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ORIGINAL PAPER

Waist circumference, body mass index, and postmenopausal breast cancer incidence in the Cancer Prevention Study-II Nutrition Cohort

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Abstract
Purpose High body mass index (BMI) is an established risk factor for postmenopausal breast cancer. However, less is known about associations with waist circumference. In particular, it is unclear whether a larger waist circumference is associated with risk more than would be expected based solely on its contribution to BMI.
Methods We examined the associations of BMI and waist circumference with risk of postmenopausal breast cancer, with and without mutual adjustment, in the Cancer Prevention Study-II Nutrition Cohort. Analyses included 28,965 postmenopausal women who reported weight and waist circumference on a questionnaire in 1997 and were not taking menopausal hormones.
Results During a median follow-up of 11.58 years, 1,088 invasive breast cancer cases were identified. Hazard ratios (HR) and 95 % confidence intervals (CI) were estimated from multivariable-adjusted Cox proportional hazard regression models. Without adjustment for BMI, a larger waist circumference was associated with higher risk of breast cancer (per 10 cm increase in waist circumference, HR = 1.13, 95 % CI 1.08–1.19). However, adjustment for BMI eliminated the association with waist circumference (per 10 cm HR = 1.00, 95 % CI 0.92–1.08). BMI was associated with risk unadjusted for waist circumference (per 1 kg/m^2 HR = 1.04, 95 % CI 1.03–1.05) and adjusted for waist circumference (per 1 kg/m^2 HR = 1.04, 95 % CI 1.02–1.06).
Conclusions Our study of predominantly white women provides evidence that a larger waist circumference is associated with higher risk of postmenopausal breast cancer, but not beyond its contribution to BMI.

Keywords Breast cancer · Obesity · Waist circumference

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Introduction

More than 42 % of US women aged 60 years and older are obese (as measured as a body mass index (BMI) >30 kg/m^2) [1]. Larger body size is an established risk factor for postmenopausal breast cancer. Most studies examining associations with body size used BMI as a proxy of overall adiposity and found that among women who do not use postmenopausal hormones, obese women had a 1.5- to 2-fold higher postmenopausal breast cancer risk than women in the normal range of BMI [2].

With aging, women lose lean body mass and gain weight as visceral fat [3]. Metabolically active visceral fat releases substantial amounts of insulin-like growth factors (IGF), inflammatory markers, free fatty acids, locally produced estrogen, and adipokines to the liver [4] that might reach the breast through systemic circulation. In epidemiologic studies, people with larger amounts of visceral fat, as measured by larger waist circumferences, have higher risk of hyperinsulinemia and type II diabetes [5], both breast cancer risk factors. Therefore, among postmenopausal women, waist circumference, which is more strongly correlated with visceral fat than BMI [6], might be a better indicator of breast cancer risk [7].

Prior cohort studies have found that women with large waist circumferences have higher risk of postmenopausal breast cancer [8–16]; however, not all studies were restricted

to women not taking postmenopausal hormones, which are known to modify relations between measures of body size with postmenopausal breast cancer, and not all studies adjusted for BMI. Adjustment for BMI is potentially informative because an association with waist circumference after adjustment for BMI would suggest that excess abdominal weight increases risk of breast cancer more than an equivalent amount of excess weight located elsewhere on the body [17].

To clarify the association between waist circumference and risk of postmenopausal breast cancer, we examined the association, with and without adjustment for BMI, among postmenopausal women not using menopausal hormones in the Cancer Prevention Study (CPS)-II Nutrition Cohort. We also examined associations by estrogen receptor (ER) status of the breast tumor. This cohort is well suited to examine this association because it includes large numbers of postmenopausal women with information on waist circumference who were not using hormones.

Methods

Description of cohort

Women in this analysis were drawn from the 97,785 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality established in 1992 as a subgroup of a larger mortality study initiated in 1982 [18]. All participants completed a mailed questionnaire in 1982 and 1992/3 that included information on demographic, medical, and behavioral factors. Follow-up questionnaires were sent to cohort members every 2 years starting in 1997 to update exposure information and ascertain cancer outcomes. Waist circumference was ascertained once as part of the 1997 follow-up survey. With the 1997 survey, study participants were provided with a tape measure and instructed to measure their waist circumference just above the navel to the nearest quarter inch, while standing, and to avoid measuring over bulky clothing. Hip circumference was not collected. BMI was calculated from weight reported on the 1997 survey and height reported on the 1982 survey. The response rate for each of the follow-up questionnaires through 2009 was at least 86 %. Informed consent for participation was assumed based on completion and return of study questionnaires. The Emory University School of Medicine Institutional Review Board approves all aspects of CPS-II.

