Body Composition and Breast Cancer in Postmenopausal Women: A Danish Prospective Cohort Study

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Abstract

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Objective: To assess the importance of body fat mass (BFM) and fat free mass (FFM) for the established positive association between BMI and breast cancer among postmenopausal women.

Research Methods and Procedures: A prospective cohort of 23,788 postmenopausal women included in the Danish study Diet, Cancer, and Health during 1993 to 1997 was linked to the Danish Cancer Registry to identify all cases of breast cancer occurring during 1993 to 2002. Breast cancer incidence rate ratios for anthropometric measurements with adjustment for known risk factors for breast cancer were calculated by Cox regression analyses.

Results: Among the most commonly used anthropometric measurements, BMI was positively associated with breast cancer among never users of hormone replacement therapy (HRT). By splitting BMI into two indices, BFM index and FFM index, we found that the incidence rate ratio with each 1 kg/m^2 among never users of HRT was 0.98 (95% confidence interval, 0.93 to 1.03) for BFM index and 1.12 (95% confidence interval, 1.00 to 1.26) for FFM index after mutual adjustment.

Discussion: The finding for BMI was in accordance with previous findings. Our results indicate that the FFM component of BMI may play a role for development of breast cancer among never users of HRT.

Key words: body fat mass, fat free mass, body fat percentage, anthropometric, breast cancer

Introduction

The association between BMI and breast cancer in postmenopausal women has been studied intensively. In a recent review from the International Agency for Research on Cancer, the conclusion was that a modest positive association between BMI and breast cancer among postmenopausal women had been demonstrated (1). The relationship between BMI and breast cancer after menopause has been explained by conversion of androgen to estrogen in fat tissue. Use of exogenous hormones obscures the relationship by elevating estrogen levels in both lean and overweight women; accordingly, the risk increase has primarily been observed among women who have never used hormone replacement therapy (HRT)[1] (2–4). As BMI depends on both fat free mass (FFM) and body fat mass (BFM), BMI most likely misclassifies some study subjects concerning body fat (BF); misclassification is more likely with age because muscle mass is lost, whereas fat is accumulated without a concomitant change in BMI (5). Therefore, using measures of BFM and FFM in studies of breast cancer risk would show whether the increased risk of breast cancer among postmenopausal obese women primarily reflects ex-

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[1] Nonstandard abbreviations: HRT, hormone replacement therapy; FFM, fat free mass; BF, body fat; BFM, body fat mass; BF%, body fat percentage; BFMI, body fat mass index; FFMI, fat free mass index; WHR, waist-to-hip ratio; CI, confidence interval; IRR, incidence rate ratio; EPIC, European Prospective Investigation into Cancer and Nutrition.

cess BFM or if FFM also plays a role. A positive change in energy balance increases both lean and fat components; thus, obese subjects tend to have both higher FFM and higher BFM (5).

Two previous prospective studies on the risk of breast cancer among postmenopausal women included a measure of BF (6,7). Both studies showed a positive association between high BF percentage (BF%) and breast cancer, and one also showed a positive association between FFM and breast cancer (7). We tried to disentangle the effect of BFM and FFM by splitting BMI into two indices: BFM index (BFMI) and FFM index (FFMI) (8). We investigated the effects of these indices and BF% and the commonly used anthropometric measurements height, weight, BMI, waist and hip circumference, and waist-to-hip ratio (WHR) on the risk for breast cancer among 23,788 postmenopausal women included in the Danish prospective cohort study Diet, Cancer, and Health.

