Research Article

Cancer Epidemiology, Biomarkers & Prevention

Overall and Abdominal Adiposity and Premenopausal Breast Cancer Risk among Hispanic Women: The Breast Cancer Health Disparities Study

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Abstract

Background: Few studies in Hispanic women have examined the relation between adult body size and risk of premenopausal breast cancer defined by hormone receptor status.

Methods: The Breast Cancer Health Disparities Study pooled interview and anthropometric data from two large U.S. population-based case–control studies. We examined associations of overall and abdominal adiposity with risk of estrogen receptor– and progesterone receptor–positive (ER^+PR^+) and –negative (ER^-PR^-) breast cancer in Hispanic and non-Hispanic White (NHW) women, calculating ORs and 95% confidence intervals.

Results: Among Hispanics, risk of ER^+PR^+ breast cancer was inversely associated with measures of overall adiposity, including young-adult and current body mass index (BMI). Risk was substantially reduced among those with high (above the median) young-adult BMI and current overweight or obesity. The findings for overall adiposity were similar for Hispanics and NHWs. In the subset of Hispanics with data on genetic ancestry, inverse associations of current BMI, and weight gain with ER^+PR^+ breast cancer were limited to those with lower Indigenous American ancestry. For ER^-PR^- breast cancer, height was associated with increased risk, and young-adult BMI was associated with reduced risk. For all breast cancers combined, positive associations were seen for waist circumference, waist-to-hip ratio, and waist-to-height ratio in Hispanic women only.

Conclusions: Our findings of body size associations with specific breast cancer subtypes among premenopausal Hispanic women were similar to those reported for NHW women.

Impact: Adiposity throughout the premenopausal years has a major influence on breast cancer risk in Hispanic women. *Cancer Epidemiol Biomarkers Prev; 24(1); 138–47. ©2014 AACR.*

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Introduction

Body mass index (BMI), a measure of overall adiposity, has been associated with decreased risk of premenopausal breast cancer (1–3), whereas waist circumference and waist-to-hip ratio (WHR), two commonly used measures of abdominal or central adiposity, have been associated with increased risk (3–5), although not consistently. These findings are based on studies conducted in primarily non-Hispanic white (NHW) women. Only a few studies have reported on body size associations in premenopausal U.S. Hispanic (6–10) and Mexican (11) women, and the findings are not consistent. Therefore, it is unclear whether the effects of overall and abdominal obesity on premenopausal breast cancer risk in Hispanics are different from those in NHWs (12). The higher prevalence of overall and abdominal obesity in Hispanic than NHW women (13, 14) warrants further investigation of the relation between body size and breast cancer risk in Hispanics.

In this report, we analyzed data for Hispanic and NHW women from two large population-based case–control studies that were harmonized and pooled for the Breast Cancer Health Disparities Study (15). We assessed associations of overall and abdominal adiposity with risk of premenopausal breast cancer defined by estrogen receptor (ER) and progesterone receptor (PR) status, which is important in characterizing risk profiles for hormone-related exposures such as body size (16). We also examined whether genetic ancestry among Hispanic women modified the body size associations, given our previous finding that overall and abdominal obesity are more common in Hispanic women with higher Indigenous American (IA) ancestry (17).

Materials and Methods

The Breast Cancer Health Disparities Study was approved by the Institutional Review Board at each institution. Written informed

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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consent was provided by all study participants. Our analysis did not include a third study that is part of the Breast Cancer Health Disparities Study (15) because no data were available on hormone receptor status. That study, the Mexico Breast Cancer Study, reported on body size associations elsewhere (11).

San Francisco Bay Area Breast Cancer Study

The San Francisco Bay Area Breast Cancer Study (SFBCS) was conducted in Hispanic, African American, and NHW women from the San Francisco Bay Area (18, 19). The Greater Bay Area Cancer Registry identified 17,537 cases ages 35 to 79 years with a first primary invasive breast cancer diagnosed between April 1995 and April 2002. Controls were identified through random-digit dialing and were frequency matched to cases on race/ethnicity and the expected 5-year age distribution of cases. Self-reported race/ethnicity and eligibility for several studies were assessed by a telephone screening interview, with participation rates of 89% among 15,573 cases contacted (alive, valid address, and no physician refusal) and 92% among 3,547 controls contacted. For the SFBCS, women eligible for an in-person interview included all Hispanic cases diagnosed from 1995 to 2002, all African American cases diagnosed from 1995 to 1999, and a sample of NHW cases diagnosed from 1995 to 1999. Given the large number of diagnoses in NHW women, they were randomly sampled at 10%. Interview data were obtained for 1,715 cases, including 1,119 (89%) Hispanics and 596 (86%) NHWs, and 2,108 controls, including 1,462 (88%) Hispanics and 646 (83%) NHWs. Median time between diagnosis and interview was 15.4 months. The pooled analysis included Hispanics and NHWs only; body size associations for African Americans were reported elsewhere (9).

4-Corners Breast Cancer Study

The 4-Corners Breast Cancer Study (4-CBCS) included NHW, Hispanic, and Native American (NA) women from nonreservation areas in Arizona, Colorado, New Mexico, and Utah (8). The state-wide cancer registries identified 5,256 cases ages 25 to 79 years with *in situ* or invasive breast cancer diagnosed between October 1999 and May 2004; controls were selected from the populations living in the four states and were frequency matched to cases on race/ethnicity and expected 5-year age distribution. A total of 3,761 cases were contacted and 2,556 completed the in-person interview, including 873 Hispanics/NAs (63%) and 1,683 NHWs (71%). Of 6,152 controls contacted, 2,605 completed the interview, including 936 (36%) Hispanics/NAs and 1,669 (47%) NHWs. The number of NAs (55 cases, 73 controls) was too small for separate analysis and they were combined with Hispanics. Cases were restricted to those with a first primary invasive breast cancer (662 Hispanics/NAs, 1,246 NHWs). Median time between diagnosis and interview was 17.8 months.

