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BRIEF COMMUNICATION

Body Fat Distribution and Risk of Premenopausal Breast Cancer in the Nurses' Health Study II

Holly R. Harris, Walter C. Willett, Kathryn L. Terry, Karin B. Michels

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Correspondence to: Karin B. Michels, ScD, PhD, Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, 221 Longwood Ave, Boston, MA 02115 (email: kmichels@rics.bwh.harvard.edu).

Body mass index is inversely associated with risk of premenopausal breast cancer, but the underlying mechanisms for this association are poorly understood. Abdominal adiposity is associated with metabolic and hormonal changes, many of which have been associated with the risk of premenopausal breast cancer. We investigated the association between body fat distribution, assessed in 1993 by self-reported waist circumference, hip circumference, and waist to hip ratio, and the incidence of premenopausal breast cancer in the Nurses' Health Study II. Cox proportional hazards regression models were used to calculate hazard ratios and 95% confidence intervals (CIs). Statistical tests were two-sided. During 426 164 person-years of follow-up from 1993 to 2005, 620 cases of breast cancer were diagnosed among 45 799 women. Hormone receptor status information was available for 84% of the breast cancers. The age-standardized incidence rates of breast cancer were 131 per 100 000 person-years among those in the lowest quintile of waist circumference and 136 per 100 000 person-years among those in the highest quintile. No statistically significant associations were found between waist circumference, hip circumference, or the waist to hip ratio and risk of breast cancer. However, each of the three body fat distribution measures was statistically significantly associated with greater incidence of estrogen receptor (ER)–negative breast cancer. The multivariable-adjusted hazard ratios of ER-negative breast cancer for the highest vs the lowest quintile of each body fat distribution measure were 2.75 (95% CI = 1.15 to 6.54; P_{trend} = .05) for waist circumference, 2.40 (95% CI = 0.95 to 6.08; P_{trend} = .26) for hip circumference, and 1.95 (95% CI = 1.10 to 3.46; P_{trend} = .01) for waist to hip ratio. Our findings suggest that body fat distribution does not play an important role in the overall incidence of premenopausal breast cancer but is associated with an increased risk for ER-negative breast cancer.

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Body mass index (BMI) has a multifaceted relation with the risk of breast cancer that varies with menopausal status. Higher BMI is positively associated with risk of postmenopausal breast cancer but inversely associated with risk of premenopausal breast cancer (1–28). The underlying mechanisms for the inverse association are poorly understood. Previous studies have found associations between body fat distribution and hormone levels and metabolic indicators in women with a range of BMIs, suggesting that body fat distribution may play a role in the risk of premenopausal breast cancer (29–32). Thus, a direct examination of the relation between body fat distribution and the risk of premenopausal breast cancer may contribute to our understanding of the mechanistic pathways of this disease.

Intra-abdominal visceral fat is metabolically distinct from subcutaneous fat. It is associated with metabolic and hormonal changes, including hyperinsulinemia and insulin resistance, increased levels of free fatty acids, lower levels of sex hormone–binding globulin, and increased bioavailability of estradiol (3,33–35), and each of these changes have been associated with an increased risk of premenopausal breast cancer (36–39). However, prospective studies that have examined the association between body fat distribution and the risk of premenopausal breast cancer have produced conflicting results, and none examined the association by hormone receptor status (7,9,13,19,40–42).

We investigated whether body fat distribution, defined by measuring waist and hip circumferences and by the waist to hip ratio, was associated with the risk of premenopausal breast cancer in the Nurses' Health Study II (NHS II), a prospective cohort of 116 430 women who have been followed since its inception in 1989. Follow-up questionnaires are sent biannually to participants so that they can update their information on disease diagnoses and anthropometric and other breast cancer risk factors. Details about the NHS II have been provided elsewhere (43). Estrogen receptor (ER) and progesterone receptor (PR) status information was obtained from pathology reports (44). Follow-up for this analysis began in 1993 when 46 607 (46.7%) premenopausal participants first reported waist and hip circumference. Participants were excluded if they were missing waist or hip circumference measurements, had any cancer diagnosed before 1995, were missing the date of diagnosis of invasive breast cancer, were missing height in 1989, or were missing weight in 1989, 1991, and 1993. After these exclusions, 45 799 premenopausal women with waist and hip circumference measurements remained.

