

Migration History, Language Acculturation, and Mammographic Breast Density

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Abstract

Background: Breast cancer incidence is lower in many U.S. ethnic minority and foreign-born population groups. Investigating whether migration and acculturation patterns in risk are reflected in disease biomarkers may help to elucidate the underlying mechanisms.

Methods: We compared the distribution of breast cancer risk factors across U.S.-born white, African American and Hispanic women, and foreign-born Hispanic women ($n = 477$, ages 40–64 years, 287 born in Caribbean countries). We used linear regression models to examine the associations of migration history and linguistic acculturation with mammographic breast density (MBD), measured using computer-assisted methods as percent and area of dense breast tissue.

Results: The distribution of most breast cancer risk factors varied by ethnicity, nativity, and age at migration. In age- and body mass index-adjusted models, U.S.-born women did not differ in average MBD according to ethnicity, but foreign-born

Hispanic women had lower MBD [e.g., -4.50% ; 95% confidence interval (CI), -7.12 to -1.89 lower percent density in foreign- vs. U.S.-born Hispanic women]. Lower linguistic acculturation and lower percent of life spent in the United States were also associated with lower MBD [e.g., monolingual Spanish and bilingual vs. monolingual English speakers, respectively, had 5.09% (95% CI, -8.33 to -1.85) and 3.34% (95% CI, -6.57 to -0.12) lower percent density]. Adjusting for risk factors (e.g., childhood body size, parity) attenuated some of these associations.

Conclusions: Hispanic women predominantly born in Caribbean countries have lower MBD than U.S.-born women of diverse ethnic backgrounds, including U.S.-born Hispanic women of Caribbean heritage.

Impact: MBD may provide insight into mechanisms driving geographic and migration variations in breast cancer risk. *Cancer Epidemiol Biomarkers Prev*; 27(5); 566–74. ©2018 AACR.

Introduction

Breast cancer is the most frequently diagnosed cancer in women in most regions of the world, but there are large variations in the incidence rates of breast cancer across countries (1). Breast cancer incidence also differs between native- and foreign-born women living in the same country. Specifically, women migrating from lower to higher incidence countries experience an increased breast cancer risk compared with native-born women remaining in their birth country but have a lower breast cancer risk compared with native-born women in their host country (2–5). Although less frequently examined than nativity status, studies have also reported a similar transition from lower to higher risk within the foreign-born generation (first-generation) according to increasing length of residence in the host country and acculturation (2, 3), the process by which immigrants adopt their host country's

predominant values, norms, behaviors, and exposures (6). Collectively, this evidence has been used to underscore the role of environmental factors (e.g., reproductive and lifestyle factors) in breast cancer etiology, based on the premise of rapid differences in the social and physical environments of migrants but stable shared genetic backgrounds. In support of this proposition, migration and acculturation patterns in breast cancer risk in Asian and Hispanic women in the United States may partially be explained by reproductive and lifestyle risk factors for breast cancer (2, 7–9).

Migrant studies of risk markers can provide important information about the process underlying the transition in breast cancer risk. Mammographic breast density (MBD) represents an ideal marker for several reasons. MBD has been consistently and strongly associated with increased breast cancer risk in women from different world regions and racial/ethnic backgrounds (10). Many breast cancer risk factors experienced across the life course show associations with MBD that are consistent with their associations with breast cancer risk. These include body size in early life (e.g., birthweight, postnatal growth, adolescent body size; refs. 11–13), reproductive events (e.g., parity, age at first birth; refs. 14, 15), and exogenous hormonal exposures [e.g., tamoxifen, hormone replacement therapy (HRT); refs. 16–19]. Furthermore, MBD is not static, and has been shown to change over time, usually declining with increasing age, particularly around the time of menopausal transition, and in response to hormonal therapies, which in turn correspond to subsequent breast cancer risk (16–21). Thus, the effects of breast cancer risk factors occurring before, during, or after migration may be reflected in MBD and map to

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doi: 10.1158/1055-9965.EPI-17-0885

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future breast cancer risk. Migrant studies of MBD that consider migration history (e.g., timing of migration, duration of stay in host country) and acculturation process can inform life course etiology of breast cancer by revealing critical or sensitive periods and/or cumulative effects of breast cancer risk factors.

Migration and acculturation take place within broader historical, sociopolitical, and cultural contexts that are rarely considered in empirical breast cancer research. This includes a consideration of race and ethnicity in diverse countries such as the United States, where immigrants may be likely to settle in communities and assimilate to the cultural norms and behaviors that predominate in their co-racial/ethnic population groups. This is particularly important given that breast cancer incidence rates have consistently varied across U.S. racial/ethnic groups, with considerably higher incidence in white and black women than in Hispanic, Asian/Pacific Islanders, and American Indian/Native Americans (22). In the United States, research on the associations of migration and acculturation with MBD has mostly been limited to women of Asian ethnicities, and have provided mixed results (23, 24). Research on MBD in Hispanic women in the United States, particularly those originating in the Caribbean countries, the majority of whom are foreign-born, is scarce. Here we examined differences in the distribution of breast cancer risk factors, and mammographic density by migration history and linguistic acculturation within a racially and ethnically diverse sample.

