Case–Control Study of Endogenous Steroid Hormones and Endometrial Cancer

*Nancy Potischman, Robert N. Hoover, Louise A. Brinton, Pentti Siiteri, Joanne F. Dorgan, Christine A. Swanson, Michael L. Berman, Rodrigue Mortel, Leo B. Twiggs, Rolland J. Barrett, George D. Wilbanks, Victoria Persky, John R. Lurain**

Background: **It has been suggested that identified risk factors for endometrial cancer operate through a single etiologic pathway, i.e., exposure to relatively high levels of unopposed estrogen (estrogen in the absence of progestins). Only a few studies, however, have addressed this issue directly.** ***Purpose:*** **We assessed the risk of developing endometrial cancer among both premenopausal and postmenopausal women in relation to the circulating levels of steroid hormones and sex hormone-binding globulin (SHBG). The independent effect of hormones was assessed after adjustment for other known risk factors.** ***Methods:*** **The data used in the analysis are from a case–control study conducted in five geographic regions in the United States. Incident cases were newly diagnosed during the period from June 1, 1987, through May 15, 1990. The case patients, aged 20-74 years, were matched to control subjects by age, race, and geographic region. The community control subjects were obtained by random-digit-dialing procedures (for subjects 20-64 years old) and from files of the Health Care Financing Administration (for subjects ≥65 years old). Additional control subjects who were having a hysterectomy performed for benign conditions were obtained from the participating centers. Women reporting use of exogenous estrogens or oral contraceptives within 6 months of interview were excluded, resulting in 68 case patients and 107 control subjects among premenopausal women and 208 case patients and 209 control subjects among postmenopausal women. The hormone analyses were performed on blood samples obtained from case patients or from hysterectomy control subjects before surgery. The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by use of an unconditional logistic regression analysis after we controlled for matching variables and potential confounders. All *P* values were two-sided.** ***Results:*** **High circulating levels of androstenedione were associated with 3.6-fold and 2.8-fold increased risks among premenopausal and postmenopausal women, respectively, after adjustment for other factors (*P* for trend = .01 and <.001, respectively). Risks related to other hormone fractions varied by menopausal status. Among postmenopausal women, a reduced risk was associated with high SHBG levels and persisted after adjustment was made for obesity and other factors (OR = 0.51; 95% CI = 0.27-0.95). High estrone levels were associated with increased risk (OR = 3.8; 95% CI = 2.2-6.6), although adjustment for other risk factors (particularly body mass index) diminished the effect (OR = 2.2; 95% CI = 1.2-4.4). Albumin-bound estradiol (E_2), a marker of the bioavailable fraction, also remained an important risk factor after adjustment was made for other factors (OR = 2.0; 95% CI = 1.0-3.9). In contrast, high concentrations of total, free, and albumin-bound E_2 were unrelated to increased risk in premenopausal women. In both premenopausal and postmenopausal groups, risks associated with obesity and fat distribution were not affected by adjustment for hormones.** ***Conclusion:*** **High endogenous levels of unopposed estrogen are related to increased risk of endometrial cancer, but their independence from other risk factors is inconsistent with being a common underlying biologic pathway through which all risk factors for endometrial cancer operate.** ***Implications:*** **Further research should focus on alternative endocrinologic mechanisms for risk associated with obesity and body fat distribution and for the biologic relevance of the increased risk associated with androstenedione in both premenopausal and postmenopausal disease. [J Natl Cancer Inst 1996; 88:1127-35]**

Epidemiologic and clinical studies have described endometrial cancer as a disease related to excessive exposure to estrogens. The strongest evidence derives from studies of exogenous estrogens that show a greatly enhanced risk of endometrial cancer with use of menopausal estrogens (*1*) and sequential oral contraceptives (*2*). In contrast, menopausal hor-

**Affiliations of authors:* N. Potischman, R. N. Hoover, L. A. Brinton, P. Siiteri, C. A. Swanson (Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics), J. F. Dorgan (Cancer Prevention Studies Branch, Division of Cancer Prevention and Control), National Cancer Institute, Bethesda, MD; M. L. Berman, Department of Obstetrics and Gynecology, University of California at Irvine Medical Center; R. Mortel, Department of Obstetrics and Gynecology, Milton S. Hershey Medical Center, Hershey, PA; L. B. Twiggs, Department of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis; R. J. Barrett, Department of Obstetrics and Gynecology, The Bowman Gray School of Medicine, Winston-Salem, NC; G. D. Wilbanks, Department of Obstetrics and Gynecology, Rush Medical College, Chicago, IL; V. Persky, Division of Epidemiology-Biostatistics, School of Public Health, The University of Illinois, Chicago; J. R. Lurain, Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago.

Correspondence to: Nancy Potischman, Ph.D., National Institutes of Health, Executive Plaza North, Suite 443, Bethesda, MD 20892-7374.

