Is Body Fat Topography a Risk Factor for Breast Cancer?

Jeanne A. Petrek, MD; Margaret Peters, BS, RN; Constance Cirrincione, MS; Deborah Rhodes, MD; and Daiva Bajorunas MD

■ *Objective*: To determine whether body fat distribution is associated with the onset of breast cancer.
■ *Design*: Case-control study.
■ *Setting*: Memorial Sloan-Kettering Cancer Center, New York, New York.
■ *Patients*: Three hundred thirteen healthy, white women, born in the United States.
■ *Measurements*: Waist and hip circumferences were measured on the day before diagnostic breast surgery, and an extensive risk assessment of clinical and family history data was done. After the results of diagnostic breast surgery were obtained, study participants were divided into three groups: women with breast cancer (n = 156); controls (n = 126) with benign tissue at biopsy and an average risk for breast cancer; and high-risk women (n = 31), defined as being at a risk for breast cancer development of 1% per year, based on rigorous histologic or clinical criteria.
■ *Results*: The waist-to-hip ratios (WHR) were identical (mean ± SD) in case patients (0.80 ± 0.06), controls (0.80 ± 0.06), and high-risk women (0.80 ± 0.08). Further, no trend could be detected between increasing WHR and breast cancer risk; the estimated relative risk for cancer incidence in women with WHR greater than or equal to 0.81 was 0.78 (95% CI, 0.36 to 1.71), compared with women with WHR of less than 0.73. No difference in WHR was noted between the case patients and controls when analyzed separately according to menopausal status, age, absolute weight, or relative weight.
■ *Conclusion*: In the women studied, body fat topography as defined by WHR was not associated with breast cancer development.

Annals of Internal Medicine. 1993;**118**:356-362.

From Memorial Sloan-Kettering Cancer Center, New York, New York. For current author addresses, see end of text.

Various chronic illnesses are related to the pattern of body fat distribution. At equal degrees of relative or absolute body fat, a predominant upper (central) body fat distribution, as defined by an increased waist-to-hip ratio (WHR), correlates positively with glucose intolerance, diabetes mellitus, hyperlipidemia, coronary artery disease, hypertension, stroke, and premature (as well as overall) death (1-5). Conversely, generally healthier populations have been shown to exhibit a decreased WHR (lower body fat distribution) (6).

Interrelations among these diverse metabolic disorders and their convincing association with the distinct WHR phenotype of upper body fat predominance suggest that the regional distribution of adipose tissue, with its site-specific hormonal activity and metabolic responsiveness (7, 8), may have relevance in other diseases associated with characteristic metabolic profiles. Indeed, endometrial cancer, a malignancy long known to be associated with obesity, diabetes, and hypertension (9-11), has recently been shown to have a significant association with upper or central body fat distribution (12, 13). This body fat pattern is a stronger predictor than body mass of endometrial, and possibly ovarian, carcinomas (6).

Breast cancer, the most prevalent malignancy occurring in white women, has generally not been associated with the other clinical entities that have been linked to an increased WHR (14, 15). A recent evaluation of mammographic breast morphologic analysis and body fat distribution found that women who had a high WHR were significantly less likely to have a putative high-risk mammographic pattern compared with women who had a low WHR, independent of age and the degree of obesity (16). More importantly, data from a population-based, prospective study have shown no association between breast cancer development and body fat topography (12). Surprisingly, however, three other clinical studies have noted a positive relation between upper or central body fat distribution and breast cancer risk (17-19).

We present the results of prospective body fat topography assessment in a large cohort of demographically homogeneous women, analyzed with particular attention to the menopausal status of the participants. Women subsequently diagnosed with breast cancer

Abbreviations

BMI = body mass index
SHBG = sex hormone binding globulin
WHR = waist-to-hip ratio

were compared with women evaluated by rigorous pathologic and clinical criteria and considered to be at low risk for breast cancer.

Methods

Participants

Consecutive white American women of any age were recruited the day before the excision of an undiagnosed breast mass between 1 August 1988 and 1 December 1989 at Memorial Sloan-Kettering Cancer Center, according to the guidelines of the Institutional Review Board. To avoid confounding variables, women were excluded if they had any major systemic illnesses because of the association between body fat topography and various metabolic disorders. Obesity alone (without diabetes or hypertension) was not considered an exclusion criterion, unless morbid obesity (> 100% above ideal body weight) was present. Women were excluded if they experienced a weight gain or loss of 10% or more of their current weight in the previous 3 years.

Because hormonal status independently affects WHR (1, 6, 20) as well as breast cancer risk (14, 15), the hormonal status of potential participants was carefully defined: Women either had to be premenopausal or to have had a known menopause with no postmenopausal hormone replacement. Premenopausal women with intact ovaries after hysterectomy were disqualified because the date of ovarian cessation could not be ascertained. Patients taking any hormonal preparation (for example, birth control pills, fertility drugs, or estrogen replacement) and pregnant patients (determined by history) were excluded.