Materials and Methods

Study population

We used data from the New York Mammographic Density (NY MaDe) Study, an ongoing study of women of racially/ethnically diverse and predominantly immigrant backgrounds who are recruited as they present for their screening mammography appointment at a facility in a Northern Manhattan community in New York City. Between 2012 and 2016, trained research personnel recruited 534 women, ages 40 to 64 years, collected sociodemographic and risk factors data through in-person interviews in English (49%) or Spanish (51%), and obtained physical anthropometric measurements. We collected copies of digital mammograms for 520 women without breast implants and a history of breast cancer. Because of small group size, we excluded Asian ($n = 16$) and non-Hispanic foreign-born ($n = 27$) women, leaving an overall sample of 477 women, consisting of 165 U.S.-born white, African American, and Hispanic women and 312 foreign-born Hispanic women. A vast majority of foreign-born women were born in the Dominican Republic, Puerto Rico, or Cuba (92%). All questionnaire, body size, and mammographic density data used in this analysis were collected at the same enrollment time.

The Institutional Review Board of Columbia University Medical Center approved this study. All participants provided written informed consent.

Measures

Breast cancer risk factors. We asked women detailed questions on reproductive, menstrual, and lifestyles factors, and used the responses to construct the following variables: menopausal status, age at natural menopause, parity, age at first live birth, age at menarche, breastfeeding history and duration, and hormonal birth control and HRT use. Additionally, women reported on their family history of breast cancer in first-degree relatives,

personal history of breast biopsy, highest educational level (ranging from less than high school to doctoral degree), and alcohol consumption (never/former drinkers, current drinkers defined as drinking in the past 12 months, and by servings per week). Using a validated nine-figure pictogram (25), women also reported their body size at age 10 (hereafter childhood body size), which was categorized into four levels. We measured women's height using a stadiometer and weight using a digital scale in light clothing and without shoes, and calculated body mass index (BMI; in kg/m^2).

Ethnicity, migration history, and linguistic acculturation. We used women's reports of race and Hispanic ethnicity identification and place of birth to create the following categories, U.S.-born non-Hispanic white, U.S.-born non-Hispanic African American, U.S.-born Hispanic, and foreign-born Hispanic. Foreign-born women also reported information on their age at migration to the United States, which we used to categorize them as early life or childhood migrants (migrated before age 20), young adult migrants (migrated at ages 20–29 years), and later adult migrants (i.e., migrated at or after age 30). We additionally used age at migration as a continuous variable, considered other categorization for age at migration (e.g., using age 13 or 15 for lower cut-off points) and developed measures that characterized the timing of migration in relation to the life stage of specific risk factors; for example, we examined migration before and after menarche and first birth. Because we obtained similar results using these different measures of migrating timing, we limit the presentation of the results to age at migration using the primary cut-points at ages 20 and 30 years. To assess linguistic acculturation, we asked participants if they spoke exclusively or mostly English, exclusively or mostly Spanish, or both languages equally in three contexts, namely at home, work, and with friends. Women were categorized as monolingual if they only or mostly spoke one language in all contexts and bilingual if they reported speaking both languages in at least one context.

Mammographic breast density. We evaluated MBD from the cranio-caudal images of the left breast for all participants in randomly sorted batches of approximately 50 mammograms. We duplicated the assessment for 10% of the mammograms within each batch and repeated the assessment of an additional 10% of the mammograms in every batch to respectively calculate within-batch and between-batch variability. We measured MBD by using a computer assisted method, in which a trained reader, blinded to all study data, used a computer thresholding software (Cumulus developed by the University of Toronto) to outline the areas corresponding to the total breast and dense breast (fibroglandular) tissue on digital mammograms (26). We then calculated two measures of MBD: dense area (cm^2) as a measure of absolute amount of dense breast tissue, and percent density (dense area/total breast area in percentage) as a measure of relative amount of dense breast tissue. We also calculated non-dense area (in cm^2 ; total breast area – dense area) to capture the amount of predominantly fat tissue in the breast. Prior studies of breast cancer risk have consistently reported positive associations with percent density and dense area and inverse associations with non-dense area (10, 27). The within-batch correlation coefficients in our study were 0.98 for percent density, 0.99 for dense area, and 0.99 for non-dense area. The between-batch intraclass correlation coefficients for mammograms, read in two waves in 2014 and

2016, were respectively 0.93 and 0.96 for percent density, 0.91 and 0.94 for dense area, and 0.95 and 0.99 for non-dense area.