See "Note" section following "References."

mone replacement therapy containing progestins has been associated with a lower risk of endometrial cancer than therapy with estrogens alone (*3,4*), and decreased risks have been observed in association with use of combination-type oral contraceptives (*5-8*). Furthermore, risk is increased among women with chronic anovulation (*9-11*) and among those with fertility problems (*6,12,13*), suggesting increased risk associated with estrogen exposure unopposed by progestins (*10,14*).

It is well established that obesity increases the risk of endometrial cancer (*15*), with the postulated mechanism being increased conversion of androgens to estrogens in the adipose tissue of postmenopausal women (*11,16-18*). In addition, obesity has been linked to higher circulating levels of free estradiol (E_2) (*19,20*) as a consequence of lower concentrations of sex hormone-binding globulin (SHBG) that tightly binds estrogens (*19-21*). The more recent association of upper-body or central fat distribution with increased risk of endometrial cancer (*22-26*) has also been linked to low SHBG levels and hormonal alterations (*24,27*). In premenopausal women, the obesity association is thought to operate through increased anovulatory cycles (*10,11,14*) and associated progesterone insufficiency (*28*).

The common etiologic hypothesis for all of these risk factors, and possibly other reproductive and lifestyle factors, is that long-term exposure to estrogens unopposed by progestins is the key endocrine anomaly linked to endometrial cancer (*10,14*).

Conflicting results have been reported from a variety of clinical studies that have investigated the relation of endogenous hormones to endometrial cancer. Higher plasma levels of endogenous estrogens and/or androgens (*20,21,29*) have been associated with endometrial cancer, but other studies do not find these relationships (*19,30-34*). An epidemiologic study (*25*) showed associations between postmenopausal endometrial cancer and high levels of estrone (E_1), E_2, and androstenedione. These associations persisted after adjustment was made for body size and other factors. These data suggested that the higher estrogen concentrations did not merely reflect the higher obesity among case patients.

We had the opportunity to evaluate the effects of hormones in a large case–control study after adjustment was made for established risk factors, e.g., body mass index, parity, and oral contraceptive use. Although endometrial cancer is principally a disease of postmenopausal women, we also were able to evaluate risks among a small group of premenopausal women.

Subjects and Methods

Case Patients and Control Subjects

The design of this multicenter, case–control study is detailed elsewhere (*12*). Briefly, case patients were accrued from seven hospitals in the following five geographic regions: Chicago, IL; Hershey, PA; Irvine and Long Beach, CA; Minneapolis, MN; and Winston-Salem, NC. Eligible case patients with endometrial cancer were newly diagnosed during the period from June 1, 1987, through May 15, 1990; were aged 20-74 years; and lived in defined geographic areas. All case patients had pathologically confirmed endometrial cancer. Community control subjects were individually matched to case patients according to age (5-year age group), race (white, black, or other), and area of residence. Random-digit-dialing (RDD) procedures were used to select control subjects aged 20-64 years with telephone exchanges similar to those of case patients. Older control subjects (≥65 years of age) were selected, with age, race, and ZIP code information provided by the Health Care Financing Administration (HCFA), Baltimore, MD. A short questionnaire was administered to all potential control subjects to determine hysterectomy status. Control subjects without an intact uterus were replaced with another eligible subject. Another control group of women who were having hysterectomies for benign conditions at one of the seven hospitals was also included. The second control group was recruited from these referral hospitals for possible greater comparability with case patients than community control subjects provided. Attempts were made to use the same matching criteria of age, race, and location of residence as were used for the community control subjects. However, it was occasionally necessary to use less stringent matching criteria; the most commonly relaxed criterion was that of age. Thus, all analyses were adjusted for age.

Primary diagnoses among the 56 premenopausal hysterectomy control subjects were uterine leiomyoma (63.0%), disorders of menstruation (16.2%), uterine hyperplasia (7.2%), genital prolapse (5.4%), and other disorders (9.0%), including uterine adhesions, noninflammatory disorders of the ovaries or fallopian tubes, ovarian cysts, benign ovarian neoplasm, and endometriosis. Among the 62 postmenopausal hysterectomy control subjects, primary diagnoses were genital prolapse (67.2%), stress incontinence (8.1%), ovarian neoplasm (6.5%), endometrial cystic hyperplasia (6.5%), uterine leiomyoma (4.8%), and other disorders (6.9%), including endometriosis and other noninflammatory disorders of the ovaries or fallopian tubes. Although some differences were noted in mean hormone levels between hysterectomy control subjects and community control subjects, the patterns of associations were similar with the use of either control group; therefore, the analyses presented use the combined control group to achieve stable estimates.

Subjects were classified into menopausal groups on the basis of the interval since their last menstrual period. A combined premenopausal and perimenopausal group, hereafter referred to as "premenopausal," was made up of women who experienced a menses in the 6 months prior to interview or blood collection. The remainder were classified as "postmenopausal."

