differences in outcome classification (categorized versus quantitative measures of breast density) or ethnic differences among study populations (28, 32). Of the women in our study population who were diabetic, 94% reported taking insulin, other oral medication, or both. The use of diabetes medication may explain the relationship we observed in our investigation. Studies are currently underway to examine the effect of the diabetes medication, metformin, on breast density (33).

Strengths of this investigation include the use of a prospective cohort study design. In using this design we may establish temporality between significant predictors and breast density. Additionally, the baseline questionnaire allowed for the collection of a comprehensive set of variables for the study including sociodemographic, reproductive, and physiological data (as well information on potential confounders) on the cohort. One limitation of our study involves the subjective assessment of breast density. We ascertained our outcome from mammography reports retrieved from screening facilities throughout Connecticut. The BI-RADS categorization listed on the report provided the radiologists' classification of density, which we used to further categorize our cohort as "dense" and "nondense". BI-RADS is a qualitative method used in determining breast density and reporting is not protected against potential bias or variation in radiologist reporting. Automated quantitation may assist in obtaining accurate and objective measurements of breast density in future studies (34). Another limitation to the study involves changes in breast density over time. We collected mammography reports from screening facilities throughout the follow-up period. Breast density has been shown to decline over time (i.e. with age) and we generally assumed breast density would not increase over the follow-up period (22, 23). As such, if a woman was reported as having nondense breasts earlier in follow-up but was later reported to be dense (based on reports received later in follow-up), she was categorized as having nondense breasts. While such changes in density categorization were likely a result of variation in radiologist reporting, this impacted very few women in our study (n=11).

This study provided an opportunity to examine breast density in the population of Hispanic and Latino women living in the Northeast region of the United States. Additionally, this investigation gives insight to a population in which prevalence of diabetes and comorbidity is high relative to the overall population of the United States (35). Breast density predictors in our cohort are consistent with predictors in the general population. We report, however, that the distribution of density in our cohort differs from that of the general population and may explain lower breast cancer risk among Hispanic and Latino women. We also found a significant inverse association between density and diabetes. Although there is some discrepancy among previous findings, this may be a unique phenomenon among this population that elicits further study along with the potential impact of diabetes medication use on density. Our results also suggest that the effect of age at menarche may be modified by BMI. In describing the breast density distribution in Hispanic and Latino women and identifying risk factors in this population, these findings not only add to the body of breast density literature but also promote our understanding of density in this understudied population and provide evidential basis for future breast density research.

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