Adiposity throughout Adulthood and Risk of Young-Onset Breast Cancer Tumor Subtypes in the Young Women's Health History Study

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ABSTRACT

Background: The role of adult adiposity in young-onset breast cancer (YOBC) subtype risk is not well understood.

Methods: In this population-based case (n = 1812)–control (n = 1,381) study of invasive YOBC (ages <50 years), cases were identified from the Los Angeles County and Metropolitan Detroit Surveillance, Epidemiology, and End Results registries, 2010 to 2015. Area-based, frequency-matched controls were sampled from the 2010 Census. General adiposity [body mass index (BMI)] and central adiposity (waist circumference and waist-to-height ratio) across adulthood and covariates were collected from in-person interviews and measurements. ORs and 95% confidence intervals (CI) for adiposity and YOBC tumor subtypes [i.e., luminal A, luminal B, HER2$^+$, and triple negative (TN)] were calculated, overall and by parity, using multivariable weighted logistic regression.

Results: Obese young adult BMI was inversely associated with luminal A YOBC (OR = 0.35, 95% CI, 0.16–0.79); other subtype associations were nonsignificant. Similarly, adult overweight and obese BMIs were inversely associated with luminal A (OR = 0.66, 95% CI, 0.48–0.91 and OR = 0.59, 95% CI, 0.46–0.87, respectively), but not other subtypes. Conversely, larger waist circumference was associated with higher odds of luminal B and TN YOBC (OR = 1.48, 95% CI, 1.01–2.15 and OR = 2.48, 95% CI, 1.52–3.88, respectively), but not other subtypes (with similar results for weight-to-height ratio); highest odds were among parous women.

Conclusions: Findings show greater general adult adiposity is associated with reduced odds of luminal A YOBC, whereas greater central adiposity is associated with increased odds of luminal B and TN YOBC, particularly among parous women.

Impact: Additional studies of central adiposity and YOBC subtype risk, especially incorporating pregnancy history, are warranted.

Introduction

Breast cancer is the most diagnosed cancer and the leading cause of cancer death among young (<50 years of age) non-Hispanic Black (NHB) and White (NHW) women in the United States, and the incidence of young-onset breast cancer (YOBC) has increased in recent years (1, 2). YOBC is more likely to be diagnosed at a later stage and to comprise subtypes with fewer effective treatment options than tumors diagnosed at later ages (3). YOBC is also etiologically distinct from later-onset breast cancer (4). This is notably illustrated by the observation that adult adiposity as measured by higher body mass index (BMI) is consistently associated with increased risk of postmenopausal breast cancer but is consistently associated with decreased risk of premenopausal breast cancer (5). Explanations for the differing effects of adiposity on pre- and postmenopausal breast cancer risk remain elusive (4, 6).

Furthermore, associations between adult adiposity and YOBC risk seem to vary by both tumor subtype and type of fat deposition (general vs. central; refs. 7–9). The observed inverse association between greater general adiposity (measured by BMI) and YOBC is hypothesized to be driven by the high prevalence of hormone receptor–positive [HR-positive, i.e., estrogen receptor (ER) and progesterone receptor (PR)] tumors (9–12). General adiposity is often not associated with risk of HR-negative YOBC (9, 10, 13–16). In contrast, evidence suggests that central adiposity [e.g., waist circumference (WC) and waist-to-height ratio (WHtR)] may be associated with increased risk for YOBC overall (8, 17) and HR-negative tumors, but not HR-positive tumors (8, 18), although associations between YOBC subtypes and adiposity are not well studied (6, 8). Moreover, many previous studies of adiposity and YOBC subtype lack information on HER2 status and tumor grade, which improve definition of tumor subtypes (19–21). Additionally, parity is hypothesized to modify breast tissue (22–24) and thus may modify associations between adiposity throughout adulthood and

[1]Epidemiology Program, Joseph J. Zilber College of Public Health, University of Wisconsin, Milwaukee, Wisconsin. [2]Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing, Michigan. [3]Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, California. [4]Center for the Study of Curriculum, College of Education, Michigan State University, East Lansing, Michigan. [5]Diabetes Institute, Heritage College of Osteopathic Medicine, Ohio University, Athens, Ohio. [6]Department of Mathematical Sciences, Montana State University, Bozeman, Montana. [7]Department of Physiology, College of Human Medicine, Michigan State University, Lansing, Michigan. [8]Department of Pharmacology, Physiology, and Cancer Biology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania. [9]Department of Oncology, School of Medicine, Wayne State University, Detroit, Michigan. [10]Department of Medicine and Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin.

Corresponding Author: Ellen M. Velie, Joseph J. Zilber College of Public Health, University of Wisconsin–Milwaukee, Milwaukee, WI 53205. E-mail: velie@uwm.edu

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YOBC risk, but few studies have evaluated potential differential effects of parity on adiposity and YOBC risk (15). Thus, further research is required to understand the role of general and central adiposity throughout adulthood on breast cancer subtype risk, particularly in young women, as well as to evaluate potential heterogeneity in associations by other factors that affect tumor microenvironment, e.g., parity (24–26).

Considering the dramatic increases in overweight and obesity in recent decades (27, 28), an increase in nulliparity (29), and an increase in YOBC incidence (3), understanding associations between adiposity and YOBC risk is critically important and may both illuminate elusive underlying biologic mechanisms and inform targeted prevention efforts. Thus, we examined associations between general and central adiposity throughout adulthood and YOBC overall and by tumor subtypes and assessed whether these associations were modified by parity (30).

Materials and Methods

Study population

Data are from the Young Women's Health History Study (YWHHS), described in detail elsewhere (31). Briefly, YWHHS is a population-based case–control study among NHB and NHW women residing in the Los Angeles (LA) County and Metropolitan (Metro) Detroit (Oakland, Wayne, and Macomb counties) Surveillance, Epidemiology, and End Results (SEER) registry areas. Eligibility criteria included that participants were 20 to 49 years of age at the "reference date" [i.e., for cases, SEER histologic date of diagnosis; for controls, 4 months before screening interview (31)], were US-born, and self-identified as NHB or NHW women. Cases were diagnosed with invasive breast cancer between 2010 and 2015 (N = 1,812; n = 682 NHB, n = 1,130 NHW). Controls were identified via three-stage area-based probability sampling from the 2010 US Census. More than 24,000 potentially eligible households were screened to identify a random sample of eligible participants frequency-matched to cases on site (Detroit/LA), five-year age intervals, and race/ethnicity (N = 1,381; n = 665 NHB, n = 716 NHW). Sample weights were incorporated in all analyses to reflect probability of selection, to weight participants to the Metro Detroit and LA County study populations (31), and to address nonresponse. Response rates, calculated in accordance with American Association for Public Opinion guidelines (32), were 60% for cases and 53% for controls. Nonresponse weights incorporated information from demographic data available from 86% of sampled controls and 100% of sampled cases (31). YWHHS participant sociodemographic characteristics have previously been described (31).

