Annals of Epidemiology 23 (2013) 227–232

Contents lists available at SciVerse ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Brief communication

Differences between Hispanic and non-Hispanic white women with breast cancer for clinical characteristics and their correlates

Avonne E. Connor PhD [a,*], Richard N. Baumgartner PhD [a], Dongyan Yang MD [a], Martha L. Slattery PhD [b], Anna R. Giuliano PhD [c], Betsy C. Risendal PhD [d], Madiha M. Abdel-Maksoud MD, PhD [d], Kathy B. Baumgartner PhD [a]

[a] Department of Epidemiology and Population Health, School of Public Health and Information Sciences, University of Louisville, KY
[b] Department of Internal Medicine, University of Utah, Salt Lake City, UT
[c] H. Lee Moffit Cancer Center and Research Institute, Tampa, FL
[d] Department of Epidemiology, Colorado School of Public Health, University of Colorado, Aurora, CO

ARTICLE INFO

Article history:
Received 27 June 2012
Accepted 26 December 2012
Available online 28 January 2013

Keywords:
Breast neoplasms
Hispanic Americans
Obesity

ABSTRACT

Purpose: Body size and ethnicity may influence breast cancer tumor characteristics at diagnosis. We compared Hispanic and non-Hispanic white (NHW) cases for stage of disease, estrogen receptor (ER) status, tumor size, and lymph node status, and the associations of these with body size in the 4-Corners Breast Cancer Study.

Methods: One thousand five hundred twenty-seven NHW and 798 Hispanic primary incident breast cancer cases diagnosed between October 1999 and May 2004 were included. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by multiple logistic regression.

Results: Hispanic women were more likely to have larger (>1 cm) ER− tumors and more than four positive lymph nodes ($P < .003$). Lymph node status was not associated with body size. However, among NHW women, obesity (body mass index >30) and increased waist circumference (>38.5 inches) were significantly positively associated with ER− tumor status (OR, 1.87; 95% CI, 1.24–2.81 and OR, 2.59; 95% CI, 1.58–4.22, respectively). In contrast, among Hispanic women, obesity and waist circumference had inverse associations with ER− tumor status (OR, 0.49; 95% CI, 0.29–0.84 and OR, 0.56; 95% CI, 0.30–1.05, respectively).

Conclusions: Hispanic ethnicity may modify the association of body size and composition with ER− breast cancer. This finding could have relevance to clinical treatment and prognosis.

Introduction

Breast cancer risk in women is associated with body size and composition; however, this finding is dependent on the menopausal status [1,2]. Breast cancer prognosis also may be associated with increased adiposity, which has been linked with poor survival and increased risk for breast cancer recurrence [3–8]. Some studies report that obesity is strongly associated with breast cancer prognostic markers, including positive estrogen receptor (ER) status [9,10], increased tumor size [11–13], advanced stage of disease [14,15], and positive nodal status [12,16]. Furthermore, breast cancer treatment is based on the evaluation of these prognostic markers, and some studies suggest that treatment is further associated with postdiagnostic changes in weight and body composition that impact survival and that this association may depend on prediagnosis body weight [17,18]. Thus, establishing the associations of body size with these markers at the time of diagnosis is important because it may illuminate the pathways by which obesity influences breast cancer prognosis.

We tested the hypothesis that the following body size measures, body mass index (BMI), waist circumference, and waist–hip ratio (WHR), are associated with baseline prognostic markers using data for breast cancer cases from the 4-Corners Breast Cancer Study (4-CBCS). The purpose of the 4-CBCS was to evaluate the associations between various risk factors for breast cancer in Hispanic and non-Hispanic white (NHW) women residing in the Southwestern United States.

Methods

Study population

The study participants in the 4-CBCS were women between the ages of 25 and 79 years living in Arizona, Colorado, New Mexico,

* Corresponding author. Department of Epidemiology and Population Health, School of Public Health and Information Sciences, University of Louisville, 485 E. Gray St, Louisville, KY 40202. Tel.: 502 852 6441; fax: 502 852 3294.
E-mail address: aeconn02@louisville.edu (A.E. Connor).

1047-2797/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.annepidem.2012.12.013

and Utah. The methods for subject selection, participation rates, data collection, and quality control procedures are described in previous publications [19–24]. Cases were ascertained through the National Cancer Institute as Surveillance Epidemiology and End Results registries in New Mexico and Utah and through the Centers for Disease Control and Prevention National Program of Cancer Registries for Colorado or Arizona. All primary incident cases diagnosed with in situ or invasive breast cancer between October 1999 and May 2004 with histological confirmation were eligible. Registries provided information on estrogen and progesterone receptor tumor status for approximately 70% of cases [22]. All study participants signed informed consent documents before the study enrollment. The study was approved by the institutional review board for human subjects at each institution.

Data description

In-person interviews were administered to participants by trained interviewers using a computerized questionnaire to collect data on demographic characteristics and breast cancer risk factors before the referent year (date of diagnosis). Ethnicity was based on self-report. Risk factors included reproductive history, medical and medication history, height, weight history, diet, physical activity, education, smoking history, and alcohol intake. All participants had a blood draw, and anthropometric measurements were obtained.

