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OBESITY, BODY FAT DISTRIBUTION, AND RISK OF BREAST CANCER SUBTYPES IN AFRICAN AMERICAN WOMEN PARTICIPATING IN THE AMBER CONSORTIUM

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Abstract

Purpose—African American (AA) women are more likely than white women to be obese and to be diagnosed with ER- and triple negative (TN) breast cancer, but few studies have evaluated the impact of obesity and body fat distribution on breast cancer subtypes in AA women. We evaluated these associations in the AMBER Consortium by pooling data from four large studies.

Methods—Cases were categorized according to hormone receptor status as ER+, ER-, and TN (ER-, PR-, and HER2-) based on pathology data. A total of 2,104 ER+ cases, 1,070 ER- cases (including 491 TN cases), and 12,060 controls were included. Odds ratios (OR) and 95% confidence intervals (CI) were computed using logistic regression, taking into account breast cancer risk factors.

Results—In postmenopausal women, higher recent (most proximal value to diagnosis/index date) BMI was associated with increased risk of ER+ cancer (OR: 1.31; 95% CI: 1.02–1.67 for

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BMI≥35 vs <25 kg/m2) and with decreased risk of TN tumors (OR: 0.60; 95% CI: 0.39–0.93 for BMI≥35 vs. <25). High young adult BMI was associated with decreased premenopausal ER+ cancer and all subtypes of postmenopausal cancer, and high recent waist-to-hip ratio (WHR) with increased risk of pre-menopausal ER+ tumors (OR: 1.35; 95% CI: 1.01–1.80) and all tumor subtypes combined in postmenopausal women (OR: 1.26; 95% CI: 1.02–1.56).

Conclusions—The impact of general and central obesity varies by menopausal status and hormone receptor subtype in AA women. Our findings imply different mechanisms for associations of adiposity with TN and ER+ breast cancers.

Keywords

Obesity; breast cancer subtypes; triple negative; African Americans; waist-to-hip ratio

INTRODUCTION

Breast cancer is a heterogeneous disease, with growing evidence that the various subtypes may have different etiologies [1,2]. African American (AA) women are more likely to develop estrogen receptor (ER) negative tumors including the subset of ER- tumors that are also lacking expression of progesterone receptor (PR-) and human epidermal growth factor receptor 2 (HER2-), known as triple negative (TN) breast cancer [3]. Both ER- and TN tumors tend to be more aggressive and have worse prognosis [3].

Obesity is currently a global public health concern, which disproportionately affects AA women in the United States. The prevalence of obesity (BMI≥30 kg/m^2) is 58.6% among AA women compared to 33.4% of non-Hispanic white women [4]. AA women more often have a fat distribution pattern consistent with central obesity [5], which has been associated with hyperinsulinemia and insulin resistance, in turn implicated in breast carcinogenesis [6]. In the majority of studies, mostly conducted in white women, obesity is associated with increased risk of postmenopausal and decreased risk of premenopausal breast cancer [7]. A few of those studies considered effects of obesity by hormone receptor subtypes: most suggest a stronger association of obesity with ER+ tumors, while the associations for ER- and TN breast cancers remain unresolved [8]. The few studies in AA women have had inconsistent results [9]. In view of the high prevalence of obesity and ER- tumors in AA women, informative data are clearly needed.

We examined general and central obesity and breast cancer subtypes in AA women participating in the AMBER (African American Breast Cancer Epidemiology and Risk) Consortium.

MATERIALS AND METHODS

The AMBER Consortium is a collaboration of four studies, the Carolina Breast Cancer Study (CBCS), the Women's Circle of Health Study (WCHS), the Black Women's Health Study (BWHS), and the Multiethnic Cohort Study (MEC) [10,11].

CBCS is a population-based case-control study of breast cancer [12]; cases were identified through the North Carolina Central Cancer Registry by rapid case ascertainment, with

oversampling of younger cases. Controls were identified through the Division of Motor Vehicles for women under 65 years and Health Care Financing Administration for women 65 or older, and were frequency matched to cases on age (±5 years) and race. Home interviews were conducted to collect information on breast cancer risk factors, as well as height and weight one year before diagnosis and weight at age 18 years, and to conduct anthropometric measurements (height, weight and waist and hip circumferences) [13,14]. Average time between diagnosis and the interview was 3–6 months.

WCHS is a case-control study of breast cancer [15,16], originally recruiting white and AA women in New York City (NYC) and New Jersey (NJ), with recruitment currently limited to AA women in ten counties in NJ. In NYC, cases were identified through hospitals with large enrollments of AA women; controls were recruited through random digit dialing (RDD), frequency matched to cases by age and race. In NJ cases are identified by rapid case ascertainment conducted by the NJ State Cancer Registry. Controls were initially identified by RDD, later complemented for the AA group with community-based recruitment [16]. During in-person home interviews information was collected on breast cancer risk factors, including height, and weight at age 20 years and 1 year before diagnosis/interview [17]. Anthropometric measurements were taken during the home interview using a standardized protocol [18]. Interviews, on average, took place approximately nine months after diagnosis.