Blood Collection

Blood samples (after fasting) were collected from case patients and hysterectomy control subjects prior to surgery and on a scheduled day for community control subjects. The day of the cycle was not ascertained on the day of blood collection for premenopausal women, but serum progesterone levels were used to classify subjects with regard to the luteal or nonluteal phase. Of the 498 eligible cases, 434 completed the interview; of these women, 325 donated blood samples. Blood samples from 49 case patients were excluded, since these women reported the use of exogenous estrogens or oral contraceptives within 6 months of interview, leaving 276 case patients in this analysis. Among the 730 eligible hysterectomy (n = 253), RDD (n = 304), and HCFA (n = 173) control subjects, 519 completed the interview; of these women, 356 donated blood samples. Blood specimens were excluded for 39 control subjects who were recent users of exogenous estrogens or oral contraceptives and for one woman who was pregnant at the time of the interview. The analysis focused on the remaining 316 control subjects.

Laboratory Analysis of Hormone Levels

Blood samples were analyzed at Nichols Institute, Inc. (San Juan Capistrano, CA); laboratory personnel were blinded as to the case status. Because of the concern for the effects of long-term storage, case patient–control subjects triplets were grouped on the basis of the duration of serum storage, and sera were analyzed together in the same batch. Levels of E_2, E_1, and androstenedione were measured by an in-house method of radioimmunoassay following extraction with 20% ethyl acetate in hexane and separation by celite chromatography (*35*). E_1 sulfate was measured by radioimmunoassay after extraction with an organic solvent (*36*), enzymatic hydrolysis, and celite chromatography (*35*). Progesterone concentration was determined for 162 women in the premenopausal group with in-house procedures of radioimmunoassay after organic extraction of progesterone and other steroids. A commercially available radioimmunoassay kit manufactured by Diagnostic Systems Laboratories, Inc., Webster, TX (catalog #DSL 6300), was used to measure SHBG levels. The percentage of E_2 that was free in serum was determined by equilibrium dialysis (*37*). To estimate the percentage bound to albumin, we subtracted the percentage free from the percentage that was non-SHBG bound. The ammonium sulfate precipitation technique was used to separate the SHBG fraction (*38*). Similarly, we estimated

the percentage of E_2 that was SHBG bound by subtracting the percentage that was non-SHBG bound from 100. The amount of E_2 in each fraction was then calculated by multiplying the percentage by the total amount of E_2 measured by radioimmunoassay as described above. Complete hormone results were available for all subjects, with the exception of missing data on albumin-bound E_2 for two premenopausal and three postmenopausal subjects and on E_1 sulfate for one postmenopausal subject as a result of insufficient volumes of sera.

Reproducibility of Laboratory Assays

Prior to this study, we conducted a feasibility study of laboratory assays and found that repeated testing of the same pools over a 10-day period resulted in acceptable estimates of reliability for most hormones analyzed by the laboratory (*39*). Lack of reproducibility in the SHBG assay, however, resulted in a new radioimmunoassay kit being employed for the case–control blood samples. Multiple, blind quality surveillance blood samples that were aliquots from the same pools were included in all batches with the blood samples from subjects to monitor quality control in this study. Repeated analyses of these pools in the same and different batches revealed the overall coefficients of variation shown in Table 1. Although the coefficients of variation were relatively high for E_2 and its related fractions, this finding was largely due to one outlier in each menopausal pool. That is, one outlier was found of the 16 times the premenopausal quality-control pool was tested, and one outlier was found of the 34 times the postmenopausal pool was tested. Exclusion of these two outliers reduced the coefficients of variation for total E_2 from 20.3 to 6.0 for premenopausal and from 16.6 to 13.7 for postmenopausal pools. Similarly, exclusion of the one outlier in androstenedione reduced the coefficient of variation from 45.1 to 10.8 for the postmenopausal pool. Removing data from subjects in the various batches containing these outliers resulted in risk estimates of a magnitude similar to those presented in this article, but the variances were reduced.

Table 1. Overall coefficients of variation of laboratory assays:* National Cancer Institute Collaborative Endometrial Cancer Study, 1987-1990

	Premenopausal, %	Postmenopausal, %
Sex hormone-binding globulin	8.2	15.2
Estradiol	20.3	16.6
Free estradiol	28.1	18.2
Albumin-bound estradiol	21.5	17.2
Estrone	7.6	11.0
Estrone sulfate	12.8	11.4
Androstenedione	10.4	45.1

*Calculated from repeated testing of the same premenopausal (n = 16) or postmenopausal (n = 34) pools inserted into batches with samples from subjects.

Statistical Analysis

Age-adjusted mean hormone values were calculated using the least-squares mean regression analysis. All hormone data were log transformed as a result of skewed distributions, but data are presented as geometric means. For both premenopausal and postmenopausal groups, subjects were divided into tertiles of hormone levels based on the distribution among the control group. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by use of an unconditional logistic regression analysis (*40*) controlling for matching variables (e.g., age and race) as well as potential confounders (e.g., body mass index and exogenous estrogen use). With the exception of age, study site, and education, other factors were expressed as dichotomous variables for inclusion in models with all potential confounders and hormone values. Small numbers in the premenopausal/perimenopausal group necessitated more parsimonious models, so variables weakly related to disease (diabetes and exogenous estrogens) were removed from the full models. Blood samples were taken more often from case patients than from control subjects in the follicular phase of the menstrual cycle; therefore, the phase of the menstrual cycle was included in logistic models for E_2 fractions. Tests for trend were obtained by ordinal scoring of the tertile variables and treating them as continuous. All *P* values were two-sided.

