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Original Contribution

Hormonal, Metabolic, and Inflammatory Profiles and Endometrial Cancer Risk Within the EPIC Cohort—A Factor Analysis

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A "Western" lifestyle characterized by physical inactivity and excess weight is associated with a number of metabolic and hormonal dysregulations, including increased circulating estrogen levels, hyperinsulinemia, hyperglycemia, and chronic inflammation. The same hormonal and metabolic axes might mediate the association between this lifestyle and the development of endometrial cancer. Using data collected within the European Prospective Investigation into Cancer and Nutrition (EPIC), a prospective cohort study carried out in 10 European countries during 1992–2000, we conducted a factor analysis to delineate important components that summarize the variation explained by a set of biomarkers and to examine their association with endometrial cancer risk. Prediagnostic levels of testosterone, androstenedione, dehydroepiandrosterone sulfate, sex hormone-binding globulin, estrone, estradiol, C-peptide, insulin-like growth factor-binding proteins 1 and 2, adiponectin, high- and low-density lipoprotein cholesterol, glucose, triglycerides, tumor necrosis factor (TNF) α, soluble TNF receptors 1 and 2, C-reactive protein, interleukin-6, and interleukin-1 receptor antagonist were measured in 233 incident endometrial cancer cases and 446 matched controls. Factor analysis identified 3 components associated with postmenopausal endometrial cancer risk that could be labeled "insulin resistance/metabolic syndrome," "steroids," and "inflammation" factors. A fourth component, "lipids," was not significantly associated with endometrial cancer. In conclusion, besides the well-known associations of risk with sex hormones and insulin-regulated physiological axes, our data further support the hypothesis that inflammation factors play a role in endometrial carcinogenesis.

endometrial neoplasms; factor analysis; hormones; inflammation; prospective studies

Abbreviations: BMI, body mass index; CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; EPIC, European Prospective Investigation into Cancer and Nutrition; HDL, high-density lipoprotein; IARC, International Agency for Research on Cancer; IGFBP, insulin-like growth factor-binding protein; IR/MS, insulin resistance/metabolic syndrome; OR, odds ratio; SHBG, sex hormone-binding globulin; TNF, tumor necrosis factor.

The higher rates of endometrial cancer in developed countries than in developing countries and the increase in incidence observed among persons who migrate from low-risk areas to high-risk areas suggest a strong influence of environmental factors on this type of cancer (1, 2). However, the mechanisms underlying this relationship still have been only partially resolved.

A "Western" lifestyle is mainly characterized by physical inactivity and a high intake of energy-dense foods resulting in excess weight and high body fatness. Excess weight and obesity are characterized by a number of metabolic and hormonal dysregulations that include increased peripheral conversion of androgens into estrogens within adipose tissue, as well as hyperinsulinemia, hyperglycemia, and chronic inflammation (3).

Although estrogens are recognized as the major physiological determinant of endometrial cancer (4–8), a number of other hormonal and metabolic axes have been associated with risk (9–11). The regulation of endometrial mucosa growth and shedding during the menstrual cycle is associated with physiologically regulated cyclic endometrial inflammation. This local inflammation process may be aggravated if it is combined with a state of chronic low-grade inflammation resulting from obesity (12, 13). In the light of these and other observations, inflammation has been hypothesized to play a role in endometrial cancer development, either by mediating estrogen action or as an independent mechanism (14). Although it is well established that insulin and estrogens play important roles in endometrial carcinogenesis, the role of inflammation, especially chronic, low-grade inflammation, still has to be demonstrated. In the European Prospective Investigation into Cancer and Nutrition (EPIC), endometrial cancer risk was increased among women with elevated levels of testosterone, estrone, estradiol, C-peptide, triglycerides, glucose, and proinflammatory cytokines and decreased among women with elevated levels of sex hormone-binding globulin (SHBG), insulin-like growth factor-binding proteins (IGFBPs) 1 and 2 (IGFBP-1 and IGFBP-2), high-density lipoprotein (HDL) cholesterol, and adiponectin (15–20).

All of the above biomarkers are physiologically interrelated and are likely to reflect a more restricted number of underlying biological pathways. Therefore, we conducted a factor analysis, using the data collected within EPIC, to delineate important components (dimensions) that summarize the variation explained by the different biomarkers. Our aims in the study were to determine how many distinct constructs could be identified in this set of markers and which of these independently contributed to endometrial cancer risk. We also examined the extent to which the risk association was independent of estrogens and how these major components might mediate the body mass index (BMI)-risk association.

