Body Size and Risk of Luminal, HER2-Overexpressing, and Triple-Negative Breast Cancer in Postmenopausal Women

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Abstract

Although the clinical relevance of molecular subtypes of breast cancer has been documented, little is known about risk factors for different tumor subtypes, especially the HER2-overexpressing and the triple-negative subtypes that have poor prognoses. Obesity may be differentially related to the risk of different subtypes given the various potential mechanisms underlying its association with breast cancer. We pooled two population-based case-control studies of postmenopausal breast cancer for an analysis, including 1,447 controls and 1,008 luminal (hormone receptor positive), 39 HER2-overexpressing (hormone receptor negative, HER2 positive), and 77 triple-negative (hormone receptor and HER2 negative) cases. Associations between anthropometric factors and the risk of different breast cancer subtypes were evaluated using polytomous logistic regression. Among women not currently using menopausal hormone therapy, body mass index (BMI) and weight were associated with the risk of luminal tumors [odds ratio (OR) comparing highest versus lowest quartiles, 1.7; 95% confidence interval (95% CI), 1.2-2.4 and OR, 1.7; 95% CI, 1.2-2.4, respectively] and suggestively associated with risk of triple-negative tumors (OR, 2.7; 95% CI, 1.0-7.5 and OR, 5.1; 95% CI, 1.1-23.0, respectively). Neither BMI nor weight was associated with the risk of any tumor subtype among hormone therapy users. The positive relationship between BMI and luminal tumors among postmenopausal women not using hormone therapy is well characterized in the literature. Although our sample size was limited, body size may also be related to the risk of postmenopausal triple-negative breast cancer among nonusers of hormone therapy. Given the expanding obesity epidemic, the widespread cessation of hormone therapy use, and the poor prognosis of triple-negative tumors, this novel finding merits confirmation. (Cancer Epidemiol Biomarkers Prev 2008;17(8):2078–86)

Introduction

Studies evaluating molecular profiles of breast cancer indicate that breast tumors can be classified into five clinically relevant subtypes on the basis of gene expression patterns (1, 2): luminal A, luminal B, HER2 overexpressing, basal-like, and unclassified. Expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) alone can be used to approximately differentiate between these subtypes (3, 4). Luminal A and B tumors are ER+, whereas HER2-overexpressing tumors are hormone receptor-negative but HER2 overexpressing (i.e., ER−/PR−/HER2+). Basal-like and unclassified tumors both have a "triple-negative" phenotype (i.e., ER−/PR−/HER2−), although approximately 70% of triple-negative tumors are basal-like (5).

Existing data point to a distinct biology of nonluminal (ER−) breast tumors. Nonluminal tumors are more likely than luminal tumors to present at an advanced stage and to have a high grade (4, 6, 7). Although luminal tumors are most likely to be responsive to hormonal therapies, such as tamoxifen, and HER2-overexpressing tumors respond favorably to treatment with trastuzumab, therapeutic options for triple-negative tumors are limited and nonspecific (8). Consistent with these differences, there are marked differences in survival among luminal, HER2-overexpressing, and triple-negative breast cancers (2, 4, 8-10). Luminal subtypes are associated with the most favorable prognoses (90% 5-year disease-specific survival; refs. 2, 4). Five-year disease-specific survival rates are only 20% to 75% for HER2-overexpressing tumors, 30% to 80% for basal-like tumors, and 50% to 85% for unclassified tumors (2, 4). Although HER2-overexpressing and triple-negative tumors account for <30% of all breast cancers (4, 11), furthering our understanding of the etiologies of these tumors is particularly important given their relatively poor prognoses.

Although the clinical relevance of these molecular subtypes of breast cancer is evident, etiologic differences among subtypes have not been well studied. Studies suggest that basal-like tumors are more common among African American women (4, 7, 12), premenopausal

women (4, 11), and women with a family history of breast cancer (11), specifically *BRCA1* mutation carriers (13). However, few studies have evaluated differences in the associations between established breast cancer risk factors and the molecular subtypes of breast cancer defined by joint ER/PR/HER2 status.

The focus of this study is on the relationship between anthropometric characteristics and the risk of breast cancer subtypes defined by ER/PR/HER2 status. It is well established that obesity, particularly among postmenopausal nonusers of hormone therapy (HT), is positively related to the risk of breast cancer (14-16). This relationship is thought to be hormonally mediated given the positive correlation between obesity and endogenous estrogen levels (17-19). Given proposed mechanisms and data from prior studies indicating that the association between body mass index (BMI) and postmenopausal breast cancer risk is stronger for hormone receptor–positive disease than hormone receptor–negative disease (20-22), it is reasonable to hypothesize that obesity would be more strongly related to the risk of luminal breast tumors. However, nonhormonal factors such as cytokine levels and genetic factors may also contribute to the association between BMI and breast cancer risk, and these factors might contribute to the risk of either luminal, HER2-overexpressing, or triple-negative tumors (23-26). Of the two prior studies to have evaluated the relationship between anthropometric characteristics and the risk of molecular subtypes of breast cancer (11, 27), the larger study (n = 172 triple-negative cases) observed that waist-to-hip ratio, a measure of central obesity, was more strongly related to the risk of triple-negative disease than to other subtypes (27). Neither study observed an association between BMI and postmenopausal triple-negative breast cancer; also, neither study stratified results by HT use.