BWHS is a prospective study among AA women across the United States [19]. The study was established in 1995, with 59,000 AA women responding to a 14-page health questionnaire. Biennial follow-up questionnaires update covariates and ascertain new cases of breast cancer. Cases are confirmed with medical records and cancer registry data. Information collected included demographic factors, family history of breast cancer, reproductive and medical history, hormone use, current weight and weight at age 18, height, and waist and hip circumferences [20].

MEC is a prospective study that includes 16,594 AA women [21]. The cohort, started in 1993–1996, is comprised of respondents to a 26-page questionnaire mailed to subjects identified through driver's license files for the state of Hawaii and Los Angeles County in California, supplemented by other sources. Cases were identified by linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County and the California State Cancer Registry. Follow-up questionnaires, sent approximately every five years collect information on demographics, medical and reproductive histories and other cancer risk factors, including current height and weight, weight at age 21 years [22], and waist and hip circumferences [23]. Given the few premenopausal participants, MEC was only included in analyses of postmenopausal women.

For both BWHS and MEC, a nested case-control approach was used to pool data with the other two studies. Controls were frequency matched to cases on 5-year age category and questionnaire completed prior to case diagnosis (index date).

Women were considered postmenopausal if their periods had stopped because of natural menopause or bilateral oophorectomy. Women who reported a hysterectomy but retained one or both ovaries were classified as premenopausal if their current age was less than the

10th percentile of age at natural menopause (<43 years), as postmenopausal if their age was greater than the 90th percentile of age at natural menopause (>56 years), and as having unknown menopausal status if their age was 43–56 years.

Pathology data from hospital records or cancer registries were used to classify cancers by subtype based on ER, PR and HER2. Pooled data from the four studies after exclusion of subjects with missing values for menopausal status, BMI, and ER receptor status, resulted in an analytical dataset with 2,104 ER+ cases, 1,070 ER- cases (which included 491 TN cases), and 12,060 controls. Data on waist and hip circumferences were available on 2,461 cases and 8,269 controls. Each study was approved by the individual Institutional Review Boards at participating institutions.

Statistical Analyses

Questionnaire data from the four studies were pooled and harmonized in the AMBER Biostatistics and Data Management Core, as described in detail elsewhere [10]. In brief, variables of interest for analyses were identified and, if categorical, categories specified. Individual studies carried out cleaning and recoding of their data, and returned to the Core for final quality checks and harmonization. Recent BMI and WHR were based on anthropometric data prior and closest to diagnosis/index date (for most women, approximately one year). Because height, weight, waist and hip measurements were continuous variables, no re-categorization was needed. Young adult BMI was based on self-reported weight at age 18 (BWHS and CBCS), 20 (WCHS), or 21 (MEC). All analyses were stratified by menopausal status. Body mass index (BMI) was computed as weight in kilograms (kg) divided by the square of height in meters (m). Waist-to-hip ratio (WHR) was computed as waist circumference (inches) divided by hip circumference (inches). Recent BMI was categorized according to the World Health Organization (WHO) International Classification. Because a large proportion of participants had a BMI below 25 as young adults (age 18–21 years), that category was further divided into BMI<20 and 20–24.9. Quartiles were used for WHR, with cutpoints based on the distribution of all controls combined. The same cutpoints were used for pre- and postmenopausal women to be able to compare estimates across menopausal status.

Odds ratios (OR) and 95% confidence intervals (CI) for ER+ and ER- tumors vs. controls were computed using polytomous logistic regression. Binary logistic regression was used to compute OR and CIs for overall breast cancer and TN breast cancer vs. controls. Multivariable models included as covariates age, education, study, time period of enrollment (1993–98, 1999–2005, 2006–2013), geographical region (South, Midwest, West, New Jersey, other Northeast), family history of breast cancer, age at menarche, parity, breastfeeding (yes/no), age at first birth, duration of oral contraceptive use, hormone therapy (HT) use, and age at menopause (for postmenopausal women). BMI and young adult BMI were further adjusted for WHR, and WHR was further adjusted for current BMI to assess potential independent effects of general and central adiposity. We also evaluated the joint effects of recent BMI and young adult BMI by modeling the two variables with low recent BMI (<25) and low young adult BMI (lowest tertile) as the reference category in separate models for ER+ and ER- cases compared to all controls. Similar joint analyses were

conducted for recent BMI and WHR. P values for trend were computed by including the median in each quartile as a continuous variable in regression models. Analyses in postmenopausal women were repeated after excluding HT users to assess possible effect modification. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary NC).