Research Methods and Procedures

The Diet, Cancer, and Health Study Population

Between December 1993 and May 1997, all women 50 to 64 years old who were born in Denmark and resided in the greater Copenhagen and Aarhus areas were identified in the Danish Central Population Register. All inhabitants of Denmark have a unique personal identification number that encodes date of birth and sex. This number was used for linkage to the Danish Cancer Registry to avoid recruiting prevalent cases of cancer. The remaining women were invited to participate in the study Diet, Cancer, and Health (9); a total of 29,875 accepted, corresponding to 37% of the women invited. The women attended a study clinic where they completed a questionnaire on reproductive factors (e.g., number of births, age at birth of first child), health-related issues (e.g., benign breast tumor, use of HRT), social factors (e.g., years of schooling), and lifestyle factors (e.g., alcohol intake). Anthropometric measurements were made by a trained technician during the visit. The self-administered questionnaires were processed using optical scanning allowing missing or unclear responses to be checked with the participant at a personal interview. The study protocol was approved by the regional scientific ethics committees on human studies.

Identification of Study Cohort

Eight women were excluded from the study cohort because they did not complete the questionnaire on background variables, and 333 were excluded because they had a diagnosis of cancer before attending the study clinic that was not captured by the preinvitation record linkage between the invitation database and the Cancer Registry.

For the present study, we excluded women who were premenopausal at study entry, i.e., 4797 women who reported at least one menstruation within the 12 months before entry and who were not current users of HRT. In addition, we excluded nine women who had never menstruated and 37 women whose HRT use was unknown. The remaining group of probably postmenopausal women included those who had not menstruated during the past 12 months (including those who had undergone bilateral oophorectomy and/or hysterectomy) and those who had menstruated within the past 12 months and were current users of HRT. Finally, we further excluded 877 who gave no information on reproductive events, surgery for benign breast tumor, duration of HRT use, length of schooling, or alcohol intake; thus, 23,814 subjects remained.

Bioelectrical Impedance

Electrical impedance was measured with a BIA 101-F device (Akern/RJL, Florence, Italy), single frequency (50 Hz), and was recorded with the participant lying relaxed on a couch with electrodes placed on the dorsal surfaces of the right hand and foot (over the wrist and the distal metacarpals and over the ankle and the metatarsals, respectively). An equation derived from a Danish population living in the same area as the Diet, Cancer, and Health population was used to calculate BFM and FFM from the impedance measurement (10). BFMI and FFMI were calculated by dividing BFM (kilograms) and FFM (kilograms), respectively, by height squared (meters squared), as suggested by Van Itallie (8). BF% was calculated as BFM (kilograms) divided by total weight (kilograms) and multiplied by 100. From the 23,814 subjects, 109 were excluded because they had no or implausible bioimpedance measurements leaving 23,705 subjects for the analyses of FFMI, BFMI, and BF%.

Anthropometric Measurements

Trained laboratory technicians obtained the anthropometric measurements at the study clinics. Height was measured when the participant was standing without shoes and was recorded to the nearest 0.5 cm. Weight was measured with a digital scale for participants wearing light clothes or underwear and recorded to the nearest 100 grams. Waist circumference was measured either at the narrowest part between the lower rib and the iliac crest (the natural waist), or, if this position could not be clearly identified, halfway between the lower rib and the iliac crest and was recorded to the nearest 0.5 cm. Hip circumference was measured at the most prominent part of the buttocks and recorded to the nearest 0.5 cm. BMI was calculated as weight (kilograms) divided by height squared (meters squared), and WHR was calculated as waist circumference divided by the hip circumference. From the 23,814 subjects, 15 were excluded because of extreme values for these anthropometric measurements, and 11 were excluded because of missing values for these measurements leaving 23,788 subjects for the analyses on anthropometric measurements.

Breast Cancer Incidence

The records of all cohort members were linked to the Central Population Register for information on vital status and emigration. Information on cancer occurrence was obtained by record linkage to the Danish Cancer Registry. Linkage was performed using the personal identification number. Each cohort member was followed for breast cancer from age at visit to the study clinic (baseline) until age at diagnosis of breast cancer, age at diagnosis of other cancers (except nonmelanoma skin cancer), age at death, emigration, or December 31, 2002, whichever came first.

