

Body Fat Distribution and Breast Cancer in the Framingham Study

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We examined the relation between central body fat distribution and breast cancer in a prospective cohort of women who participated in the Framingham Study. At the baseline examination in 1948, a total of 2,201 women aged 30-62 years were analyzed. An index of central to peripheral body fat (the central adiposity ratio) was calculated from the sum of the trunkal skinfolds (chest, subscapular, and abdominal) divided by the sum of the extremity skinfolds (triceps and thigh). These skinfolds were measured at the fourth examination in 1954. The cohort was followed for up to 28 years and yielded 106 cases of breast cancer. When divided into quartiles based on the central adiposity ratio, only women in the fourth quartile (those with the highest central to peripheral body fat distribution) demonstrated an increased risk for breast cancer. The age- and adiposity-adjusted relative risk estimate for having an increased central adiposity ratio (fourth quartile) compared to lower central adiposity ratios was 1.8 (95% confidence interval, 1.2-2.6). Adjustment for potential confounders of height, parity, and education did not appreciably alter this estimate (1.7, 1.1-2.5). There was no association between degree of adiposity, as measured by the sum of the five skinfolds or by body mass index (weight in kg divided by height in m²), and subsequent breast cancer. The results of this study suggest that increased central to peripheral body fat distribution predicts breast cancer risk independently of the degree of adiposity and may be a more specific marker of a premalignant hormonal pattern than degree of adiposity. [J Natl Cancer Inst 82:286-290, 1990]

Increases in bioavailable estrogen are thought to be one of the likely mechanisms for the increased breast cancer risk associated with obesity (1). Recent studies suggest that changes in estrogen protein binding in obese women may be a major determinant of the increases in bioavailable estrogen seen in obese women compared to women of normal weight (2,3). Estrogen binding also appears to be influenced by differences in body fat distribution (4). Therefore, based on endocrine studies, it is plausible that the distribution of body fat might contribute to a woman's breast cancer risk independent of her level of general obesity (1-7). Studies in cardiovascular disease suggest that abdominal obesity increases the risk of cardiovascular disease independent of body mass (8,9). Pre-

liminary research suggests that body fat distribution may be a stronger predictor of endometrial and ovarian carcinomas than is body mass (10).

The present study was undertaken to assess the influence of body fat distribution on breast cancer occurrence in a prospective cohort of women who participated in the Framingham Study (11).

Methods

The Cohort

The Framingham Study, a population-based prospective cohort study of risk factors for cardiovascular disease, was initiated in 1948. The original cohort contained 2,873 women and 2,336 men, aged 30-62 years at the first examination. This cohort was followed with biennial examinations for a 34-year period (examination No. 1-18) with minimal (<3%) loss to follow-up. Data available from each examination include information from a medical history, a physical examination, and a series of laboratory tests (11).

Identification of Cases

All cohort records with any mention of malignancy were reviewed in detail, and 139 incident cases of breast cancer (International Classification of Diseases for Oncology, code 174) that occurred after examination 4 were identified. Follow-up information was not available after examination 18 and thus we have follow-up information on 28 years.

Determination of Body Fat Distribution and Other Covariates

Five skinfold measures (chest, subscapular, triceps, abdominal, and thigh), three girths (waist, wrist, and upper arm),

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and weight and height were measured at examination 4 (11). Metropolitan relative weight (MRW) based on the 1959 tables was calculated from weight and height at examination 4. From these measurements we also calculated two potential measures of degree of adiposity, the sum of the five skinfolds and the body mass index (BMI). BMI was calculated as weight in kilograms divided by height in meters squared. We created an index of central to peripheral body fat distribution by dividing the sum of the trunkal skinfolds (chest, subscapular, and abdominal) by the sum of the extremity skinfolds (triceps and thigh). This is subsequently referred to as the central adiposity ratio. It showed only small correlations with the measures of degree of adiposity [Pearson correlation coefficient (*r*) of 0.03 (*P* =.11) for sum of skinfolds and 0.09 (*P* <.01) for BMI].

