Body Mass Index, Serum Sex Hormones, and Breast Cancer Risk in Postmenopausal Women

Endogenous Hormones and Breast Cancer Collaborative Group

Background: **Obesity is associated with increased breast cancer risk among postmenopausal women. We examined whether this association could be explained by the relationship of body mass index (BMI) with serum sex hormone concentrations.** *Methods:* **We analyzed individual data from eight prospective studies of postmenopausal women. Data on BMI and prediagnostic estradiol levels were available for 624 case subjects and 1669 control subjects; data on the other sex hormones were available for fewer subjects. The relative risks (RRs) with 95% confidence intervals (CIs) of breast cancer associated with increasing BMI were estimated by conditional logistic regression on case–control sets, matched within each study for age and recruitment date, and adjusted for parity. All statistical tests were two-sided.** *Results:* **Breast cancer risk increased with increasing BMI (P_{trend} = .002), and this increase in RR was substantially reduced by adjustment for serum estrogen concentrations. Adjusting for free estradiol reduced the RR for breast cancer associated with a 5 kg/m^2 increase in BMI from 1.19 (95% CI = 1.05 to 1.34) to 1.02 (95% CI = 0.89 to 1.17). The increased risk was also substantially reduced after adjusting for other estrogens (total estradiol, non–sex hormone–binding globulin–bound estradiol, estrone, and estrone sulfate), and moderately reduced after adjusting for sex hormone–binding globulin, whereas adjustment for the androgens (androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone) had little effect on the excess risk.** *Conclusion:* **The results are compatible with the hypothesis that the increase in breast cancer risk with increasing BMI among postmenopausal women is largely the result of the associated increase in estrogens, particularly bioavailable estradiol. [J Natl Cancer Inst 2003;95:1218–26]**

Breast cancer risk among postmenopausal women increases with increasing body mass index (BMI) *(1,2)*. From a recent meta-analysis, it was estimated that there is a 3% increase in risk per 1 kg/m^2 increase in BMI *(3)*. The mechanism for the association between obesity and breast cancer risk is not established, but it may result, at least in part, from an increase in the serum concentration of bioavailable estradiol, which results in turn from both an increase in the production of estrogens by aromatase in the adipose tissue and a decrease in the serum concentration of sex hormone–binding globulin (SHBG) *(4,5)*.

The Endogenous Hormones and Breast Cancer Collaborative Group was established to conduct pooled re-analyses of individual data from prospective studies of endogenous hormones and breast cancer. In an earlier article *(6)*, we described the overall associations of sex hormones with breast cancer risk in postmenopausal women, and we observed that the largest increases in risk were associated with high serum concentrations of bioavailable estradiol, estimated as free estradiol and non–SHBG-bound estradiol. Here, we examine whether sex hormone levels could explain the relationship between BMI and breast cancer risk in postmenopausal women.

Correspondence to: Timothy J. Key, DPhil, Endogenous Hormones and Breast Cancer Collaborative Group, Cancer Research U.K. Epidemiology Unit, University of Oxford, Gibson Bldg., Radcliffe Infirmary, Oxford OX2 6HE, U.K. (e-mail: Tim.Key@cancer.org.uk).

See "Appendix" for affiliations of the Endogenous Hormones and Breast Cancer Collaborative Group.

See "Notes" following "References."

SUBJECTS AND METHODS

Data Collection

Published studies were eligible for the re-analysis if they contained data on endogenous hormones and breast cancer risk using prospectively collected blood samples from postmenopausal women, as described previously (6). Nine eligible studies were identified: Columbia, MO (7,8); Guernsey, UK (9); Nurses' Health Study, USA (10); New York University Women's Health Study (NYU WHS), USA (11,12); Study of Hormones and Diet in the Etiology of Breast Tumors (ORDET), Italy (13); Rancho Bernardo, USA (14,15); Radiation Effects Research Foundation (RERF), Japan (16); Study of Osteoporotic Fractures (SOF), USA (17); and Washington County, MD, USA (18–20). Details of the recruitment of participants, informed consent, assay methods, and definitions of reproductive variables are in the original publications (7–20). Height and weight were measured by clinicians in three studies (Guernsey, ORDET, and Rancho Bernardo) and were self-reported in four studies (Columbia, Nurses' Health Study, NYU WHS, and RERF), whereas weight was measured and height at age 25 was self-reported (because women had to be at least 65 years of age at recruitment and some may have experienced osteoporotic height loss secondary to vertebral fractures) in the SOF study. Height and weight were not available for women in the Washington County study; therefore, data from this study were excluded from the current analysis.

Collaborators were asked to provide data on concentrations of the hormones estradiol (total), free estradiol, non–SHBG-bound estradiol (free plus albumin-bound estradiol), estrone, estrone sulfate, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), testosterone, and SHBG, where available. Technically, SHBG is not a hormone, but for convenience it will be referred to as such throughout this paper. Collaborators also provided data on reproductive and anthropometric factors for each woman in their study. Women with missing data for any of the following factors were excluded from the analysis: date of diagnosis of case patients, date of birth, date of blood collection, height, and weight.

All studies that contributed data to the analysis were cohorts in which blood samples were collected from healthy women who were then followed to identify those subjects who developed breast cancer. Women who were using hormone replacement therapy or other exogenous sex hormones at the time of blood collection were excluded from our analysis.

Statistical Analysis

BMI was calculated as weight in kilograms divided by the square of height in meters and categorized as less than 22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, and greater than or equal to 30.0 kg/m^2, respectively, on the basis of standard categories of BMI. Hormone concentrations were logarithmically transformed, and geometric mean concentrations by BMI category among control subjects, adjusted for study and age at blood collection (categorized as aged <55, 55–59, 60–64, 65–69, and ≥70 years), were calculated using analysis of variance. The F test was used to test for linear trends in the geometric mean hormone concentrations between the BMI categories, with the BMI categories scored 1, 2, 3, 4, and 5.

