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# Central and peripheral adiposity and premenopausal breast cancer risk: a pooled analysis of 440,179 women

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## Abstract

**Background** Among premenopausal women, higher body mass index (BMI) is associated with lower breast cancer risk, although the underlying mechanisms are unclear. Investigating adiposity distribution may help clarify impacts on breast cancer risk. This study was initiated to investigate associations of central and peripheral adiposity with premenopausal breast cancer risk overall and by other risk factors and breast cancer characteristics.

**Methods** We used individual-level data from 14 prospective cohort studies to estimate hazard ratios (HRs) for premenopausal breast cancer using Cox proportional hazards regression. Analyses included 440,179 women followed for a median of 7.5 years (interquartile range: 4.0–11.3) between 1976 and 2017, with 6,779 incident premenopausal breast cancers.

**Results** All central adiposity measures were inversely associated with breast cancer risk overall when not controlling for BMI (e.g. for waist circumference, HR per 10 cm increase: 0.92, 95% confidence interval (CI): 0.90–0.94) whereas in models adjusting for BMI, these measures were no longer associated with risk (e.g. for waist circumference: HR 0.99, 95% CI: 0.95–1.03). This finding was consistent across age categories, with some evidence that BMI-adjusted associations differed by breast cancer subtype. Inverse associations for in situ breast cancer were observed with waist-to-height and waist-to-hip ratios and a positive association was observed for oestrogen-receptor-positive breast cancer with hip circumference (HR per 10 cm increase: 1.08, 95% CI: 1.10–1.14). For luminal B, HER2-positive breast cancer, we observed an inverse association with hip circumference (HR per 10 cm: 0.84, 95% CI: 0.71–0.98), but positive associations with waist circumference (HR per 10 cm: 1.18, 95% CI: 1.03–1.36), waist-to-hip ratio (HR per 0.1 units: 1.29, 95% CI: 1.15–1.45) and waist-to height ratio (HR per 0.1 units: 1.46, 95% CI: 1.17–1.84).

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**Conclusions** Our analyses did not support an association between central adiposity and overall premenopausal breast cancer risk after adjustment for BMI. However, our findings suggest associations might differ by breast cancer hormone receptor and intrinsic subtypes.

**Keywords** Breast cancer, Cohort study, Adiposity

## Introduction

Breast cancer accounts for 25% of incident female cancers globally, and a higher percentage among young women [1]. Understanding the role of adiposity in breast cancer risk is important because it is a potentially modifiable factor, and the prevalence of obesity has been increasing worldwide. The relationship between adiposity and breast cancer risk is unusual in that there is an inverse association with body mass index (BMI) before menopause and a positive association with BMI after menopause [2]. The association after menopause is likely driven by sex hormone levels, but the inverse association with premenopausal breast cancer is largely unexplained [3, 4]. However, the explanatory power of BMI has limitations in that it does not reflect the distribution of fat versus lean tissue: women with the same BMI may carry fat more centrally or more peripherally [5].

There is evidence that body fat deposition at different anatomical locations has different metabolic effects [6, 7], but the role of fat distribution in the etiology of premenopausal breast cancer is unclear. Central adiposity, around the trunk and upper body, reflects both abdominal subcutaneous and visceral fat, and its association with cardiometabolic outcomes and cancer risk, including postmenopausal breast cancer, is thought to be related to the metabolic actions of visceral fat [2, 6]. Peripheral adiposity, around the buttocks, hips and thighs, is metabolically different, and confers a protective effect on cardiovascular health and mortality [8–11].

To understand the potential unique contribution of central adiposity to premenopausal breast cancer risk, investigations must simultaneously account for measures of overall adiposity, such as BMI. However, not all studies report results with BMI adjustment (or other analytic approaches to account for overall adiposity). Relatively few studies have investigated hip circumference or waist-to-height ratio, the latter being reported to be a better global screening tool for cardiovascular disease risk than waist circumference [12]. Moreover, there is some evidence that the association between central adiposity and premenopausal breast cancer varies according to hormone receptor or molecular subtypes of breast cancer, but few studies have been large enough to examine differences by subtype [3] or by potential modifying factors, such as age at exposure assessment, parity, or other relevant characteristics.

In the study reported here, we pooled data from 14 prospective cohort studies of premenopausal women to investigate in detail the role of central and peripheral adiposity measures on premenopausal breast cancer risk.