BMI for the referent year was based on the self-reported weight and the measured height collected by the interviewer at the time of interview and expressed as weight (kilogram)/height (square meter). Levels of body size were defined using international BMI cut points of less than 25 as normal weight, 25–29.9 as overweight, and 30+ as obese. Self-reported BMIs at ages 15, 30, and 50 years were also considered in the analyses. BMI levels at ages 15 and 30 years were defined as the following quartiles: BMI at age 15, less than 17.9, 17.9–19.5, 19.5–21.2, and greater than 21.2 kg/m^2 and BMI at age 30, less than 20.5, 20.5–22.1, 22.1–24.4, and greater than 24.4 kg/m^2. BMI at age 50 years was analyzed using the international cut points. Changes in BMI between ages and the referent year were calculated and analyzed as continuous variables. Waist and hip circumferences were measured in duplicate at the time of interview and to the nearest 0.5 inches. For the analyses, waist circumferences were categorized into quartiles, based on the normal distribution of the sample as follows: <30.6 (referent), 30.6–34.1, 34.1–38.5, and >38.5 inches. WHRs were calculated and categorized as >0.8, 0.8–0.9, and >0.9.

An algorithm based on age younger than 57 years at referent date and responses to eight questions regarding menstrual status, hormone replacement use, and surgical or medical menopause was used to determine menopausal status, as previously described [22]. Postmenopausal women were further stratified based on their recent exposure to hormones, which was defined as hormone replacement therapy use within the past 2 years or pre- or perimenopausal status during the 2 years before the referent date [22]. Women who were perimenopausal at the time of interview were grouped with premenopausal women in analyses. Parity, or number of live births, was categorized as nulliparous, one to two live births, three to four live births, and five or more live births. Family history of breast cancer was determined by the report of first-degree relatives. Education was categorized as less than high school graduate, high school graduate or General Educational Development, some college, and bachelors or more. Cigarette smoking status was categorized as current, former, or never smoker. Recent hormone exposure was based on the recent hormone exposure within 2 years of the referent year. Age at menarche was categorized as younger than 12, 12, 13, and 14 years or older. Self-reported history of diabetes was based on the following responses: “yes,” “no,” or “borderline.” Self-reported history of mammography screening was recorded as “yes” or “no.”

The clinical and tumor characteristics, such as stage, lymph node status, tumor size, and ER status, were obtained from the cancer registries [25]. Cancer stage groupings were coded as in situ (stage 0) versus invasive disease. ER status and lymph node status were both coded as positive versus negative. Tumor size was coded as less than 1 cm or greater than or equal to 1 cm.

Data analysis

A total of 2325 breast cancer cases were included for the analyses (1527 NHW and 798 Hispanic/American Indian and Alaska Native). Descriptive statistics were calculated using chi-squared tests for categorical variables and *t* tests for continuous variables. Multiple logistic regression models were used for this case–case comparison to calculate the association of body composition and obesity measures with the breast cancer prognostic markers. Covariates included in the analysis were age, ethnicity, menopausal status, education, family history, age at menarche, parity, smoking status, time to interview, study center, recent hormone exposure, history of diabetes, and history of mammography screening. Models were then stratified by ethnicity to test for effect modification and divergent patterns within the data, and *P* values for interaction tests were calculated by including multiplicative interaction terms in the multivariable logistic regression models if there was evidence of divergent patterns. The statistical significance of the interactions was evaluated using the difference in maximum likelihood estimates. All *P* values are two sided. SAS statistical software (version 9.2; SAS Institute, Cary, NC) was used to conduct all analyses.

Results

The mean age of women in the present analyses was 54.2 years (SD = 11.2). Hispanic women were somewhat younger than NHW women, with a mean age of 52.2 years (SD = 11.2) for Hispanic women and 55.3 years (SD = 11.1) for NHW women. NHW women, in comparison to Hispanic women, reported higher education levels, lower parity, more family history of breast cancer, and more recent exposure to exogenous hormones (Table 1).

Hispanic women had larger tumors ($P < .0001$), were more likely to have positive lymph node involvement ($P = .0034$), and had ER– tumors ($P = .0020$) (Table 2). Hispanic women had significantly higher means for all body composition measures than NHW women (Table 3). The higher waist circumferences in Hispanic women suggest more centralized adiposity than NHW women (Hispanic mean = 36.0, SD = 5.5 vs. NHW mean = 34.2, SD = 5.7) (Table 3). The ethnic groups were closely similar for BMI at age of 15 years, with mean BMI = 19.8, (SD = 3.2) for Hispanic women versus mean BMI = 19.7 (SD = 2.9) for NHW women (Table 3).