Conditional logistic regression was used to calculate the relative risk (RR) of breast cancer by BMI category, relative to those

with a BMI of less than 22.5 kg/m^2 (category 1). For our analyses, we preserved the original matching in the six studies that used a nested matched case–control design [details of this matching are provided in the original publications (7–13,16)]. For two studies, which had a case–cohort (17) or full cohort (14,15) design, nested case–control sets were generated from within the cohorts and matched as closely as possible for age and date of blood collection so that the same statistical analysis could be conducted across all eight studies, as described previously (6). Because matching was conducted within studies, only women from the same study are compared directly. Within this pooled dataset, there was no statistically significant heterogeneity between studies regarding the associations between serum hormone concentrations and breast cancer risk (6).

We investigated the association between BMI and breast cancer risk after adjusting for various established risk factors for breast cancer: age at menarche (<12, 12–13, ≥14 years); type of menopause (natural, surgical); age at menopause (<45, 45–49, 50–54, ≥55 years; natural postmenopausal women only); time since menopause (0–4, 5–14, ≥15 years; natural postmenopausal women only); parity (0, 1, 2, 3, ≥4 full-term pregnancies); age at first full-term pregnancy (<20, 20–24, 25–29, ≥30 years; parous women only); previous use of oral contraceptives (never, ever); and previous use of hormone replacement therapy (never, ever).

To assess the extent to which hormone concentrations might account for the association between BMI and breast cancer risk, the RR of breast cancer associated with BMI was calculated with and without adjustment for the within-study quintile of hormone concentration for each hormone in succession. To facilitate comparison of the adjusted and unadjusted RRs, the analysis for each hormone was restricted to informative matched sets of women with both BMI and hormone measurements. Unfortunately, not all of the hormones were measured in each of the studies, so that the comparisons for each hormone were made using data from different subsets of the studies.

All analyses were performed using STATA (21). Mean hormone concentrations and RRs were calculated with their 95% confidence intervals (CIs). Heterogeneity between RRs and linear trends in RRs (obtained by scoring the BMI categories from 1 to 5) were assessed by χ^2 tests. All statistical tests were two-sided.

RESULTS

BMI was available for a total of 630 case subjects and 1704 control subjects. Table 1 shows the numbers of case and control subjects in each study with a BMI measurement, mean age, time to diagnosis in case subjects, the numbers in each BMI category, and the mean BMI. In six of the eight studies, mean BMI was higher in the case subjects than in the control subjects. Overall, mean BMI among case subjects was 26.5 (standard deviation [SD] ± 4.6) kg/m^2 compared with 25.8 (SD ± 4.4) kg/m^2 among control subjects, and there was a higher proportion of case subjects than control subjects in each of the three heaviest BMI categories.

BMI was positively associated with breast cancer risk. When women with a BMI of less than 22.5 kg/m^2 were the reference group for the whole dataset, the RRs of breast cancer in ascending order of BMI categories were 1.10 (95% CI = 0.83 to 1.46), 1.45 (95% CI = 1.08 to 1.95), 1.62 (95% CI = 1.17 to 2.24), and 1.36 (95% CI = 1.00 to 1.85), respectively (P_{trend} = .004);

Table 1. Characteristics and body mass index (BMI) by case–control status and study*

Study†	Subjects	No.	Mean age, y	Mean y to diagnosis	BMI, kg/m²					
					<22.5	22.5–24.9	25.0–27.4	27.5–29.9	≥30.0	Mean (SD)
Columbia, MO, USA (7,8)	Case	71	61.4	3.3	6 (8.5)	23 (32.4)	16 (22.5)	16 (22.5)	10 (14.1)	26.5 (3.8)
	Control	133	61.8	—	23 (17.3)	39 (29.3)	29 (21.8)	13 (9.8)	29 (21.8)	26.6 (5.3)
Guernsey, UK (9)	Case	61	58.6	7.7	9 (14.8)	15 (24.6)	18 (29.5)	11 (18.0)	8 (13.1)	26.0 (3.2)
	Control	177	58.5	—	33 (18.6)	49 (27.7)	48 (27.1)	26 (14.7)	21 (11.9)	25.6 (3.8)
Nurses' Health Study, USA (10)	Case	155	61.8	2.4	32 (20.6)	28 (18.1)	36 (23.2)	20 (12.9)	39 (25.2)	26.9 (5.5)
	Control	310	61.8	—	68 (21.9)	83 (26.8)	59 (19.0)	37 (11.9)	63 (20.3)	26.2 (4.7)
NYU WHS, USA (11,12)	Case	127	58.7	2.0	21 (16.5)	33 (26.0)	31 (24.4)	23 (18.1)	19 (15.0)	26.1 (4.2)
	Control	246	58.5	—	73 (29.7)	71 (28.9)	48 (19.5)	20 (8.1)	34 (13.8)	25.1 (4.5)
ORDET, Italy (13)	Case	65	58.6	2.6	8 (12.3)	17 (26.2)	14 (21.5)	14 (21.5)	12 (18.5)	26.5 (4.0)
	Control	264	58.1	—	41 (15.5)	60 (22.7)	58 (22.0)	56 (21.2)	49 (18.6)	26.7 (4.1)
Rancho Bernardo, USA (14,15)	Case	31	64.3	10.4	9 (29.0)	8 (25.8)	7 (22.6)	4 (12.9)	3 (9.7)	24.8 (3.3)
	Control	286	64.9	—	86 (30.1)	100 (35.0)	50 (17.5)	26 (9.1)	24 (8.4)	24.5 (3.7)
RERF, Japan (16)	Case	23	62.6	7.5	9 (39.1)	4 (17.4)	8 (34.8)	2 (8.7)	0 (0.0)	23.5 (3.3)
	Control	45	62.3	—	22 (48.9)	11 (24.4)	7 (15.6)	3 (6.7)	2 (4.4)	22.3 (4.3)
SOF, USA (17)	Case	97	70.9	3.2	16 (16.5)	24 (24.7)	17 (17.5)	14 (14.4)	26 (26.8)	27.6 (5.4)
	Control	243	71.8	—	35 (14.4)	63 (25.9)	53 (21.8)	45 (18.5)	47 (19.3)	26.5 (4.3)
Total	Case	630	62.0	3.6	110 (17.5)	152 (24.1)	147 (23.3)	104 (16.5)	117 (18.6)	26.5 (4.6)
	Control	1704	62.4	—	381 (22.4)	476 (27.9)	352 (20.7)	226 (13.3)	269 (15.8)	25.8 (4.4)

*SD = standard deviation; NYU WHS = New York University Women's Health Study; ORDET = Study of Hormones and Diet in the Etiology of Breast Tumors; RERF = Radiation Effects Research Foundation; SOF = Study of Osteoporotic Fractures.

