Research Article

Cancer Epidemiology, Biomarkers & Prevention

Body Size Throughout Adult Life Influences Postmenopausal Breast Cancer Risk among Hispanic Women: The Breast Cancer Health Disparities Study

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Abstract

Background: Few studies have assessed the association of body size with postmenopausal breast cancer risk in Hispanic women. Findings are inconsistent and appear to contradict those reported for non-Hispanic white (NHW) women.

Methods: We pooled interview and anthropometric data for 2,023 Hispanic and 2,384 NHW women from two U.S. population-based case–control studies. Using logistic regression analysis, we examined associations of overall and abdominal adiposity with risk of postmenopausal breast cancer defined by estrogen receptor (ER) and progesterone receptor (PR) status.

Results: Weight gain was associated with increased risk of ER^+PR^+ breast cancer in Hispanics not currently using menopausal hormone therapy (HT), but only among those with a low young-adult body mass index (BMI). In the subset of Hispanics with data on genetic ancestry, the association with weight gain was limited to women with lower Indigenous American ancestry. Young-adult BMI was inversely associated with both ER^+PR^+ and ER^-PR^- breast cancers for both ethnicities combined, with similar, although nonsignificant, inverse trends in Hispanics and NHWs. Among all Hispanics, regardless of HT use, height was associated with risk of ER^-PR^- breast cancer and hip circumference with risk of breast cancer overall.

Conclusions: Body size throughout adult life is associated with breast cancer risk among postmenopausal Hispanic women, as has been reported for NHW women. Associations were specific for breast cancer subtypes defined by hormone receptor status.

Impact: Avoiding weight gain and maintaining a healthy weight are important strategies to reduce the risk of postmenopausal ER^+PR^+ breast cancer, the most common breast cancer subtype. *Cancer Epidemiol Biomarkers Prev; 24(1); 128–37. ©2014 AACR.*

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Introduction

In studies of non-Hispanic white (NHW) women, both overall and abdominal adiposity have been associated with increased risk of postmenopausal breast cancer (1, 2). Data on body size associations are sparse and inconsistent for U.S. Hispanic (3–7) and Mexican (8) women, who have a higher prevalence of obesity than NHWs (9). Most studies in Hispanics had small sample sizes, and most did not consider tumor hormone receptor status (10) or factors that modify body size associations, such as use of hormone therapy (HT; refs. 11–13) or young-adult body size (14, 15). Only three studies (4, 7, 8) have assessed associations with abdominal adiposity, and there remains uncertainty about the independent effects of abdominal versus overall adiposity.

We pooled data for U.S. Hispanic and NHW women to assess associations of body size with risk of postmenopausal breast cancer defined by hormone receptor status and evaluate the modifying effects of HT use and young-adult body mass index (BMI). We also investigated whether associations with body size varied by genetic ancestry, given the higher prevalence of obesity in women with higher Indigenous American (IA) ancestry (16).

Materials and Methods

The study population consists of U.S. Hispanic, native American (NA), and NHW women included in the Breast Cancer Health Disparities Study (17) that pooled interview and anthropometric data from two population-based case–control studies. The study was approved by the institutional review board at each institution. All study participants provided written informed consent.

San Francisco Bay Area Breast Cancer Study

Through the Greater Bay Area Cancer Registry, the San Francisco Bay Area Breast Cancer Study (SFBCS) identified 17,537 cases ages 35 to 79 years diagnosed with a first primary invasive breast cancer

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between April 1995 and April 2002 (18, 19). 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. A telephone screening interview assessing self-identified race/ethnicity and eligibility for several studies was completed by 89% of 15,573 cases contacted (alive, valid address, no physician refusal) and 92% of 3,547 controls contacted. Hispanic cases diagnosed from 1995 to 2002, African American cases diagnosed from 1995 to 1999, and a 10% random sample of NHW cases diagnosed from 1995 to 1999 were eligible for an in-person interview. NHW cases were sampled, given the large number of incident cases during the ascertainment period. This analysis is based on interview data 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 14.2 months (range, 5.0–46.5) for Hispanic cases, and 16.4 months (range, 6.5–45.8) for NHW cases. Findings on body size associations for African Americans are reported elsewhere (7).

4-Corners Breast Cancer Study

The 4-Corners Breast Cancer Study (4-CBCS) was conducted in Hispanic, NA, and NHW women living in nonreservation areas in Arizona, Colorado, New Mexico, and Utah (4). A total of 5,256 cases ages 25 to 79 years and diagnosed with *in situ* or invasive breast cancer between October 1999 and May 2004 were identified through the state-wide cancer registries. 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. Of 3,761 cases contacted, 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. We combined the small number of NAs (55 cases, 73 controls) with Hispanics, and restricted cases to those with a first primary invasive breast cancer (662 Hispanics/NAs, 1,246 NHWs). Median time between diagnosis and interview was 19.7 months (range, 3.4–58.3) for Hispanic cases and 16.7 months (range, 2.5–59.0) for NHW cases.

Data collection and harmonization

In-person interviews were conducted in English or Spanish by trained bilingual interviewers using similar structured questionnaires translated into Spanish. Information on risk factors was collected up to the referent year, defined as the calendar year before diagnosis for cases or selection into the study for controls. Standing height (with shoes removed) and weight (with light clothing) were measured 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 was measured to the nearest 0.2 kilogram (kg). Three measurements of height and two of weight were taken and averaged (20). In 4-CBCS, height was measured to the nearest 0.25 inches (in), weight was measured to the nearest 0.5 pound (lb), and waist and hip circumferences were measured to the nearest 0.5 in. Two measurements of height and weight were taken (if they differed by >0.5 in or >1.0 lb, respectively, a third measurement was taken) and averaged (4). Data on estrogen receptor (ER) and progesterone receptor (PR) status were obtained from the respective cancer registries for most postmenopausal cases (85% in SFBCS, 76% in 4-CBCS).