The research nurse reviewed the admission history and physical examination of 400 white American women before their diagnostic breast surgery. Three refused participation (all three were later noted to have benign biopsy results). Ten patients were eliminated for hormone use or uncertain date of menopause (six were benign; four had cancer on biopsy). One patient with cancer was eliminated for weight change. Seventy-two patients were eliminated for illnesses: 40 had cancer and 33 had benign findings on biopsy. In order of frequency, the most common illnesses were hypertension, diabetes, and asthma. These conditions were responsible for more than 80% of the illness exclusions. The total number of patients excluded was 87 (45 with cancer and 42 with benign findings on subsequent biopsy). The remaining 313 women, found to be eligible and having consented to participation, formed the study group.

Study Protocol

The study parameters (clinical variables and the anthropometric measurements) were obtained from all participants before the diagnostic breast operation. Clinical information about the major breast cancer risk factors (age, heredity, and hormonal and reproductive factors) was obtained by interview. More minor or controversial risk factors, such as alcohol consumption, smoking history, or mammographic parenchymal patterns, were not considered. Data were collected on the number of pregnancies and deliveries as well as on the age of first full-term delivery. An extensive family history confirmed the status of all first-degree relatives: their current age or age at death, the presence or absence of unilateral or bilateral breast cancer, and the age at breast cancer diagnosis. After the interview, anthropometric measurements were done according to the method of Ashwell and colleagues (21) by a single examiner to reduce intertester errors.

Waist circumference was measured with the participant standing with abdomen relaxed, arms at sides, and feet together without footwear. The research nurse faced the participant and measured with a tape to the nearest 0.5 cm in the horizontal plane on the bare skin at the level of the natural waist, the narrowest part of the torso at the end of a normal expiration.

Hip circumference was measured with the participant standing in the same position. The research nurse measured with a tape to within 0.5 cm around the buttocks in the horizontal plane at the largest circumference between the waist and thigh. The measurement was usually over the greater trochanters.

Participants were weighed without footwear or underwear and wore the standard lightweight cotton hospital gown. Using the Detecto Floor Scales Model II (Detecto, Inc., Brooklyn, New York), each participant's weight was measured to the nearest 0.5 kg.

Height was measured to the nearest 0.5 cm using the standard vertical attached rod on the Detecto Floor Scales Model II. Participants did not wear shoes during height measurements.

Case-Control Assignment

The results of the paraffin histologic sections obtained from the diagnostic breast surgery of study participants were made available by the Department of Pathology in several days. Of the 313 women studied, 156 had invasive breast carcinoma (stage I or II). These women constituted the "cases." Because the remaining women with benign breast biopsies evaluated at a comprehensive cancer center may not be typical of women nationwide, we conducted a rigorous assessment to separate those at high risk from those at average risk. Of the 157 women who did not have invasive breast cancer, 126 were considered to be without high risk ("controls"), and 31 were considered to be at high risk for invasive breast cancer.

Histologic and Clinical Risk Assessment

The breast tissue of 157 women without invasive breast cancer was studied for histologic changes associated with an increased risk for breast cancer, that yielding a breast cancer incidence of at least 1% per year (22). A histologic diagnosis of ductal or lobular carcinoma in situ or a benign biopsy sample showing atypical proliferative disease as defined by the classification of Page and coworkers, adopted in 1986 by the consensus meeting of the American College of Pathologists (23) and modified in 1991 (22), conferred a high-risk status.

Of the 157 patients without invasive breast cancer, 22 had ductal or lobular carcinoma in situ (15 had ductal carcinoma in situ, 3 had lobular carcinoma in situ, and 4 had both ductal and lobular carcinoma in situ). Four patients had atypical hyperplasia. Therefore, 26 patients (22 with in-situ carcinoma and 4 with atypical hyperplasia) were considered to be at high risk for developing breast cancer of 1% per year based on histologic criteria. Of the remaining 131 patients with benign biopsy results, 110 had Page and Dupont classification (1991) (22), diagnoses that conferred no increased risk (fibroadenoma, cyst, fibrosis, or adenosis), and 21 had sclerosing adenosis, papilloma with fibrovascular core, or moderate or florid hyperplasia, diagnoses that conferred a detectable but clinically irrelevant risk.

A family history of breast cancer diagnoses in first-degree relatives, depending on their age at diagnosis and whether the disease is bilateral, can place a woman at a risk for breast cancer development of 1% per year (24). Five patients had such a family history and were added to the high-risk category due to clinical criteria. No other patients were at this level of risk when evaluated by a combination criteria of specific clinical and histologic risk factors (25).

Thirty-one patients (26 for histologic criteria and 5 for clinical criteria) therefore were removed from the group of 157 patients without invasive breast cancer and were analyzed separately as a group at high risk for invasive breast cancer. The other 126 women without breast cancer were estimated to have a risk similar to that of the average white American woman and thus served as controls.