Data collection

The two studies used similar structured questionnaires in English or Spanish to collect information on body size and other breast cancer risk factors up to the reference year (defined as the calendar year before diagnosis for cases or selection into the study for controls). Trained professional bilingual interviewers administered the questionnaires in English or Spanish and also measured standing height (with shoes removed) and weight (with light clothing) at the time of interview, using a portable stadiometer and scale, respectively. Waist and hip circumferences were measured using a linen tape (in SFBCS) or a flexible tape (in 4-CBCS). In SFBCS, height was measured to the nearest millimeter, weight to the nearest 0.20 kg, and waist and hip circumferences to the nearest millimeter. For each, three measurements were taken (except for two measurements of weight) and averaged (9). In 4-CBCS, height was measured to the nearest 0.25 inch (in), weight to the nearest 0.50 pound (lb), and waist and hip circumferences to the nearest 0.50 in. For each, two measurements were taken (if they differed by >0.5 in for height, >1.0 in for waist or hip circumferences, or >1.0 lb for weight, a third measurement was taken) and averaged (8). Information on ER and PR status was obtained from the respective cancer registries and was available for most premenopausal cases (84% in SFBCS, 79% in 4-CBCS).

Study variables

Data from the two studies were harmonized according to common definitions (15). Women were classified as premenopausal if they reported having menstrual periods during the reference year. On the basis of current language usage, a three-level acculturation index was created for Hispanics (low, Spanish speaking only; moderate, speaking more Spanish than English or Spanish and English equally; high, speaking more English than Spanish or English only).

Current BMI was calculated as weight (in kg) divided by height (in meter) squared, based on measured height at interview and self-reported weight in the reference year. Self-reported weight before diagnosis was used because weight measured at interview may have been affected by disease- or treatment-related weight gain or loss. For study participants who declined the height measurement, self-reported height was used (3% of cases, 2% of controls); for individuals without self-reported weight, measured weight was used (1% of cases, 2% of controls). The two studies used slightly different approaches to assess young-adult weight. In SFBCS, young-adult BMI was based on self-reported weight at age 25 to 30 years for cases diagnosed from 1995–1998 and their matched controls, or on self-reported weight at age 20 to 29 years for cases diagnosed from 1998 to 2002 and their matched controls. In 4-CBCS, young-adult BMI was based on the average of weights reported at ages 15 years and 30 years. Weight gain was calculated as the difference between self-reported young-adult weight and self-reported weight in the reference year (or measured weight at interview if self-reported weight was not available). We calculated WHR as a measure of body fat distribution that reflects both adipose tissue (waist circumference) and muscle mass (hip circumference), and waist-to-height ratio (WHtR) as a measure of visceral adiposity independent of height (20). Current BMI was classified as underweight to normal weight (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥ 30.0 kg/m^2). All other body size variables were categorized according to the tertile or quartile distribution among premenopausal controls.

For a subset of study participants with stored DNA (in SFBCS, biospecimen collection began with cases diagnosed in April 1997 or later and their matched controls), we estimated genetic ancestry using 104 ancestry informative markers (AIM; ref. 15). Hispanic women were classified according to being above or below the median (46%) of IA ancestry among premenopausal controls.

Statistical analyses

Unconditional logistic regression was used to calculate ORs and 95% confidence intervals (CI) for the associations with body size variables. Polytomous logistic regression was used to compare ER^+PR^+ and ER^-PR^- case groups to a common control group. Other case groups in premenopausal women (97 ER^+PR^-, 41 ER^-PR^+) were too small for separate analyses. We also stratified the analyses of Hispanic women by median IA ancestry. To directly compare OR estimates for Hispanics and NHWs, we categorized the body size variables according to the quartile or tertile distribution among Hispanic and NHW controls combined. Given the distinctly different distribution of body size measures between the two populations, we also used ethnicity-specific quantiles.

Multivariate analyses were adjusted for age (continuous) and study, and additionally, for factors significantly associated with risk of ER^+PR^+ or ER^-PR^- breast cancer in our dataset. For ER^+PR^+ breast cancer, analyses were adjusted for education, breast cancer family history, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, lifetime duration of breast feeding, oral contraceptive use, and alcohol consumption; for ER^-PR^- breast cancer, analyses were adjusted for alcohol consumption. Analyses in Hispanics additionally adjusted for language acculturation. Additional adjustment for genetic ancestry did not alter the results. Variables were categorized as noted in the footnotes of the tables. Linear trends were assessed across ordinal values of categorical variables. Significant differences in ORs between case groups were tested using the Wald statistic P value, calculated from the polytomous regression model. Two-sided P values are reported for tests of trend and tests of heterogeneity, with P values <0.05 considered statistically significant.

Analyses in premenopausal women included 1,262 Hispanics (497 cases and 765 controls) and 1,101 NHWs (448 cases and 653 controls), after excluding individuals with missing data on covariates (89 cases and 92 controls) or ER/PR status (241 cases). The analyses by genetic ancestry were based on 861 Hispanics (327 cases and 534 controls). Given the possibility of treatment- or disease-related weight gain among cases, we restricted the analysis of abdominal adiposity to 207 cases and 963 controls with anthropometric measurements taken <12 months after diagnosis (cases) or selection into the study (controls), hereafter referred to as the reduced dataset. Statistical analyses used SAS version 9.3 software (SAS Institute, Inc.).