Cohort for analysis

Of the 87,257 women in the CPS-II Nutrition Cohort who completed the 1997 questionnaire, we excluded from the analytical dataset women who reported a history of cancer prior to enrollment (except non-melanoma skin cancer, $n = 14{,}273$), were not postmenopausal or had missing age at menopause ($n = 2{,}081$), had missing or outlier data (<39 cm or >139 cm for waist circumference ($n = 11{,}510$)), or had missing data for BMI ($n = 4{,}809$). In preliminary analyses, we found that the associations of waist circumference and BMI with breast cancer risk did not differ for women who were classified as never and former postmenopausal hormone users in 1997 (p value for interaction = 0.45 and 0.92, respectively); therefore, only women who reported current postmenopausal hormone use in 1997 were excluded ($n = 25{,}475$).

Breast cancer cases

In the analysis, we included invasive breast cancer cases (ICD-9 code: 174 or ICD-10/O code: C50) that were diagnosed between the return of the 1997 survey and June 30, 2009. Most incident breast cancer diagnoses were first self-reported on follow-up questionnaires and then were verified through medical records ($n = 836$) or linkage with state registries ($n = 221$) [21]. An additional 22 cases, not self-reported, for which breast cancer was listed as an underlying or contributory cause of death on the death certificate, were initially identified through linkage with the National Death Index (NDI). Finally, nine more cases of breast cancer were identified during registry linkage conducted to verify a self-report of, or NDI-ascertained death from, a different type of cancer [19]. A total of 140 women who reported a breast cancer diagnosis that could not be verified were excluded from analyses. Clinical characteristics of the tumor were obtained from state registries or abstracted from medical records.

Statistical methods

Waist circumference was converted to centimeters and categorized into approximate quintiles that were rounded and incorporated the World Health Organization (WHO) cut-points of 80 and 88 cm [20]. BMI was categorized into <25.0, 25.0–29.9, and ≥30.0 kg/m^2. Waist circumference and BMI were normally distributed so we also examined continuous versions of the variables (per 10 cm and per kg/m^2 unit, respectively). Age-adjusted Spearman's correlation coefficient between continuous waist circumference and BMI were calculated. Participants contributed person-time to the analysis from the return of the 1997 questionnaire until they were censored at the date of any cancer diagnosis, date of death, date of last survey returned, or the end of follow-up June 30, 2009. Age-adjusted breast cancer incidence rates were calculated for categories of waist circumference and BMI. Cox proportional hazards regression was

used to estimate the associations of waist circumference and BMI with breast cancer risk. All Cox models were stratified on single year of age in 1997 by including age in the STRATA statement. Multivariable-adjusted models included known breast cancer risk factors: age and other known or suspected breast cancer risk factors, including race (white, black, other/missing), education (<high school graduate/missing, high school graduate, some college, college graduate), parity and age at first birth (no children, 1–2 births with first birth <25 years of age, 1–2 births with first birth at 25 years or older, three or more births with first birth <25 years of age, three or more births with first birth at 25 years or older), age at menopause (<50, 50–54, ≥55 years, missing/unknown), height (0–159, 160–164, 165–169, ≥170 cm), first-degree family history of breast cancer (0, ≥1 female members, missing), personal history of benign breast disease (yes, no, missing), diabetes (yes, no, missing), physical activity (0–6.9, 7–17.4, 17.5–20.4, and 20.5 + MET/hours, missing), alcohol use (never, former, current drinker <1, 1, and ≥2 drinks per day, missing), smoking status (never, former, current, missing), use of oral contraceptives (never, ever, missing), former use of postmenopausal hormones (never, former), and recent mammogram (yes, no, missing). Mutually adjusted models included all covariates as well as continuous BMI variable in the waist circumference models and continuous waist circumference variable in the BMI models. Tests of trend were examined by assessing every 10 cm for waist circumference and every 1 kg/m^2 for BMI. The statistical significance of the interaction between waist circumference and BMI was estimated comparing the −2 log likelihood of models with and without an interaction variable created using continuous variables for waist circumference and BMI. We also examined interaction by age (<60, 60–69, and ≥70 years) and years since menopause (<10, 10–14, 15–19, ≥20 years). We evaluated whether associations differed by ER status of the tumor using a joint Cox proportional hazards model [21]. The proportional hazard assumption was evaluated for associations of BMI and waist circumference with risk; no violations were observed. All analyses were conducted in SAS, version 9.3 (SAS Institute, Inc, Cary, NC).