RESULTS

Selected characteristics of the AMBER studies are shown in Table 1. CBCS oversampled younger AA women and had a higher proportion of cases younger than 40 years. Consistent with national trends [1], the younger CBCS population had higher proportions of ER-and TN breast cancers compared to the other studies. MEC had the highest proportion of older women (≥60 years). The prevalence of obesity (BMI≥30) was higher in CBCS and WCHS, and WCHS, CBCS and MEC subjects had higher prevalence of central obesity (WHR>0.8) than BWHS participants.

As shown in Table 2, recent BMI was not significantly associated with premenopausal ER+, ER-, or TN cancer. For postmenopausal women, high recent BMI was associated with increased risk of ER+ cancer (OR= 1.31, 95% CI 1.02–1.67) and with reduced risk of TN disease (OR=0.60, 95% CI 0.39–0.93).

Regarding BMI as a young adult (Table 3), in premenopausal women, higher BMI was associated with reduced risk of ER+ breast cancer (OR: 0.65; 95% CI: 0.42–1.01 for BMI ≥30 vs <20), with no associations with ER- or TN cancer. In contrast, there was a suggestion that a higher young adult BMI was associated with reduced risk of postmenopausal breast cancer (overall and for each subtype), although most risk estimates were not statistically significant.

Higher WHR (Table 4) was associated with increased risk of ER+ cancer (OR: 1.35, 95% CI 1.01–1.80 for WHR >0.88 vs. ≤0.64) and with non-significant increases of ER- and TN cancer among premenopausal women. Among postmenopausal women, there was elevated risk with higher WHR for each subtype, with stronger risk for TN breast cancer (OR: 1.73; 95% CI 1.02–2.91 and 1.60; 95% CI: 0.94–2.73 for third and fourth quartiles, respectively, compared to lowest). When analyses were repeated in postmenopausal women excluding hormone therapy users, results did not substantially change (data not shown).

In joint effects analyses for recent and young adult BMI (Table 5), there were no clear patterns and no significant associations with ER+ or ER- breast cancer among premenopausal women. Among postmenopausal women, those who were thin as young adults (BMI<19.48, lowest tertile), but had a high recent BMI (≥35) had almost double the risk of ER+ breast cancer (OR: 1.91; 95% CI 1.32–2.75, p for interaction: 0.08), compared with women with low recent and young adult BMI. Moreover, being heavy as an adult was associated with reduced risk of postmenopausal ER- cancer regardless of young adult BMI.

DISCUSSION

There are several major findings from this largest study, to date, evaluating anthropometric factors and breast cancer subtypes in AA women.. Among postmenopausal women, higher

recent BMI was associated with increased risk of ER+ cancer, and the risk was even greater if the women were thin as young adults. Conversely, higher recent BMI was associated with a reduced risk of TN breast cancer. Higher young adult BMI was associated with reduced risk of premenopausal ER+ cancer and each subtype of postmenopausal cancer. Higher WHR was associated with increased risk in pre- and postmenopausal women for all subtypes combined, and for ER+ in premenopausal women and TN in postmenopausal women.

There is strong evidence that recent obesity increases risk of breast cancer in postmenopausal women, based largely on studies of white women, with weaker evidence that higher BMI reduces premenopausal breast cancer risk [7]. In the few studies on breast cancer subtypes, the association of recent obesity appears to be stronger for hormone-receptor positive tumors (ER+/PR+) [8,24,25]. To our knowledge, only five studies have been published reporting on BMI and breast cancer by hormone receptor (HR) status in AA women, including earlier reports from the BWHS [20], WCHS [18], and CBCS [26], which are included in this consortium, as well as two other case-control studies, the Women's CARE Study [27] and the San Francisco Bay Area Breast Cancer Study [28,29]. Consistent with the present findings, the other two studies found that higher recent BMI was associated with lower risk of ER+/PR+ cancer in premenopausal women [28,27] and ER-/PR- cancer in postmenopausal women [27,29]. We also found that risk of ER+ postmenopausal breast cancer was only elevated for obese women who were thin during young adulthood, while women who were obese in both periods were not at increased risk. It is not surprising that this weight trajectory has the worst risk profile, given the well-established association between BMI and ER+ breast cancer, with obese women having reduced risk before menopause and increased risk after menopause. Our findings are also consistent with results from the multi-ethnic San Francisco Bay Area Breast Cancer Study [29] and the California Teachers Study Cohort, which included mostly whites [30].

Results on recent BMI and ER-/PR- tumors have been mixed and two meta-analyses found no significant association for pre- or postmenopausal women [8,25]. While few studies have evaluated these associations in AA women and results have generally been inconclusive, a recent meta-analysis suggested that the impact of obesity may be different in AA women compared to white women [25], with a stronger positive association for hormone receptor (HR) positive tumors (OR: 1.38; 95% CI: 1.00–1.91) and stronger inverse association (OR: 0.73; 95% CI: 0.49–1.10) for HR negative tumors among postmenopausal AA women compared to white women. However, estimates were based on 4 studies among whites and 2 among AA women.