The data from the two studies were harmonized and pooled, and common analytic variables were generated (17). Postmenopausal status was defined according to study-specific definitions. Women who were taking menopausal HT and were still having periods were classified as postmenopausal if they were at or above the 95th percentile of age for race/ethnicity of those who reported having a natural menopause (i.e., $\geq$12 months since their last period) within their study. This age (in years) was 55 for NHWs and 56 for Hispanics in SFBCS, and 58 for NHWs and 56 for Hispanics in 4-CBCS. For Hispanics, an acculturation index based on language spoken was created (low: Spanish only; moderate: more Spanish than English or Spanish and English equally; high: more English than Spanish or English only).

Body size variables

Current BMI was calculated as weight (kg) divided by height (m) squared, based on height measured at interview and self-reported weight in the reference year. Because cases may have experienced disease- or treatment-related weight gain or loss, we used self-reported weight before diagnosis for the BMI calculation. For individuals without self-reported weight, measured weight was used (1% of cases, 2% of controls) and for those who declined the height measurement, self-reported height was used (3% of cases, 2% of controls). In SFBCS, young-adult BMI was based on self-reported weight at age of 25 to 30 years for cases diagnosed before May 1998 and their matched controls, or on self-reported weight at age of 20 to 29 years for cases diagnosed in May 1998 or later and their matched controls. In 4-CBCS, young-adult BMI was calculated as the average of weights reported at ages 15 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 waist-to-hip ratio (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 (21). Current BMI was classified as underweight to normal weight (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese ($\geq$30.0 kg/m^2). All other body size variables were categorized according to the tertile or quartile distribution among postmenopausal controls. To facilitate the comparison of OR estimates between Hispanics and NHWs, we used the same cut-points for the two groups. Given the different distributions of body size characteristics, we also used ethnicity-specific quantiles.

Genetic ancestry

We estimated genetic ancestry for a subset of study participants with available DNA. In SFBCS, biospecimens were collected only for cases diagnosed in April 1997 or later and their matched controls. Genetic admixture of European and IA ancestry was estimated based on 104 ancestry informative markers (AIM; ref. 17).

Statistical analyses

ORs and 95% confidence intervals (CI) were calculated using unconditional logistic regression. Given prior findings of effect modification by HT use (12, 22, 23), we stratified the analyses by

HT use (current vs. former or never use). Polytomous logistic regression was used to compare the major subtypes, ER^+PR^+ and ER^-PR^- breast cancer, to a common control group. Hispanic women were also stratified by median IA ancestry (44%) among Hispanic postmenopausal controls.

Multivariate analyses were adjusted for age (continuous) and study, and factors significantly associated with breast cancer risk in our dataset. For overall and ER^+PR^+ breast cancer, analyses were adjusted for education, breast cancer family history in first-degree relatives, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, lifetime duration of breast feeding, and alcohol consumption. Variables were categorized as noted in the footnotes of the tables. For ER^-PR^- breast cancer, analyses were adjusted for breast cancer family history and age at menarche. Analyses that were not stratified by HT use were also adjusted for HT use. Analyses in Hispanics were additionally adjusted for language acculturation. Additional adjustment for genetic ancestry did not alter the results. 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 postmenopausal women were based on 2,023 Hispanics (759 cases, 1,264 controls) and 2,384 NHWs (937 cases, 1,447 controls), after excluding subjects with missing data on covariates (91 cases, 231 controls) or ER/PR status (448 cases). Analyses by genetic ancestry were based on 1,338 Hispanics (493 cases, 845 controls). Because of concern about treatment- or disease-related weight gain among cases, we restricted the analysis of abdominal adiposity to cases and controls with anthropometric measurements taken <12 months after diagnosis or selection into the study (400 cases, 1,740 controls), hereafter referred to as the reduced dataset. Statistical analyses were conducted using SAS version 9.3 software (SAS Institute, Inc., Cary, NC).

Results

Compared with controls, higher proportions of cases had a higher education, breast cancer family history in first-degree relatives, young age at menarche, no or few full-term pregnancies, late age at first full-term pregnancy, no or short duration of breast feeding, a history of current HT use, and higher English language acculturation (among Hispanics; Supplementary Table S1). Hispanic controls were shorter and had higher overall and abdominal body size measures than NHW controls (Supplementary Table S2). Hispanic controls with higher IA ancestry (>44%) had shorter height, higher current BMI, higher WHR, and lower WHtR.

