

Endogenous Sex Hormones and Breast Cancer in Postmenopausal Women: Reanalysis of Nine Prospective Studies

The Endogenous Hormones and Breast Cancer Collaborative Group

Background: Reproductive and hormonal factors are involved in the etiology of breast cancer, but there are only a few prospective studies on endogenous sex hormone levels and breast cancer risk. We reanalyzed the worldwide data from prospective studies to examine the relationship between the levels of endogenous sex hormones and breast cancer risk in postmenopausal women. **Methods:** We analyzed the individual data from nine prospective studies on 663 women who developed breast cancer and 1765 women who did not. None of the women was taking exogenous sex hormones when their blood was collected to determine hormone levels. The relative risks (RRs) for breast cancer associated with increasing hormone concentrations were estimated by conditional logistic regression on case-control sets matched within each study. Linear trends and heterogeneity of RRs were assessed by two-sided tests or chi-square tests, as appropriate. **Results:** The risk for breast cancer increased statistically significantly with increasing concentrations of all sex hormones examined: total estradiol, free estradiol, non-sex hormone-binding globulin (SHBG)-bound estradiol (which comprises free and albumin-bound estradiol), estrone, estrone sulfate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone. The RRs for women with increasing quintiles of estradiol concentrations, relative to the lowest quintile, were 1.42 (95% confidence interval [CI] = 1.04 to 1.95), 1.21 (95% CI

= 0.89 to 1.66), 1.80 (95% CI = 1.33 to 2.43), and 2.00 (95% CI = 1.47 to 2.71; $P_{\text{trend}} < .001$); the RRs for women with increasing quintiles of free estradiol were 1.38 (95% CI = 0.94 to 2.03), 1.84 (95% CI = 1.24 to 2.74), 2.24 (95% CI = 1.53 to 3.27), and 2.58 (95% CI = 1.76 to 3.78; $P_{\text{trend}} < .001$). The magnitudes of risk associated with the other estrogens and with the androgens were similar. SHBG was associated with a decrease in breast cancer risk ($P_{\text{trend}} = .041$). The increases in risk associated with increased levels of all sex hormones remained after subjects who were diagnosed with breast cancer within 2 years of blood collection were excluded from the analysis. **Conclusion:** Levels of endogenous sex hormones are strongly associated with breast cancer risk in postmenopausal women. [J Natl Cancer Inst 2002;94:606-16]

Breast cancer risk is partially determined by several hormone-related factors, such as age at menarche, parity, and age at menopause, and it has long been hypothesized that high levels of

Correspondence to: Timothy J. Key, D.Phil., 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."

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endogenous sex hormones, especially estrogens, may increase breast cancer risk. Early epidemiologic studies compared the hormone levels in women diagnosed with breast cancer with those in healthy control subjects. The overall results of these studies suggested that postmenopausal women with breast cancer had higher levels of estradiol and estrone than did healthy postmenopausal women; however, these studies (1) did not clarify whether such differences were caused by the disease or represented risk factors for the disease. To eliminate the former possibility, data are needed from prospective studies that collect blood samples from healthy women and then examine the relationship between hormone levels and the risk of subsequently developing breast cancer. During the last 10 years, nine research groups have published results from prospective studies of endogenous hormones and breast cancer: Columbia, MO, United States (2,3); Guernsey, United Kingdom (4); Nurses' Health Study, United States (5); New York University Women's Health Study (NYU WHS), United States (6,7); Study of Hormones and Diet in the Etiology of Breast Tumors (ORDET), Italy (8); Rancho Bernardo, United States (9,10); Radiation Effects Research Foundation (RERF), Japan (11); Study of Osteoporotic Fractures (SOF), United States (12); Washington County, United States (13,14). Most of these studies have concluded that high levels of estrogens and other sex hormones are associated with an increase in breast cancer risk in postmenopausal women. However, none of the individual studies has been large enough to produce precise estimates of the risks.

The Endogenous Hormones and Breast Cancer Collaborative Group was established to conduct pooled analyses of the original data from these nine studies. The specific aims of the group were 1) to obtain more precise estimates of the relative risks (RRs) of breast cancer than were obtained from the single studies, 2) to look at the relationship between time from blood collection to diagnosis and the risks associated with endogenous levels of hormones, 3) to investigate whether the association between endogenous hormone concentrations and breast cancer risk varies according to the history of use of hormone replacement therapy (HRT), 4) to evaluate whether estradiol is the hormone most closely associated with risk, 5) to examine whether sex hormone levels may explain the relationship between body mass index (BMI) and breast cancer risk, and 6) to examine the associations between hormone levels and breast cancer risk in premenopausal women. In this article, we present our findings for the first four of these aims.

SUBJECTS AND METHODS

Identification of Prospective Studies of Hormones and Breast Cancer Risk

Studies were identified by computer-aided literature searches, within relevant review articles, and through our discussions with colleagues. Studies were eligible for inclusion in this analysis if they had published data on endogenous hormone concentrations and breast cancer risk using prospectively collected blood samples from postmenopausal women. Ten eligible studies (2–15) were identified, and data were contributed for nine of them. The tenth study (15) was not included in the analysis because the data could not be retrieved; this study included 39 cases of breast cancer among postmenopausal women.

Collection of Data

Authors of the included studies were asked to provide their data on the following factors and hormone concentrations for each woman in their study: case or control status and matched set identifier, where applicable; date of diagnosis and stage of the disease for case patients; date of birth; date and time of blood collection with details of any overnight fasting or concurrent drug use; age at menarche; number of full-term pregnancies and age at first and last full-term pregnancy, where applicable; menopausal status at blood collection (natural menopause, bilateral ovariectomy, hysterectomy without bilateral ovariectomy, surgical but details unknown) and age at menopause; height and weight; smoking habits; previous use of hormonal contraceptives; previous use of HRT; concentrations of total estradiol, free estradiol, non-sex hormone-binding globulin (SHBG)-bound estradiol (free plus albumin-bound estradiol), estrone, estrone sulfate, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), testosterone, and SHBG. Not all of the hormone and SHBG measurements were available for each study. Women who were missing data for any of the following factors were excluded from the analysis: matched set identifier, where applicable; dates of diagnosis for case patients; date of birth; and date of blood collection.

In general, the data sent to us for analysis were identical to the data analyzed and published previously by the original researchers. The two exceptions were the ORDET study (8), for which extra follow-up data and laboratory measurements had been obtained and analyzed but not yet published since the original report from that study, and the Rancho Bernardo study (9,10), for which additional follow-up data had been obtained and could be analyzed in relation to the assays conducted at the outset in this cohort.

