

Body Size and Composition and Risk of Postmenopausal Breast Cancer

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Abstract

Background: Studies of postmenopausal breast cancer have reported positive associations with body size and composition but it is uncertain whether these are due to non-adipose, adipose mass, or central adiposity, and whether they are limited to subgroups defined by age or tumor characteristics.

Methods: In a prospective cohort study of women ages 27 to 75, body measurements were taken directly; fat mass and fat-free mass being estimated by bioelectrical impedance analysis, and central adiposity by waist circumference. Among 13,598 women followed on average for 9.1 years, 357 invasive breast cancers were ascertained via the population cancer registry. Data were obtained on estrogen receptor and progesterone receptor status, grade, and stage.

Results: Estimates of body size such as fat-free mass [hazard ratio per 10 kg increase = 1.45, 95% confidence

interval (CI) 1.16-1.82], fat mass (hazard ratio per 10 kg increase = 1.18, 95% CI, 1.06-1.31), and waist circumference (hazard ratio per 10 cm increase = 1.13, 95% CI, 1.03-1.24) were associated with breast cancer risk. There was no association with risk before 15 years postmenopause. About 15 years after menopause, risk increased sharply and remained elevated. There was some evidence that this association might be stronger for estrogen receptor-positive and poorly differentiated tumors but no evidence that it differed by stage.

Conclusion: Given that elements of body size and composition are positively associated with breast cancer risk, although not until 15 or more years postmenopause, it is possible that women could reduce risk by maintaining ideal body weight after menopause. (Cancer Epidemiol Biomarkers Prev 2004;13(12):2117-25)

Introduction

Whereas many cohort studies of postmenopausal breast cancer have found positive associations with body mass index (BMI; ref. 1), it is uncertain whether this relationship is due to non-adipose mass, adipose mass, or the distribution of adipose mass such as central adiposity. Only a few cohort studies have reported findings with respect to central adiposity (2), and none have reported any associations with non-adipose mass. It is also uncertain whether any association with elements of body size and composition might be limited to a particular tumor subgroup identified, for example, by estrogen receptor (ER) and progesterone receptor (PR) status, grade or stage.

The risk of breast cancer associated with increased body size is not uniform across a woman's lifetime. For example, heavier women have a decreased risk of premenopausal breast cancer (1, 3). The point at which the association between increased body size and breast cancer

changes from being protective to being detrimental is still uncertain. It could occur at menopause, or sometime before or after menopause, whereas there may also be an intermediate period where increased body size has virtually no relationship to breast cancer risk. In premenopausal women, circulating estrogen and progesterone is produced largely from the ovaries. After menopause, when ovarian hormone production has stopped, estrogens are primarily locally produced by aromatase activity in adipose tissue (4). Thus for postmenopausal women, the number of years since menopause is a reasonable estimate of the time in which peripheral production has been the main source of endogenous estrogen exposure.

We assessed the relationship between estimates of body size and composition, and risk of invasive breast cancer in postmenopausal women in a prospective cohort study by using direct anthropometric measurements including estimates of non-adipose mass and adipose mass from bioelectrical impedance analysis. Further analyses were done as a function of years since menopause. We also analyzed risk by tumor ER and PR status, and by tumor stage and grade.

Materials and Methods

The Cohort. The Melbourne Collaborative Cohort Study is a prospective cohort study of 41,528 people (24,479 women) ages between 27 and 75 at baseline, 99.3%

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of whom were ages 40-69 (5). Recruitment occurred between 1990 and 1994. The study protocol was approved by The Cancer Council Victoria's Human Research Ethics Committee. Southern European migrants to Australia (including 3,008 Italian women and 2,461 Greek women) were deliberately over-sampled to extend the range of lifestyle exposures and to increase genetic variation.

Subjects were recruited via the Electoral Rolls (registration to vote is compulsory for adults in Australia), advertisements and community announcements in local media (e.g., television, radio, and newspapers). Comprehensive lists of Italian and Greek surnames were also used to target southern European migrants in the phone book and Electoral Rolls.

Subjects. We recruited 24,479 women, of whom 13,974 (57%) were classified as postmenopausal at baseline. Of these, 260 were excluded from analysis because they had a diagnosis of breast cancer before baseline, and 116 women were excluded because they did not have a complete set of valid measurements, leaving 13,598 women available for analysis.

Measurements. Height, weight, and waist and hip circumferences were measured once at baseline attendance for each participant according to written protocols that were based on standard procedures (6). Weight was measured to 100 g using digital electronic scales, height to 1 mm using a stadiometer, and waist and hips circumferences were measured to 1 mm using a 2-meter metal anthropometric tape. Bioelectrical impedance analysis was done with a single frequency (50 kHz) electric current produced by a BIA-101A RJL system analyzer (RJL systems, Detroit, MI, USA). Resistance and reactance were measured with subjects in a supine position. Blood samples were collected from all subjects. Details of this have been published (7). These blood samples have been used to measure sex hormones (including total estradiol) on a total of 2,920 women not currently using hormone replacement therapy (HRT) at baseline, which includes a random subcohort and all incident cases of breast and colorectal cancer, type 2 diabetes, and cardiovascular deaths identified during follow-up.