There are few studies of recent BMI and TN breast cancer, with inconsistent results. A meta-analysis [31] reported an increased risk for premenopausal women and no association for postmenopausal women, but it was based on few studies, most with small sample sizes, and some of the included estimates were unadjusted for any covariates. Our study is the first to report results separately on AA women. Our results for premenopausal women are consistent with an earlier report from the CBCS on basal-like tumors [32], two other case-control studies [33,34] and a pooled analysis of 12 studies, which found non-significant increases in risk of TN breast cancer for premenopausal obese women [24]. For postmenopausal women, higher BMI was associated with lower risk of TN cancer,

consistent with the findings of an earlier report from the CBCS on basal-like tumors [32]. Three case-control studies have reported results for TN tumors in postmenopausal women, each based on small numbers (56–87 TN cases):one reported an OR above one [35], another study reported an OR below one (for basal-like tumors) [33], and the third found no association [36]. The Women's Health Initiative [37] suggested elevated risk of TN breast cancer with higher BMI (HR: 1.37; 95% CI: 0.98–1.93), based on 307 TN cases, of which only 50 were AA.

Previous studies, largely in white populations, have generally reported lower breast cancer risk with higher BMI in early adulthood [38]. However, the few studies in AA women reported inconsistent results perhaps due to small sample sizes and unstable risk estimates, with some studies suggesting an inverse association for both pre- and postmenopausal women [20], for premenopausal women [27], or no association [39,40,22,28,17]. Only two of these, the Women's CARE Study [27] and the San Francisco Bay Area Breast Cancer Study [28,29], both case-control studies, reported results by HR status. In agreement with our findings, these two studies suggested an inverse association for ER+/PR+ breast cancer in premenopausal and postmenopausal women, but risk estimates were only statistically significant among premenopausal women in both studies.

To our knowledge, this is the first study reporting on the association of young-adult BMI and TN breast cancer in premenopausal women, and we therefore cannot compare our null findings with other studies. For postmenopausal women, the Women's Health Initiative [37] found no association with TN breast cancer (307 cases, 79% white). In the Nurses' Health Study [41], there was a suggestion of an inverse association between BMI at age 18 and the basal-like subtype (n=226), but the confidence interval included the null and analyses were not stratified by menopausal status.

Because other studies reported increased risk associated with higher BMI in postmenopausal women to be stronger or limited to nonusers of female hormone [8,25], we repeated analyses excluding current users. Results in postmenopausal women remained essentially unchanged, which has also been reported by others [27].

The evidence for central obesity, most often measured with WHR, and breast cancer has been generally inconsistent for white populations, particularly for premenopausal breast cancer [5,42], but tends to suggest an association in postmenopausal women [7]. However, in two meta-analyses of studies that adjusted for BMI, the association with WHR became weaker and non- significant among postmenopausal women [6,7]. Although the data are scant, studies have suggested a distinct impact of WHR by race/ethnicity and hormone receptor status [42]. In agreement with our findings of increases in risk associated with high WHR, a recent meta-analysis reported an association between WHR and premenopausal breast cancer, which was stronger in AA than in white women [43]. Furthermore, the San Francisco Bay Area Breast Cancer Study reported elevated risk for ER+/PR+ breast cancer in premenopausal [28] and postmenopausal [29] AA women, albeit not statistically significant. Little is known about the impact of central adiposity on risk of TN breast cancer. Our study is consistent with the earlier finding from the CBCS including whites and AA women [32], suggesting elevated risk of basal-like breast cancer in premenopausal and

postmenopausal women. In contrast, no association with WHR for postmenopausal women was found in the Women's Health Initiative [35]. Both studies adjusted for BMI.

It should be pointed out that, as in most observational studies, we used self-reported body size measures. However, studies have shown a strong correlation (>0.9) between self-reported and measured weight and height [44,18,45,46], with weaker but still good correlation (0.74–0.93) for waist and hip circumferences [44,45,47].

The complex relationship of obesity and breast cancer has mostly been attributed to endogenous estrogen exposure, which varies greatly throughout life, with the major source being the ovaries in premenopausal women, and adipose tissue after menopause. For ER+ breast cancer, the inverse association found in premenopausal women has been postulated to be due to more frequent anovulatory cycles and faster clearance rate of free estrogens in obese than lean women, while, after menopause, excess adipose tissue results in increased estrogen production from aromatization of androgen in peripheral fat tissue [8]. In addition, both general obesity and central obesity are associated with elevated levels of insulin and insulin-like growth factor (IGF-I), chronic systemic inflammation, increased leptin, and oxidative stress [42]. We found that risk of TN tumors was reduced for women with a high BMI, but elevated for those with a body fat distribution pattern compatible with central obesity. While these findings need to be replicated by other studies, they support the notion that TN tumors may be more influenced by components of the metabolic syndrome (central obesity, insulin resistance, dyslipidemia, and hypertension) than by estrogens, as hypothesized by others [48].