Results

The mean age of the subjects at interview showed case patients and community control subjects to be somewhat older (58.9 and 57.5 years, respectively) than hysterectomy control subjects (54.8 years). Hysterectomy control subjects were more educated than case patients or community control subjects, so analyses were adjusted for education. Case patients and control subjects were comparable on race; 90.7% of these subjects classified themselves as white and 9.3% as nonwhite. Previously identified risk factors for endometrial cancer (*4,7,12,22,41-44*) among women with hormone data are presented in Table 2. Compared with control subjects, case patients were more likely to use menopausal estrogens, to report a history of diabetes, to have low cholesterol concentrations, to have high body mass indices, to have high waist-to-thigh ratios (predominance of upper-body fat distribution), and to have high saturated fat intakes; however, they were less likely to use oral contraceptives, consume alcohol, be current smokers, and be parous.

Among postmenopausal subjects (Table 3), the age-adjusted mean concentration of SHBG was lower, and concentrations of total E_2, free E_2, albumin-bound E_2, E_1, E_1 sulfate, and androstenedione were higher for case patients than for control subjects (P = .0001 for each). Among premenopausal women (Table 4), case patients had significantly lower concentrations of SHBG (P = .001) and higher concentrations of E_1 (P = .03) and androstenedione (P = .01) than control subjects. In contrast to postmenopausal women, the premenopausal case patients had slightly lower mean concentrations of total and free E_2 than the control subjects, but the case–control differences were not significant (P = .18 and .32, respectively). Concentrations of albumin-bound E_2 and E_1 sulfate were similar between premenopausal case patients and control subjects.

The date of the last menstrual cycle was not ascertained from premenopausal women at the time of the blood collection. Therefore, we classified women as being in the follicular or anovulatory luteal phase of the menstrual cycle on the basis of a progesterone concentration of 50 ng/dL or less (the cutpoint routinely used by our laboratory). After we adjusted for slight differences in the age distributions of case patients and control subjects, more control subjects (46%) than case patients (27%) were noted to be in the luteal phase of an ovulatory cycle at the time of phlebotomy. Examination of the age-adjusted means for case patients and control subjects with progesterone values 50 ng/dL or less (Table 4) revealed findings similar to those in the overall premenopausal group. Of note was that the total E_2 levels remained lower among case patients (51.4 pg/mL) than among control subjects (60.8 pg/mL), although this difference was not significant (P = .52).

In general, ORs adjusted for age, study site, race, and education revealed results consistent with the comparison of means. Among postmenopausal women (Table 5), a trend of reduced risk with increasing SHBG levels was observed (P for trend <.001). High concentrations of all E_2 fractions were associated with a threefold to fourfold increased risk compared with low E_2 levels. E_1 showed a strong relation with disease (OR = 3.8; 95% CI = 2.2-6.6 in highest tertile), with a linear trend in risks as concentrations increased (P for trend <.001). Risk of disease also increased significantly with E_1 sulfate levels and andro-

Table 2. Distribution of endometrial cancer case patients and control subjects for selected risk factors: National Cancer Institute Collaborative Endometrial Cancer Study, 1987-1990

	Case patients, %* (n = 276)	Control subjects, %* (n = 316)	Odds ratio† (95% confidence interval)
Exogenous estrogen use, mo			
<4	89.9	94.9	1.0 (referent)
≥4	9.8	5.1	2.3 (1.1-4.6)
History of diabetes			
No	83.3	94.3	1.0 (referent)
Yes	15.6	5.7	2.7 (1.5-5.0)
Serum cholesterol level, mg/dL			
>255	18.8	23.1	1.0 (referent)
227-255	18.5	22.2	1.1 (0.6-1.8)
195-226	26.1	22.5	1.7 (1.0-2.7)
≤194	29.0	24.7	1.9 (1.1-3.2)
Body mass index, kg/m^2			
<23.0	18.5	26.9	1.0 (referent)
23.0-26.0	10.9	23.4	0.7 (0.4-1.2)
26.1-30.0	13.8	25.3	0.8 (0.5-1.4)
>30.0	56.5	24.4	3.7 (2.3-6.0)
Waist-to-thigh ratio			
<1.62	10.5	21.8	1.0 (referent)
1.62-1.78	18.8	28.8	1.5 (0.8-2.6)
1.79-1.99	26.1	22.2	2.4 (1.4-4.3)
>1.99	38.0	24.7	3.3 (1.9-5.7)
Saturated fat intake, g/day‡			
<12	15.9	23.4	1.0 (referent)
12-18	27.9	24.1	1.8 (1.1-3.0)
19-25	23.6	25.0	1.5 (0.9-2.6)
>25	31.5	26.9	1.8 (1.0-3.3)
Oral contraceptive use			
Never	81.9	62.3	1.0 (referent)
Ever	18.1	37.7	0.4 (0.2-0.6)
Alcohol intake, g/wk			
0	27.5	22.5	1.0 (referent)
<15	38.0	38.6	0.9 (0.5-1.4)
15-60	21.7	23.7	0.9 (0.5-1.4)
>60	12.7	15.2	0.8 (0.4-1.5)
Current smoker			
No	92.4	84.2	1.0 (referent)
Yes	6.5	15.8	0.4 (0.2-0.7)
No. of births			
0	21.7	11.1	1.0 (referent)
1-2	34.8	40.2	0.4 (0.3-0.7)
≥3	43.5	48.8	0.4 (0.2-0.7)

*Some percents do not add up to 100% because of rounding, insufficient blood volume for serum cholesterol, and missing data for waist-to-thigh ratio.