Odds ratios (ORs) for body composition measures and prognostic characteristics are shown in Table 4. All ORs are stratified by ethnicity and have been adjusted for age, menopausal status, education, study center, and time to interview. There were divergent results between the ethnic groups for the association of current waist circumference with ER– tumor status. Among NHW women, increased waist circumference (>38.5 inches vs. <30.6 inches) was associated significantly with an increased risk for ER– tumor status (OR, 2.59; 95% confidence interval [CI], 1.58–4.22) (Table 4). In contrast, there was an inverse association with increased centralized adiposity and ER– status, among Hispanic women; however, the point estimate was not statistically significant (OR, 0.56; 95% CI, 0.30–1.05) (Table 4). We also examined waist circumference using the cut points for the clinical identification of metabolic syndrome among women [26] (0–35 vs. >35 inches) and found a significant positive association for ER– breast cancer among NHW women with a waist circumference greater than 35 inches (OR, 1.74; 95% CI,

Table 1
Baseline data on selected study population characteristics, 4-CBCS (1999–2004)

Characteristics	Hispanic ($n = 798$)	NHW ($n = 1527$)	X^2 P
	N (%)	*N* (%)	
Age at diagnosis (y)			<.0001
<29	8 (1.00)	9 (0.59)	
30–39	85 (10.65)	90 (5.9)	
40–49	266 (33.34)	433 (28.36)	
50–59	228 (28.57)	453 (29.67)	
60–69	148 (18.54)	356 (23.32)	
70–79	63 (7.89)	186 (12.18)	
Education			<.0001
Under high school	245 (30.70)	64 (4.19)	
High school	221 (27.69)	308 (20.17)	
Some college	218 (27.32)	562 (36.80)	
Bachelors or more	114 (14.29)	593 (38.83)	
Age at menarche (y)			.0064
<12	181 (22.68)	314 (20.56)	
12	207 (25.94)	407 (26.65)	
13	178 (22.31)	431 (28.23)	
≥14	232 (29.07)	375 (24.56)	
Menopause status			.0021
Pre/perimenopausal	333 (41.73)	538 (35.23)	
Postmenopausal	465 (58.27)	989 (64.77)	
Number of live births			<.0001
None	77 (9.65)	260 (17.03)	
1–2	327 (40.98)	696 (45.58)	
3–4	283 (35.46)	478 (31.30)	
≥5	111 (13.91)	93 (6.09)	
Family history			.0005
Yes	127 (15.91)	345 (22.59)	
No	654 (81.95)	1160 (75.97)	
Unknown	17 (2.13)	22 (1.44)	
Recent hormone exposure			.0052
Yes	611 (76.57)	1244 (81.47)	
No	187 (23.43)	283 (18.53)	
History of type 2 diabetes			<.0001
Yes	121 (15.2)	109 (7.1)	
Borderline	16 (2.0)	25 (1.6)	
No	661 (82.8)	1392 (91.2)	
Smoking status			<.0001
Current	96 (12.03)	204 (13.36)	
Former	172 (21.55)	482 (31.57)	
Never	530 (66.42)	842 (55.08)	
	Hispanic ($n = 798$)	NHW ($n = 1527$)	*t* test *P*
	Mean (SD)	Mean (SD)	
Time to interview (mo)	21.54 (11.25)	18.17 (9.32)	<.001

Table 2
Baseline data on prognostic factors, 4-CBCS (1999–2004)

Prognostic factor	Hispanic ($n = 798$)	NHW ($n = 1527$)	X^2 P
	N (%)	*N* (%)	
Stage			.0594
In situ	129 (17.4)	259 (16.4)	
Localized	361 (46.0)	806 (54.0)	
Regional	264 (33.6)	371 (24.9)	
Distant	7 (0.9)	17 (1.1)	
Unstaged	24 (3.1)	40 (2.7)	
Tumor size (cm)			<.0001
<1	117 (14.66)	325 (21.28)	
≥1	548 (68.67)	934 (61.17)	
Unknown	133 (16.67)	268 (17.55)	
	Hispanic ($n = 662$)	NHW ($n = 1246$)	
	N (%)	*N* (%)	
ER status*			
Positive	449 (67.82)	915 (73.43)	.0020
Negative	138 (20.85)	191 (15.33)	
Unknown	75 (11.33)	140 (11.24)	
Lymph node status*			.0034
1–3 nodes positive	161 (24.32)	222 (17.82)	
≥4 nodes positive	74 (11.18)	95 (7.62)	
All nodes examined negative	342 (51.67)	760 (61.0)	
Not examined	42 (6.34)	83 (6.66)	
Unknown	43 (6.50)	86 (6.90)	

* Based on the invasive breast cancer cases only.

1.25–2.42) and a nonsignificant association among Hispanic cases (OR, 0.98; 95% CI, 0.65–1.47). The corresponding interaction between ethnicity and waist circumference on ER status was highly significant ($P_{interaction} = .0001$). Waist circumference was also associated with increased tumor size among NHW women; however, the largest effect found was among cases who had waist circumferences between 34.1 and 38.5 inches compared with less than 30.6 inches (OR, 1.71; 95% CI, 1.17–2.49) (Table 4).