Statistical analysis

We examined descriptive statistics for breast cancer risk factors and sociodemographic variables by racial/ethnic and migration groups. For multivariable analysis, we performed linear regression models for percent density, dense area and non-dense area in their original measurement scale and transformed as squared roots; we restrict our presentation of results to models using original measurement scales because the overall results and interpretation were not materially different using transformed density measures. We first fit models that adjusted for age and BMI, as continuous variables as *a priori* confounders. We then fit more fully adjusted models that included breast cancer risk factors that individually changed the estimates of the age and BMI adjusted associations between migration and acculturation factors and any measures of mammographic density by more than 10%. We performed all analyses as two-sided tests with 0.05 significance level, using SAS 9.4 (SAS Institute, Cary, NC).

Results

The overall sample had a mean age of 51.2 [standard deviation (SD) = 5.8] and BMI of 30.1 (SD = 5.6). About 12% of women were nulliparous, 55% were postmenopausal, and 6% reported ever using HRT. Table 1 displays the sample characteristics for U.S.-born women by race/ethnicity and for foreign-born women by age at migration to the United States. Higher educational attainment, age at first birth, and duration of breastfeeding differed by nativity status, by race/ethnicity in U.S.-born women, and by age at migration in foreign-born women. Alcohol consumption differed by nativity status and by race/ethnicity in U.S.-born women, but no significant differences were observed by age at migration in foreign-born women. U.S.-born African American and Hispanic women relative to U.S.-born white women and early life migrants relative to adult migrants had younger average at first birth, lower education, and lower alcohol consumption. U.S.-born African Americans were more likely to have never breastfed (41%) than U.S.-born white (14%) and U.S.-born Hispanic (27%) women, and foreign-born women migrating in their 30s were more likely to have breastfed for 6 months or longer (78%) than those migrating in early life (44%) or in their 20s (49%). Average age at menarche was similar for U.S.-born white (12.8 years) and foreign-born Hispanic women migrating in their 20s (13.2 years) or in or after age 30 (12.9 years), and was substantially greater than age at menarche in U.S.-born African American (12.3 years), U.S.-born Hispanic (12.2 years), and early life Hispanic migrants (12.4 years) women. U.S.-born Hispanic women were on average younger than all other groups, and they, along with U.S.-born white women were less likely to be postmenopausal (38% and 36%, respectively) than U.S.-born African American (59%) or any of the foreign-born Hispanic groups (range of 55%–64%). The prevalence of benign breast disease and family history of breast cancer was relatively low in the overall sample (6.3% and 12%, respectively) and was highest in U.S.-born white women (12% and 23%, respectively). History of breast biopsy was reported by 22% of the overall sample with minimal differences by nativity, race/ethnicity, or migration age.

The distribution of percent density and dense area were not substantially different across U.S.-born racial/ethnic and across

migrant groups, but there were differences for non-dense area with U.S.-born African Americans having on average larger non-dense and U.S.-born white women having the smallest non-dense area (Table 1). Most risk factors for breast cancer did not substantially alter the associations of migration and acculturation variables with MBD, and only childhood body size, parity, and age at first live birth, along with age and BMI, were included in multivariable analyses.

Tables 2 to 4 respectively show the results of the multivariable models of percent density, dense area, and non-dense area with migration history and acculturation. In age- and BMI-adjusted models (model 1, Tables 2 and 3), monolingual and bilingual Spanish-speaking women had lower percent density and smaller dense area than monolingual English-speaking women [e.g., $\beta = -5.09$; 95% confidence interval (CI): -8.33 to -1.85 ; and $\beta = -3.34$; 95% CI, -6.57 to -0.12 for monolingual Spanish-speaking and bilingual women respectively, relative to monolingual English-speaking women for percent density]. In general, foreign-born women had lower percent density and dense area, as shown in age- and BMI-adjusted models for nativity alone, and nativity with race/ethnicity. For example, foreign-born Hispanic women had on average 4.32% (95% CI, -8.36 to -0.27) lower percent density and 6.52 cm² (95% CI, -15.22 to 2.18) smaller dense area, both relative to U.S.-born Hispanic women (model 1, Tables 2 and 3). As compared with U.S.-born women, there was also a trend toward lower percent density and dense area with spending a smaller proportion of life in the United States among foreign-born women, but statistically significant differences were only observed for those spending less than 50% of their lives in the United States and percent density ($\beta = -5.10$; 95% CI, -9.48 to -0.72 relative to U.S.-born Hispanic women; model 1, Table 2). There was no clear trend in percent density or dense area by age at migration, but foreign-born Hispanic women migrating at or after age 30 had significantly lower percent density than U.S.-born Hispanic women ($\beta = -5.37$; 95% CI, -10.10 to -0.64).

We examined whether observed associations of migration and acculturation with percent density and dense area were affected by further adjustment for breast cancer risk factors, namely childhood body size, parity, and age at first birth; nativity, and linguistic acculturation models were also adjusted for race/ethnicity (model 2, Tables 2 and 3). There were some attenuation in these associations, but most associations remained statistically significant for percent density (e.g., $\beta = -4.84$; 95% CI, -8.78 to -0.91 for foreign-born vs. U.S.-born women).