Results

Compared with controls, cases had higher education, younger age at menarche, fewer full-term pregnancies, later age at first full-term pregnancy, shorter duration of breast feeding, and were more likely to have a first-degree family history of breast cancer (Supplementary Table S1). Among Hispanics, cases had higher English language acculturation than controls. Compared with NHW controls, higher proportions of Hispanic controls were currently overweight or obese (72% vs. 45 and had a young-adult BMI above the median of 21.7 kg/m^2 (63% vs. 35%; Supplementary Table S2). Hispanic controls had significantly higher abdominal obesity than NHWs. Furthermore, Hispanics with higher IA ancestry (above the median of 46%) had higher body size measures than those with lower IA ancestry.

Height, overall adiposity, and ER^+PR^+ breast cancer

For ER^+PR^+ breast cancer (Table 1), a suggestive positive trend ($P_{trend} = 0.08$) with height was seen for Hispanic women only. Young-adult BMI and current BMI were associated with reduced risk, with similar ORs associated with high (high vs. low quartile) young-adult BMI for Hispanics (OR, 0.53; $P_{trend} < 0.01$) and NHWs (OR, 0.58; $P_{trend} < 0.01$). For current obesity ($\geq$30 vs. <25 kg/m^2), risk was significantly reduced for Hispanics (OR, 0.63; $P_{trend} = 0.01$); for NHWs the inverse trend was of borderline significance ($P_{trend} = 0.10$). No significant associations were seen for weight gain in either population. Use of ethnicity-specific quartiles produced similar results (Table 1). Considering both young-adult and current BMI, reduced risks associated with current BMI were seen only in women with higher young-adult BMI (above the median, $\geq$21.8 kg/m^2), with similar findings for Hispanics and NHWs. For overweight (25–29.9 vs. <25 kg/m^2), ORs were 0.47 (95% CI, 0.30–0.74) and 0.55 (95% CI, 0.31–0.97), respectively; for obesity, ORs were 0.53 (95% CI, 0.35–0.81) and 0.66 (95% CI, 0.42–1.05), respectively. Adjustment for waist circumference did not alter OR estimates for overall body size (assessed in the reduced dataset, data not shown).

Height, overall adiposity, and ER^-PR^- breast cancer

For ER^-PR^- breast cancer (Table 2), significant associations were limited to Hispanic women. Using common tertile cutoff points, we found a positive association with height (OR, 1.91; $P_{trend} = 0.01$) and an inverse association with young-adult BMI (OR, 0.41; $P_{trend} < 0.01$), with slightly attenuated associations using ethnicity-specific tertiles. Adjustment for abdominal adiposity (assessed in the reduced dataset, data not shown) did not alter the associations.

Abdominal adiposity and breast cancer risk

In the reduced dataset, the analyses of abdominal adiposity were not stratified by ER/PR status, given the small number of ER^-PR^- cases (Table 3). Positive associations, adjusted for BMI, were limited to Hispanic women (71 cases and 561 controls). Using continuous measures, ORs were elevated for waist circumference (per 2 cm: OR, 1.09; 95% CI, 1.02–1.16), WHR (per 0.1: OR, 1.70; 95% CI, 1.03–2.81), and WHtR (per 0.1: OR, 1.92; 95% CI, 1.12–3.28).

Overall adiposity, genetic ancestry, and ER^+PR^+ breast cancer among Hispanics

In the subset of premenopausal Hispanics with available DNA (Supplementary Table S3), high young-adult BMI was associated with similar reductions in risk of ER^+PR^+ breast cancer (OR, 0.51) among Hispanics with higher or lower IA ancestry, although the inverse trend was statistically significant only for women with lower IA ancestry ($P_{trend} = 0.03$). For current BMI ($P_{trend} = 0.01$) and weight gain ($P_{trend} = 0.05$), inverse associations were limited to Hispanics with lower IA ancestry, although the interactions by genetic ancestry did not reach statistical significance. The reduced dataset was too small to assess interactions for abdominal adiposity by genetic ancestry.

Discussion

This pooled case–control analysis of more than 1,200 premenopausal Hispanic women is the largest study to date to

Table 1. Height and overall adiposity associations with ER^+PR^+ breast cancer in premenopausal women, by ethnicity

