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Body fat distribution and obesity in pre- and postmenopausal breast cancer

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Background Excessive body weight is known to increase the risk of postmenopausal, but not premenopausal breast cancer. Some studies have suggested that being overweight is protective against premenopausal breast cancer, but the evidence is not compelling. Much less is known about the role of body fat distribution in either pre- or postmenopausal breast cancer.

Methods Breast cancer risk was examined in relation to body weight, height, Quetelet index (kg/m^2), and waist/hip ratio (WHR) in the New York University Women's Health Study, a prospective cohort study. Cases were 109 premenopausal and 150 postmenopausal women diagnosed with breast cancer between 1985 and 1994. Non-cases were 8157 cohort members free of breast cancer.

Results Among premenopausal women, there was an increasing risk of breast cancer with increasing WHR. The relative risk (RR) of breast cancer increased to 1.72 (95% confidence interval [CI] : 1.0–3.1) in the upper quartile of WHR. The association was limited to subjects who had elevated Quetelet index, but not among those with lower weight. Overall, Quetelet index itself was not related to breast cancer risk in the premenopausal group, but there was a protective association among those ranking below the median WHR. In postmenopausal women, the RR for breast cancer increased to 2.36 (95% CI : 1.4–3.9) in the upper quartile of Quetelet index, but there was no association with WHR. Height was not associated with breast cancer in this study.

Conclusions The study confirms that excessive body weight increases breast cancer risk in postmenopausal women. On the contrary, in premenopausal women, excessive body weight may be protective among women who have a lower-body type of fat accumulation (low WHR). An upper-body fat accumulation (high WHR) is a predictor of breast cancer risk in premenopausal women, and this effect is especially pronounced among subjects who are overweight.

Keywords Breast neoplasms, body fat distribution, body weight, cohort studies, epidemiology, obesity

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Epidemiological studies of breast cancer suggest that body weight, relative weight and height alter disease risk.[1–3] Many studies show that in postmenopausal women, breast cancer risk is increased in heavier women, although not all observations are consistent. After menopause, obesity is associated with an increased level of circulating oestrone and a reduced level of sex-hormone binding globulin (SHBG).[4] With evidence accumulating that endogenous sex hormones are associated with an increased risk of breast cancer,[4–7] this explanation for the effect of body size on breast cancer risk deserves further attention.

Overweight premenopausal women may experience a reduced risk of breast cancer,[8] possibly owing to an increased frequency of anovulatory cycles[8] or a reduction in serum progesterone levels.[5] Obesity may lower risk as a result of increased parity,[9] which is protective, or because it is accompanied

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by reduced mammographic density,[10] which is inversely related to breast cancer risk. Detection bias, resulting from leaner women being diagnosed earlier, appears not to account fully for the observed difference in risk.[1,11,12]

In 1987, Bruning[13] proposed that the distribution of body fat affects breast cancer risk by influencing sex hormone availability. Evidence supporting this hypothesis came from observations showing that women with a predominance of upper body or truncal fat have lower SHBG levels and increased percentage of free testosterone, independent of overall adiposity.[14–19] Epidemiological studies of body fat distribution using waist/hip ratio (WHR) or skinfold thickness have produced contradictory results, some being positively related to breast cancer,[20–25] others showing no association.[7,26–31] Some of these inconsistencies may reflect differences between prospective and cross-sectional studies, or perhaps small sample size. It should be noted also that skinfold thickness and WHR are poorly correlated with each other,[32] thus reflecting different mechanisms of body fat distribution.[32,33] WHR is more commonly used than skinfold thickness because it is considered a better predictor of type 2 diabetes, hypertension, and metabolic abnormalities[33] and because it is more easily obtained in large epidemiological studies.

In this paper we evaluated the role of body fat distribution and other anthropometric variables among women enrolled in the New York University Women's Health Study, an ongoing prospective cohort study of breast cancer and endogenous sex hormones. Of particular interest was to assess the role of height, Quetelet index (weight in kg/height in m^2) and WHR as they related to subsequent breast cancer risk in pre- and postmenopausal women.

Materials and Methods

Study subjects and body size measurements

The New York University Women's Health Study cohort includes 14 275 women aged 35–65 who were recruited at a breast screening clinic in New York City from March 1985 through June 1991.[6,34] At entry, and at each subsequent annual visit, cohort members completed a questionnaire on demographic data, reproductive history and personal and family history of cancer, and reported current weight and height. Venous blood serum was obtained and stored at –80°C for subsequent analysis.