†For each study and in total, the numbers of case and control subjects with a BMI measurement, their mean age at blood collection, and years from blood collection to diagnosis (case subjects only), the numbers (percentage) in each BMI category, and the mean (SD) BMI are shown.

there was no statistically significant heterogeneity between studies in the linear relationship between BMI and breast cancer risk ($\chi^2_7 = 3.18$, $P = .87$). We also examined the association between BMI and breast cancer risk after adjustment for each of nine risk factors for breast cancer: age at menarche, type of menopause, age at menopause, years since menopause (in natural postmenopausal women only), number of full-term pregnancies, age at first full-term pregnancy, past use of oral contraceptives, past use of hormone replacement therapy, and past use of either oral contraceptives or hormone replacement therapy. With the exception of number of full-term pregnancies and, to a lesser extent, age at first full-term pregnancy (in parous women only), adjustment for these risk factors had a negligible effect on the association between BMI and breast cancer risk (changes in the RR in the highest category of BMI were ≤1%; data not shown). Adjustment for number of full-term pregnancies and age at first full-term pregnancy both increased the magnitude of the association between BMI and breast cancer risk. Data on number of full-term pregnancies were available for almost all subjects; therefore, we chose to adjust all subsequent analyses of the association between BMI and breast cancer risk for the number of full-term pregnancies. After adjusting for the number of full-term pregnancies, relative to women with a BMI of less than 22.5 kg/m², the RRs of breast cancer in ascending order of BMI categories were 1.17 (95% CI = 0.87 to 1.57), 1.50 (95% CI = 1.10 to 2.04), 1.78 (95% CI = 1.27 to 2.49), and 1.50 (95% CI = 1.09 to 2.06), respectively ($P_{\text{trend}} = .001$).

We next considered the geometric mean hormone concentrations among control subjects by BMI category, adjusted for study and age at blood collection (Table 2). Each of the estrogens (estradiol, free estradiol, non–SHBG-bound estradiol, estrone, and estrone sulfate) was strongly and statistically significantly positively associated with BMI, with the mean concentration in obese women (i.e., women with BMI ≥30.0 kg/m²)

between 60% and 219% higher than that in thin women (i.e., women with BMI <22.5 kg/m²). There were no statistically significant associations between DHEA or DHEAS and BMI. There was a weak positive association between androstenedione and BMI, with the mean concentration in obese women being 12% higher than the mean concentration in thin women. Testosterone was positively associated with BMI, with the mean concentration in obese women being 20% higher than the mean concentration in thin women, whereas SHBG was strongly inversely associated with BMI, with the mean concentration in obese women being 44% lower than the mean concentration in thin women.

We evaluated the associations between BMI and hormone levels among control subjects, and the RR of breast cancer in relation to BMI before and after adjustment for serum hormone concentration (Fig. 1). For each hormone, the geometric mean hormone concentrations by BMI among control subjects (adjusted for study and age at blood collection) are shown in the left panels, scaled such that the mean concentration in the lowest BMI category equals 1.0. The right panels show the RRs for breast cancer by BMI category, unadjusted and adjusted for each hormone individually. The numbers of case and control subjects vary considerably with each hormone because each study measured levels of some but not all hormones, with the exception of estradiol, which was measured in all studies. Therefore, the unadjusted RRs, and their χ^2 values for linear trend, also vary considerably from one hormone to another. However, because the same women were included in the unadjusted and adjusted conditional logistic regression analyses for each hormone, the adjusted RRs and their χ^2 values for linear trend are directly comparable to the corresponding unadjusted values. For each of the five estrogens measured, the association of BMI with breast cancer risk was substantially attenuated after adjustment for the concentration of that estrogen in serum (Fig. 1). By contrast,

Table 2. Geometric mean hormone concentrations among controls by body mass index (BMI), adjusted for study and age at blood collection*

Hormone	No. of case/control subjects	BMI (kg/m²)					P†
		<22.5	22.5–24.9	25.0–27.4	27.5–29.9	≥30.0	
Estradiol, pmol/L	624/1669	30.0 (28.3 to 31.8)	34.8 (33.0 to 36.7)	37.3 (35.1 to 39.7)	43.2 (40.0 to 46.6)	54.9 (51.2 to 58.9)	<.001
Free estradiol, pmol/L	447/925	0.40 (0.37 to 0.44)	0.51 (0.47 to 0.55)	0.56 (0.51 to 0.62)	0.68 (0.61 to 0.77)	1.00 (0.91 to 1.11)	<.001
Non–SHBG-bound estradiol, pmol/L	472/971	7.5 (6.8 to 8.3)	10.0 (9.2 to 11.0)	11.9 (10.8 to 13.2)	16.2 (14.2 to 18.5)	23.9 (21.4 to 26.6)	<.001
Estrone, pmol/L	439/1130	72.8 (68.2 to 77.6)	80.0 (75.5 to 84.7)	85.4 (79.6 to 91.5)	95.7 (87.5 to 104.7)	116.7 (108.0 to 126.1)	<.001
Estrone sulfate, pmol/L	312/664	400 (356 to 450)	457 (415 to 503)	523 (468 to 584)	585 (512 to 669)	733 (657 to 819)	<.001
Androstenedione, nmol/L	346/954	1.73 (1.60 to 1.86)	1.74 (1.64 to 1.85)	1.87 (1.74 to 2.02)	1.82 (1.65 to 2.01)	1.94 (1.79 to 2.11)	.021
DHEA, nmol/L	209/405	6.1 (5.3 to 6.9)	6.1 (5.5 to 6.9)	7.1 (6.2 to 8.1)	6.5 (5.4 to 7.7)	5.7 (5.0 to 6.4)	.583
DHEAS, nmol/L	552/1466	1737 (1605 to 1879)	1887 (1760 to 2024)	1881 (1729 to 2047)	1903 (1716 to 2111)	1720 (1569 to 1886)	.949
Testosterone, nmol/L	583/1595	0.76 (0.72 to 0.81)	0.77 (0.73 to 0.81)	0.78 (0.73 to 0.83)	0.82 (0.75 to 0.88)	0.91 (0.85 to 0.98)	<.001
SHBG, nmol/L	343/1117	52.8 (49.1 to 56.9)	42.0 (39.5 to 44.7)	38.6 (35.9 to 41.5)	32.3 (29.5 to 35.2)	29.6 (27.2 to 32.3)	<.001

*DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone–binding globulin. Table shows the numbers of case and control subjects with both a hormone level and a BMI measurement for each hormone, plus the geometric mean hormone concentration (95% confidence interval) among control subjects in each BMI category, adjusted for study and age at blood collection.