Height, overall adiposity, and breast cancer risk by ER/PR status

Among women currently using HT (554 cases, 920 controls), height, and overall adiposity measures were not associated with ER^+PR^+ breast cancer risk (data not shown). In women not currently using HT (Table 1), height was not related to risk of ER^+PR^+ breast cancer and young-adult BMI, independent of current BMI, was associated with reduced risk among the two ethnicities combined ($P_{trend} = 0.04$), with similar inverse trends among Hispanics and NHWs, although of borderline significance among Hispanics only (high vs. low quartile: OR = 0.61, $P_{trend} = 0.07$). There was no association with current BMI in either ethnic group. Weight gain, adjusted for current BMI, was associated with increased risk of ER^+PR^+ breast cancer among Hispanics only (high vs. low quartile: OR = 1.68, $P_{trend} = 0.04$), but the association was limited to those with a low (below the median) young-adult BMI (per 5 kg: OR, 1.42; 95% CI, 1.09–1.86). Women with both elevated young-adult BMI and current obesity were not at increased risk of ER^+PR^+ breast cancer in either ethnic group. In the reduced dataset, OR estimates for overall adiposity were not altered after additional adjustment for hip circumference (among Hispanics) or WHR (among NHWs), two measures associated with breast cancer risk (Supplementary Tables S3 and S4).

Height and overall adiposity associations with ER^-PR^- breast cancer did not significantly vary by HT use; therefore, results shown in Table 2 are not stratified by HT use. Height was marginally associated with increased risk among Hispanics (per 5 cm: OR, 1.16; 95% CI, 1.00–1.34). Young-adult BMI was inversely associated with risk among both ethnicities combined (high vs. low tertile: OR = 0.67, $P_{trend} = 0.03$), with similar inverse trends for Hispanics and NHWs, but of borderline significance among NHWs only ($P_{trend} = 0.05$). A suggestive inverse trend was also seen for current BMI, with similar findings for Hispanics (per 5 kg/m^2: OR, 0.76; 95% CI, 0.57–1.01) and NHWs (per 5 kg/m^2: OR, 0.63; 95% CI, 0.43–0.92). Weight gain was associated with increased risk in NHWs only (per 5 kg: OR, 1.18; 95% CI, 1.02–1.37).

Abdominal adiposity and breast cancer risk

In the reduced dataset, associations with abdominal adiposity did not significantly differ by ER/PR status. For all breast cancers combined (Table 3), there were no associations with waist circumference, WHR, and WHtR in either population. Among Hispanics, hip circumference was associated with a 2-fold increased risk (high vs. low tertile: OR = 2.03, $P_{trend} = 0.04$; Table 3). This association was limited to women not currently using HT (Supplementary Table S3), although the interaction by HT was not statistically significant. Among NHWs, there was evidence of significant interaction by HT use for WHR ($P_{interaction}$ <0.01), with an increased risk limited to those not currently using HT (Supplementary Table S4).

Overall adiposity, genetic ancestry, and breast cancer among Hispanics

In the subset of cases and controls with information on genetic ancestry, we found that the overall adiposity associations in Hispanic women were limited to those with lower IA ancestry (Supplementary Table S5). Among noncurrent HT users, weight gain was associated with a 3-fold increased risk of ER^+PR^+ breast cancer (high vs. low tertile: OR = 3.46, $P_{trend} = 0.01$), whereas current obesity was associated with a significantly reduced risk (≥30 vs. <25 kg/m^2: OR = 0.31, $P_{trend} = 0.02$). Similarly, for young-adult BMI, an inverse association with breast cancer risk (all subtypes combined) was found only among Hispanics with lower IA ancestry (high vs. low tertile: OR, 0.42; 95% CI, 0.23–0.77, P_{trend}<0.01; data not shown). None of the interactions by genetic ancestry, however, reached statistical significance. For abdominal adiposity, the reduced dataset was too small to assess interactions by genetic ancestry.

Table 1. Height and overall adiposity associations with ER^+PR^+ breast cancer in postmenopausal women not currently using hormone therapy, by ethnicity