Beginning in August 1986, 18 months after enrolment began, waist and hip circumference measurements were added for all new and returning cohort members and are therefore available for a subset of approximately 65% of the original cohort. After excluding cohort members with missing height, weight or other essential information (reproductive history, family history of breast cancer and previous benign breast biopsy) 8416 subjects, or 59% of the original cohort, were available for analyses. Of these, 3941 women (47%) were classified as postmenopausal at cohort enrolment having reported no menstrual cycles for the preceding 6 months, or a history of bilateral oophorectomy.

New breast cancer cases were identified by active follow-up and by record linkage with the New York State Tumor Registry. The present analysis included 55 377 person-years with an average follow-up of 6.6 years. Cases were women diagnosed with invasive or *in situ* breast cancer after cohort enrolment and before 1 January 1994. There were 259 women with breast cancer, 109 premenopausal and 150 postmenopausal at the time of cohort enrolment. Mean time to diagnosis was 3.8 years for premenopausal cases and 4.4 years for postmenopausal cases. Non-cases were the 8157 cohort members who had not been diagnosed with breast cancer as of 1 January 1994.

Waist and hip circumferences were measured with subjects undressed from the waist up, in a standing position. Waist was measured just above the level of the lateral iliac crest, below the lowest rib, and hip circumference under the inferior rim of the symphysis, in the midline. The same technician performed all measurements using a cloth tape and recording to the nearest centimetre.

Statistical analysis

Cox proportional hazards regression analysis was used to calculate relative risks (RR) for breast cancer according to quartiles of height, Quetelet index, waist circumference, hip circumference, and WHR. Waist and hip circumferences were adjusted for height using residual analysis.[35] Covariates in multivariate analyses were known risk factors for breast cancer, including age at cohort entry, age at menarche, age at first full-term pregnancy, age at menopause, history of breast biopsy, and history of breast cancer in mother and in sisters. Quetelet index and WHR are known to be positively correlated, as was the case in our data (Pearson correlation coefficients were 0.41 in premenopausal women and 0.38 in postmenopausal women), so that analysis of Quetelet index and WHR were further adjusted for each other. Risk associated with anthropometric variables was evaluated separately for pre- and postmenopausal subjects. Menopausal status at study baseline, rather than at diagnosis, was used because information concerning the occurrence of menopause during follow-up was not available for most individuals.

Results

Reproducibility of the technician's measurements of hip and waist was high, with an intraclass correlation (for WHR) >0.99, as described previously.[36] We evaluated the intra-individual variability of WHR over time based on the 1851 cohort members who were measured on three or more occasions. WHR tended to increase with age, but repeated annual measurements were moderately stable, with an intraclass correlation of 0.68.[36]

Differences in mean anthropometric variables between breast cancer cases and non-cases are shown in Table 1. Premenopausal cases had a significantly greater WHR than the non-cases (0.753 versus 0.742, $P = 0.05$), and a smaller hip circumference (94.6 cm versus 97.3 cm, $P = 0.01$). They were also 1.7 kg lighter in weight than the non-cases (a non-significant difference), but had no differences in height, Quetelet index, or waist. In contrast, postmenopausal cases were heavier than the non-cases, (69.0 versus 66.8 kg, $P = 0.03$), but showed no appreciable case-control differences in height, Quetelet index, waist circumference, hip circumference, or WHR.

In multivariate analyses in premenopausal subjects (Table 2), there was an evident increase in risk of breast cancer with increasing WHR. The adjusted RR increased to 1.72 (95% CI : 1.0–3.1) in the highest quartile of WHR (P for trend = 0.03) and increased even further after adjustment for Quetelet index. The risk of breast cancer did not vary with increasing height

Table 1 Age-adjusted means (standard error) of anthropometric measurements in breast cancer cases and non-cases, by menopausal status. New York University Women's Health Study, 1985–1994

	Premenopausal			Postmenopausal		
	Cases N = 109	Non-cases N = 4366		Cases N = 150	Non-cases N = 3791	
Variables	Mean (SE)	Mean (SE)	*P*-value	Mean (SE)	Mean (SE)	*P*-value
Weight (kg)	63.1 (1.24)	64.8 (0.20)	0.17	69.0 (0.99)	66.8 (0.20)	0.03
Height (m)	1.63 (0.006)	1.63 (0.001)	0.67	1.63 (0.005)	1.62 (0.001)	0.24
Quetelet index	23.8 (0.44)	24.3 (0.07)	0.20	26.1 (0.36)	25.5 (0.07)	0.10
Waist (cm)	71.4 (1.05)	72.3 (0.17)	0.43	78.7 (0.93)	77.2 (0.19)	0.13
Hip (cm)	94.6 (1.05)	97.3 (0.17)	0.01	100.2 (0.86)	99.2 (0.17)	0.24
Waist/hip ratio	0.753 (0.006)	0.742 (0.001)	0.05	0.784 (0.006)	0.777 (0.001)	0.21