Questionnaire Measures. At interview, questions were asked about conventional risk factors such as reproductive history, country of birth, alcohol, physical activity, and highest level of education. Additionally, women were asked to report their use of HRT and oral contraceptives.

Age at menopause was determined by the age at which a woman's periods had ceased naturally for at least the past 12 months or at which they had a bilateral oophorectomy (if this was the reason for cessation of periods). Of the 4,450 women who indicated having a hysterectomy without bilateral oophorectomy, 367 had measures of estradiol available. From this, 272 women who indicated that they had had a hysterectomy without having a bilateral oophorectomy, were considered postmenopausal with unknown age at menopause as their concentration of total estradiol was <109 pmol/L (the level at which 90% of women were correctly classified as premenopausal or naturally postmenopausal in the randomly selected subcohort). The remaining women who indicated

having a hysterectomy without bilateral oophorectomy were considered postmenopausal with unknown age at menopause if their age at baseline was >55 years (age at which natural menopause had occurred in 90% of the total cohort).

Cohort Follow-up and Case Ascertainment. Passive follow-up has been conducted by record linkage to the Electoral Rolls, electronic phone books and the Victorian Cancer Registry and death records until June 30, 2002. At this time, 165 women had left Victoria (1.2%), and 657 (4.8%) had died.

All subjects gave written consent allowing access to their medical records to confirm diagnoses. Cases were identified from notifications to the Victorian Cancer Registry of diagnoses of adenocarcinoma of the breast (International Classification of Diseases 9th revision rubric 174.0-174.9, or 10th revision rubric C50.0-C50.9). Women with *in situ* breast cancers were not included as cases. Medical records of reported breast cancers were reviewed and classified according to stage of disease, histologic tumor grade, and ER/PR status. Stage was defined as groups I-IV based on the standard guidelines of the tumor-node-metastasis, system for staging cancer classification system (8) but collapsed into localized (stage I) and nonlocalized (stage II-IV) for analysis. Cases that only had information on size of tumor were classified as localized if the diameter was ≤ 15 mm ($n = 41$), whereas tumors >20 mm were classified as nonlocalized ($n = 6$). Grade was used to categorize breast cancer into well (grade I), moderately (grade II), and poorly (grade III) differentiated tumors. We obtained both ER and PR status of the tumor from either the histopathology report held at the Victorian Cancer Registry or through a written request to the pathology laboratory that had issued the diagnostic histopathology report.

Statistical Analysis. Cox's proportional hazard regression models, with age as the time axis (9), were used to estimate the hazard ratios associated with each anthropometric measure at baseline. Calculation of person-time began at baseline and ended at the earliest of the following: date of diagnosis of breast cancer, date of diagnosis of cancer of unknown primary site, date of death, the date last known to be in Victoria or June 30, 2002 (the date that ascertainment of breast cases by the Victorian Cancer Registry was complete).

The temporal nature of the associations with body size and composition was assessed by estimating the hazard ratio for each anthropometric measure as a function of years since menopause using a time-varying covariate. We initially compared hazard ratios in two time-varying strata, <15 and ≥ 15 years since menopause, because this cut point approximately equally divided the number of women and cases. Women who were both <15 and ≥ 15 years postmenopause at any time during follow-up were included in both time-varying strata. These women left the first stratum at the age in which they became 15 years postmenopause and entered the second stratum at the same age. Subsequent analyses using a similar approach were done with time since menopause grouped into four time-varying strata, 0-9, 10-14, 15-19, and ≥ 20 years.

We used bioelectrical impedance analysis to estimate non-adipose mass, hereafter termed fat-free mass (FFM), as $7.7435 + (0.4542 \times \text{height}^2/\text{resistance}) + (0.1190 \times$

weight) + (0.0455 × reactance; ref. 10). Adipose mass, hereafter termed fat mass (weight – FFM), and percent-age fat (fat mass divided by weight), were subsequently calculated. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist-to-hips ratio (WHR) was also computed.

Initially, all anthropometric measures were fitted as continuous covariates to estimate linear trends on the log hazard scale. In addition, analysis of BMI was also done using WHO categories that describe overweight and obesity (<25, 25-29, and ≥30 kg/m²), whereas the other anthropometric measures were categorized into approximate quartiles according to their baseline distribution in the entire study population.³ The lowest category was used as the referent category.