Current evidence suggests that there are important differences in the association of obesity with overall breast cancer risk between AA and white women, which may be due, in part, to AA women being more likely to have ER- and TN breast cancer tumors. However, even for HR negative tumors, obesity appears to have a distinct impact in AA women. Important differences have been found between AA and white women in the relationship of BMI with body composition. AA women tend to have higher lean mass and lower fat than white women for a given BMI [49] and lower visceral adipose tissue (VAT) and higher subcutaneous adipose tissue (SAT) for a given amount of body fat [50] compared to white women. However, there is also evidence that despite less VAT, AA women are more insulin resistant than white women at the same level of BMI [51]. Differences in obesity-related circulating adipokines and inflammatory biomarkers have also been noted between AA and white women, with AA women having higher levels of leptin, C-reactive protein and interleukin-6, and lower levels of adiponectin, even after adjusting for BMI [52]. Furthermore, correlations between BMI and these biomarkers seemed to be stronger in AA than in white women in that study. Clearly, studies are needed to understand biological mechanisms underlying the impact of adiposity on breast cancer risk in AA women, in particular by HR subtypes and menopausal status.

In conclusion, effects of adiposity appear to differ by both menopausal status and breast cancer subtype. Further work is needed to understand the complex impact of obesity on the various cancer subtypes and underlying mechanisms. This is particularly important for AA women, given the high prevalence of general and central obesity in this population.

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Table 1

Characteristics of cases and controls by study in the AMBER Consortium.

	BWHS		CBCS		WCHS		MEC		AMBER	
	Cases n (%)	**Controls n (%)**	**Cases n (%)**	**Controls n (%)**	**Cases n (%)**	**Controls n (%)**	**Cases n (%)**	**Controls n (%)**	**Cases n (%)**	**Controls n (%)**
Total	1129	7317	686	666	725	905	634	3172	3174	12060
HR status										
ER+	735 (65.1)		371 (54.1)		521 (71.9)		477 (75.2)		2104 (66.3)	
ER-	394 (34.9)		315 (45.9)		204 (28.1)		157 (24.8)		1070 (33.7)	
TN	*138*		*180*		*116*		*57*		*491 (15.5)*	
Age at dx (y)										
< 40	96 (8.5)	885 (12.1)	127 (18.5)	100 (15)	97 (13.4)	133 (14.7)	0 (0)	0 (0)	320 (10.1)	1118 (9.3)
40–49	322 (28.5)	2167 (29.6)	205 (29.9)	220 (33)	205 (28.3)	268 (29.6)	1 (1.2)	24 (0.8)	733 (23.1)	2679 (22.2)
50–59	356 (31.5)	2100 (28.7)	145 (21.1)	145 (21.8)	233 (32.1)	311 (34.4)	48 (7.6)	299 (9.4)	782 (24.6)	2855 (23.7)
≥ 60	355 (31.4)	2165 (29.6)	209 (30.5)	201 (30.2)	190 (26.2)	193 (21.3)	585 (92.3)	2849 (89.8)	1339 (42.2)	5408 (44.8)
Recent BMI (kg/m^2)										
<25	273 (24.2)	1818 (24.9)	132 (19.2)	128 (19.2)	132 (18.2)	187 (20.7)	147 (23.2)	765 (24.1)	684 (21.6)	2898 (24.0)
25–29.99	393 (34.8)	2438 (33.3)	193 (28.1)	190 (28.5)	214 (29.5)	269 (29.7)	228 (36)	1230 (38.8)	1028 (32.4)	4127 (34.2)
30–34.99	265 (23.5)	1653 (22.6)	177 (25.8)	169 (25.4)	191 (26.3)	207 (22.9)	153 (24.1)	711 (22.4)	786 (24.8)	2740 (22.7)
≥35	198 (17.5)	1408 (19.2)	184 (26.8)	179 (26.9)	188 (25.9)	242 (26.7)	106 (16.7)	466 (14.7)	676 (21.3)	2295 (19.0)
Recent WHR										
≤0.74	281 (28.6)	1924 (30.0)	55 (8.1)	90 (13.6)	35 (4.8)	40 (4.4)	4 (5.4)	23 (8.2)	375 (15.2)	2077 (25.1)
0.75–0.81	255 (25.9)	1669 (26.0)	150 (22)	152 (22.9)	98 (13.6)	159 (17.6)	13 (17.6)	64 (22.7)	516 (21)	2044 (24.7)
0.82–0.88	235 (23.9)	1515 (23.6)	227 (33.3)	213 (32.1)	237 (32.8)	282 (31.2)	21 (28.4)	73 (25.9)	720 (29.3)	2083 (25.2)
>0.88	212 (21.6)	1311 (20.4)	249 (36.6)	208 (31.4)	353 (48.8)	424 (46.9)	36 (48.7)	122 (43.3)	850 (34.5)	2065 (25.0)