Results

During a median follow-up time of 11.58 years, 1,088 invasive breast cancer cases were diagnosed among 28,965 women at risk. Former users of menopausal hormones comprised 38.8 % of the study population. Many women (44.6 %) had a waist circumference of 88 cm or larger, whereas only 18.5 % of the women were obese (BMI ≥30 kg/m^2). The age-adjusted correlation between waist

Table 1 Distribution of breast cancer risk factors by categories of waist circumference in women from the CPS-II Nutrition Cohort who were never/former HRT users in 1997

	Categories of waist circumference (cm)						Total percent
	39–79 n = 8,717		80–87 n = 7,322		88–139 n = 12,926		
	n	%	n	%	n	%	
Age in 1997							
<60	911	10.5	606	8.3	1,098	8.5	9.0
60–64	1,921	22.0	1,513	20.7	2,623	20.3	20.9
65–69	2,456	28.2	2,151	29.4	3,682	28.5	28.6
70–74	2,122	24.3	1,907	26.0	3,508	27.1	26.0
75+	1,307	15.0	1,145	15.6	2,015	15.6	15.4
Race							
White	8,491	97.4	7,138	97.5	12,650	97.9	97.6
Black	96	1.1	124	1.7	191	1.5	1.4
Other/ missing	130	1.5	60	0.8	85	0.7	0.9
Education level							
Less than high school/ missing	411	4.7	428	5.9	867	6.7	5.9
High school graduate	2,637	30.3	2,487	34.0	4,833	37.4	34.4
Some college	2,723	31.2	2,188	29.9	3,924	30.4	30.5
College graduate	2,946	33.8	2,219	30.3	3,302	25.6	29.2
Smoking status in 1997							
Never smoker	4,860	55.8	4,110	56.1	7,254	56.1	56.0
Current smoker	619	7.1	437	6.0	644	5.0	5.9
Former smoker	3,092	35.5	2,656	36.3	4,818	37.3	36.5
Missing	146	1.7	119	1.6	210	1.6	1.6
Age at first birth							
No births	703	8.1	570	7.8	949	7.3	7.7
Age <20	612	7.0	594	8.1	1,233	9.5	8.4
Age 20–24	3,913	44.9	3,322	45.4	6,027	46.6	45.8
Age 25–29	2,576	29.6	2,097	28.6	3,376	26.1	27.8
Age 30+	734	8.4	573	7.8	1,081	8.4	8.2
Missing	179	2.1	166	2.3	260	2.0	2.1
Number of live births							
None	703	8.1	570	7.8	949	7.3	7.7
1	696	8.0	486	6.6	912	7.1	7.2
2–3	4,818	55.3	3,765	51.4	6,350	49.1	51.6
4+	2,351	27.0	2,367	32.3	4,491	34.7	31.8
Missing	149	1.7	134	1.8	224	1.7	1.8
Benign breast disease							
No	6,532	74.9	5,710	78.0	10,502	81.3	78.5
Yes	2,185	25.1	1,612	22.0	2,424	18.8	21.5