## Methods

We used data from prospective studies included in the Premenopausal Breast Cancer Collaborative Group [13], a collaboration of 22 prospective studies that each included at least 100 incident breast cancer cases diagnosed before age 55 years, which was formed through the National Cancer Institute Cohort Consortium [14]. We included all of the 14 (out of 22) prospective studies from the working group for which premenopausal waist circumference was available at one or more time points (see Supplemental Methods).

We harmonized individual-level data to a common template from the baseline questionnaire plus 0–16 rounds of follow-up questionnaires, depending on the study. Studies were carried out in North America (n = 7), Europe (n = 5), Asia (n = 1) and Australia (n = 1), with participants recruited between 1976 and 2013 and follow-up through 2017.

Women were included in the analysis if they were premenopausal at enrollment, with no history of breast cancer, with information on premenopausal waist (± hip) circumference and BMI available at the same age or, if missing at that age, up to 3 years earlier. Extreme values of anthropometric measures (across different cohorts) were set to missing: height (< 100 or > 195 cm), weight (< 30 or > 200 kg), BMI (< 15 or > 49 kg/m$^2$), waist circumference (< 50 or > 160 cm), hip circumference (< 50 or > 180 cm), waist-to-hip ratio (< 0.4 or > 1.5), waist-to-height ratio (< 0.2 or > 1.0). We determined menopausal status during follow-up from information reported at multiple questionnaire rounds and, if missing, assumptions based on attained age and the latest information provided as defined in the Supplemental Methods.

The main analytical endpoint was diagnosis with premenopausal breast cancer. We also conducted analyses by invasiveness (in situ vs. invasive) and hormone receptor status of breast cancer (oestrogen (ER)-receptor positive vs. ER-negative), combined ER-receptor and progesterone (PR)-receptor status, and by a clinicopathological surrogate definition of intrinsic

breast cancer subtypes (luminal A-like; luminal B-like, HER2-negative; luminal B-like, HER2-positive; HER2-enriched; triple-negative, as defined in the Supplemental Methods) [15].

### Statistical methods

We conducted analyses using STATA 14.2 [16]. Our analyses were restricted to premenopausal person-time. Follow-up for breast cancer started at the age of the first report of waist circumference and ended with the first of: breast cancer diagnosis, menopause, last follow-up, death, or age 55 years. Menopause status and age at menopause were updated across follow-up rounds, as available, and included premenopausal uterectomy with retention or one or both ovaries. We estimated relative hazards (HR) for breast cancer with 95% confidence intervals (CI) using Cox proportional hazards models, treating age as the underlying time scale [17]. We included the following covariates, which were updated over follow-up where possible (if appropriate): study, birth cohort (< 1930, 1930–9, 1940–9, 1950–9, 1960–9, 1970–9, ≥ 1980), age at menarche, parity, age at first birth, adult height, and time since most recent birth. Missing data were coded as a separate category. Across covariates, missingness levels were highest for time since most recent birth and lowest for height (adult height: 0%, age at menarche: 2.2%, parity: 6.0%, age at first birth: 6.7%, and time since most recent birth: 21.2%).

We estimated HRs for waist and hip circumference, waist-to-hip ratio and waist-to-height ratio, with and without adjustment for BMI. Because of the strong correlation of waist-to-hip ratio with BMI, we additionally fit a model including BMI and the residuals of waist or hip circumference after regressing waist and hip circumference on BMI [18]. Adiposity measures were analyzed in categories and as a linear trend. We estimated separate HRs for breast cancer subtypes using an augmentation method [19].

Effect modification was assessed by cohort, birth cohort < 1950 versus ≥ 1950, age at waist/hip assessment, age at follow-up, parity/nulliparity, breastfeeding (among parous women), race and ethnicity, family history of breast cancer and method of assessment of waist/hip circumference as described in the Supplemental Methods [20].

We conducted sensitivity analyses by: excluding subjects whose BMI was carried forward from a previous round if BMI at the time of waist circumference assessment was missing; adjusting analyses for BMI at ages 18–24 years instead of concurrent BMI, given that BMI at these younger ages is more strongly associated with breast cancer risk than BMI at later premenopausal ages [21]; restricting follow-up time from participants who did not have a self-reported age at menopause (for whom age at menopause was imputed as 55 years); adjusting, in separate models, for each of alcohol consumption, cigarette smoking, physical activity, family history of breast cancer, history of mammographic screening and race and ethnicity.