HR: Hormone Receptor; ER: Estrogen Receptor; TN; Triple Negative (ER-, PR-, HER2-); PR: progesterone receptor; HER: human epidermal growth factor receptor; dx; diagnosis; BMI: Body Mass Index; WHR: Waist-to-Hip Ratio. Recent BMI and WHR: based on most proximal value to diagnosis/index date

Table 2

Association of recent body mass index and breast cancer risk by menopausal status and subtype in the AMBER Consortium[1]

	Pre-menopausal						Post-menopausal					
	Cases	**Controls**	**OR1**	**95% CI**	**OR2**	**95% CI**	**Cases**	**Controls**	**OR1**	**95% CI**	**OR2**	**95% CI**
Overall												
Recent BMI (kg/m^2)												
<25	300	1185	Ref		Ref		384	1713	Ref		Ref	
25–29.99	359	1253	1.04	0.86–1.26	1.00	0.82–1.22	669	2874	1.02	0.88–1.18	1.05	0.87–1.27
30–34.99	269	814	1.12	0.91–1.37	1.14	0.91–1.42	517	1926	1.10	0.94–1.29	1.00	0.81–1.22
≥35	221	835	0.85	0.69–1.06	0.83	0.66–1.05	455	1460	1.14	0.96–1.34	1.08	0.88–1.34
p for trend				*0.20*		*0.21*				*0.08*		*0.57*
ER+												
Recent BMI (kg/m^2)												
<25	187	1185	Ref		Ref		254	1713	Ref		Ref	
25–29.99	205	1253	0.96	0.77–1.21	0.93	0.73–1.18	469	2874	1.10	0.93–1.30	1.18	0.94–1.48
30–34.99	169	814	1.14	0.89–1.46	1.20	0.92–1.55	361	1926	1.21	1.01–1.45	1.14	0.90–1.46
≥35	130	835	0.82	0.63–1.06	0.81	0.61–1.07	329	1460	1.32	1.09–1.60	1.31	1.02–1.67
p for trend				*0.26*		*0.32*				*0.002*		*0.06*
ER-												
Recent BMI (kg/m^2)												
<25	113	1185	Ref		Ref		130	1713	Ref		Ref	
25–29.99	154	1253	1.18	0.90–1.54	1.12	0.84–1.48	200	2874	0.87	0.69–1.11	0.86	0.64–1.14
30–34.99	100	814	1.08	0.80–1.47	1.06	0.77–1.46	156	1926	0.90	0.70–1.17	0.78	0.57–1.06
≥35	91	835	0.92	0.67–1.27	0.89	0.64–1.24	126	1460	0.82	0.63–1.08	0.75	0.54–1.04
p for trend				*0.45*		*0.38*				*0.23*		*0.09*
TN (ER-/PR-/HER2-)												
Recent BMI (kg/m^2)												
<25	47	1185	Ref		Ref		60	1713	Ref		Ref	

	Pre-menopausal						Post-menopausal					
	Cases	**Controls**	**OR1**	**95% CI**	**OR2**	**95% CI**	**Cases**	**Controls**	**OR1**	**95% CI**	**OR2**	**95% CI**
25–29.99	73	1253	1.37	0.92–2.05	1.29	0.85–1.94	71	2874	0.66	0.46–0.95	0.55	0.37–0.84
30–34.99	56	814	1.54	1.00–2.36	1.43	0.91–2.23	77	1926	0.91	0.63–1.31	0.72	0.47–1.08
≥35	51	835	1.25	0.80–1.94	1.13	0.71–1.80	56	1460	0.68	0.46–1.02	0.60	0.39–0.93
p for trend				*0.39*		*0.72*				*0.25*		*0.12*

OR1 adjusted for age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding (ever/never), age at first birth, hormone therapy use (ever/never), duration of oral contraceptive use, and age at menopause (for postmenopausal women). OR2 further adjusted for WHR for BMI analyses, and further adjusted for BMI for WHR analyses.

[1] Analyses in premenopausal women excluded MEC.