Statistical Analyses

The analyses were based on Cox regression models, with age as the time axis to ensure that the estimation was based on comparisons of individuals of the same age to prevent confounding by age (11). The analyses were corrected for delayed entry by considering individuals at risk from the age at entry into the study cohort. All models were adjusted for known risk factors for breast cancer such as parity (entered as two variables: the categorical variable parous/nulliparous and the linear variable number of births), age at birth of first child (linear), duration of HRT (linear), alcohol intake (linear), previous benign breast tumor surgery (yes/no), and length of schooling (low, ≤7 years; medium, 8 to 10 years; high, >10 years). In addition, because the underlying time scale was age and not time in study, all analyses were adjusted for time in study by a linear spline with one knot (<1 year/≥1 year) to allow for a possible healthy participant effect. Most of the analyses were stratified on use of HRT into never users and ever users [current and past users (defined as women who responded yes to the question of ever use of hormones but no to the question of use at the time of the interview)], except for the analyses on height, which were adjusted for use of HRT entered categorized (current/past/never).

In the initial analyses, each of the continuous variables, including the previously mentioned confounders, was modeled in the Cox regression model as a linear spline with three knots. For the anthropometric measurements, we defined knots at the boundaries of the quartiles among cases in the subcohort of women who never used HRT to ensure an even distribution of cases within the quartile intervals, except for BMI, where the boundaries were chosen according to the World Health Organization definitions of underweight (<18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and severe overweight (≥30 kg/m^2) (12). The linear spline method uses the continuous information of the variables and considers the within-category variation in risk with varying values of the variables, and the risk pattern is estimated as piece-wise linear associations within each interval, allowing the curves to change direction at the knots (13). It was tested whether the linear splines of the variables could be simplified to straight lines.

Association with the exposure variables of interest was illustrated with the exposure variables modeled as categorized or continuous (linear) according to the aforementioned boundaries. In the categorical analyses, the reference group was defined as the group with the largest number of noncases to minimize random error in the presented pair-wise comparisons. The SAS procedure PHREG (SAS, Cary, NC) was used for statistical analyses.

Tests were based on the likelihood ratio test statistics calculated from Cox's partial likelihood. Confidence intervals (CIs) were based on Wald's test of the corresponding regression parameters, i.e., on the log scale for the incidence rate ratios (IRRs).

Results

Among the 23,788 postmenopausal women, 633 cases of breast cancer were identified during a median follow-up of 6.7 years (1st and 99th percentiles, 1.1 and 8.7 years). The median age at entry was 57 years (range, 50 to 65 years). Table 1 shows the distribution on the known risk factors for breast cancer for the entire cohort and for women who developed breast cancer during follow-up and rate ratios for each variable. All of the associations were in the expected direction, i.e., a negative association with the number of children and positive associations with age at birth of first child, having had a benign breast tumor, years of schooling, use of HRT and duration of HRT use, and consumption of alcohol. The distributions of anthropometric measurements at baseline among all women and cases are shown in Table 2. Among all women, the age-specific rate of breast cancer among postmenopausal women was 1.08 times higher for each 5-cm higher height (95% CI, 1.01 to 1.15) after adjustment for confounders.

The IRR for postmenopausal breast cancer was slightly higher for higher weight and BMI among the 11,796 women who had never used HRT, whereas there was no increase in the rate with higher weight and BMI among the 11,992 women who were ever users of HRT (Table 3). After adjustment for waist and hip circumference, the association with BMI found among never users of HRT was slightly strengthened (IRR, 1.13; 95% CI, 0.84 to 1.51). There were no associations between waist circumference and breast cancer between both never and ever HRT users. A tendency toward a weak positive association between hip circumference and breast cancer was observed among never and ever HRT users. The associations became stronger after adjustment for waist circumference and BMI among never HRT users (IRR, 1.08; 95% CI, 0.94 to 1.24) and, in particular, among ever HRT users (IRR, 1.15; 95% CI, 1.03 to 1.28). A weak negative association between WHR and breast cancer was seen in both never and ever users of HRT.