	All			Hispanics			NHWs		
	ER^+PR^+ cases ($n = 575$)	Controls ($n = 1,418$)		ER^+PR^+ cases ($n = 285$)	Controls ($n = 765$)		ER^+PR^+ cases ($n = 290$)	Controls ($n = 653$)	
	n	*n*	OR[a] (95% CI)	*n*	*n*	OR[a] (95% CI)	*n*	*n*	OR[b] (95% CI)
Current height (cm)[c,d]									
Q1: <155.5	110	354	1.0	93	309	1.0	17	45	1.0
Q2: 155.5–160.0	139	357	1.12 (0.82–1.52)	80	229	1.07 (0.74–1.54)	59	128	1.14 (0.59–2.21)
Q3: 160.1–165.4	171	351	1.39 (1.02–1.89)	81	161	1.41 (0.97–2.06)	90	190	1.23 (0.65–2.34)
Q4: >165.4	155	354	1.26 (0.90–1.77)	31	64	1.34 (0.80–2.23)	124	290	1.20 (0.64–2.25)
			$P_{trend} = 0.09$			$P_{trend} = 0.08$			$P_{trend} = 0.61$
Current height (cm)[d,e]									
Quartile 1				55	189	1.0	76	173	1.0
Quartile 2				62	197	0.98 (0.64–1.52)	69	157	1.06 (0.70–1.59)
Quartile 3				75	188	1.21 (0.79–1.86)	74	167	1.06 (0.71–1.58)
Quartile 4				93	189	1.34 (0.88–2.04)	70	155	1.20 (0.79–1.82)
						$P_{trend} = 0.10$			$P_{trend} = 0.41$
Per 5 cm			1.06 (0.97–1.15)			1.04 (0.93–1.17)			1.07 (0.95–1.20)
Young-adult BMI (kg/m^2)[c,f]									
Q1: <20.1	190	337	1.0	59	117	1.0	131	220	1.0
Q2: 20.1–21.7	163	338	0.84 (0.64–1.10)	83	149	1.09 (0.70–1.69)	80	189	0.71 (0.50–1.01)
Q3: 21.8–24.1	120	338	0.66 (0.49–0.88)	78	210	0.81 (0.52–1.26)	42	128	0.55 (0.36–0.85)
Q4: >24.1	91	338	0.51 (0.37–0.70)	60	250	0.53 (0.33–0.84)	31	88	0.58 (0.36–0.95)
			$P_{trend} < 0.01$			$P_{trend} < 0.01$			$P_{trend} < 0.01$
Young-adult BMI (kg/m^2)[f,g]									
Quartile 1				86	182	1.0	94	155	1.0
Quartile 2				99	181	1.22 (0.84–1.78)	79	157	0.83 (0.56–1.23)
Quartile 3				50	183	0.69 (0.45–1.06)	63	156	0.66 (0.44–0.99)
Quartile 4				45	180	0.59 (0.38–0.93)	47	156	0.50 (0.32–0.78)
						$P_{trend} < 0.01$			$P_{trend} < 0.01$
Per 5 kg/m^2			0.74 (0.63–0.86)			0.76 (0.62–0.93)			0.71 (0.55–0.93)
Current BMI (kg/m^2)[h]									
<25.0	294	576	1.0	119	212	1.0	178	364	1.0
25.0–29.9	148	446	0.69 (0.53–0.88)	84	286	0.60 (0.42–0.86)	64	160	0.79 (0.55–1.13)
≥30.0	133	394	0.67 (0.51–0.87)	82	265	0.63 (0.44–0.92)	51	129	0.74 (0.50–1.10)
			$P_{trend} < 0.01$			$P_{trend} = 0.01$			$P_{trend} = 0.10$
Per 5 kg/m^2			0.86 (0.78–0.94)			0.81 (0.71–0.92)			0.92 (0.82–1.05)
Weight gain (kg)[c,i]									
Q1: <6.8	170	349	1.0	75	154	1.0	95	195	1.0
Q2: 6.8–11.3	69	222	0.66 (0.47–0.92)	36	124	0.62 (0.38–1.01)	33	98	0.67 (0.41–1.09)
Q3: 11.3–19.8	139	350	0.83 (0.63–1.10)	67	206	0.73 (0.48–1.09)	72	144	0.99 (0.66–1.47)
Q4: >19.8	124	307	0.80 (0.59–1.07)	64	178	0.78 (0.51–1.19)	60	129	0.85 (0.56–1.30)
			$P_{trend} = 0.21$			$P_{trend} = 0.30$			$P_{trend} = 0.68$

(Continued on the following page)

Table 1. Height and overall adiposity associations with ER^+PR^+ breast cancer in premenopausal women, by ethnicity (Cont'd)

	All			Hispanics			NHWs		
	ER^+PR^+ cases ($n = 575$)	Controls ($n = 1,418$)		ER^+PR^+ cases ($n = 285$)	Controls ($n = 765$)		ER^+PR^+ cases ($n = 290$)	Controls ($n = 653$)	
	n	*n*	OR[a] (95% CI)	*n*	*n*	OR[a] (95% CI)	*n*	*n*	OR[b] (95% CI)
Weight gain (kg)[i,j]									
Quartile 1				79	166	1.0	60	136	1.0
Quartile 2				46	161	0.62 (0.40–0.96)	56	133	0.94 (0.60–1.48)
Quartile 3				54	166	0.77 (0.50–1.18)	69	140	1.06 (0.68–1.66)
Quartile 4				63	169	0.82 (0.54–1.24)	74	156	0.95 (0.62–1.48)
						$P_{trend} = 0.45$			$P_{trend} = 0.96$
Per 5 kg			0.98 (0.94–1.03)			0.96 (0.89–1.04)			1.01 (0.94–1.07)
Young-adult BMI (kg/m^2)[f,k] and current BMI (kg/m^2)[h]									
<21.8/<25	242	436	1.0	89	136	1.0	153	300	1.0
<21.8/25–25.9	83	185	0.82 (0.59–1.12)	38	98	0.68 (0.42–1.10)	45	85	0.95 (0.62–1.47)
<21.8/≥30	28	56	0.89 (0.54–1.47)	15	32	0.85 (0.42–1.74)	13	24	0.97 (0.47–2.00)
≥21.8/<25	48	113	0.80 (0.54–1.18)	29	64	0.78 (0.45–1.34)	19	49	0.77 (0.42–1.39)
≥21.8/25–25.9	63	245	0.52 (0.37–0.73)	45	177	0.47 (0.30–0.74)	18	68	0.55 (0.31–0.97)
≥21.8/≥30	100	318	0.58 (0.43–0.78)	64	219	0.53 (0.35–0.81)	36	99	0.66 (0.42–1.05)
			$P_{interaction} = 0.73$			$P_{interaction} = 0.95$			$P_{interaction} = 0.81$

[a]ORs and 95% CIs, adjusted for age (years, continuous), study (SFBCS, 4-CBCS), ethnicity/English language acculturation (low, moderate, high, and NHW), education (less than high school, high school graduate, after high school education), family history of breast cancer in first-degree relatives (no or yes), age at menarche (<12, 12, 13, ≥14), number of full-term pregnancies (nulliparous, 1–2, 3–4, ≥5), age at first full-term pregnancy (<20, 20–24, 25–29, ≥30, nulliparous), lifetime number of months of breastfeeding (nulliparous, 0, 1–6, 7–12, 13–24, >24), hormonal contraception use (never, former, current), and average alcohol consumption in reference year (g/d; 0, 0.1–4.9, 5–9.9, 10–19.9, ≥20).