Table 1 continued

	Categories of waist circumference (cm)						Total percent
	39–79 $n = 8,717$		80–87 $n = 7,322$		88–139 $n = 12,926$		
	n	%	*n*	%	*n*	%	
Family history of breast cancer							
No	6,392	73.3	5,416	74.0	9,670	74.8	74.2
Yes	1,634	18.7	1,359	18.6	2,304	17.8	18.3
Missing	691	7.9	547	7.5	952	7.4	7.6
HRT use in 1997							
Never	5,274	60.5	4,437	60.6	8,029	62.1	61.2
Former	3,443	39.5	2,885	39.4	4,897	37.9	38.8
Age at menopause							
<50	3,630	41.6	3,169	43.3	5,846	45.2	43.7
50–54	4,016	46.1	3,351	45.8	5,531	42.8	44.5
55+	1,071	12.3	802	11.0	1,549	12.0	11.8
Years since menopause							
<5	286	3.3	174	2.4	331	2.6	2.7
5–9	958	11.0	685	9.4	1,132	8.8	9.6
10–14	1,398	16.0	1,085	14.8	1,783	13.8	14.7
15–19	2,264	26.0	1,970	26.9	3,380	26.2	26.3
20+	3,811	43.7	3,408	46.5	6,300	48.7	46.7
Oral contraceptive use							
Never user	5,775	66.3	4,862	66.4	8,747	67.7	66.9
Ever user	2,850	32.7	2,376	32.5	4,025	31.1	31.9
Missing/ unknown	92	1.1	84	1.2	154	1.2	1.1
Recent mammography							
Never	518	5.9	359	4.9	774	6.0	5.7
≤2 years	7,273	83.4	6,227	85.1	10,741	83.1	83.7
2+ years	906	10.4	725	9.9	1,384	10.7	10.4
Unknown	20	0.2	11	0.2	27	0.2	0.2
Alcohol use (drinks/day)							
Non-drinker	3,194	36.6	2,922	39.9	6,200	48.0	42.5
<1	3,667	42.1	2,839	38.8	4,016	31.1	36.3
1	736	8.4	596	8.1	772	6.0	7.3
2+	181	2.1	142	1.9	248	1.9	2.0
Former drinker	694	8.0	628	8.6	1,217	9.4	8.8
Missing	245	2.8	195	2.7	473	3.7	3.2
BMI in 1997							
<25	7,873	90.3	4,175	57.0	1,880	14.5	48.1
25–29.9	794	9.1	2,857	39.0	6,032	46.7	33.4
30+	50	0.6	290	4.0	5,014	38.8	18.5
Diabetes							
No	7,755	89.0	6,357	86.8	10,235	79.2	84.1
Yes	251	2.9	324	4.4	1,470	11.4	7.1
Missing	711	8.2	641	8.8	1,221	9.5	8.9
Exercise (METs/hour)							
<7	1,367	15.7	1,453	19.8	3,863	29.9	23.1
7–17.5	3,760	43.1	3,445	47.1	5,864	45.4	45.1
17.6–24.4	826	9.5	612	8.4	882	6.8	8.0
24.5	2,708	31.1	1,756	24.0	2,171	16.8	22.9
Missing	56	0.6	56	0.8	146	1.1	0.9

circumference and BMI was 0.80 (data not shown in tables). Women with smaller waists tended to be younger, more educated, exercise participant, and a current smoker and drinker at baseline, than women with larger waists (Table 1). Women with larger waists were more likely to be 20 or more years since menopause and to report type 2 diabetes mellitus.

In multivariable-adjusted models without adjustment for BMI, waist circumference was statistically significantly positively associated with risk of postmenopausal breast cancer; for every 10 cm increase in waist circumference, there was a 13 % higher risk (Table 2). Upon further adjustment for BMI, the association with waist circumference was eliminated. Without adjustment for waist circumference, BMI was statistically significant positively associated with risk [per 1 kg/m^2 hazard ratios (HR) = 1.04, 95 % confidence intervals (CI) 1.03–1.05] and controlling for waist circumference did not attenuate the association (per 1 kg/m^2 HR = 1.04, 95 % CI 1.02–1.06).

There was no evidence of statistical interaction between waist circumference and BMI (p value for interaction = 0.95; Table 3). The association between waist circumference and risk of breast cancer, controlled for BMI, did not differ by age in 1997 or by years since menopause (p value for interaction >0.05; data not otherwise shown).

In analyses stratified on ER status, waist circumference, after adjustment for BMI, was not associated with ER+ or ER− breast cancer risk (Table 4). Adjusting for waist circumference, obesity (BMI ≥ 30.0 kg/m^2) was associated with higher risk of ER+ breast cancer (HR = 1.41, 95 % CI 1.08–1.85), but not ER− breast cancer risk (HR = 0.61, 95 % CI 0.35–1.08; p value for tumor heterogeneity = 0.02).