We used Cox proportional hazards regression models to calculate the hazard ratio for developing premenopausal breast cancer associated with quintiles of waist circumference, hip circumference, and waist to hip ratio, with the lowest quintile of each measure as the reference category. Proportionality of hazards was evaluated by adding an interaction term for each body fat distribution variable and age and questionnaire period to the models; these terms were not statistically significant by the likelihood ratio test, confirming the assumption. Models were adjusted for age (continuous), height (continuous), history of benign breast disease (yes or no), family history of breast cancer (yes or no), age at menarche (≤10, 11, 12, 13, 14, or ≥15 years) and at birth of first child (≤24, 25–30, or

CONTEXT AND CAVEATS

Prior knowledge

Body mass index is inversely associated with risk of premenopausal breast cancer, but the underlying mechanisms for this association are poorly understood. Abdominal fat is associated with metabolic and hormonal changes, many of which have been associated with the risk of premenopausal breast cancer.

Study design

Prospective study of the association between body fat distribution, defined by waist and hip circumferences and by the waist to hip ratio, and the risk of premenopausal breast cancer among women in the Nurses' Health Study II.

Contribution

Abdominal adiposity was not associated with the overall incidence of premenopausal breast cancer. However, abdominal adiposity was more strongly associated with risk of estrogen receptor–negative breast cancer than with the risk of estrogen receptor–positive breast cancer in premenopausal women.

Implications

Abdominal adiposity may influence the risk of premenopausal breast cancer through sex hormone–independent pathways.

Limitations

Waist and hip circumferences were self-measured by participants and are subject to measurement error. Abdominal circumference measurements, which comprise both visceral and subcutaneous fat, are an indirect measure of intra-abdominal visceral fat, which is metabolically distinct from other types of body fat and the true variable of interest.

From the Editors

>30 years), parity (0, 1, 2, 3, or ≥4 births), oral contraceptive use (never, in the past for <5 years, in the past for ≥5 years, currently for <5 years, currently for 5–9 years, or currently for ≥10 years), physical activity (<3, 3–8, 9–17, 18–26, 27–41, or ≥42 metabolic equivalents per week), alcohol consumption (none, 0.1–7.4, 7.5–14, 15–29, ≥30 g/d), and BMI (continuous). Variable categories were chosen to create approximately equally spaced category boundaries (45). Covariates were updated throughout the analysis whenever new information was available.

Effect modification by BMI and family history of breast cancer was assessed by adding a cross-product term and comparing models with and without this term by use of a likelihood ratio test. Competing risks analyses were used to examine whether the associations between each of the three body fat distribution variables and the risk of breast cancer differed by hormone receptor status among the 45,792 women with that information available (46). Using likelihood ratio tests, a model with separate hazard ratios for hormone receptor subtypes was compared with a model with a common hazard ratio for all breast cancer cases to generate *P* values for heterogeneity. Tests of statistical significance were two-sided, and a statistical significance level of .05 was used. Statistical analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC). Implied consent was assumed upon completion and return of the questionnaire. This study was approved by the institutional review boards of the Harvard School of Public Health and Brigham and Women's Hospital.

During 426 164 person-years of follow-up from 1993 to 2005, 620 incident cases of invasive premenopausal breast cancer were diagnosed. The age-standardized incidence rates of breast cancer were 131 per 100 000 person-years among those in the lowest quintile of waist circumference and 136 per 100 000 person-years among those in the highest quintile. The Spearman correlation coefficients for the association between BMI and waist circumference, hip circumference, and waist to hip ratio were .82, .85, and .33, respectively (all *P*s < .001). Neither waist circumference nor hip circumference nor the waist to hip ratio was associated with breast cancer incidence in any of the models (Table 1). For example, the multivariable-adjusted hazard ratio of breast cancer for the highest vs the lowest quintile of waist circumference was 1.27 (95% confidence interval [CI] = 0.88 to 1.84; P_{trend} = .17). The hazard ratios of breast cancer for the highest vs the lowest quintile of hip circumference and of the waist to hip ratio were 1.17 (95% CI = 0.78 to 1.74; P_{trend} = .41) and 1.14 (95% CI = 0.88 to 1.48; P_{trend} = .13), respectively (Table 1). The association between body fat distribution and the risk of breast cancer did not vary by BMI or family history of breast cancer (all $P_{interaction}$ > .05).