Table 4 shows the IRRs for FFMI, BFMI, and BF%. Among never users of HRT, the IRR for FFMI was 1.12 (95% CI, 1.00 to 1.26) for each 1 kg/m^2 increment after

Table 1. Number of postmenopausal cohort members and number of cases with postmenopausal breast cancer according to different levels of breast cancer risk factors in the Danish Diet, Cancer, and Health study

	Total cohort (n = 23,788)			Cases (n = 633)			Mutually adjusted*	
Known risk factor for breast cancer	**PY**	**No.**	**(%)**	**PY**	**No.**	**(%)**	**IRR**	**95% CI**
Parity								
Nulliparous	19,563	2926	(12)	369	94	(15)	0.90†	0.66 to 1.23
One	23,971	3632	(15)	453	126	(20)	0.84‡	0.76 to 0.94
Two to three	102,369	15,582	(66)	1,297	383	(61)		
Four+	10,906	1648	(7)	106	30	(5)		
Age at first childbirth								
≤19	21,017	3163	(15)§	245	72	(13)§		
20 to 24	65,546	9929	(48)§	857	243	(44)§		
25 to 29	38,881	5963	(29)§	548	166	(31)§	1.03¶	0.92 to 1.15
30 to 34	9,254	1420	(7)§	158	46	(9)§		
35+	2,540	386	(2)§	48	12	(2)§		
Benign breast tumor								
Yes	20,465	3140	(13)	495	139	(22)	1.79	1.48 to 2.16
No	136,344	20,648	(87)	1,730	494	(78)	1.00	
Years of schooling								
≤7	53,140	7991	(34)	731	199	(31)	1.00	
8 to 10	77,119	11,728	(49)	1,053	304	(48)	0.96	0.80 to 1.15
≥11	26,550	4069	(17)	441	130	(21)	1.13	0.90 to 1.43
HRT use								
Never	78,120	11,796	(50)	785	217	(34)	1.00	
Past	24,781	3747	(16)	289	81	(13)	1.10	0.83 to 1.46
Current	53,908	8245	(35)	1,152	335	(53)	2.01	1.62 to 2.50
Duration of HRT (years)								
<1	20,207	3067	(26)**	254	75	(18)**		
1 to 4	20,713	3143	(26)**	339	99	(24)**	1.11††	0.88 to 1.40
5 to 9	18,091	2768	(23)**	421	117	(28)**	1.05§§	0.96 to 1.15
10+	19,677	3014	(25)**	427	125	(30)**		
Alcohol intake (g/d)								
Abstainers	4,705	716	(3)	37	15	(2)	0.94	0.56 to 1.58
>0 to 11	92,539	13,953	(59)	1,134	321	(51)	1.10‡‡	1.04 to 1.16
12 to 35	46,066	7050	(30)	828	228	(36)		
36+	13,498	2069	(9)	225	69	(11)		

* Mutually adjusted for the other risk factors in the table.
† Rate ratio for nulliparous vs. one birth at age 35 years.
‡ Rate ratio per birth larger than 1.
§ Percentage of all women giving birth.
¶ Rate ratio per 5-year increment in age at first birth.
** Percentage of all women using HRT
†† Rate ratio per 5-year increment among past users of HRT.
§§ Rate ratio per 5-year increment among current users of HRT.
‡‡ Rate ratio per 12 g alcohol/d.
PY, person-years; HRT, hormone replacement therapy.

Table 2. Distribution of anthropometric measurements at baseline among all postmenopausal cohort members and cases developing breast cancer in the Danish Diet, Cancer, and Health study

Anthropometric measure	Percentiles					
	Total cohort (n = 23,788)			Cases (n = 633)		
	5	50 (median)	95	5	50 (median)	95
Height (m)	1.54	1.64	1.74	1.55	1.65	1.75
Weight (kg)	52.4	67.1	91.3	52.8	66.9	89.7
BMI (kg/m^2)	19.9	24.9	33.8	20.0	24.8	33.4
Waist circumference (cm)	67	80	104	68	79	102
Hip circumference (cm)	89	101	118	89	101	118
WHR	0.70	0.80	0.94	0.70	0.79	0.94
FFMI (kg/m^2)*	14.6	16.3	19.0	14.7	16.3	18.9
BFMI (kg/m^2)*	4.6	8.7	15.5	4.4	8.3	14.9
BF%*	22.5	34.8	46.1	21.9	34.0	46.1

* Due to missing values for bioimpedance measurements, percentiles for BFMI, and FFMI covered 23,705 women in the total cohort and 631 cases.