Statistical Analysis

A series of anthropometric measurements (height, weight, waist circumference, hip circumference, WHR, body mass index [BMI]) and clinical parameters (age at diagnosis, menopausal status, any family history of breast cancer, age at first full-term pregnancy, number of pregnancies) were examined in case patients, high-risk participants, and controls. Body mass index (weight in kg divided by height in m^2) was used as the

Table 1. Demographic Characteristics of Case Patients and Controls*

Characteristics	Controls	High-Risk Women	Case Patients
	← n(%) →		
Age, *y*			
≤ 30	5 (4)	5 (16)	5 (3)
31 to 40	25 (19)	6 (19)	20 (12)
41 to 50	52 (41)	6 (19)	53 (34)
51 to 60	26 (20)	10 (32)	34 (22)
61 to 70	20 (15)	4 (13)	36 (23)
71 to 80	1 (1)	0 (0)	7 (5)
≥ 81	0 (0)	0 (0)	1 (1)
Children, *n*			
0	35 (28)	3 (10)	31 (20)
1 to 3	78 (61)	23 (74)	107 (69)
≥ 4	15 (11)	5 (16)	18 (11)
Menopausal status			
Premenopausal	84 (66)	17 (55)	82 (53)
Postmenopausal	44 (34)	14 (45)	73 (47)

* The mean age (± SD) at first full-term delivery was 24.8 (± 4.4) years for controls, 23.0 (± 5.2) years for high-risk women, and 25.5 (± 5.2) for case patients.

measure of obesity. Except for menopausal status, variables were analyzed as continuous data.

As an initial comparison of case patients and controls, univariate testing was done on continuous variables using the Student *t*-test and on categoric variables using chi-square tests. Because of the disparity in sample size between high-risk participants (n = 31) and controls and case patients (n = 126 and 156, respectively), a three-way analysis was deemed statistically inaccurate. We therefore compared all patients with benign biopsy results (high-risk participants plus controls, n = 157) with case patients (n = 156). To avoid bias, we also compared the lowest-risk population (the controls, n = 126) with the "maximal-risk" population (the case patients, n = 156).

Stepwise logistic regression with forward inclusion of variables was used to model the probability of breast cancer as a function of the variables considered simultaneously. The binary response variable was breast cancer diagnosis compared with benign biopsy, as defined here. To test the hypothesis that the coefficient of a variable is zero, the maximum likelihood estimate chi-square statistic was used. The model likelihood ratio chi-square was also calculated to test the difference between each model and a model based only on the intercept. This measure was used to determine the significance of the model.

The relative risk, defined as the ratio of the risk for developing breast cancer in the presence of a factor to the risk in the absence of that factor, was estimated by the odds ratio. An odds ratio of 1.00 indicated that the probability of breast cancer was unchanged by the presence or absence of a particular factor, thereby indicating no association between that factor and breast cancer. Confidence intervals (CIs) of 95% are provided where appropriate.

Results

The demographic and clinical characteristics of the patients with breast cancer, the high-risk participants, and the controls are presented in Table 1. The three groups were similar in age at presentation, parity, and age at first full-term delivery. Two thirds of patients with benign biopsy results were premenopausal, and one third was postmenopausal; the patients with breast cancer were equally divided in terms of menopausal status.

Table 2 shows the mean anthropometric values for the three study groups. No difference in body fat distribution, as represented by the WHR (the main end point of the study), was shown to exist between case patients and controls; the mean WHR (± SD) was 0.80 ± 0.06 in both groups. Results for the 31 patients at high risk were also similar, with a mean WHR (± SD) of 0.80 ± 0.08. Women with breast cancer differed significantly only in age, whether analyzed with or without the high-risk group added to the controls. Although case patients appeared leaner than women without cancer, as determined by smaller waist and hip measurements, these data did not differ significantly.

The classification of women as pre- or postmenopausal is the most clinically relevant criterion in the assessment of breast cancer risk. Our data were analyzed further, separately, according to menopausal status. Because the analysis with or without the high-risk group added to controls yielded identical results, we present only the data regarding comparison of case patients with controls (Table 3). Premenopausal women with breast cancer were leaner than controls, as determined by significantly lower BMI, waist circumference, and hip circumference. Patients with breast cancer were also of lower weight and greater height, although these differences were not significant (P = 0.07 and P = 0.06, respectively). Despite those differences, the body fat distribution, as represented by WHR, was the same in the two groups. Comparisons between the postmenopausal patients with breast cancer and controls yielded no significant differences in any of the anthropometric measurements. In case patients and controls alike, the age, relative weight, and absolute weight were similar. The mean WHR was identical in the two groups.