The point estimates for the association between each of the three body fat distribution measures and the risk of breast cancer were greater for women with ER-negative breast cancer than for those with ER-positive breast cancer (*P* values for heterogeneity ≤ .003) (Table 2). The multivariable-adjusted hazard ratios of ER-negative breast cancer for the highest vs the lowest quintile of each body fat distribution measure were 2.75 (95% CI = 1.15 to 6.54; P_{trend} = .05) for waist circumference, 2.40 (95% CI = 0.95 to 6.08; P_{trend} = .26) for hip circumference, and 1.95 (95% CI = 1.10 to 3.46; P_{trend} = .01) for waist to hip ratio. No difference in associations between each of the body fat distribution variables and breast cancer was observed according to PR status (*P* values for heterogeneity > .05); however, for each of the three body fat distribution variables, the quintile point estimates for breast cancer risk were larger for PR-negative breast cancer than for PR-positive breast cancer (data not shown).

Epidemiological data from prospective studies that examined the association between body fat distribution and the risk of premenopausal breast cancer are inconsistent. To our knowledge, seven prospective studies have examined the association between body fat distribution and premenopausal breast cancer (7,9,13,19,40–42): all seven studies examined waist to hip ratio, six (7,9,13,19,40,42) also examined waist circumference, and five (7,9,13,19,40) examined hip circumference. Two studies (13,41) reported a statistically significant positive association between the waist to hip ratio and the risk of breast cancer, another study (19) reported an inverse association, and four studies (7,9,40,42) reported null or non-statistically significant positive associations. Two meta-analyses (34,47) reported that a greater waist to hip ratio was associated with 1.5-fold increased risk of premenopausal breast cancer. The studies that examined the associations with waist and hip circumferences also found inconsistent results (7,9,13,19,40–42).

These inconsistent findings may be due, in part, to the fact that none of the seven published prospective studies reported the associations with breast cancer by hormone receptor status. Of the two case–control studies that did, one (48) reported that the association between waist to hip ratio and

Table 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) of premenopausal breast cancer associated with waist circumference, hip circumference, waist to hip ratio, and body mass index in the Nurses' Health Study II, 1993–2005

Measure, quintiles	No. of incident breast cancers (n = 620)	Follow-up, person-years (n = 426 164)	HR (95% CI)		
			Age-adjusted	Multivariable*	Multivariable†
Waist circumference, in					
<27.0	103	78411	1.0 (referent)	1.0 (referent)	1.0 (referent)
27.0–28.75	135	95887	1.05 (0.81 to 1.36)	1.00 (0.77 to 1.30)	1.06 (0.82 to 1.38)
29.0–30.75	128	83085	1.10 (0.85 to 1.43)	1.06 (0.81 to 1.38)	1.19 (0.90 to 1.56)
31.0–34.0	143	87324	1.16 (0.90 to 1.50)	1.12 (0.86 to 1.45)	1.36 (1.02 to 1.82)
≥34.25	111	81457	0.91 (0.69 to 1.19)	0.86 (0.65 to 1.14)	1.27 (0.88 to 1.84)
P_{trend}‡			.38	.25	.17
Hip circumference, in					
<36.25	127	98639	1.0 (referent)	1.0 (referent)	1.0 (referent)
36.25–37.75	113	75257	1.15 (0.89 to 1.48)	1.11 (0.86 to 1.44)	1.16 (0.90 to 1.51)
38.0–39.25	128	84555	1.10 (0.86 to 1.41)	1.03 (0.80 to 1.32)	1.13 (0.87 to 1.47)
39.5–42.0	144	87374	1.13 (0.89 to 1.44)	1.05 (0.82 to 1.35)	1.25 (0.93 to 1.66)
≥42.25	108	80339	0.89 (0.69 to 1.16)	0.82 (0.62 to 1.08)	1.17 (0.78 to 1.74)
P_{trend}‡			.28	.09	.41
Waist to hip ratio					
<0.73	137	89943	1.0 (referent)	1.0 (referent)	1.0 (referent)
0.73–0.75	104	82591	0.84 (0.65 to 1.08)	0.84 (0.65 to 1.09)	0.85 (0.66 to 1.10)
0.76–0.78	118	80340	0.97 (0.76 to 1.24)	0.97 (0.75 to 1.24)	1.01 (0.79 to 1.30)
0.79–0.83	138	91845	0.98 (0.77 to 1.25)	0.99 (0.78 to 1.26)	1.07 (0.83 to 1.36)
≥0.84	123	81445	0.97 (0.76 to 1.24)	1.00 (0.78 to 1.28)	1.14 (0.88 to 1.48)
P_{trend}‡			.82	.66	.13
Body mass index,§ kg/m^2					
<20.5	132	89799	1.0 (referent)	1.0 (referent)	1.0 (referent)
20.6–22.0	128	84987	0.97 (0.76 to 1.24)	0.98 (0.76 to 1.25)	0.99 (0.77 to 1.27)
22.1–23.9	129	87947	0.92 (0.72 to 1.18)	0.94 (0.74 to 1.20)	0.96 (0.74 to 1.24)
24.0–27.4	135	88065	0.91 (0.72 to 1.16)	0.94 (0.74 to 1.20)	0.98 (0.73 to 1.29)
≥27.5	96	75366	0.74 (0.57 to 0.96)	0.75 (0.57 to 0.99)	0.81 (0.53 to 1.21)
P_{trend}‡			.02	.03	.32