Country of birth (Australia, Greece, Italy, United Kingdom) was included in all models. Potential confounders were included in all final analyses if they changed the hazard ratios of any of the anthropometric measures by at least 5%. Initially, education (primary school, some high/technical school, completed high school, and completed tertiary degree/diploma), current level of physical activity (none, low, moderate, high; see ref. 11 for further details), current alcohol consumption (grams per day), maternal family history of cancer (yes/no), parity, total months of lactation for all live births, age at first gestation >24 weeks (regardless of whether the pregnancy was live or not), age at menarche, HRT (never, former, current), and oral contraceptive pill usage (never, ever) were added. The hazard ratios from the models with HRT, physical activity and education differed by more than 5% from the model with all of them in and, thus, they were retained for further analysis. Finally, age at menopause was tested for women with a natural menopause or a bilateral oophorectomy in the same way, but had little effect.

Effect modification by HRT use was assessed by fitting interactions between HRT use and the continuous form of the anthropometric measures. To test for heterogeneity in the hazard ratios for stage (localized versus non-localized), and grade (well versus moderately versus poorly differentiated) of disease and for ER and PR status (ER+ versus ER-, PR+ versus PR-, and ER+/PR+ versus ER-/PR-), Cox's proportional hazards regression models were fitted using a data duplication method (12). Statistical analyses were done using STATA/SE 7.0 (Stata Corporation, College Station, TX, USA). Tests based on Schoenfeld residuals and graphical methods using Kaplan-Meier curves (13) showed no evidence that proportional hazard assumptions were violated for any of the anthropometric measures.

Results

We identified 357 histologically verified incident invasive breast cancer cases over an average of 9.1 person-years of follow-up between 1990 and 2002. The mean age at diagnosis of breast cancer was 66.1 years (range 48.2-79.4 years). Information on stage was available for 335

(94%) cases. Of these, 197 (59%) were localized, and 138 (41%) were nonlocalized. Information on grade was available for 311 (87%) cases. Of these, 69 (22%) were well-differentiated, 141 (45%) were moderately differentiated, and 101 (32%) were poorly differentiated. ER and PR status was available for 286 (80%) cases (90% from reports held at the Victorian Cancer Registry), determined using methods that were immunohistochemical (81%), biochemical (11%), or unknown (8%). There were 173 ER+ PR+, 42 ER+ PR-, 15 ER- PR+, and 56 ER- PR- cases. Since 1997, 92% of cases had ER and PR status recorded, whereas only 63% of the cases had this information recorded prior to 1997. Tumors 20 mm or less were more likely to have missing data on ER and PR status than larger tumors (22% versus 6%).

A history of HRT use was reported by 28% of all postmenopausal women. Of these, 59% were current users and 41% were past users. Compared with never users, the hazard ratios (adjusted for age) were 1.7 [95% confidence interval (CI), 1.3-2.2] for current users and 1.0 (95% CI, 0.7-1.5) for former users.

Table 1 shows the hazard ratios by quartiles and continuously for each anthropometric variable after adjusting for age, ethnicity, education level, physical activity, and HRT use. Apart from WHR, women within the highest quartile of each body size measurement had higher rates of breast cancer compared with those in the lowest quartile of body size. The hazard ratio ranged from 1.5 for waist and hips circumference to 1.7 for weight, fat mass and percent fat. Using the WHO cut points and compared with women in the reference range of BMI, the hazard ratio for overweight women was 1.2 (95% CI, 0.9-1.5), whereas the hazard ratio for obese women was 1.4 (95% CI, 1.0-1.9). For all anthropometric variables, similar overall associations were seen using the continuous measure. The associations with FFM, fat mass, waist and hips circumference remained virtually unchanged after further adjustment for height (data not shown). Modeling both FFM and fat mass together reduced the hazard ratios of both measures (FFM 1.30, 95% CI, 1.00-1.72; fat mass 1.10, 95% CI, 0.96-1.25).

The following additional analyses were performed but did not materially change the hazard ratios (results not shown): excluding the first 2 years of follow-up, using only women with natural menopause, and excluding women with any cancer within 5 years before baseline attendance.

Although all tests for HRT-body size interactions had large *P* values (i.e., all *P* > 0.4), the hazard ratios for all anthropometric measures apart from height were larger among women who had never used HRT than for current users, whereas the hazard ratios among past users of HRT were intermediate. For example, the hazard ratios for fat mass were 1.20, 95% CI, 1.06-1.37 (never users); 1.14, 95% CI, 0.80-1.63 (former users); and 1.09, 95% CI, 0.86-1.40 (current users). Conversely, the hazard ratios for height were similar across HRT status, i.e., 1.27, 95% CI, 1.03-1.58 (never users); 1.20, 95% CI, 0.71-2.01 (former users); and 1.30, 95% CI, 0.91-1.87 (current users).

Women who were postmenopausal for 15 years or more accounted for virtually all the elevated rates associated with increased body size (Table 2). Apart from height and WHR, the *P* values for the tests for interactions between each measure and time since

³ The cut points used for the body size measurements were: height 155, 160, and 164 cm; weight 60, 66, and 75 kg; waist circumference 71, 78, and 87 cm; hip circumference 95, 100, and 107 cm; WHR 0.74, 0.78, and 0.83; FFM 37, 40, and 43 kg; fat mass 21, 26, and 33 kg; and percent fat 35%, 40%, and 45%.