Specific variables of case patients and controls (age, weight, height, BMI, waist, hips, WHR, and menopausal status) were considered simultaneously in a logistic regression analysis. As a first step in modeling the relations of these factors to the diagnosis of breast cancer, all variables were considered. Patient age (and therefore menopausal status) was the factor that correlated most highly with the diagnosis of carcinoma. This result is not surprising because univariate testing indicated that the two patient groups differed by age. We next controlled for age and included each variable separately in a logistic regression to determine its univariate significance in predicting carcinoma. In this multi-

Table 2. Anthropometric Measurements for Case Patients and Controls*

Variable	Controls (n = 126)	Case Patients (n = 156)	High-Risk Women (n = 31)
Waist-hip ratio	0.80 (0.06)	0.80 (0.06)	0.08 (0.08)
Waist, *cm*	82.2 (13.4)	79.5 (12.4)	80.9 (14.0)
Hips, *cm*	102.1 (13.1)	99.0 (14.7)	100.0 (14.9)
Body mass index	26.6 (5.4)	25.4 (4.9)	26.7 (6.7)
Weight, *kg*	69.8 (18.0)	66.7 (12.9)	69.9 (20.1)
Height, *cm*	161.5 (7.3)	161.9 (7.5)	163.0 (6.0)
Age, *y*†	48.0 (10.9)	51.8 (11.8)	48.5 (15.0)

* All data expressed as mean (SD).
† Significant by t test at P = 0.05.

Table 3. Anthropometric Measurements for Case Patients and Controls According to Menopausal Status*

Variable	Premenopausal			Postmenopausal		
	Controls (n = 82)	Case Patients (n = 84)	P Value†	Controls (n = 44)	Case Patients (n = 72)	P Value†
Waist-hip ratio	0.79 (0.06)	0.79 (0.05)	‡	0.83 (0.06)	0.82 (0.06)	‡
Waist, *cm*	79.8 (12.7)	75.4 (10.2)	0.01	86.4 (14.1)	84.1 (13.1)	‡
Hips, *cm*	101.1 (13.0)	95.8 (9.3)	0.003	103.4 (13.7)	102.4 (11.3)	‡
BMI, kg/m^2	26.2 (5.5)	24.1 (4.5)	0.03	27.3 (6.3)	26.9 (5.1)	‡
Weight, *kg*	69.4 (15.2)	65.0 (12.0)	0.07	69.9 (15.5)	68.5 (13.8)	‡
Height, *cm*	162.1 (7.4)	164.1 (6.3)	0.06	160.2 (6.9)	159.9 (7.7)	‡
Age, *y*	41.9 (7.0)	42.9 (6.5)	‡	59.7 (6.5)	61.7 (7.8)	‡

* All data expressed as mean (SD).
† Results from t test.
‡ $P > 0.1$.

variate logistic regression, after adjusting for age, BMI was the only factor found to be related significantly to a diagnosis of breast cancer (P = 0.032). Weight, height, and menopausal status were not significant variables, and WHR was clearly not a significant predictor ($P > 0.2$). The final model consisted of an adjustment for patient age (P = 0.003) and BMI (P = 0.03). The overall model, which showed that age was the most predictive factor and BMI the next most predictive factor, was highly significant (P = 0.003; chi-square = 12.02; df = 2).

Table 4 shows the unadjusted odds ratios for the development of breast cancer for the four patient characteristics of particular interest: WHR, age, BMI, and absolute weight. Analyzed independently, odds ratios for WHR, BMI, and weight did not change substantially with increasing levels of the respective characteristics. When WHR, the variable of primary interest, was adjusted separately for age, relative weight, or absolute weight, the odds ratio of developing breast cancer was also similar (data not shown). Because the 95% CIs of these odds ratios included 1.0, these odds ratios did not differ significantly when analyzed without (*see* Table 4) or with (data not shown) the high-risk group added to the controls. The only exception was a significant risk for breast cancer diagnosis in patients older than 60 years. Specifically, the odds of a woman older than 60 years developing breast cancer was 2.69 times greater than that of a woman younger than 42 years of age (CI, 1.33 to 5.44) when analyzed without the high-risk group and 2.75 (CI, 1.31 to 5.41) when the high-risk group was included.

Table 4. Unadjusted Odds Ratio for Breast Cancer Related to Variables Listed

Variable	Controls	Case Patients	Unadjusted Odds Ratio	(95% CI)
Waist-hip ratio				
< 0.73	13	20	1.00	*
0.73 to 0.76	24	25	0.650	0.264 to 1.60
0.77 to 0.80	32	39	0.797	0.341 to 1.86
≥ 0.81	59	71	0.780	0.358 to 1.71
Age, *y*				
< 42	40	30	1.00	*
42 to 47	34	39	1.54	0.791 to 3.01
48 to 59	32	41	1.73	0.882 to 3.37
≥ 60	23	45	2.69	1.33 to 5.44
BMI, kg/m^2				
< 23	35	54	1.00	*
23 to 24.9	28	31	0.720	0.367 to 1.41
25 to 26.9	19	23	0.785	0.372 to 1.65
≥ 27	44	46	0.665	0.365 to 1.20
Weight, *kg*				
< 56	20	33	1.00	*
57 to 64	40	49	0.727	0.361 to 1.46
65 to 73	34	33	0.606	0.289 to 1.27
≥ 74	34	40	0.700	0.336 to 1.43

* Reference group.