The YWHHS protocol was approved by the Institutional Review Boards at University of Wisconsin—Milwaukee (UWM), Milwaukee, WI (Medical College of Wisconsin deferred to UWM); Michigan State University, East Lansing, MI; Wayne State University, Detroit, MI; Michigan Department of Community Health, MI; University of Southern California Health Sciences, Los Angeles, CA; California Committee for the Protection of Human Subjects, CA; and California Cancer Registry. All study participants provided written informed consent.

Outcome assessment

Histopathologic diagnosis of invasive breast tumor status, tumor grade, and expression of ER, PR, and HER2 was collected by SEER registries and provided to YWHHS (33).

Tumor subtypes

Tumor subtypes were classified as luminal A (ER-positive and/or PR-positive and HER2-negative and grade 1 or 2); luminal B (either ER-positive and/or PR-positive and HER2-positive or ER-positive and/or PR-positive and HER2-negative with grade 3); triple negative (TNBC; ER-negative, PR-negative, and HER2-negative); or HER2-type (ER-negative, PR-negative, and HER2-positive). Participants missing tumor pathology information for receptor status (n = 63) and/or tumor grade (n = 71) were removed from subtype analyses (n = 130 total) but included in analyses of YOBC overall. Participants missing tumor subtype were more likely to be from LA than Metro Detroit (57.5% vs. 42.5% of missing, respectively) but did not vary by other sociodemographic characteristics or measures of adiposity.

Exposure and covariate assessment

Recalled lifetime adiposity and covariates were ascertained via an in-person computer-assisted interview with life history calendars to facilitate recall (34); current body size was measured by trained interviewers. Measures of *general adiposity* throughout adulthood include BMI at 18, 25, and 35 years of age and 12 months before reference date (from recalled weights) and percent body fat (%BF) measured at interview; measures of adult *central adiposity* include measured WC (measured on bare skin between the lowest rib and iliac crest) and WHtR (from measured WC and measured height). Weight and %BF were measured using a Tanita SC-240 scale (35), with a 440 pound maximum; participants reporting weighing >400 pounds were assigned their self-reported weight (n = 4). Height was measured using a portable stadiometer. Height, weight, and WC measurements were taken twice. If differences in measurements were >1%, a third was taken, and the closest two measures were averaged.

General adiposity

BMI values at 18 years of age (hereafter, "young adult BMI") and 12 months before reference date (hereafter, "adult BMI") were calculated using recalled weights and height measured at interview and categorized as <18.5 kg/m^2 (underweight), 18.5 to <25 kg/m^2 (normal weight), 25 to <30 kg/m^2 (overweight), and ≥30 kg/m^2 (obese; ref. 36). If measured height was unavailable (n = 157), recalled adult height was used; measured height and recalled height at interview are highly correlated (case r = 0.95, control r = 0.94; data not shown). Adult BMI was calculated using "corrected" recalled weight, created by applying the ratio of self-reported to measured weight at interview (self-reported vs. measured weight correlation r = 0.98 for cases and r = 0.96 for controls); if measured or recalled weight at interview was unavailable (n = 105), uncorrected recalled weight 12 months before reference date was used.

Additional measures of general adiposity throughout adulthood include recalled weights at 25 and 35 years of age (used to calculate BMI) and %BF measured at interview. BMI at 25 and 35 years of age was available for participants who were diagnosed with breast cancer after each age (n = 1,797 and n = 1,604, respectively) and their frequency-matched controls (n = 1,279 and n = 904, respectively). %BF was calculated from measured fat mass divided by overall body weight and categorized according to the American College of Sports Medicine categories for women by 10-year age group (lower, high, highest; ref. 37). Associations between these additional measures and YOBC odds were evaluated in supplemental analyses.

Central adiposity

WC was categorized as <80 (hereafter, "smaller WC"), 80 to <88 ("larger WC"), or ≥88 cm ("largest WC"), based on World Health Organization thresholds (38). WHtR was calculated by dividing WC by measured or recalled height. WHtR was categorized as <0.49 (hereafter, "smaller WHtR"), 0.49 to <0.59 ("larger WHtR"), and ≥0.59 ("largest WHtR") based on tertiles from the control distribution; 0.59 is also the clinical threshold used to define visceral obesity in women ages 20 to 59 years (39, 40).

Covariates

Potential confounders assessed include family history of breast cancer (yes/no/do not know), alcohol use (ever/never, cumulative lifetime average alcohol use), parous (ever/never), age at first full-term pregnancy (AFFTP, continuous and centered at mean AFFTP 25.42 years for parous women; nulliparous participants were assigned a value of 0), number of full-term births (i.e., parity; continuous), lifetime duration of breastfeeding (nulliparous/parous, never breastfed/parous, breastfed <6 months/parous, breastfed ≥6 months), lifetime duration of smoking (never smoker/<5/5–19/≥20 pack-years), oral contraceptive use (ever/never), age at menarche, and adult height.

Missingness

Participants missing anthropometric exposures of interest were excluded from those analyses (young adult BMI $n = 110$, adult BMI $n = 81$, WC $n = 165$, WHtR $n = 167$). Missing data ranged from 1.9% of the sample for adult BMI to 5.0% for WHtR. For participants missing covariate information, those who did not know or were missing information on first-degree family history of breast cancer ($n = 156$) were categorized as "do not know" and retained in analyses. For all other covariates, missing data were imputed; for age at menarche ($n = 76$) and smoking history ($n = 24$), values were imputed using the median value for site, case/control status, household percent poverty [HPP; from recalled total income in the 12 months before reference date and number of adults and children supported by it, compared with the federal poverty level (31)], race/ethnicity, and joint parity/age at first full-term pregnancy, and for cumulative lifetime alcohol consumption ($n = 20$) values were imputed using the median value for case/control status, HPP, race/ethnicity, and smoking status.

Statistical analyses

We conducted descriptive analyses to summarize the weighted distribution of covariates among women without breast cancer by measures of general and central adiposity. We then used multivariable weighted logistic regression to calculate OR and 95% confidence intervals (CI) estimating associations between adult adiposity and risk of YOBC overall and by subtype. We considered BMI, WC, and WHtR as continuous variables to evaluate linear trends with the Wald test. All models were adjusted for study site (Detroit/LA) and age at reference date; additional potential confounders (described above) were evaluated separately for each YOBC subtype and exposure of interest using postselection inference ($\alpha \leq 0.15$; ref. 41). Age at menarche and at reference date were evaluated for linear or quadratic fit and determined to best fit as quadratic distributions. AFFTP and parity were modeled to accommodate structural zeros for nulliparous women [see **Table 2** (footnote a); ref. 42]. All covariates were significant and included in all models. Models of WC and WHtR were additionally adjusted for BMI at interview as a linear term (18). We assessed heterogeneity in odds by tumor subtype using multinomial logistic regression, adjusting for all covariates.