	All			Hispanics			NHWs		
	ER^+PR^+ cases ($n = 586$)	Controls ($n = 1,775$)		ER^+PR^+ cases ($n = 294$)	Controls ($n = 961$)		ER^+PR^+ cases ($n = 292$)	Controls ($n = 814$)	
	n	*n*	OR (95% CI)[a]	*n*	*n*	OR (95% CI)[a]	*n*	*n*	OR (95% CI)[b]
Current height (m)[c,d]									
Q1: <153.2	139	442	1.0	111	354	1.0	28	88	1.0
Q2: 153.2–157.7	138	443	0.95 (0.72–1.26)	77	283	0.85 (0.61–1.20)	61	160	1.22 (0.72–2.09)
Q3: 157.8–162.9	147	443	0.97 (0.73–1.30)	72	213	1.01 (0.71–1.44)	75	230	1.05 (0.63–1.76)
Q4: >162.9	161	440	1.06 (0.78–1.45)	33	108	0.92 (0.57–1.48)	128	332	1.26 (0.76–2.09)
			$P_{trend} = 0.65$			$P_{trend} = 0.88$			$P_{trend} = 0.47$
Current height (m)[d,e]									
Quartile 1				65	240	1.0	69	213	1.0
Quartile 2				81	251	1.16 (0.79–1.71)	78	192	1.24 (0.84–1.83)
Quartile 3				62	228	0.97 (0.65–1.46)	66	203	1.01 (0.68–1.51)
Quartile 4				85	239	1.26 (0.85–1.88)	79	202	1.23 (0.82–1.85)
						$P_{trend} = 0.42$			$P_{trend} = 0.52$
Per 5 cm			1.07 (0.98–1.16)			1.09 (0.97–1.22)			1.04 (0.93–1.17)
Young-adult BMI (kg/m^2)[c,f,g]									
Q1: <20.4	159	426	1.0	67	161	1.0	92	265	1.0
Q2: 20.4–22.1	133	424	0.84 (0.64–1.11)	55	208	0.61 (0.40–0.94)	78	216	1.03 (0.71–1.49)
Q3: 22.2–24.4	145	427	0.87 (0.66–1.16)	74	256	0.69 (0.46–1.05)	71	171	1.07 (0.72–1.59)
Q4: >24.4	121	426	0.69 (0.50–0.95)	74	281	0.61 (0.40–0.95)	47	145	0.68 (0.42–1.11)
			$P_{trend} = 0.04$			$P_{trend} = 0.07$			$P_{trend} = 0.27$
Young-adult BMI (kg/m^2)[f,g,h]									
Quartile 1				85	227	1.0	71	201	1.0
Quartile 2				59	226	0.69 (0.47–1.02)	70	197	0.99 (0.66–1.47)
Quartile 3				65	226	0.79 (0.53–1.17)	79	199	1.01 (0.67–1.52)
Quartile 4				61	227	0.71 (0.46–1.09)	68	200	0.73 (0.46–1.14)
						$P_{trend} = 0.18$			$P_{trend} = 0.23$
Per 5 kg/m^2			0.81 (0.68–0.96)			0.83 (0.66–1.04)			0.77 (0.59–1.00)
Current BMI (kg/m^2)[i,j]									
<25.0	158	517	1.0	57	180	1.0	101	337	1.0
25.0–29.9	202	615	1.02 (0.77–1.35)	99	364	0.81 (0.52–1.25)	103	251	1.16 (0.79–1.70)
≥30.0	225	635	0.96 (0.67–1.37)	137	413	0.91 (0.55–1.51)	88	222	0.89 (0.52–1.52)
			$P_{trend} = 0.80$			$P_{trend} = 0.84$			$P_{trend} = 0.77$
Per 5 kg/m^2			0.87 (0.74–1.02)			0.81 (0.65–1.01)			0.94 (0.74–1.19)
Weight gain (kg)[c,g,k]									
Q1: <8.6	128	388	1.0	52	188	1.0	76	200	1.0
Q2: 8.6–14.5	100	396	0.83 (0.61–1.13)	53	218	0.96 (0.62–1.50)	47	178	0.71 (0.46–1.10)
Q3: 14.6–22.7	124	348	1.17 (0.86–1.61)	64	202	1.32 (0.84–2.09)	60	146	1.05 (0.67–1.65)
Q4: >22.7	165	418	1.40 (0.96–2.06)	82	234	1.68 (0.98–2.89)	83	184	1.15 (0.66–2.00)
			$P_{trend} = 0.04$			$P_{trend} = 0.04$			$P_{trend} = 0.49$
Weight gain (kg)[g,k,l]									
Quartile 1				62	232	1.0	62	177	1.0
Quartile 2				51	192	1.06 (0.69–1.63)	49	162	0.91 (0.58–1.43)
Quartile 3				65	212	1.31 (0.85–2.02)	72	185	1.10 (0.70–1.72)
Quartile 4				73	206	1.75 (1.02–3.02)	83	184	1.29 (0.73–2.29)
						$P_{trend} = 0.04$			$P_{trend} = 0.36$
Per 5 kg			1.09 (1.01–1.18)			1.11 (1.00–1.22)			1.08 (0.96–1.21)
Young-adult BMI (kg/m^2)[f,m] and weight gain (kg)[g,k]									
<22.2/ 5 kg	292	850	1.26 (1.05–1.50)	122	369	1.42 (1.09–1.86)	170	481	1.15 (0.90–1.47)
≥22.2/5 kg	266	853	1.05 (0.93–1.19)	148	537	1.03 (0.87–1.21)	118	316	1.09 (0.89–1.33)

[a]ORs and 95% CIs, adjusted for age (years, continuous), study (SFBCS, 4-CBCS), ethnicity/English language acculturation (low, moderate, high, NHW), education (less than high school, high school graduate, post high school education), family history of breast cancer in first-degree relatives (no, 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 breast feeding (nulliparous, 0, 1–6, 7–12, 13–24, >24), and average alcohol consumption in reference year (g/day; 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 postmenopausal controls not currently using hormone therapy.

[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 postmenopausal controls not currently using hormone therapy in each ethnic group. Quartile cutpoints by ethnicity are <151.2, 151.2–154.9, 155.0–159.4, and >159.4 for Hispanics, and <156.9, 156.9–161.5, 161.6–165.5, and >165.5 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]Adjusted additionally for current BMI (continuous).

[h]Based on ethnicity-specific quartiles among postmenopausal controls not currently using hormone therapy in each ethnic group. Quartile cutpoints by ethnicity are <21.0, 21.0–22.7, 22.8–25.1, and >25.1 for Hispanics, and <19.9, 19.9–21.5, 21.6–23.3, and >23.3 for NHWs.

[i]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).

[j]Adjusted additionally for weight gain (continuous).

[k]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.

[l]Based on ethnicity-specific quartiles among postmenopausal controls not currently using hormone therapy in each ethnic group. Quartile cutpoints by ethnicity are <9.1, 9.1–15.4, 15.5–23.6, and >23.6 for Hispanics, and <7.1, 7.1–13.6, 13.7–22.7, and >22.7 for NHWs.

[m]Based on median among postmenopausal controls not currently using hormone therapy.