## Results

The analyses included 440,179 women who provided data on premenopausal waist circumference (including 437,421 (99.4%) with waist *and* hip circumference) and concomitant BMI (93%) or BMI up to 3 years earlier (7%). Waist and hip circumference were examiner-measured for 23.3% of subjects, with the remainder having self-reported/self-measured circumferences or unknown method. The median age at reported waist circumference was 42.6 years (interquartile range: 36.6–46.9), and follow-up was for a median of 7.5 (interquartile range: 4.0–11.3) premenopausal years, during which 6,779 women were diagnosed with breast cancer (Table 1). Most study participants were white (80.9%), and the greatest proportion was from North America (40.8%) (Table S1).

Waist circumference was on average greater among women with earlier menarche, or with earlier first childbirth, higher parity and among Black women and women from North America (Table S1). Correlations with BMI were strong for waist and hip circumference and waist-to-height ratio (correlation coefficients ranging 0.77–0.85, with stronger associations at older ages), and modest with waist-to-hip ratio (0.30–0.39) (Table S2).

All central and peripheral adiposity measures (Fig. 1, left) showed statistically significant inverse associations with breast cancer risk in models that did not account for BMI. The inverse association was notably weaker for waist-to-hip ratio than for the other measures.

In models that adjusted for BMI (Fig. 1, right), no associations with overall breast cancer risk were observed. These findings were supported by analyses of residuals of BMI-adjusted waist and hip circumference instead of waist and hip circumference on their own, thereby removing correlation between each variable and BMI (Table S3). In all models, BMI was strongly inversely associated with risk, with risk reduction estimated as 12% per 5 $kg/m^2$ increase in BMI (HR: 0.88, 95% CI: 0.86–0.91).

We found little to no evidence for between-cohort heterogeneity in effect for either waist or hip circumference and cohort-specific effect estimates were overall consistent with the main findings (Figure S1). In analyses by age at adiposity assessment, there was weak (p heterogeneity = 0.045 for analyses of trend) evidence for effect modification by age at waist-to-hip ratio

**Table 1** Cohort characteristics and number of premenopausal breast cancer cases included in the analyses of central and peripheral adiposity, by cohort study

| Cohort | Age at start follow-up, years | | Follow-up, median (y) | Number of participants | Number of breast cancer cases | BMI, median ($kg/m^2$) | Waist circumference, median (cm) | Hip circumference, median (cm) | Waist-to-hip ratio, median | Waist-to-height Ratio, median |
|---|---|---|---|---|---|---|---|---|---|---|
| | Median (a) | Minimum, maximum (a) | | | | | | | | |
| BWHS | 35 | 20–52 | 11 | 38,897 | 717 | 25 | 78 | 101 | 0.78 | 0.47 |
| CSDLH (b) | 42 | 23–52 | 6 | 1078 | 210 | 22 | 76 | 99 | 0.77 | 0.46 |
| CTS | 43 | 24–54 | 7 | 26,488 | 345 | 22 | 76 | 99 | 0.77 | 0.46 |
| E3N | 48 | 44–54 | 4 | 25,647 | 442 | 22 | 73 | 95 | 0.77 | 0.45 |
| EPIC | 41 | 19–54 | 7 | 79,914 | 961 | 23 | 74 | 97 | 0.76 | 0.45 |
| GS | 38 | 18–54 | 7 | 58,902 | 699 | 23 | 78 | 98 | 0.80 | 0.47 |
| HUNT2 | 37 | 20–54 | 12 | 16,527 | 117 | 24 | 76 | 99 | 0.77 | 0.45 |
| MCCS | 45 | 31–54 | 4 | 8085 | 86 | 24 | 74 | 99 | 0.76 | 0.46 |
| NHS | 49 | 39–54 | 5 | 29,630 | 520 | 23 | 76 | 99 | 0.76 | 0.46 |
| NHS2 | 41 | 28–54 | 9 | 63,872 | 1388 | 23 | 77 | 99 | 0.78 | 0.47 |
| NYUWHS | 43 | 33–54 | 8 | 4472 | 155 | 23 | 70 | 96 | 0.73 | 0.42 |
| SISTER | 46 | 35–54 | 4 | 15,163 | 395 | 25 | 81 | 102 | 0.79 | 0.49 |
| SWHS | 44 | 40–54 | 6 | 33,687 | 216 | 22 | 74 | 94 | 0.79 | 0.46 |
| WLHS | 40 | 29–54 | 9 | 37,817 | 528 | 22 | 76 | 98 | 0.77 | 0.45 |
| Total | 42 | 18–54 | 7 | 440,179 | 6779 | 23 | 76 | 98 | 0.78 | 0.46 |