Discussion

Our study did not show an association between body fat distribution (as measured by WHR) and breast cancer diagnosis. Case patients (those diagnosed with early breast cancer) and controls (those with a benign diagnosis and an average risk for breast cancer) had identical WHRs, even when case patients and controls were analyzed separately according to age, menopausal status, absolute weight, or relative weight (BMI). A small group of women at high risk for breast cancer, but with benign tissue on diagnostic surgery, also showed similar results. Moreover, we observed no significant differences or evidence for a trend in breast cancer incidence when we used relative risk analysis and grouped women according to WHR.

Body fat distribution is related to many factors, with perhaps 25% of variance resulting from genetic factors (26); many reports have noted interracial (27, 28) and intercountry differences in regional adipose distribution as well (29). Thus, our current conclusions must be limited to the population under study—white, otherwise healthy, U.S.-born women presenting for excision of an undiagnosed breast mass. The referral patterns to our institution have assured a similarly homogeneous population for both case patients and controls. Despite concern about "overmatching" with bias toward showing no effect of the outcome variable, the unanalyzed factors in these patients (that is, college education and higher socioeconomic class) were considered such minor risk factors for breast cancer (25) that their contribution was presumed to be negligible. Nevertheless, further studies should include a more diverse sample of American women to expand these findings.

Women serving as controls in our study were not prone to investigator bias because they were not "chosen" as in typical case-control studies: According to

study design, controls were determined by benign histologic findings at the time of diagnostic breast surgery and a low-risk clinical profile, in each instance defined subsequent to data collection. Because women with suspicious breast masses are referred more frequently to a comprehensive cancer center for excision, we predicted, and indeed noted, a high prevalence of malignancy (50%) on diagnostic biopsy. In the same fashion, one could argue that a benign finding on surgical biopsy might indicate a high risk for breast cancer, not typical of the general population of American women, thereby precluding the use of these women as appropriate controls. According to the 1986 consensus statement of the College of American Pathologists (23), recently updated (22), diagnostic breast surgery per se does not constitute a risk factor for subsequent breast cancer development. Moreover, we did a rigorous risk assessment to identify women at high risk and selected as controls only women who met specific and strict criteria. Detailed histologic features and comprehensive clinical data were evaluated to validate the selection of the control group. Major risk factors, alone or combined, were used to identify and eliminate women at high risk, defined as a breast cancer incidence rate of at least 1% per year (25), from serving as controls; minor (conferring less than twofold relative risks) and more controversial risk factors, such as alcohol consumption and mammographic patterns, were not considered (14, 15, 25). The use of such stringent criteria resulted in the objective exclusion of high-risk women and the formation of a valid control group.

No data exist to suggest that a particular illness or nonhormonal medication use significantly alters breast cancer risk (14, 15). To avoid the confounding influence (potential as well as proven) of systemic illness on regional fat patterns, however, we eliminated any patient with illnesses from consideration in the study. The exclusions were done at study entry and, therefore, did not affect the case-control status of any participant. When analyzed, the proportion and the nature of exclusions were similar for women who later were found to have either breast cancer or benign tissue at biopsy.

Our patients with breast cancer had a slightly lower mean BMI than did controls (25.4 compared with 26.6) ($P > 0.05$). We specifically excluded patients with a weight change exceeding 10% of their current weight occurring in the preceding 3 years. Nevertheless, some weight change related to whether a possible cancer diagnosis might have occurred. Because patients who were later considered to be controls or case patients shared in the anxiety associated with an undiagnosed breast mass, any weight loss attributable to anxiety would have been the same in both groups. Moreover, the study design mandated the anthropometric measurements to be uniformly done the day before breast surgery specifically to minimize the impact of the breast cancer diagnosis on subsequent anxiety and weight change. In any event, it is unlikely that undetected preoperative weight change occurring in this sample could appreciably alter the study participants' WHR, as supported by data from several laboratories (30, 31).

The mean age of all study participants was approximately 50 years. When considered according to their menopausal status, premenopausal patients with breast cancer had a significantly lower mean BMI (24.1) than did premenopausal controls (26.2) ($P = 0.03$). This finding is consistent with the large body of information showing a significant inverse relation between body mass and breast cancer risk before menopause (14, 15). Although relative weight and WHR are positively, albeit weakly, correlated (1, 5, 31), BMI was controlled in the current analysis, and WHR was therefore unrelated to case-control status. The mean WHR of the premenopausal patients with breast cancer and that of controls were identical, thus underscoring the specificity of these findings. As expected, the postmenopausal women, both case patients and controls, were heavier than the premenopausal study participants. In agreement with the known increase in WHR associated with age (1, 5, 32), lack of ovarian hormones (1, 6, 20), and obesity (1, 5, 31), postmenopausal women had comparably higher WHR measurements.