Study Designs

All nine studies examined cohorts in which blood samples were collected from healthy women who were then followed to identify those who developed breast cancer. As shown in Table 1, seven studies used a nested matched case-control design: Columbia, MO (2,3), Guernsey, United Kingdom (4), Nurses' Health Study (5), NYU WHS (6,7), ORDET (8), RERF (11), and Washington County (13,14). In these studies, the subjects were followed for a defined time interval, and then assays of their serum hormone concentrations were conducted for case patients with incident breast cancer and for control subjects matched to the case patients on criteria such as age and date at blood collection. The SOF (12) used a case-cohort design; study subjects were followed for a defined time interval, and then assays of their serum hormone concentrations were conducted for case patients with incident breast cancer and for control subjects selected at random as a subsample of the whole cohort. The Rancho Bernardo study (9,10) used a full cohort design, in which hormone assays were conducted on stored serum collected from the whole cohort before incident cases of breast cancer were identified; all the women in the cohort were followed for a defined time interval after blood collection. In all nine studies, women who were using HRT or other exogenous sex hormones at the time of blood collection were not eligible for inclusion in the analyses of endogenous hormones and breast cancer risk.

Table 1. Study designs*

Study, country (reference No.)	Control subjects and case patients	Matching criteria				
		Age	Date of blood collection	Time of blood collection†	Fasting status at blood collection†	Other
Columbia, MO, United States (2,3)	Matched 2 : 1	±1 y	±1 y	±2 h	None	None
Guernsey, U.K. (4)	Matched 3 : 1	±2 y	±1 y	None	None	<3 y versus ≥3 y post menopause
Nurses' Health Study, United States (5)	Matched 2 : 1	±2 y	Same month	±2 h	<10 h versus ≥10 h	None
NYU WHS, United States (6,7)	Matched 2 : 1	±6 mo	±3 mo	None	None	Subsequent samples collected
ORDET, Italy (8)	Matched 4 : 1	±5 y	±89 days	All 8:00 AM to 9:30 AM	All fasting	Center, daylight saving period
Rancho Bernardo, United States (9,10)	Full cohort	—	—	—	—	—
RERF, Japan (11)	Matched 2 : 1	±3 y	±3 mo	None	None	Radiation exposure
SOF, United States (12)	Subcohort	—	—	—	—	—
Washington County, United States (13,14)	Matched 2 : 1	±1 y	±4 mo	Yes, not specified	±2 h for time since previous meal	±1 y for time since menopause

*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; — = not applicable.

†“None” means that there was no attempt made to match on this variable.

Details of the assay methods for the different hormones and SHGB are presented in the original publications. For estradiol, estrone, and testosterone, we examined the results according to whether the assay incorporated purification steps, such as extraction and chromatography, or used a direct, no-extraction method. For estradiol, five studies (4,5,9,12,14) used assays incorporating purification and four studies (2,6,8,11) used direct methods; for estrone, four studies (5,9,12,14) used assays incorporating purification and two studies (2,6) used direct assays; for testosterone, three studies (5,9,12) used assays incorporating purification and four studies (2,4,7,8) used direct assays.

Statistical Analysis

The basic method of analysis used throughout this study was conditional logistic regression. Seven of the nine studies were already in the form of matched case-control data, and for these studies, the original matching was preserved. For the other two studies, which had case-cohort and full cohort designs, nested case-control data sets were generated from within the cohorts so that the same statistical analysis could be conducted across all nine studies. In keeping with the designs of the other seven studies, control subjects in the latter two studies were matched to case patients as closely as possible by age and time between diagnosis and blood collection. Analysis of the data from these two studies before such matching (i.e., as they were originally published) and after the imposition of matching provided very similar results for the associations between hormone levels and breast cancer risk (results not shown). Because matching was conducted within studies, only women from the same study were directly compared.

Measurements of steroid hormone concentrations are subject to substantial between-laboratory variations because different laboratories use different assay methods. It is not surprising, therefore, that there were considerable differences between the different studies in the median values and interquartile ranges (25th to 75th percentiles) for the serum concentrations of most of the hormones in the control subjects. Given this variability, it is clear that the reported hormone concentrations are not directly

comparable between studies and that any pooled estimate of breast cancer risk in relation to such measures would have to take this into account.

Although the reported values of a given hormone concentration may vary considerably among studies, we expected that the RR of breast cancer in women with hormone levels at the top end of each study-specific distribution of hormone concentrations compared with that of women at the bottom of that distribution would be comparable across studies. The first approach used here, therefore, was to carry out an analysis of breast cancer risk in which each hormone concentration was divided into five groups with cut-points defined by the study-specific quintiles of its distribution within the control subjects.

The analyses of breast cancer risk according to quintiles of hormone concentration suggested trends of increasing risk with increasing hormone concentrations. To provide summary measures that would quantify these trends and that could easily be compared across studies and subgroups, we also calculated a linear trend in breast cancer risk in relation to the logarithm serum hormone concentrations. The rationale for such an analysis is as follows: If true hormone concentrations are the same for all the studies and if the effect of an assay method is multiplicative, then for a woman in study *i*:

$$X = m_i H,$$

where *X* is her measured hormone concentration, *H* is her underlying hormone concentration (subject to within-subject and within-laboratory error), and *m_i* is a study-specific multiplicative constant representing the effect of the assay method on the measured hormone concentration. The effect of a logarithmic transformation of this equation,

$$Z = \log(X) = \log(m_i) + \log(H),$$

is to make the effect of the assay method additive. Consequently, comparisons of risk based on differences in *Z* will not depend on *m_i*. We used a log₂ transformation so that a unit increase in *Z* would represent a doubling in *H* (other transformations, such as log₁₀ and ln, would have produced identical results, based on

tests of statistical significance, but different and less easily interpretable RR estimates). Pooling the risk estimates from the separate cohorts assumes that a doubling in hormone concentration has the same effect on RR in each cohort.

The possible influences of other variables on the association between the doubling of a hormone concentration and breast cancer risk were examined by adjusting for established risk factors and by subgroup analyses. The established risk factors we examined were: age at menarche (<12 years, 12–13 years, ≥14 years); parity (zero, one, two, three, four or more full-term pregnancies); previous use of oral contraceptives (never, past); type of menopause (natural, surgical); time since menopause (0–4 years, 5–14 years, ≥15 years); previous use of HRT (never, past); and BMI (<22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, ≥30.0 kg/m²). The subgroups we examined were: time from blood collection to diagnosis (<2 years, ≥2 years); previous use of HRT (never, past); age at diagnosis (<60 years, ≥60 years); parity (nulliparous, parous); previous use of oral contraceptives (never, past); type of menopause (natural, surgical); and BMI (<25 kg/m², ≥25 kg/m²).

The associations of estradiol, the androgens, and SHBG with breast cancer risk were further examined by entering estradiol and each androgen and SHBG in turn into a conditional logistic regression model. All statistical analyses were performed using Stata Statistical Software (Stata Corp., College Station, TX) (16). RRs and their 95% confidence intervals (CIs) were calculated. Heterogeneity of RRs and, where appropriate, linear trends in RRs were assessed by χ^2 tests. Linear trends and heterogeneity of RRs were assessed by two-sided tests or chi-square tests, as appropriate.