Increased body size, measured as BMI at referent year, was associated with ER– tumor status and with a divergent pattern between the ethnic groups. Among NHW women, there was a statistically significant positive association for risk of ER– tumor status in obese compared with normal weight (BMI ≥ 30 vs. <25 kg/m^2; OR, 1.87; 95% CI, 1.24–2.81); conversely, an inverse association was found for Hispanic women (OR, 0.49; 95% CI, 0.29–0.84) (Table 4). The formal test of interaction between ethnicity and BMI was statistically significant ($P_{interaction} = .0003$). Although WHR had a statistically significant positive association with the risk of ER– tumors in NHW women (WHR, 0.8–0.9; OR, 1.99; 95% CI, 1.40–2.82 and WHR, >0.9; OR, 2.09; 95% CI, 1.20–3.66), there was no association in Hispanic women; therefore, a similar divergent pattern between the ethnic groups was not found (Table 4). Changes in BMI between ages and referent year were also modeled. There was evidence for effect modification of the association between change in BMI between the age of 15 years and the referent year (Hispanics OR, 0.96; 95% CI, 0.93–1.00 vs. NHW OR, 1.04; 95% CI, 1.01–1.07; $P_{interaction} = .001$) (Table 4). These associations for ER– tumor status were similar when stratified by menopausal status (data not shown).

Table 4 also shows the associations between measures of body size and breast cancer stage by ethnicity. Multiple logistic regression models were constructed comparing in situ versus invasive cancer. Invasive stage was significantly associated with the highest tertiles of BMI at referent year compared with normal BMI in NHW women (OR, 1.64; 95% CI, 1.14–2.36); however, there was no

Table 3
Body composition data for all breast cancer cases, 4-CBCS (1999–2004)

Body composition	Hispanic ($n = 798$)	NHW ($n = 1527$)	*t* test *P*
	Mean (SD)	Mean (SD)	
BMI (kg/m^2)			
Referent year	28.1 (5.8)	26.8 (6.1)	<.0001
At age 15 y	19.8 (3.2)	19.7 (2.9)	<.0001
At age 30 y	23.8 (4.1)	22.5 (3.9)	<.0001
At age 50 y	27.2 (5.1)	25.9 (5.6)	<.0001
Unknown			
15–30 y	4.1 (3.8)	3.0 (3.4)	<.0001
15–50 y	7.2 (5.3)	6.1 (4.9)	.002
15 to referent year	8.2 (5.7)	7.3 (5.7)	.002
30–50 y	3.6 (4.1)	3.4 (4.1)	.430
30 to referent year	4.3 (3.9)	4.4 (4.1)	.652
50 to referent year	1.4 (3.9)	1.6 (3.5)	.298
Waist circumference (in)*	36.0 (5.5)	34.2 (5.7)	<.0001
WHR*	0.84 (0.07)	0.80 (0.07)	<.0001

* Anthropometrics that were measured at time of interview.

Table 4
Baseline data on association of body composition with prognostic markers, stratified by ethnicity, 4-CBCS