Lower values for WHR determinations than those noted here have been reported; the mean WHR of 0.78 for the current premenopausal study participants and 0.82 for postmenopausal study participants is higher than that reported in samples with mean relative weights closer to the ideal (33, 34). Our study participants were generally overweight, however, possibly due to the exclusion of any confounding systemic illness or simply as a consequence of the inherent characteristics of our patient referral base. In light of the known association between increased BMI and WHR, the anthropometric values in our study are typical of the general American population (31, 32); moreover, they compare favorably with data recently reported for postmenopausal women in Iowa with (WHR, 0.85; BMI, 27.7) and without (WHR, 0.84; BMI, 27.1) breast cancer (17). Given the smaller number of postmenopausal control subjects than patients with breast cancer in our study, the similarity in data between these two diverse American populations is all the more reassuring.

The lack of an association between breast cancer and WHR found in the current study contrasts markedly with the only other case-control study (19) to address this issue. Schapira and colleagues (19) studied pre- and postmenopausal women and found an increasing risk for breast cancer with increasing WHR. Their study patients, grouped according to WHRs of greater than 0.73, 0.73 to 0.76, 0.77 to 0.80, and 0.81 or more, had relative risks of 1.00, 1.90 (CI, 1.06 to 3.40), 2.83 (CI, 1.58 to 5.06) and 6.46 (CI, 3.76 to 11.10), respectively, compared with 1.00, 0.65 (CI, 0.26 to 1.60), 0.80 (CI, 0.34 to 1.86), and 0.78 (CI, 0.36 to 1.71), respectively, obtained in our study.

Schapira and colleagues (19), however, do not group study participants by age or menopausal status to determine the independent association of these factors with obesity. The relation of obesity to breast cancer incidence is complex, as recently reviewed (14, 15). In premenopausal women, obesity is significantly related inversely to breast cancer development, and its association with postmenopausal breast cancer appears to be either limited to or strongest in the oldest postmenopausal women. As many as two thirds of the women studied by Schapira and colleagues could be considered

premenopausal or early postmenopausal; for these women, the association of breast cancer with obesity should be inverse or null. The investigators, however, noted an overall significant association of breast cancer with obesity. This finding suggests a selection bias for less obesity in the controls (age-matched women from 10 businesses and two retirement communities, the so-called "healthy worker effect" [35]), possibly permitting a spurious association of breast cancer with an increased WHR, given the known relation of obesity with WHR. Indeed, when other investigators have matched patients with breast cancer with controls for age and BMI, no difference in WHR has been shown (36). Other differences exist between our study design and that of Schapira and coworkers (19). In the former study, women were accrued up to 3 months after the diagnosis of breast cancer was made, and the study controls, although matched in age, were more frequently premenopausal and nonwhite than the respective group with cancer.

Three prospective cohort studies (12, 17, 18) have reported on body fat distribution and its relation to breast cancer incidence, with two (17, 18) finding this disease correlated to central or truncal fat distribution. In 1986, Folsom and colleagues (17) conducted a mail survey of postmenopausal women who self-reported their waist and hip circumferences. Compared with controls, women later diagnosed with breast cancer had a higher age-adjusted mean WHR (0.850 compared with 0.837) ($P = 0.03$) as well as a trend toward a greater mean weight ($P = 0.07$) and increased BMI ($P = 0.08$). The WHR ($r = 0.41$) correlated significantly with the BMI (the most common measurement of obesity), thereby limiting the importance of WHR as an independent variable in postmenopausal breast cancer development. Finally, when women were divided into tertiles of increasing WHR, no significant trend for breast cancer incidence could be shown. A WHR of less than 0.794 yielded a reference risk of 1.00, a WHR of 0.794 to 0.873 yielded an odds ratio of 0.93 (CI, 0.65 to 1.35), and a WHR greater than 0.873 yielded an odds ratio of 1.39 (CI, 0.99 to 1.96).

Ballard-Barbash and colleagues (18), using a Framingham cohort, recently reported that breast cancer correlated significantly with truncal (compared with extremity) fat predominance. Only 5% of their patients with breast cancer were premenopausal. Differences in the choice of anthropometric end points further limit comparison with the current study. Skinfold measurements from the upper and lower trunk were summed and were then divided by the sum of skinfold measurements from the upper and lower extremities. The waist and hip circumferences were not measured, and, thus, the distribution of upper to lower body fat is unclear. Swedish investigators (12), assessing body fat topography by the standard WHR measurement as well as by skinfold thickness measurements, could not find a positive association with breast cancer. This last population-based prospective study supports our current results.

In general, theories on breast cancer pathogenesis stress the importance of estrogenic exposure that is prolonged in duration or increased in intensity (14, 15). Increased WHR and increased abdominal fat cell size have been associated with decreased binding of estrogen to sex hormone binding globulin (SHBG) (8, 37); this mechanism, as well as the potential effect of increased levels of free fatty acids seen in abdominal obesity on the bioavailability of estrogen (5), has been cited to support the putative association of breast cancer risk with increasing WHR (19). Although the role of estrogens in regional fat distribution has not been clarified, upper body fat predominance generally indicates androgenic over estrogenic influence (8, 38). The decline in SHBG noted with abdominal obesity results in much greater change in unbound testosterone than in unbound estradiol because the affinity of SHBG for testosterone is considerably higher than that for estradiol (39).