WHR, waist-to-hip ratio; FFMI, fat free mass index; BFMI, body fat mass index; BF%, body fat percentage.

adjustment for BFMI, and among ever users of HRT, the IRR was 1.00 (95% CI, 0.91 to 1.09) for each 1 kg/m^2 increment after adjustment for BFMI. For BFMI, the IRR was 0.98 (95% CI, 0.93 to 1.03) among never HRT users and 1.00 (95% CI, 0.96 to 1.04) among ever HRT users for each 1 kg/m^2 increment in BFMI after adjustment for FFMI. The associations with BFMI and FFMI among never HRT users were not significantly different ($p = 0.10$). Among never HRT users, BF% was also positively associated with breast cancer with an IRR of 1.08 (95% CI, 0.88 to 1.33) for each 10% increase but not among ever users. BF% was positively correlated with FFMI among never HRT users (Spearman's correlation coefficient, 0.44; $p < 0.0001$) and among ever HRT users (Spearman's correlation coefficient, 0.35; $p < 0.0001$). After adjusting the analysis of FFMI for BF% among never HRT users, the positive association remained, but after adjusting the analysis of BF% for FFMI, the positive association disappeared. The positive association found for FFMI adjusted for BFMI among never HRT users was largely the same after adjustment for height (IRR, 1.11; 95% CI, 0.99 to 1.26). All analyses were repeated after excluding all past users of HRT from the group of ever users of HRT, but the results were largely the same for current and ever users of HRT.

Discussion

Unexpectedly, we found no association between BFMI and breast cancer among postmenopausal women who had never used HRT, whereas a weak positive association with FFMI was indicated. The weak positive association found for BMI was also restricted to never HRT users. Hip circumference slightly increased the breast cancer risk, whereas no effect of waist circumference was found independently of HRT use.

The Diet, Cancer, and Health database includes anthropometric measurements of high quality; they were obtained by a trained laboratory technician in a standardized way as opposed to self-report. The accuracy of body composition estimated by bioelectrical impedance depends on the equation used. We used an equation developed in a Danish population (10) that has previously been applied on impedance measurements from the Diet, Cancer, and Health cohort (10). In this study, the robustness of the results was evaluated using other equations, and most of the findings were reproduced (14). To date, BFMI and FFMI have not been widely applied, but a recent study from Switzerland reported reference values in apparently healthy white adults (15). The percentiles for BFMI and FFMI for our population corresponded closely to those in the Swiss study of 386 women 55 to 74 years old, except for percentiles at and above 75% for BFMI, where our values were somewhat larger. Some weight changes are likely to have occurred during follow-up; however, considering the relatively short time period covered, these probably had no major impact on the breast cancer incidence. There has been some concern that adiposity delays the detection of a breast tumor. However, because the women in our cohort were not screened for breast cancer at baseline, a potential postponement of

Table 3. IRRs and 95% CIs for breast cancer in relation to weight, BMI, waist and hip circumference, and WHR among postmenopausal never and ever users of HRT in the Danish Diet, Cancer, and Health study