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

	All			Hispanics			NHWs		
	ER$^-$PR$^-$ cases (n = 286)	Controls (n = 2,711)		ER$^-$PR$^-$ cases (n = 153)	Controls (n = 1,264)		ER$^-$PR$^-$ cases (n = 133)	Controls (n = 1,447)	
	n	*n*	OR (95% CI)[a]	*n*	*n*	OR (95% CI)[a]	*n*	*n*	OR (95% CI)[b]
Current height (m)[c,d]									
T1: <155.3	79	890	1.0	70	654	1.0	9	236	1.0
T2: 155.3–161.8	106	895	1.41 (1.02–1.95)	57	417	1.24 (0.84–1.82)	49	478	2.44 (1.17–5.09)
T3: >161.8	100	917	1.40 (0.98–2.00)	25	190	1.25 (0.76–2.07)	75	726	2.32 (1.13–4.78)
			P_{trend} = 0.07			P_{trend} = 0.28			P_{trend} = 0.08
Current height (m)[d,e]									
Tertile 1				57	504	1.0	28	429	1.0
Tertile 2				47	404	1.25 (0.80–1.95)	51	489	1.27 (0.80–2.02)
Tertile 3				48	353	1.47 (0.94–2.30)	54	522	1.27 (0.80–2.02)
						P_{trend} = 0.10			P_{trend} = 0.34
Per 5 cm			1.12 (1.01–1.25)			1.16 (1.00–1.34)			1.11 (0.96–1.29
Young-adult BMI (kg/m^2)[c,f,g]									
T1: <20.6	103	865	1.0	42	287	1.0	61	578	1.0
T2: 20.6–23.0	89	866	0.81 (0.59–1.10)	51	391	0.90 (0.57–1.42)	38	475	0.69 (0.44–1.07)
T3: >23.0	86	893	0.67 (0.47–0.96)	53	520	0.69 (0.42–1.12)	33	373	0.60 (0.35–1.03)
			P_{trend} = 0.03			P_{trend} = 0.13			P_{trend} = 0.05
Young-adult BMI (kg/m^2)[f,g,h]									
Tertile 1				47	348	1.0	49	464	1.0
Tertile 2				48	389	0.92 (0.59–1.44)	43	481	0.79 (0.51–1.23)
Tertile 3				51	461	0.79 (0.49–1.28)	40	480	0.58 (0.35–0.97)
						P_{trend} = 0.34			P_{trend} = 0.04
Per 5 kg/m^2			0.87 (0.70–1.09)			0.86 (0.64–1.17)			0.85 (0.61–1.19)
Current BMI (kg/m^2)[i,j]									
<25.0	92	885	1.0	45	267	1.0	47	618	1.0
25.0–29.9	98	900	0.91 (0.64–1.29)	53	478	0.71 (0.43–1.16)	45	422	1.00 (0.61–1.66)
≥30.0	95	915	0.66 (0.41–1.05)	54	515	0.60 (0.32–1.11)	41	400	0.57 (0.28–1.17)
			P_{trend} = 0.09			P_{trend} = 0.11			P_{trend} = 0.16
Per 5 kg/m^2			0.82 (0.66–1.00)			0.76 (0.57–1.01)			0.63 (0.43–0.92)
Weight gain (kg)[c,g,k]									
T1: <10.2	68	771	1.0	44	340	1.0	24	431	1.0
T2: 10.2–20.4	95	798	1.49 (1.06–2.11)	55	380	1.37 (0.87–2.17)	40	418	1.80 (1.04–3.11)
T3: >20.4	91	810	1.61 (1.02–2.53)	36	390	1.08 (0.57–2.04)	55	420	2.74 (1.39–5.41)
			P_{trend} = 0.03			P_{trend} = 0.66			P_{trend} < 0.01
Weight gain (kg)[g,k,l]									
Tertile 1				47	363	1.0	24	430	1.0
Tertile 2				52	357	1.37 (0.87–2.17)	38	403	1.77 (1.02–3.08)
Tertile 3				36	390	1.08 (0.57–2.02)	57	435	2.76 (1.41–5.40)
						P_{trend} = 0.67			P_{trend} < 0.01
Per 5 kg			1.10 (1.00–1.22)			1.04 (0.91–1.20)			1.18 (1.02–1.37)
Young-adult BMI (kg/m^2)[f,m] and weight gain (kg)[g,k]									
<21.8/5 kg	143	1,312	1.11 (0.88–1.40)	62	480	0.86 (0.57–1.29)	81	832	1.23 (0.92–1.64)
≥21.8/5 kg	135	1,311	1.13 (0.97–1.32)	84	718	1.20 (0.97–1.50)	51	593	1.09 (0.85–1.40)

[a]ORs and 95% CIs, adjusted for age (years, continuous), study (SFBCS, 4-CBCS), ethnicity/English language acculturation (low, moderate, high, NHW), family history of breast cancer in first-degree relatives (no, yes), age at menarche (<12, 12, 13, ≥14), and use of menopausal hormone therapy (never, past, current, unknown).
[b]Adjusted for all variables above except English language acculturation.
[c]Based on tertiles among all postmenopausal 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 all postmenopausal controls in each ethnic group. Tertile cutpoints by ethnicity are <152.8, 152.8–157.8, and >157.8 for Hispanics, and <158.8, 158.8–164.5, and >164.5 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]Adjusted additionally for current BMI (continuous).
[h]Based on ethnicity-specific tertiles among all postmenopausal controls in each ethnic group. Tertile cutpoints by ethnicity are <21.2, 21.2–23.8, and >23.8 for Hispanics, and <20.2, 20.2–22.2, and >22.2 for NHWs.
[i]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).
[j]Adjusted additionally for weight gain (continuous).
[k]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.
[l]Based on ethnicity-specific tertiles among all postmenopausal controls in each ethnic group. Tertile cutpoints by ethnicity are <10.7, 10.7–20.4, and >20.4 for Hispanics, and <10.0, 10.0–19.3, and >19.3 for NHWs.
[m]Based on median among all postmenopausal controls.