Materials and Methods

Given the rarity of HER2-overexpressing and triple-negative tumors, cases and controls were pooled from two population-based case-control studies of breast cancer. Both studies were approved by the Fred Hutchinson Cancer Research Center institutional review board, and written informed consent was obtained from all study participants. In both studies, cases were identified through the Cancer Surveillance System of western Washington State as women with incident invasive breast cancer who had no prior history of *in situ* or invasive breast cancer and were residents of King, Pierce, or Snohomish counties. Both studies have been described in detail elsewhere (28, 29). Briefly, cases were eligible for the earlier study if they were diagnosed with breast cancer between April 1, 1997, and May 31, 1999, were ages 65 to 79 y at diagnosis, and had a Health Care Financing Administration record (28). Potential controls without a prior breast cancer were identified through Health Care Financing Administration records and frequency-matched to cases on age. Enrolled in and completing the study interview were 80.6% (n = 975) of eligible cases and 73.6% (n = 1,007) of eligible controls. Cases were eligible for the more recently completed study if they were diagnosed with invasive breast cancer

between January 1, 2000, and March 31, 2004, and were ages 55 to 74 y at diagnosis (29). All incident lobular breast cancer cases and a 25% random sample of incident ductal cases were eligible. Women diagnosed with breast cancers that were neither ductal nor lobular were excluded. Controls were identified through random-digit dialing (30) and frequency-matched to cases on age. Enrolled in and completing the study interview were 83.5% (n = 1,044) of eligible cases and 71.1% (n = 469) of eligible controls. This analysis was restricted to ductal cases from both studies (n = 1,233) because the only other histologic type of breast cancer included in the more recent study was lobular carcinoma, and HER2-overexpressing and triple-negative tumors are very rarely lobular. Specifically, >92% of lobular carcinomas are ER+ (i.e., luminal; ref. 31). Thus, because the risk factors for lobular breast cancer differ from those for ductal disease (32) and lobular breast cancer cases were oversampled in the more recent of the two pooled studies, the inclusion of lobular cases in this analysis could have skewed subtype-specific associations. Histologic classifications were based on centralized reviews of pathology reports for all cases.

Both studies used nearly identical protocols and materials, and used very similar questionnaires that were administered in person. Both questionnaires included information on a wide range of breast cancer risk factors, including medical history, demographics, reproductive history, hormone use, lifestyle factors, and family history of cancer. Women were asked about exposures occurring before their reference date, defined as the date of diagnosis for cases; control reference dates were assigned based on the expected distribution of case reference dates. Both studies collected physical measurements for weight and height at the time of the interview, and self-reported measures for height, weight at reference year, maximum lifetime weight, and weight at age 30 years. Adult weight change was defined as the difference between self-reported weight in the reference year and self-reported weight at age 30 years. BMI in the reference year was estimated based on measured height and self-reported weight in the reference year. When measured height was not available, self-reported height was used (5% of cases, 4% of controls). Similarly, measured weight was used when self-reported weight was not provided (1% of cases, 1% of controls). A high level of agreement was observed between self-reported and measured anthropometric characteristics (r = 0.87 for height and r = 0.93 for weight) and between quartile categorizations of self-reported and measured body size (r = 0.81 for height, r = 0.89 for weight).

ER and PR data were identified from Cancer Surveillance System records, whereas HER2 expression status data were taken from centralized pathology testing at the Fred Hutchinson Cancer Research Center (completed for 411 ductal cases from the more recent study) and Cancer Surveillance System records (reviewed for all cases). If HER2 data were available from both sources and were discrepant, Cancer Surveillance System results were given primacy because such results were based on the original diagnostic testing that used complete specimens, whereas centralized testing at the Fred Hutchinson Cancer Research Center research laboratory used the tissue remaining after clinical workup. A total of 401 (33%) cases were missing data for at least one tumor

marker: 52 (4%) cases had missing ER status, 53 (4%) had missing PR status, and HER2 status could not be determined for 386 (31%) cases. All ER and PR results, and most HER2 results, were based on immunohisto-chemistry testing. However, Cancer Surveillance System records of fluorescence *in situ* hybridization (FISH) testing for HER2 were available for 32 cases. When available, FISH results were given precedence over immunohistochemistry results. Cases were classified as HER2 negative if their FISH test was negative or they had an immunohistochemistry score of 0, 1+, or 2+, and were classified as HER2 positive if their FISH test was positive or they had an immunohistochemistry score of 3+. Clinically, an immunohistochemistry score of 2+ is considered indeterminate and warrants a confirmatory FISH test. In the absence of FISH testing for cases with 2+ immunohistochemistry results for HER2 ($n = 80$), we classified 2+ results as HER2 negative because of data indicating that 80% of these tumors are HER2 negative when tested by FISH (33, 34). Because all ER+ cases were classified as luminal regardless of HER2 status (see below), we conducted sensitivity analyses that only excluded the five triple-negative cases that were ER−/PR− and had a 2+ HER2 status without a FISH result. Because our results did not change with this exclusion, and to be consistent with prior studies (4), all ER−/PR− cases with a HER2 immunohistochemistry result of 2+ without FISH confirmation were included as triple-negative cases in our final analyses.

Classification of tumor subtypes was based on ER, PR, and HER2 data as follows, consistent with the criteria used by Carey et al. (4): luminal (ER+), HER2 over-expressing (ER−/PR−/HER2+), and triple negative (ER−/PR−/HER2−). Previous studies have subclassi-fied luminal tumors as luminal A or luminal B; however, because these luminal subtypes are clinically similar and not well distinguished on the basis of only ER, PR, and HER2 status (4), all luminal tumors were grouped together in this analysis. Previous studies have also subclassified triple-negative tumors as basal-like or unclassified based on epidermal growth factor receptor and cytokeratin 5/6 expression (4, 11), but because epidermal growth factor receptor and cytokeratin 5/6 expression data were not available for the present analysis, we grouped together all triple-negative tumors; however, given that approximately 70% of triple-negative breast tumors are basal-like (5), the triple-negative phenotype has previously been used as an approximation of the basal-like subtype (12, 35).