†Odds ratios are adjusted for age, race, study site, and education. Subjects with missing data for a risk factor were included in the analyses, but risk estimates related to missing data are not presented.

‡Further adjusted for carbohydrate calories.

stenedione concentrations (P for trend <.001 for both). Adjustment for other risk factors substantially reduced the strength of all of these associations, with the exception of androstenedione. The relationship with total E_2 was eliminated, whereas the other risk estimates remained significant, although at a reduced level. The vast majority of these changes in ORs were the result of control for the anthropometric variables of body mass index and waist-to-thigh ratio. Control for body mass index in finer categories showed no further reduction in ORs for hormones or SHBG. Although E_1 and E_2 were too highly correlated to evaluate separate effects (r = .87), simultaneous adjustment of E_1, androstenedione (r = .45 with E_1), and SHBG (r = –.06 with E_1) showed risk estimates similar to those presented. Comparison of those with a high-risk profile (tertile 1 of SHBG, tertile 2 or 3 of E_1, and tertile 2 or 3 of androstenedione) to those with a low-risk profile (tertile 2 or 3 of SHBG, tertile 1 of E_1, and tertile 1 of androstenedione) demonstrated independent and additive effects of these three factors (OR = 4.6; 95% CI = 1.7-12).

Before adjustment for potential confounders, similarities to some risks in postmenopausal women were observed among premenopausal women (Table 6). Significantly lower risk of disease was associated with high SHBG concentrations, whereas high concentrations of E_1 and androstenedione were associated with increased risk (P for trend = .05, .04, and .04, respectively). Unlike findings in postmenopausal women, high levels of total E_2 and its fractions were associated with reduced risk of endometrial cancer, and a high E_1 sulfate concentration was not significantly related to disease (P for trend = .54). Adjustment

Table 3. Age-adjusted geometric mean (95% confidence interval) hormone values* by case–control status among postmenopausal subjects: National Cancer Institute Collaborative Endometrial Cancer Study, 1987-1990

Hormone	Geometric mean (95% confidence interval)	
	Case patients (n = 208)	Control subjects (n = 209)
Sex hormone-binding globulin, nmol/L	30.6 (28.1-33.3)	41.5 (38.1-45.1)
Total estradiol, pg/mL	10.8 (9.8-12.0)	7.4 (6.7-8.2)
Free estradiol, pg/mL	0.17 (0.15-0.19)	0.11 (0.10-0.12)
Albumin-bound estradiol, pg/mL	3.0 (2.6-3.4)	1.6 (1.4-1.8)
Estrone, pg/mL	43.7 (40.7-47.0)	33.1 (30.9-35.6)
Estrone sulfate, pg/mL	493 (436-558)	350 (309-395)
Androstenedione, ng/dL	76 (71-81)	62 (58-66)

*All means were statistically significantly different between case patients and control subjects ($P = .0001$). Conversion to moles per liter: estradiol (pmol/L) = estradiol (pg/mL)/272.37 × 1000; estrone (pmol/L) = estrone (pg/mL)/270.36 × 1000; estrone sulfate (pmol/L) = estrone sulfate (pg/mL)/350.42 × 1000; androstenedione (nmol/L) = androstenedione (ng/dL)/286.40 × 10.

of the association with SHBG for body mass index and waist-to-thigh ratio did not materially alter the estimates (e.g., OR = 0.6 and 95% CI = 0.2-1.8 for tertile 3). Inclusion of the other risk factors eliminated the association of SHBG with disease; no single variable was uniquely responsible for this change. The reduced risks associated with high total E_2 and free E_2 concentrations became less apparent with adjustment for other factors, including phase of the cycle (P for trend = .25 and .10, respectively). Adjustment for other risk factors did not appreciably alter the relationships for albumin-bound E_2 and E_1 sulfate but caused a moderate decline in E_1. The risk estimate for androstenedione changed from 2.3 (95% CI = 1.0-5.3) to 3.1 (95% CI = 1.2-7.8) with adjustment for body mass index and waist-to-thigh ratio, whereas control for other risk factors enhanced risk further. To minimize the influence of perimenopausal women in the overall premenopausal group, we restricted analyses to women younger than 45 years of age (30 case patients and 50 control subjects). This analysis showed results similar to those presented in Table 6, with the exception that risk was not elevated for young women with high E_1 levels (OR = 0.8; 95% CI = 0.2-3.7).