Study acronyms: BWHS: Black Women's Health Study; BGS: Breakthrough Generations Study; CTS: Californian Teachers Study; CSDLH: Canadian Study of Diet, Lifestyle, and Health; EPIC: European Prospective Study into Cancer and Nutrition; E3N: Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; HUNT2: Helseundersøkelsen i Nord-Trøndelag MCCS: Melbourne Collaborative Cohort Study; NHS1: Nurses' Health Study 1; NHS2: Nurses' Health Study 2; NYUWHS: New York University Women's Health Study; SISTER: Sister Study; SMC: Swedish Mammography Cohort; SWHS: Shanghai Women's Health Study; WLHS: Women's Lifestyle and Health Study

(a) Follow-up starts at waist (±hip) assessment

(b) This study was provided as a case-cohort dataset

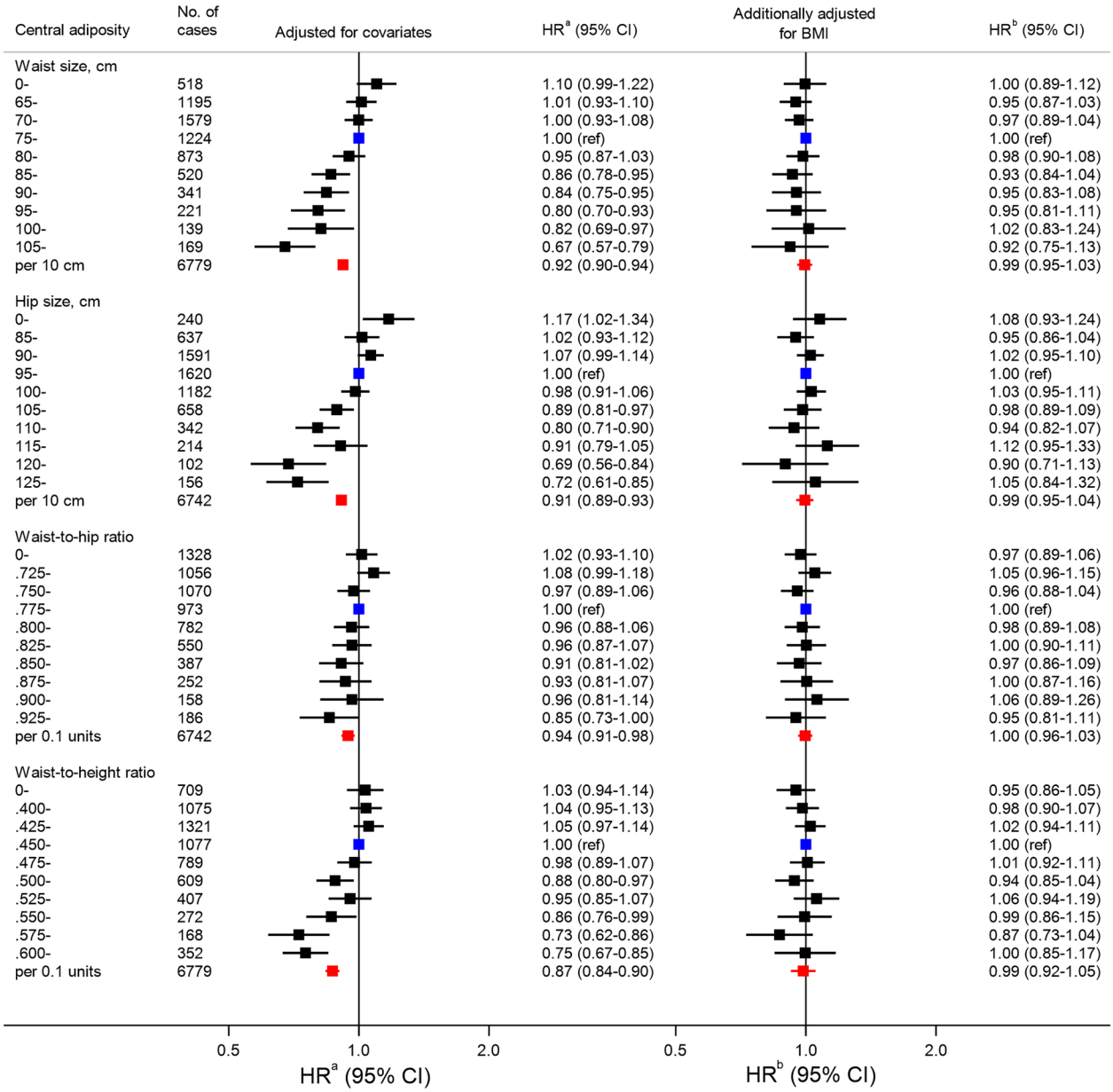


**Fig. 1** Hazard ratios of premenopausal breast cancer overall in relation to central and peripheral adiposity measures. BMI, body mass index; CI, confidence interval; HR, hazard ratio. (a) Adjusted for study centre, attained age, birth cohort, age at menarche, age at first birth, number of births, time since last birth and adult height. (b) Adjusted for study centre, attained age, birth cohort, age at menarche, age at first birth, number of births, time since last birth and adult height plus BMI at the time of the waist circumference (see supplementary methods)

assessment only, with a positive association for waist-to-hip ratio at ages 18–34 (HR per 0.1 units: 1.07, 95% CI: 1.00–1.15) but no association at older ages (Table S4). There was little evidence that HRs differed by race (Table S5).

In BMI-adjusted analyses, statistically significant inverse associations with waist-to-height and waist-to-hip ratio were observed for in situ, but not invasive, breast cancer (Table 2). Results were similar when we restricted analyses to women who reported ever having had a screening mammogram (not shown). Analyses by ER status showed no significant associations except for hip circumference, for which there was evidence of heterogeneity by ER status (HR per 10 cm for ER-positive breast cancer: 1.08, 95% CI: 1.01–1.14, ER-negative: 0.91, 95% CI: 0.83–1.01, p