Cases missing ER expression data ($n = 52$) and cases who were ER−/PR− but were missing HER2 data ($n = 32$) were excluded as we were unable to classify these cases as luminal, HER2 overexpressing, or triple negative. However, cases excluded due to insufficient tumor marker data did not significantly differ from other cases with respect to body size measurements, including BMI in the reference year (27.3 kg/m² versus 28.1 kg/m², respectively; $P = 0.29$), height (162.0 cm versus 161.3 cm; $P = 0.40$), and BMI at age 30 years (22.6 kg/m² versus 22.9 kg/m²; $P = 0.46$), or with regard to the prevalence of current HT use (46% versus 48%; $P = 0.75$). All cases that were ER−/PR+ were also excluded due to the rarity of this phenotype ($n = 9$). After excluding individuals with insufficient tumor marker data or incomplete anthropometric data, final

analyses were based on 1,447 controls and 1,124 cases (1,008 or 90% luminal, 39 or 3% HER2-overexpressing, and 77 or 7% triple-negative).

Polytomous logistic regression (36) was used to compare luminal, HER2-overexpressing, and triple-negative case groups with a common control group. Body size measures were analyzed both continuously and as categorical variables, with categories defined according to the quartile distribution in controls; BMI was also analyzed using categories based on the National Heart Blood and Lung Institute definitions for normal weight (BMI <25.0 kg/m²), overweight (BMI 25.0-29.9 kg/m²), and obese (BMI ≥30 kg/m²; ref. 37). Because HT use is an established effect modifier of the relationship between obesity and the risk of breast cancer among postmenopausal women (14, 15), we evaluated interactions between current use of HT (never use versus current use) and both BMI and weight in relation to breast cancer risk through the inclusion of interaction terms. All analyses were adjusted for age (continuous) and reference year (continuous); because there was no overlap in reference years between the two pooled studies, adjustment for reference year resulted in implicit adjustment for study population. The following breast cancer risk factors were evaluated as potential confounders with respect to the two largest case groups, luminal and triple-negative: education level (≤high school degree/post–high school/college graduate), age at menarche (≤11/12-13/≥14 y), age at menopause (<50/50-54/≥55 y), current HT use (no/estrogen only/ estrogen + progestin), family history of breast cancer in first-degree relatives (yes/no), parity (nulliparous/par-ous), age at first live birth (nulliparous/<25 y/≥25 y), smoking status (yes/no), and alcohol consumption (nondrinker/≤7 drinks per week/>7 drinks per week). Adjustment for these potential confounders did not alter our risk estimates by more than 10% for either tumor subtype. The exception to this was that the association between BMI and the risk of triple-negative disease among current HT users was altered by slightly greater than 10% with the adjustment for alcohol consumption, but this did not alter the risk of luminal disease. Therefore, none of these factors were included in the final analyses as confounders. Heterogeneity of effect estimates between case groups was examined through a series of polytomous regression models comparing HER2-overexpressing and triple-negative case groups with the luminal case group. All statistical analyses were done using STATA/SE version 8.2 (StataCorp).

Results

Relative to other cases and controls, women with triple-negative breast cancer were slightly younger and more likely to have never used HT (Table 1). Luminal cases were more likely to have a first-degree family history of breast cancer and to be current users of combined estrogen + progestin HT. HER2-overexpressing cases were less likely to be college graduates and to have had their first live birth before the age of 20 years.

Associations with BMI and weight at the reference date varied by tumor subtype (Table 2). Overall, we did not find BMI to be related to the risk of either lumi-nal, HER2-overexpressing, or triple-negative disease,

Table 1. Distributions of demographic characteristics and established breast cancer risk factors among controls and luminal, HER2-overexpressing, and triple-negative cases

	Controls (n = 1,447), n (%)	Cases		
		Luminal (ER+; n = 1,008), n (%)	HER2-overexpressing (ER−/PR−/HER2+; n = 39) n (%)	Triple-negative (ER−/PR−/HER2−; n = 77), n (%)
Age, y				
55-59	131 (9)	120 (12)	5 (13)	16 (21)
60-64	119 (8)	106 (11)	7 (18)	12 (16)
65-69	440 (30)	275 (27)	10 (26)	27 (35)
70-74	470 (32)	332 (33)	9 (23)	12 (16)
75-79	287 (20)	175 (17)	8 (21)	10 (13)
Mean	69.3	68.6	67.6	66.0
Race/ethnicity				
Non-Hispanic White	1,323 (91)	945 (94)	32 (82)	71 (92)
African American	42 (3)	16 (2)	2 (5)	3 (4)
Asian/Pacific Islander	38 (3)	29 (3)	3 (8)	1 (1)
Hispanic White	25 (2)	8 (1)	2 (5)	1 (1)
Other	19 (1)	10 (1)	0 (0)	1 (1)
Education				
High school or less	682 (47)	441 (44)	18 (46)	33 (43)
Some college	460 (32)	332 (33)	17 (44)	28 (36)
College graduate	304 (21)	235 (23)	4 (10)	16 (21)
First-degree family history of breast cancer				
No	1,131 (83)	727 (77)	33 (85)	61 (87)
Yes	226 (17)	219 (23)	6 (15)	9 (13)
Missing	90	38	0	7
Hormone therapy use				
Never use	539 (37)	340 (34)	10 (27)	32 (42)
Former use	247 (17)	165 (17)	11 (30)	13 (17)
Current use of unopposed estrogen	450 (31)	246 (25)	10 (27)	21 (27)
Current use of estrogen + progestin	207 (14)	246 (25)	6 (16)	11 (14)
Missing	4	11	2	0
Parity				
0	125 (9)	113 (11)	3 (8)	7 (9)
1	114 (8)	93 (9)	4 (10)	9 (12)
2	346 (24)	267 (26)	16 (41)	21 (27)
3	389 (27)	256 (25)	4 (10)	18 (23)
≥4	473 (33)	279 (28)	12 (31)	22 (29)
Age at first live birth, y				
<20	268 (20)	176 (20)	4 (11)	14 (20)
20-24	640 (49)	427 (48)	24 (67)	33 (47)
25-29	299 (23)	197 (22)	6 (17)	19 (27)
≥30	112 (8)	92 (10)	2 (6)	4 (6)