Several further analyses were conducted to minimize possible sources of error or bias. Although the blood samples were taken late in the natural history of the disease, we did not observe any trends of higher hormone levels or lower SHBG levels with stage of disease, which suggested that the tumor was not responsible for the observed associations. To eliminate women whose hormone levels were in transition to postmenopausal levels, we removed from the postmenopausal group women who reported a menstrual period within 2 years of the interview. Results were unchanged from those presented. Since exogenous estrogens and oral contraceptives influence risk and possibly hormone levels for many years after cessation of use (*4*,*7*), we repeated the analyses after we excluded women who had ever used either preparation. Results in both menopausal groups were not appreciably different. With the intent of removing disorders likely to be associated with hormonal alterations, we eliminated hysterectomy control subjects with a description of hyperplasia in their pathology reports. Results were similar to or slightly stronger than those presented in both menopausal groups. Hirsutism (i.e., presence of excessive facial and body hair) was associated with an approximate twofold excess risk in this study, but adjustment for this factor had no effect on hormone

Table 4. Age-adjusted geometric mean (95% confidence interval) hormone values by case–control status among all premenopausal subjects and the subset with progesterone levels less than or equal to 50 ng/dL: National Cancer Institute Collaborative Endometrial Cancer Study, 1987-1990

Hormone	Geometric mean (95% confidence interval)			Geometric mean (95% confidence interval)		
	All case patients (n = 68)	All control subjects (n = 107)	P*	Case patients with progesterone levels ≤50 ng/dL (n = 45)	Control subjects with progesterone levels ≤50 ng/dL (n = 55)	P*
Sex hormone-binding globulin, nmol/L	33.7 (29.1-39.0)	46.3 (41.2-52.0)	.001	31.2 (26.2-37.3)	45.4 (38.7-53.3)	.003
Total estradiol, pg/mL	58.1 (43.9-76.9)	74.5 (59.6-93.1)	.18	51.4 (35.4-74.8)	60.8 (43.3-85.3)	.52
Free estradiol, pg/mL	0.90 (0.68-1.18)	1.07 (0.86-1.33)	.32	0.80 (0.56-1.17)	0.89 (0.64-1.24)	.69
Albumin-bound estradiol, pg/mL	13.7 (10.3-18.2)	13.8 (11.0-17.3)	.95	11.9 (8.2-17.3)	11.2 (8.0-15.7)	.81
Estrone, pg/mL	82.9 (71.8-95.8)	67.5 (60.2-75.7)	.03	79.5 (66.2-95.5)	58.1 (49.2-68.5)	.01
Estrone sulfate, pg/mL	1234 (979-1554)	1101 (917-1324)	.45	1014 (771-1332)	918 (717-1176)	.60
Androstenedione, ng/dL	111 (100-123)	94 (86-102)	.01	101 (89-114)	89 (79-99)	.13

*All P values were two-sided.

Table 5. Odds ratios and 95% confidence intervals for endometrial cancer associated with levels of hormones and sex hormone-binding globulin among postmenopausal women: National Cancer Institute Collaborative Endometrial Cancer Study, 1987-1990

	No. of case patients	No. of control subjects	Odds ratio* (95% confidence interval)	Odds ratio† (95% confidence interval)
Sex hormone-binding globulin, nmol/L				
<35	119	71	1.0 (referent)	1.0 (referent)
35-58	57	70	0.45 (0.28-0.72)	0.66 (0.38-1.2)
≥59	32	68	0.28 (0.16-0.47)	0.51 (0.27-0.95)
Total estradiol, pg/mL				
<6.0	47	75	1.0 (referent)	1.0 (referent)
6.0-9.9	44	68	1.0 (0.59-1.7)	0.80 (0.43-1.5)
≥10.0	117	66	3.0 (1.8-5.0)	1.3 (0.70-2.5)
Free estradiol, pg/mL				
<0.08	41	67	1.0 (referent)	1.0 (referent)
0.08-0.13	37	76	0.79 (0.45-1.4)	0.63 (0.33-1.2)
≥0.14	130	66	3.5 (2.1-5.9)	1.7 (0.87-3.3)
Albumin-bound estradiol, pg/mL‡				
<1.07	39	70	1.0 (referent)	1.0 (referent)
1.07-2.24	39	69	1.0 (0.58-1.8)	0.86 (0.45-1.7)
≥2.25	128	69	3.7 (2.2-6.2)	2.0 (1.0-3.9)
Estrone, pg/mL				
<26	31	70	1.0 (referent)	1.0 (referent)
26-40	65	69	2.3 (1.3-4.1)	2.2 (1.2-4.3)
≥41	112	70	3.8 (2.2-6.6)	2.2 (1.2-4.4)
Estrone sulfate, pg/mL‡				
<232	43	69	1.0 (referent)	1.0 (referent)
232-481	52	70	1.3 (0.75-2.2)	1.3 (0.68-2.4)
≥482	112	70	2.9 (1.8-4.9)	1.9 (1.1-3.6)
Androstenedione, ng/dL				
<52	38	69	1.0 (referent)	1.0 (referent)
52-77	74	70	2.0 (1.2-3.4)	1.8 (1.0-3.2)
≥78	96	70	2.7 (1.6-4.6)	2.8 (1.5-5.2)

*Adjusted for age, study site, race, and education.
†Further adjusted for body mass index, waist-to-thigh ratio, parity, current smoking, use of oral contraceptives, diabetes, exogenous estrogen use, serum cholesterol level, alcohol intake, saturated fat, and carbohydrate calories.
‡Missing data because of insufficient volumes of sera.

risk estimates. Finally, results among those with no history of diabetes were similar to those among the overall group.