Recent BMI based on most proximal value to diagnosis/index date

Table 3

Association of young adult body mass index and breast cancer risk by menopausal status and subtype in the AMBER Consortium[1]

	Pre-menopausal						Post-menopausal					
	Cases	*Controls*	OR1	95% CI	OR2	95% CI	*Cases*	*Controls*	OR1	95% CI	OR2	95% CI
Overall												
Young adult BMI (kg/m^2)												
<20	424	1548	1.06	0.90–1.24	1.02	0.86–1.20	812	3184	1.10	0.98–1.23	1.09	0.95–1.26
20–24.9	517	1811	Ref		Ref		890	3440	Ref	0	Ref	
25–29.9	125	470	0.83	0.65–1.05	0.83	0.65–1.07	173	642	0.93	0.77–1.14	0.98	0.78–1.25
≥30	59	224	0.77	0.55–1.07	0.78	0.55–1.10	48	199	0.71	0.50–1.01	0.67	0.45–1.01
p for trend				*0.02*		*0.06*				*0.01*		*0.02*
ER+												
Young adult BMI (kg/m^2)												
<20	259	1548	1.06	0.87–1.28	0.99	0.81–1.20	554	3184	1.06	0.93–1.21	1.06	0.90–1.25
20–24.9	317	1811	Ref		Ref		628	3440	Ref		Ref	
25–29.9	68	470	0.75	0.56–1.01	0.75	0.55–1.01	125	642	0.97	0.78–1.21	1.07	0.82–1.39
≥30	30	224	0.65	0.42–0.99	0.65	0.42–1.01	31	199	0.68	0.45–1.03	0.62	0.38–1.01
p for trend				*0.005*		*0.02*				*0.05*		*0.12*
ER-												
Young adult BMI (kg/m^2)												
<20	165	1548	1.06	0.84–1.33	1.07	0.84–1.35	258	3184	1.19	0.99–1.44	1.17	0.93–1.46
20–24.9	200	1811	Ref		Ref		262	3440	Ref		Ref	
25–29.9	57	470	0.95	0.68–1.33	0.98	0.70–1.37	48	642	0.85	0.61–1.19	0.81	0.55–1.19
≥30	29	224	0.97	0.62–1.51	1.00	0.63–1.58	17	199	0.78	0.46–1.34	0.78	0.44–1.41
p for trend				*0.58*		*0.69*				*0.02*		*0.04*
TN (ER-/PR-/HER2-)												
Young adult BMI (kg/m^2)												
<20	72	1548	0.91	0.65–1.27	0.92	0.65–1.30	110	3184	1.13	0.86–1.49	1.03	0.75–1.41

	Pre-menopausal						Post-menopausal					
	Cases	***Controls***	**OR1**	**95% CI**	**OR2**	**95% CI**	***Cases***	***Controls***	**OR1**	**95% CI**	**OR2**	**95% CI**
20–24.9	99	1811	Ref		Ref		121	3440	Ref		Ref	
25–29.9	36	470	1.25	0.81–1.93	1.29	0.83–2.00	16	642	0.57	0.33–0.98	0.53	0.29–0.96
≥30	17	224	1.08	0.60–1.95	1.08	0.59–1.98	8	199	0.77	0.35–1.66	0.68	0.29–1.56
p for trend				*0.30*		*0.31*				*0.03*		*0.06*

OR1 adjusted for age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding (ever/never), age at first birth, hormone therapy use (ever/never), duration of oral contraceptive use, and age at menopause (for postmenopausal women). OR2 further adjusted for recent WHR.

[1] Analyses in premenopausal women excluded MEC.

Young adult BMI: BMI at age 18, 20 or 21.

Table 4

Body fat distribution and breast cancer risk by menopausal status and tumor subtype in the AMBER Consortium[1]

	Pre-menopausal						Post-menopausal					
	Cases	*Controls*	OR1	95% CI	OR2	95% CI	*Cases*	*Controls*	OR1	95% CI	OR2	95% CI
Overall												
Recent WHR												
≤0.74	188	1006	Ref		Ref		187	1071	Ref		Ref	
0.75–0.81	260	938	1.09	0.87–1.36	1.09	0.87–1.37	256	1106	1.02	0.82–1.27	1.02	0.82–1.27
0.82–0.88	313	851	1.21	0.97–1.51	1.23	0.98–1.55	407	1232	1.13	0.92–1.40	1.14	0.92–1.40
>0.88	320	853	1.21	0.96–1.53	1.26	0.99–1.60	530	1212	1.26	1.02–1.56	1.26	1.02–1.56
p for trend				*0.07*		*0.04*				*0.01*		*0.01*
ER+												
Recent WHR												
≤0.74	107	1006	Ref		Ref		125	1071	Ref		Ref	
0.75–0.81	149	938	1.08	0.82–1.43	1.09	0.82–1.44	174	1106	1.04	0.80–1.34	1.03	0.80–1.34
0.82–0.88	187	851	1.26	0.96–1.66	1.30	0.98–1.72	269	1232	1.10	0.86–1.41	1.09	0.86–1.40
>0.88	200	853	1.28	0.96–1.69	1.35	1.01–1.80	362	1212	1.26	0.98–1.61	1.24	0.97–1.60
p for trend				*0.05*		*0.02*				*0.04*		*0.05*
ER-												
Recent WHR												
≤0.74	81	1006	Ref		Ref		62	1071	Ref		Ref	
0.75–0.81	111	938	1.09	0.79–1.50	1.09	0.79–1.50	82	1106	1.00	0.70–1.42	1.00	0.71–1.43
0.82–0.88	126	851	1.13	0.82–1.55	1.14	0.82–1.57	138	1232	1.21	0.86–1.68	1.23	0.88–1.72
>0.88	120	853	1.12	0.81–1.56	1.14	0.81–1.59	168	1212	1.27	0.91–1.77	1.31	0.93–1.83
p for trend				*0.51*		*0.47*				*0.09*		*0.06*
TN (ER-/PR-/HER2-)												
Recent WHR												
≤0.74	33	1006	Ref		Ref		21	1071	Ref		Ref	