There were no statistically significant differences in percent density or dense area among U.S.-born racial/ethnic groups, and changing the referent group from U.S.-born Hispanic to U.S.-born white or U.S.-born African American women, yielded the same overall results, but larger estimates of inverse associations of migration variables and acculturation with percent density and dense area.

In age- and BMI-adjusted models, bilingual vs. monolingual English speakers had smaller non-dense area, but these differences were attenuated and no longer significant in the final model (Table 4). African American women had significantly larger non-dense area than other U.S.-born groups as well as foreign-born Hispanics, which remained statistically significant in the fully adjusted model (e.g., $\beta = 31.24$; 95% CI, 9.09–53.40 compared with U.S.-born Hispanic women; model 2, Table 4).

Table 1. Sample characteristics by birthplace and race/ethnicity (*n* = 477)

	U.S.-Born by Race/ethnicity			Foreign-Born Hispanic by Age at Migration*		
	White (<i>n</i> = 49)	African American (<i>n</i> = 62)	Hispanic (<i>n</i> = 54)	<20 years (<i>n</i> = 93)	20–29 years (<i>n</i> = 128)	≥30 years (<i>n</i> = 90)
Mean (SD)						
Age at mammogram (year) ^{a,b}	51.1 (5.8)	51.8 (5.2)	48.3 (5.3)	51.6 (6.1)	51.2 (5.6)	52.4 (6.0)
Age at menarche (year) ^{a,c}	12.8 (1.3)	12.3 (1.9)	12.2 (1.5)	12.4 (1.9)	13.2 (1.9)	12.9 (1.8)
Parity ^a	1.3 (1.0)	1.8 (2.0)	1.8 (1.4)	2.5 (1.2)	2.4 (1.2)	2.4 (1.2)
Age at first live birth (in parous women, year) ^{a,b,c}	33.8 (6.9)	21.9 (5.5)	25.0 (7.1)	22.6 (5.0)	24.5 (5.0)	25.6 (6.3)
Age at natural menopause (year) ^b	52.2 (2.1)	45.9 (4.6)	44.3 (8.1)	48.4 (4.2)	48.3 (5.0)	48.6 (5.1)
Body mass index (kg/m ²) ^b	28.4 (5.3)	32.5 (7.4)	30.2 (6.2)	30.0 (5.2)	29.9 (5.0)	29.9 (4.6)
Percent density ^a	31.0 (19.1)	25.8 (16.4)	30.3 (17.7)	23.8 (14.4)	25.2 (14.4)	22.5 (11.6)
Premenopausal	34.4 (18.6)	28.3 (14.7)	33.9 (17.8)	28.6 (14.5)	30.2 (15.4)	26.8 (12.1)
Postmenopausal	25.6 (18.8)	24.0 (17.7)	22.1 (13.1)	20.7 (13.6)	21.1 (12.1)	20.2 (10.7)
Dense area (cm ²) ^a	48.2 (27.0)	54.9 (36.5)	54.3 (34.7)	45.3 (26.6)	45.3 (30.2)	42.8 (28.1)
Premenopausal	51.0 (27.9)	61.5 (38.1)	55.2 (34.2)	51.6 (25.7)	51.2 (30.7)	47.0 (31.0)
Postmenopausal	44.7 (26.0)	49.2 (35.0)	51.2 (35.8)	41.4 (26.7)	40.5 (29.1)	40.8 (26.6)
Non-dense area (cm ²) ^b	126.0 (79.4)	193.0 (110.4)	141.5 (81.3)	157.0 (63.3)	143.1 (65.3)	151.7 (61.8)
Premenopausal ^b	109.4 (63.9)	183.0 (111.5)	121.6 (75.2)	141.9 (60.5)	124.2 (56.1)	131.9 (56.0)
Postmenopausal ^a	151.5 (95.0)	198.4 (111.9)	185.3 (80.2)	166.5 (63.8)	158.7 (68.5)	163.3 (63.0)
N (%)						
Educational Attainment ^{a,b,c}						
High school graduate or less education	1 (2.04)	26 (41.9)	12 (22.2)	47 (50.5)	83 (64.8)	53 (58.9)
Some college	6 (12.2)	21 (33.9)	16 (29.6)	31 (33.3)	27(21.1)	16 (17.8)
Bachelor's degree or more	42 (85.7)	15 (24.2)	26 (48.2)	15 (16.1)	18 (14.1)	21 (23.3)
Body size at age 10 ^{a,b}						
Level 1	7 (14.3)	22 (36.1)	14 (25.9)	48 (51.6)	74 (57.8)	54 (60.0)
Level 2	12 (24.5)	10 (16.4)	15 (27.8)	15 (16.1)	27 (21.1)	11 (12.2)
Level 3	24 (49.0)	18 (29.5)	13 (24.1)	18 (19.4)	22 (17.2)	15 (16.7)
Level 4	6 (12.2)	11 (18.0)	12 (22.2)	12 (12.9)	5 (3.9)	10 (11.1)
Current Alcohol Consumption ^{a,b}						
Never or former drinker	10 (20.4)	38 (61.3)	26 (48.2)	52 (55.9)	76 (60.3)	55 (61.8)
Fewer than 3 servings/week	23 (46.9)	12 (19.4)	13 (24.1)	26 (28.0)	36 (28.6)	26(28.3)
3–7 servings/week	12 (24.5)	7 (11.3)	12 (22.2)	8 (8.6)	8 (6.4)	5 (5.6)
7 or more servings/week	4 (8.2)	5 (8.1)	3 (5.6)	7 (7.5)	6 (4.8)	4 (4.5)
Duration of lifetime breastfeeding (in parous women) ^{a,b,c}						
Never breastfed	5 (14.3)	19 (41.3)	12 (26.7)	16 (18.2)	22 (18.0)	5 (6.1)
Less than 6 months	7 (20.0)	17 (37.0)	19 (42.2)	33 (37.5)	40 (32.8)	13 (15.9)
6–11 months	5 (14.3)	6 (13.0)	8 (17.8)	14 (15.9)	23 (18.9)	27 (32.9)
12 or more months	18 (51.4)	4 (8.7)	6 (13.3)	25 (28.4)	37 (30.3)	37 (45.1)
Duration of lifetime hormonal contraceptive use						
Less than 1 year	5 (14.3)	11 (26.8)	9 (25.0)	15 (24.6)	25 (31.3)	13 (29.6)
1–4 years	9 (25.7)	14 (34.2)	14 (38.9)	23 (37.7)	27 (33.8)	16 (36.4)
5 or more years	21 (60.0)	16 (39.0)	13 (36.1)	23 (37.7)	28 (35.0)	15 (34.1)
Ever hormone replacement therapy	5 (10.2)	3 (4.8)	4 (7.4)	6 (6.5)	5 (3.9)	4 (4.4)
Menopausal status ^{a,b}						
Premenopausal	30 (63.8)	25 (41.0)	31 (62.0)	36 (38.7)	58 (45.3)	32 (36.0)
Postmenopausal	17 (36.2)	36 (59.0)	19 (38.0)	57 (61.3)	70 (54.7)	57 (64.0)
Personal History of Breast Biopsy	11 (22.5)	7 (11.30)	12 (22.2)	23 (24.7)	34 (26.6)	19 (21.1)
Personal History of Benign Breast Disease ^c	6 (12.2)	3 (4.8)	3 (5.6)	4 (4.3)	14 (10.2)	1 (1.1)
Family history of breast cancer ^a	11 (22.5)	10 (16.1)	5 (9.3)	11 (11.8)	11 (8.6)	8 (8.9)