We additionally evaluated whether associations between adult adiposity and YOBC odds were modified by parity (ever/never)—or attained age (<40 years vs. ≥40 years), given the 30-year age range in our sample—by calculating Wald tests of interaction terms and by conducting stratified analyses. We did not adjust for multiple comparisons; our analyses were guided by *a priori* determined hypotheses based on the underlying biology and previous literature.

In supplemental analyses, we evaluated effect modification by HPP (<250% vs. ≥250%) and by race/ethnicity (NHB vs. NHW), associations between additional measures of general adiposity and YOBC risk, and associations among premenopausal women (87.4% of participants).

All analyses were conducted in SAS 9.4 (SAS Institute, Inc.)

Data availability

Data are available from the corresponding author upon reasonable request and contingent upon approval by appropriate institutional review boards.

Results

Younger participants were more likely to have obesity in young adulthood (e.g., 11.3% of those ages 20–29 vs. 4.3% of those ages 40–49 years) and less likely to have larger central adiposity (e.g., 33.3 vs. 53.7% with WC ≥88 cm; **Table 1**). The frequency of general and central adiposity was higher among NHB women and those with HPP <250% (i.e., poorer). Additionally, parous participants, and especially those who had their first child before 25 years of age, had a higher frequency of visceral obesity (e.g., 57.0% of women with AFFTP <25 years/1–2 children vs. 34.6% of nulliparous women with WC ≥88 cm).

Obesity in young adulthood and adulthood was inversely associated with YOBC overall (OR = 0.53; 95% CI, 0.33–0.86 and OR = 0.71; 95% CI, 0.54–0.92, respectively) and luminal A YOBC (OR = 0.35; 95% CI, 0.16–0.79 and OR = 0.59; 95% CI, 0.46–0.87, respectively) but was not significantly associated with other subtypes (**Table 2**). Overweight adult BMI was also associated with lower odds of luminal A YOBC (OR = 0.66; 95% CI, 0.48–0.91). Additionally, underweight adult BMI was inversely associated with YOBC overall (OR = 0.47; 95% CI, 0.25–0.87) and luminal A YOBC (OR = 0.18, 95% CI, 0.06–0.50). An inverse linear trend between adult BMI and luminal A odds was also evident ($P_{trend} = 0.02$), although few women diagnosed with luminal A YOBC had an underweight adult BMI. We did not observe significant heterogeneity of associations between general adiposity and YOBC subtype–potentially due in part to the smaller sample size of nonluminal subtypes.

WC was not associated with luminal A and HER2-type YOBC but was positively associated with luminal B and TNBC. Compared with a smaller WC, both larger and largest WC were associated with luminal B YOBC (OR = 1.55; 95% CI, 1.09–2.20 and OR = 1.48; 95% CI, 1.01–2.15, respectively), and largest WC was associated with TNBC (OR = 2.48; 95% CI, 1.58–3.88). Similar results were observed with WHtR, in which largest versus smaller WHtR was nonsignificantly associated with higher odds of luminal B (OR = 1.29; 95% CI, 0.78–2.13) and significantly associated with higher odds of TN YOBC (OR = 2.20; 95% CI, 1.20–4.03). We also observed a dose response in which greater central adiposity was

Table 1. Weighted characteristics of a population-based sample of NHB and NHW women without breast cancer in LA County and Metro Detroit by adiposity throughout adulthood, 2010 to 2015.

		Young adult BMI (kg/m^2)[a]				Adult BMI (kg/m^2)[a]				Adult WC (cm)[a]			Adult WHtR[a]		
	Overall	<18.5	18.5 to <25	25 to <30	≥30	<18.5	18.5 to <25	25 to <30	≥30	<0.80	0.80 to <88	≥0.88	<0.49	0.49 to <0.59	≥0.59
	N = 1,381	*n* = 201	*n* = 858	*n* = 167	*n* = 101	*n* = 43	*n* = 486	*n* = 334	*n* = 480	*n* = 368	*n* = 205	*n* = 747	*n* = 361	*n* = 456	*n* = 501
	N	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]	W%[b]
Birth cohort															
1961–1965	192	20.0	66.6	6.5	2.2	3.2	26.8	33.8	36.0	19.8	18.8	58.7	19.8	38.4	39.1
1966–1975	584	17.7	63.3	9.2	5.7	3.1	36.9	21.2	36.8	28.9	14.3	53.0	28.3	29.7	38.3
1976–1985	425	14.7	66.4	10.6	7.0	6.7	39.9	21.5	25.8	31.5	16.6	41.9	31.5	30.8	27.4
1986–1995	192	3.8	63.1	16.2	14.1	4.8	45.4	26.3	21.9	45.0	17.9	36.3	39.5	34.1	23.3
Age at reference date															
20–29	246	7.1	64.8	14.5	11.3	7.6	45.1	25.0	19.4	44.0	18.3	33.3	39.6	32.0	22.2
30–39	482	16.0	61.1	12.5	8.2	3.1	37.1	20.6	33.6	28.1	13.7	51.1	28.2	30.5	33.9
40–49	653	17.2	67.4	6.7	4.3	3.1	34.4	25.9	35.7	26.0	17.0	53.7	25.6	33.7	37.3
Study site															
Metro Detroit	717	10.3	62.4	13.9	11.0	2.9	34.5	25.5	33.5	28.4	16.6	52.6	26.7	33.4	36.3
LA County	664	17.3	67.7	7.4	3.8	7.3	45.9	21.8	22.7	40.2	16.3	35.0	38.5	30.2	22.7
Race/ethnicity															
NHB	665	8.0	54.1	20.8	13.4	2.0	21.1	31.9	43.2	15.4	15.9	67.0	14.0	38.5	45.8
NHW	716	15.9	70.1	6.3	5.2	6.2	48.7	19.8	21.7	42.6	16.7	34.1	40.8	28.8	22.8
Adult HPP															
<250%	716	12.6	59.9	14.8	8.2	5.4	27.6	28.1	34.8	25.3	16.1	55.5	23.9	34.0	37.7
≥250%	622	13.5	71.4	6.1	7.7	4.3	51.4	19.6	23.2	41.3	17.3	34.4	39.4	30.2	23.5
First degree family history of breast cancer															
Yes	116	0.39	21.3	68.1	5.3	4.3	51.5	21.6	20.0	44.6	15.3	37.0	40.3	29.0	27.7
No	1,198	2.85	12.8	64.2	11.7	4.9	38.7	23.7	29.5	33.3	16.2	45.4	31.7	31.7	30.7
Do not know	67	9.5	5.1	66.4	13.9	1.3	26.1	33.9	37.1	11.6	22.9	62.0	12.5	46.1	38.0
Lifetime smoking (pack-years)															
Never	902	13.0	65.2	11.0	8.5	4.7	40.7	23.6	28.4	33.7	16.8	44.5	31.0	33.4	29.5
<5	226	11.9	61.2	13.2	8.4	4.6	38.8	21.0	28.5	32.7	16.7	45.0	31.8	31.1	31.6
5 to <20	186	12.7	66.5	11.6	5.0	3.5	34.1	31.4	30.3	36.0	12.9	47.0	37.9	23.4	34.6
≥20	67	21.5	61.9	7.3	8.5	8.7	29.7	20.7	39.4	18.8	20.4	58.3	20.4	40.1	37.1
Lifetime cumulative alcohol use (g/day)															
None	120	9.5	60.7	17.8	6.7	3.5	33.5	34.2	26.3	26.6	15.8	53.9	25.6	31.4	38.6
0.1 to <7	642	11.8	70.4	9.2	6.3	2.1	42.8	23.6	27.8	31.7	20.6	41.7	30.3	34.4	29.3
7 to <14	272	13.0	60.3	12.4	11.8	5.1	41.2	15.2	35.0	36.6	8.3	50.5	30.4	25.0	36.9
14 to <28	224	19.7	57.0	11.5	7.4	13.8	36.7	26.1	21.4	41.6	14.6	39.5	40.7	34.7	20.3
≥28	123	11.3	62.2	13.5	11.2	1.2	25.4	33.2	38.9	23.2	18.5	56.6	28.5	33.2	36.6