It was also of interest to evaluate the influence of the hormones on risk estimates related to anthropometric variables. In both menopausal groups, the ORs for body mass index and waist-to-thigh ratio were not significantly altered by adjustment for hormones. For example, the risk associated with high waist-to-thigh ratio among postmenopausal women (OR = 2.2; 95% CI = 1.1-4.7) remained significantly elevated and ranged from 1.9 to 2.2 with adjustment for hormones or SHBG. Of particular interest was the minimal effect of adjustment for SHBG on risk associated with body mass index. In postmenopausal women, the adjusted OR for a body mass index of 30.0 kg/m^2 or more compared with one lower than 30.0 kg/m^2 was 3.8 (95% CI = 2.2-6.4), which was reduced to 3.1 (95% CI = 1.8-5.4) after adjustment for SHBG. The OR for body mass index remained substantially elevated at approximately 3.0 after adjustment for any of the hormones.

Discussion

The results of this investigation of endometrial cancer support many of the prevailing theories concerning the hormonal etiology of this disease, but at the same time they raise some questions about the completeness of these theories. The most popular unifying hypothesis is that endometrial cancer is a disease of the proliferative effects of estrogen on the endometrium, particularly when unopposed by the differentiating action of progesterone (*14*). Furthermore, it has been proposed that this hormonal profile explains virtually all of the reproductive, anthropometric, medical, pharmacologic, and other risk factors for this cancer (*45*). The increased risks associated with elevated levels of various estrogens and diminished risks associated with elevated levels of SHBG are consistent with this hypothesis. In addition, differences between premenopausal and postmenopausal women in patterns of these associations imply differing relative contributions of various aspects of this hypothesis to these two groups. Among postmenopausal women, the elevation in risks with several serum estrogen fractions and the inverse relationship of risk with SHBG concentration point to the importance of estrogenicity. Among premenopausal women, the lack of any evidence of a positive association of endometrial cancer risk with any estrogen determination (particularly after exclusion of perimenopausal subjects) and the finding that substantially more control subjects than case patients had elevated progesterone levels, indicating the luteal phase of ovulatory cycles, suggest that the periodic effects of progesterone exposure rather than the estrogen level may be the overwhelming determinant of endo-

Table 6. Odds ratios and 95% confidence intervals for endometrial cancer associated with levels of hormones and sex hormone-binding globulin among premenopausal women: National Cancer Institute Collaborative Endometrial Cancer Study, 1987-1990

	No. of case patients	No. of control subjects	Odds ratio* (95% confidence interval)	Odds ratio† (95% confidence interval)
Sex hormone-binding globulin, nmol/L				
<39	38	34	1.0 (referent)	1.0 (referent)
39-60	11	37	0.27 (0.11-0.66)	0.26 (0.08-0.81)
≥61	19	36	0.49 (0.22-1.1)	1.2 (0.41-3.5)
Total estradiol, pg/mL				
<61	37	35	1.0 (referent)	1.0‡ (referent)
61-148	19	36	0.54 (0.25-1.2)	1.0 (0.34-2.9)
≥149	12	36	0.32 (0.14-0.76)	0.52 (0.17-1.6)
Free estradiol, pg/mL				
<0.96	40	35	1.0 (referent)	1.0‡ (referent)
0.96-2.04	14	36	0.36 (0.16-0.82)	0.52 (0.18-1.5)
≥2.05	14	36	0.34 (0.15-0.78)	0.42 (0.15-1.2)
Albumin-bound estradiol, pg/mL§				
<10.2	26	35	1.0 (referent)	1.0‡ (referent)
10.2-27.5	22	36	0.89 (0.40-2.0)	0.97 (0.35-2.7)
≥27.6	19	35	0.82 (0.36-1.9)	0.76 (0.26-2.2)
Estrone, pg/mL				
<53	12	35	1.0 (referent)	1.0 (referent)
53-89	30	36	2.9 (1.2-7.0)	2.0 (0.69-6.1)
≥90	26	36	2.8 (1.1-7.0)	2.3 (0.74-6.7)
Estrone sulfate, pg/mL				
<768	19	35	1.0 (referent)	1.0 (referent)
768-1830	25	36	1.2 (0.50-2.7)	1.3 (0.45-3.5)
≥1831	24	36	1.3 (0.56-3.0)	0.91 (0.33-2.5)
Androstenedione, ng/dL				
<83	16	35	1.0 (referent)	1.0 (referent)
83-118	20	36	1.2 (0.49-2.9)	1.6 (0.51-4.7)
≥119	32	36	2.3 (1.0-5.3)	3.6 (1.2-11)

*Adjusted for age, study site, race, and education.