Discussion

In this large prospective study of predominantly white, postmenopausal women, we found a statistically significant positive association between waist circumference and

Table 2 Age-adjusted, multivariable-adjusted, and mutually adjusted associations of invasive breast cancer risk with waist circumference and body mass index among never and former postmenopausal hormone users, Cancer Prevention Study-II Nutrition Cohort (1997–2009)

	Cases	Person-years	Rate[a]	Age adjusted			Multivariable adjusted[b]			Mutually adjusted[b,c]		
				RR	95 % CI	*p* value	RR	95 % CI	*p* value	RR	95 % CI	*p* value
Waist circumference (quintiles)												
39–74 cm	183	51,549	355.3	1.00	–		1.00	–		1.00	–	
75–79 cm	108	33,400	303.0	0.91	(0.72, 1.15)		0.90	(0.71, 1.14)		0.82	(0.65, 1.05)	
80–87 cm	231	71,583	322.2	0.90	(0.74, 1.09)		0.90	(0.74, 1.09)		0.76	(0.62, 0.94)	
88–96 cm	270	61,546	417.4	1.22	(1.01, 1.48)		1.25	(1.03, 1.52)		0.96	(0.77, 1.19)	
97–139 cm	296	61,586	454.8	1.34	(1.11, 1.61)		1.36	(1.12, 1.65)		0.85	(0.65, 1.12)	
Per 10 cm				1.12	(1.08, 1.17)	1.3E−07	1.13	(1.08, 1.19)	9.3E−08	1.00	(0.92, 1.08)	0.99
Body mass index (kg/m^2)												
<25	441	133,947	329.5	1.00	–		1.00	–		1.00	–	
25–29.9	401	94,402	403.5	1.29	(1.13, 1.48)		1.34	(1.17, 1.54)		1.26	(1.07, 1.48)	
30+	246	51,316	462.1	1.48	(1.27, 1.74)		1.60	(1.36, 1.89)		1.40	(1.10, 1.78)	
Per 1 BMI unit				1.04	(1.02, 1.05)	1.3E−09	1.04	(1.03, 1.05)	1.2E−11	1.04	(1.02, 1.06)	6.1E−05

[a] Rate per 100,000 person-years and adjusted to the person-year distribution of the cohort

[b] Multivariable analyses adjust for height, education, parity, age at first birth, smoking and alcohol use, race, family history of breast cancer, oral contraceptive use, diabetes, age at menopause, exercise, benign breast disease, recent mammography screening, and postmenopausal hormone use

[c] Models of waist circumference were adjusted also for BMI as a continuous variable. Models of BMI were adjusted also for waist circumference as a continuous variable

postmenopausal breast cancer risk; however, the association was eliminated after adjusting for BMI. The positive association between BMI and risk was statistically significant even after adjusting for waist circumference and was limited to tumors expressing the ER.

The World Cancer Research Fund/American Institute for Cancer Research concluded that there is "probable" evidence that central obesity is associated with risk of postmenopausal breast cancer [22]. However, few cohort studies have investigated whether central obesity contributes to risk of postmenopausal breast cancer beyond its contribution to overall obesity. While nine prospective studies [8–16, 23, 24] presented associations of waist circumference and BMI with risk, only five studies presented results for waist circumference and/or BMI after mutual adjustment [10, 12, 13, 15, 24]. Consistent with the results from the CPS-II Nutrition cohort, larger waist circumference was associated with higher risk of breast cancer but attenuated toward the null in the mutually adjusted models in the Iowa Women's Health Study (IWHS), the Women's Health Initiative (WHI), and the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts [10, 12, 24]. In the Nurses' Health Study (NHS), the association between waist circumference and postmenopausal breast cancer was unaffected with the inclusion of BMI in the model (Q5 vs. Q1: RR = 1.88–1.83) [13]. Possible reasons for these discrepancies are unclear. BMI was significantly positively associated with postmenopausal breast cancer incidence even after controlling for waist circumference or waist-to-hip ratio in the NHS, the New York University Women's Health Study, and the WHI [10, 13, 15], as we found in the CPS-II Nutrition cohort. In a subset of the WHI participants with dual energy X-ray absorptiometry (DXA) measurements, similar positive associations with postmenopausal breast cancer risk were reported for whole body fat mass (HR = 1.88) and fat mass of the trunk (HR = 2.05); however, the HRs were not mutually adjusted [25].