SD, standard deviation; * one (1) Hispanic foreign-born participant missing age at migration.

^aComparison of U.S.-born versus foreign-born women; *P*-value <0.05.^bComparisons among racial/ethnic groups in U.S.-born women; *P*-value <0.05.^cComparisons among women migrated at different ages in foreign-born women; *P*-value <0.05.

Discussion

We investigated the associations of migration history and linguistic acculturation with mammographic density in a sample of U.S.-born racially/ethnically diverse and foreign-born Hispanic women in their midlife. Specifically, we were interested in examining whether any observed associations corresponded to the established migration and acculturation patterns in breast cancer risk. Our results provide some support for these patterns by showing lower MBD in foreign-born women and with increasing use of Spanish language and decreasing proportion of life residing in the United States. We also considered racial/ethnic back-

grounds in relation to nativity and migration timing, and did not observe significant MBD differences in U.S.-born women of different racial/ethnic backgrounds, with all three groups having higher MBD as compared with foreign-born Hispanic women. The observed associations were consistent for percent density and dense area, both strong risk factors for breast cancer that respectively represent relative and absolute amount of mammographically dense breast tissue (28–30). The distribution of breast cancer risk factors differed by race/ethnicity and by migration history, with U.S.-born white women having an overall higher prevalence of most risk factors except for younger age at menarche, lack of and

Table 2. Multivariable associations of migration and linguistic acculturation with percent density