* Hazard ratios adjusted for age, height, history of benign breast disease, family history of breast cancer, age at menarche, age at first birth, parity, oral contraceptive use, alcohol consumption, and physical activity.

† Hazard ratios for waist circumference, hip circumference, and waist to hip ratio were adjusted for body mass index in addition to age, height, history of benign breast disease, family history of breast cancer, age at menarche, age at first birth, parity, oral contraceptive use, alcohol consumption, and physical activity. Hazard ratios for body mass index adjusted for waist circumference in addition to age, height, history of benign breast disease, family history of breast cancer, age at menarche, age at first birth, parity, oral contraceptive use, alcohol consumption, and physical activity.

‡ Tests for trend were performed using the midpoint of the interval for each quintile; *P* values are two-sided.

§ Body mass index measure in 1993.

the risk of premenopausal breast cancer did not vary by ER status, but this study had limited statistical power (n = 132 cases). The second study (49) reported no statistically significant association between waist to hip ratio and ER- and PR-negative breast cancer (n = 151 cases) and a statistically significant positive association between waist to hip ratio and ER- and PR-positive breast cancer (n = 168 cases).

Our finding that abdominal adiposity, as defined by waist circumference and the waist to hip ratio, was more strongly associated with risk of ER-negative breast cancer than with the risk of ER-positive breast cancer suggests that abdominal adiposity may influence the risk of premenopausal breast cancer through sex hormone–independent pathways. Data from both human and in vitro studies provide evidence to support this hypothesis. Although abdominal adiposity is associated with lower levels of sex hormone–binding globulin and increased bioavailability of estradiol (3,33,35), it is also associated with hyperinsulinemia and insulin resistance (3,34). Hyperinsulinemia may play a role in the etiology of breast cancer (50), given that insulin receptors are expressed in most breast cancers (51) and have been shown to stimulate the growth of breast cancer cells in vitro (52–55). In addition, insulin binds the insulin-like growth factor 1 receptor, which is expressed in breast cancer cell lines (56). Finally, the mitogenic effect of insulin on breast cancer cells may be more apparent in ER-negative tumors given evidence that suggests these tumors are not as susceptible to risk factors that are mediated through estrogen exposure (49,57).

A limitation of this study is that waist and hip circumferences were self-measured by participants and are subject to measurement error (58). However, the validity of self-reported waist and hip circumference measurements assessed in the NHS was found to be high (59). We expect that the errors in these measurements, including systematic within-person errors, would likely cause an attenuation of the true effect (58,60). In addition, intra-abdominal visceral fat is metabolically distinct from other types of body fat. Therefore, abdominal circumference measurements, which comprise both visceral and subcutaneous fat, are an indirect measure of the true var-

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between waist circumference, hip circumference, and waist to hip ratio and premenopausal breast cancer by estrogen receptor status among 45 792 women in the Nurses'Health Study II, 1993–2005*