A limited number of cohort studies have examined the statistical interaction between waist circumference and BMI. Early results from the IWHS suggested a statistically significant multiplicative interaction between age, BMI, and waist-to-hip ratio [14]. Recently interaction results from larger cohorts, including the NHS [13] and the California Teachers Study [16], were not statistically significant, consistent with the results from the CPS-II Nutrition cohort.

There is consistent evidence that larger BMI is a risk factor only for ER+ breast tumors [11, 16, 24, 26, 27]. Our results further support this evidence for BMI, and we showed that this association persists after controlling for waist circumference. Waist circumference also appears to be associated with ER+ breast cancer in postmenopausal women [11, 16, 24, 25, 27]; however, adjusting for BMI attenuates the associations with risk [24, 27], as we observed in the CPS-II Nutrition cohort.

Table 3 Multivariable-adjusted[b] HR and 95 % CI of invasive breast cancer with waist circumference by body mass index among never and former users of postmenopausal hormone therapy, Cancer Prevention Study-II Nutrition Cohort (1997–2009)

Waist circumference (cm)	1997 BMI categories (WHO format)														*p* value for interaction
	<25					25–29.9				30+					
	Cases	Rate[a]	RR[c]	95 % CI	*p* value	Cases	Rate[a]	RR[c]	95 % CI	*p* value	Cases	Rate[a]	RR[c]	95 % CI	*p* value	
<79	270	348.1	1.00			19	220.9	0.75	(0.47, 1.20)		2	437.0	1.41	(0.35, 5.68)		0.95
80–87	103	272.1	0.70	(0.56, 0.88)		121	411.6	1.25	(1.01, 1.55)		7	203.4	0.81	(0.38, 1.72)		
88+	68	289.5	1.07	(0.82, 1.41)		261	427.1	1.28	(1.08, 1.53)		237	476.4	1.51	(1.25, 1.81)		
Per 10 cm			0.92	(0.82, 1.05)	0.22			1.01	(0.95, 1.07)	0.74			1.01	(0.97, 1.06)	0.54	

[a] Rate per 100,000 person-years and adjusted to the person-year distribution of the cohort

[b] Multivariable analyses adjust for age, height, education, parity, age at first birth, smoking and alcohol use, race, family history of breast cancer, oral contraceptive use, diabetes, age at menopause, exercise, benign breast disease, recent mammography screening, and postmenopausal hormone use

[c] Models of waist circumference were adjusted also for BMI as a continuous variable

Both systemic and local biologic mechanisms have been hypothesized to underlie the association between obesity and postmenopausal breast cancer risk. The most widely accepted systemic effects related to breast cancer risk are those due to higher levels of circulating free estradiol resulting from the conversion of androgens to estrogens by aromatase from adipocytes; these effects may work in concert with or independently of insulin resistance leading to hyperinsulinemia and perturbations of the insulin/IGF axis [7]. In the WHI, 23.8 % of excess breast cancer cases attributed to obesity are due to elevated estradiol levels and 65.8 % due to perturbations in the insulin pathways [28]. Low circulating levels of adiponectin might also contribute to the increased risk of breast cancer [29, 30], although in at least one study, the association with adiponectin was substantially attenuated after controlling for estradiol [30].

Because the amount of fat in the breast is proportional to total body adipose tissue mass [31–33], the association between BMI and postmenopausal breast cancer might reflect the local microenvironment of adipocytes in the breast. Obesity is associated with low grade, chronic inflammation that, at the local level, leads to the recruitment of macrophages around necrotic adipocytes, visualized as crown-like structures (CLS) [34]. In human breast tissue, higher proportion of CLS was observed in overweight and obese women with breast cancer than in normal weight patients [35] or women without breast cancer [36]. As a paracrine and autocrine organ, mammary adipose tissue also produces estradiol, adipokines, and factors involved in the insulin/IGF axis [37]. In summary, the association between BMI and postmenopausal breast cancer might be mediated by local and/or systemic mechanisms. Much of the research in the local breast environment has been conducted in premenopausal women; however, the breast tissue of postmenopausal women who undergo only partial age-related lobular involution [38] might experience the same obesity-related mechanisms.