Body size measures	Stage		ER status*		Lymph node status*		Tumor size	
	In situ vs. invasive		ER+ vs. ER−		Negative vs. positive		<1.0 cm vs. ≥1.0 cm	
	Hispanic	NHW	Hispanic	NHW	Hispanic	NHW	Hispanic	NHW
BMI (kg/m^2), referent								
<25.00	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25.00–30.00	1.08 (0.68–1.70)	1.33 (0.97–1.84)	1.18 (0.74–1.87)	1.86 (1.26–2.74)	0.84 (0.55–1.29)	1.11 (0.81–1.52)	1.07 (0.65–1.76)	1.25 (0.92–1.70)
≥30.00	1.19 (0.74–1.91)	1.64 (1.14–2.36)	0.49 (0.29–0.84)	1.87 (1.24–2.81)	1.02 (0.67–1.57)	1.06 (0.75–1.51)	1.08 (0.65–1.80)	1.09 (0.79–1.51)
P_{trend}	.33	.002	.01	.002	.93	.99	.82	.24
N	790	1507	585	1103	577	1077	662	1256
BMI (kg/m^2), age 15								
<17.90	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
17.90–19.50	1.40 (0.80–2.44)	1.43 (0.98–2.08)	0.96 (0.54–1.69)	1.12 (0.72–1.75)	0.64 (0.38–1.08)	1.23 (0.84–1.79)	0.68 (0.38–1.22)	1.02 (0.70–1.47)
19.50–21.20	1.30 (0.76–2.21)	1.22 (0.85–1.76)	0.77 (0.44–1.36)	0.92 (0.58–1.46)	0.84 (0.51–1.40)	1.09 (0.74–1.60)	1.23 (0.66–2.31)	1.03 (0.71–1.49)
≥21.2	1.47 (0.85–2.51)	1.49 (1.01–2.19)	0.87 (0.50–1.52)	1.18 (0.75–1.85)	1.11 (0.67–1.83)	0.93 (0.65–1.43)	0.95 (0.53–1.71)	1.11 (0.76–1.60)
P_{trend}	.20	.11	.63	.76	.48	.90	.67	.68
N	754	1456	559	1060	552	1034	633	1211
BMI (kg/m^2), age 30								
<20.49	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
20.49–22.09	1.94 (1.04–3.63)	1.27 (0.89–1.81)	1.60 (0.83–3.08)	0.99 (0.62–1.56)	1.07 (0.60–1.93)	1.21 (0.84–1.74)	1.75 (0.90–3.40)	1.08 (0.76–1.52)
22.09–24.40	1.55 (0.88–2.75)	1.15 (0.81–1.63)	1.17 (0.61–2.24)	1.20 (0.77–1.87)	1.27 (0.72–2.23)	1.14 (0.78–1.65)	1.48 (0.80–2.72)	1.42 (0.99–2.03)
>24.40	1.48 (0.88–2.52)	2.05 (1.33–3.14)	0.88 (0.47–1.67)	1.20 (0.76–1.91)	1.21 (0.70–2.07)	0.93 (0.62–1.38)	1.56 (0.87–2.78)	1.22 (0.85–1.77)
P_{trend}	.20	.001	.08	.03	.85	.50	.98	.44
N	758	1478	558	1077	554	1056	258	418
BMI (kg/m^2), age 50								
<25.00	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25.00–30.00	1.41 (0.78–2.56)	1.12 (0.75–1.68)	1.08 (0.50–2.34)	1.27 (0.74–2.16)	0.78 (0.42–1.45)	1.00 (0.67–1.51)	0.97 (0.51–1.82)	0.88 (0.61–1.28)
≥30.00	1.63 (0.79–3.34)	1.30 (0.78–2.17)	0.89 (0.36–2.19)	1.50 (0.82–2.75)	0.78 (0.39–1.59)	0.72 (0.43–1.21)	0.83 (0.40–1.72)	0.87 (0.56–1.35)
P_{trend}	.04	.40	.42	.11	.63	.82	.50	.64
N	383	900	269	651	273	656	324	764
Changes in BMI (kg/m^2) by age								
15–30 y	1.01 (0.96–1.07)	1.06 (1.02–1.11)	0.96 (0.91–1.02)	1.05 (1.00–1.10)	0.99 (0.94–1.04)	0.98 (0.94–1.03)	0.99 (0.93–1.04)	1.04 (1.00–1.09)
P_{trend}	.61	.001	.17	.04	.60	.46	.60	.06
N	738	1431	544	1037	539	1015	618	1190
15–50 y	1.02 (0.96–1.07)	1.01 (0.97–1.05)	0.95 (0.88–1.03)	1.03 (0.99–1.08)	0.97 (0.92–1.02)	1.00 (0.96–1.04)	1.03 (0.97–1.09)	1.00 (0.97–1.04)
P_{trend}	.58	.70	.22	.14	.20	.86	.35	.97
N	364	859	254	618	258	623	309	727
15 to referent year	1.00 (0.97–1.04)	1.04 (1.01–1.07)	0.96 (0.93–1.00)	1.04 (1.01–1.07)	1.00 (0.97–1.03)	1.00 (0.97–1.02)	0.99 (0.96–1.03)	1.02 (1.00–1.05)
P_{trend}	.81	.01	.05	.004	.81	.81	.66	.09
N	751	1453	556	1059	550	1032	631	1208
30–50 y	1.03 (0.96–1.11)	0.98 (0.94–1.03)	1.03 (0.96–1.11)	1.03 (0.97–1.08)	0.95 (0.89–1.02)	1.03 (0.98–1.07)	1.00 (0.93–1.07)	0.99 (0.95–1.03)
P_{trend}	.42	.40	.43	.36	.18	.22	.95	.49
N	375	895	264	647	269	654	317	759
30 to referent year	1.00 (0.96–1.04)	1.02 (0.99–1.05)	0.96 (0.92–1.01)	1.04 (1.01–1.08)	0.99 (0.95–1.03)	1.01 (0.98–1.04)	0.99 (0.95–1.04)	1.01 (0.98–1.04)
P_{trend}	.97	.19	.11	.02	.70	.63	.75	.43
N	755	1475	555	1076	552	1054	631	1228
50 to referent year	0.96 (0.89–1.04)	1.04 (0.99–1.09)	0.96 (0.88–1.04)	1.06 (0.99–1.13)	1.05 (0.97–1.12)	1.00 (0.94–1.05)	0.97 (0.90–1.06)	1.02 (0.97–1.06)
P_{trend}	.31	.17	.30	.09	.22	.87	.52	.49
N	381	898	267	650	271	655	322	762
Waist circumference (in), interview								
<30.6	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
30.6–34.1	1.39 (0.78–2.47)	1.14 (0.81–1.62)	0.68 (0.37–1.25)	1.73 (1.05–2.88)	1.19 (0.67–2.13)	0.96 (0.66–1.40)	1.72 (0.91–3.24)	1.35 (0.95–1.92)
34.1–38.5	2.21 (1.18–4.14)	1.47 (1.00–2.17)	0.73 (0.40–1.34)	3.22 (1.98–5.23)	1.25 (0.70–2.24)	1.12 (0.76–1.66)	1.82 (0.96–3.45)	1.71 (1.17–2.49)
>38.5	1.24 (0.70–2.19)	1.79 (1.20–2.67)	0.56 (0.30–1.05)	2.59 (1.58–4.22)	0.99 (0.55–1.79)	0.98 (0.67–1.43)	1.33 (0.72–2.46)	1.46 (1.01–2.09)
P_{trend}	.59	<.001	.09	<.001	.83	.91	.99	.03
N	774	1486	575	1085	567	1063	650	1238
WHR, interview								
<0.8	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.8–0.9	1.21 (0.78–1.89)	1.23 (0.92-1.64)	1.18 (0.67–1.66)	1.99 (1.40–2.82)	1.19 (0.79–1.80)	1.05 (0.79–1.41)	1.22 (0.77–1.94)	1.10 (0.83–1.44)
>0.9	0.87 (0.49–1.56)	1.64 (1.14–2.36)	1.05 (0.67–1.66)	2.09 (1.20–3.66)	0.85 (0.48–1.53)	1.09 (0.68–1.75)	1.37 (0.70–2.67)	1.40 (0.87–2.25)
P_{trend}	.82	.04	.35	<.001	.82	.65	.31	.18
N	793	1510	587	1106	579	1080	665	1259