**Table 2** Hazard ratios for premenopausal breast cancer in relation to central/peripheral adiposity, by breast cancer characteristics

| Breast cancer characteristics, Type(a) | Analyses based on waist circumference | | | Analyses based on hip and waist circumference | | |
|---|---|---|---|---|---|---|
| | | Waist circumference, per 10 cm | Waist-to-height ratio, per 0.1 units | | Hip circumference, per 10 cm | Waist-to-hip ratio, per 0.1 units |
| | No. cases | HR (95% CI) | HR (95% CI) | No. cases | HR (95% CI) | HR (95% CI) |
| *Invasiveness* | | | | | | |
| In situ | 1224 | 0.93 (0.85–1.02) | 0.82 (0.70–0.95) | 1216 | 1.02 (0.93–1.12) | 0.91 (0.83–0.99) |
| Invasive | 5143 | 1.01 (0.97–1.06) | 1.04 (0.97–1.11) | 5115 | 0.99 (0.94–1.04) | 1.02 (0.98–1.06) |
| | | p-het = 0.08 | p-het = 0.005 | | p-het = 0.5 | p-het = 0.02 |
| *ER-status* | | | | | | |
| ER + | 3764 | 1.03 (0.98–1.08) | 1.02 (0.94–1.11) | 3746 | 1.08 (1.01–1.14) | 0.98 (0.94–1.03) |
| ER- | 1122 | 0.97 (0.89–1.06) | 1.04 (0.90–1.20) | 1114 | 0.91 (0.83–1.01) | 1.03 (0.94–1.12) |
| | | p-het = 0.25 | p-het = 0.84 | | p-het = 0.003 | p-het = 0.4 |
| *Combined ER and PR status* | | | | | | |
| ER + PR + | 2970 | 1.03 (0.98–1.09) | 1.02 (0.94–1.12) | 2958 | 1.10 (1.03–1.17) | 0.98 (0.92–1.03) |
| ER + PR- | 439 | 0.99 (0.85–1.15) | 0.95 (0.74–1.23) | 437 | 1.07 (0.91–1.24) | 0.95 (0.82–1.10) |
| ER-PR + | 185 | 1.10 (0.90–1.36) | 1.57 (1.14–2.15) | 185 | 0.97 (0.79–1.18) | 1.10 (0.92–1.31) |
| ER-PR- | 889 | 0.98 (0.90–1.08) | 1.01 (0.86–1.18) | 882 | 0.91 (0.81–1.01) | 1.05 (0.95–1.15) |
| | | p-het = 0.7 | p-het = 0.065 | | p-het = 0.019 | p-het = 0.35 |
| *Breast cancer intrinsic subtype (b)* | | | | | | |
| Luminal A | 1472 | 0.99 (0.91–1.07) | 0.94 (0.82–1.07) | 1471 | 1.09 (0.99–1.21) | 0.95 (0.87–1.04) |
| Luminal B-HER2-neg | 238 | 0.95 (0.78–1.16) | 0.93 (0.67–1.31) | 238 | 1.10 (0.89–1.36) | 0.88 (0.72–1.08) |
| Luminal B-HER2-pos | 383 | 1.18 (1.03–1.36) | 1.46 (1.17–1.84) | 383 | 0.84 (0.71–0.98) | 1.29 (1.15–1.45) |
| HER2-enriched (ER-PR-) | 150 | 1.19 (0.93–1.52) | 1.30 (0.86–1.96) | 150 | 1.34 (1.03–1.75) | 1.00 (0.78–1.27) |
| Triple Negative | 308 | 1.03 (0.88–1.20) | 1.08 (0.83–1.41) | 306 | 0.94 (0.78–1.13) | 1.07 (0.92–1.25) |
| | | p-het = 0.1 | p-het = 0.01 | | p-het = 0.01 | p-het < 0.001 |