(Continued on the following page)

Table 1. Weighted characteristics of a population-based sample of NHB and NHW women without breast cancer in LA County and Metro Detroit by adiposity throughout adulthood, 2010 to 2015. (Cont'd)

		Young adult BMI (kg/m^2)[a]				Adult BMI (kg/m^2)[a]				Adult WC (cm)[a]			Adult WHtR[a]		
	Overall	**<18.5**	**18.5 to <25**	**25 to <30**	**≥30**	**<18.5**	**18.5 to <25**	**25 to <30**	**≥30**	**<0.80**	**0.80 to <88**	**≥0.88**	**<0.49**	**0.49 to <0.59**	**≥0.59**
	***N* = 1,381**	***n* = 201**	***n* = 858**	***n* = 167**	***n* = 101**	***n* = 43**	***n* = 486**	***n* = 334**	***n* = 480**	***n* = 368**	***n* = 205**	***n* = 747**	***n* = 361**	***n* = 456**	***n* = 501**
	N	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**	**W%[b]**
Age at menarche (years)															
≤11	402	5.7	64.9	13.6	10.7	2.7	33.2	27.0	34.0	27.4	16.3	52.1	24.3	32.0	37.2
12 to ≤13	728	15.1	66.4	11.0	5.8	5.3	41.4	23.9	26.4	34.0	17.8	42.8	32.8	34.4	27.3
>13	251	20.7	57.8	7.6	10.4	6.9	43.0	18.4	29.0	41.7	12.2	41.6	41.0	24.7	29.8
Parity/age at first full-term pregnancy (children; years)															
Nulliparous	403	13.8	63.1	11.7	11.0	7.4	45.7	23.5	23.2	43.2	14.3	34.6	41.7	25.0	23.9
1–2; <25	298	7.8	59.9	14.7	10.2	3.0	33.5	24.2	38.1	25.3	16.1	57.0	20.9	38.6	38.9
1–2; ≥25	320	16.6	71.8	7.1	3.7	3.8	43.8	23.6	20.4	34.7	23.2	38.3	33.8	39.7	22.4
3+; <25	274	13.4	61.3	12.7	5.5	2.2	24.5	27.8	42.2	16.4	14.1	66.8	16.6	32.4	48.3
3+; ≥25	86	13.2	73.6	8.8	3.5	2.6	34.1	16.8	37.5	30.2	12.9	51.2	28.3	30.9	35.2
Lifetime breastfeeding (months)															
Parous, never	261	10.9	62.8	14.9	7.5	1.4	31.8	23.8	40.4	20.0	12.4	63.2	15.5	34.9	44.7
>0 to <6	250	14.3	59.8	12.6	6.4	4.5	30.7	29.7	32.4	26.8	16.5	54.2	27.7	34.0	35.7
≥6	467	12.8	70.0	8.2	5.5	3.1	38.8	21.6	29.4	30.2	21.3	46.1	28.2	39.2	30.1
Measured adult height (cm)															
Mean (SE)	164.5 (0.2)	166.3 (0.5)	164.4 (0.3)	165.0 (0.8)	161.9 (1.1)	165.9 (1.2)	165.4 (0.4)	163.8 (0.4)	164.0 (0.4)	165.2 (0.5)	163.6 (0.5)	164.5 (0.3)	166.0 (0.4)	164.5 (0.3)	163.5 (0.4)

[a]Participants missing exposure of interest removed from that analysis: young adult BMI ($n = 110$), adult BMI ($n = 81$), adult WC ($n = 165$), and adult WHtR ($n = 167$).
[b]Row percentages are weighted to LA County and Metro Detroit populations of NHB and NHW women ages 20 to 49 years in the 2010 Census; weights also account for nonresponse.

Table 2. Adiposity throughout adulthood and odds of breast cancer overall and by tumor subtype in the YWHHS.[a]

	Control	Overall cases[b]		Luminal A		Luminal B		TNBC		HER2-type		
	N = 1,381	*N* = 1812		*n* = 697		*n* = 567		*n* = 314		*n* = 104		
	N	*N*	aOR (95%CI)	*N*	aOR (95%CI)	*N*	aOR (95%CI)	*N*	aOR (95%CI)	*N*	aOR (95%CI)	P_{het}[c]
General adiposity												
Young adult BMI (age 18 years; kg/m^2)												
<18.5	201	331	1.02 (0.77–1.35)	118	0.89 (0.63–1.25)	104	1.00 (0.71–1.41)	56	1.11 (0.72–1.72)	28	1.58 (0.80–3.12)	
18.5 to <25	858	1,191	REF	471	REF	388	REF	187	REF	65	REF	0.49
25 to <30	167	178	1.15 (0.82–1.62)	75	1.20 (0.80–1.78)	41	0.88 (0.56–1.38)	40	1.44 (0.84–2.46)	7	0.91 (0.36–2.28)	
≥30	101	56	**0.53 (0.33–0.86)**	13	**0.35 (0.16–0.79)**	22	0.72 (0.41–1.28)	11	0.56 (0.24–1.26)	4	—	
P_{trend}[d]			0.13		0.26		0.17		0.35		0.24	
Adult BMI (1 year before diagnosis; kg/m^2)[e]												
<18.5	43	41	**0.47 (0.25–0.87)**	9	**0.18 (0.06–0.50)**	19	0.78 (0.37–1.64)	2	0.16 (0.03–0.88)	5	1.05 (0.23–4.74)	0.39
18.5 to <25	486	750	REF	315	REF	235	REF	109	REF	40	REF	
25 to <30	334	448	0.84 (0.65–1.09)	152	**0.66 (0.48–0.91)**	148	0.91 (0.71–1.32)	93	1.24 (0.86–1.80)	21	0.73 (0.40–1.36)	
≥30	480	530	**0.71 (0.54–0.92)**	207	**0.59 (0.46–0.87)**	147	0.69 (0.55–1.02)	102	0.88 (0.59–1.29)	36	0.88 (0.48–1.64)	
P_{trend}[d]			0.01		0.02		0.08		0.26		0.99	
Central adiposity												
Adult WC measured at interview (cm)[f]												
<80	368	490	REF	209	REF	159	REF	63	REF	28	REF	<0.01
80 to <88	205	301	1.14 (0.87–1.49)	110	0.92 (0.66–1.29)	108	**1.55 (1.09–2.20)**	39	1.33 (0.79–2.23)	17	0.95 (0.45–2.01)	
≥88	747	917	1.27 (0.98–1.65)	341	0.96 (0.69–1.33)	262	**1.48 (1.01–2.15)**	194	**2.48 (1.58–3.88)**	55	0.89 (0.43–1.82)	
P_{trend}[d]			0.88		0.11		0.40		<0.01		0.14	
Adult WC-to-height ratio measured at interview[g]												
<0.49	361	502	REF	210	REF	166	REF	64	REF	29	REF	
0.49 to <0.59	456	616	1.15 (0.93–1.42)	236	0.95 (0.72–1.24)	200	1.32 (0.98–1.77)	106	**1.72 (1.16–2.55)**	29	0.79 (0.40–1.56)	<0.01
≥0.59	501	590	1.10 (0.76–1.60)	214	0.71 (0.43–1.15)	163	1.29 (0.78–2.13)	126	**2.20 (1.20–4.03)**	42	1.21 (0.48–3.05)	
P_{trend}[d]			0.92		0.10		0.45		<0.01		0.17	