MATERIALS AND METHODS

Study population

EPIC is a large prospective cohort study designed to investigate the associations between nutritional, lifestyle, metabolic, and genetic factors and cancer incidence. It was initiated in 1992 in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) and involves approximately 370,000 women and 150,000 men. Norway was not included in the present study because at the time the first set of biomarkers was measured, only a few cases of endometrial cancer had been diagnosed after blood donation. Sweden was not included because their separate study did not include lipid measurements. The study population and baseline data and blood collection have been previously described in detail (21).

Follow-up for cancer incidence and vital status

Incident cancer cases were identified through several methods, including record linkage with population-based cancer registries (Denmark, Italy, the Netherlands, Spain, and the United Kingdom), health insurance records, pathology registries, and active follow-up of study subjects (France, Germany, and Greece). Data on vital status were obtained from mortality registries at the regional or national level, in combination with data collected through active follow-up (Greece). For each EPIC center, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status, as of 2005 when the first set of biomarkers was measured (from December 1999 to November 2003).

Selection of case and control subjects

Women who reported hysterectomy, use of exogenous hormones (oral contraceptives or hormone replacement therapy) at blood donation, or a previous diagnosis of cancer (except nonmelanoma skin cancer) were excluded from the study.

A total of 233 primary incident epithelial endometrial cancer cases (50 premenopausal, 183 postmenopausal) were identified and individually matched to 446 controls (incidence density sampling) on recruitment center, menopausal status (premenopausal or postmenopausal), age (in years, ±6 months) at enrollment, time of day of blood collection (±1 hour), fasting status (<3, 3–6, or >6 hours), and, for premenopausal women, phase of the menstrual cycle (follicular, periovulatory, or luteal) as previously described (22).

All participants had given their consent for participation in the EPIC study. The Ethical Review Board of the International Agency for Research on Cancer (IARC) and local institutional review boards at participating study centers approved the study protocol.

Laboratory assays

Measurement of the biomarkers has been described in detail elsewhere (15–20). In brief, blood samples from cases and matched controls were analyzed within the same analytical batch, and laboratory technicians were blinded to the case-control status of the study subjects. The number of missing values (due to failed laboratory analyses or a limited amount of sample material available) varied between 0% for C-peptide and 7% for estrone (Table 1). Most of the assays were performed in the laboratory of the Hormone and Cancer Group at IARC (Lyon, France) using commercially available immunoassays. Interleukin-1 receptor antagonist and soluble tumor necrosis factor (TNF) receptors were measured in the laboratory of the Cancer Epidemiology Division at the German Cancer Research Center (Deutsches Krebsforschungszentrum, Heidelberg, Germany) using the

Table 1. Baseline Characteristics of Endometrial Cancer Cases and Matched Controls in the European Prospective Investigation into Cancer and Nutrition, 1992–2000

Variable	% of Values Missing	Cases ($n = 233$)		Controls ($n = 446$)		*P* Value[a]
		Mean (SD)	%	Mean (SD)	%	
Age at blood donation, years	0	57.7 (7.1)		57.7 (7.2)		Matched
Age at diagnosis, years	0	60.6 (7.3)				
Lag time between blood donation and diagnosis, years	0	3.0 (2.1)				
Body mass index[b]	0	28.1 (5.9)		26.4 (4.5)		<0.0001
Waist circumference, cm	0	87.0 (13.1)		83.4 (11.3)		0.0001
Nulliparity	0		21.5		9.7	<0.0001
No. of full-term pregnancies[c]	1	2.3 (1.0)		2.4 (1.1)		0.14
Age at menarche, years	2	13.0 (1.6)		13.3 (1.7)		0.09
Age at menopause, years[d]	7	51.2 (4.0)		49.8 (4.0)		0.0006
Previous use of oral contraceptives	0		33.0		40.2	0.05
Previous use of hormone replacement therapy[d]	0		22.0		14.5	0.03
History of diabetes	2		3.9		4.4	0.77
Alcohol consumption, g/day	0	7.1 (10.6)		7.3 (10.3)		0.97
Smoking status	0					0.19
Never smoker			68.1		62.0	
Former smoker			19.0		21.2	
Current smoker			12.9		17.3	
Physical activity	0					0.65
Inactive			26.4		27.1	
Moderately inactive			34.6		38.0	
Moderately active			23.4		19.5	
Active			15.6		15.4	

Abbreviation: SD, standard deviation.
[a] Paired *t* test.
[b] Weight (kg)/height $(m)^2$.
[c] Among parous women only.
[d] Among postmenopausal women only.

same general procedures (e.g., the same study batches) as in the IARC laboratory. The lipids were measured at the Hôpital Edouard Herriot (Lyon, France) using an enzymatic colorimetric test.