	N	Model 1 ^a		Model 2 ^b	
		β	(95% CI)	β	(95% CI)
Linguistic Acculturation^c					
Monolingual English	117	Ref		Ref	
Bilingual	181	-3.34	(-6.57, -0.12)	-3.90	(-8.94, 1.14)
Monolingual Spanish	179	-5.09	(-8.33, -1.85)	-5.83	(-11.14, -0.51)
Nativity^c					
U.S.-born	165	Ref		Ref	
Foreign-born	312	-4.50	(-7.12, -1.89)	-4.84	(-8.78, -0.91)
Race/ethnicity and Nativity					
U.S.-born white	49	1.16	(-4.22, 6.54)	1.28	(-4.32, 6.88)
U.S.-born African American	62	-0.44	(-5.53, 4.64)	0.23	(-4.92, 5.37)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born Hispanic	312	-4.32	(-8.36, -0.27)	-4.54	(-8.68, -0.40)
Race/ethnicity and % Life Spent in the U.S.					
U.S.-born white	49	1.19	(-5.49, 4.68)	1.18	(-4.41, 6.78)
U.S.-born African American	62	-0.41	(-4.19, 6.56)	0.30	(-4.84, 5.44)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born, 50%-99%	178	-3.67	(-7.94, 0.61)	-3.77	(-8.15, 0.61)
Foreign-born, <50%	133	-5.10	(-9.48, -0.72)	-5.43	(-9.88, -0.97)
Race/ethnicity and Age at Migration to the United States					
U.S.-born white	49	1.13	(-4.24, 6.51)	1.19	(-4.41, 6.79)
U.S.-born African American	62	-0.47	(-5.55, 4.61)	0.22	(-4.92, 5.36)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born Hispanic, migrated < 20 years	93	-4.54	(-9.20, 0.13)	-4.32	(-9.05, 0.41)
Foreign-born Hispanic, migrated 20-29 years	128	-3.48	(-7.89, 0.94)	-3.92	(-8.44, 0.59)
Foreign-born Hispanic, migrated 30+ years	90	-5.37	(-10.10, -0.64)	-5.68	(-10.47, -0.90)

^aModel 1 is adjusted for age and BMI (kg/m²) at the time of mammogram.

^bModel 2 is adjusted by age, BMI (kg/m²) at the time of mammogram, parity, age at first birth, and childhood body size.

^cModel 2 is also adjusted for race/ethnicity.

shorter breastfeeding, and large BMI, which were more prevalent in U.S.-born African American women. Foreign-born women migrating in later adult years had the lowest risk factor profile.

Accounting for differences in risk factors for breast cancer had smaller effects on the estimates of the associations of migration and acculturation with percent density than with dense area.

Table 3. Multivariable associations of migration and linguistic acculturation with dense area (cm²)

	N	Model 1 ^a		Model 2 ^b	
		β	(95% CI)	β	(95% CI)
Linguistic Acculturation^c					
Monolingual English	117	Ref		Ref	
Bilingual	181	-5.78	(-12.71, 1.15)	-5.42	(-16.13, 5.28)
Monolingual Spanish	179	-7.49	(-14.45, -0.52)	-7.08	(-18.36, 4.21)
Nativity^c					
U.S.-born	165	Ref		Ref	
Foreign-born	312	-6.58	(-12.21, -0.95)	-4.45	(-12.82, 3.92)
Race/ethnicity and Nativity					
U.S.-born white	49	-2.31	(-13.88, 9.27)	-1.01	(-12.92, 10.90)
U.S.-born African American	62	2.04	(-8.91, 12.98)	4.98	(-5.96, 15.93)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born Hispanic	312	-6.52	(-15.22, 2.18)	-5.35	(-14.15, 3.45)
Race/ethnicity and % Life Spent in the U.S.					
U.S.-born white	49	-2.26	(-13.83, 9.31)	-1.15	(-13.06, 10.75)
U.S.-born African American	62	2.10	(-8.84, 13.04)	5.10	(-5.84, 16.04)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born Hispanic, 50%-99%	178	-5.43	(-14.63, 3.77)	-4.13	(-13.45, 5.18)
Foreign-born Hispanic, <50%	133	-7.85	(-17.28, 1.59)	-6.74	(-16.21, 2.73)
Race/ethnicity and Age at Migration to the United States					
U.S.- born white	49	-2.33	(-13.91, 9.24)	-1.16	(-13.08, 10.75)
U.S.- born African American	62	2.02	(-8.92, 12.96)	5.0	(-5.94, 15.94)
U.S.- born Hispanic	54	Ref		Ref	
Foreign-born Hispanic, migrated < 20 years	93	-5.95	(-16.0, 4.09)	-4.09	(-14.16, 5.97)
Foreign-born Hispanic, migrated 20-29 years	128	-6.20	(-15.71, 3.31)	-5.54	(-15.15, 4.06)
Foreign-born Hispanic, migrated 30+ years	90	-7.65	(-17.83, 2.52)	-6.45	(-16.64, 3.74)

^aModel 1 is adjusted for age and BMI (kg/m²) at the time of mammogram.

^bModel 2 is adjusted by age, BMI (kg/m²) at the time of mammogram, parity, age at first birth, and childhood body size.

^cModel 2 is also adjusted for race/ethnicity.