†The P value refers to an F test of trend in the geometric mean hormone concentrations across the five BMI categories, with the categories scored 1, 2, 3, 4, and 5.

adjustment for each of the androgen concentrations had a negligible effect on the association between BMI and breast cancer risk (Fig. 1). Adjustment for SHBG produced a moderate attenuation of this association.

The effects of adjustment for serum hormone concentrations on the association of BMI with breast cancer risk are summarized in Table 3. The number of studies contributing data varies between hormones; therefore, the unadjusted RRs associated with a 5 kg/m² increase in BMI (equivalent to the difference between the upper level of normal [25.0 kg/m²] and the lower level of obese [30.0 kg/m²]) varied according to which hormone was examined. We calculated the estimated RR for breast cancer associated with an increase in BMI of 5 kg/m² and the corresponding estimate after adjustment for each hormone in turn (Table 3). Adjusting for free estradiol resulted in the greatest reduction in RR for breast cancer associated with a 5 kg/m² increase in BMI from 1.19 (95% CI = 1.05 to 1.34) to 1.02 (95% CI = 0.89 to 1.17). Adjustments for other estrogens also resulted in substantial reductions in the RR from 1.18 to 1.07 for total estradiol, from 1.20 to 1.05 for non–SHBG-bound estradiol, from 1.20 to 1.10 for estrone, and from 1.14 to 1.07 for estrone sulfate (Table 3). Adjustment for the androgens (androstenedione, DHEA, DHEAS, and testosterone) and for SHBG reduced the RR associated with increasing BMI by much less than adjustment for the estrogens (Table 3).

We next examined whether the associations of BMI and hormones with breast cancer risk varied according to whether women had previously used hormone replacement therapy. Among women who had never used hormone replacement therapy (296 case subjects and 571 control subjects with estradiol measurements), the unadjusted RR per 5 kg/m² increase in BMI was 1.22 (95% CI = 1.04 to 1.44); the RR was reduced to 1.09 (95% CI = 0.91 to 1.30) after adjusting for estradiol. Among women who had previously used hormone replacement therapy (89 case subjects and 114 control subjects with estradiol measurements), the unadjusted RR per 5 kg/m² increase in BMI was 1.16 (95% CI = 0.85 to 1.59); the RR was reduced to 1.09 (95% CI = 0.75 to 1.58) after adjusting for estradiol. Similar patterns were observed for all other hormones, but the numbers of case subjects were smaller for all other hormones than for estradiol.

Further analyses were conducted to examine whether the as-

sociations of the hormones with breast cancer risk would be altered by adjustment for BMI. Adjustment for BMI did not substantially change the associations between any hormone level and breast cancer risk, and all associations remained statistically significant. For example, the RR of breast cancer for women in the top quintile of total estradiol compared with those in the lowest quintile was 2.00 (95% CI = 1.47 to 2.71) without adjustment for BMI and 1.92 (95% CI = 1.37 to 2.67) after adjustment for BMI; for free estradiol, the RR of breast cancer for women in the top quintile compared with those in the lowest quintile was 2.62 (95% CI = 1.77 to 3.88) without adjustment for BMI and 2.73 (95% CI = 1.76 to 4.22) after adjustment for BMI.

DISCUSSION

The results of this collaborative analysis suggest that the increase in breast cancer risk with increasing BMI among postmenopausal women is largely the result of the associated increase in estrogens. The strengths of this analysis are that the data and serum samples were all collected prospectively and that we have been able to analyze all the available data from published studies worldwide. However, the pooled dataset is still relatively small, with data on BMI and endogenous estradiol levels available for just over 600 women who developed breast cancer and data on the other hormones studied available for fewer women. BMI was calculated from self-reported data in five of the eight studies, but validation studies have consistently shown high correlations between measured and self-reported data on both height and weight (22). Because BMI is based only on height and weight, it does not allow for variation among women in the proportions of lean mass and fat mass in the body; however, in these cohorts of postmenopausal women, it is unlikely that there are many very muscular individuals, and BMI is likely to be strongly associated with fat mass.