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

	All			Hispanics			NHWs		
	Cases ($n = 400$)	Controls ($n = 1{,}740$)		Cases ($n = 127$)	Controls ($n = 913$)		Cases ($n = 273$)	Controls ($n = 827$)	
	n	*n*	OR (95% CI)[a]	*n*	*n*	OR (95% CI)[a]	*n*	*n*	OR (95% CI)[b]
Waist (cm)[c]									
T1: <83.2	126	544	1.0	33	214	1.0	93	330	1.0
T2: 83.2–94.6	120	551	1.19 (0.86–1.63)	43	317	1.03 (0.59–1.79)	77	234	1.20 (0.81–1.77)
T3: >94.6	136	559	1.40 (0.93–2.10)	46	352	1.23 (0.62–2.43)	90	207	1.44 (0.86–2.43)
			$P_{trend} = 0.11$			$P_{trend} = 0.54$			$P_{trend} = 0.16$
Waist (cm)[d]									
Tertile 1				45	292	1.0	77	253	1.0
Tertile 2				37	291	0.97 (0.57–1.64)	71	256	0.85 (0.57–1.28)
Tertile 3				40	300	1.23 (0.63–2.41)	112	262	1.24 (0.75–2.06)
						$P_{trend} = 0.58$			$P_{trend} = 0.47$
Per 2 cm			1.02 (0.99–1.05)			1.02 (0.97–1.07)			1.01 (0.98–1.05)
Hip (cm)[c]									
T1: <102.3	123	546	1.0	37	276	1.0	86	270	1.0
T2: 102.3–111.8	115	549	0.98 (0.72–1.34)	38	272	1.43 (0.84–2.43)	77	277	0.80 (0.54–1.19)
T3: >111.8	144	558	1.31 (0.87–1.96)	47	334	2.03 (1.05–3.94)	97	224	1.02 (0.60–1.73)
			$P_{trend} = 0.23$			$P_{trend} = 0.04$			$P_{trend} = 0.92$
Hip (cm)[e]									
Tertile 1				39	295	1.0	82	257	1.0
Tertile 2				39	287	1.53 (0.90–2.60)	68	254	0.77 (0.51–1.15)
Tertile 3				44	300	2.31 (1.17–4.56)	110	260	1.04 (0.63–1.70)
						$P_{trend} = 0.02$			$P_{trend} = 0.98$
Per 2 cm			1.01 (0.98–1.04)			1.02 (0.97–1.08)			1.00 (0.96–1.05)
Waist-to-hip ratio[c]									
T1: <0.80	147	546	1.0	33	200	1.0	114	346	
T2: 0.80–0.86	106	544	0.88 (0.65–1.19)	39	302	0.88 (0.52–1.50)	67	242	0.84 (0.58–1.22)
T3: >0.86	129	563	1.10 (0.81–1.50)	50	380	0.87 (0.52–1.47)	79	183	1.22 (0.83–1.81)
			$P_{trend} = 0.55$			$P_{trend} = 0.62$			$P_{trend} = 0.39$
Waist-to-hip ratio[f]									
Tertile 1				47	292	1.0	76	252	
Tertile 2				32	290	0.78 (0.47–1.31)	79	257	1.00 (0.68–1.47)
Tertile 3				43	300	0.93 (0.57–1.53)	105	262	1.32 (0.89–1.96)
						$P_{trend} = 0.79$			$P_{trend} = 0.16$
Per 0.1			1.09 (0.91–1.31)			0.99 (0.72–1.37)			1.10 (0.87–1.38)
Waist-to-height ratio[c]									
T1: <0.53	150	545	1.0	34	180	1.0	116	365	1.0
T2: 0.53–0.60	108	547	0.91 (0.66–1.25)	39	316	0.77 (0.44–1.36)	69	231	0.88 (0.60–1.31)
T3: >0.60	124	562	0.98 (0.65–1.49)	49	387	0.87 (0.44–1.75)	75	175	0.99 (0.58–1.70)
			$P_{trend} = 0.89$			$P_{trend} = 0.74$			$P_{trend} = 0.87$
Waist-to-height ratio[g]									
Tertile 1				49	290	1.0	82	254	1.0
Tertile 2				37	290	0.86 (0.51–1.46)	74	254	0.80 (0.53–1.20)
Tertile 3				36	301	0.86 (0.43–1.71)	104	263	0.91 (0.54–1.54)
						$P_{trend} = 0.64$			$P_{trend} = 0.69$
Per 0.1			1.07 (0.85–1.35)			1.03 (0.70–1.52)			1.07 (0.80–1.43)

[a]ORs and 95% CIs, adjusted for age (years, continuous), study (SFBCS, 4-CBCS), ethnicity/English language acculturation (low, moderate, high, NHW), education (less than high school, high school graduate, post high school education), family history of breast cancer in first-degree relatives (no, 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 breast feeding (nulliparous, 0, 1–6, 7–12, 13–24, >24), use of menopausal hormone therapy (never, past, current, unknown), average alcohol consumption in reference year (g/day; 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 postmenopausal controls measured <12 months after selection into the study.