Table 2 Relative risks (RR) of breast cancer according to quartiles of anthropometric measurements among premenopausal subjects. New York University Women's Health Study, 1985–1994

Variables	No. of cases/ non-cases	RR1[a] (95% CI)	RR2[b] (95% CI)
Height (cm)			
<161	31/1165	1.00	NA
161–165	29/1210	0.91 (0.55–1.52)	
165–170	27/1130	0.93 (0.55–1.56)	
>170.1	22/861	0.96 (0.55–1.66)	
Quetelet index			
<21.5	31/1082	1.00	1.00
21.5–23.25	29/1110	0.95 (0.57–1.56)	0.90 (0.54–1.51)
23.25–26.36	24/1105	0.85 (0.50–1.47)	0.77 (0.44–1.33)
>26.36	25/1069	1.00 (0.58–1.73)	0.81 (0.45–1.45)
Waist/hip ratio			
<0.698	19/1100	1.00[c]	1.00[d]
0.698–0.735	23/1099	1.20 (0.65–2.20)	1.22 (0.66–2.25)
0.735–0.778	36/1090	1.80 (1.03–3.15)	1.86 (1.06–3.28)
>0.778	31/1077	1.72 (0.96–3.08)	1.86 (1.01–3.45)

[a] Adjusted for age at enrolment, age at menarche, age at first full-term pregnancy, history of breast biopsy and history of breast cancer in mother and sisters.

[b] Further adjusted for waist/hip ratio in analyses of Quetelet index and for Quetelet index in analyses of waist/hip ratio.

[c] *P*-value for trend = 0.03.

[d] *P*-value for trend = 0.02.

Table 3 Relative risks (RR) of breast cancer according to quartiles of anthropometric measurements among postmenopausal subjects. New York University Women's Health Study, 1985–1994

Variables	No. of cases/ non-cases	Relative risk[a] (95% CI)	Relative risk[b] (95% CI)
Height (cm)			
<155	23/674	1.00	NA
155–161	38/1117	1.07 (0.64–1.80)	
161–166	53/1077	1.55 (0.94–2.53)	
>166	36/923	1.28 (0.75–2.18)	
Quetelet index			
<22.32	23/962	1.00[c]	1.00[c]
22.32–24.69	32/938	1.45 (0.85–2.49)	1.45 (0.84–2.48)
24.69–27.46	47/919	2.31 (1.40–3.82)	2.29 (1.37–3.82)
>27.46	48/972	2.36 (1.43–3.91)	2.40 (1.42–4.08)
Waist/hip ratio			
<0.73	30/949	1.00	1.00
0.73–0.773	38/953	1.20 (0.74–1.94)	1.10 (0.68–1.78)
0.773–0.817	45/941	1.50 (0.94–2.39)	1.22 (0.76–1.96)
>0.817	37/948	1.28 (0.78–2.08)	0.94 (0.56–1.57)

[a] Relative risk adjusted for age at enrolment, age at menarche, age at first full-term pregnancy, history of breast biopsy and history of breast cancer in mother and sisters.

[b] Relative risk further adjusted for waist/hip ratio in analyses of Quetelet index and for Quetelet index in analyses of waist/hip ratio.

[c] *P*-value for trend < 0.001.

or Quetelet index, nor did it change with increasing hip circumference (data not shown).

Among postmenopausal women (Table 3) there was an appreciable increase in the risk of breast cancer with increasing Quetelet index. The RR increased to 2.36 (95% CI : 1.4–3.9) in the highest quartile (*P* for trend < 0.001). WHR was not associated with breast cancer, either before or after adjustment for Quetelet index. Risk of breast cancer appeared to increase with increasing waist and hip circumferences, but this association disappeared after controlling for Quetelet index (data not shown). There was no change in risk with increasing height.

Subsequent analyses explored the interrelationships between WHR, Quetelet index and breast cancer risk in premenopausal subjects. The risk of breast cancer increased with increasing WHR among women who ranked above the median for Quetelet index, but not among those who ranked below the median (Table 4). Among the overweight group, the adjusted RR for the highest category of WHR was 2.42 (95% CI : 0.8–7.0; *P* for trend 0.01). Conversely (Table 5), among subjects ranking below median for WHR, Quetelet index was inversely associated with breast cancer risk. In these subjects, the adjusted RR for the highest category of Quetelet index was 0.34 (95% CI : 0.1–1.5; *P* for trend 0.04), but there was no evident trend among those with a WHR above median.