RESULTS

Estradiol data were available for a total of 663 case patients and 1765 control subjects who were enrolled in the nine studies. Data for the other hormones and for SHBG were available from

three to eight studies. Among the control subjects, the mean age at recruitment ranged from 58.1 to 71.8 years, the proportion of nulliparous women ranged from 9% to 22%, the proportion of women with a natural menopause ranged from 71% to 95%, the proportion of women who had previously used HRT ranged from 18% to 37%, and the mean BMI ranged from 22.3 kg/m² to 26.7 kg/m². Among the case patients, the median time between blood collection and diagnosis ranged from 2.0 years to 12.1 years (Table 2).

Table 3 summarizes the median hormone concentrations (and interquartile ranges) reported in each of the individual studies. The median concentrations for most of the hormones in most of the studies were higher in the case patients than in the control subjects. By contrast, most of the studies reported a lower median concentration of SHBG in case patients than in control subjects.

Associations Between Individual Hormone Levels and Breast Cancer Risk

In a pooled analysis that examined the RR of breast cancer associated with quintiles of hormone concentrations, we found that all of the hormones were statistically significantly associated with an increase in breast cancer risk and that there was evidence for a dose–response relationship between hormone levels and risk (Fig. 1). The RR of breast cancer for women whose estradiol levels were in the top quintile compared with women whose estradiol levels were in the bottom quintile was 2.00 (95% CI = 1.47 to 2.71). For the other hormones, the RRs of breast cancer for women whose levels were in the top quintile compared with those whose levels were in the bottom quintile were all approximately 2. The highest RRs were for women in the top quintiles for free estradiol (RR = 2.58; 95% CI = 1.76 to 3.78) and for non-SHBG-bound estradiol (RR = 2.39; 95% CI = 1.62 to 3.54). By contrast, there was a statistically sig-

Table 2. Subject characteristics by study and case–control status*

Study, country	Subjects	No.	Mean age, y	% Nulliparous	% Natural menopause	% Previous HRT	Mean BMI, kg/m ²	Median years to diagnosis†
Columbia, MO, United States	Case	71	61.4	20	76	N/A	26.5	2.9
	Control	133	61.8	14	72	N/A	26.6	—
Guernsey, U.K.	Case	61	58.6	23	95	20	26.0	7.8
	Control	178	58.5	15	95	26	25.6	—
Nurses' Health Study, United States	Case	155	61.8	5	75	45	26.9	2.6
	Control	310	61.8	9	74	37	26.2	—
NYU WHS, United States	Case	129	58.6	26	79	19	26.1	2.0
	Control	247	58.5	22	79	18	25.1	—
ORDET, Italy	Case	67	58.7	10	84	26	26.5	2.3
	Control	264	58.1	11	79	19	26.7	—
Rancho Bernardo, United States	Case	31	64.3	10	63	N/A	24.8	9.0
	Control	287	64.9	12	71	N/A	24.5	—
RERF, Japan	Case	23	62.6	20	N/A	N/A	23.5	7.2
	Control	45	62.3	19	N/A	N/A	22.3	—
SOF, United States	Case	97	70.9	19	86	34	27.6	2.9
	Control	243	71.8	21	86	32	26.5	—
Washington County, United States	Case	29	60.9	N/A	N/A	N/A	N/A	12.1
	Control	58	60.9	N/A	N/A	N/A	N/A	—

*HRT = hormone replacement therapy; BMI = body mass index; 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; — = not applicable; N/A = data not available in this study.

†Median time between blood collection and diagnosis for case patients.

Table 3. Median (interquartile range) hormone concentrations by study and case-control status*

Study, country	Study subjects	No.†	Estradiol, pmol/L	Free estradiol, pmol/L	Non-SHBG estradiol, pmol/L	Estrone, pmol/L	Estrone sulfate, pmol/L	Androstenedione, nmol/L	DHEA, nmol/L	DHEAS, nmol/L	Testosterone, nmol/L	SHBG, nmol/L
Columbia, MO, United States	Case	71	55.1 (36.7–84.4)	0.70 (0.49–1.22)	27.3 (15.7–41.1)	129.4 (103.6–177.5)	509 (358–718)	3.46 (2.58–4.43)	7.04 (4.40–10.19)	2776 (1551–4027)	0.76 (0.49–1.25)	49.4 (36.0–69.9)
	Control	133	51.4 (29.4–88.1)	0.62 (0.31–1.17)	22.1 (11.3–38.8)	129.4 (85.1–162.7)	526 (372–761)	3.11 (2.23–4.26)	5.58 (3.22–8.81)	2204 (1333–3184)	0.59 (0.35–0.90)	53.4 (33.3–73.9)
Guernsey, U.K.	Case	61	45.5 (34.0–57.0)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1.14 (0.77–1.73)	54.0 (37.0–66.0)
	Control	178	35.0 (29.0–47.0)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.91 (0.64–1.34)	63.0 (42.0–83.5)
Nurses' Health Study, United States	Case	155	29.4 (18.4–44.1)	0.44 (0.29–0.77)	7.2 (3.8–13.4)	114.6 (85.1–155.3)	662 (383–1089)	2.16 (1.61–2.79)	7.28 (4.54–10.89)	2367 (1605–3973)	0.80 (0.59–1.14)	n/a
	Control	310	25.7 (18.4–40.4)	0.40 (0.29–0.62)	5.9 (3.6–10.7)	103.6 (77.7–140.5)	549 (363–770)	1.99 (1.43–2.71)	7.11 (4.54–9.83)	2136 (1333–3347)	0.76 (0.52–1.07)	n/a
NYU WHS, United States	Case	129	134.0 (84.4–172.5)	1.94 (1.22–2.53)	79.5 (52.0–119.3)	52.7 (37.9–78.7)	n/a	n/a	n/a	2540 (1340–4150)	1.14 (0.78–1.50)	n/a
	Control	247	101.0 (69.8–154.2)	1.29 (0.84–2.15)	52.9 (34.0–93.6)	41.0 (28.0–76.4)	n/a	n/a	n/a	2320 (1310–3430)	1.01 (0.70–1.42)	n/a
ORDET, Italy	Case	67	21.9 (15.6–30.0)	n/a	n/a	n/a	n/a	n/a	n/a	1747 (1057–3160)	1.21 (0.91–1.69)	39.8 (28.5–53.3)
	Control	264	21.7 (15.8–30.3)	n/a	n/a	n/a	n/a	n/a	n/a	2004 (1275–3031)	1.17 (0.90–1.58)	41.5 (29.8–53.3)
Rancho Bernardo, United States	Case	31	36.7 (25.7–58.7)	n/a	n/a	114.6 (88.8–166.4)	n/a	1.82 (1.55–2.62)	n/a	2150 (1197–3238)	0.85 (0.59–1.07)	32.0 (18.0–51.0)
	Control	287	40.4 (29.4–62.4)	n/a	n/a	107.3 (81.4–151.6)	n/a	1.94 (1.40–2.72)	n/a	1850 (1088–2993)	0.75 (0.51–1.06)	28.0 (17.0–44.0)
RERF, Japan	Case	23	63.1 (49.4–88.1)	n/a	28.2 (22.1–45.6)	n/a	n/a	n/a	n/a	1034 (898–1524)	n/a	51.4 (36.5–71.3)
	Control	45	64.5 (41.9–95.0)	n/a	24.7 (13.9–42.4)	n/a	n/a	n/a	n/a	898 (571–1333)	n/a	68.7 (42.6–95.0)
SOF, United States	Case	97	29.4 (18.4–40.4)	0.44 (0.29–0.66)	4.8 (3.0–8.7)	88.8 (62.9–122.0)	632 (398–953)	1.54 (1.01–2.20)	n/a	2041 (1279–3238)	0.73 (0.52–1.11)	38.0 (30.0–54.0)
	Control	243	22.0 (18.4–29.4)	0.37 (0.26–0.51)	3.8 (2.2–6.8)	74.0 (51.8–103.6)	475 (306–758)	1.26 (0.84–1.78)	n/a	1742 (1007–2721)	0.62 (0.42–0.94)	43.0 (29.0–59.0)
Washington County, United States	Case	29	62.4 (40.4–77.1)	0.98 (0.63–1.14)	n/a	144.2 (111.0–199.7)	n/a	3.11 (2.20–4.33)	7.03 (4.77–10.33)	2260 (1190–3050)	n/a	58.7 (37.0–69.7)
	Control	58	58.7 (29.4–77.1)	0.81 (0.41–1.19)	n/a	140.5 (107.3–196.0)	n/a	2.74 (1.99–3.42)	6.25 (4.23–8.09)	1815 (850–3280)	n/a	55.8 (37.6–79.9)