All models adjusted for study center, menopausal status, age, education, and time to interview.
BMI for the referent year.
OR (95% CI); P_{trend} values by chi-squared test for linear trend.
* ER status and lymph node status in logistic regression analysis restricted to invasive cases.

association in Hispanic women in the same risk category (OR, 1.19; 95% CI, 0.74–1.91) (Table 4). Invasive stage was also positively associated with changes in BMI between ages 15–30 years and age 15 years to referent year, for increased waist circumference, and WHR (Table 4). The addition of family history, age at menarche, parity, history of diabetes, history of mammography screening, and smoking status did not alter the divergent pattern or greatly change the effect estimates (data not shown).

Discussion

In this population-based case–case analysis, various markers for adiposity were hypothesized to be associated with clinical breast cancer prognostic markers, including ER status, breast cancer stage, tumor size, and lymph node status. Our findings suggest that obesity, as measured by BMI, waist circumference, and WHR, is associated with invasive stage and ER– tumor status in NHW women with breast cancer. Moreover, the associations with ER– tumor status by BMI are modified by Hispanic ethnicity.

In a previous 4-CBCS publication, Slattery et al. [22] reported that the relationship between obesity and breast cancer risk differs between Hispanic and NHW women. Their case–control analysis evaluated the association between ER status with BMI at referent year and at age of 15 years, height, weight gain between age 15 years and referent year, and WHR. BMI at referent year was associated with a reduction in risk for ER– tumors among obese Hispanics (OR, 0.45; 95% CI, 0.26–0.76), whereas a nonsignificant positive association was observed among obese NHW women (OR, 1.40; 95% CI, 0.95–2.07) [22]. An increased risk for ER– breast cancer was also found among NHW women with WHR greater than 0.9 compared with less than 0.8 (OR, 2.04; 95% CI, 1.20–3.50), whereas a nonsignificant inverse association was found among Hispanics (OR, 0.79; 95% CI, 0.39–1.57) [22]. A recent 4-CBCS report analyzed the relationships between behavioral risk factors and tumor characteristics [27], including the association between BMI and ER status. Among women younger than 50 years, ethnicity modified the association between obesity and ER status; there was an inverse association among obese Hispanic cases for ER– tumors (OR, 0.29; 95% CI, 0.13–0.66) but a significant positive association among NHW cases (OR, 2.47; 95% CI, 1.08–5.67) [27]. For this research, our analyses not only investigated the associations between BMI and ER status but also examined the effects of waist circumference, BMI at ages 30 and 50 years, and changes in BMI between selected ages. We also evaluated the associations between these measures of adiposity and other clinical markers for breast cancer. Based on our findings, waist circumference is an important marker of central adiposity among NHW breast cancer cases that should be considered in the obesity and ER status relationship.

Although we found a significant association for high WHR and ER– breast cancer among NHW women, ethnic-specific results were more divergent for waist circumference. Waist circumference has been suggested to be a better predictor of central, abdominal, or visceral obesity than WHR, BMI, or percent body fat [28]. Increased waist circumference is positively correlated with circulating levels of inflammatory markers, type 2 diabetes, and insulin resistance [29]. In the general population, Hispanic women have a higher prevalence of obesity and type 2 diabetes [30] and for our study, Hispanics had higher levels for all BMI and waist circumference at all ages when compared with NHW women. Nevertheless, the underlying mechanisms for these divergent associations are unknown.

The relationship between obesity and ER tumor status and the potential mechanisms contributing to these relationships and subsequent phenotypes have been explored in the epidemiologic literature. In a study of Hispanic and NHW breast cancer cases from New Mexico, none of the relevant adiposity measures (BMI, waist circumference, and WHR) were found to be associated with a risk of ER– tumors [12]. Paradoxically, other studies have found that obesity, measured by BMI, is linked to postmenopausal ER+ breast cancer and not ER– breast cancer [31–34]. The relationship between obesity and ER+ breast cancer is thought to reflect increased estrogen synthesis in adipose stores and greater bioavailability [35]. With the case of the association between obesity and ER– tumors, it has been speculated that insulin and the adipocytokine leptin may play a role in this relationship [36]. Leptin, vascular endothelial growth factor, and heparin-binding epidermal growth factor–like growth factor may stimulate ER– tumors. Moreover, there is the assumption that the action of estrogen is not influenced by mechanisms related to hormonal, paracrine, and autocrine factors [37]. It is plausible that leptin and insulin act synergistically in the development of this metastatic tumor phenotype [36], as plasma leptin and insulin levels have been reported to be positively correlated with ER– tumors [38]. Clearly, more research is warranted to obtain a better understanding of the possible mechanisms behind the obesity and ER– breast cancer association.