Discussion

In this prospective cohort study, fat accumulation as measured by WHR was significantly related to breast cancer in premenopausal women, but not in postmenopausal women. Conversely, Quetelet index, a measure of body weight, was

Table 4 Relative risks (RR) of breast cancer according to quartiles of waist/hip ratios (WHR) stratified on Quetelet index (above or below the median) among premenopausal subjects. New York University Women's Health Study, 1985–1994

	Quetelet index below median		Quetelet index above median	
Variable	No. cases/ non-cases	RR (95% CI)	No. cases/ non-cases	RR (95% CI)
Waist/hip ratio[a]				
<0.698	15/772	1.00	4/328	1.00[b]
0.698–0.734	20/654	1.51 (0.8–3.0)	3/445	0.56 (0.1–2.5)
0.734–0.778	19/518	1.66 (0.8–3.3)	17/572	2.39 (0.8–7.1)
>0.778	6/248	1.15 (0.4–3.0)	25/829	2.42 (0.8–7.0)

[a] Adjusted for age at enrolment, age at menarche, first full-term pregnancy, history of breast biopsy and history of breast cancer in mother and sisters.

[b] *P*-value for trend = 0.01.

Table 5 Relative risks (RR)[a] of breast cancer according to quartiles of Quetelet index (QI) stratified on waist/hip ratio (above or below the median) among premenopausal subjects. New York University Women's Health Study, 1985–1994

	Waist/hip ratio below median		Waist/hip ratio above median	
Variable	No. cases/ non-cases	RR (95% CI)	No. cases/ non-cases	RR (95% CI)
Quetelet index				
<21.16	22/768	1.00[b]	9/314	1.00
21.16–23.25	13/658	0.75 (0.4–1.5)	16/452	1.37 (0.6–3.1)
23.25–26.37	5/512	0.42 (0.2–1.1)	19/593	1.35 (0.6–3.0)
>26.37	2/261	0.34 (0.1–1.5)	23/808	1.32 (0.6–2.9)

[a] Adjusted for age at enrolment, age at menarche, age at first full-term pregnancy, history of breast biopsy, and history of breast cancer in mother and sisters.

[b] *P*-value for trend = 0.04.

related to breast cancer in the postmenopausal, but not in the premenopausal group. In our data, height was not associated with breast cancer risk in either pre- or postmenopausal subjects.

Previous studies of WHR and premenopausal breast cancer included a prospective cohort study,[25] which reported an appreciable effect on risk for WHR, and three case-control studies,[24,29,31] which reported no effect. In the prospective study,[25] based on 56 premenopausal cases from the Netherlands, age-adjusted RR for breast cancer increased with increasing WHR among premenopausal women under 45. In women over 45, there was an inverse association between breast cancer and WHR, waist, hip, and Quetelet index. It is unfortunate that this study was too small to provide convincing evidence. The largest case-control study of WHR and premenopausal breast cancer,[31] based on 1588 cases, was also restricted to women under 45 years of age at diagnosis. No association of WHR (adjusted for height and weight) and breast cancer was reported, but height and being lean were significantly related to breast cancer. In our data, risk of breast cancer was not related to WHR or to any other anthropometric variable in subjects who were 45 or younger. In another case-control study, Bruning *et al.*[24] reported that WHR was not related to breast cancer risk in premenopausal women, but that Quetelet index was significantly protective. Neither Quetelet index nor WHR were related to risk in a case-control study in New York City[29] that utilized as controls women diagnosed with benign breast disease.

As for postmenopausal women, the results of previous studies of WHR and breast cancer were mixed. Four studies, two prospective cohort[7,25] and two case-control,[28,29] reported observations consistent with our finding of no association and three studies, one prospective cohort[21] and two case-control,[23,24] reported a positive association. Of three prospective cohort studies of breast cancer in postmenopausal women, only the Iowa Women's Health Study[21] reported a significant association for WHR and breast cancer, particularly in older, heavier women. The other two prospective cohort studies[7,25] did not report a significant association, but they were based on only 23 and 36 cases, respectively.