[b]Adjusted for all variables above except English language acculturation.

[c]Based on quartiles among all premenopausal controls.

[d]Based on measured height at interview (or self-reported adult height when measured height was not available).

[e]Based on ethnicity-specific quartiles among premenopausal controls in each ethnic group. Quartile cut points by ethnicity are <152.7, 152.7–156.9, 157.0–161.1, and >161.1 for Hispanics, and <160.0, 160.0–164.5, 164.6–168.9, and >168.9 for NHWs.

[f]Based on self-reported averaged weight at age 15 and age 30 for 4-CBCS cases and controls, self-reported weight in the 20s for SFBCS cases and controls (between ages 25–30 for cases diagnosed from April 1995 to April 1998 and matched controls and between ages 20–29 for cases diagnosed from May 1998 to April 2002 and matched controls), and measured height at interview (or self-reported adult height when measured height was not available).

[g]Based on ethnicity-specific quartiles among premenopausal controls in each ethnic group. Quartile cut points by ethnicity are <20.9, 20.9–22.9, 23.0–25.3, and >25.3 for Hispanics, and <19.4, 19.4–20.8, 20.9–22.7, and >22.7 for NHWs.

[h]Based on self-reported weight in reference year (or measured weight at interview when self-reported weight in reference year was not available) and measured height at interview (or self-reported adult height when measured height was not available).

[i]Based on self-reported weight in reference year (or measured weight at interview when self-reported weight was not available) minus self-reported young-adult weight; excludes 62 premenopausal ER^+PR^+ cases and 125 premenopausal controls who lost weight.

[j]Based on ethnicity-specific quartiles among premenopausal controls in each ethnic group. Quartile cut points by ethnicity are <7.5, 7.5–12.5, 12.6–20.4, and >20.4 for Hispanics, and <5.0, 5.0–10.2, 10.3–18.1, and >18.1 for NHWs.

[k]Based on the median among all premenopausal controls.

Table 2. Height and overall adiposity associations with ER^-PR^- breast cancer in premenopausal women, by ethnicity

	All			Hispanics			NHWs		
	ER^-PR^- cases ($n = 247$)	Controls ($n = 1,418$)		ER^-PR^- cases ($n = 142$)	Controls ($n = 765$)		ER^-PR^- cases ($n = 105$)	Controls ($n = 653$)	
	n	*n*	OR[a] (95% CI)	*n*	*n*	OR[a] (95% CI)	*n*	*n*	OR[b] (95% CI)
Current height (cm)[c,d]									
T1: <157.1	70	468	1.0	59	394	1.0	11	74	1.0
T2: 157.1–163.2	75	466	1.07 (0.75–1.55)	45	252	1.11 (0.72–1.70)	30	214	0.93 (0.44–1.97)
T3: >163.2	102	482	1.50 (1.03–2.19)	38	117	1.91 (1.19–3.07)	64	365	1.13 (0.57–2.26)
			$P_{trend} = 0.03$			$P_{trend} = 0.01$			$P_{trend} = 0.51$
Current height (cm)[d,e]									
Tertile 1				33	252	1.0	34	215	1.0
Tertile 2				44	252	1.20 (0.73–1.98)	29	216	0.85 (0.50–1.45)
Tertile 3				65	259	1.64 (1.03–2.63)	42	221	1.13 (0.69–1.85)
						$P_{trend} = 0.01$			$P_{trend} = 0.51$
Per 5 cm			1.12 (1.01–1.25)			1.22 (1.05–1.41)			1.03 (0.87–1.21)
Young-adult BMI (kg/m^2)[c,f]									
T1: <20.6	88	446	1.0	46	157	1.0	42	289	1.0
T2: 20.6–23.1	84	446	0.90 (0.64–1.26)	51	230	0.76 (0.48–1.20)	33	216	1.06 (0.65–1.75)
T3: >23.1	59	459	0.63 (0.43–0.93)	38	339	0.41 (0.25–0.68)	21	120	1.23 (0.69–2.21)
			$P_{trend} = 0.02$			$P_{trend} < 0.01$			$P_{trend} = 0.50$
Young-adult BMI (kg/m^2)[f,g]									
Tertile 1				64	239	1.0	28	206	1.0
Tertile 2				41	240	0.67 (0.43–1.05)	32	206	1.16 (0.67–2.01)
Tertile 3				30	247	0.50 (0.31–0.81)	36	212	1.26 (0.74–2.17)
						$P_{trend} < 0.01$			$P_{trend} = 0.50$
Per 5 kg/m^2			0.88 (0.72–1.08)			0.73 (0.55–0.95)			1.20 (0.88–1.64)
Current BMI (kg/m^2)[h]									
<25.0	106	576	1.0	53	212	1.0	53	364	1.0
25.0–29.9	76	446	0.99 (0.71–1.38)	48	286	0.77 (0.50–1.20)	28	160	1.34 (0.81–2.22)
≥30.0	65	394	0.98 (0.69–1.40)	41	265	0.71 (0.45–1.12)	24	129	1.45 (0.85–2.48)
			$P_{trend} = 0.93$			$P_{trend} = 0.15$			$P_{trend} = 0.14$
Per 5 kg/m^2			0.98 (0.88–1.10)			0.83 (0.71–0.98)			1.16 (0.99–1.35)
Weight gain (kg)[c,i]									
T1: <8.2	75	414	1.0	46	183	1.0	29	231	1.0
T2: 8.2–16.3	63	397	0.90 (0.63–1.30)	36	229	0.65 (0.40–1.06)	27	168	1.35 (0.76–2.38)
T3: >16.3	76	417	1.05 (0.74–1.50)	44	250	0.73 (0.46–1.17)	32	167	1.68 (0.96–2.93)
			$P_{trend} = 0.79$			$P_{trend} = 0.21$			$P_{trend} = 0.07$
Weight gain (kg)[i,j]									
Tertile 1				55	233	1.0	23	194	1.0
Tertile 2				28	204	0.60 (0.36–0.98)	29	173	1.52 (0.84–2.75)
Tertile 3				43	225	0.86 (0.54–1.35)	36	198	1.71 (0.96–3.06)
						$P_{trend} = 0.21$			$P_{trend} = 0.07$
Per 5 kg			1.02 (0.95–1.09)			0.96 (0.87–1.05)			1.07 (0.98–1.17)