Bold values indicate statistical significance at the 5% level.

[a]Models adjusted for site (Detroit/LA), age at diagnosis (continuous, quadratic), first-degree family history of breast cancer (yes/no/do not know), parous (ever/never), parity [included as "number of full-term births" × "parous (ever/never)"], age at first full-term birth [included as "centered age at first full-term birth" × "parous (ever/never)"], age at menarche (continuous, quadratic), lifetime cigarette smoking (never/<5/5–19/≥20 pack years), lifetime alcohol use [ever/never and cumulative average amount of alcohol consumed (g/day)], lifetime breastfeeding (nulliparous/parous never breastfed/parous and breastfed <6 months/parous and breastfed ≥6 months), oral contraceptive use (ever/never), and measured height (cm). Models of WC and WHtR additionally adjusted for current measured BMI (continuous).

[b]Includes participants missing tumor subtype ($n = 130$).

[c]*P* value for heterogeneity calculated from multinomial regression model adjusting for all covariates.

[d]*P* value for continuous linear trend from Wald test statistic.

[e]The year of diagnosis for cases and four months before the screening interview for controls.

[f]Based on World Health Organization thresholds for risk of metabolic complications.

[g]Based on tertiles among the control population.

associated with increased odds of TNBC ($P_{trend} < 0.01$ for WC and WHtR), although not luminal B ($P_{trend} \geq 0.40$). There was also evidence for heterogeneity in associations between WC and WHtR with YOBC by subtype ($P_{het} < 0.01$).

As shown in **Table 3**, parity modified associations between WC and TNBC, with stronger positive associations of central adiposity with TNBC among parous than nulliparous women (e.g., largest vs. smaller WC OR = 2.99; 95% CI, 1.83–4.90 and OR = 1.87; 95% CI, 0.61–5.76, respectively; $P_{int} < 0.01$). Similarly, associations between WHtR and TNBC were stronger among parous than nulliparous women (e.g., largest vs. normal WHtR OR = 3.03; 95% CI, 1.49–6.13 and OR = 1.13; 95% CI, 0.25–5.03, respectively; $P_{int} < 0.01$). Associations between young adult BMI, adult BMI, WC, and WHtR with YOBC overall, luminal A, and luminal B were not modified by parity (all $P_{int} > 0.05$).

We found little evidence that the effect of adult adiposity on YOBC subtype odds was modified by attained age (**Table 4**; $P_{int} \geq 0.06$), HPP (Supplementary Table S1; $P_{int} \geq 0.12$), or race/ethnicity (Supplementary Table S2; $P_{int} \geq 0.07$).

We did observe, however, that obese adult BMI seemed protective for luminal B YOBC among women ages <40 but not ≥40 years, whereas overweight young adult BMI was associated with increased TNBC risk among women ages ≥40 but not <40 years. Similarly, larger central adiposity was only significantly associated with higher risk of luminal B and TN YOBC among women ages ≥40 but not <40 years of age.

In analyses of additional adiposity measures (Supplementary Table S3), larger BMI at 25 or 35 years of age was not associated with YOBC subtypes, but larger %BF at interview was significantly associated with higher odds of luminal A YOBC.

Results from sensitivity analyses restricted to premenopausal women examining adiposity and YOBC (Supplemental Table S4) were similar to main results reported in **Table 2**.

Discussion

In this population-based case–control study, greater general adiposity in young adulthood and adulthood was associated with lower

Table 3. Adiposity throughout adulthood and odds of breast cancer overall and by subtype in the YWHHS, by parity.[a]