although there was a suggestion that women in the highest BMI quartile had an elevated risk of triple-negative disease compared with women in the lowest quartile [odds ratio (OR), 1.7; 95% confidence interval (95% CI), 0.9-3.3; P = 0.12]. However, stratification by HT use (nonusers versus current users) indicated an association between BMI and breast cancer risk for luminal and triple-negative subtypes confined to women who were not current HT users (OR comparing highest versus lowest quartiles, 1.7; 95% CI, 1.2-2.4; P < 0.01 for the luminal subtype; and OR, 2.7; 95% CI, 1.0-7.5; P = 0.05 for the triple-negative subtype). Effect modification by current HT use was also evident when BMI was analyzed as a categorical variable with categories defined by National Heart Blood and Lung Institute cutpoints for normal/overweight/obese. Among nonusers of HT, however, effect estimates for breast cancer risk in obese women relative to women of normal BMI were not statistically significant and were smaller in magnitude than those observed when comparing women in the highest versus lowest quartiles of BMI (OR, 1.3; 95% CI, 1.3-1.7; P = 0.10 for the luminal subtype; and OR, 1.7; 95%

CI, 0.8-3.6; P = 0.19 for the triple-negative subtype). Similar to observations with regard to BMI, among nonusers of HT, women in the highest weight quartile had a 5.1-fold (95% CI, 1.1-23.0; P = 0.03) increased risk of triple-negative breast cancer and a 1.7-fold (95% CI, 1.2-2.4; P < 0.01) increased risk of luminal breast cancer compared with those in the lowest quartile. With respect to triple-negative disease, however, there was no linear trend or dose-response of increasing risk with increasing weight or BMI; in fact, effect estimates comparing women in the second lowest quartile with women in the lowest quartile were similar or larger in magnitude than those comparing women in the highest versus lowest quartiles of weight or BMI. When analyzed as continuous terms, weight and BMI were positively associated with breast cancer risk only among nonusers of HT, and these associations were statistically significant only for luminal disease (OR, 1.01; 95% CI, 1.00-1.02; P <0.01; and OR, 1.03; 95% CI, 1.01-1.05; P <0.01, respectively), although ORs were similar but not statistically significant for both triple-negative and HER2-overexpressing case groups.