Consistent with other studies of postmenopausal women conducted in many parts of the world, breast cancer risk in the eight studies increased with increasing BMI. The magnitude of this association, an increase in risk of about 18% per 5 kg/m² increase in BMI, is similar to the estimate from a recent meta-analysis of a 16% increase in risk per 5 kg/m² increase in BMI (3). The association of BMI with breast cancer risk varied some-
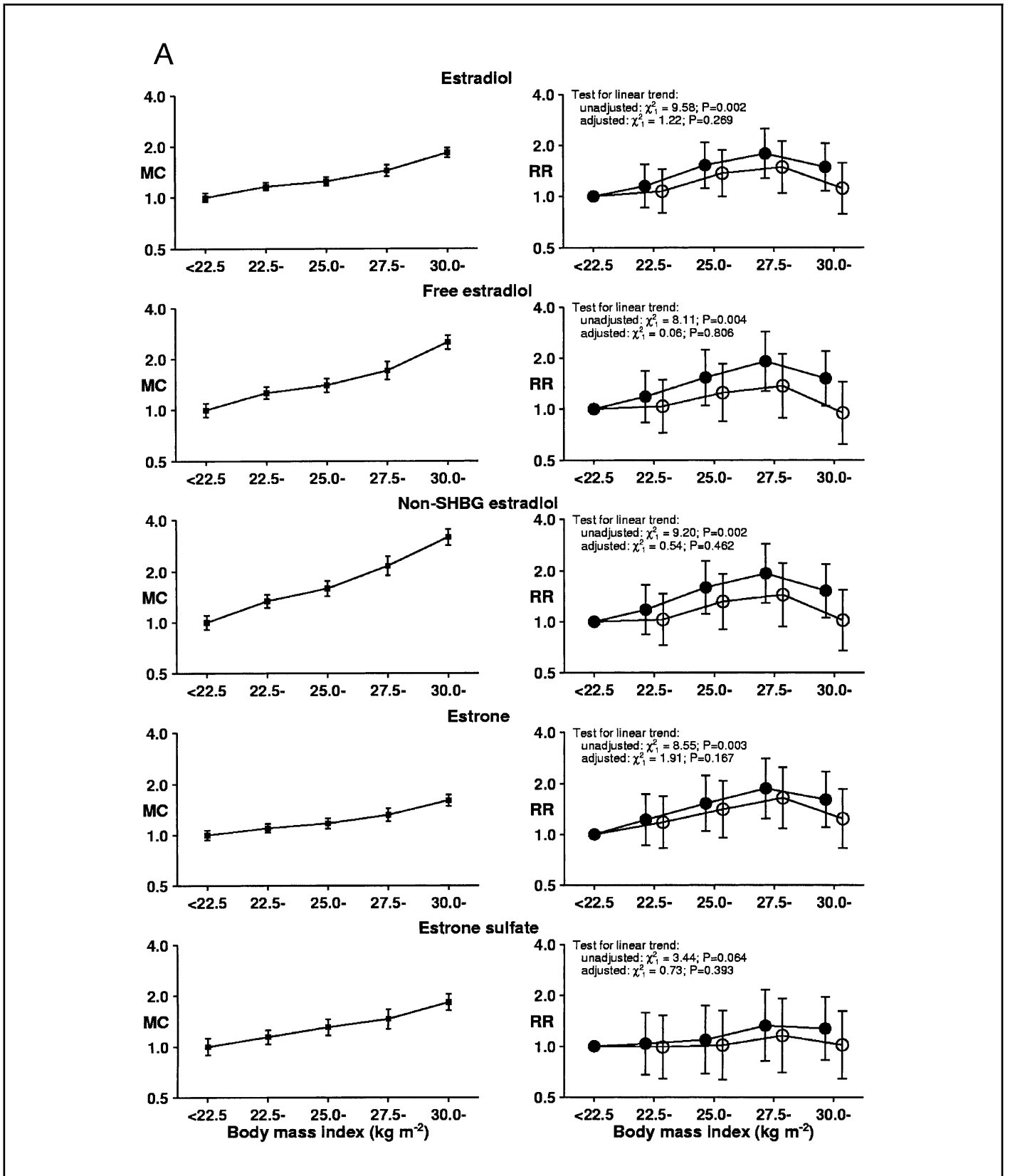
Fig. 1. Geometric mean hormone concentration (MC) and relative risk (RR) for breast cancer by body mass index (BMI) category, showing 95% confidence intervals and the effects of adjusting for hormone concentration. **Left panels:** geometric mean hormone concentration among control subjects in each BMI category, adjusted for study and age at blood collection and scaled such that the mean concentration in the lowest BMI category equals 1. **Filled squares** indicate the mean concentration (relative to the mean in the lowest BMI category), and **vertical lines** show the 95% confidence interval. **Right panels:** relative risk for breast cancer for women in each BMI category compared with those in the lowest category. **Filled circles** indicate the relative risks adjusted only for the number of full-term pregnancies, and **open circles** indicate the relative risks further adjusted for quintile of hormone concentration, with **vertical lines** showing the 95% confidence intervals. DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone–binding globulin. (Continued on facing page).
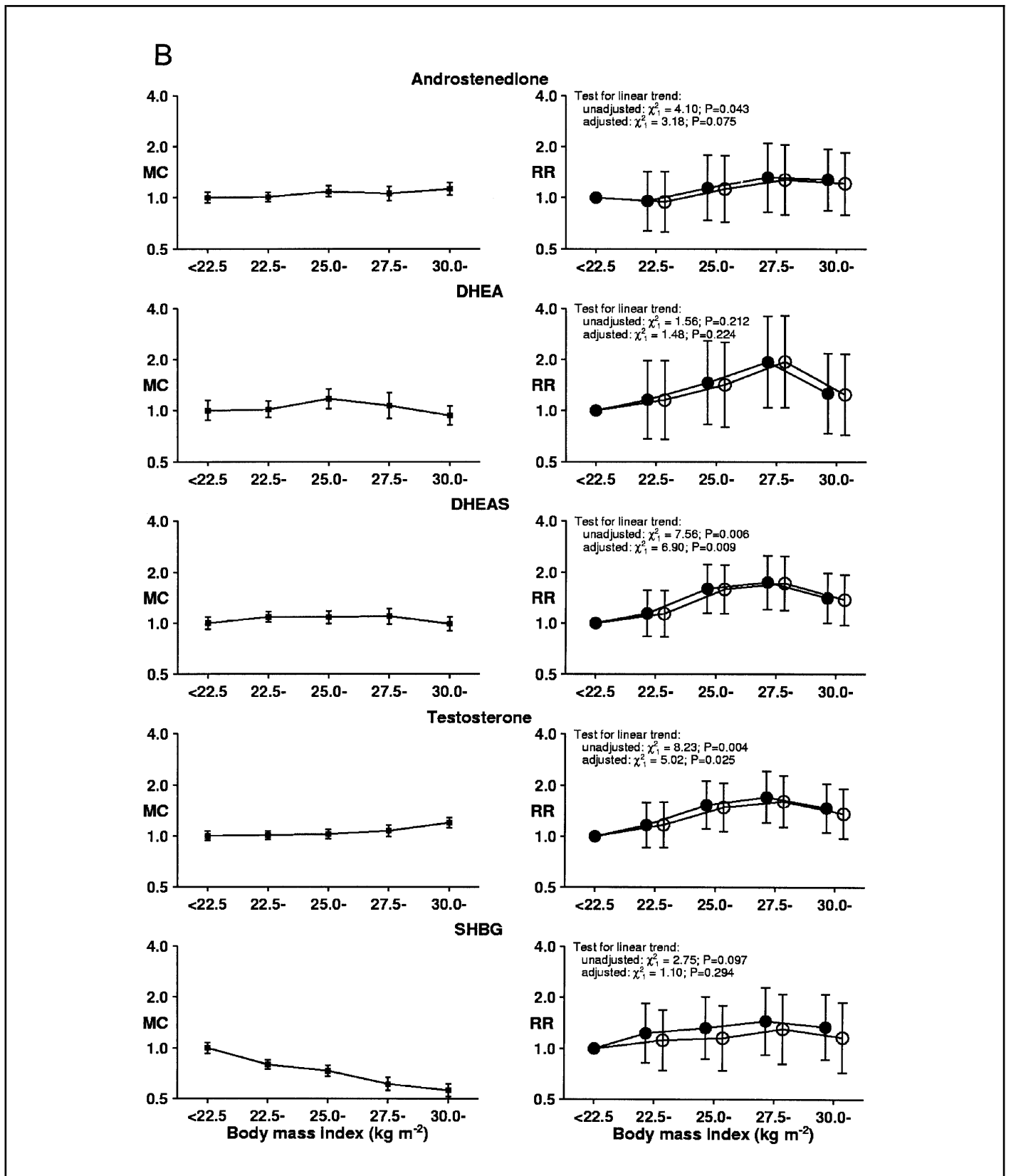
Fig. 1. (Continued from facing page).