Four case-control studies examined WHR and breast cancer in postmenopausal women. Schapira *et al.*[23] using a case group in which 80% of the 216 breast cancer cases were postmenopausal, reported a strong association of WHR and breast cancer. The RR of breast cancer for increasing quartiles of WHR were 1.0, 1.73, 3.01 and 5.21, respectively, but no adjustment was made for Quetelet index. Bruning *et al.*[24] reported that WHR was significantly associated with postmenopausal breast cancer and that Quetelet index was not. In the latter study, WHR was not related to risk in premenopausal women as noted above, but when all subjects were combined both WHR and Quetelet index (adjusted for each other) were significantly, positively associated with breast cancer. The two remaining case-control studies, by den Tonkelaar *et al.*[28] and by Petrek *et al.*[29] reported that breast cancer was not related to WHR in postmenopausal women. Two additional studies did not stratify on menopausal status, and thus were not directly comparable to our study. A cohort study in Sweden[26] reported no link between WHR and breast cancer in 21 pre- and postmenopausal cases. Likewise, a case-control study in Germany[27] (89 pre- and postmenopausal cases) reported no association between WHR and breast cancer, using age- and Quetelet index-matched controls.

Centralized or truncal fat accumulation, measured, for example by the ratio of subscapular to triceps skinfold thickness, has been evaluated in four breast cancer studies with mixed results. In the Framingham study,[20] risk for breast cancer (primarily postmenopausal) was increased in women with greater truncal skinfold thickness. In a case-control study in Russia, Berstein reported that breast cancer cases had increased centralized adiposity.[22] A prospective cohort study[39] and a case-control study,[28] both from the DOM project in the Netherlands, reported no association between breast cancer risk and skinfold thickness. Two case-control studies in the USA[23,31] evaluated WHR and skinfold thicknesses as risk factors for breast cancer. Both exposure variables were significantly associated with breast cancer in the study by Schapira *et al.*[23] and neither one was related to risk in the study by Swanson.[31]

Our observations on Quetelet index are consistent with a growing body of epidemiological evidence suggesting that increasing body mass is associated with postmenopausal breast cancer—findings more consistently reported in case-control studies than in prospective cohort studies.[3] In premenopausal

women, evidence suggests that Quetelet index is either protective or, as in the present study, not related to risk. In a recent report, oestrogen levels were elevated in premenopausal women with a lean body mass, thus suggesting a possible mechanism for this association.[37]

WHR might influence breast cancer risk in premenopausal women through sex hormones, especially oestrogens and androgens, which have been implicated in breast cancer aetiology.[5–7,38,40] An important hormonal factor that could be associated with WHR is reduced SHBG, which would increase the bioavailability of sex hormones. In the model proposed by Bruning,[13] upper body fat accumulation leads to increased triglycerides, which in turn lead to reduced SHBG and increased circulating unbound oestradiol. Excessive circulating androgens appear to be related to increased upper body fat. For example premenopausal women with increased androgenicity, as reflected by elevated free testosterone and decreased SHBG, have higher WHR, adjusted for body weight, than controls.[14] Women with hirsutism—a symptom of androgen excess—tend to have higher WHR than non-hirsute subjects, after adjustment for age and weight.[15] Kirschner *et al.*[17] in a study of morbidly obese premenopausal women, reported that testosterone, oestradiol, free testosterone and free oestradiol were elevated, and SHBG reduced, in women with upper body obesity, as compared to women with lower body obesity.

In our data, WHR was associated with premenopausal breast cancer in subjects who were overweight (Quetelet index above median) but not in normal-weight subjects. Such effect modification might explain some of the inconsistencies between our results and those of previous studies, if the participants of these studies were of lighter weight than our study population. We compared average body weight and Quetelet index in our study with previous studies in the Netherlands and in the USA[24,25,29,31] that did not observe an association with WHR. Average weight and Quetelet index were not dissimilar, or were even lower in our study population.

We observed also that in premenopausal women a low Quetelet index was associated with increased breast cancer risk among those ranking below the median in WHR, but not among the others. Previous studies of Quetelet index and breast cancer in premenopausal women have been inconsistent,[24,25,29,31] so we examined whether studies in which WHR were low reported a significant inverse association with breast cancer for Quetelet index. The study that reported the highest WHR[24] was the only one of four that reported a significant protective effect for Quetelet index.

In conclusion, our study offers new evidence that upper body fat accumulation, as estimated by WHR, may be associated with breast cancer in premenopausal, but not in postmenopausal women. Conversely, body weight, as estimated by the Quetelet index, appeared to be associated with breast cancer exclusively in postmenopausal women. The most intriguing findings had to do with the premenopausal group in which WHR appeared to increase the risk of breast cancer only among subjects who were overweight. We observed also that being overweight was clearly protective against breast cancer among premenopausal subjects with a lower body fat accumulation (low WHR). These effect modifications, not previously reported, suggest that WHR and Quetelet index interact in a way that might carry important aetiological implications for breast cancer. In order to address the issue of their interaction, studies with a sufficiently large sample size should be conducted, perhaps in populations with a broad range of values in weight and WHR.

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