†Adjusted for age, study site, race, education, body mass index, waist-to-thigh ratio, parity, smoking, use of oral contraceptives, alcohol intake, saturated fat, carbohydrate calories, and serum cholesterol level.

‡Further adjusted for luteal or nonluteal phase of the menstrual cycle.

§Missing data because of insufficient volumes of sera.

metrial cancer risk. This hypothesis has been suggested before (*14*), but it was never tested. While our results are suggestive, an appropriate test would require a study with substantially greater numbers of premenopausal women than what we studied. Such an investigation might also be able to address the issue of whether there was any residual effect on risk by level of estrogen after adequate control for presence and level of progesterone exposure.

Three observations from this study would be unexpected under the hypothesis relating to circulating levels of unopposed estrogens. These observations raise the question as to whether this hypothesis is sufficient to explain endometrial cancer.

Two of these observations are interrelated: 1) the relatively low magnitude of risk associated with increased estrogen levels and decreased SHBG levels among postmenopausal women and 2) the apparently independent effects of these hormone associations and the anthropometric risk factors they were hypothesized to explain. We had expected to see substantial elevations in relative risk with elevated estrogen levels (i.e., higher than for body mass index), and we anticipated that control for the hormonal variables would eliminate the apparent associations with adiposity. Instead, we saw only a doubling of risk for those in the highest third of various serum estrogen fractions and for those in the lower third of serum SHBG levels. In addition, control for these hormone levels had little impact on the ORs for elevated body mass index and waist-to-thigh ratio. It is possible that both of these observations could be a result of imprecision in our hormonal assessment of these women. We had only one specimen for each woman. This specimen was drawn at the time of diagnosis (or at the time of the case-matched diagnosis for control subjects), and there is documented laboratory variability in these measurements. Thus, it is possible that cumulative error in our attempt to characterize a woman's hormonal milieu could have resulted in random misclassification and resulted in lower estimates for the ORs and an uncoupling of the link between the risks for hormone levels and adiposity. However, the fact that these observations applied to those measurements with the least laboratory error (e.g., SHBG and E_1 sulfate) and that endometrial cancer risk is substantially influenced by recent exogenous hormone use (*4,46*) both suggest that alternative interpretations should also be entertained. The simplest alternative is that estrogen alone does not adequately explain risk, including the risk associated with adiposity. Indeed, the endometrial cancer risk factors of body mass index, waist-to-thigh ratio, diabetes, and even SHBG level are all associated with alterations in levels of other growth-related factors—nota-

bly insulin. A variety of metabolic alterations have been described with insulin resistance (*47,48*). These metabolic alterations could play a role in the etiology of endometrial cancer and certainly deserve some analytic attention, along with an assessment of other growth factors.

The third observation at variance with the hypothesis concerning circulating levels of unopposed estrogen, the positive association with level of androstenedione in both premenopausal and postmenopausal women, is particularly provocative. We included an assessment of this androgen, secreted by the adrenals and ovaries, since it is the primary substrate used for peripheral production of E_1 (*18*). If androstenedione were related to disease only because of its relationship with E_1, then it would have appeared unimportant after adjustment for circulating E_1. However, androstenedione itself showed the strongest and most consistent relationship to risk of endometrial cancer even after control for E_1. In fact, the only previous case–control study of any substantial size to measure hormone levels also observed an elevation of androstenedione levels in case patients, but the investigators did not comment on the potential significance of this elevation (*25*). The relationship with androstenedione takes on added meaning in the light of a report (*49*) of increased aromatase activity in malignant endometrial tumors. Thus, there is the possibility that, early in the neoplastic process, abnormal endometrial cells gain the ability to produce E_1 locally from the plasma pool of androstenedione and thus gain a growth advantage independent of circulating estrogen levels. Alternatively, while the normal endometrium is thought not to have aromatase activity (*49*), perhaps the true stem cells for the endometrium, and those that eventually become malignant, have this capability and can use the androstenedione pool to produce E_1 locally.

In the interpretation of the results of this study, a methodologic limitation merits further attention. Of note was the limited response rate to the blood component of this study. Nonetheless, the recognized risk factors were of the same magnitude in this hormone analysis (Table 2) as those in our previous publications with higher response rates for the questionnaire component (*4,7,12,22,41-44*) and in accordance with that in other published studies of these risk factors (*14*).

In summary, postmenopausal women with high concentrations of E_1, androstenedione, and albumin-bound E_2 had a twofold to threefold increased risk of endometrial cancer. Premenopausal women with high androstenedione concentrations also had a substantially increased risk of the disease. The fact that the indices of obesity were not affected by adjustment for the hormones suggested that alternative mechanisms by which these factors impart their risk should be investigated. Furthermore, although local conversion of androstenedione to E_1 and subsequently to E_2 may explain the increased risk associated with this androgen, alternative mechanisms should be investigated.

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Note

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