what because not all studies included all hormones, but this variation may reasonably be attributed to chance. The only risk factor for breast cancer that appreciably confounded the relationship between BMI and breast cancer risk was parity; high parity is associated with reduced breast cancer risk and with higher BMI, and therefore adjustment for parity slightly strengthened the association of BMI with breast cancer risk.

Although breast cancer risk increased with increasing BMI, risk did not increase further when BMI exceeded 30 kg/m^2. Indeed, the RR was lower in women with the highest BMI than

Table 3. Increase in risk for breast cancer associated with a 5 kg/m^2 increase in body mass index (BMI) before and after adjustment for serum hormone concentration*

Hormone measurement adjusted for	No. of studies included	No. of case/control subjects	Relative risk (95% CI) per 5 kg/m^2 increase in BMI†	Relative risk (95% CI) per 5 kg/m^2 increase in BMI, adjusted for hormone level
Estradiol	8	606/1440	1.18 (1.06 to 1.31)	1.07 (0.95 to 1.20)
Free estradiol	4	443/906	1.19 (1.05 to 1.34)	1.02 (0.89 to 1.17)
Non–SHBG-bound estradiol	5	465/946	1.20 (1.07 to 1.35)	1.05 (0.92 to 1.20)
Estrone	5	425/932	1.20 (1.06 to 1.35)	1.10 (0.96 to 1.25)
Estrone sulfate	3	308/643	1.14 (0.99 to 1.30)	1.07 (0.92 to 1.23)
Androstenedione	4	332/749	1.15 (1.00 to 1.31)	1.13 (0.99 to 1.29)
DHEA	2	207/373	1.11 (0.94 to 1.32)	1.11 (0.94 to 1.32)
DHEAS	7	534/1239	1.17 (1.05 to 1.31)	1.16 (1.04 to 1.30)
Testosterone	7	569/1371	1.17 (1.05 to 1.31)	1.13 (1.02 to 1.27)
SHBG	6	329/906	1.13 (0.98 to 1.32)	1.09 (0.93 to 1.28)

*DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone–binding globulin.

†Relative risks for breast cancer per 5 kg/m^2 increase in BMI were estimated using conditional logistic regression analysis on case–control sets matched within each study for age and date of recruitment, adjusted for number of full-term pregnancies.

in those in the next lowest category (27.5–29.9 kg/m^2). A similar pattern was observed in a pooled analysis of prospective studies (1), in which the authors noted that breast cancer risk among postmenopausal women statistically significantly increased with increasing BMI but did not increase further when BMI exceeded 28 kg/m^2. One possible explanation for this apparent plateau in the relationship between BMI and breast cancer risk is that it might be associated with the residual effect of the lower RR for breast cancer among obese premenopausal women that has been observed in Western countries. The pooled analysis of prospective studies (1) and the recent review by the International Agency for Research on Cancer (2) observed that this reduction in risk in premenopausal women does not appear to be observed below a BMI of 28 kg/m^2. Thus, postmenopausal women with a BMI of 30 kg/m^2 and above, many of whom would also have been obese before menopause, may have only a moderate increase in breast cancer risk because of a residual reduction in postmenopausal risk accumulated during their premenopausal life (23,24).

The analyses among control women showed strong associations between BMI and serum concentrations of most hormones, as was expected from the results of previous studies (25,26). All of the estrogen measures increased with increasing BMI, with the largest proportional increases for free estradiol and non–SHBG-bound estradiol. First described by Siiteri et al. (5), the increase in free estradiol is the result of the dual effect of obesity in increasing estrogen production and depressing SHBG levels, leading to a marked increase in the amount of estradiol that is not bound to SHBG. Among the androgens, DHEA and DHEAS levels were not associated with BMI, whereas both androstenedione and testosterone levels were moderately higher in obese women than in thin women, but the magnitude of these associations was much smaller than those for estrogens.

The result of adjusting for serum hormones on the association of BMI with breast cancer risk showed large effects for the estrogens, a moderate effect for SHBG, and negligible impact for the androgens. The biggest impact was seen after adjusting for free estradiol, which reduced the excess risk for breast cancer associated with a 5 kg/m^2 increase in BMI from 19% to 2%. Adjusting for non–SHBG-bound estradiol, or for total estradiol, also substantially reduced the association of BMI with breast cancer risk. The results do not allow us to determine which measure of estradiol is most important but strongly suggest that the increased breast cancer risk in obese postmenopausal women

is largely due to the associated increase in bioavailable estradiol (as estimated by either free estradiol or non–SHBG-bound estradiol).