There are possible limitations and strengths to the present study. Response rates were consistently lower among Hispanic cases for all study sites, and it is possible that the nonrespondents' characteristics could be different from those who participated in the study, which could create selection bias. Response rates were also fairly low among NHW cases. However, our study is one of the few that included a substantial number of Hispanic cases from a multisite population-based study, unlike previous studies with similar research aims. There is the possibility for recall bias in relation to self-reported body weight and height at the various time points selected; nonetheless, the accuracy of recalled body weight and height is good. In a previous report of the validity of self-reported past body weight in U.S. men and women, recalled past weight was strongly correlated with previously measured weight, with correlations reported as 0.74 for women, and 41% of women estimating their past weight within 5 pounds [39].

In spite of these limitations, our data suggest that obesity measured by BMI and waist circumference is significantly and positively associated with ER– breast cancer among NHW but inversely associated in Hispanic women. Our results also suggest a possible association between BMI, waist circumference, WHR, and invasive stage of disease. Our findings for ER– breast cancer build on those previously reported by other researchers from the 4-CBCS [22,27] as well as a previous report from the New Mexico site of the Healthy Eating, Activity, and Lifestyle study, which suggests that Hispanic ethnicity may modify the hormone-mediated effects of obesity on breast cancer [12]. It could be speculated that the effect modification presented in our results could be because of the genetic differences between Hispanic and NHW women and that certain genetic variants could alter obesity-related risk factors for ER– tumors. These hypotheses should be investigated further and explored with other tumor phenotypes, including triple-negative breast cancer. A previous 4-CBCS case–case analysis that included a subset of cases from Colorado reported that Hispanics were almost three times more likely to have HER2+ breast tumors when compared with NHW cases; however, this study did not test the hypothesis that obesity markers are major contributing factors to the association between ethnicity and tumor phenotypes [40]. In conclusion, our findings suggest that there is more to the estrogen, obesity, and ER status relationship, as leptin and insulin might play significant roles in the obesity and ER–breast cancer association. Furthermore, these findings could have relevance to clinical treatment and prognosis.

Acknowledgments

This study was funded by CA 078682, CA 078762, CA 078552, and CA 078802 grants. This research also was supported by the Utah Cancer Registry, which is funded by Contract N01-PC-67000 from the National Cancer Institute, with additional support from the state of Utah Department of Health, the New Mexico Tumor Registry, and the Arizona and Colorado Cancer Registries, funded by the Centers for Disease Control and Prevention National Program of Cancer Registries and additional state support. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official view of the National Cancer

Institute. We also acknowledge the contributions of Tim Byers, Sandra Edwards, and Roger Edwards.

References

[1] Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, Kuller L, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 2002;13(8):741–51.

[2] Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997; 278(17):1407–11.

[3] Chen X, Lu W, Zheng W, Gu K, Chen Z, Zheng Y, et al. Obesity and weight change in relation to breast cancer survival. Breast Cancer Res Treat 2010; 122(3):823–33.

[4] Conroy SM, Maskarinec G, Wilkens LR, White KK, Henderson BE, Kolonel LN. Obesity and breast cancer survival in ethnically diverse postmenopausal women: the Multiethnic Cohort Study. Breast Cancer Res Treat 2011;129(2):565–74.

[5] Carmichael AR. Obesity and prognosis of breast cancer. Obes Rev 2006;7(4): 333–40.

[6] Carmichael AR, Bendall S, Lockerbie L, Prescott RJ, Bates T. Does obesity compromise survival in women with breast cancer? Breast 2004;13(2):93–6.

[7] Dal Maso L, Zucchetto A, Talamini R, Serraino D, Stocco CF, Vercelli M, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. Int J Cancer 2008;123(9):2188–94.

[8] Petrelli JM, Calle EE, Rodriguez C, Thun MJ. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control 2002;13(4):325–32.

[9] Maehle BO, Tretli S. Pre-morbid body-mass-index in breast cancer: reversed effect on survival in hormone receptor negative patients. Breast Cancer Res Treat 1996;41(2):123–30.

[10] Canchola AJ, Anton-Culver H, Bernstein L, Clarke CA, Henderson K, Ma H, et al. Body size and the risk of postmenopausal breast cancer subtypes in the California Teachers Study cohort. Cancer Causes Control 2012;23(3):473–85.

[11] Maehle BO, Tretli S, Skjaerven R, Thorsen T. Premorbid body weight and its relations to primary tumour diameter in breast cancer patients; its dependence on estrogen and progesteron receptor status. Breast Cancer Res Treat 2001;68(2):159–69.

[12] Baumgartner KB, Hunt WC, Baumgartner RN, Crumley DD, Gilliland FD, McTiernan A, et al. Association of body composition and weight history with breast cancer prognostic markers: divergent pattern for Hispanic and non-Hispanic White women. Am J Epidemiol 2004;160(11):1087–97.

[13] Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 2001;92(4):720–9.