Serum estradiol levels were measured only in postmenopausal women because of the large intraindividual variation in estradiol levels during the menstrual cycle among premenopausal women. Glucose levels were not measured in samples from women recruited in Oxford, United Kingdom, because these samples were kept at room temperature for more than 24 hours before processing and freezing, and glucose levels could have degraded.

Statistical analyses

Although 75% of the subjects had values for all of the biomarkers and 98% had fewer than 2 biomarkers missing, deletion of subjects with at least 1 missing biomarker in the factor analysis procedure would have resulted in the loss of 173 study subjects (25%) with measured data on most of the biomarkers. Because no clear pattern of missing values was observed by center or case-control status, we imputed missing values using center- and menopausal status-specific means. All biomarker data were subsequently transformed using the natural logarithm to normalize their distributions, and residuals were calculated using linear regression models including center, age, and fasting status, separately for pre- and postmenopausal women.

The application of factor analysis follows standard, well-established methods (23). Principal-components factor analysis was conducted using the FACTOR procedure in SAS software (version 9; SAS Institute Inc., Cary, North Carolina). Prior communalities (the part of the variance of the variable that is explained by the factors) were estimated using squared multiple correlations between the markers. The principal-components method was used as the initial extraction method. This method searches for values of the loadings that bring the estimate of the total communality as

close as possible to the sum of the observed variances. On the basis of scree plot analysis (see Web Figure 1, available at http://aje.oxfordjournals.org/) and evaluation of the final factor solutions in terms of interpretability of the factor structure, 4 uncorrelated factors were retained. These factors were rotated using a varimax rotation which maintains the statistical independence between the factors (orthogonal rotation) but maximizes or minimizes factor loadings in order to simplify the factor structure and interpretability. Markers with factor loadings $\geq|0.4|$ and therefore sharing at least 15% of variance with the factor were used to interpret and label the factors. Analyses were conducted separately for premenopausal and postmenopausal women. To adjust for the effect of estrogens, additional analyses based on variable residuals from center, age, and fasting status and estrogen levels (estrone in premenopausal women, estrone and estradiol in postmenopausal women) were also performed. The robustness of the factor patterns to multivariate outliers was evaluated by computing Mahalanobis distance. Six outliers were identified in postmenopausal women and 5 in premenopausal women. Results from analyses excluding these subjects were almost unchanged and therefore are not presented.

Factor scores (linear combinations of all of the variables, weighted by the corresponding factor loadings, with a higher score referring to higher adherence to the identified factor) were calculated for each subject. Factor scores were categorized into tertiles based on the distribution in controls to distinguish subjects with low, medium, or high scores for a specific factor. Odds ratios and 95% confidence intervals for endometrial cancer in relation to tertiles of factor scores were calculated by means of conditional logistic regression models for pre- and postmenopausal women separately. Linear trends in odds ratios were assessed using the assigned quantitative scores 1, 2, and 3 for the tertiles. Odds ratios for endometrial cancer were calculated for World Health Organization BMI categories (weight (kg)/height $(m)^2$; <25, 25–29, or ≥30), before and after adjustment for factor scores (individually and for all 4 factors together).

The effects of the following potential confounders (additional to the matching criteria, controlled for by design) were examined by including additional terms in the logistic regression models: BMI, waist circumference, parity, number of full-term pregnancies, age at menarche, age at menopause, alcohol consumption, previous use of oral contraceptives or hormone replacement therapy, and physical activity. Only BMI and waist circumference affected risk estimates by more than 10%.

RESULTS

Baseline characteristics of the study subjects are presented in Table 1. On average, cases were diagnosed at the age of 60.6 years, approximately 3 years after recruitment. Cases had higher BMI and waist circumference, were older at menopause, had less often used oral contraceptives, and had more often used hormone replacement therapy compared with controls.