[d]Based on ethnicity-specific tertiles among postmenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cutpoints by ethnicity are <86.4, 86.4–96.6, and >96.6 for Hispanics, and <80.1, 80.1–91.8, and >91.8 for NHWs.

[e]Based on ethnicity-specific tertiles among postmenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cutpoints by ethnicity are <102.9, 102.9–112.7, and >112.7 for Hispanics, and <101.6, 101.6–110.5, and >110.5 for NHWs.

[f]Based on ethnicity-specific tertiles among postmenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cutpoints by ethnicity are <0.82, 0.82–0.87, and >0.87 for Hispanics, and <0.77, 0.77–0.84, and >0.84 for NHWs.

[g]Based on ethnicity-specific tertiles among postmenopausal controls measured <12 months after selection into the study in each ethnic group. Tertile cutpoints by ethnicity are <0.56, 0.56–0.63, and >0.63 for Hispanics, and <0.50, 0.50–0.57, and >0.57 for NHWs.

Discussion

In this pooled analysis of over 2,000 postmenopausal Hispanic women, breast cancer risk was associated with several body size measures and associations were specific for breast cancer subtypes defined by hormone receptor status. Among Hispanics not currently using HT, weight gain was associated with an increased risk

of ER^+PR^+ breast cancer among those with a low young-adult BMI. Suggestive inverse trends for young-adult BMI were found for both ER^+PR^+ and ER^-PR^- breast cancers. Among all Hispanics, regardless of HT use, height was associated with ER^-PR^- breast cancer risk and hip circumference with breast cancer risk overall.

Data on the association of height and overall adiposity with postmenopausal breast cancer risk in Hispanic women are sparse, with reports from one cohort study (6) and four case–control studies (3, 4, 7, 8), two of which were included in this pooled analysis (4, 7). For height, we found no association with ER^+PR^+ breast cancer and a suggestive positive association with ER^-PR^- breast cancer among Hispanic women. The Mexico study reported a positive association (8), whereas the multiethnic cohort found no association (6). Neither study considered ER/PR status. For all breast cancers combined, regardless of HT use, we found a positive association with height in Hispanics only (high vs. low quartile: OR, 1.51; 95% CI, 1.12–2.03, P_{trend} <0.01). Studies in NHW women reported positive associations with overall breast cancer (24, 25) or ER^+PR^+ breast cancer (15, 26, 27).

As reported for NHW women (6, 13, 15, 22, 28), we found that weight gain was a better predictor of risk in Hispanics than current BMI and that the association was limited to ER^+PR^+ breast cancer and women not currently using HT, consistent with recent meta-analyses of weight gain and BMI by hormone receptor status (10, 29, 30) or HT use (29, 30). However, the association with weight gain was seen only in Hispanics with a low young-adult BMI. In women with both elevated young-adult BMI and current obesity, there was no evidence of association, consistent with reports for NHW women (15, 28, 31), and likely explained by the residual protective effect associated with obesity before menopause. Other studies in Hispanics reported nonsignificant elevations in risk of ER^+PR^+ breast cancer (3), or no associations for breast cancer overall (6). In the Mexico study, increasing body shape silhouette size since childhood was strongly associated with increased risk of postmenopausal breast cancer (8). In NHW women, we failed to find associations with current BMI or weight gain, contrary to other studies in NHWs (1, 2).

Our findings for Hispanics emphasize the importance of considering young-adult BMI when evaluating associations with weight gain in populations with a high prevalence of young-adult overweight and obesity. Positive associations between postmenopausal breast cancer and overall adiposity may be masked in contemporary studies where the prevalence of young-adult obesity is higher than in past studies. Adult weight gain is a marker of body fat deposition (32), which serves as a source of estrogen production in postmenopausal women through the conversion of androgen to estrogen in adipose tissue (33), resulting in higher circulating concentrations of estrogens (34). Obesity may also affect breast cancer risk through other pathways, including effects on hyperinsulinemia and glucose levels, insulin and insulin-like growth factors, cytokines, and adipokines (2, 35).

We found inverse associations with young-adult BMI for both ER^+PR^+ breast cancer (among non-HT users) and ER^-PR^- breast cancer, with similar inverse trends in Hispanics and NHWs. For all breast cancers combined, results were similar for Hispanics (high vs. low quartile: OR, 0.66; 95% CI, 0.46–0.95, P_{trend} = 0.07) and NHWs (OR, 0.52; 95% CI, 0.34–0.81, P_{trend}<0.01) not currently using HT, and in agreement with reports for NHWs (12, 14, 22, 28, 36–39). Inverse associations have also been reported for childhood and adolescent obesity (38–41), including Hispanics in our studies (4, 5). Together, these findings suggest that early-life and young-adult adiposity exerts a strong and long-lasting influence on breast cancer risk that extends into the postmenopausal years. Underlying mechanisms, however, remain uncertain.

The role of overall adiposity in relation to ER^-PR^- breast cancer is not well understood; data on the association with current BMI and weight gain are not consistent. Our finding of suggestive inverse associations with current BMI both in Hispanics and NHWs agrees with some studies (28, 42), but not others (10, 15, 31). For weight gain, we found a positive association among NHWs only, consistent with some (15, 43) but not other (29) reports. Compared with ER^+PR^+ breast cancer, few risk factors have been identified for ER^-PR^- breast cancer, a subtype that is more common in Hispanics than NHWs (44). Thus, further investigation of the role of overall adiposity in studies with larger numbers of ER^-PR^- breast cancer cases is warranted.