	Controls=	Overall[b]		Luminal A		Luminal B		TNBC	
	N	*N*	aOR (95%CI)	*N*	aOR (95%CI)	*N*	aOR (95%CI)	*N*	aOR (95%CI)
General adiposity									
Young adult BMI (age 18 years; kg/m^2)									
$P_{interaction}$[c]			0.21		0.49		0.22		0.21
Nulliparous									
<18.5	57	91	0.80 (0.48–1.35)	29	0.66 (0.34–1.30)	28	0.63 (0.31–1.29)	18	1.06 (0.46–2.44)
18.5 to <25	241	330	REF	126	REF	124	REF	53	REF
25 to <30	61	46	0.68 (0.35–1.34)	20	0.77 (0.32–1.90)	14	0.51 (0.23–1.15)	8	0.91 (0.42–1.98)
≥30	40	18	0.46 (0.17–1.23)	4	—	8	0.56 (0.16–2.01)	3	—
P_{trend}[d]			0.14		0.27		0.33		0.17
Parous									
<18.5	144	240	1.10 (0.78–1.56)	89	0.97 (0.64–1.46)	76	1.18 (0.79–1.75)	38	1.12 (0.66–1.91)
18.5 to <25	617	861	REF	345	REF	264	REF	134	REF
25 to <30	106	132	1.41 (0.94–2.10)	55	1.45 (0.91–2.30)	27	1.07 (0.60–1.89)	32	1.80 (0.97–3.34)
≥30	61	38	**0.56 (0.33–0.95)**	9	**0.35 (0.14–0.83)**	14	0.80 (0.42–1.52)	8	0.72 (0.30–1.75)
P_{trend}[d]			0.33		0.54		0.16		0.88
Adult BMI (1 year before diagnosis; kg/m^2)[e]									
$P_{interaction}$[c]			0.59		0.70		0.42		0.17
Nulliparous									
<18.5	19	16	0.57 (0.25–1.32)	1	—	10	1.03 (0.36–2.93)	1	—
18.5 to <25	171	246	REF	96	REF	88	REF	43	REF
25 to <30	88	104	0.74 (0.47–1.18)	37	0.64 (0.36–1.15)	33	0.65 (0.36–1.16)	21	0.86 (0.41–1.78)
≥30	124	124	**0.56 (0.35–0.91)**	47	**0.49 (0.27–0.88)**	44	0.64 (0.35–1.20)	20	0.48 (0.20–1.12)
P_{trend}[d]			0.18		0.39		0.30		0.22
Parous									
<18.5	24	25	**0.45 (0.21–0.94)**	8	**0.20 (0.07–0.62)**	9	0.69 (0.25–1.92)	1	0.15 (0.01–1.67)
18.5 to <25	315	504	REF	219	REF	147	REF	66	REF
25 to <30	246	344	0.89 (0.67–1.17)	115	**0.69 (0.48–0.98)**	115	1.15 (0.82–1.62)	72	1.33 (0.86–2.04)
≥30	356	406	0.77 (0.57–1.02)	160	**0.69 (0.48–0.99)**	103	0.81 (0.58–1.13)	82	1.05 (0.68–1.62)
P_{trend}[d]			0.01		0.01		0.03		0.83
Central adiposity									
Adult WC measured at interview (cm)[f]									
$P_{interaction}$[c]			0.07		0.35		0.11		<0.01
Nulliparous									
<80	136	169	REF	65	REF	59	REF	27	REF
80 to <88	55	90	1.26 (0.69–2.27)	30	0.91 (0.38–2.14)	36	1.79 (0.92–3.50)	16	2.25 (0.89–5.67)
≥88	179	198	0.85 (0.41–1.74)	72	0.58 (0.22–1.52)	69	1.03 (0.40–2.65)	37	1.87 (0.61–5.76)
P_{trend}[d]			**0.04**		0.13		**0.03**		0.11
Parous									
<80	232	321	REF	144	REF	100	REF	36	REF
80 to <88	150	211	1.09 (0.79–1.51)	80	0.89 (0.59–1.32)	72	1.57 (1.00–2.48)	23	1.11 (0.55–2.23)
≥88	568	719	**1.40 (1.09–1.80)**	269	1.06 (0.77–1.48)	193	**1.79 (1.18–2.73)**	157	**2.99 (1.83–4.90)**
P_{trend}[d]			0.68		0.22		0.74		0.03
Adult WC-to-height ratio measured at interview[g]									
$P_{interaction}$[c]			0.13		0.32		0.33		<0.01
Nulliparous									
<0.49	138	179	REF	72	REF	61	REF	29	REF
0.49 to <0.59	110	155	0.97 (0.56–1.67)	51	0.63 (0.29–1.36)	59	1.27 (0.64–2.53)	31	1.55 (0.63–3.83)
≥0.59	121	123	0.60 (0.21–1.68)	44	0.25 (0.05–1.11)	44	1.00 (0.26–3.91)	20	1.13 (0.25–5.03)
P_{trend}[d]			0.08		0.04		0.15		0.70
Parous									
<0.49	223	323	REF	138	REF	105	REF	35	REF
0.49 to <0.59	346	461	1.20 (0.96–1.51)	185	1.05 (0.77–1.43)	141	1.42 (1.00–2.00)	75	**1.88 (1.13–3.14)**
≥0.59	380	467	1.30 (0.89–1.90)	170	0.91 (0.55–1.50)	119	1.52 (0.89–2.59)	106	**3.03 (1.49–6.13)**
P_{trend}[d]			0.22		0.02		0.75		0.02

Bold values indicate statistical significance at the 5% level.

[a]Models adjusted for site (Detroit/LA), age at diagnosis (continuous, quadratic), first-degree family history of breast cancer (yes/no/do not know), parity (number of full-term births), age at first full-term birth (centered on mean), age at menarche (continuous, quadratic), lifetime cigarette smoking (never/<5/5–19/≥20 pack years), lifetime alcohol use [ever/never and cumulative average amount of alcohol consumed (g/day)], lifetime breastfeeding (nulliparous/parous never breastfed/parous and breastfed <6 months/parous and breastfed ≥6 months), oral contraceptive use (ever/never), and measured height (cm). Models of WC and WHtR additionally adjusted for current measured BMI (continuous).

[b]Includes participants missing tumor subtype ($n = 130$); analyses of HER2-enriched YOBC omitted from stratified tables due to small sample size.

[c]*P* value for interaction calculated from the Wald test for the cross-product term.

[d]*P* value for trend calculated using continuous value of exposure.

[e]The year of diagnosis for cases and four months before the screening interview for controls.

[f]Based on World Health Organization thresholds for risk of metabolic complications.

[g]Based on tertiles among the control population.

odds of invasive luminal A YOBC—which was also reflected in YOBC overall. Furthermore, central obesity was associated with increased odds of both luminal B and TN YOBC, particularly among parous women and women ages ≥40 years at diagnosis. Although previous literature has identified adult general adiposity as a breast cancer risk factor, with positive associations for post- and inverse associations for premenopausal breast cancer (9–11), little research has explored the risk associated with both general and central adiposity among young women and by tumor subtype. Thus, findings from this study are an important contribution to the literature.

The biologic mechanisms linking adiposity to breast cancer risk, particularly by subtype and among young women, remains poorly understood (43). Hypothesized mechanisms for the decreased risk of luminal A YOBC associated with general adiposity include that women with either general or central obesity may be more likely to experience anovulation (44), which lowers levels of circulating hormones, including estrogen (24), and possibly rates of breast cell division (45) thereby reducing risk of ER-positive tumors (46). However, menstrual cycle characteristics and ovulatory disorders did not explain the protective effect of larger BMI on risk of premenopausal breast cancer (which includes a high proportion of luminal A tumors) in a prior cohort study (47). Additionally, general and central adiposity can lead to chronic inflammation of the immune, lymphatic, and vascular systems, which is associated with oxidative stress and contributes to tumor initiation and progression (48, 49). Central obesity, a marker of visceral obesity, is thought to be more pathogenic than general adiposity and may exert a stronger effect on circulating hormones and inflammatory markers (50). Thus, measures of central adiposity may be strongly associated with breast cancer risk, independent of general adiposity (18, 51). Obesity, and particularly central obesity (52), has also been associated with lower levels of the anti-inflammatory adipokine adiponectin, which has been found to both stimulate the growth of ER-positive breast cancer cells and inhibit the proliferation of ER-negative breast cancer cells (53). Thus, the positive association between central obesity and TN YOBC after adjustment for adult BMI we observed may be driven by factors such as reduced adiponectin levels.