The analyses reported in this article were all based on single hormone measures for each woman. Measurements of hormone concentrations are subject to error associated with assay variation and short-term fluctuations in serum levels within individual women. These sources of variation are thought to be effectively random; therefore, it is likely that the observed associations between hormone concentrations and breast cancer risk are underestimates of the true associations (10). Furthermore, any change in the estimates of the risk associated with increasing BMI after adjustment for specific hormones would be related to the degree of measurement error in that hormone. Therefore, some of the differences in the apparent effect of hormones on the association of BMI with risk may be due not to intrinsic biologic effects but to artifacts of differences in the precision of hormone assays. Data were not available to allow us to estimate the impact of measurement error in hormone concentrations on the attenuation of the association between BMI and breast cancer risk caused by adjustment for estrogens. However, in one case–control study of endometrial cancer, endogenous hormones, and BMI, Potischman et al. (27) concluded that adjustment for measurement error in hormone determinations had only a small impact on the degree of attenuation of the association of BMI with risk effected by adjustment for estrone.

The possible role of serum androgens in the etiology of breast cancer remains unclear. We previously reported that androgens are associated with breast cancer risk in postmenopausal women (6), but the analyses here show that, by contrast with the impact of adjusting for estrogens, adjusting for androgens had little effect on the association between BMI and breast cancer risk. This is consistent with the absence of strong associations between BMI and serum androgen concentrations.

It is possible that the association between BMI and breast cancer risk might be partly explained by other biochemical variables that we did not measure. Other hormones that may be associated with breast cancer risk are prolactin, insulin-like growth factor-I, and insulin. Prolactin and insulin-like growth factor-I are poor candidates to explain this relationship, however, because neither is positively associated with BMI in postmenopausal women (28,29). Levels of insulin-like growth factor binding protein 1 decrease with increasing adiposity, which might increase the bioavailability of insulin-like growth factor-I

(30), but available prospective data have not shown any definite association between insulin-like growth factor binding protein 1 and breast cancer risk *(31,32).* Insulin itself is strongly positively correlated with BMI and has been hypothesized to be an intermediate factor in the relationship between obesity and breast cancer risk *(33).* However, prospective data relating to this hypothesis involving insulin, C-peptide, and glucose have not shown any clear association with breast cancer risk in postmenopausal women *(32,34–36).*

Obesity is a modifiable risk factor for breast cancer, whereas several of the long-established risk factors are either fixed (family history and genotype) or not amenable to modification (age at menarche, number of pregnancies and ages at pregnancy, and age at menopause). The association between obesity and breast cancer risk is important because obesity may be the principal contributing factor for a substantial number of cases of breast cancer and because the prevalence of obesity is high and increasing. In the United States, for example, the estimated prevalence of obesity in women aged 60–74 years increased from 29% in 1988–1994 to 40% in 1999–2000 *(37).* Furthermore, obesity is associated with poor survival among women with breast cancer, and the association of obesity with mortality from breast cancer appears to be stronger than the association with incidence *(38).* The results reported here suggest that the increase in breast cancer risk with increasing BMI among postmenopausal women is largely the result of the associated increase in estrogens, particularly bioavailable estradiol.

APPENDIX: MEMBERS AND AFFILIATIONS OF THE ENDOGENOUS HORMONES AND BREAST CANCER COLLABORATIVE GROUP

Affiliation of the analysis and writing group: T. J. Key, P. N. Appleby, G. K. Reeves, A. Roddam, Cancer Research U.K. Epidemiology Unit, University of Oxford.

Columbia, MO, United States: J. F. Dorgan, Fox Chase Cancer Center, Philadelphia, PA; C. Longcope, Departments of Obstetrics and Gynecology and Medicine, University of Massachusetts Medical School, Worcester; F. Z. Stanczyk, Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles; H. E. Stephenson, Jr., Department of Surgery, University of Missouri Health Sciences Center, Columbia; R. T. Falk, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; R. Miller, Cancer Screening Services, Ellis Fischel Cancer Center, Columbia, MO; A. Schatzkin, Division of Cancer Epidemiology and Genetics, National Cancer Institute.

Guernsey, United Kingdom: D. S. Allen, I. S. Fentiman, T. J. Key, D. Y. Wang, Cancer Research U.K., Oxford; M. Dowsett, Department of Academic Biochemistry, Royal Marsden Hospital, London; H. V. Thomas, Department of Psychological Medicine, University of Wales College of Medicine, Cardiff.

Nurses' Health Study, United States: S. E. Hankinson for the Nurses' Health Study Research Group, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and Department of Epidemiology, Harvard School of Public Health, Boston.

NYU WHS, United States: P. Toniolo, A. Akhmedkhanov, Department of Obstetrics and Gynecology, New York University School of Medicine, New York, NY; K. Koenig, R. E. Shore, A. Zeleniuch-Jacquotte, Nelson Institute of Environmental Medicine, New York University School of Medicine.

ORDET, Italy: F. Berrino, Division of Epidemiology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan; P. Muti, Department of Social and Preventive Medicine, University at Buffalo, State University of New York, and Istituto Nazionale per lo Studio e la Cura dei Tumori; A. Micheli, V. Krogh, S. Sieri, V. Pala, E. Venturelli, G. Secreto, Istituto Nazionale per lo Studio e la Cura dei Tumori.

Rancho Bernardo, United States: E. Barrett-Connor, G. A. Laughlin, Department of Family and Preventive Medicine, University of California at San Diego.

RERF, Japan: M. Kabuto, Environmental Risk Research Division, National Institute for Environmental Studies, Ibaraki; S. Akiba, Department of Public Health, Faculty of Medicine, Kagoshima University, Kagoshima; R. G. Stevens, Department of Community Medicine, University of Connecticut Health Center, Farmington; K. Neriishi, Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima; C. E. Land, Radiation Epidemiology Branch, National Cancer Institute, Bethesda, MD.

SOF, United States: J. A. Cauley, L. H. Kuller, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA; S. R. Cummings, Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco; and the Study of Osteoporotic Fractures Research Group.