Table 2. Age-adjusted ORs for BMI and weight by tumor subtype and current HT use

	Controls	Luminal cases		HER2-overexpressing cases		Triple-negative cases	
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)
BMI, kg/m²							
Overall							
NHLBI category							
<25.0	560 (39)	365 (36)	1.0 (Reference)	15 (38)	1.0 (Reference)	24 (31)	1.0 (Reference)
25.0-29.9	484 (33)	346 (34)	1.1 (0.9-1.3)	11 (28)	0.8 (0.4-1.8)	26 (34)	1.2 (0.7-2.1)
≥30.0	403 (28)	297 (29)	1.1 (0.9-1.3)	13 (33)	1.1 (0.5-2.4)	27 (35)	1.4 (0.8-2.5)
Trend test			P = 0.33		P = 0.78		P = 0.26
Quartiles							
<23.4	365 (25)	211 (21)	1.0 (Reference)	10 (26)	1.0 (Reference)	14 (18)	1.0 (Reference)
23.4-26.5	358 (25)	274 (27)	1.3 (1.0-1.7) †	7 (18)	0.7 (0.3-1.9)	21 (27)	1.5 (0.7-3.0)
26.6-30.5	363 (25)	252 (25)	1.2 (0.9-1.5)	10 (26)	1.0 (0.4-2.4)	15 (19)	1.0 (0.5-2.2)
>30.5	361 (25)	271 (27)	1.3 (1.0-1.6)	12 (31)	1.1 (0.5-2.7)	27 (35)	1.7 (0.9-3.3)
Trend test			P = 0.13		P = 0.62		P = 0.21
Continuous (per kg/m²)			1.01 (1.00-1.03)		1.02 (0.97-1.08)		1.02 (0.97-1.08)
No current HT use							
NHLBI category							
<25.0	279 (36)	156 (30)	1.0 (Reference)	8 (35)	1.0 (Reference)	11 (24)	1.0 (Reference)
25.0-29.9	260 (33)	182 (35)	1.2 (0.9-1.6)	6 (26)	0.8 (0.3-2.3)	15 (33)	1.4 (0.6-3.1)
≥30.0	245 (31)	177 (34)	1.3 (1.0-1.7)	9 (39)	1.2 (0.4-3.1)	19 (42)	1.7 (0.8-3.6)
Trend test			P = 0.10		P = 0.73		P = 0.18
Quartiles							
<23.4	191 (24)	83 (16)	1.0 (Reference)	6 (26)	1.0 (Reference)	5 (11)	1.0 (Reference)
23.4-26.5	170 (22)	134 (26)	1.8 (1.3-2.5) †	3 (13)	0.5 (0.1-2.2)	13 (29)	2.8 (1.0-7.9)
26.6-30.5	202 (26)	131 (25)	1.5 (1.1-2.1) †	6 (26)	0.9 (0.3-2.9)	8 (18)	1.5 (0.5-4.6)
>30.5	221 (28)	167 (32)	1.7 (1.2-2.4) †	8 (35)	1.0 (0.3-3.1)	19 (42)	2.7 (1.0-7.5)
Trend test			P = 0.02		P = 0.74		P = 0.14
Continuous (per kg/m²)			1.03 (1.01-1.05) †		1.04 (0.98-1.11)		1.04 (0.99-1.08)
Current HT use							
NHLBI category							
<25.0	281 (42)	209 (42)	1.0 (Reference)	7 (44)	1.0 (Reference)	13 (41)	1.0 (Reference)
25.0-29.9	224 (34)	164 (33)	1.0 (0.7-1.3)	5 (31)	0.9 (0.3-2.8)	11 (34)	1.0 (0.4-2.2)
≥30.0	158 (24)	120 (24)	1.0 (0.7-1.4)	4 (25)	0.9 (0.3-3.2)	8 (25)	1.0 (0.4-2.4)
Trend test			P = 0.97		P = 0.88		P = 0.92
Quartiles							
<23.4	174 (26)	128 (26)	1.0 (Reference)	4 (25)	1.0 (Reference)	9 (28)	1.0 (Reference)
23.4-26.5	188 (28)	140 (28)	1.0 (0.7-1.4)	4 (25)	0.9 (0.2-3.7)	8 (25)	0.8 (0.3-2.2)
26.6-30.5	161 (24)	121 (25)	1.0 (0.7-1.4)	4 (25)	1.0 (0.2-4.2)	7 (22)	0.8 (0.3-2.2)
>30.5	140 (21)	104 (21)	1.0 (0.7-1.4)	4 (25)	1.1 (0.3-4.7)	8 (25)	1.0 (0.4-2.6)
Trend test			P = 0.96		P = 0.82		P = 0.94
Continuous (per kg/m²)			1.00 (0.98-1.02)		0.98 (0.89-1.07)		1.00 (0.93-1.06)
Weight, lb							
Overall							
Quartiles							
<121	366 (25)	200 (20)	1.0 (Reference)	8 (21)	1.0 (Reference)	9 (13)	1.0 (Reference)
121-139	380 (26)	285 (28)	1.3 (1.1-1.7) †	11 (28)	1.3 (0.5-3.2)	26 (33)	2.5 (1.2-5.4) †
140-162	346 (24)	250 (25)	1.3 (1.0-1.6)	7 (18)	0.9 (0.3-2.4)	19 (24)	1.9 (0.9-4.4)
>162	355 (25)	273 (27)	1.3 (1.1-1.7) †	13 (33)	1.5 (0.6-3.7)	23 (31)	2.1 (1.0-4.7)
Trend test			P = 0.04		P = 0.50		P = 0.20
Continuous (per lb)			1.01 (1.00-1.01) †		1.01 (0.99-1.03)		1.01 (1.00-1.02)
No current HT use							
Quartiles							
<121	188 (24)	82 (16)	1.0 (Reference)	5 (22)	1.0 (Reference)	2 (4)	1.0 (Reference)
121-139	205 (26)	134 (26)	1.5 (1.1-2.1) †	7 (30)	1.2 (0.4-4.0)	17 (38)	7.2 (1.6-31.6) †
140-162	176 (22)	133 (26)	1.7 (1.2-2.4) †	2 (9)	0.4 (0.1-2.1)	11 (24)	5.1 (1.1-23.7) †
>162	215 (27)	166 (32)	1.7 (1.2-2.4) †	9 (39)	1.4 (0.4-4.3)	15 (33)	5.1 (1.1-23.0) †
Trend test			P < 0.01		P = 0.79		P = 0.18
Continuous (per lb)			1.01 (1.01-1.02) †		1.01 (0.98-1.03)		1.01 (0.99-1.03)
Current HT use							
Quartiles							
<121	178 (27)	118 (24)	1.0 (Reference)	3 (19)	1.0 (Reference)	7 (22)	1.0 (Reference)
121-139	175 (26)	151 (31)	1.2 (0.9-1.7)	4 (25)	1.2 (0.3-5.6)	9 (28)	1.1 (0.4-3.2)
140-162	170 (26)	117 (24)	1.0 (0.7-1.4)	5 (31)	1.5 (0.4-6.6)	8 (25)	1.0 (0.3-2.8)
>162	140 (21)	107 (22)	1.1 (0.8-1.5)	4 (25)	1.5 (0.4-6.7)	8 (25)	1.2 (0.4-3.3)
Trend test			P = 0.97		P = 0.54		P = 0.87
Continuous (per lb)			1.00 (0.99-1.01)		1.00 (0.97-1.04)		1.01 (0.98-1.03)

Abbreviation: NHLBI, National Heart Blood and Lung Institute.
*OR adjusted for age and reference year.
†P < 0.05.