Table 1. Breast cancer risk in relation to anthropometric measurements (in approximate quartiles): hazard ratios and 95% CI

	Quartile*			Hazard ratio designated increase of measure ¹	P value
	Hazard ratio per (95% CI)				
	2	3	4 (highest)		
Height (per 10 cm)	1.4 (1.0-1.9)	1.5 (1.1-2.0)	1.6 (1.1-2.2)	1.27 (1.07-1.52)	0.008
Weight (per 10 kg)	1.3 (1.0-1.8)	1.3 (1.0-1.8)	1.7 (1.2-2.3)	1.15 (1.06-1.25)	0.001
BMI (per 5 kg/m ²) [‡]	1.2 (0.9-1.5)	1.4 (1.0-1.9)		1.14 (1.02-1.27)	0.02
Waist circumference (per 10 cm)	1.3 (0.9-1.8)	1.2 (0.8-1.7)	1.5 (1.1-2.1)	1.13 (1.03-1.24)	0.007
Hip circumference (per 10 cm)	1.3 (0.9-1.8)	1.2 (0.9-1.6)	1.5 (1.1-2.1)	1.16 (1.05-1.28)	0.005
WHR (per 0.1 unit)	1.0 (0.7-1.3)	1.1 (0.8-1.5)	1.2 (0.8-1.6)	1.10 (0.94-1.29)	0.23
FFM (per 10 kg)	1.2 (0.8-1.6)	1.8 (1.3-2.4)	1.6 (1.2-2.3)	1.45 (1.16-1.82)	0.001
Fat mass (per 10 kg)	1.4 (1.0-1.9)	1.3 (0.9-1.8)	1.7 (1.3-2.4)	1.18 (1.06-1.31)	0.003
Percent fat (per 10%)	1.3 (1.0-1.8)	1.2 (0.8-1.6)	1.7 (1.2-2.3)	1.21 (1.03-1.42)	0.02

NOTE: All models adjusted for age at attendance, country of birth, highest level of education, physical activity, and HRT use.

*Quartiles shown are compared with quartile 1 (lowest).

¹Hazard ratio for model where fitted as a linear effect.

[‡]BMI categorized into three groups: <25, 25-29, ≥30.

menopause were between 0.01 and 0.08. The results were similar when analyses were restricted to never users of HRT. Further stratification of years since menopause (0-9, 10-14, 15-19, ≥20) revealed that there were sharp increases in hazard ratios after 15 years postmenopause rather than gradual increases by time since menopause for all measures apart from height (see Fig. 1). For example, the hazard ratios for fat mass were: 0.97, 95% CI, 0.74-1.28 (0-9 years postmenopausal) per 10 kg; 1.00, 95% CI, 0.78-1.27 (10-14 years postmenopausal); 1.28, 95% CI, 1.02-1.61 (15-19 years postmenopausal); and 1.36, 95% CI, 1.10-1.68 (≥20 years postmenopausal). Similar patterns in fat mass were seen for weight and percent fat, whereas no discernible pattern was observed for WHR (graphs not shown).

Overall, only minor differences were observed in the hazard ratios between body size measures and grade of disease, and between localized and nonlocalized diseases (all tests of homogeneity of trends, $P > 0.1$). Among women at least 15 years postmenopause, the associations between breast cancer and most body size measures including weight, waist and hips circumference, fat mass

BMI and percent fat were stronger for poorly differentiated tumors than for moderate or well-differentiated tumors (Table 3), although the statistical evidence for heterogeneity was weak ($0.04 < P < 0.18$). Also, among women at least 15 years postmenopause, the hazard ratio for FFM was greater for nonlocalized cancer (test of homogeneity of trends, $P = 0.11$), whereas the converse was seen for percent fat (test of homogeneity of trends, $P = 0.07$). The corresponding hazards ratios for non-localized and localized breast cancer were 2.31 (95% CI, 1.58-3.38) and 1.50 (95% CI, 1.02-2.20) per 10 kg FFM, and 1.07 (95% CI, 0.70-1.64), and 1.74 (95% CI, 1.26-2.41) per 10% fat. The hazard ratios for the other body size measures showed little difference, with all tests of homogeneity at $P > 0.2$.