[a]ORs and 95% CIs, adjusted for age (years, continuous), study (SFBCS, 4-CBCS), ethnicity/English language acculturation (low, moderate, high, and NHW), and average alcohol consumption in reference year (g/d; 0, 0.1–4.9, 5–9.9, 10–19.9, ≥20).

[b]Adjusted for all variables above except English language acculturation.

[c]Based on tertiles among all premenopausal controls.

[d]Based on measured height at interview (or self-reported adult height when measured height was not available).

[e]Based on ethnicity-specific tertiles among premenopausal controls in each ethnic group. Tertile cut points by ethnicity are <154.0, 154.1–159.4, and >159.4 for Hispanics, and <161.8, 161.8–167.0, and >167.0 for NHWs.

[f]Based on self-reported averaged weight at age 15 and age 30 for 4-CBCS cases and controls, self-reported weight in the 20s for SFBCS cases and controls (between ages 25–30 for cases diagnosed from April 1995 to April 1998 and matched controls and between ages 20–29 for cases diagnosed from May 1998 to April 2002 and matched controls), and measured height at interview (or self-reported adult height when measured height was not available).

[g]Based on ethnicity-specific tertiles among premenopausal controls in each ethnic group. Tertile cut points by ethnicity are <21.5, 21.5–24.3, and >24.3 for Hispanics, and <20.0, 20.0–21.8, and >21.8 for NHWs.

[h]Based on self-reported weight in reference year (or measured weight at interview when self-reported weight in reference year was not available) and measured height at interview (or self-reported adult height when measured height was not available).

[i]Based on self-reported weight in reference year (or measured weight at interview when self-reported weight was not available) minus self-reported young-adult weight; excludes 17 premenopausal ER^-PR^- cases and 125 premenopausal controls who lost weight.

[j]Based on ethnicity-specific tertiles among premenopausal controls in each ethnic group. Tertile cut points by ethnicity are <9.1, 9.1–17.3, and >17.3 for Hispanics, and <6.8, 6.8–14.7, and >14.7 for NHWs.

evaluate associations between body size and premenopausal breast cancer risk in Hispanic women. We found inverse associations of young-adult and current BMI with risk of ER^+PR^+ breast cancer, with a nearly 50% reduced risk among those with elevated young-adult BMI and current obesity. These inverse associations were similar for Hispanics and NHWs. Genetic ancestry appeared to modify the inverse associations with current BMI and weight gain; reduced risks were limited to Hispanics with lower IA ancestry. For ER^-PR^- breast cancer, we found a positive association with height and an inverse

Table 3. Abdominal adiposity associations with breast cancer risk in premenopausal women measured <12 months after diagnosis/selection, by ethnicity