Information on several breast cancer risk factors was available in this cohort. We determined education and parity at examination 1 and menopausal status and age at examination 4. Information on other reproductive factors or on family history of breast cancer was not available.

Population for Analysis

A total of 602 women (including 33 women who subsequently developed breast cancer) were missing skinfold measurements at examination 4 and were excluded from this analysis. Also excluded were 21 women who developed breast cancer and 49 women who died or were lost to follow-up prior to examination 4. The analytic cohort consisted of 2,201 women, including 106 women who developed breast cancer after examination 4.

Statistical Analysis

Crude incidence rates for quartiles of the central adiposity ratio (quartiles based on the analytic cohort values) were calculated by dividing the number of breast cancer cases occurring in that quartile by the total number of person-years contributed by all women in that quartile. We calculated age-adjusted incidence rates using the age distribution of the entire analytic cohort as the standard (12).

We used Cox's proportional hazards regression technique to analyze the simultaneous effect of body fat distribution, age, and other potential breast cancer risk factors on breast cancer incidence in the cohort (13). For the multivariate analyses, all variables were modeled as indicator variables as follows: age (<40, 40-50, >50 yr), sum of skinfolds (quartiles), height (quartiles), parity (0, 1-3, 4+), and education (<12, 12, >12 yr). A linear test for trend of the central adiposity ratio was modeled as a quartile trend variable. These analyses were performed with the PROC PHGLM procedure available in the SAS statistical package.

Results

At examination 4, the mean age of the analytic cohort was 50 years. Twenty-five percent of the women in the analytic cohort were less than 43 years of age, and 30% were over 55 years of age. Forty percent of women had not completed high school; 28% had completed some education beyond high school. Of the 106 women with breast cancer in this

cohort, 99 were postmenopausal at the time of diagnosis, six were premenopausal at the time of diagnosis, and one woman's menopausal status at diagnosis was unknown.

The relation of the central adiposity ratio to other previously suggested breast cancer risk factors is shown in table 1. The proportion of women in the fourth quartile of the central adiposity ratio was greater among women who were older, who were in the midrange of the sum of skinfolds, who were shorter, who were premenopausal, and who had lower parity, and who had higher education.

The age-adjusted incidence rates for the first three quartiles of the central adiposity ratio were similar (180, 200, and 150 per 100,000, respectively) and markedly less than that of the fourth quartile (310 per 100,000) (table 2).

Relative risk estimates for breast cancer from proportional hazards models for quartiles of the central adiposity ratio, as well as for quartiles of the two measures of degree of adiposity, are presented in table 3. When women in the highest quartile of the central adiposity ratio were compared to women in the lower three quartiles combined, the age-adjusted relative risk estimate was 1.8 (95% confidence interval, 1.2-2.6). The relative risk estimates for the second and third quartiles compared to the first quartile did not vary significantly from 1.0. The relative risk estimates for the second through the fourth quartiles of the two measures of degree of adiposity, the sum of skinfolds and the BMI, also did not vary significantly from 1.0. Simultaneous inclusion of the central adiposity ratio with the sum of skinfolds, or of these

Table 1. Elevated central adiposity ratio in relation to breast cancer risk factors

Risk factor [mean \pm SD] (<i>N</i> , %)	% in fourth quartile of central adiposity ratio*
Age (50 \pm 9 yr)	
<40 (263, 12.0)	22.1
40-50 (946, 43.0)	24.7
>50 (992, 45.0)	25.9
Sum of skinfolds (83.2 \pm 25.5 mm)	
\leq 66 (558)	20.8
66.1-81 (526)	27.8
81.1-97 (560)	28.4
>97 (557)	22.3
Height (1.59 \pm 0.06 m)	
\leq 1.55 (563)	26.1
1.56-1.58 (536)	28.0
1.59-1.63 (554)	23.4
>1.63 (543)	20.8
Parity	
0 (526, 24.0)	25.8
1-3 (1,170, 53.5)	25.0
4+ (491, 22.5)	22.8
Education (yr)	
<12 (860, 40.1)	23.6
12 (675, 31.5)	26.0
>12 (609, 28.4)	26.0
Menopausal status (examination No. 4)	
Premenopausal (843, 39.0)	27.1
Postmenopausal (1,317, 61.0)	25.0

*Percentiles (except for age category) adjusted to age distribution of entire analytic cohort (12).