The rate of breast cancer in relation to body size measures did not differ greatly between the ER/PR subtypes (all tests for homogeneity of trends, $P > 0.05$). Further analyses to investigate whether these relationships differed among women at least 15 years postmenopause are shown in Table 4. All measures, apart from height and FFM, showed positive associations

Table 2. Hazard ratios (95% CI in parentheses) of breast cancer risk in relation to anthropometric measurements stratified by years since menopause

No. of cases (No. of women)	Time since menopause (years)		P value*
	<15 <i>n</i> = 140 (<i>n</i> = 8,057)	≥15 <i>n</i> = 158 (<i>n</i> = 8,390)	
Height (per 10 cm)	1.12 (0.85-1.46)	1.36 (1.05-1.75)	0.29
Weight (per 10 kg)	1.00 (0.87-1.15)	1.26 (1.12-1.42)	0.01
BMI (per 5 kg/m ²)	0.98 (0.82-1.18)	1.26 (1.08-1.46)	0.04
Waist circumference (per 10 cm)	1.01 (0.88-1.18)	1.23 (1.08-1.40)	0.05
Hip circumference (per 10 cm)	0.98 (0.82-1.16)	1.28 (1.10-1.48)	0.02
WHR (per 0.1 unit)	1.06 (0.83-1.36)	1.17 (0.94-1.47)	0.54
FFM (per 10 kg)	1.09 (0.74-1.62)	1.72 (1.24-2.38)	0.08
Fat mass (per 10 kg)	0.99 (0.82-1.18)	1.32 (1.13-1.54)	0.02
Percent fat (per 10%)	0.99 (0.77-1.27)	1.41 (1.11-1.79)	0.04

NOTE: All models adjusted for age at attendance, country of birth, highest level of education, physical activity, and HRT use.

*Test of interaction between body size measure and years postmenopause grouping.