	All			Hispanics			NHWs		
	Cases ($n = 199$)	Controls ($n = 937$)		Cases ($n = 71$)	Controls ($n = 561$)		Cases ($n = 128$)	Controls ($n = 376$)	
	n	*n*	OR[a] (95% CI)	*n*	*n*	OR[a] (95% CI)	*n*	*n*	OR[b] (95% CI)
Waist (cm)[c]									
T1: <79.5	82	310	1.0	16	127	1.0	66	183	1.0
T2: 79.5–91.4	64	308	1.16 (0.81–1.66)	32	204	1.79 (0.83–3.86)	32	104	0.85 (0.47–1.53)
T3: >91.4	53	318	1.29 (0.91–1.84)	23	229	1.98 (0.74–5.27)	30	89	0.90 (0.38–2.13)
			$P_{trend} = 0.34$			$P_{trend} = 0.17$			$P_{trend} = 0.72$
Waist (cm)[d]									
Tertile 1				25	184	1.0	40	124	1.0
Tertile 2				24	186	1.51 (0.74–3.08)	47	125	1.20 (0.68–2.12)
Tertile 3				22	190	2.27 (0.92–5.61)	41	127	1.06 (0.48–2.37)
						$P_{trend} = 0.07$			$P_{trend} = 0.81$
Per 2 cm			1.03 (0.99–1.08)			1.09 (1.02–1.16)			0.99 (0.93–1.05)
Hip (cm)[c]									
T1: <101.1	72	311	1.0	27	165	1.0	45	146	1.0
T2: 101.1–111.1	69	308	1.06 (0.74–1.50)	23	191	0.94 (0.47–1.88)	46	117	1.20 (0.69–2.07)
T3: >111.1	58	318	1.27 (0.91–1.79)	21	205	0.95 (0.39–2.36)	37	113	1.13 (0.51–2.51)
			$P_{trend} = 0.27$			$P_{trend} = 0.90$			$P_{trend} = 0.68$
Hip (cm)[e]									
Tertile 1				28	185	1.0	42	125	1.0
Tertile 2				23	186	1.11 (0.55–2.21)	44	124	1.06 (0.61–1.85)
Tertile 3				20	190	1.16 (0.48–2.85)	42	127	1.06 (0.49–2.33)
						$P_{trend} = 0.73$			$P_{trend} = 0.86$
Per 2 cm			1.02 (0.98–1.07)			1.04 (0.97–1.11)			1.00 (0.94–1.07)
Waist-to-hip ratio[c]									
T1: <0.77	81	308	1.0	10	107	1.0	71	201	1.0
T2: 0.77–0.83	60	309	1.35 (0.95–1.93)	24	204	1.60 (0.66–3.86)	36	105	1.01 (0.59–1.72)
T3: >0.83	58	319	1.34 (0.92–1.95)	37	249	2.67 (1.10–6.49)	21	70	0.86 (0.44–1.68)
			$P_{trend} = 0.75$			$P_{trend} = 0.02$			$P_{trend} = 0.71$
Waist-to-hip ratio[f]									
Tertile 1				22	185	1.0	52	125	1.0
Tertile 2				21	185	1.04 (0.50–2.16)	33	123	0.63 (0.36–1.11)
Tertile 3				28	190	1.96 (0.95–4.06)	43	128	0.73 (0.41–1.33)
						$P_{trend} = 0.06$			$P_{trend} = 0.29$
Per 0.1			1.12 (0.84–1.51)			1.70 (1.03–2.81)			0.89 (0.61–1.31)
Waist-to-height ratio[c]									
T1: <0.50	88	307	1.0	13	101	1.0	75	206	1.0
T2: 0.50–0.58	56	310	1.22 (0.85–1.75)	29	216	2.13 (0.90–5.05)	27	94	0.76 (0.41–1.41)
T3: >0.58	55	319	1.40 (0.97–2.03)	29	243	3.57 (1.25–10.18)	26	76	0.73 (0.29–1.79)
			$P_{trend} = 0.48$			$P_{trend} = 0.02$			$P_{trend} = 0.42$
Waist-to-height ratio[g]									
Tertile 1				29	185	1.0	46	124	1.0
Tertile 2				22	184	1.19 (0.59–2.40)	44	124	0.83 (0.47–1.48)
Tertile 3				20	191	1.46 (0.59–3.60)	38	128	0.64 (0.28–1.48)
						$P_{trend} = 0.42$			$P_{trend} = 0.30$
Per 0.1			1.13 (0.79–1.61)			1.92 (1.12–3.28)			0.72 (0.43–1.21)

[a]ORs and 95% CIs, adjusted for age (years, continuous), study (SFBCS, 4-CBCS), ethnicity/English language acculturation (low, moderate, high, and NHW), education (less than high school, high school graduate, after high school education), family history of breast cancer in first-degree relatives (no or yes), age at menarche (<12, 12, 13, ≥14), number of full-term pregnancies (nulliparous, 1–2, 3–4, ≥5), age at first full-term pregnancy (<20, 20–24, 25–29, ≥30, nulliparous), lifetime number of months of breastfeeding (nulliparous, 0, 1–6, 7–12, 13–24, >24), hormonal contraception use (never, former, current), average alcohol consumption in reference year (g/d; 0, 0.1–4.9, 5–9.9, 10–19.9, ≥20), and current BMI (continuous).

[b]Adjusted for all variables above except English language acculturation.

[c]Based on tertiles among premenopausal controls measured <12 months after selection into the study.

[d]Based on ethnicity-specific tertiles among premenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cut points by ethnicity are <82.9, 82.9–94.0, and >94.0 for Hispanics and <74.3, 74.3–86.5, and >86.5 for NHWs.

[e]Based on ethnicity-specific tertiles among premenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cut points by ethnicity are <101.9, 101.9–111.8, and >111.8 for Hispanics and <99.7, 99.7–109.2, and >109.2 for NHWs.

[f]Based on ethnicity-specific tertiles among premenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cut points by ethnicity are <0.80, 0.80–0.85, and >0.85 for Hispanics and <0.74, 0.74–0.80, and >0.80 for NHWs.

[g]Based on ethnicity-specific tertiles among premenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cut points by ethnicity are <0.53, 0.53–0.60, and >0.60 for Hispanics and <0.45, 0.45–0.53, and >0.53 for NHWs.

association with young-adult BMI among Hispanics only. Positive associations with waist circumference, WHR, and WHtR were limited to Hispanics. These findings provide evidence that body size does play a role in breast cancer etiology among premenopausal Hispanic women, as has been reported for NHWs.

Our finding of an increased risk associated with height (statistically significant for ER^-PR^- breast cancer and borderline

significance for ER^+PR^+ breast cancer) for Hispanic women is consistent with the positive associations for all breast cancers combined reported for Mexican women (11). Unlike other studies (21, 22), we failed to find an association for NHWs.

Adult obesity has been associated with reduced risk of premenopausal breast cancer risk in meta-analyses of primarily NHW women (3, 21, 23). Similarly for Hispanic women, we found an inverse association with current obesity, but only for ER^+PR^+ breast cancer. An even greater reduction in risk was noted for women who also had an elevated young-adult BMI. No associations with BMI were seen in women with a lower young-adult BMI. An inverse association for all breast cancers combined was also reported for Mexican women (11), but not in two U.S. studies that had small samples sizes (6, 7). In analyses of current BMI, the consideration of young-adult BMI is particularly important for populations, such as Hispanics, who have a high prevalence of overweight and obesity even at young ages (13). In our pooled dataset, 34% of premenopausal Hispanic controls had a young-adult BMI in the highest quartile (>24.1 kg/m^2) compared with 14% among NHWs. The lower breast cancer risk among obese premenopausal women has been attributed to more frequent anovulatory menstrual cycles and lower estrogen concentrations (24), although there is evidence that menstrual cycle characteristics, self-reported infertility, and polycystic ovary syndrome do not explain the inverse associations with obesity (25, 26), suggesting the importance of other mechanisms yet to be identified.