*SHBG = sex hormone-binding globulin; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; 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; n/a = hormone measurement not available in this study.

†These numbers correspond to the numbers of case patients and control subjects for whom estradiol measurements were obtained in each study; the numbers of case patients and control subjects for whom measurements for the other hormones were obtained varied slightly for the different hormones.

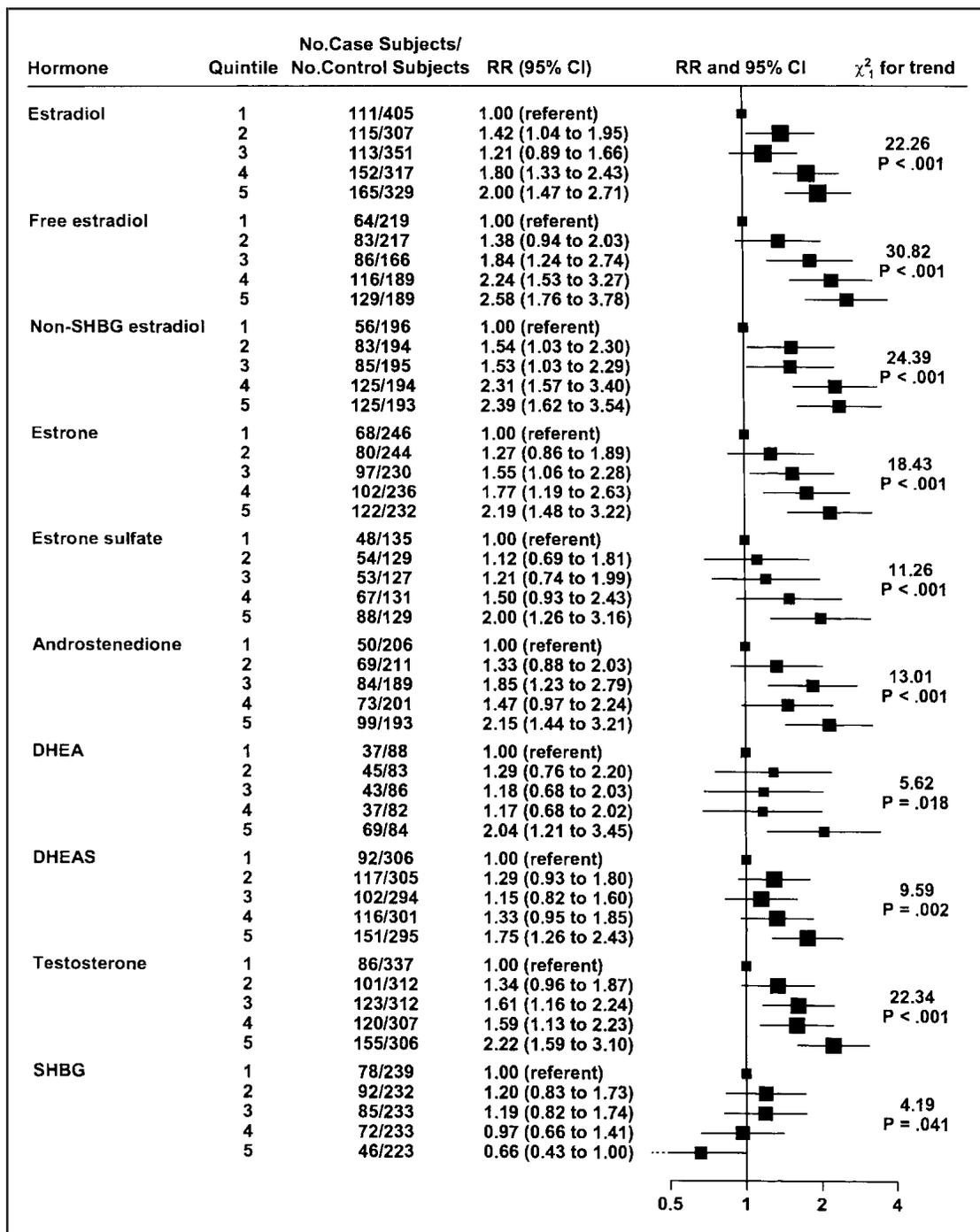
nificant inverse association between SHBG levels and breast cancer risk (RR in the top versus the bottom quintile = 0.66; 95% CI = 0.43 to 1.00, $P_{\text{trend}} = .041$). The RRs for breast cancer also increased with increasing percentages of free and non-SHBG-bound estradiol; RRs in the top versus the bottom quintiles were 1.55 (95% CI = 1.06 to 2.27) for percentage free estradiol and 1.88 (95% CI = 1.31 to 2.69) for percentage non-SHBG-bound estradiol (data not shown).