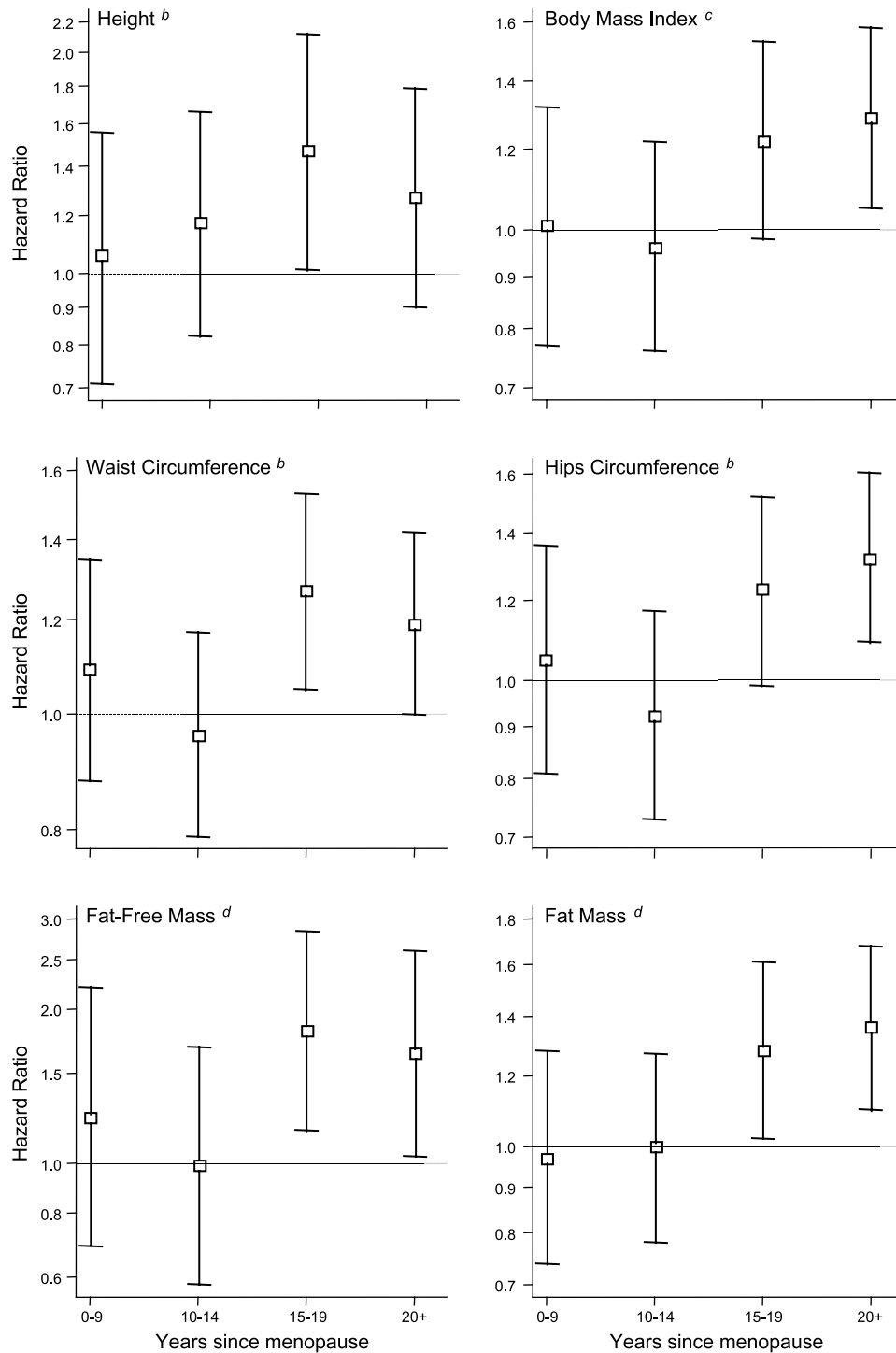


Figure 1. Hazard ratios and 95% CIs of breast cancer risk in relation to anthropometric measurements stratified by years since menopause. *Hazard Ratios*, all models adjusted for age at attendance, country of birth, highest level of education, physical activity and HRT use; *Height, Waist, and Hip Circumference*, hazard ratios are per 10 cm increase of the corresponding body size measure; *BMI*, hazard ratios are per 5 kg/m² increase of body mass index; *FFM and Fat mass*, hazard ratios are per 10 kg increase of the corresponding body size measure.

Table 3. Hazard ratios (95% CIs in parenthesis) of well, moderately, and poorly differentiated breast cancer risk in relation to anthropometric measurements for women 15 or more years postmenopause

No. of cases	Well-differentiated <i>n</i> = 36	Moderately differentiated <i>n</i> = 59	Poorly differentiated <i>n</i> = 44
Height (per 10 cm)	1.75 (1.10-2.78)	1.92 (1.25-2.95)	1.20 (0.74-1.95)
Weight (per 10 kg)	1.12 (0.90-1.39)	1.31 (1.11-1.53)	1.42 (1.15-1.74)
BMI (per 5 kg/m ²)*	1.00 (0.74-1.36)	1.21 (0.97-1.52)	1.50 (1.17-1.93)
Waist circumference (per 10 cm)	1.06 (0.80-1.39)	1.27 (1.06-1.54)	1.37 (1.06-1.76)
Hip circumference (per 10 cm)	1.12 (0.83-1.51)	1.26 (1.02-1.56)	1.54 (1.18-2.02)
WHR (per 0.1 unit)	0.95 (0.56-1.62)	1.33 (0.94-1.89)	1.10 (0.70-1.71)
FFM (per 10 kg)	1.42 (0.80-2.52)	2.04 (1.38-3.02)	1.80 (1.17-2.77)
Fat mass (per 10 kg)	1.12 (0.82-1.54)	1.33 (1.07-1.65)	1.58 (1.19-2.09)
Percent fat (per 10%)	1.14 (0.69-1.88)	1.39 (0.95-2.02)	1.86 (1.09-3.16)

NOTE: All hazard ratios (per unit of change) adjusted for age, country of birth, exercise, HRT use, and highest level of education.

*Tests for interaction between well-differentiated and poorly differentiated tumors, *P* = 0.04.

with ER+ tumors and weak negative associations with ER- tumors (all tests for homogeneity of trends, $0.01 < P < 0.07$). The associations were weaker for PR+ tumors compared with ER+ tumors, and stronger for PR- tumors compared with ER- tumors. Differences in rates were not marked between PR+ and PR- tumors, except perhaps for FFM, which showed a stronger positive association with PR- tumors. When we stratified by joint ER/PR status, we found that the strengths of the joint ER+/PR+ associations were intermediate compared with ER+ and PR+, and also joint ER-/PR- compared with ER- and PR- (results not shown). There was weak evidence that the association with increased waist circumference was stronger for ER+/PR+ tumors (hazard ratio 1.22, 95% CI, 1.02-1.46) compared with ER- PR- tumors (hazard ratio 0.85, 95% CI, 0.61-1.19), with the test for homogeneity of trends, *P* = 0.06. Similar trends were seen for fat mass and BMI.

Discussion

We found that non-adipose mass, adipose mass, and central adiposity were all positively associated with breast cancer rates in postmenopausal women. There seemed to be virtually no association with body size and risk of breast cancer for women <15 years postmenopause, but at ~15 years postmenopause, the rate increased sharply, and then remained constant. We also found that the obesity-breast cancer relationship may be stronger for tumors that are either ER-positive or of high grade, but there was no compelling evidence that the effect of increased body size differed by tumor stage. When interpreting these differences in subgroup analyses, some caution is required because the statistical evidence for heterogeneity was weak.