	Estrogen receptor–positive breast cancer			Estrogen receptor–negative breast cancer		
Body fat distribution measure, quintiles	**No. of incident breast cancers (n = 393)**	**Multivariable HR (95% CI)†**	**Multivariable HR (95% CI)‡**	**No. of incident breast cancers (n = 131)**	**Multivariable HR (95% CI)†**	**Multivariable HR (95% CI)‡**
Waist circumference, in						
<27.0	66	1.0 (referent)	1.0 (referent)	12	1.0 (referent)	1.0 (referent)
27.0–28.75	89	1.03 (0.75 to 1.42)	1.11 (0.80 to 1.53)	28	1.81 (0.91 to 3.61)	1.89 (0.95 to 3.78)
29.0–30.75	85	1.07 (0.77 to 1.49)	1.23 (0.88 to 1.73)	24	1.79 (0.89 to 3.62)	1.94 (0.94 to 3.99)
31.0–34.0	84	1.00 (0.72 to 1.39)	1.27 (0.88 to 1.83)	37	2.55 (1.31 to 4.98)	2.94 (1.43 to 6.04)
≥34.25	69	0.82 (0.58 to 1.17)	1.32 (0.83 to 2.11)	30	2.09 (1.04 to 4.19)	2.75 (1.15 to 6.54)
P_{trend}§		.16	.25		.09	.05
				$P_{heterogeneity}$‖ = .0004		
Hip circumference, in						
<36.25	86	1.0 (referent)	1.0 (referent)	15	1.0 (referent)	1.0 (referent)
36.25–37.75	64	0.89 (0.64 to 1.23)	0.94 (0.67 to 1.31)	30	2.94 (1.54 to 5.61)	2.98 (1.56 to 5.73)
38.0–39.25	88	0.97 (0.72 to 1.32)	1.10 (0.80 to 1.51)	28	2.25 (1.16 to 4.34)	2.30 (1.16 to 4.56)
39.5–42.0	89	0.90 (0.66 to 1.22)	1.11 (0.78 to 1.59)	28	2.06 (1.06 to 4.00)	2.15 (1.03 to 4.46)
≥42.25	66	0.71 (0.50 to 1.00)	1.11 (0.68 to 1.82)	30	2.19 (1.12 to 4.28)	2.40 (0.95 to 6.08)
P_{trend}§		.05	.56		.26	.26
				$P_{heterogeneity}$‖ = .001		
Waist to hip ratio						
<0.73	91	1.0 (referent)	1.0 (referent)	21	1.0 (referent)	1.0 (referent)
0.73–0.75	71	0.87 (0.64 to 1.19)	0.89 (0.65 to 1.21)	18	0.95 (0.50 to 1.78)	0.95 (0.50 to 1.79)
0.76–0.78	73	0.92 (0.67 to 1.25)	0.96 (0.70 to 1.32)	26	1.37 (0.77 to 2.45)	1.38 (0.77 to 2.48)
0.79–0.83	85	0.92 (0.68 to 1.24)	1.00 (0.74 to 1.36)	29	1.33 (0.75 to 2.35)	1.35 (0.76 to 2.41)
≥0.84	73	0.91 (0.66 to 1.24)	1.07 (0.77 to 1.48)	37	1.88 (1.09 to 3.27)	1.95 (1.10 to 3.46)
P_{trend}§		.67	.53		.009	.01
				$P_{heterogeneity}$‖ = .003		

* Estrogen and progesterone receptor status was available for 84% of the incident breast cancers.

† Hazard ratios adjusted for age, height, history of benign breast disease, family history of breast cancer, age at menarche, age at first birth, parity, oral contraceptive use, alcohol consumption, and physical activity.

‡ Hazard ratios adjusted for body mass index, age, height, history of benign breast disease, family history of breast cancer, age at menarche, age at first birth, parity, oral contraceptive use, alcohol consumption, and physical activity.

§ Tests for trend were performed using the midpoint of the interval for each quintile; *P* values are two-sided.

‖ *P* value (two-sided) from likelihood ratio test comparing the model with separate estimates for hormone receptor subtypes with a model with a single estimate across the subtypes.

iable of interest (intra-abdominal visceral fat), even when measured with limited error (58). However, Soto González et al. (61) reported correlations of visceral fat and subcutaneous fat with waist circumference of 0.59 ($P < .001$) and 0.37 ($P < .001$), and with waist to hip ratio of 0.37 ($P < .001$) and −0.16 ($P = .12$), respectively. Because waist circumference and the waist to hip ratio are more strongly correlated with visceral fat than with subcutaneous fat, it is likely that we have captured the exposure of interest.

In conclusion, our findings suggest that abdominal adiposity may play a role in the risk of premenopausal ER-negative breast cancer. These findings may suggest that an insulin-related pathway of abdominal adiposity is involved in the etiology of premenopausal breast cancer.

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Affiliations of authors: Department of Epidemiology, Harvard School of Public Health, Boston, MA (HRH, WCW, KLT, KBM); Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics and Gynecology (HRH, KLT, KBM) and Channing Laboratory, Department of Medicine (WCW, KLT, KBM), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Nutrition, Harvard School of Public Health, Boston, MA (WCW).