Lower body fat predominance is the norm in women, as well as the tendency in men exposed to exogenous estrogens (40, 41). Administration of estrogen in combination with progesterone favors gluteal-femoral fat distribution (20, 41, 42). In-vitro studies in adipose tissue show regional differences in estrogen formation, with cells derived from abdominal fat having a lower ratio of estrone to 5α-reduced androgens than cells from the thigh-buttock area; upper-body fat predominance thus has been found to favor lowered overall estrogen formation (40, 43). Given that decreased estrogen and increased androgen exposure, such as that which occurs with castration at an early age and in various other situations, is protective against the development of breast cancer (14, 15), it is difficult to reconcile the complex hormonal aspects of upper-body fat distribution with the theories of breast cancer pathogenesis. Our findings do not support a relation between regional fat distribution (as measured by WHR) and the risk for breast cancer and suggest continued research for clarification of this important issue. It is hoped that our results will stimulate further investigation into the role of body fat distribution in breast cancer development.

Grant Support: In part by American Cancer Society Award PDT-331.

Requests for Reprints: Jeanne A. Petrek, MD, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

Current Author Addresses: Drs. Petrek and Bajournas and Ms. Peters: Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

Ms. Cirrincione: Duke University, Comprehensive Care Center, Biostatistics Department, 20 West Main Street, Durham NC 27705.

Dr. Rhodes: New York Hospital-Cornell Medical Center, 525 East 70th Street, New York NY 10021.

References

1. **Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, et al.** Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab. 1982;54:254-60.
2. **Kissebah AH, Freedman DS, Peiris AN.** Health risks of obesity. Med Clin North Am. 1989;73:111-38.
3. **Bray GA.** Obesity: basic considerations and clinical approaches. Dis Mon. 1989;35:449-537.
4. **Seidell JC, Hautvast JG, Deurenberg P.** Overweight: fat distribution and health risks. Epidemiologic observations. A review. Infusionstherapie. 1989;16:276-81.
5. **Björntorp P.** Obesity and adipose tissue distribution as risk factors for the development of disease. A review. Infusionstherapie. 1990; 17:24-7.
6. **Björntorp P.** The associations between obesity, adipose tissue distribution and disease. Acta Med Scand Suppl. 1988;723:121-34.