We found no associations of waist circumference, WHR, and WHtR with breast cancer risk among Hispanics. The Mexico study reported inverse associations with waist circumference and WHR (8), but limited to women with <10 years since menopause; among those with ≥10 years since menopause, there was no association with abdominal obesity. The sample size for our analysis was limited because we included only women with anthropometric measurements taken <12 months after diagnosis/selection because of concern about treatment- or disease-related weight gain among cases (45), especially in the abdominal area (46). The Mexico study took anthropometric measurements shortly after diagnosis (8). Unlike the Mexico study (8), we found a positive association between hip circumference and breast cancer risk overall among Hispanic women, but no association among NHWs. Some studies in NHWs reported positive associations with hip circumference (12, 47), although the evidence is not consistent (48, 49).

For NHW women, we found that WHR was the only abdominal obesity measure significantly associated with breast cancer risk, but only among those not currently using HT. This finding is in agreement with both case–control (23, 50, 51) and prospective (28, 52–54) studies, including a meta-analysis (55). In contrast, some case–control (56) and prospective (12, 47, 49, 57–59) studies found no association with WHR in NHW women. In some studies, associations with abdominal obesity were limited to (12, 23, 28, 54) or stronger in (47) noncurrent HT users, but not all studies evaluated the potential modifying effects of HT use. The data are also mixed for the association with specific breast cancer subtypes, with reports of positive associations with waist (15, 47, 60), WHR (61), or WHtR (15) limited to ER^+PR^+ or ER^+ breast cancer; association with WHR independent of hormone receptor status (50); or no associations with WHR (49, 60, 62) and waist circumference (48, 49, 62), regardless of hormone receptor status. Thus, the data on the relation between abdominal adiposity and breast cancer risk in NHW women are inconclusive.

In postmenopausal women, waist circumference has been associated with sex hormone-binding globulin (SHBG) and free estradiol and testosterone levels, independently of BMI (63), and low SHBG levels have been more strongly associated with abdominal adiposity than overall adiposity (64). In a prospective study, adjustment for serum estrogen attenuated the association between waist circumference and breast cancer

risk somewhat, although an increased risk remained (65), suggesting that other metabolic or hormonal factors, such as insulin resistance or other growth-related factors may play a role (66, 67).

Our findings suggest that genetic ancestry may modify the body size associations in Hispanic women. The inverse associations with young-adult BMI and current BMI and the positive association with weight gain were limited to Hispanics with lower IA ancestry. Our sample size, however, was too small to consider weight gain in relation to young-adult BMI. The 4-CBCS is the only other study that examined variations in body size associations by genetic ancestry, but used different AIMs (4). Larger studies will be needed to determine whether body size associations vary by genetic ancestry among Hispanic women.

Our study has some limitations and several strengths. Participation was less than optimal and differed between the SFBCS and 4-CBCS, although the results for Hispanics were generally consistent. The evaluation of several modifying factors jointly resulted in limited sample sizes, and the many comparisons may have led to potentially false-positive results. Nevertheless, the analyses were hypothesis-driven, building upon prior findings. Past weight was based on self-report, and exposure misclassification may have attenuated the associations due to inaccurate recall. However, the correlation between self-reported and measured weight was high both in postmenopausal cases ($r = 0.87$) and controls ($r = 0.91$) and similar in Hispanic and NHW cases ($r = 0.84$ and $r = 0.90$, respectively) and controls ($r = 0.91$ and $r = 0.91$, respectively). Furthermore, a sensitivity analysis in women with both measured and self-reported weight and height found similar associations with BMI based on self-reported or measured weight and height. The use of BMI as a measure of body fat does not distinguish between lean and fat mass (68) or between individuals with the same BMI but differing percent fat mass (69). The relation between body fat and BMI has been shown to vary by race/ethnicity (70–72). Nevertheless, an analysis of the Women's Health Initiative reported similar associations for measurement-based BMI and dual-energy X-ray absorptiometry–based body fat measures (73). We had to rely on waist and hip circumferences measured after diagnosis and had no data available on prediagnostic measures. To minimize exposure misclassification due to treatment- or disease-related weight gain, we restricted the analyses of abdominal adiposity to women with anthropometric measurements <12 months after diagnosis or selection into the study.

The main strengths include the population-based design, the use of standardized protocols to take body measurements rather than relying on self-report or self-measurement, and the comprehensive assessment of other breast cancer risk factors by in-person interview. Our pooled sample size was considerably larger than previous studies in U.S. Hispanics which allowed us to evaluate the role of several modifying factors. The availability of information on hormone receptor status for most cases allowed us to investigate the role of body size for specific subtypes.

In conclusion, our pooled analysis shows that weight gain is an important risk factor for postmenopausal ER^+PR^+ breast cancer in Hispanic women with a low young-adult BMI, and that a high young-adult BMI is inversely associated with breast cancer risk, regardless of ER/PR status. These findings emphasize that body size throughout life should be considered when assessing postmenopausal breast cancer risk. In light of the high prevalence of overweight and obesity, particularly among Hispanics, avoiding weight gain and maintaining a healthy weight are important strategies to reduce the risk of ER^+PR^+ breast cancer, the most common breast cancer subtype. For ER^-PR^- breast cancer, the role of overweight and obesity throughout adult life warrants further investigation in larger studies, given our finding of suggestive inverse associations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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