We had virtually complete follow-up in this prospective study as the identification of incident breast cancers was done by record linkage to the Victorian

Table 4. Hazard ratios (95% CIs in parenthesis) of ER and PR breast cancer risk in relation to anthropometric measurements for women 15 or more years postmenopause

	Positive	Negative	<i>P</i> value*
ER			
No. of cases	<i>n</i> = 97	<i>n</i> = 29	
Height (per 10 cm)	1.43 (1.01-2.04)	1.41 (0.78-2.56)	0.96
Weight (per 10 kg)	1.27 (1.11-1.46)	0.91 (0.69-1.19)	0.03
BMI (per 5 kg/m ²)	1.25 (1.05-1.49)	0.82 (0.55-1.24)	0.06
Waist circumference (per 10 cm)	1.24 (1.06-1.46)	0.79 (0.58-1.07)	0.008
Hip circumference (per 10 cm)	1.29 (1.08-1.54)	0.84 (0.60-1.16)	0.02
WHR (per 0.1 unit)	1.19 (0.88-1.61)	0.69 (0.41-1.16)	0.07
FFM (per 10 kg)	1.77 (1.21-2.59)	1.06 (0.54-2.10)	0.20
Fat mass (per 10 kg)	1.33 (1.11-1.60)	0.84 (0.56-1.24)	0.04
Percent fat (per 10%)	1.44 (1.05-1.97)	0.79 (0.48-1.32)	0.05
PR			
No. of cases	<i>n</i> = 84	<i>n</i> = 42	
Height (per 10 cm)	1.27 (0.89-1.81)	1.81 (1.04-3.14)	0.26
Weight (per 10 kg)	1.17 (1.00-1.36)	1.24 (1.00-1.53)	0.67
BMI (per 5 kg/m ²)	1.17 (0.95-1.44)	1.11 (0.86-1.45)	0.78
Waist circumference (per 10 cm)	1.18 (0.99-1.40)	1.05 (0.82-1.33)	0.43
Hip circumference (per 10 cm)	1.21 (1.00-1.48)	1.12 (0.86-1.47)	0.65
WHR (per 0.1 unit)	1.13 (0.82-1.57)	0.93 (0.58-1.49)	0.49
FFM (per 10 kg)	1.28 (0.79-2.07)	2.26 (1.48-3.44)	0.08
Fat mass (per 10 kg)	1.23 (1.01-1.51)	1.18 (0.87-1.61)	0.83
Percent fat (per 10%)	1.36 (0.97-1.90)	1.05 (0.66-1.66)	0.36

NOTE: All hazard ratios (per unit of change) adjusted for age, country of birth, exercise, HRT use, and highest level of education.

*Test of homogeneity in the hazard ratios between positive receptor and negative receptor breast cancer.

population cancer registry, which has complete coverage of the cohort participants. As only 165 women identified as postmenopausal at baseline have left Victoria, it is unlikely that we have missed more than two or three cases. Cases diagnosed later in the study were more likely to have ER and PR status recorded than earlier cases. It is unlikely that this would create any selection bias, as the pathologist would be uninformed with respect to a patient's anthropometric measures. Detection bias was possible, as women who self-detect their tumors may be more likely to have nonlocalized tumors (14). Yet, our hazard ratios for nonlocalized disease, for which the incidence would not be as influenced by early detection, were very similar to those for localized disease. A recent review showed that the relationship between central obesity and breast cancer risk was not consistently stronger in studies that used only screen-detected cases compared with results from other studies (2).

Our study used measures of body size made by direct physical examination according to standard protocols. Issues concerning the measurement of FFM and fat mass have been addressed previously (11, 15). Briefly, we chose a formula that had been developed using subjects whose ethnicity, age and BMI distribution (10) were similar to our own study. As the algorithm to compute FFM and fat mass includes height, weight, resistance, and reactance; in theory, any measurement errors in these would have reduced the precision of FFM and fat mass estimates. In practice, however, these measurement errors are generally small so the consequences for precision are likely to have been minimal. On the other hand, the associations would have been attenuated if the baseline measures were not representative of the participant's body size during the etiologically relevant period. Although it is possible that current alcohol consumption, parity, and age at menopause could have confounded these relationships, the hazard ratios did not differ by more than 5% after adjustment for our measures of these factors. Lactation, oral contraceptive use, age of menarche, and age at first live birth show little or no association with postmenopausal breast cancer (16, 17), and are thus unlikely to have confounded these relationships. We did not adjust for dietary factors, including dietary fat, as the evidence of a relationship with breast cancer risk is weak (18). Other potential confounders such as family history of breast cancer and history of benign breast disease were not collected at baseline attendance, thus we could not assess their possible impact. We did find, however, that the inclusion of maternal history of cancer, which was an independent risk factor for breast cancer in our study, did not materially affect the results.

The majority of studies to date have shown a positive relationship between height and breast cancer in both premenopausal and postmenopausal women (19). Height and FFM are correlated, and our analyses suggest that FFM is an independent risk factor that diminishes, if not fully explains, the association of cancer risk with height. Height and FFM, as well as age at menarche, reflect the net result of nutrition during childhood and adolescence and the action of growth factors including androgens and insulin-like growth factor (20, 21).

All our other associations remained after adjustment for height. Due to high correlations, we were unable to adequately test whether central or total adiposity is the more important risk factor. When FFM and fat mass were modeled together, the hazard ratios were reduced but remained above unity, suggesting that, although moderately correlated, both might be important independent risk factors.