Table 3. Age-adjusted ORs for quartiles of other anthropometric characteristics by tumor subtype

	Controls	Luminal cases		HER2-overexpressing cases		Triple-negative cases	
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)
Height, cm							
Quartiles							
<157	362 (25)	222 (22)	1.0 (Reference)	11 (28)	1.0 (Reference)	13 (17)	1.0 (Reference)
157-160	362 (25)	227 (23)	1.0 (0.8-1.3)	10 (26)	0.9 (0.4-2.1)	15 (19)	1.1 (0.5-2.3)
161-165	395 (27)	301 (30)	1.2 (1.0-1.5)	11 (28)	0.9 (0.4-2.0)	26 (34)	1.6 (0.8-3.3)
>165	328 (23)	258 (26)	1.2 (1.0-1.5)	7 (18)	0.6 (0.2-1.6)	23 (30)	1.5 (0.7-3.1)
Trend test			$P = 0.05$		$P = 0.34$		$P = 0.13$
Continuous (per cm)			1.01 (1.00-1.02)		1.00 (0.95-1.05)		1.02 (0.98-1.05)
Lifetime maximum BMI, kg/m^2							
Quartiles							
<25.0	362 (25)	235 (23)	1.0 (Reference)	12 (31)	1.0 (Reference)	15 (19)	1.0 (Reference)
25.0-27.9	361 (25)	241 (24)	1.0 (0.8-1.3)	7 (18)	0.6 (0.2-1.5)	17 (22)	1.1 (0.5-2.3)
28.0-32.3	363 (25)	261 (26)	1.1 (0.9-1.4)	7 (18)	0.6 (0.2-1.5)	21 (27)	1.4 (0.7-2.8)
>32.3	361 (25)	271 (27)	1.1 (0.9-1.4)	13 (33)	1.0 (0.5-2.3)	24 (31)	1.5 (0.7-2.8)
Trend test			$P = 0.22$		$P = 0.91$		$P = 0.21$
Continuous (per kg/m^2)			1.01 (1.00-1.02)		1.00 (0.95-1.05)		1.03 (1.00-1.06)
Lifetime maximum weight, lb							
Quartiles							
≤140	369 (26)	224 (22)	1.0 (Reference)	13 (33)	1.0 (Reference)	11 (14)	1.0 (Reference)
141-160	380 (26)	277 (27)	1.2 (0.9-1.5)	7 (18)	0.5 (0.2-1.3)	18 (23)	1.5 (0.7-3.2)
161-185	349 (24)	245 (24)	1.1 (0.9-1.4)	9 (23)	0.7 (0.3-1.7)	24 (31)	2.2 (1.0-4.5) [†]
>185	349 (24)	262 (26)	1.2 (0.9-1.5)	10 (26)	0.7 (0.3-1.7)	24 (31)	1.9 (0.9-4.0)
Trend test			$P = 0.23$		$P = 0.60$		$P = 0.05$
Continuous (per lb)			1.00 (1.00-1.01) [†]		1.00 (0.99-1.01)		1.01 (1.00-1.01) [†]
Weight at age 30 y, lb							
Quartiles							
<120	389 (27)	263 (26)	1.0 (Reference)	15 (38)	1.0 (Reference)	20 (26)	1.0 (Reference)
120-128	367 (25)	215 (21)	0.9 (0.7-1.1)	8 (21)	0.6 (0.2-1.4)	12 (16)	0.7 (0.3-1.5)
129-140	323 (22)	270 (27)	1.2 (1.0-1.5)	6 (15)	0.5 (0.2-1.2)	16 (21)	0.9 (0.5-1.8)
>140	368 (25)	260 (26)	1.1 (0.8-1.3)	10 (26)	0.7 (0.3-1.6)	29 (38)	1.5 (0.8-2.7)
Trend test			$P = 0.22$		$P = 0.31$		$P = 0.11$
Continuous (per lb)			1.00 (0.99-1.01)		0.99 (0.96-1.03)		1.01 (1.00-1.03)
BMI at age 30 y, kg/m^2							
Quartiles							
<20.8	362 (25)	258 (26)	1.0 (Reference)	11 (28)	1.0 (Reference)	21 (27)	1.0 (Reference)
20.8-22.3	361 (25)	233 (23)	0.9 (0.7-1.2)	9 (23)	0.8 (0.3-2.0)	18 (23)	0.9 (0.5-1.7)
22.4-24.3	362 (25)	279 (28)	1.1 (0.9-1.4)	6 (15)	0.6 (0.2-1.6)	11 (14)	0.6 (0.3-1.2)
>24.3	362 (25)	238 (24)	0.9 (0.8-1.2)	13 (33)	1.2 (0.5-2.8)	27 (35)	1.4 (0.8-2.5)
Trend test			$P = 0.91$		$P = 0.74$		$P = 0.41$
Continuous (per kg/m^2)			1.00 (0.97-1.02)		0.99 (0.90-1.08)		1.03 (0.98-1.09)
Weight change (age 30 y vs reference, lb)							
Overall							
Weight loss	201 (14)	71 (7)	0.5 (0.3-0.6) [†]	3 (8)	0.5 (0.1-1.8)	9 (12)	1.1 (0.5-2.4)
Weight gain (tertiles)							
<18	407 (28)	320 (32)	1.0 (Reference)	13 (33)	1.0 (Reference)	20 (26)	1.0 (Reference)
18-37	416 (29)	289 (29)	0.9 (0.7-1.1)	10 (26)	0.7 (0.3-1.7)	25 (32)	1.1 (0.6-2.0)
>37	423 (29)	328 (33)	1.0 (0.8-1.2)	13 (33)	0.9 (0.4-2.0)	23 (30)	1.0 (0.5-1.8)
Continuous (per lb)			1.00 (1.00-1.01) [†]		1.01 (0.99-1.02)		1.00 (0.99-1.01)

*OR adjusted for age and reference year.
[†]$P < 0.05$.