Greater adult general adiposity, measured by BMI, was associated with a reduced odds of luminal A in this study, and larger adult BMI was protective for luminal B among women <40 years and premenopausal women. Our observation that overweight/obese adult BMI is associated with lower odds of luminal-like (HR-positive) YOBC, but not associated with TNBC, aligns with findings from two recent pooled cohort studies and a meta-analysis (9, 10, 13). Additionally, our observation of no statistically significant association between young adult and adult BMI with TNBC in this study is consistent with several previous case–control and cohort studies, which found no association between HR-negative YOBC and adult BMI or silhouette (10, 14, 15, 54, 55). In contrast, three case-only (56–58) and five case–control (46, 59–63) studies observed a positive association between adult BMI and risk of HR-negative or TN YOBC, whereas one case–control and one cohort study each found larger BMI to be associated with lower risk of HR-negative and ER-negative or PR-negative YOBC (9, 64). Adult adiposity parameterizations vary between studies, which may contribute to the observed heterogeneity in associations. For example, several studies grouped overweight and obese BMI (62, 65), or used other BMI cut points (10, 66, 67), making it difficult to compare associations with the present findings (59). Additionally, some studies lacked adequate sample size of young women with TNBC, making it difficult to draw inferences (67).

Similar to our findings, both case–control and prospective studies have generally found WC to be positively associated with TN (18, 64) and luminal B (56, 68) and unassociated with breast cancer defined as HR-positive in young women (51, 61, 69). In contrast to our findings, one cohort and two case–control studies observed no associations between WC and HR-negative YOBC (51, 61, 69), two cohort studies observed inverse associations of WC and HR-positive YOBC (18, 51), one case–control study observed positive associations of WC with HR-positive YOBC (70), and three cohort studies found that WC was not associated with HR-positive, HR-negative, or TN YOBC (7, 55, 71). Our WHtR results are consistent with one of the two previous studies that evaluated WHtR and YOBC risk and found that higher WHtR was associated with more than two times higher odds of HR-negative premenopausal breast cancer (16). Unlike our findings, the other study observed inverse associations between WHtR and HR-positive premenopausal breast cancer, although this protective association seemed to be restricted to Hispanic women (54). It is important to note that central adiposity was measured at interview in our study and may be affected by breast cancer treatment or changes in weight-related behaviors, although the effect of breast cancer treatment on adiposity is yet unclear and has been observed to vary by treatment type (72). Radiotherapy and hormone therapies used to treat HR-positive tumors are not typically associated with weight change, and although some studies have found chemotherapy to be associated with weight gain, significant changes in central adiposity were not detected (73). There is also evidence that, although older chemotherapy regimens are associated with weight gain, modern regimens are less associated with weight gain (72). In YWHHS, 68% of cases received chemotherapy treatment before the study interview. Additional studies of prediagnosis central adiposity and YOBC subtype risk are warranted to confirm our findings.

We observe that parity modified associations between central adiposity and TNBC, with positive associations observed among parous but not nulliparous women. Although age at diagnosis did not significantly modify associations of central adiposity and YOBC subtypes, greater central adiposity was only positively associated with TNBC among older women (ages ≥40 years). In our sample, older women were more likely to be parous (78% ≥40 years of age) and more likely to have greater central adiposity. Pregnancy has been associated with a short-term increase in breast cancer risk followed by a lifetime reduction in risk (23, 24). Parous women in our sample, who experience changes in breast tissue associated with pregnancy (24, 26), may thus be more susceptible to the increased risk of breast cancer associated with central adiposity, compared with nulliparous women. To the best of our knowledge, associations between adult general or central adiposity and YOBC subtypes by parity have not yet been evaluated; future studies to confirm these findings are warranted.

In this study, associations between adiposity and YOBC subtype were not significantly modified by HPP or race/ethnicity. Larger central adiposity and TNBC are more prevalent among women with lower HPP and NHB women, thus additional analyses are needed to evaluate whether or how much central adiposity contributes to the increased risk of TNBC among women with lower HPP and NHB women.

Table 4. Adiposity throughout adulthood and odds of breast cancer overall and by subtype in the YWHHS, by attained age.[a]

	Control	Overall[b]		Luminal A		Luminal B		TNBC	
	N	*N*	aOR (95%CI)	*N*	aOR (95%CI)	*N*	aOR (95%CI)	*N*	aOR (95%CI)
General adiposity									
Young adult BMI (age 18 years; kg/m^2)									
$P_{interaction}$[c]			0.06		0.08		0.90		0.06
Ages <40 years									
<18.5	89	92	1.10 (0.73−−1.65)	30	1.21 (0.68−2.13)	36	1.10 (0.66−1.85)	15	0.99 (0.50−1.96)
18.5 to <25	431	337	REF	97	REF	135	REF	68	REF
25 to <30	117	51	0.65 (0.41−1.03)	15	0.62 (0.31−1.22)	18	0.63 (0.35−1.14)	12	0.69 (0.30−1.58)
≥30	70	18	**0.38 (0.23–0.64)**	3	—	10	0.60 (0.29−1.14)	2	—
P_{trend}[d]			<0.01		<0.01		0.02		<0.01
Ages ≥40 years									
<18.5	112	239	0.99 (0.71−1.38)	88	0.84 (0.57−1.25)	68	0.98 (0.64−1.50)	41	1.16 (0.68−2.00)
18.5 to <25	427	854	REF	374	REF	253	REF	119	REF
25 to <30	50	127	1.46 (0.94−2.25)	60	1.46 (0.91−2.34)	23	1.03 (0.53−1.99)	28	**2.19 (1.14–4.20)**
≥30	31	38	0.59 (0.30−1.13)	10	0.37 (0.14−1.03)	12	0.76 (0.32−1.83)	9	0.84 (0.31−2.28)
P_{trend}[d]			0.63		0.65		0.41		0.61
Adult BMI 12 (1 year before diagnosis; kg/m^2)[e]									
$P_{interaction}$[c]			0.46		0.51		0.92		0.23
Ages <40 years									
<18.5	25	15	0.60 (0.26−1.39)	3	0.34 (0.08−1.36)	9	0.85 (0.33−2.19)	0	—
18.5 to <25	277	240	REF	79	REF	95	REF	39	REF
25 to <30	159	113	0.86 (0.62−1.19)	29	**0.60 (0.38–0.96)**	40	0.78 (0.46−1.32)	34	0.59 (0.33−1.07)
≥30	237	116	**0.50 (0.35–0.71)**	31	**0.39 (0.23–0.66)**	44	**0.53 (0.34–0.82)**	26	0.91 (0.59−1.43)
P_{trend}[d]			<0.01		<0.01		<0.01		0.03
Ages ≥40 years									
<18.5	18	26	**0.42 (0.19–0.97)**	6	**0.14 (0.04–0.49)**	10	0.72 (0.23−2.25)	2	—
18.5 to <25	209	510	REF	236	REF	140	REF	70	REF
25 to <30	175	335	0.84 (0.62−1.15)	123	**0.68 (0.46–0.99)**	108	1.03 (0.67−1.57)	59	1.12 (0.71−1.78)
≥30	243	414	0.76 (0.55−1.05)	176	**0.68 (0.47–0.99)**	103	0.82 (0.54−1.25)	76	0.94 (0.57−1.54)
P_{trend}[d]			0.11		0.08		0.32		0.96
Central adiposity									
Adult WC measured at interview (cm)[f]									
$P_{interaction}$[c]			0.22		0.11		0.61		0.38
Ages <40 years									
<80	217	171	REF	55	REF	67	REF	28	REF
80 to <88	103	94	1.32 (0.90−1.95)	31	1.23 (0.66−2.29)	41	1.49 (0.89−2.48)	14	1.27 (0.60−2.70)
≥88	368	219	1.07 (0.70−1.63)	56	0.67 (0.36−1.26)	80	1.01 (0.58−1.76)	57	1.62 (0.73−3.59)
P_{trend}[d]			0.92		0.11		0.84		0.09
Ages ≥40 years									
<80	151	319	REF	154	REF	92	REF	35	REF
80 to <88	102	207	1.10 (0.80−1.53)	79	0.87 (0.59−1.30)	67	1.56 (0.98−2.51)	25	1.32 (0.65−2.70)
≥88	379	698	1.32 (0.97−1.80)	285	1.03 (0.71−1.51)	182	**1.64 (1.03–2.61)**	137	**2.81 (1.53–5.16)**
P_{trend}[d]			0.85		0.13		0.46		<0.01
Adult WC-to-height-ratio measured at interview[g]									
$P_{interaction}$[c]			0.31		0.34		0.43		0.60
Ages <40 years									
<0.49	213	179	REF	62	REF	69	REF	29	REF
0.49 to <0.59	227	169	1.07 (0.77−1.49)	45	0.70 (0.40−1.22)	73	1.13 (0.70−1.81)	31	1.32 (0.72−2.40)
≥0.59	246	136	0.85 (0.47−1.53)	35	0.42 (0.16−1.07)	46	0.71 (0.34−1.49)	39	1.95 (0.78−4.91)
P_{trend}[d]			0.92		0.11		0.84		0.09
Ages ≥40 years									
<0.49	148	323	REF	148	REF	97	REF	35	REF
0.49 to <0.59	229	447	1.18 (0.92−1.52)	191	1.03 (0.76−1.41)	127	1.38 (0.93−2.03)	75	**1.90 (1.11–3.28)**
≥0.59	255	454	1.17 (0.75−1.84)	179	0.81 (0.44−1.48)	117	1.55 (0.83−2.91)	87	**2.32 (1.03–5.24)**
P_{trend}[d]			0.85		0.13		0.46		<0.01