The RRs for breast cancer associated with a doubling of estradiol levels in each of the nine studies ranged from 0.76 to 1.69, and this RR was greater than 1.0 in six of the nine studies (Fig. 2). The all-studies estimate of the RR of breast cancer associated with the doubling of estradiol levels was 1.29 (95% CI = 1.15 to 1.44; $P < .001$). The variation in RRs between studies was not statistically significant (test for heterogeneity, $\chi^2_{8df} = 14.45$, $P = .071$). We conducted similar analyses for

the other hormones. For each of the hormones, the all-studies estimate of the RR associated with a doubling of their concentrations was greater than 1.0, whereas the all-studies RR estimate associated with a doubling in SHBG levels was 0.88 (95% CI = 0.76 to 1.03). There was no statistically significant heterogeneity between studies for the association of any of the hormones or SHBG with breast cancer risk.

We examined the RRs of breast cancer associated with a doubling in the concentrations of estradiol, estrone, and testosterone according to whether the assay that measured the level of each hormone had used a method that incorporated a purification step or had used a direct, no-extraction approach. There were no statistically significant differences in these RRs according to the assay method used. The RRs associated with a doubling of estradiol levels were 1.35 (95% CI = 1.15 to 1.58) for the five studies that used an assay that incorporated a purification step

Fig. 1. Relative risk (RR) of breast cancer by increasing quintiles of hormone concentrations. The position of each square indicates the magnitude of the RR, and the area of the square is proportional to the amount of statistical information available (inverse of the variance of the logarithm of the RR). The length of the horizontal line through the square indicates the 95% confidence interval (CI); the 95% CI that extends beyond the scale of the horizontal axis is indicated by a dotted line. The numbers of case patients and control subjects reported in the figure include only those from informative matched case-control sets. Estimates are from conditional logistic regression on case-control sets matched within each study. Linear trends and heterogeneity of RRs were assessed by two-sided tests or chi-square tests, as appropriate. DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin.



(4,5,9,12,14) and 1.23 (95% CI = 1.04 to 1.44) for the four studies that used a direct assay (2,6,8,11). The RRs associated with a doubling of estrone levels were 1.46 (95% CI = 1.18 to 1.79) for the four studies that used an assay that incorporated a purification step (5,9,12,14) and 1.45 (95% CI = 1.08 to 1.96) for the two studies that used a direct assay (2,6). The RRs associated with a doubling of testosterone levels were 1.37 (95% CI = 1.15 to 1.65) for the three studies that used an assay that incorporated a purification step (5,9,12) and 1.44 (95% CI = 1.21 to 1.72) for the four studies that used a direct assay (2,4,7,8).

Adjustment for Established Risk Factors for Breast Cancer

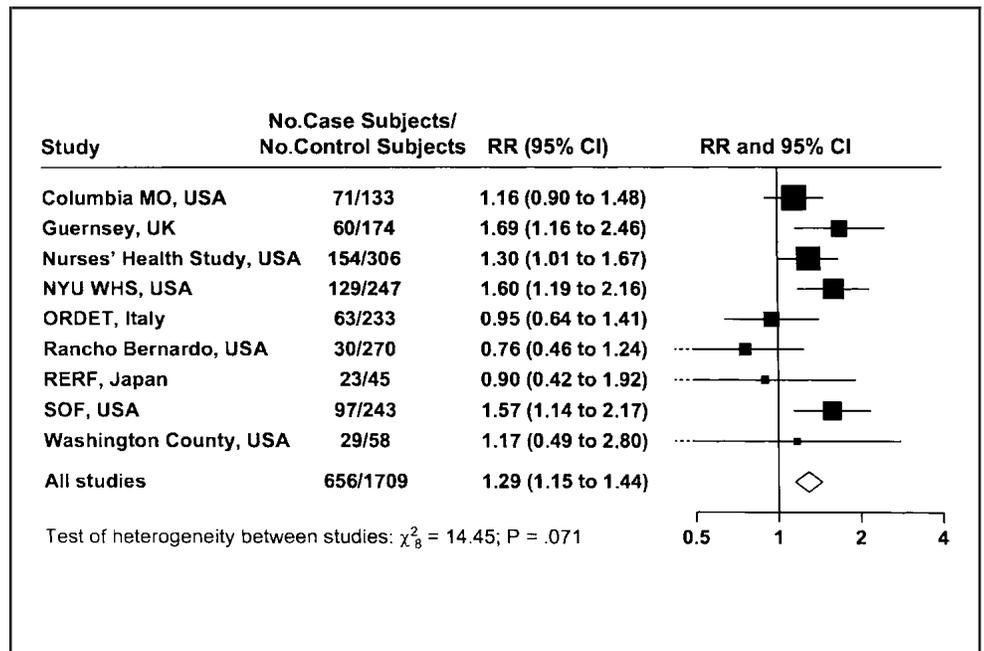
We examined the associations between the levels of all the hormones and breast cancer risk after adjusting, one factor at a

time, for the following established risk factors for breast cancer: age at menarche, parity, previous use of oral contraceptives, type of menopause, time since menopause, previous use of HRT, and BMI. None of these adjustments substantially altered the associations between the levels of any of the hormones and breast cancer risk (results not shown).

Time From Blood Collection to Diagnosis

We found no evidence to suggest that the RRs of breast cancer associated with a doubling in hormone concentrations were substantially greater for case patients whose blood was collected within 2 years of diagnosis than for case patients whose blood was collected 2 or more years before diagnosis (Fig. 3). Indeed, for all five types of estrogens examined, the

Fig. 2. Relative risk (RR) of breast cancer associated with a doubling of serum estradiol levels by study. The position of each square indicates the RR, and the area of the square is proportional to the amount of statistical information (inverse of the variance of the logarithm of the RR). The length of the horizontal line through the square indicates the 95% confidence interval (CI); 95% CIs that extend beyond the scale of the horizontal axis are indicated by dotted lines. The diamond indicates the RR and 95% CI for all studies combined. The numbers of case patients and control subjects reported in the figure include only those from informative matched case-control sets. Estimates are from conditional logistic regression on case-control sets matched within each study. Linear trends and heterogeneity of RRs were assessed by two-sided tests or chi-square tests, as appropriate. 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.



RR of breast cancer associated with a doubling of hormone concentration was lower among case patients who were diagnosed within 2 years of blood collection than among case patients who were diagnosed 2 years or more from the time of blood collection.

Previous Use of HRT

For all the hormones except DHEA, and for SHBG, the RRs for breast cancer associated with a doubling in their concentrations were greater among women who had never used HRT than among women who had previously used HRT (Fig. 4). Although these differences in RRs according to previous use of HRT were not statistically significant, the differences in RRs were more marked for the estrogens than for the androgens.