Washington County (MD), United States: K. J. Helzlsouer, A. J. Alberg, T. L. Bush, G. W. Comstock, Department of Epidemiology, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD; G. B. Gordon, Oncology Center and Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine; S. R. Miller, Department of Health Policy and Management, The Johns Hopkins University School of Hygiene and Public Health; C. Longcope, Department of Obstetrics and Gynecology and Medicine, University of Massachusetts Medical School, Worcester.

REFERENCES

(1) van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000;152:514–27.

(2) International Agency for Research on Cancer (IARC). Weight and weight control: breast cancer. In: IARC Handbooks of Cancer Prevention. Weight control and physical activity. Lyon (France): IARC Press; 2002. p. 95–112.

(3) Bergström A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001;91:421–30.

(4) Judd HL, Shamonki IM, Frumar AM, Lagasse LD. Origin of serum estradiol in postmenopausal women. Obstet Gynecol 1982;59:680–6.

(5) Siiteri PK, Hammond GL, Nisker JA. Increased availability of serum estrogens in breast cancer: a new hypothesis. In: Pike MC, Siiteri PK, Welsch CW, editors. Banbury Report 8. Hormones and breast cancer. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 1981. p. 87–106.

(6) Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.

(7) Dorgan JF, Longcope C, Stephenson HE, Falk RT, Miller R, Franz C, et al. Relation of prediagnostic serum estrogen and androgen levels to breast cancer risk. Cancer Epidemiol Biomarkers Prev 1996;5:533–9.

(8) Dorgan JF, Stanczyk FZ, Longcope C, Stephenson HE, Chang L, Miller R, et al. Relationship of serum dehydroepiandrosterone (DHEA), DHEA sulfate, and 5-androstene-3 beta, 17 beta-diol to risk of breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 1997;6:177–81.

(9) Thomas HV, Key TJ, Allen DS, Moore JW, Dowsett M, Fentiman IS, et al. A prospective study of endogenous serum hormone concentrations and breast cancer risk in post-menopausal women on the island of Guernsey. Br J Cancer 1997;76:401–5.

(10) Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 1998;90:1292–9.

(11) Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE, et al. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 1995;87:190–7.

(12) Zeleniuch-Jacquotte A, Bruning PF, Bonfrer JM, Koenig KL, Shore RE, Kim MY, et al. Relation of serum levels of testosterone and dehydroepiandrosterone sulfate to risk of breast cancer in postmenopausal women. Am J Epidemiol 1997;145:1030–8.

(13) Berrino F, Muti P, Micheli A, Bolelli G, Krogh V, Sciajno R, et al. Serum sex hormone levels after menopause and subsequent breast cancer. J Natl Cancer Inst 1996;88:291–6.

(14) Barrett-Connor E, Friedlander NJ, Khaw KT. Dehydroepiandrosterone sulfate and breast cancer risk. Cancer Res 1990;50:6571–4.

(15) Garland CF, Friedlander NJ, Barrett-Connor E, Khaw KT. Sex hormones and postmenopausal breast cancer: a prospective study in an adult community. Am J Epidemiol 1992;135:1220–30.

(16) Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE. A prospective study of estradiol and breast cancer in Japanese women. Cancer Epidemiol Biomarkers Prev 2000;9:575–9.

(17) Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W, Cummings SR. Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1999;130:270–7.

(18) Gordon GB, Bush TL, Helzlsouer KJ, Miller SR, Comstock GW. Relationship of serum levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate to the risk of developing postmenopausal breast cancer. Cancer Res 1990;50:3859–62.

(19) Helzlsouer KJ, Alberg AJ, Bush TL, Longcope C, Gordon GB, Comstock GW. A prospective study of endogenous hormones and breast cancer. Cancer Detect Prev 1994;18:79–85.

(20) Wysowski DK, Comstock GW, Helsing KJ, Lau HL. Sex hormone levels in serum in relation to the development of breast cancer. Am J Epidemiol 1987;125:791–9.

(21) StataCorp. 2001. Stata Statistical Software: Release 7.0. College Station, TX. Stata Corporation.

(22) Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr 2002;5:561–5.

(23) Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol 2000;152:950–64.

(24) Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997;278:1407–11.

(25) Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11:1531–43.

(26) Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. Proc Nutr Soc 2001;60:81–9.

(27) Potischman N, Gail MH, Troisi R, Wacholder S, Hoover RN. Measurement error does not explain the persistence of a body mass index association with endometrial cancer after adjustment for endogenous hormones. Epidemiology 1999;10:76–9.

(28) Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995;87:1297–302.

(29) Lukanova A, Toniolo P, Akhmedkhanov A, Hunt K, Rinaldi S, Zeleniuch-Jacquotte A, et al. A cross-sectional study of IGF-I determinants in women. Eur J Cancer Prev 2001;10:443–52.

(30) McGuire WL, Jackson JG, Figueroa JA, Shimasaki S, Powell DR, Yee D. Regulation of insulin-like growth factor-binding protein (IGFBP) expression by breast cancer cells: use of IGFBP-1 as an inhibitor of insulin-like growth factor action. J Natl Cancer Inst 1992;84:1336–41.

(31) Kaaks R, Lundin E, Rinaldi S, Manjer J, Biessy C, Soderberg S, et al. Prospective study of IGF-I, IGF-binding proteins, and breast cancer risk, in northern and southern Sweden. Cancer Causes Control 2002;13:307–16.

(32) Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, Schunemann HJ, et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002;11:1361–8.

(33) Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control 1996;7:605–25.

(34) Mink PJ, Shahar E, Rosamond WD, Alberg AJ, Folsom AR. Serum insulin and glucose levels and breast cancer incidence: the atherosclerosis risk in communities study. Am J Epidemiol 2002;156:349–52.

(35) Toniolo P, Bruning PF, Akhmedkhanov A, Bonfrer JM, Koenig KL, Lukanova A, et al. Serum insulin-like growth factor-I and breast cancer. Int J Cancer 2000;88:828–32.

(36) Manjer J, Kaaks R, Riboli E, Berglund G. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmö Preventive Project. Eur J Cancer Prev 2001;10:33–42.

(37) Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002;288:1723–7.

(38) Petrelli JM, Calle EE, Rodriguez C, Thun MJ. Body mass index, height, and postmenopausal breast cancer mortality in a prospective cohort of US women. Cancer Causes Control 2002;13:325–32.

NOTES