Bold values indicate statistical significance at the 5% level.

[a]Models adjusted for site (Detroit/LA), age at diagnosis (continuous, quadratic), first-degree family history of breast cancer (yes/no/do not know), parous (ever/never), parity (included as "number of full-term births" × "parous"), age at first full-term birth (included as "centered age at first full-term birth" × "parous"), age at menarche (continuous, quadratic), lifetime cigarette smoking (never/<5/5–19/≥20 pack years), lifetime alcohol use [ever/never and cumulative average amount of alcohol consumed (g/day)], lifetime breastfeeding (nulliparous/parous never breastfed/parous and breastfed <6 months/parous and breastfed ≥6 months), oral contraceptive use (ever/never), and measured height (cm). Models of WC and WHtR additionally adjusted for current measured BMI (continuous).

[b]Includes participants missing tumor subtype ($n = 130$); analyses of HER2-enriched YOBC omitted from stratified tables due to small sample size.

[c]*P* value for interaction calculated from the Wald test for the cross-product term.

[d]*P* value for trend calculated using continuous value of exposure.

[e]The year of diagnosis for cases and four months before the screening interview for controls.

[f]Based on World Health Organization thresholds for risk of metabolic complications.

[g]Based on tertiles among the control population.

This study has several limitations. First, we relied primarily on self-reported weight, which may introduce recall bias. In our study, however, self-reported and measured current weight are highly correlated among both case and control participants ($r = 0.98$ and 0.96, respectively), and we applied a correction factor to recalled adult to reduce this potential bias. Previous studies also observe good correlation between measured adult weight and the weight recalled after a 10-year follow-up ($r = 0.74$) among women ages 25 to 74 years (74). As mentioned above, an additional limitation is that WC and WHtR were measured at the interview and may have been impacted by breast cancer or breast cancer treatment. However, because the correlation between measured current BMI at interview and recalled BMI 12 months before diagnosis was high among cases ($r = 0.90$, data not shown), we expect that central adiposity before and after diagnosis are similarly correlated. The associations we observed between central adiposity and YOBC were also largely consistent with the literature, including prospective studies (10, 18). Finally, we had limited power to assess associations between some measures of adiposity and YOBC risk for rarer tumor subtypes, particularly in stratified analyses.

Study strengths include the population-based design with case ascertainment from two well-established NCI SEER registries and area-based controls sampled from more than 24,000 households from the US Census (31), which improves the generalizability of findings. Also, in contrast with many previous studies, which classified tumor subtypes based only on ER and PR status (11), we additionally evaluated HER2 status and tumor grade, which improve subtype classification (20); ER/PR/HER2 information from SEER registries has been shown to be highly valid (75). Additionally, to the best of our knowledge, this is the first study to evaluate WHtR and YOBC tumor subtype risk.

Our results suggest that general adiposity in both young adulthood and adulthood is associated with a decreased risk of overall YOBC, driven largely by luminal A tumors, whereas larger adult central adiposity is associated with increased odds of luminal B and TNBC tumors, particularly among parous women. Future studies to confirm the positive association between central adiposity and risk of luminal B and TN YOBC—and the modifying effect of parity—that we observe are warranted.

Authors' Disclosures

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Authors' Contributions

L. Marcus Post: Conceptualization, data curation, formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **D.R. Pathak:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, visualization, methodology, project administration, writing–review and editing. **A.S. Hamilton:** Conceptualization, resources, data curation, formal analysis, funding acquisition, investigation, visualization, methodology, project administration, writing–review and editing. **K.A. Hirko:** Visualization, methodology, writing–review and editing. **R.T. Houang:** Conceptualization, data curation, formal analysis, funding acquisition, validation, visualization, methodology, writing–review and editing. **E.H. Guseman:** Conceptualization, investigation, methodology, writing–review and editing. **D. Sanfelippo:** Data curation, writing–review and editing. **N. Bohme Carnegie:** Formal analysis, validation, visualization, writing–review and editing. **L.K. Olson:** Conceptualization, funding acquisition, writing–review and editing. **H. Rui:** Data curation, writing–review and editing. **A.G. Schwartz:** Funding acquisition, writing–review and editing. **E.M. Velie:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, visualization, methodology, project administration, writing–review and editing.

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Note

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