Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

*Breast Cancer Res Treat*. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

*Breast Cancer Res Treat*. 2015 April ; 150(3): 655–666. doi:10.1007/s10549-015-3353-z.

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

**Elisa V. Bandera**[1,2], **Urmila Chandran**[1,3], **Chi-Chen Hong**[4], **Melissa A. Troester**[5], **Traci N. Bethea**[6], **Lucile L. Adams-Campbell**[7], **Christopher A. Haiman**[8], **Song-Yi Park**[9], **Andrew F. Olshan**[5], **Christine B. Ambrosone**[4], **Julie R. Palmer**[6], and **Lynn Rosenberg**[6]

[1]Cancer Prevention and Control, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

[2]Department of Epidemiology, Rutgers School of Public Health, Piscataway, NJ

[3]Janssen Pharmaceuticals, Johnson & Johnson, Raritan, NJ

[4]Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY

[5]Cancer Epidemiology, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill NC

[6]Slone Epidemiology Center at Boston University, Boston, MA

[7]Cancer Prevention and Control, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

[8]Department of Preventive Medicine and Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine, Los Angeles, CA

[9]Cancer Epidemiology, University of Hawaii Cancer Center, Honolulu, HI

## 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

**Corresponding author**: Dr. Elisa V. Bandera; Rutgers Cancer Institute of New Jersey; 195 Little Albany St., New Brunswick, NJ 08903, USA; elisa.bandera@rutgers.edu; Phone: (732) 235-9874; Fax: (732) 235-8808.

**Conflict of interest**: None

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## ACKNOWLEDGEMENTS

We thank participants and staff of the contributing studies. We wish also to acknowledge the late Robert Millikan, DVM, MPH, PhD, who was instrumental in the creation of this consortium. Pathology data were obtained from numerous state cancer registries (Arizona, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Illinois, Indiana, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, North Carolina, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas, Virginia). The results reported do not necessarily represent their views or the views of the NIH.

**Financial support**: This research was funded by the National Cancer Institute: P01CA151135 (all investigators), R01CA058420 and UM1CA164974 (T.N. Bethea, J.R. Palmer, L. Rosenberg), R01CA100598 (C.B. Ambrosone, E.V. Bandera). P50CA58223 (A.F. Olshan, M.A. Troester); the University Cancer Research Fund of North Carolina (A.F. Olshan, M.A. Troester) and the Breast Cancer Research Foundation (C.B. Ambrosone). The results do not necessarily reflect the views of the sponsors, who had no role in study design; data collection, analysis, or interpretation; or writing and submission of the manuscript.

## REFERENCES

1. Anderson WF, Rosenberg PS, Prat A, Perou CM, Sherman ME. How many etiological subtypes of breast cancer: two, three, four, or more? Journal of the National Cancer Institute. 2014; 106(8)
2. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast cancer research and treatment. 2014; 144(1):1–10. [PubMed: 24477977]
3. Amend K, Hicks D, Ambrosone CB. Breast cancer in African-American women: differences in tumor biology from European-American women. Cancer Res. 2006; 66(17):8327–8330. [PubMed: 16951137]
4. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012; 307(5):491–497. [PubMed: 22253363]
5. Rose DP, Haffner SM, Baillargeon J. Adiposity, the metabolic syndrome, and breast cancer in African-American and white American women. Endocrine reviews. 2007; 28(7):763–777. [PubMed: 17981890]
6. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2003; 4(3):157–173. [PubMed: 12916817]
7. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report Summary ( 2010) Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer.
8. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. International journal of cancer Journal international du cancer. 2009; 124(3):698–712. [PubMed: 18988226]
9. Chandran U, Hirshfield KM, Bandera EV. The role of anthropometric and nutritional factors on breast cancer risk in African-American women. Public health nutrition. 2012; 15(4):738–748. [PubMed: 22122844]
10. Palmer JR, Ambrosone CB, Olshan AF. A collaborative study of the etiology of breast cancer subtypes in African American women: the AMBER consortium. Cancer causes & control : CCC. 2014; 25(3):309–319. [PubMed: 24343304]
11. Palmer JR, Viscidi E, Troester MA, Hong CC, Schedin P, Bethea TN, Bandera EV, Borges V, McKinnon C, Haiman CA, Lunetta K, Kolonel LN, Rosenberg L, Olshan AF, Ambrosone CB. Parity, Lactation, and Breast Cancer Subtypes in African American Women: Results from the AMBER Consortium. Journal of the National Cancer Institute. 2014; 106(10)
12. Newman B, Moorman PG, Millikan R, Qaqish BF, Geradts J, Aldrich TE, Liu ET. The Carolina Breast Cancer Study: integrating population-based epidemiology and molecular biology. Breast cancer research and treatment. 1995; 35(1):51–60. [PubMed: 7612904]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