Table 2. Age-adjusted incidence rates of breast cancer by quartiles of the central adiposity ratio in Framingham cohort of 2,201 women

Central adiposity ratio quartiles	Cases/person-years at risk	Incidence rate* (per 100,000)
<1.4	24/13,198	180
1.4-1.5	23/11,784	200
1.51-1.6	20/13,337	150
>1.6	39/12,554	310

* Adjusted to age distribution of entire analytic cohort (12).

latter two variables with other potential breast cancer risk factors, did not alter these estimates (table 4).

The association of increased central body fat with increased breast cancer risk was unchanged when we examined the subset of overweight women (MRW \geq 110%). It was also unchanged for the subset of women who were not markedly obese (MRW \leq 150%) as shown in table 5. For younger women and for those who were premenopausal at the time of skinfold measurement, the relative risk estimate for the fourth quartile of the central adiposity ratio compared to the lower three quartiles combined was lower and did not vary significantly from 1.0. Conversely, the relative risk estimate increased slightly and remained significant among older women and those who were postmenopausal at the time of skinfold measurement (table 5). The test for trend of this ratio was significant for older women ($P < .05$) and was near significance for postmenopausal women ($P = .10$).

Discussion

In this prospective study of a subset of women from the Framingham Study, women with increased central adiposity at examination 4 (as measured by the sum of the chest, abdomen, and subscapular skinfolds divided by the sum of the triceps and thigh skinfolds) experienced an elevated risk for breast cancer over the subsequent 28-year interval. A number of studies on cardiovascular disease, diabetes mellitus, and hypertension, and some preliminary research on endometrial and ovarian carcinomas, suggest that body fat dis-

Table 3. Relative risk estimates for breast cancer by the central adiposity ratio and by obesity measures in Framingham cohort of 2,201 women

Model*	Relative risk estimates (95% confidence interval)			
	Quartiles			
	1	2	3	4
Central adiposity ratio†	1.0	1.1 (0.6-1.9)	0.8 (0.5-1.5)	1.7 (1.0-2.9)
Sum of skinfolds	1.0	1.2 (0.7-2.0)	1.2 (0.7-2.0)	1.3 (0.7-2.2)
Body mass index	1.0	1.0 (0.6-1.7)	1.0 (0.6-1.7)	0.9 (0.5-1.6)

* Age-adjusted proportional hazards models with 106 breast cancer cases (99 postmenopausal, six premenopausal, and one unknown).

† Test for trend yielded $P = .07$.

Table 4. Relative risk estimates for breast cancer by the central adiposity ratio in Framingham cohort of 2,201 women

Models	Relative risk estimates (95% confidence interval)				
	Quartiles of central adiposity ratio				
	1	2	3	4	4/1-3*
Model 1†	1.0	1.1 (0.6-1.9)	0.8 (0.4-1.5)	1.7 (1.0-2.8)	1.8 (1.2-2.6)
Model 2‡	1.0	1.1 (0.6-1.8)	0.8 (0.4-1.5)	1.6 (0.9-2.6)	1.7 (1.1-2.5)

* Model with fourth quartile of the central adiposity ratio as indicator variable with the first three quartiles as reference.

† Model includes age and the sum of skinfolds; $n = 106$ cases. Test for trend yielded $P = .07$.

‡ Model includes age (<40, 40-50, >50), sum of skinfolds (quartiles), height (quartiles), parity (0, 1-3, 4+), and education (<12, 12, >12 yr); $n = 103$ cases. Test for trend yielded $P = .14$.

tribution, in particular increased central adiposity, increases the risk of developing these diseases (8-10,14-16). However, to our knowledge, this is the first report of an association between central adiposity, as measured by subcutaneous fat distribution, and breast cancer. Our results are supported by recent findings from the Iowa Women's Health Study of an increased risk of breast cancer among postmenopausal women with an increased waist to hip ratio (17). Another study with only 21 breast cancer cases did not find an association between a waist to hip ratio and breast cancer, but was limited by the small number of cases (18).