The strengths of this study include the prospective collection of anthropometric data and the large number of cases diagnosed over a long follow-up time. Limitations include the use of anthropometry as indirect measures of body fatness; however, similar positive associations with postmenopausal breast cancer risk were reported for BMI and DXA, a direct measure of body fatness [25]. The self-assessment of waist circumference in the CPS-II Nutrition cohort also might have limited our conclusions. However, in other studies of older women, waist circumference was measured with good validity (Pearson $r = 0.87$ for BMI, $r = 0.85$ for waist circumference) [10, 16]; thus, we expect random measurement error would have only modestly attenuated the observed associations. Moreover, we were only able to examine waist circumference at one point in time.

Table 4 Age-adjusted, and mutually adjusted[b,c] associations of ER+ and ER− breast cancer risk with waist circumference and body mass index among never and former postmenopausal hormone users, Cancer Prevention Study-II Nutrition Cohort (1997–2009)

	ER+							ER−							*p* value for tumor heterogeneity[d]
	Age adjusted[b]				Mutually adjusted[b,c]			Age adjusted[b]				Mutually adjusted[b,c]			
	Cases	Rate[a]	RR[b]	95 % CI	RR[b,c]	95 % CI	*p* value	Cases	Rate[a]	RR[b]	95 % CI	RR[b,c]	95 % CI	*p* value	
Waist circumference (cm)															
<79	215	244.3	1.00		1.00			39	45.7	1.00		1.00			0.01
80–87	163	223.3	0.90	(0.73, 1.11)	0.82	(0.67, 1.02)		38	57.2	1.18	(0.75, 1.84)	1.07	(0.68, 1.69)		
≥88	413	310.3	1.37	(1.16, 1.63)	1.09	(0.87, 1.36)		51	40.2	0.95	(0.62, 1.44)	0.75	(0.48, 1.17)		
Per 10 cm			1.15	(1.09, 1.21)	1.04	(0.95, 1.15)	0.37			0.95	(0.83, 1.09)	0.87	(0.75, 1.00)	0.06	
Body mass index (kg/m2)															
<25.0	319	228.6	1.00		1.00			65	53.4	1.00		1.00			0.02
25.0–29.9	294	294.0	1.37	(1.17, 1.61)	1.28	(1.06, 1.54)		46	46.1	1.03	(0.70, 1.51)	0.96	(0.65, 1.43)		
≥30.0	178	332.2	1.64	(1.35, 1.99)	1.41	(1.08, 1.85)		17	31.6	0.71	(0.41, 1.22)	0.61	(0.35, 1.08)		
Per 1 BMI unit			1.04	(1.03, 1.06)	1.04	(1.01, 1.06)	0.003			1.00	(0.96, 1.04)	0.99	(0.95, 1.04)	0.76	

[a] Rate per 100,000 person-years and adjusted to the person-year distribution of the cohort

[b] Relative risks (RR) and 95 % confidence intervals (CI) estimated from joint Cox proportional hazards models, adjusted for age, height, education, parity, age at first birth, smoking and alcohol use, race, family history of breast cancer, oral contraceptive use, diabetes, age at menopause, exercise, benign breast disease, recent mammography screening, and postmenopausal hormone use

[c] Mutually adjusted models of waist circumference were adjusted also for BMI as a continuous variable. Mutually adjusted models of BMI were adjusted also for waist circumference as a continuous variable

[d] *p* value compares the mutually adjusted models

Conclusions

Our study of predominantly white women provides further evidence that waist circumference is associated with risk of postmenopausal breast cancer but not beyond its contribution to overall obesity. Whether these observations are valid across the age range (i.e., premenopausal women) is unclear. Pathways driven by central obesity do not appear to completely explain the biologic mechanisms through which obesity increases risk of breast cancer. To better understand the local influence of obesity on the development of postmenopausal breast cancer, research on the breast microenvironment and improved techniques to non-invasively sample non-malignant breast tissue in postmenopausal women are necessary. Our data support the value of measuring BMI to capture the increased risk of postmenopausal breast cancer associated with larger body size.

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Conflict of interest The author(s) declare that they have no competing interests.

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