BMI, body mass index; CI, confidence interval; ER, oestrogen-receptor; HR, hazard ratio; p-het, P-value for heterogeneity test; PR, progesterone-receptor

(a) Adjusted for study centre, attained age, birth cohort, age at menarche, age at first birth, number of births, time since last birth, adult height and additionally for the main effect of BMI plus an interaction term for BMI with breast cancer subtype (see supplementary methods)

(b) Luminal A-like: ER + PR + HER2-; Luminal B-like, HER2-: ER + PR – HER2- and ER – PR + HER2-; luminal B-like, HER2 + : [ER + and/or PR +] and HER2 + ; HER2-enriched: ER – PR – HER2 + ; and Triple-negative: ER – PR – HER2- as proposed by St Gallen Expert Consensus. [13]

heterogeneity = 0.003). Heterogeneity in the association with hip circumference was also observed in analyses by combined ER and PR status (p heterogeneity = 0.02).

Analyses by breast cancer intrinsic subtype showed positive associations with luminal-B, HER2-positive breast cancer for waist circumference, waist-to-hip ratio and waist-to-height ratio, but an inverse association with hip circumference (Table 2). Additionally, HER2-enriched breast cancer was positively associated with hip circumference but not associated with other measures.

Results from all sensitivity analyses, including those restricted to the 5 cohorts with examiner-measured waist and hip circumference, did not materially differ from the main findings (*data not shown*). Estimates restricted to subjects with only concurrent BMI available; adjusted for BMI at age 18–24; and restricted to only documented premenopausal follow-up time are shown in Table S6.

## Discussion

In this large, pooled analysis, waist and hip size measures were not associated with risk of overall premenopausal breast cancer or most subtypes after adjusting for BMI. Most waist and hip measures were strongly correlated with BMI, which was strongly inversely associated with risk regardless of whether central/peripheral measures were taken into account. There was some evidence, however, that central adiposity measures are independently associated with some subtypes of breast cancer, particularly in situ disease and luminal-B, HER2-positive tumors.

Our analysis included individual-level data from 14 studies; of these, 9 studies (NHS [22, 23], NHS2 [23, 24], EPIC [25], E3N [26], NYU [27], SWHS [28], SIS [29], BWHS [30, 31], CSDLH [32]) have separately published their individual results and/or were included in a previous meta-analysis of prospective studies [33, 34]. In two prior meta-analyses, the BMI-adjusted HRs

for the association between waist circumference and premenopausal breast cancer (per 10-cm increase) were 1.09 (95% CI: 1.02, 1.16) and 1.15 (1.05, 1.26) based on 5 [33] and 4 [34] studies, respectively; all of which are included in our analysis as well. For WHR (per 0.1 unit) and premenopausal breast cancer, these estimates were 1.12 (95% CI: 0.94, 1.34) and 1.14 (95% CI: 1.00, 1.29) based on 8 [33] and 7 [34] studies, respectively; all of which were included in our analysis except the Italian ORDET study [35]. There has been one meta-analytic estimate of the association between hip circumference and premenopausal breast cancer adjusted for BMI: HR = 1.05 per 10 cm (95% CI: 0.80, 1.36) based on three studies (all also included in our analysis) [34].

Meta-analysis of published aggregate data has several additional sources of heterogeneity, including that dose–response analyses frequently involve deriving study-specific dose–response trends from published relative risks referring to categorized data and that the meta-analysis summarizes individual-study estimates with wide confidence intervals. Published estimates are also based on models with heterogeneous inclusion of covariates and differing definitions of menopausal status. These challenges, in addition to the larger number of cohorts included in our analysis, may contribute to differences in the estimates between the prior meta-analyses and our current pooled analysis.