Other Subgroups

There were no statistically significant differences in the associations of any of the hormone levels with breast cancer risk when women were categorized according to age at diagnosis, parity, type of menopause, previous use of oral contraceptives, or BMI (results not shown).

Adjustment of Estradiol for Androgens and SHBG

Estradiol levels were positively correlated with the levels of the other sex hormones and inversely correlated with levels of SHBG. For example, the median correlations calculated from data reported in the individual studies were $r = .96$ for free estradiol, $r = .87$ for non-SHBG-bound estradiol, $r = .59$ for estrone, $r = .60$ for estrone sulfate, $r = .35$ for androstenedione, $r = .20$ for DHEA, $r = .29$ for DHEAS, $r = .37$ for testosterone, and $r = -.17$ for SHBG. The strong correlations between the levels of estradiol and those of the other estrogens made it inappropriate to include more than one of these hormones in the same logistic regression model. To examine the simultaneous associations between estradiol and each of the androgens and SHBG and breast cancer risk, we calculated the RRs associated with a doubling of estradiol and the androgens and SHBG, with and without adjustment for each androgen and SHBG, in turn (Table 4). In all cases, the magnitudes of the RRs associated with

a doubling of estradiol levels were somewhat reduced after adjustment but remained statistically significant or approached statistical significance. Similarly, the RRs associated with a doubling of androgen levels or SHBG levels either remained statistically significant or approached statistical significance after adjustment for estradiol, although the magnitudes of the associations were also slightly reduced.

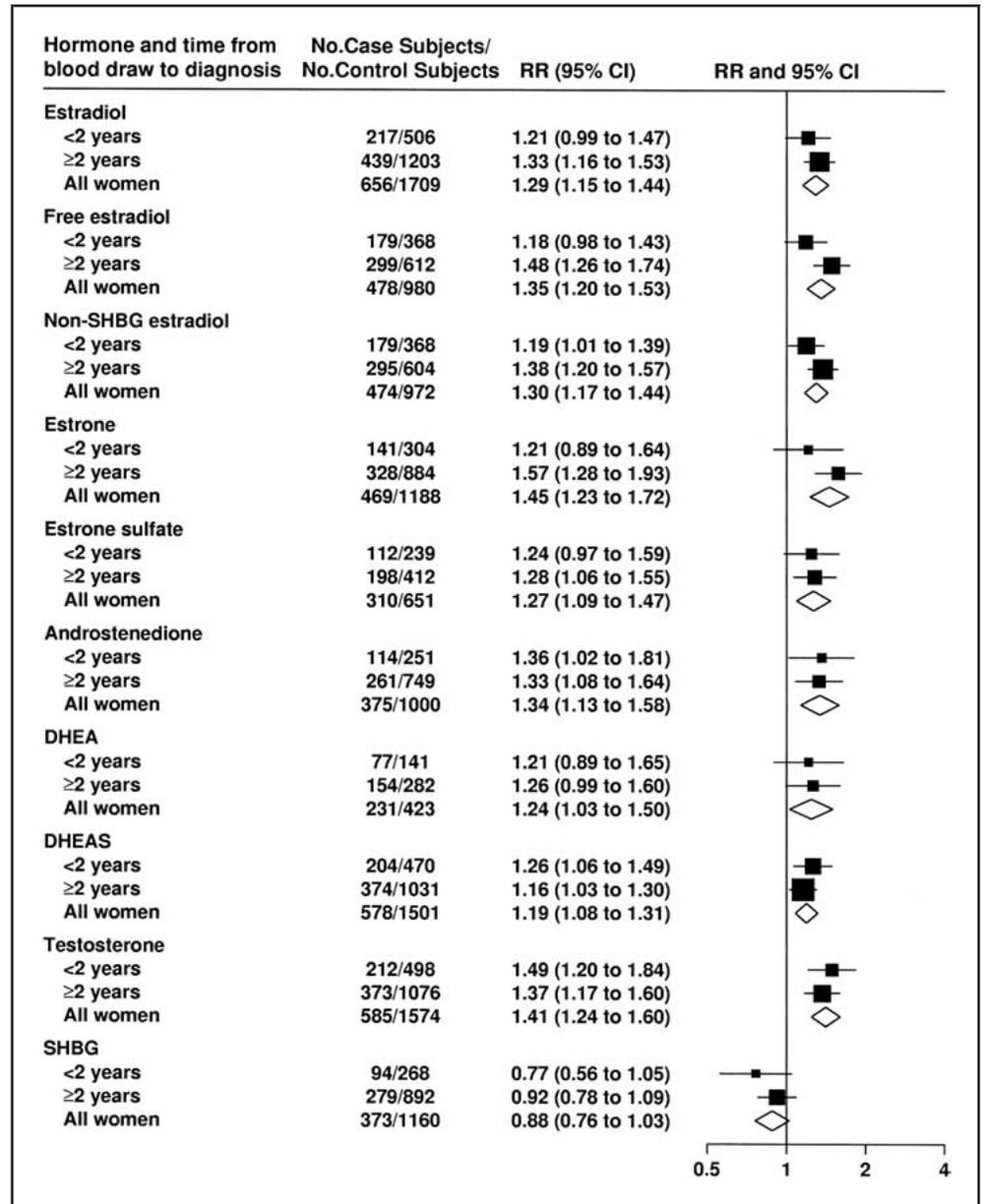
DISCUSSION

The main finding of our study was that postmenopausal women with relatively high serum concentrations of sex hormones had a roughly twofold higher risk for breast cancer than did postmenopausal women with relatively low serum concentrations of sex hormones. These results were highly statistically significant, were not statistically significantly heterogeneous between the nine studies we analyzed, and were not altered by adjusting for established risk factors for breast cancer. These results support the long-hypothesized role of endogenous hormones in the etiology of breast cancer.

One specific aim of our analysis was to examine the risks of breast cancer associated with sex hormone concentrations by subdividing the data according to the time interval between blood collection and diagnosis of breast cancer. This subgroup analysis showed that, for all of the sex hormones studied, the association with risk was not limited to the case patients who were diagnosed with breast cancer shortly after blood collection; indeed, for most of the hormones examined, the increase in risk was somewhat greater among the case patients who were diagnosed 2 or more years after blood collection than in the case patients who were diagnosed earlier than 2 years after blood collection. These results suggest that it is more likely that the positive associations we observed between sex hormone levels and breast cancer risk were the result of an effect of the hormones on the development of clinical cancer rather than an effect of preclinical tumors on hormone metabolism.

Another hypothesis that we sought to test was that the associations between the levels of different estrogens and breast cancer risk would be stronger among women who had not used HRT than among women who had used HRT. This hypothesis

Fig. 3. Relative risk (RR) of breast cancer associated with a doubling of hormone concentration according to years from blood collection to diagnosis. The position of each square indicates the RR, and the area of the square is proportional to the amount of statistical information (inverse of the variance of the logarithm of the RR). The length of the horizontal line through the square indicates the 95% confidence interval (CI). The diamonds indicate the RRs and 95% CIs for all women contributing data for each hormone. The numbers of case patients and control subjects reported in the figure include only those from informative matched case-control sets. Estimates are from conditional logistic regression on case-control sets matched within each study. DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin.