Anthropometric measurements	Never HRT users (*N* = 11,796)					Ever HRT users (*N* = 11,992)				
	PY	Cases	IRR*	95% CI	*p*‡	PY	Cases	IRR*†	95% CI	*p*‡
Weight (kg)										
<62.6	25,055	55	1.00			26,650	144	1.00		
62.6 to <68.1	15,568	53	1.60	1.09 to 2.33		17,184	97	1.07	0.83 to 1.39	
68.1 to <75.5	16,724	54	1.53	1.05 to 2.23		17,108	87	1.00	0.77 to 1.31	
≥75.5	20,773	55	1.32	0.90 to 1.92		17,746	88	1.07	0.82 to 1.39	
Per 10 kg			1.07	0.97 to 1.19	0.17			1.02	0.94 to 1.11	0.66
BMI (kg/m^2)										
<18.5	1,037	1	−§	−§		946	7	1.23	0.58 to 2.63	
18.5 to <25	37,183	96	1.00			40,713	237	1.00		
25 to <30	26,707	85	1.34	1.00 to 1.80		27,700	130	0.88	0.71 to 1.09	
≥30	13,193	35	1.17	0.79 to 1.73		9,331	42	0.94	0.67 to 1.31	
Per 4 kg/m^2			1.06	0.95 to 1.19	0.28			0.98	0.89 to 1.09	0.74
Waist circumference (cm)										
<74	17,208	52	1.05	0.72 to 1.53		18,866	111	1.00	0.78 to 1.30	
74 to <81	20,176	56	1.00			22,766	129	1.00		
81 to <89	18,974	54	1.06	0.73 to 1.54		19,406	93	0.87	0.67 to 1.14	
≥89	21,762	55	0.97	0.66 to 1.41		17,650	83	0.94	0.71 to 1.24	
Per 5 cm			1.01	0.95 to 1.06	0.88			0.98	0.93 to 1.03	0.39
Hip circumference (cm)										
<97	21,724	51	0.77	0.53 to 1.13		23,570	121	0.95	0.73 to 1.23	
97 to <102	19,266	56	1.00			20,511	108	1.00		
102 to <107	16,169	48	1.04	0.70 to 1.53		16,901	100	1.18	0.90 to 1.55	
≥107	20,961	62	1.07	0.74 to 1.53		17,706	87	1.06	0.80 to 1.40	
Per 5 cm			1.05	0.98 to 1.13	0.15			1.03	0.97 to 1.09	0.33
WHR										
<0.75	14,623	49	1.29	0.88 to 1.89		15,623	104	1.27	0.98 to 1.65	
0.75 to <0.79	16,931	49	1.13	0.77 to 1.65		18,463	101	1.06	0.82 to 1.38	
0.79 to <0.85	23,790	59	1.00			24,919	126	1.00		
≥0.85	22,775	60	1.08	0.75 to 1.55		19,683	85	0.89	0.68 to 1.17	
Per 0.05			0.95	0.86 to 1.04	0.24			0.92	0.86 to 0.99	0.03

* Adjusted for parity, age at birth of first child, benign breast tumor, years of schooling, and alcohol intake.
† Also adjusted for current use of HRT and duration of HRT.
‡ *p* value for trend.
§ Insufficient numbers to provide a stable estimate.
IRR, incidence rate ratio; CI, confidence interval; WHR, waist-to-hip ratio; HRT, hormone replacement therapy; PY, person-years.

diagnoses among the obese women is not likely to reduce the incidence of breast cancer in this group; the diagnoses will merely be displaced.

The database also provides opportunities for adjustment for various confounders for breast cancer, with the exception of family history of breast cancer, which was not available. Furthermore, the linkage by the unique personal identification number to the Danish Cancer Registry ensures valid data on incident cases of breast cancer that were recorded independently of participation in the study. Of the women invited, 37% chose to participate in the study, which may limit the generalization of the results, although the internal validity is not affected. The Diet, Cancer, and Health cohort is part of the European Prospective Investi-

Table 4. IRRs and 95% CIs for breast cancer in relation to FFMI, BFMI, and BF% among postmenopausal never and ever users of HRT in the Danish Diet, Cancer, and Health study