Table 4. Multivariable associations of migration and linguistic acculturation with non-dense area (cm²)

	N	Model 1 ^a		Model 2 ^b	
		β	(95% CI)	β	(95% CI)
Linguistic Acculturation^c					
Monolingual English	117	Ref		Ref	
Bilingual	181	-14.27	(-28.21, -0.33)	-0.39	(-22.13, 21.36)
Monolingual Spanish	179	-6.62	(-20.62, 7.39)	10.14	(-12.78, 33.06)
Nativity^c					
U.S.-born	165	Ref		Ref	
Foreign-born	312	-3.84	(-15.21, 7.53)	15.26	(-1.72, 32.24)
Race/ethnicity and Nativity					
U.S.-born white	49	-5.72	(-28.88, 17.43)	-2.53	(-26.64, 21.57)
U.S.-born African American	62	27.73	(5.84, 49.62)	31.24	(9.09, 53.40)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born Hispanic	312	4.83	(-12.57, 22.23)	10.57	(-7.24, 28.39)
Race/Ethnicity and % Life Spent in the United States					
U.S.-born white	49	-5.71	(-28.86, 17.44)	-2.50	(-26.62, 21.62)
U.S.-born African American	62	27.75	(5.86, 49.64)	31.22	(9.06, 53.38)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born Hispanic, 50%-99%	178	5.13	(-13.29, 23.55)	10.31	(-8.56, 29.18)
Foreign-born Hispanic, <50%	133	4.46	(-14.42, 23.34)	10.88	(-8.30, 30.06)
Race/ethnicity and Age at Migration to the U.S.					
U.S.-born white	49	-5.66	(-28.75, 17.44)	-2.75	(-26.85, 21.35)
U.S.-born African American	62	27.81	(5.98, 49.65)	31.38	(9.26, 53.50)
U.S.-born Hispanic	54	Ref		Ref	
Foreign-born Hispanic, migrated < 20 years	93	11.60	(-8.44, 31.64)	14.90	(-5.45, 35.25)
Foreign-born Hispanic, migrated 20-29 years	128	-0.72	(-19.70, 18.26)	6.24	(-13.19, 25.66)
Foreign-born Hispanic, migrated 30+ years	90	5.98	(-14.32, 26.28)	12.17	(-8.44, 32.77)

^aModel 1 is adjusted for age and BMI (kg/m²) at the time of mammogram.

^bModel 2 is adjusted by age, BMI (kg/m²) at the time of mammogram, parity, age at first birth, and childhood body size.

^cModel 2 is also adjusted for race/ethnicity.

Importantly, although percent density is highly correlated with body size and breast fat, associations of migration and acculturation with percent density remained after adjustment for women's childhood body size and midlife BMI. These associations were also unlikely due to breast fat given minimal differences in the amount of mammographically non-dense, primarily fat, tissue in the breast, with mostly inverse associations with breast cancer in prior studies (27, 30, 31). Reasons for differences in the associations of breast cancer risk factors with dense area and percent density, reported in some studies (32-34), remain mostly unknown, and along with confirmation of our findings in other ethnic and migrant populations, warrant more research.

Our results with respect to lower MBD in women born primarily in the Caribbean countries as compared with U.S.-born women are aligned with international variations in breast cancer risk (e.g., age-standardized incidence rate of 91.9 in the United States vs. 46.1 in the Caribbean countries; ref. 1), as well as with variations in MBD that show lower average MBD in women from regions with lower breast cancer incidence than in women from higher incidence regions (21, 33). Only a few studies have examined MBD differences between native- and foreign-born women residing in the same country. A U.K. study reported lower percent density and dense area in foreign-born Afro-Caribbean and South Asian women relative to white women (35), whereas the Study of Women's Health Across the Nation (SWAN) found higher percent density in foreign-born Chinese and Japanese women relative to U.S.-born Chinese and Japanese women (23). Another study of foreign-born Asian women in the U.S., a vast majority of whom (~90%) were born in China, Hong Kong, or Taiwan, showed increased probability of higher MBD category with increasing U.S. acculturation, which is consistent with our results and with the expected acculturation patterns in breast cancer risk (24). In contrast, the SWAN study reported a trend

of higher percent density and larger dense area in less acculturated Chinese and Japanese descent women (23). Reconciling different results across the limited number of studies is made difficult by variations in the measurements of MBD and acculturation, as well as differences in the racial/ethnic composition of the study populations. Racial/ethnic differences in MBD have been reported in a number of studies, generally showing lower MBD in Asian women, similar MBD in Hispanic women and mixed results for African American women compared with white women (23, 36-41); however, most studies have not been able to tease apart the effect of ethnicity from that of migration. Additional studies are necessary to clarify whether a universal process of increasing risk operate within the context of migration and acculturation, or whether and how this process is shaped by unique and varied experiences of immigrant women, including upheaval and changes in the country of origin, reasons for migration, and the circumstances under which migration and resettlement into the host country occur. This research could benefit from a multidisciplinary approach that integrates more complex and multidimensional theories of acculturation with life course epidemiology of breast cancer.