13. Hall IJ, Newman B, Millikan RC, Moorman PG. Body size and breast cancer risk in black women and white women: the Carolina Breast Cancer Study. American journal of epidemiology. 2000; 151(8):754–764. [PubMed: 10965972]

14. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. American journal of epidemiology. 2000; 151(7):703–714. [PubMed: 10752798]

15. Ambrosone CB, Ciupak GL, Bandera EV, Jandorf L, Bovbjerg DH, Zirpoli G, Pawlish K, Godbold J, Furberg H, Fatone A, Valdimarsdottir H, Yao S, Li Y, Hwang H, Davis W, Roberts M, Sucheston L, Demissie K, Amend KL, Tartter P, Reilly J, Pace BW, Rohan T, Sparano J, Raptis G, Castaldi M, Estabrook A, Feldman S, Weltz C, Kemeny M. Conducting Molecular Epidemiological Research in the Age of HIPAA: A Multi-Institutional Case-Control Study of Breast Cancer in African-American and European-American Women. Journal of oncology. 2009:871250. [PubMed: 19865486]

16. Bandera EV, Chandran U, Zirpoli G, McCann SE, Ciupak G, Ambrosone CB. Rethinking sources of representative controls for the conduct of case-control studies in minority populations. BMC medical research methodology. 2013; 13:71. [PubMed: 23721229]

17. Bandera EV, Chandran U, Zirpoli G, Ciupak G, Bovbjerg DH, Jandorf L, Pawlish K, Freudenheim JL, Ambrosone CB. Body size in early life and breast cancer risk in African American and European American women. Cancer causes & control : CCC. 2013; 24(12):2231–2243. [PubMed: 24113797]

18. Bandera EV, Chandran U, Zirpoli G, Gong Z, McCann SE, Hong CC, Ciupak G, Pawlish K, Ambrosone CB. fatness and breast cancer risk in women of African ancestry. BMC cancer. 2013) Body; 13:475. [PubMed: 24118876]

19. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. Journal of the American Medical Women's Association. 1995; 50(2):56–58.

20. Palmer JR, Adams-Campbell LL, Boggs DA, Wise LA, Rosenberg L. A prospective study of body size and breast cancer in black women. Cancer Epidemiol Biomarkers Prev. 2007; 16(9):1795–1802. [PubMed: 17855697]

21. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, Stram DO, Monroe KR, Earle ME, Nagamine FS. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. American journal of epidemiology. 2000; 151(4):346–357. [PubMed: 10695593]

22. White KK, Park SY, Kolonel LN, Henderson BE, Wilkens LR. Body size and breast cancer risk: the Multiethnic Cohort. International journal of cancer Journal international du cancer. 2012; 131(5):E705–E716. [PubMed: 22120517]

23. Steinbrecher A, Heak S, Morimoto Y, Grandinetti A, Kolonel LN, Maskarinec G. Various Adiposity Measures Show Similar Positive Associations With Type 2Diabetes in Caucasians, Native Hawaiians, and Japanese Americans: The Multiethnic Cohort. Asia-Pacific journal of public health / Asia-Pacific Academic Consortium for Public Health. 2012

24. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, Gaudet M, Schmidt MK, Broeks A, Cox A, Fasching PA, Hein R, Spurdle AB, Blows F, Driver K, Flesch-Janys D, Heinz J, Sinn P, Vrieling A, Heikkinen T, Aittomaki K, Heikkila P, Blomqvist C, Lissowska J, Peplonska B, Chanock S, Figueroa J, Brinton L, Hall P, Czene K, Humphreys K, Darabi H, Liu J, Van 't Veer LJ, van Leeuwen FE, Andrulis IL, Glendon G, Knight JA, Mulligan AM, O'Malley FP, Weerasooriya N, John EM, Beckmann MW, Hartmann A, Weihbrecht SB, Wachter DL, Jud SM, Loehberg CR, Baglietto L, English DR, Giles GG, McLean CA, Severi G, Lambrechts D, Vandorpe T, Weltens C, Paridaens R, Smeets A, Neven P, Wildiers H, Wang X, Olson JE, Cafourek V, Fredericksen Z, Kosel M, Vachon C, Cramp HE, Connley D, Cross SS, Balasubramanian SP, Reed MW, Dork T, Bremer M, Meyer A, Karstens JH, Ay A, Park-Simon TW, Hillemanns P, Arias Perez JI, Menendez Rodriguez P, Zamora P, Benitez J, Ko YD, Fischer HP, Hamann U, Pesch B, Bruning T, Justenhoven C, Brauch H, Eccles DM, Tapper WJ, Gerty SM, Sawyer EJ, Tomlinson IP, Jones A, Kerin M, Miller N, McInerney N, Anton-Culver H, Ziogas A, Shen CY, Hsiung CN, Wu PE, Yang SL, Yu JC, Chen ST, Hsu GC, Haiman CA, Henderson BE, Le Marchand L, Kolonel LN, Lindblom A, Margolin S, Jakubowska A, Lubinski J, Huzarski T, Byrski T, Gorski B, Gronwald J, Hooning MJ, Hollestelle A, van den Ouweland AM,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Jager A, Kriege M, Tilanus-Linthorst MM, Collee M, Wang-Gohrke S, Pylkas K, Jukkola-Vuorinen A, Mononen K, Grip M, Hirvikoski P, Winqvist R, Mannermaa A, Kosma VM, Kauppinen J, Kataja V, Auvinen P, Soini Y, Sironen R, Bojesen SE, Orsted DD, Kaur-Knudsen D, Flyger H, Nordestgaard BG, Holland H, Chenevix-Trench G, Manoukian S, Barile M, Radice P, Hankinson SE, Hunter DJ, Tamimi R, Sangrajrang S, Brennan P, McKay J, Odefrey F, Gaborieau V, Devilee P, Huijts PE, Tollenaar RA, Seynaeve C, Dite GS, Apicella C, Hopper JL, Hammet F, Tsimiklis H, Smith LD, Southey MC, Humphreys MK, Easton D, Pharoah P, Sherman ME, Garcia-Closas M. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. Journal of the National Cancer Institute. 2011; 103(3):250–263. [PubMed: 21191117]

25. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiologic reviews. 2014; 36(1):114–136. [PubMed: 24375928]
26. Robinson WR, Tse CK, Olshan AF, Troester MA. Body size across the life course and risk of premenopausal and postmenopausal breast cancer in Black women, the Carolina Breast Cancer Study, 1993–2001. Cancer causes & control : CCC. 2014; 25(9):1101–1117. [PubMed: 24924530]
27. Berstad P, Coates RJ, Bernstein L, Folger SG, Malone KE, Marchbanks PA, Weiss LK, Liff JM, McDonald JA, Strom BL, Simon MS, Deapen D, Press MF, Burkman RT, Spirtas R, Ursin G. A case-control study of body mass index and breast cancer risk in white and African-American women. Cancer Epidemiol Biomarkers Prev. 2010; 19(6):1532–1544. [PubMed: 20501755]
28. John EM, Sangaramoorthy M, Phipps AI, Koo J, Horn-Ross PL. Adult body size, hormone receptor status, and premenopausal breast cancer risk in a multiethnic population: the San Francisco Bay Area breast cancer study. American journal of epidemiology. 2011; 173(2):201–216. [PubMed: 21084558]
29. John EM, Phipps AI, Sangaramoorthy M. Body size, modifying factors, and postmenopausal breast cancer risk in a multiethnic population: the San Francisco Bay Area Breast Cancer Study. SpringerPlus. 2013; 2(1):239. [PubMed: 23762816]
30. Canchola AJ, Anton-Culver H, Bernstein L, Clarke CA, Henderson K, Ma H, Ursin G, Horn-Ross PL. Body size and the risk of postmenopausal breast cancer subtypes in the California Teachers Study cohort. Cancer causes & control : CCC. 2012
31. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast cancer research and treatment. 2013; 137(1):307–314. [PubMed: 23179600]
32. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, Smith LV, Labbok MH, Geradts J, Bensen JT, Jackson S, Nyante S, Livasy C, Carey L, Earp HS, Perou CM. Epidemiology of basal-like breast cancer. Breast cancer research and treatment. 2008; 109(1):123–139. [PubMed: 17578664]
33. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, Hewitt SM, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Cartun R, Mandich D, Rymkiewicz G, Ligaj M, Lukaszek S, Kordek R, Garcia-Closas M. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev. 2007; 16(3):439–443. [PubMed: 17372238]
34. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, Malone KE. Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1157–1166. [PubMed: 19336554]
35. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2008; 17(8):2078–2086. [PubMed: 18664548]
36. Gaudet MM, Press MF, Haile RW, Lynch CF, Glaser SL, Schildkraut J, Gammon MD, Douglas Thompson W, Bernstein JL. Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger. Breast cancer research and treatment. 2011; 130(2):587–597. [PubMed: 21667121]
37. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Stefanick ML, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Vitolins M, Kabat GC, Rohan TE, Li CI. Body size, physical