Some studies have shown that excess central adiposity, usually measured by WHR, is related to an increased risk of breast cancer (1). This has led to the hypothesis that hyperinsulinemia may be a direct risk factor for breast cancer (2, 16). Although we failed to observe a notable relationship between WHR and breast cancer risk, waist circumference may be a better indicator of central adiposity than WHR. A recent study using computed tomography found that, for women, waist circumference was the best overall predictor of abdominal visceral obesity (or deep abdominal obesity) when compared with WHR, percent body fat and BMI (22). In particular, WHR was a poor indicator of abdominal visceral fat. It is reasonable to assume that the increased risk of breast cancer due to an increased waist circumference may be due to visceral fat as waist circumference correlates better with visceral than with abdominal subcutaneous fat (trunk-abdominal obesity; ref. 23). There is good evidence that increases of visceral adipose tissue have a strong relationship with the development of insulin resistance (24), although subcutaneous fat and in particular "deep" subcutaneous fat may play a similar role in the development of insulin resistance (25). Thus chronically elevated insulin levels may be a direct risk factor for breast cancer (26, 27). There is also evidence that visceral fat accumulation may relate predominantly to insulin resistance after the age of 60 years in women (28). Our finding that risk due to increased waist circumference is most pronounced in women who were at least 15 years postmenopausal supports this finding.

Women with a high BMI have been found to have a decreased risk of premenopausal breast cancer (1, 3). The possible reasons behind this observation are complex. One hypothesis is that this may be attributed to an increased frequency of anovulatory cycles and decreased levels of sex hormone-binding globulin, which results in lower levels of estradiol due to its increased clearance (29). Production of estrogen from adipose tissue is relatively low for premenopausal women, and therefore, the increased production of estrogen from the abundant adipose tissue associated with increased body size is not strong enough to offset the reduction of estrogen due to an increased frequency of anovulatory cycles. It is also unclear whether this protective effect is consistent throughout the years before menopause or is confined to teenage years only (30). The situation changes after menopause because the ovarian production of estrogen is greatly diminished. The main source of estrogen then is from aromatase converting the androgen precursor androstenedione to estrone in the adipose tissue (31).

Our results suggest that the change in the relationship between body size and breast cancer risk is not linear during the postmenopausal years and that it does

not manifest until ~15 years postmenopause. A few studies have found that risk associated with increased BMI is higher in older age (32-34), whereas others have reported no difference (35, 36), and one study even found a stronger effect for younger postmenopausal women (37). The report from the Nurses' Health Study also stratified analysis by years since menopause and found no clear variation in association (35). The differing results between our study and the Nurses' Health Study may be due to our cohort being older and of longer postmenopausal duration on average, and thus, the range of exposure would be greater. Time since menopause is likely to be a more meaningful measure than age as this reflects the amount of time in which peripheral production is the main source of endogenous estrogens.

There is evidence that the body size and breast cancer relationship may be stronger for never users of HRT (32, 35, 37-39). Our results are in concordance with others, although all tests for interaction had large *P* values. The rationale for this effect modification is that current HRT users have elevated estrogen levels, regardless of their body weight, which greatly reduces the impact on total circulating estrogen of the aromatization of androgens to estrogens in adipose tissue (37).

Several studies have reported on breast cancer risk stratified by the tumor's ER and PR status (40-47). ER+ tumors and PR+ tumors are likely to be sensitive to exposure to estrogen and progesterone, respectively, whereas ER- and PR- tumors may involve mechanisms independent of hormonal exposure (41). Many of these studies have also examined ER and PR tumors jointly as this may be a more meaningful approach biologically. The "estrogen augmented by progesterone" hypothesis of breast cancer developed by Pike and colleagues (17) clearly details why relationships with both ER and PR should be examined. We observed that the hazard ratios for ER+/PR+ tumors due to increased waist circumference, fat mass, and BMI were moderately positive, whereas the risk of ER-/PR- tumors had modest negative point estimates, although tests for homogeneity between these two subtypes were weak. Due to the small numbers of cases, we were unable to adequately assess ER+ /PR- and ER-/PR+ tumors. The evidence of an increased risk of ER+ and PR+ tumors separately is less conclusive. Some studies have found that the association with BMI differed according to PR (but not ER) status (41, 44, 47). This is in contrast to our findings, where we found that BMI (and other measures such as fat mass and waist circumference) and breast cancer relationship differed more by ER status than by PR status in women 15 years or more postmenopause. As the distribution of ER and PR tumors varies by age at diagnosis (47), it is possible that the ER status of the tumor may gain greater importance later in life.

In conclusion, our prospective study has found evidence that body size was positively associated with the risk of breast cancer in postmenopausal women. This relationship was only apparent for women who were 15 or more years postmenopause, and this raises the possibility that women could reduce their risk of breast cancer by maintaining ideal body weight after menopause. Although height and non-adipose tissue are not

amenable to intervention, increases in physical activity and/or decreases in dietary energy intake may have a beneficial effect on breast cancer risk through control of obesity.

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