Although not statistically significant, women in the highest lifetime weight quartile, women in the highest weight at age 30 years quartile, and women in the tallest height quartile had 1.9-fold, 1.5-fold, and 1.5-fold elevated risks of triple-negative tumors, compared with 1.2-fold, 1.1-fold, and 1.2-fold elevated risks of luminal tumors, respectively (Table 3). All of these estimates, however, were within the limits of chance. Women who self-reported a lower weight in the reference year than at age 30 years had a significantly reduced risk of luminal breast cancer relative to women in the lowest tertile of weight gain (OR, 0.5; 95% CI, 0.3-0.6) and a similarly reduced (but not statistically significant) risk of HER2-overexpressing disease (OR, 0.5; 95% CI, 0.1-1.8); this measure was not, however, associated with the risk of triple-negative breast cancer. When analyzed as continuous terms, lifetime maximum weight was positively associated with the risk of luminal and triple-negative tumors (OR, 1.00; 95% CI, 1.00-1.01; $P = 0.02$; and OR, 1.01; 95% CI, 1.00-1.01; $P = 0.04$, respectively) and adult weight change was positively associated with the risk of luminal tumors (OR, 1.01; 95% CI, 1.00-1.01; $P < 0.01$). BMI at age 30 years and lifetime maximum BMI were not associated with the risk of any disease subtype. None of the factors assessed were strongly related to the risk of HER2-overexpressing tumors, although these analyses were limited by the inclusion of only 39 HER2-overexpressing cases.

Discussion

It is important to acknowledge the limitations of this study before interpreting our results. We had to exclude 84 (7%) eligible cases because they were missing sufficient tumor marker data to be categorized into a molecular subtype. However, cases that could not be classified did not differ markedly from other cases with respect to height, weight, or BMI at the reference year. We therefore assume that the exclusion of cases with insufficient tumor marker data did not differentially bias the study findings. Another limitation was the lack of information on other tumor markers that would have enabled us to more precisely classify case groups. Specifically, without data on epidermal growth factor receptor or cytokeratin 5/6 expression, we were unable to distinguish between basal-like and unclassified tumors within our triple-negative case group (3). Although this distinction seems to be significant with respect to overall survival and therapeutic response (4, 38), findings from the Polish Breast Cancer Study (11) and the Carolina Breast Cancer Study (27) do not indicate substantial differences in the epidemiologies of basal-like triple-negative and unclassified triple-negative tumors; thus, we anticipate that the distinction between basal-like and unclassified tumors may be more important in clinical settings than in the context of epidemiologic studies. Misclassification of case subtypes may also result from the use of tumor marker data from multiple laboratories in the Seattle-Puget Sound region, given that assays and practices for interpreting results vary across institutions.

Although a certain degree of misclassification of tumor subtype is present due to these differences, it is reasonable to assume that this misclassification is non-differential with respect to anthropometric factors and would have biased our risk estimates toward the null. Last, this analysis included limited numbers of triple-negative and HER2-overexpressing cases; as such, some categories of the anthropometric characteristics contained very few cases and resulting effect estimates need to be interpreted with caution. The observed small numbers for triple-negative and HER2-overexpressing cases reflect the rarity of these tumor types relative to luminal breast cancers overall and the fact that we had to exclude a number of nonluminal cases due to missing HER2 data ($n = 32$). Additionally, the distribution of these subtypes is reflective of the demographic characteristics of our study population. Specifically, existing data suggest that nonluminal breast cancers, particularly triple-negative cancers, are associated with African American and Hispanic White race/ethnicity and early age at diagnosis (12, 27, 39). Thus, the fact that the studies pooled for this analysis involved populations that were predominantly non-Hispanic White (92%) and exclusively postmenopausal likely contributed to the observed low prevalence of the triple-negative and HER2-overexpressing phenotypes. Given that only 4% and 2% of cases eligible for the earlier and more recently completed studies, respectively, died before an interview could be conducted, we assume that survivor bias did not appreciably influence the distribution of case subtypes, although nonluminal breast cancers are associated with a less favorable prognosis than luminal disease (2, 4, 8-10).

Limitations to this study may also exist with regard to the ascertainment and classification of exposures. In particular, misclassification of exposure categories might have occurred if women were unable to accurately recall or report their weight in the reference year or at age 30 years. Although we measured the weight of cases and controls at the time of the interview, self-reported weight data were given primacy over actual measurements due to the fact that interviews were conducted up to 3 years after breast cancer diagnosis, and cancer treatments could have contributed to weight changes during that intervening period. Additionally, our analyses could be biased if women who participated in these studies differed from those who did not participate with regard to body size.

Our results suggest that there may be heterogeneity in the associations between anthropometric measures and postmenopausal breast cancer risk by tumor subtype, although differences between subtypes were not statistically significant. Consistent with prior studies that assessed the association between BMI and breast cancer risk by joint ER/PR status (21, 22, 40-44), we observed that BMI was positively associated with the risk of luminal (i.e., ER+) breast cancer among postmenopausal women not using HT. This association is likely largely attributable to the positive relationship between BMI and endogenous estrogen levels because adipose tissue is the primary source of estrogen in postmenopausal women. However, we found that among nonusers of HT, postmenopausal BMI and weight may also be related to the risk of triple-negative breast cancer. Due to the small numbers of triple-negative cases in the lowest weight and BMI quartiles, and given the lack of a clear dose-response or linear trend in effect estimates with increasing weight or BMI, we cannot rule out the possibilities that these may be chance findings or may reflect particularly low risks among persons with a low weight or BMI, rather than reflecting an elevated risk among persons with a high weight or BMI.