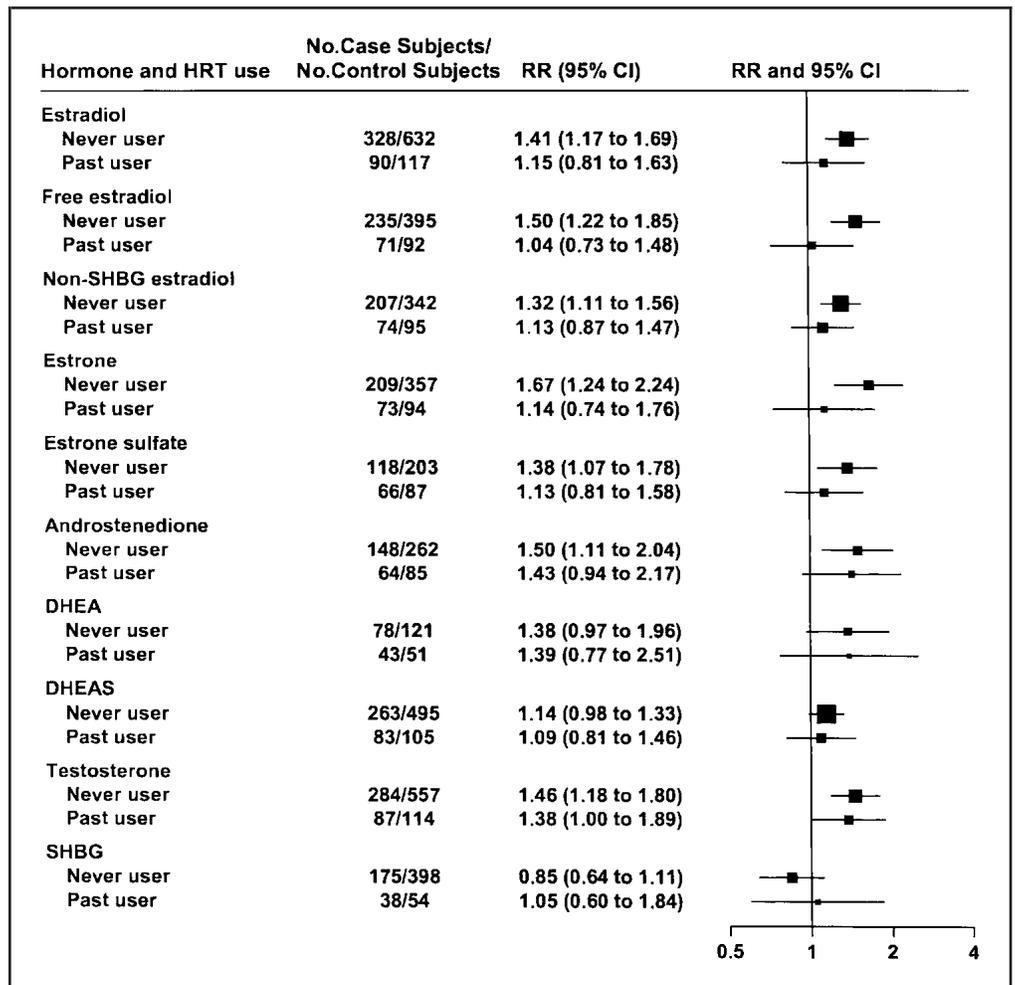
was originally proposed by Hankinson et al. (5) on the basis of their observations in the Nurses' Health Study. In our analysis, the RRs associated with a twofold increase in the levels of all the hormones except DHEA were larger among the women who had never used HRT than among the women who had previously used HRT, although none of these differences was statistically significant. Thus, further data are required to confirm this hypothesis.

The levels of all nine hormones or hormone fractions examined were statistically significantly associated with breast cancer risk. However, identifying which of these hormones is the most biologically important is not straightforward because they are all biochemically closely related. We therefore focused our analyses on estradiol, because this hormone was *a priori* of primary interest and because all nine studies reported measurements of estradiol levels. In theory, we would expect that the effect of estradiol on breast cancer risk would be observed most strongly for the fraction of estradiol that is not tightly bound by SHBG because this fraction of estradiol (which comprises free and albumin-bound estradiol) is readily able to enter cells, whereas

SHBG-bound estradiol is not (17). Our results supported this hypothesis: The highest RRs for breast cancer we observed were for women in the top quintiles of free estradiol and non-SHBG-bound estradiol. Levels of estrone and estrone sulfate were also strongly associated with breast cancer risk, but it was not possible to say whether this is because they are converted into estradiol, because they are correlated with estradiol levels or, in the case of estrone, because of a direct biologic effect on breast cells.

The levels of all four androgens studied were also associated with breast cancer risk, although we observed somewhat stronger associations for androstenedione and testosterone than for DHEA and DHEAS. Androstenedione and testosterone can be converted in one step into estrone and estradiol, respectively. DHEA (and, indirectly, its sulfate DHEAS) can be converted into androstenedione, which can then be converted into both estrone and testosterone. Thus, DHEA and DHEAS are farther away from estradiol in the metabolic pathway than are androstenedione and testosterone. The results of the statistical analyses that entered both estradiol and each androgen in turn into the

Fig. 4. Relative risk (RR) of breast cancer associated with a doubling of hormone concentration according to use of hormone replacement therapy (HRT). The position of each square indicates the RR, and the area of the square is proportional to the amount of statistical information (inverse of the variance of the logarithm of the RR). The length of the horizontal line through the square indicates the 95% confidence interval (CI). The numbers of case patients and control subjects reported in the figure include only those from informative matched case-control sets. Estimates are from conditional logistic regression on case-control sets matched within each study. DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; SHBG = sex hormone-binding globulin.



same model suggested that the associations of estradiol and the androgens with breast cancer risk were essentially independent and, indeed, that androstenedione and testosterone might be more strongly associated with risk than estradiol. However, caution is required in drawing such conclusions from these analyses because the measurements of androgens may be more precise than those of estradiol, making it easier to detect associations with the former than the latter. However, because the circulating levels of androgens are much higher than the circulating levels of estrogens in postmenopausal women, and because androgens can be converted to estrogens in the breast, serum androgens could be an important source of estrogens in the breast. In addition, androgens might also affect breast cancer risk by directly stimulating the growth and division of breast cells.