[14] Ewertz M, Jensen MB, Gunnarsdottir KA, Hojris I, Jakobsen EH, Nielsen D, et al. Effect of obesity on prognosis after early-stage breast cancer. J Clin Oncol 2011;29(1):25–31.

[15] Cui Y, Whiteman MK, Flaws JA, Langenberg P, Tkaczuk KH, Bush TL. Body mass and stage of breast cancer at diagnosis. Int J Cancer 2002;98(2):279–83.

[16] Daniell HW. Increased lymph node metastases at mastectomy for breast cancer associated with host obesity, cigarette smoking, age, and large tumor size. Cancer 1988;62(2):429–35.

[17] Thivat E, Therondel S, Lapirot O, Abrial C, Gimbergues P, Gadea E, et al. Weight change during chemotherapy changes the prognosis in non metastatic breast cancer for the worse. BMC Cancer 2010;10:648.

[18] Caan BJ, Kwan ML, Hartzell G, Castillo A, Slattery ML, Sternfeld B, et al. Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. Cancer Causes Control 2008; 19(10):1319–28.

[19] Murtaugh MA, Herrick JS, Sweeney C, Baumgartner KB, Guiliano AR, Byers T, et al. Diet composition and risk of overweight and obesity in women living in the southwestern United States. J Am Diet Assoc 2007;107(8):1311–21.

[20] Slattery ML, Baumgartner KB, Byers T, Guiliano A, Sweeney C, Herrick J, et al. Genetic, anthropometric, and lifestyle factors associated with IGF-1 and IGFBP-3 levels in Hispanic and non-Hispanic white women. Cancer Causes Control 2005;16(10):1147–57.

[21] Slattery ML, Edwards S, Murtaugh MA, Sweeney C, Herrick J, Byers T, et al. Physical activity and breast cancer risk among women in the southwestern United States. Ann Epidemiol 2007;17(5):342–53.

[22] Slattery ML, Sweeney C, Edwards S, Herrick J, Baumgartner K, Wolff R, et al. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. Breast Cancer Res Treat 2007;102(1): 85–101.

[23] Slattery ML, Sweeney C, Herrick J, Wolff R, Baumgartner K, Giuliano A, et al. ESR1, AR, body size, and breast cancer risk in Hispanic and non-Hispanic white women living in the Southwestern United States. Breast Cancer Res Treat 2007;105(3):327–35.

[24] Sweeney C, Edwards SL, Baumgartner KB, Herrick JS, Palmer LE, Murtaugh MA, et al. Recruiting Hispanic women for a population-based study: validity of surname search and characteristics of nonparticipants. Am J Epidemiol 2007; 166(10):1210–9.

[25] Division of Cancer Control and Population Sciences. The SEER program code manual. 3rd ed. Bethesda, MD: National Cancer Institute, U.S. Department of Health and Human Services; 1998.

[26] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486–97.

[27] Abdel-Maksoud MF, Risendal BC, Slattery ML, Giuliano AR, Baumgartner KB, Byers TE. Behavioral risk factors and their relationship to tumor characteristics in Hispanic and non-Hispanic white long-term breast cancer survivors. Breast Cancer Res Treat 2012;131(1):169–76.

[28] Rankinen T, Kim SY, Perusse L, Despres JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. Int J Obes Relat Metab Disord 1999;23(8):801–9.

[29] Ackermann D, Jones J, Barona J, Calle MC, Kim JE, LaPia B, et al. Waist circumference is positively correlated with markers of inflammation and negatively with adiponectin in women with metabolic syndrome. Nutr Res 2011;31(3):197–204.

[30] Zhang Q, Wang Y, Huang ES. Changes in racial/ethnic disparities in the prevalence of Type 2 diabetes by obesity level among US adults. Ethn Health 2009;14(5):439–57.

[31] Vrieling A, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. Breast Cancer Res Treat 2010;123(3):641–9.

[32] Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst 2011;103(3):250–63.

[33] Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis. Int J Cancer 2009;124(3):698–712.

[34] Setiawan VW, Monroe KR, Wilkens LR, Kolonel LN, Pike MC, Henderson BE. Breast cancer risk factors defined by estrogen and progesterone receptor status: the multiethnic cohort study. Am J Epidemiol 2009;169(10):1251–9.

[35] Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev 2004;13(10): 1558–68.

[36] Stephenson GD, Rose DP. Breast cancer and obesity: an update. Nutr Cancer 2003;45(1):1–16.

[37] Vona-Davis L, Rose DP. Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression. Endocr Relat Cancer 2007;14(2): 189–206.

[38] Goodwin PJ, Ennis M, Fantus IG, Pritchard KI, Trudeau ME, Koo J, et al. Is leptin a mediator of adverse prognostic effects of obesity in breast cancer? J Clin Oncol 2005;23(25):6037–42.

[39] Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF. The validity of self-reports of past body weights by U.S. adults. Epidemiology 1995;6(1): 61–6.

[40] Hines LM, Risendal B, Byers T, Mengshol S, Lowery J, Singh M. Ethnic disparities in breast tumor phenotypic subtypes in Hispanic and non-Hispanic white women. J Womens Health (Larchmt) 2011;20(10):1543–50.