	Never HRT users (*N* = 11,575)					Ever HRT users (*N* = 11,948)				
Body composition	**PY**	**Cases**	**IRR***	**95% CI**	***p*†**	**PY**	**Cases**	**IRR*‡**	**95% CI**	***p*†**
FFMI (kg/m^2)										
<15.7	22,981	55	1.00§¶			22,253	107	1.00§‖		
15.7 to <16.4	17,657	55	1.33§¶	0.91 to 1.95		18,761	115	1.30§‖	1.00 to 1.70	
16.4 to <17.3	18,653	52	1.28§¶	0.86 to 1.91		20,631	116	1.21§‖	0.92 to 1.60	
≥17.3	18,559	55	1.52§¶	0.98 to 2.37		16,741	76	1.02§‖	0.73 to 1.42	
Per 1 kg/m^2 adjusted for BFMI			1.12¶	1.00 to 1.26	0.06			1.00‖	0.91 to 1.09	0.94
Per 1 kg/m^2 adjusted for BF%			1.10	0.99 to 1.23	0.09			1.00	0.91 to 1.09	0.93
BFMI (kg/m^2)										
<6.9	19,198	55	1.25§¶	0.80 to 1.96		22,849	133	0.98§‖	0.71 to 1.34	
6.9 to <8.8	19,687	54	1.23§¶	0.80 to 1.88		20,590	121	1.01§‖	0.75 to 1.37	
8.8 to <10.8	16,385	53	1.40§¶	0.93 to 2.09		16,817	72	0.77§‖	0.56 to 1.07	
≥10.8	22,580	55	1.00§¶			18,130	88	1.00§‖		
Per 1 kg/m^2 adjusted for FFMI			0.98¶	0.93 to 1.03	0.43			1.00‖	0.96 to 1.04	0.79
Per 1 kg/m^2 adjusted for BF%			0.97	0.83 to 1.12	0.67			1.01	0.89 to 1.15	0.87
BF%										
<30.1	16,987	47	0.95	0.64 to 1.42		20,453	115	0.97	0.73 to 1.30	
30.1 to <35.3	21,607	59	1.00	0.69 to 1.45		22,757	132	1.03	0.78 to 1.36	
35.3 to <39.3	17,252	56	1.22	0.84 to 1.78		17,748	83	0.89	0.66 to 1.21	
≥39.3	22,004	55	1.00			17,428	84	1.00		
Per 10%			1.08	0.88 to 1.33	0.45			0.97	0.83 to 1.13	0.67
Per 10% adjusted for BFMI			1.28	0.58 to 2.82	0.54			0.92	0.48 to 1.74	0.79
Per 10% adjusted for FFMI			0.96	0.75 to 1.22	0.74			0.97	0.81 to 1.16	0.74

* Adjusted for parity, age at birth of first child, benign breast tumor, years of schooling, and alcohol intake.
† *p* value for trend.
‡ Also adjusted for current use of HRT and duration of HRT.
§ Mutually adjusted for FFMI and BFMI in categories.
¶ Spearman's correlation coefficient = 0.59 ($p < 0.0001$) for FFMI and BFMI among never HRT users.
‖ Spearman's correlation coefficient = 0.50 ($p < 0.0001$) for FFMI and BFMI among ever HRT users.
IRR, incidence rate ratio; FFMI, fat free mass index; BFMI, body fat mass index; BF%, body fat percentage; HRT, hormone replacement therapy; PY, person-years.

gation into Cancer and Nutrition (EPIC) study, for which results on body size and breast cancer were recently published on 103,344 postmenopausal women from nine European countries (4). In comparison with the Danish data in the EPIC study, the Danish data presented here included more postmenopausal women and longer follow-up (median of 6.7 years), with an additional 400 extra breast cancer cases. Besides, body composition was not investigated in the EPIC publication.