Waist-to-height ratio has rarely been investigated in breast cancer etiology research, even though it is reportedly a better predictor of whole-body fat percentage and visceral adipose tissue than BMI, waist circumference or waist-to-hip ratio [35] and a better screening tool for cardiometabolic risk [12]. Waist-to-hip ratio is more complex to interpret than waist-to-height ratio because an increased waist-to-hip ratio can be a consequence of increased abdominal fat or a decrease in lean muscle mass around the hips. In our study, waist-to-hip ratio was more weakly associated with risk than were other adiposity measures. If overall adiposity were driving the inverse associations, this finding would be expected, given that its correlation with BMI was considerably lower than for other measures.

Hip circumference on its own, a proxy of peripheral adiposity, also has received little attention beyond being evaluated as part of waist-to-hip ratio. In the cardiovascular literature, gluteofemoral fat mass is associated with a protective lipid and glucose profile in part by trapping excess fatty acids and preventing chronic exposure to elevated lipid levels [8, 9]. In our analyses, hip circumference was not associated with premenopausal breast cancer risk (after adjustment for BMI) with the exception of results for some breast cancer subtypes.

In line with the relationships that pertain to BMI and weight change [21, 37], we found stronger inverse associations of central/peripheral adiposity measures with in situ than with invasive breast cancer. The relative absence of in situ diagnoses among the heaviest women could be due to differences in stage-specific etiology or an artifact if heavier women are less likely to receive recommended breast cancer screening, or if they present later because breast self-examination and lump detection is more difficult [38]. We lacked detailed information on mammography screening behaviors and site-specific recommendations; however, we observed similar results in analyses restricted to women who reported ever participating in breast cancer screening.

We also observed some subtype-specific associations with hormonally defined and intrinsic subtypes, but those results did not appear to follow a consistent pattern across adiposity measures. Some of these findings are based on modest numbers, despite this being a pooling study, and may therefore be due to chance. We are unaware of other prospective cohorts with intrinsic subtype-specific results for the association between central adiposity measures and premenopausal breast cancer risk (beyond those already represented in our analysis). However, a recent U.S.-based case–control study of breast cancer before age 50 (1,812 cases, 1,391 controls) assessed examiner-measured waist circumference in relation to Luminal A, Luminal B, HER2-type, and Triple Negative Breast Cancer [39]. After adjustment for BMI, waist circumference ≥ 88 cm (vs. < 80) was positively associated with Luminal B (OR = 1.48; 95% CI: 1.01–2.15) and triple negative (OR = 2.48; 95% CI: 1.58, 3.88), but not Luminal A (OR = 0.96; 95% CI: 0.69–1.33) or HER2-type (OR = 0.89; 95% CI: 0.43–1.82) disease. These results align with the positive association between continuous waist circumference and premenopausal Luminal B-HER2 + disease and null findings for Luminal A tumors in our analysis but differ from our results for HER-2 enriched and triple negative tumors. The authors also reported heterogeneity by subtype according to waist-to-height ratio (p-heterogeneity < 0.01, adjusted for BMI), as observed in our analysis, however; our findings indicated a positive association between waist-to-height and luminal B, HER2 + tumors, while the positive trend in the case–control study was strongest for triple-negative tumors [39].

An Italian case-only investigation of 596 premenopausal patients reported a positive association between higher waist circumference (> 80 vs. ≤ 80 cm) and Luminal B subtypes (OR = 2.55; 95% CI: 1.53, 4.24 and 2.11; 95% CI: 1.03, 4.35 for HER2- and HER2 + Luminal B disease, respectively), but not HER2 +, ER-/PR- (OR = 1.03; 95% CI: 0.42, 2.53) or triple

negative subtypes (OR = 1.28; 95% CI: 0.50, 3.27), relative to Luminal A tumors [40], providing further partial support for etiologic heterogeneity in the association between central adiposity and premenopausal breast cancer risk after adjustment for BMI.

Visceral adiposity has been implicated in tumorigenesis because of the involvement of several mechanistic pathways including alterations in adipokine secretion and cell signaling pathways, insulin resistance and stimulation of the insulin-like growth factor-1 (IGF-1) axis as a consequence of hyperinsulinaemia, and systemic inflammation in visceral adipose tissue [41]. Our findings, however, suggest that these mechanisms may not be highly influential for premenopausal breast cancer. The high levels of oestrogens in premenopausal women might counteract some of these processes given the ability for oestrogens to modulate metabolism-related inflammation [42].