Geographic, migration, and acculturation variations in breast cancer risk are widely attributed to differential exposures to risk factors for breast cancer. However, the significant differences in the prevalence of many breast cancer risk factors across racial/ethnic and migrant groups have not fully explained migration and acculturation patterns in MBD in prior studies (23, 35), and in percent density in our study. Breast cancer risk is shaped across the life course, but factors operating in earlier life periods such as prenatal, childhood, and adolescence are difficult to reliably assess in most studies of MBD, which similar to our study, focus on the midlife period when women undergo screening mammography. In our study, we considered recalled body size at age

10 using a validated pictogram as used in other studies of MBD (11, 25). To further explore whether exposures experienced in earlier life periods may be at play, we examined the timing of migration according to age groups representing different life stages and windows of susceptibility (e.g., migration in childhood/adolescence, young, or later adulthood) and in relation to key reproductive events (e.g., migration prior to menarche). We obtained similar results in models using different cut-points for age at migration (e.g., age 13, 15, 20) or when using age at migration as a continuous variable. The consistent inverse association of MBD with foreign birth along with relatively small differences in MBD by the timing of migration in foreign-born women may point to possibility of differences in breast cancer-relevant prenatal or infancy exposures. These exposures associated with MBD in prior studies include prenatal tobacco exposures (42), birthweight, and postnatal growth (11, 13, 43), all of which are likely to vary between foreign- and native-born populations. Carefully designed studies such as family-based studies of siblings discordant in their early life environments and retrieval of early life data from family and health records may help to provide the necessary data for future investigations.

Our study limitations included the small size of U.S.-born racial/ethnic groups and early life migrant group, which may have limited the power to detect small differences in MBD by ethnicity and migration timing; nonetheless, we observed statistically significant association for percent density even in fully adjusted model. The likelihood of bias in our results is small given that women and interviewers were unaware of MBD measures, and participant selection and recruitment were not contingent on migration history, language proficiency or MBD. Our study sample reflect the sociodemographic composition and migration experiences of the patient population and community from which we enrolled women, comprised primarily of Hispanic immigrants. The rate of and access to (e.g., wait time, availability of facilities) mammography screening in our catchment community is higher than New York City average (44), and the availability of low-cost mammography and bilingual research staff enabled the recruitment of an ethnically and socioeconomically diverse sample. Of Hispanic women in our sample, 86% and 6% were born, respectively, in the Dominican Republic and in Puerto Rico, and 30% and 43% of U.S.-born women respectively had parents born in the Dominican Republic and in Puerto Rico. Thus, our study results are most generalizable to Hispanic women of Caribbean descent, a population that is underrepresented in research on MBD, and has higher breast cancer incidence and mortality than women of Mexican and Central American backgrounds (1, 45–47). Additionally, we lacked data on many early life factors relevant to breast cancer risk and other measures of acculturation. The strengths of this study include the use of all digital mammograms performed at a single institution, and highly reproducible quantitative assessments of MBD, which help to minimize MBD measurement error. We further minimized possible measurement bias by collecting physical measurements of height and weight to calculate BMI, a necessary covariate in studies of MBD, rather than

relying on self-reported anthropometric data whose accuracy depends on women's sociodemographic backgrounds including race/ethnicity and education (48–51). We also utilized a standardized protocol to collect in-person detailed data on factors related to breast cancer risk and migration history. Of note, more than half of the interviews were conducted in Spanish using a professionally translated questionnaire, enabling the enrollment of foreign-born and more recent immigrants with limited English proficiency.

In conclusion, we provide the first data to show that Hispanic women born predominantly in Caribbean countries have lower mammographic density than U.S.-born women of diverse racial/ethnic backgrounds, including U.S.-born Hispanic women of Caribbean heritage. Additionally, mammographic density is lower in women with lower linguistic acculturation and proportion of life spent in the United States, proxies for adaptation to U.S.-prevalent sociocultural, behavioral, and environmental exposures. These associations are consistent with those observed for breast cancer risk, suggesting that mammographic density may reflect the process that increases the risk of breast cancer in migrants from low- to high-incidence regions. These findings, if confirmed in other populations, highlight the importance of mammographic density for better understanding breast cancer etiology and epidemiology with the potential to inform strategies for reducing population level risk profiles.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: P. Tehraniyar

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P. Tehraniyar, C.B. Rodriguez, A.K. April-Sanders, K.M. Schmitt

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P. Tehraniyar, C.B. Rodriguez, A.K. April-Sanders

Writing, review, and/or revision of the manuscript: P. Tehraniyar, C.B. Rodriguez, A.K. April-Sanders, E. Desperito, K.M. Schmitt

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P. Tehraniyar, C.B. Rodriguez, A.K. April-Sanders, E. Desperito

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Acknowledgments

This research was funded by the NIH/National Cancer Institute K07CA151777 (to principal investigator P. Tehraniyar).

We thank the study participants for contributing data to this research and the research staff for data collection and management.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 29, 2017; revised December 18, 2017; accepted February 2, 2018; published first February 23, 2018.

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