There are explanations other than causality that could have produced the findings observed here. The relatively large number of exclusions from the original Framingham Heart Study cohort due to women missing skinfold measurements, for example, could have biased our findings upward from the null, but this should occur only if the excluded group included a disproportionately large number of women of low central adiposity who subsequently developed breast cancer. We have no a priori reason to suspect such a differential bias in our exclusions. The majority of women excluded for lack of skinfold measurements lacked these data because they were not examined at examination 4. In addition, there were negligible differences between the analytic cohort and the excluded group in the available potential breast cancer risk factors of age, parity, education, menopausal status, height, and body mass as measured at examination 1 (data not shown). Loss to follow-up was also minimal, and information was objectively determined and prospective in nature.

The central adiposity ratio used in this analysis appears to have characteristics similar to those of other central to peripheral body fat ratios, such as the waist to hip ratio. Regional adiposity appears to have metabolic and physiologic consequences. Recent studies suggest that increased central adiposity is positively correlated with increases in systolic blood pressure, total cholesterol, and triglycerides (5-7,19). In these data, the central adiposity ratio showed a small but statistically significant association with systolic blood pressure and cholesterol measurements at examination 4 ($r = 0.09$ and 0.10 , respectively, $P = .0001$). Although

Table 5. Relative risk estimates for breast cancer by central adiposity ratios in subgroups of the Framingham cohort of 2,201 women

Models*	Cases/cohort	Relative risk estimates (95% confidence interval)				
		Quartiles of central adiposity ratio				
		1	2	3	4	4/1-3†
Lean excluded MRW \geq 110%	67/1,457	1.0	0.9 (0.4-1.9)	0.9 (0.4-1.9)	1.7 (0.9-3.4)	1.8 (1.1-3.0)
Markedly obese excluded MRW \leq 150%	99/1,927	1.0	1.0 (0.6-1.9)	0.9 (0.5-1.6)	1.6 (0.9-2.8)	1.7 (1.1-2.5)
Age at examination 4 (yr)						
\leq 50	57/1,173	1.0	0.8 (0.4-1.6)	0.5 (0.2-1.2)	1.1 (0.6-2.2)	1.4 (0.8-2.6)
$>$ 50‡	46/953	1.0	1.4 (0.5-3.8)	1.3 (0.5-3.4)	2.8 (1.1-6.8)	2.4 (1.2-4.1)
Menopausal status at examination 4						
Premenopausal	47/821	1.0	0.9 (0.4-1.9)	0.6 (0.2-1.5)	1.2 (0.6-2.4)	1.4 (0.8-2.6)
Postmenopausal	55/1,267	1.0	1.2 (0.5-2.7)	1.0 (0.4-2.3)	2.1 (1.0-4.6)	2.0 (1.2-3.5)

* Models include age, sum of skinfolds, height, parity, and education. For cuts of variables in models see table 4.

† Model with fourth quartile of the central adiposity ratio as indicator variable with the first three quartiles as reference.

‡ Test for trend yielded $P < .05$; remainder of tests for trend for other models were nonsignificant.

other potential measures of central adiposity, such as waist or waist-height have been used in previous Framingham studies (20,21), recent studies suggest that there are marked differences in subcutaneous adipocyte physiology based on location (abdominal vs. femoral) (22). This argues for the use of a ratio that includes both the abdominal and thigh skinfolds.

While increased central adiposity was associated with an increased risk of breast cancer in this cohort, neither of the two measures of degree of adiposity (the sum of the five skinfolds or the BMI) examined here was associated with a significant increase in breast cancer. Although many studies demonstrate an association between the degree of adiposity and postmenopausal breast cancer (23-26), our results are similar to several recent cohort studies that did not demonstrate this association (27,28). Because adjustment for degree of adiposity by these two measures did not alter the positive association between central adiposity and breast cancer, central adiposity appears to predict breast cancer risk independently of the degree of adiposity. The isolation of an elevated risk to the fourth quartile of the central adiposity ratio is similar to findings in cardiovascular disease. While women in the first quartile of the central adiposity ratio have an increased peripheral or gynecoid body fat distribution, women in the second and third quartiles have more uniform body fat distributions. Given the markedly different body fat distributions estimated by the quartiles of these ratios, one would not necessarily expect a linear dose-response pattern of risk with measures of body fat distribution.