We have previously considered reasons for the strong inverse association between BMI and premenopausal breast cancer risk [21], including the hypothesis that the inverse association is likely to originate in childhood [43], with childhood body circumference being inversely associated with adult breast cancer risk and intermediate phenotypes including mammographic density [44]and benign breast disease [45]. However, we have previously shown that BMI and weight gain in adulthood are also inversely associated with premenopausal breast cancer risk [21, 37], and it is plausible that such associations are at least in part due to a direct role of fat. Leptin, secreted by adipocytes, is associated with decreased risk in premenopausal women [46]. Mammographic density, the ratio of fibroglandular to fatty tissue in the breast, is a strong risk factor for breast cancer [47, 48] but the amount of fatty tissue may also be independently inversely associated with risk [49]. The amount of breast fat and overall breast circumference correlates strongly with overall adiposity [50], and it is likely that the mammary fat pad is the factor of interest, being a source of IGF-1, leptin, adiponectin and bioactive vitamin D, affecting extracellular matrix and tissue stiffness [49]. Furthermore, differences in levels of hormones and IGF-1 by body circumference in adulthood may contribute [51–59].

Strengths of our study are that we used individual-level pooled data from prospective studies, with time-updated information on menopausal status. Also, we were able to explore differences in association by age, participant characteristics and breast cancer subtypes. One limitation of our study is that anthropometric measures were self-reported for the majority of study participants; however, our overall findings were highly similar in analyses limited to those with examiner-measured central adiposity metrics and previous literature indicates high correlation between self-reported and measured anthropometric variables including waist circumference (r = 0.89; ICC = 0.96), hip circumference (r = 0.84, ICC = 0.97), and weight-to-height ratio (r = 0.86) [60, 61]. Most cohorts (12/14) included in our analysis were based in North America and Europe. This may limit the generalizability of our findings to other populations. Similarly, some studies had a greater number of repeated measurements and correspondingly lower measurement error across the lifecourse. Although we had reasonable numbers of breast cancer cases overall to compare results between Black and White women, we did not have large enough numbers for Asian women, or to compare race specific associations by subtype of breast cancer. As in all observational epidemiologic studies, we cannot directly assess causality, and our analyses may include potential residual confounding due to imperfect or unmeasured covariate data. More exact adiposity measures such as those derived from DEXA or CT scans provide an opportunity to examine biological correlates of breast cancer risk in a clinical setting [62, 63]. However, they remain challenging in large scale epidemiologic cohort studies across multiple clinical settings and countries.

We conclude that among premenopausal women, higher adiposity was associated with lower premenopausal breast cancer risk regardless of whether it was central or peripheral. When both central and peripheral adiposity were taken into account simultaneously, peripheral adiposity (BMI) remained associated, but central adiposity did not. This suggests that the contribution of central adiposity to premenopausal breast cancer risk (beyond overall adiposity) is not substantial. However, our findings indicate associations might differ by breast cancer subtype. Waist-related measures were independently positively associated, and hip circumference inversely associated, with Luminal B-HER2 + breast cancer risk.

## Supplementary Information

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Additional file 1.

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**Author contributions**
Conceptualization: MJS, HBN, DPS, AJS. Data curation: MJS, HBN, LBW, MEJ, KMO, HOA, LB, KAB, YC, JD, AHE, GGG, SCH, VAK, RLM, JRP, HLP, TEH, GS, XOS, RMT, LV, EW, WCW, AZJ, WZ, DPS, AJS. Formal analysis: MJS, LBW, MEJ. Writing – original draft: MJS, TE. Writing – critical review & editing: All authors.

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**Availability of data and materials**
The datasets analyzed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

## Declarations

**Ethical approval and consent to participate**
Individual study protocols were approved by the relevant institutional review boards and obtained informed consent from participants.

**Competing interests**
The authors have no competing interests as defined by BMC, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

**Disclaimer**
The opinions, findings, and conclusions expressed herein are those of the author(s) and do not necessarily reflect the official views of the State of California, Department of Public Health, the National Cancer Institute, the National Institutes of Health, the Centers for Disease Control and Prevention or their Contractors and Subcontractors, or the Regents of the University of California, or any of its programs, or the state cancer registries. Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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## Publisher's Note