	Pre-menopausal						Post-menopausal					
	Cases	***Controls***	**OR1**	**95% CI**	**OR2**	**95% CI**	***Cases***	***Controls***	**OR1**	**95% CI**	**OR2**	**95% CI**
0.75–0.81	55	938	1.27	0.79–2.04	1.26	0.78–2.03	40	1106	1.33	0.76–2.31	1.33	0.76–2.31
0.82–0.88	63	851	1.20	0.75–1.93	1.18	0.73–1.91	72	1232	1.70	1.01–2.86	1.73	1.02–2.91
>0.88	71	853	1.44	0.89–2.33	1.40	0.85–2.31	81	1212	1.55	0.91–2.64	1.60	0.94–2.73
p for trend				*0.18*		*0.24*				*0.12*		*0.09*

OR1 adjusted for age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding (ever/never), age at first birth, hormone therapy use (ever/never), duration of oral contraceptive use, and age at menopause (for postmenopausal women). OR2 further adjusted for BMI.

[1] Analyses in premenopausal women excluded MEC.

Table 5

Joint associations of young adult and recent BMI in relation to ER+ and ER- breast cancer risk by menopausal status.

	Premenopausal			Postmenopausal		
	Young adult BMI (tertiles)			Young adult BMI (tertiles)		
	1 (≤19.48)	2 (19.49–21.97)	3 (>21.97)	1 (≤19.48)	2 (19.49–21.97)	3 (>21.97)
ER+						
Recent BMI						
<25	Ref (1.00)	1.14 (0.81–1.62)	0.68 (0.38–1.22)	Ref (1.00)	0.98 (0.72–1.33)	0.59 (0.36–0.97)
25–29.99	1.17 (0.82–1.68)	0.98 (0.71–1.37)	0.72 (0.48–1.09)	1.02 (0.79–1.32)	1.00 (0.77–1.28)	0.92 (0.68–1.23)
30–34.99	1.02 (0.62–1.68)	1.15 (0.78–1.71)	1.22 (0.86–1.72)	1.03 (0.75–1.42)	1.19 (0.90–1.56)	1.13 (0.86–1.49)
≥35	1.12 (0.54–2.31)	0.71 (0.40–1.23)	0.79 (0.57–1.11)	1.91 (1.32–2.75)	1.14 (0.83–1.58)	1.06 (0.81–1.38)
p for interaction		*0.31*			*0.08*	
ER-						
Recent BMI						
<25	Ref (1.00)	0.60 (0.37–0.97)	1.03 (0.56–1.90)	Ref (1.00)	0.84 (0.55–1.28)	0.70 (0.37–1.32)
25–29.99	1.37 (0.91–2.07)	0.96 (0.65–1.43)	0.85 (0.54–1.34)	0.89 (0.63–1.25)	0.73 (0.51–1.04)	0.74 (0.49–1.11)
30–34.99	0.88 (0.49–1.61)	0.90 (0.54–1.49)	1.09 (0.72–1.65)	0.91 (0.60–1.39)	0.91 (0.62–1.32)	0.67 (0.45–1.00)
≥35	1.44 (0.65–3.18)	0.86 (0.46–1.59)	0.69 (0.46–1.03)	0.60 (0.31–1.17)	0.61 (0.38–0.99)	0.73 (0.51–1.05)
p for interaction		*0.32*			*0.71*	

Adjusted for age, education, study, time period, geographical region, family history of breast cancer, age at menarche, parity, breastfeeding (yes/no), age at first birth, duration of oral contraceptive use, hormone therapy use, and age at menopause for postmenopausal women

[1] Analyses in premenopausal women excluded MEC

Recent BMI based on most proximal value to diagnosis/index date. Young adult BMI: BMI at age 18, 20 or 21.