Pooling data on hormone concentrations and breast cancer risk is a biologically reasonable approach to these analyses. The true hormone concentrations among the women in the different cohort studies are likely to be very similar [with the possible exception of the RERF cohort, because there is evidence that Japanese women have lower serum concentrations of some sex hormones than Western women (18)]. Furthermore, there is no reason to expect that the association of hormone levels with breast cancer risk is fundamentally different in different populations. The two methods of statistical analysis that we present (i.e., risks associated with increasing hormone concentrations across quintiles of the distribution and with the doubling of hormone concentrations) were carefully chosen because they

assume only that the distributions of true hormone concentrations, and not the measured concentrations, were similar in the different studies. For individual hormones, there was no statistically significant heterogeneity between studies for the association between a doubling of hormone concentration and breast cancer risk. There was also no suggestion that the associations between the levels of estradiol, estrone, and testosterone and breast cancer risk differed markedly according to the method used to measure the levels of these hormones.

Tests for heterogeneity in the associations of hormones with breast cancer risk according to various characteristics of the women did not demonstrate any statistically significant heterogeneity for any of the hormones or for SHBG. The only hormone that approached statistical significance with respect to heterogeneity was estradiol. The only variable that appeared to modify the relationship between estradiol levels and breast cancer risk was previous use of HRT. However, this modification was not statistically significant, and previous use of HRT did not explain the weak heterogeneity between studies in the association between estradiol and breast cancer risk.

One limitation of our study is that the RRs we calculated are all based on single measurements of serum hormone concentrations for each woman. These single measures provide an imperfect estimate of an individual woman's long-term serum hormone levels. In the Nurses' Health Study, the authors used intraclass correlation coefficients from a reliable

Table 4. Risk of breast cancer associated with a doubling of hormone concentration, with and without adjustment for another hormone*

Hormones in the model	RR (95% CI) associated with a doubling in hormone concentration	
	Unadjusted	Adjusted for other hormone
Estradiol and androstenedione†		
Estradiol	1.25 (1.08 to 1.44)	1.15 (0.99 to 1.35)
Androstenedione	1.35 (1.14 to 1.60)	1.27 (1.06 to 1.53)
Estradiol and DHEA‡		
Estradiol	1.24 (1.03 to 1.49)	1.19 (0.98 to 1.44)
DHEA	1.24 (1.03 to 1.50)	1.19 (0.98 to 1.45)
Estradiol and DHEAS§		
Estradiol	1.25 (1.11 to 1.41)	1.19 (1.05 to 1.35)
DHEAS	1.20 (1.08 to 1.32)	1.15 (1.04 to 1.27)
Estradiol and testosterone		
Estradiol	1.31 (1.17 to 1.48)	1.18 (1.04 to 1.34)
Testosterone	1.42 (1.25 to 1.61)	1.32 (1.15 to 1.51)
Estradiol and SHBG¶		
Estradiol	1.21 (1.05 to 1.40)	1.20 (1.04 to 1.38)
SHBG	0.88 (0.76 to 1.02)	0.91 (0.80 to 1.06)

*CI = confidence interval; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; 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; SHBG = sex hormone-binding globulin; SOF = Study of Osteoporotic Fractures; RR = relative risk.

†374 case patients, 986 control subjects from Columbia, MO, United States; Nurses' Health Study, United States; Rancho Bernardo, United States; SOF, United States; and Washington County, United States.

‡231 case patients, 423 control subjects from Columbia, MO, United States; Nurses' Health Study, United States; Washington County, United States.

§577 case patients, 1483 control subjects from Columbia, MO, United States; Nurses' Health Study, United States; NYU WHS, United States; ORDET, Italy; Rancho Bernardo, United States; RERF, Japan; SOF, United States; Washington County, United States.

||583 case patients, 1555 control subjects from Columbia, MO, United States; Guernsey, U.K.; Nurses' Health Study, United States; NYU WHS, United States; ORDET, Italy; Rancho Bernardo, United States; SOF, United States; Washington County, United States.

¶371 case patients, 1137 control subjects from Columbia, MO, United States; Guernsey, U.K.; ORDET, Italy; Rancho Bernardo, United States; RERF, Japan; SOF, United States; Washington County, United States.

bility study to correct their RR estimates and observed that the RR for the upper fourth versus the lower fourth of the distribution for total estradiol levels increased from 1.77 (uncorrected) to 2.42 (corrected) (5). Thus, it is likely that the RRs we report here are also underestimates of the true associations between hormone levels and breast cancer risk.

This pooled analysis of the worldwide data from prospective studies has established that serum concentrations of endogenous sex hormones are strongly associated with breast cancer risk in postmenopausal women. Because the levels of the hormones studied here are positively correlated with each other, it is difficult to identify which single hormone is most strongly associated with breast cancer risk. For estrogens, however, the observed association between their levels and breast cancer risk is probably causal for two reasons: 1) estrogens stimulate cell division (19) and 2) anti-estrogenic agents, such as tamoxifen, have been shown to be an effective treatment for early breast cancer (20), to reduce the incidence of contralateral breast

cancer (20), and to reduce the primary occurrence of breast cancer (21,22). More research is needed on the roles of other hormones and growth factors in breast cancer risk, the roles of hormones in premenopausal women, and the roles of lifestyle and genetic determinants on hormone levels. In the future, the measurement of endogenous hormone levels might help to identify those women who are at increased risk for breast cancer.

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

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

Columbia, MO, United States: J. F. Dorgan, Fox Chase Cancer Center, Philadelphia, PA; C. Longcope, C. Franz, Departments of Obstetrics and Gynecology and Medicine, University of Massachusetts Medical School, Worcester; F. Z. Stanczyk, L. C. Chang, 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; L. Kahle, Information Management Services, Inc., Silver Spring, MD; R. Miller, Cancer Screening Services, Ellis Fischel Cancer Center, Columbia; J. A. Tangrea, W. S. Campbell, Division of Cancer Prevention and Control, National Cancer Institute; A. Schatzkin, Division of Cancer Epidemiology and Genetics, National Cancer Institute.

Guernsey, United Kingdom: T. J. Key, Cancer Research U.K., Oxford; D. S. Allen, I. S. Fentiman, J. W. Moore, D. Y. Wang, Cancer Research U.K., London; 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.

New York University Women's Health Study, United States: P. G. Toniolo, A. Akhmedkhanov, Division of Epidemiology, Department of Obstetrics and Gynecology, and Nelson Institute of Environmental Medicine, 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.

Study of Hormones and Diet in the Etiology of Breast Tumors, Italy: F. Berrino, Division of Epidemiology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano; 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.

Radiation Effects Research Foundation, Japan: M. Kabuto, Environmental Risk Research Division, National Institute for Environmental Studies, Ibaraki; S. Akiba, Department of Public Health, Faculty of Medicine, Kagoshima University; 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.

Study of Osteoporotic Fractures, United States: J. A. Cauley, L. H. Kuller, Department of Epidemiology, University of 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 (PA), 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.

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NOTES

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

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