Only two prior population-based studies, the Polish Breast Cancer Study (11) and the Carolina Breast Cancer Study (27), have assessed differences in breast cancer risk factors among nonluminal breast cancer subtypes. Similar to our study, these analyses were based on large overall case populations ($n = 804$ for the Polish Breast Cancer Study and $n = 1,424$ for the Carolina Breast Cancer Study), but included limited numbers of post-menopausal nonluminal cases ($n = 99$ and $n = 172$ postmenopausal triple-negative cases, respectively, and $n = 47$ and $n = 70$ postmenopausal HER2-overexpressing cases). Neither study observed an association between BMI and the risk of basal-like or unclassified triple-negative breast cancer among postmenopausal women, but neither study presented estimates stratified by HT use. To our knowledge, there are no previously published data on the relationship between height, weight, or weight gain and the risk of triple-negative or HER2-overexpressing tumors. The Carolina Breast Cancer Study did, however, identify a significant positive association between waist-hip ratio and the risk of postmenopausal basal-like breast cancer (OR for highest versus lowest tertile, 2.7; 95% CI, 1.3-5.4). Given that most postmenopausal weight gain is central weight gain (45), our finding of no association between adult weight gain and the risk of triple-negative breast cancer is not entirely consistent with the finding of the Carolina Breast Cancer Study with respect to waist-hip ratio; however,

this might be attributable to small numbers in both studies or to differences in the distribution of race/ethnicity between studies contributing to differences in adiposity patterns.

The observed associations between BMI and weight and the risk of triple-negative breast cancer among nonusers of HT are somewhat unexpected given the predominating theory that the effects of anthropometric factors on postmenopausal breast cancer risk are mediated through hormonal pathways. The possibility that hormonal mechanisms may underlie the etiology or promotion of triple-negative breast tumors is consistent with the findings of two recent studies. The Breast and Prostate Cancer Cohort Consortium recently reported that two haplotypes of the 17β-hydroxysteroid dehydrogenase 1 gene (*17HSD1*), which catalyses the final step of the conversion of estrone to estradiol, were associated with risk of ER− but not ER+ breast tumors (46). Additionally, Gupta et al. used a xenograft mouse-model to show that ER− tumors required circulating estrogens for their formation; this study suggested that estrogens may affect the growth of ER− tumors by enhancing angiogenesis and stromal cell recruitment to promote tumor growth (47).

Nonhormonal mechanisms underlying the association between postmenopausal breast cancer and anthropometric factors have not been well elucidated, although it has been suggested that obesity may be associated with insulin resistance and increased concentrations of insulin, which may have a mitogenic effect on breast tumors (24, 26). Observed associations between anthropometric factors and breast cancer may also be reflective of the increased levels of leptin (48) and markers of inflammation associated with obesity, such as tumor necrosis factor-α and interleukin-6 (49). Specifically, elevated leptin levels in obese women may increase breast cancer risk through angiogenic effects (48) whereas obesity-associated chronic inflammation may increase risk through the activation of redox-sensitive transcription factors such as nuclear factor-κB (50).

It is also important to note that grouping cases according to joint ER/PR/HER2 status assumes that the combination of these markers is of greater relevance with respect to anthropometric risk factors than each marker independently. However, at least one prior study has suggested that HER2 status may be inversely associated with BMI independent of ER status (51). Overall, we found no difference in associations with height, weight, or BMI by HER2 status, although comparison of BMI and of weight among nonusers of HT revealed slightly, but not significantly, stronger effect estimates with respect to HER2− breast cancer than with respect to HER2+ breast cancer (OR comparing highest versus lowest quartiles of BMI, 1.8; 95% CI, 1.2-2.6 and OR, 0.9; 95% CI, 0.5-1.8, respectively; *P* for heterogeneity = 0.09; OR comparing highest versus lowest quartiles of weight, 1.8; 95% CI, 1.2-2.6 and OR, 1.0; 95% CI, 0.5-2.1, respectively; *P* for heterogeneity = 0.17). Given that approximately 89% of luminal cases with known HER2 expression status were HER2−, the fact that we observed similar effect estimates with respect to luminal and triple-negative but not the HER2-overexpressing case groups is consistent with a role of HER2 independent of ER. Additional studies with sufficient numbers of HER2+

and HER2− tumors would help clarify the association between HER2 expression status and BMI.

Although clinical differences between breast tumor subtypes defined by ER, PR, and HER2 expression status are increasingly well documented, the differences in etiologic pathways leading to these distinct subtypes are not well defined. Our results suggest that, similar to previously observed associations with respect to ER+ breast cancer, body size may also be associated with a woman's risk for developing postmenopausal triple-negative breast cancer, either through an elevated risk in women with a high weight or through a reduced risk in women with a low weight. Given the ongoing obesity epidemic in the United States, the continued decline in menopausal hormone use, and the relatively poor prognosis of triple-negative breast cancers, these findings require confirmation in other studies. In particular, studies that include larger numbers of African Americans and Hispanics are needed given that the triple-negative phenotype is more common among these women compared with non-Hispanic Whites (12, 27).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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Body Size and Risk of Luminal, HER2-Overexpressing, and Triple-Negative Breast Cancer in Postmenopausal Women

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