Body composition estimated from bioelectrical impedance was used in three previous studies of breast cancer among postmenopausal women (6,7,16), of which one study was based on only 36 cases (16). In a prospective cohort study from Sweden including 246 cases of breast cancer, the risk of incident breast cancer was 3.41 (95% CI, 1.75 to 6.67) times higher for women in the highest quintile above 36% BF vs. the lowest quintile of <27% BF among women who did not use HRT (6). The effect of FFM was not investigated (6). In a recent prospective cohort study from Australia including 357 cases of breast cancers among postmenopausal women, the risk of breast cancer increased with increasing FFM and BFM, but only when 15 or more years had passed after menopause (7). Here, the risk estimates for each 10-kg increment in FFM and BFM were 1.72 (95% CI, 1.24 to 2.38) and 1.32 (95% CI, 1.13 to 1.54), respectively. Neither of these two studies adjusted estimates of BF% for

FFM, but at least for the Swedish study, it seems unlikely that the strong effect could be entirely explained by an effect of FFM. Our cohort was younger than both the Swedish and, in particular, the Australian cohort, which may possibly explain why we found very weak effects for FFM and no effect for BFM. Our cohort is currently too young for investigation of the risk of breast cancer during the time interval of 15 or more years since menopause.

It has been hypothesized that the underlying explanation for an increase in breast cancer risk among overweight women is that adipose tissue is an internal source of estrogen production after menopause because the enzyme aromatase converts androgens to estrogens. Women who have never used HRT are presumed to be of particular interest concerning the effects of obesity on breast cancer because exogenous female hormones would surmount any effect of endogenous hormone production in adipose tissue. In line with this, we found no relationship between BFMI and breast cancer among ever users of HRT, whereas the finding of no relationship between BFMI and breast cancer among never HRT users disagreed with the hypothesis. The association with FFMI was confined to never HRT users, so endogenous estrogen production may still be an underlying factor if other sources related to FFM are important for endogenous estrogen production in postmenopausal women. In addition to adipose tissue, the enzyme aromatase is also found in skin fibroblasts, bone, and the brain (17) and, according to a recent study, also in skeletal muscles (18). The activity of aromatase is low in muscles, but considering the amount of muscle tissue in the body, the production of estrogens may still pose a risk.

The results for height were in close agreement with those obtained in the EPIC study (4) and the pooled analysis of seven prospective studies (2). The pooled project included 3208 cases of breast cancer in postmenopausal women in Canada, The Netherlands, Sweden, and the U.S.

A recent meta-analysis gave evidence that a positive association between waist circumference or WHR and breast cancer among postmenopausal women was explained by general obesity and not abdominal adiposity because adjustment for BMI abolished the relationships with waist circumference and WHR (19). We saw no association with waist circumference in our study even without adjustment for BMI as a proxy for general obesity. However, among both never and ever HRT users, we saw a weak positive association with hip circumference that was slightly strengthened after adjustment for BMI and waist circumference, especially among ever HRT users. Some previous studies also have reported a positive association with hip circumference, although only among nonusers of HRT (3,4,20); adjustment for BMI was performed in the EPIC study (4) and the Women's Health Initiative Observational study (3) without changing the association. In the Nurses' Health study (21), a larger hip circumference was moderately associated with breast cancer in all postmenopausal women, but the association was attenuated toward the null after adjusting for BMI or waist circumference. In respect to BMI, we found a weak positive association with breast cancer after adjustment for standard confounders among never users of HRT that was relatively close to the association found in the EPIC study (4) and the pooled analysis (2). The association was slightly enhanced after further adjustment for waist and hip circumference in our study. None of the previous studies adjusted the analyses of BMI for waist and/or hip circumference. As in previous studies (2,4), our categorical analyses of BMI did not show a higher risk of breast cancer among those with severe overweight compared with those with more moderate overweight.

On the basis of data collected in the prospective cohort study Diet, Cancer, and Health, we found a weak positive association between BMI and breast cancer among postmenopausal women. When splitting BMI into BFMI and FFMI, a positive association with FFMI was seen. These associations were observed among never users of HRT but not among ever users. Because there is previous evidence also indicating a role for the lean component of body mass in breast cancer development, this deserves further attention.

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