Because most of the breast cancer cases occurred in postmenopausal women in this cohort (99 of 106), we could not assess the relation of central adiposity ratio to premenopausal breast cancer. With regard to postmenopausal breast cancer, it appears that premenopausal measurement of body fat dis-

tribution was not predictive of postmenopausal breast cancer risk, whereas postmenopausal measurement of body fat distribution was predictive of postmenopausal breast cancer risk. When women were stratified by menopausal status at examination 4 (the time of skinfold measurement), central adiposity (the fourth quartile of the ratio) was associated with an increased breast cancer risk only in women who were postmenopausal at examination 4 (table 5).

When this stratified analysis was repeated excluding all premenopausal person-years (and therefore excluding women with premenopausal breast cancer), the results were unaltered. A similar pattern was seen when women were stratified by age at examination 4 (\leq 50 and $>$ 50 yr). The increased breast cancer risk seen with increased central adiposity was observed only in women over age 50 at the time of measurement of skinfolds. It is known that central adiposity increases with aging (29), and abdominal adipocytes increase in size during menopause (22). Therefore, body fat distribution may change with menopause in a subgroup of women, which may explain the lack of an association between central adiposity and breast cancer when body fat distribution is measured in premenopausal women.

A variety of biological mechanisms have been proposed to explain the increased risk for breast cancer observed among obese women. These include alterations in estrogen protein binding (4), postmenopausal estrogen production (1), and 2- versus 16-hydroxylation of estradiol (30). All of these alterations result in increases in the biological availability and activity of estrogen. Few of these potential mechanisms have been examined relative to body fat distribution. Abdominal obesity and increased abdominal fat cell size have been associated with decreased binding of estrogen to sex hormone binding globulin (SHBG) (4), and to de-

creases in androstenedione and the ratio of luteinizing hormone to follicle-stimulating hormone (2). Kirschner et al. (31) found that women with abdominal (i.e., central) obesity had higher concentrations of free E₂ while women with femoral (i.e., peripheral) obesity had increased amounts of E₁ due to increased peripheral aromatization of androstenedione. A recent report suggests that estrogen protein binding may be influenced by body fat distribution due to alterations in the blood levels of free fatty acids and subsequently of triglycerides (4). Women with abdominal adiposity have increased levels of free fatty acids and triglycerides compared to women with femoral adiposity (5-7). Increases in free fatty acids have been reported to increase the level of bioavailable estrogen by displacing estrogen from SHBG where it is tightly bound, to albumin where it is less tightly bound (4). These studies suggest that although both phenotypes of obese women have increases in various forms of estrogen, women with abdominal obesity may have greater increases in biologically significant estrogen. Future studies should examine whether other possible mechanisms are influenced by body fat distribution.

The findings reported here suggest that body fat distribution, in particular, central adiposity, may influence a woman's risk of developing breast cancer independent of the level of general obesity. Recent studies suggest that weight loss results in greater decreases in blood glucose, triglycerides, and total cholesterol in women with central adiposity compared to women with femoral adiposity (32). If metabolic parameters influenced by body fat distribution, such as triglycerides, significantly influence the level of bioavailable estrogen and hence influence breast cancer promotion, weight loss and the associated reduction in triglycerides may reduce subsequent breast cancer development to a greater extent in women with central compared to femoral adiposity.

This finding of an increased risk for breast cancer among women with increased central adiposity is preliminary but coincides with preliminary findings of the Iowa Women's Health Study (17). Should these findings be confirmed, serial measurements over time of body fat distribution and associated metabolic parameters are needed to predict whether changes in central adiposity influence the subsequent risk of breast cancer.

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