7. **Leibel RL, Edens NK, Fried SK.** Physiologic basis for the control of body fat distribution in humans. Annu Rev Nutr. 1989;9:417-43.
8. **Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH.** Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. J Clin Endocrinol Metab. 1983;57:304-10.
9. **Elwood JM, Cole P, Rothman KJ, Kaplan SD.** Epidemiology of endometrial cancer. J Natl Cancer Inst. 1977;59:1055-60.
10. **Kelsey JL, LiVolsi VA, Holford TR, Fischer DB, Mostow ED, Schwartz PE, et al.** A case-control study of cancer of the endometrium. Am J Epidemiol. 1982;116:333-42.
11. **Kelsey JL, Hildreth NG.** Breast and Gynecological Cancer Epidemiology. Boca Raton, Florida: CRC Press, Inc.; 1983:71-92.
12. **Lapidus L, Helgesson O, Merck C, Björntorp P.** Adipose tissue distribution and female carcinomas. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Int J Obes. 1988;12:361-8.
13. **Schapira DV, Kumar NB, Lyman GH, Cavanagh D, Roberts WS, LaPolla J.** Upper-body fat distribution and endometrial cancer risk. JAMA. 1991;266:1808-11.
14. **Kelsey JL, Gammon MD.** The epidemiology of breast cancer. CA Cancer C Clin. 1991;41:146-65.
15. **Miller AB, Henderson BE, Bernstein L, Willett W, London SJ, Garber JE, et al.** Causes of breast cancer and high-risk groups. In: Harris JR, Hellman S, Henderson IC, Kinne DW; eds. Breast Diseases II. Philadelphia: J. B. Lippincott Company; 1991:119-63.
16. **Beijerinck D, van Noord PA, Seidell JC, den Tonkelaar I, Rombach JJ, Bruning PF.** Abdominal fat predominance in women is associated with a decreased prevalence of the high risk P2, DY mammographic breast patterns. Int J Obes. 1991;15:89-93.
17. **Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB.** Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. Am J Epidemiol. 1990;131:794-803.
18. **Ballard-Barbash R, Schatzkin A, Carter CL, Kannel WB, Kreger BE, D'Agostino RB, et al.** Body fat distribution and breast cancer in the Framingham study. J Natl Cancer Ins. 1990;82:286-90.
19. **Schapira DV, Kumar NB, Lyman GH, Cox CE.** Abdominal obesity and breast cancer risk. Ann Intern Med. 1990;112:182-86.
20. **Rebuffe-Scrive M.** Regional adipose tissue metabolism in women during and after reproductive life and in men. In: Berry EM; eds. Recent Advances in Obesity Research. V. London: John Libbey, Inc.; 1987:82-91.
21. **Ashwell M, Chinn S, Staley S, Garrow JS.** Female fat distribution—a simple classification based on two circumference measurements. Int J Obes. 1982;6:143-52.
22. **Page DL, Dupont WD.** Histologic indicators of breast cancer risk. Bull Am Coll Surg. 1991;76:16-23.
23. **Winchester DP.** Consensus Statement. The relationship of fibrocystic disease to breast cancer. Bull Am Coll Surg. 1986:71:29-31.
24. **Ottman R, Pike, MC, King MC, Henderson BE.** Practical guide for estimating risk for familial breast cancer. Lancet 1983;2:556-8.
25. **Kelly PT.** Evaluation of breast cancer risk. In: Kelly PT; ed. Understanding Breast Cancer Risk. Philadelphia: Temple University Press; 1991:29-44.
26. **Bouchard C.** Genetic factors in the regulation of adipose tissue distribution. Acta Med Scand Suppl. 1988;723:135-41.
27. **Adams-Campbell LL, Nwankwo M, Ukoli F, Omene J, Haile GT, Kuller LH.** Body fat distribution patterns and blood pressure in black and white women. J Natl Med Assoc. 1990;82:573-6.
28. **Folsom AR, Burke GL, Ballew C, Jacobs DR Jr, Haskell WL, Donahue RP, et al.** The relation of body fatness and its distribution to cardiovascular risk factors in young blacks and whites. The role of insulin. Am J Epidemiol. 1989;130:911-24
29. **Seidell JC, Cigolini M, Charzewska J, Ellsinger BM, Contaldo F.** Regional obesity and serum lipids in European women born in 1948. A multicenter study. Acta Med Scand Suppl. 1988;723:189-97.
30. **Campaigne BN.** Body fat distribution in females: metabolic consequences and implications for weight loss. Med Sci Sports Exerc. 1990;22:291-7.
31. **Hartz AJ, Rupley DC, Rimm AA.** The association of girth measurements with disease in 32 856 women. Am J Epidemiol. 1984;119:71-80.
32. **Shimokata H, Tobin JD, Muller DC, Elahi D, Coon PJ, Andres R.** Studies in the distribution of body fat: I. Effects of age, sex and obesity. J Gerontol. 1989;44:M66-73.
33. **den Tonkelaar I, Seidell JC, van Noord PA, Baanders-van Halewijn EA, Ouwehand LJ.** Fat distribution in relation to age, degree of obesity, smoking habits, parity and estrogen use: a cross-sectional study in 11 825 Dutch women participating in the DOM-project. Int J Obes. 1990;14:753-61.
34. **Seidell JC, Cigolini M, Deurenberg P, Oosterlee A, Doornbos G.** Fat distribution, androgens, and metabolism in nonobese women. Am J Clin Nutr. 1989;50:269-73.
35. **Last JM; ed.** A Dictionary of Epidemiology. New York: Oxford University Press; 1983.
36. **Sönnischen AC, Richter WO, Schwandt P.** Body fat distribution and risk for breast cancer [Letter]. Ann Intern Med. 1990;112:882.
37. **Haffner SM, Katz MS, Dunn JF, Stern MP.** Decreased sex hormone binding globulin is associated with hyperinsulinemia in premenopausal Mexican American women [Abstract]. Clin Res 1988;36: 482A.
38. **Kissebah AH, Peiris AN.** Biology of regional body fat distribution: relationship to non-insulin-dependent diabetes mellitus. Diabetes Metab Rev. 1989;5:83-109.
39. **Vermeulen A, Verdonck L, Van Der Straeten M, Orie N.** Capacity of the testosterone-binding globulin in human plasma and influence of specific binding of testosterone on its metabolic clearance rate. J Clin Endocrinol Metab. 1969;29:1470-80.
40. **Kirschner MA, Samojlik E, Drejka F, Szmal E, Schneider G, Ertel N.** Androgen-estrogen metabolism in women with upper body versus lower body obesity. J Clin Endocrinol Metab. 1990;70:473-9.
41. **Krotkiewski M, Björntorp P.** The effects of estrogen treatment of carcinoma of the prostate on regional adipocyte size. J Endocrinol Invest. 1978;1:365-8.
42. **Rebuffe-Scrive M, Lönnroth P, Mårin P, Wesslau C, Björntorp P, Smith U.** Regional adipose tissue metabolism in men and postmenopausal women. Int J Obes. 1987;11:347-55.
43. **Killinger DW, Perel E, Daniilescu, Kharlip L, Lindsay WR.** The relationship between aromatase activity and body fat distribution. Steroids. 1987;50:61-72.