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

activity, and risk of triple-negative and estrogen receptor-positive breast cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20(3):454–463. [PubMed: 21364029]

38. Michels KB, Willett WC. Breast cancer--early life matters. The New England Journal of Medicine. 2004; 351(16):1679–1681. [PubMed: 15483288]
39. Mayberry RM. Age-specific patterns of association between breast cancer and risk factors in black women, ages 20 to 39 and 40 to 54. Ann Epidemiol. 1994; 4(3):205–213. [PubMed: 8055121]
40. Zhu K, Caulfield J, Hunter S, Roland CL, Payne-Wilks K, Texter L. Body mass index and breast cancer risk in African American women. Ann Epidemiol. 2005; 15(2):123–128. [PubMed: 15652717]
41. Tamimi RM, Colditz GA, Hazra A, Baer HJ, Hankinson SE, Rosner B, Marotti J, Connolly JL, Schnitt SJ, Collins LC. Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast cancer research and treatment. 2012; 131(1):159–167. [PubMed: 21830014]
42. Amadou A, Hainaut P, Romieu I. Role of obesity in the risk of breast cancer: lessons from anthropometry. Journal of oncology. 2013:906495. [PubMed: 23431300]
43. Amadou A, Ferrari P, Muwonge R, Moskal A, Biessy C, Romieu I, Hainaut P. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2013; 14(8):665–678. [PubMed: 23615120]
44. Wise LA, Palmer JR, Spiegelman D, Harlow BL, Stewart EA, Adams-Campbell LL, Rosenberg L. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology. 2005; 16(3):346–354. [PubMed: 15824551]
45. Cairns BJ, Liu B, Clennell S, Cooper R, Reeves GK, Beral V, Kuh D. Lifetime body size and reproductive factors: comparisons of data recorded prospectively with self reports in middle age. BMC medical research methodology. 2011; 11:7. [PubMed: 21241500]
46. McAdams MA, Van Dam RM, Hu FB. Comparison of self-reported and measured BMI as correlates of disease markers in US adults. Obesity. 2007; 15(1):188–196. [PubMed: 17228047]
47. Roberts CA, Wilder LB, Jackson RT, Moy TF, Becker DM. Accuracy of self-measurement of waist and hip circumference in men and women. Journal of the American Dietetic Association. 1997; 97(5):534–536. [PubMed: 9145094]
48. Davis AA, Kaklamani VG. Metabolic syndrome and triple-negative breast cancer: a new paradigm. International journal of breast cancer. 2012:809291. [PubMed: 22295251]
49. Flegal KM, Shepherd JA, Looker AC, Graubard BI, Borrud LG, Ogden CL, Harris TB, Everhart JE, Schenker N. Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. The American journal of clinical nutrition. 2009; 89(2):500–508. [PubMed: 19116329]
50. Katzmarzyk PT, Bray GA, Greenway FL, Johnson WD, Newton RL Jr, Ravussin E, Ryan DH, Smith SR, Bouchard C. Racial differences in abdominal depot-specific adiposity in white and African American adults. The American journal of clinical nutrition. 2010; 91(1):7–15. [PubMed: 19828714]
51. Goedecke JH, Levitt NS, Evans J, Ellman N, Hume DJ, Kotze L, Tootla M, Victor H, Keswell D. The role of adipose tissue in insulin resistance in women of African ancestry. Journal of obesity. 2013:952916. [PubMed: 23401754]
52. Morimoto Y, Conroy SM, Ollberding NJ, Kim Y, Lim U, Cooney RV, Franke AA, Wilkens LR, Hernandez BY, Goodman MT, Henderson BE, Kolonel LN, Le Marchand L, Maskarinec G. Ethnic differences in serum adipokine and C-reactive protein levels: the multiethnic cohort. International journal of obesity. 2014

Author Manuscript Author Manuscript Author Manuscript Author Manuscript





*Breast Cancer Res Treat*. Author manuscript; available in PMC 2016 April 01.

**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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



**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 | |

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



| | 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript





*Breast Cancer Res Treat*. Author manuscript; available in PMC 2016 April 01.

**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 |

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



| | 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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



**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 | |

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



| | 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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



**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.