Consistent with studies in NHW women (27–30), we found strong inverse associations with young-adult BMI in Hispanic women, both for ER^+PR^+ and ER^-PR^- breast cancer. Two small U.S. studies found no association with BMI (6) or weight (7) at age 18 years. We previously reported inverse associations with adolescent obesity in Hispanics (8, 10) and NHWs (8). Inverse associations with childhood or adolescent obesity have also been reported for NHW women (25, 31–34). Although the underlying mechanisms remain unclear, these findings suggest that adolescent and young-adult adiposity exert a long-lasting influence on premenopausal breast cancer risk, both in Hispanic and NHW women.

We found elevated ORs associated with waist circumference, WHR, and WHtR for Hispanic women only, independent of current BMI. In contrast, in Mexican women (11), these abdominal obesity measures were associated with reduced breast cancer risk, independent of BMI. Studies in NHW women have also produced mixed results, with reports of positive associations with WHR (3, 35, 36), associations limited to ER^+PR^+ (37) or ER^- (38) breast cancer, or no association (9, 39–42), in agreement with our finding of no association for NHW women. The reasons for the differences in abdominal obesity associations between Hispanics and NHWs in our pooled analysis are not obvious. Power in the reduced dataset was limited because we included only women with anthropometric measurements taken <12 months after diagnosis or selection into the study. Given the opposite associations with BMI (reduced risk) and abdominal obesity (increased risk), larger studies will be needed to assess the association with abdominal adiposity in obese and nonobese women. Abdominal obesity may affect premenopausal breast cancer risk through hormonal, metabolic, and inflammatory mechanisms (2, 43), and it has been suggested that abdominal adipose tissue may be metabolically more active than peripheral adipose tissue (44).

The 4-CBCS, to our knowledge, is the only study that examined possible variations in body size associations among Hispanics by genetic ancestry (8). Using a different set of AIMs in a population with a more limited range of genetic admixture than in the SFBCS, associations with BMI and WHR did not differ by genetic ancestry in the 4-CBCS. In contrast, in our pooled analyses, we found that inverse associations of ER^+PR^+ breast cancer with BMI and weight gain were limited to Hispanics with lower IA ancestry, whereas for young-adult BMI, the inverse associations were similar for the two ancestry groups. These results call for further evaluation in larger datasets.

This pooled analysis contributes to the sparse and inconsistent epidemiologic data on body size and premenopausal breast cancer risk in Hispanics (6–9, 11) and has several strengths, including the population-based design, the large sample size, measurements of body size, comprehensive assessment of other breast cancer risk factors by in-person interview, and availability of information on tumor ER and PR status for most cases. The use of measured height for BMI calculation was particularly important, because in the SFBCS, 22% of Hispanics did not know their height. Although we measured weight at interview, we used self-reported weight during the reference year to calculate BMI because of concern about treatment- and disease-related weight gain among cases. In a sensitivity analysis limited to women with both measured and self-reported weight and height, we found similar associations with BMI based on self-reported or measured height and weight. Furthermore, the correlation between self-reported and measured weight was high both in premenopausal cases ($r = 0.88$) and controls ($r = 0.91$). Some limitations also need to be considered. Participation rates differed between the two studies, but the results for Hispanic women were generally consistent across the two studies. Although the pooled analysis included a large sample of premenopausal Hispanic women and was hypothesis driven, the sample size was limited for certain subgroup analyses that considered multiple factors jointly, analyses of ER^-PR^- breast cancer, and analyses by genetic ancestry. Furthermore, the investigation of modifying factors resulted in many comparisons, possibly leading to false-positive results. We relied on self-reported young-adult weight and the two studies assessed weight at different ages. Data harmonization to estimate average weight in a woman's twenties may not have been optimal and introduced nondifferential misclassification, possibly causing the associations with weight gain to be attenuated. BMI, a widely used measure of body fat, does not distinguish between lean and fat mass (45), or account for differences in body fat between individuals with the same BMI or across different racial/ethnic groups (46–48). The analyses of abdominal obesity were based on measurements taken after diagnosis. To reduce the possibility of misclassification due to treatment-related weight gain among cases, we restricted the analyses to women with anthropometric measurements taken <12 months after diagnosis/selection. Finally, our analyses by genetic ancestry were limited by the range of admixture, as only U.S. Hispanics were included.

In conclusion, our findings highlight that body size throughout the premenopausal years has a major influence on breast cancer risk. For Hispanics, inverse associations of young-adult and current adiposity with ER^+PR^+ breast cancer are similar to those for NHWs, and consistent with previous reports for NHW women. For some body size measures, we found associations

among Hispanic women only, including height (increased risk) and young-adult BMI (reduced risk) for ER^-PR^- breast cancer, and abdominal adiposity (increased risk) for all breast cancers combined. Given that obesity and weight gain are associated with increased breast cancer risk after menopause, when breast cancer is diagnosed more frequently than at younger ages, avoiding weight gain and maintaining a healthy weight are important in both Hispanic and non-Hispanic populations, even at a young age, because of the long-term adverse effects of obesity on breast cancer and other chronic disease risk later in life.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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