Levels of cytokines, triglycerides, glucose, C-peptide, testosterone, estrone, and postmenopausal estradiol were higher in cases than in controls, whereas levels of HDL cholesterol, adiponectin, IGFBPs, and SHBG were lower in cases than in controls (Table 2).

Correlations with BMI and waist circumference were strongest for C-reactive protein, interleukin-6, interleukin-1 receptor antagonist, triglycerides, C-peptide, and estradiol ($r = 0.24$–0.38), while negative correlations were observed for HDL cholesterol, adiponectin, IGFBP-1, IGFBP-2, and SHBG ($r \leq -0.39$) (Web Table 1). Inflammation markers were all intercorrelated and correlated with lipids, glucose, adiponectin, C-peptide, IGFBPs, SHBG, and estradiol. Triglycerides showed positive correlations with low-density lipoprotein cholesterol ($r = 0.44$) and C-peptide ($r = 0.37$) and negative correlations with HDL cholesterol, adiponectin, IGFBPs, and SHBG ($r \leq -0.3$). Glucose was not strongly associated with the other markers. C-peptide was negatively correlated with adiponectin, IGFBPs, and SHBG ($r \approx -0.4$). Strong correlations were observed between androgens and between estrogens ($r \approx 0.6$). Correlations between androgens and estrogens ranged from 0.38 to 0.49. Postmenopausal estradiol had some degree of correlation with most of the markers studied.

Factor analysis identified 4 main factors that explained 41.4% of the total variance in premenopausal women and 44.3% in postmenopausal women (Table 3). Pearson correlations between the factors were less than 0.10, except between factor 1 and factor 4 (0.10 and 0.13 in pre- and postmenopausal women, respectively). The communalities were highest for testosterone, IGFBP-2, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and C-peptide in premenopausal women (communalities ≥ 0.55) and highest for soluble TNF receptors, DHEAS, testosterone, estrone, and androstenedione in postmenopausal women (communalities ≥ 0.55). They were lowest for glucose, interleukin-1 receptor antagonist, and tumor necrosis factor α (TNF-α) (communalities ≤ 0.22).

SHBG, IGFBPs, adiponectin, and HDL cholesterol had loadings greater than 0.43 on factor 1, while C-peptide and C-reactive protein had loadings less than −0.46 on factor 1. In postmenopausal women, glucose, estradiol, interleukin-6, C-reactive protein, interleukin-1 receptor antagonist, and triglycerides showed loadings less than −0.28 on this factor. This factor could thus be interpreted as the "insulin resistance/metabolic syndrome" ("IR/MS") factor.

On factor 2 ("steroids"), androgens showed loadings greater than 0.74 irrespective of menopausal status. Estrone and estradiol showed loadings greater than 0.70 on this factor in postmenopausal women.

Factor 3, which we labeled "inflammation" factors, showed loadings between 0.21 and 0.81 for cytokines in postmenopausal women. Interleukin-1 receptor antagonist and TNF-α were not associated with this factor in premenopausal women (loadings ≤ 0.10).

Factor 4 ("lipids") was defined by loadings greater than 0.50 for triglycerides and low-density lipoprotein cholesterol and negative loadings for HDL cholesterol. C-reactive protein was more strongly associated with the "lipids" factor than with the "inflammation" factor in premenopausal women (loadings of 0.43 and 0.26, respectively).

When physiological markers were further adjusted for estrogen levels, factor analysis gave very similar results

Table 2. Geometric Mean Values for Hormonal, Metabolic, and Inflammatory Markers in Endometrial Cancer Cases and Matched Controls, European Prospective Investigation into Cancer and Nutrition, 1992–2000

Marker	% With Missing Values	Cases		Controls		*P* Value[a]
		Geometric Mean	95% CI	Geometric Mean	95% CI	
C-reactive protein, ng/mL	3	1,421	1,241, 1,627	1,209	1,096, 1,334	0.07
Interleukin-1 receptor antagonist, pg/mL	2	51.5	44.4, 59.8	36.3	32.6, 40.4	0.0005
Interleukin-6, pg/mL	4	1.47	1.36, 1.60	1.30	1.23, 1.38	0.01
TNF-α, pg/mL	1	1.13	1.04, 1.23	1.05	0.99, 1.11	0.09
TNF receptor 1, pg/mL	1	1,017	978, 1,058	985	958, 1,014	0.12
TNF receptor 2, pg/mL	1	1,918	1,854, 1,984	1,866	1,821, 1,912	0.32
Triglycerides, nmol/L	1	1.25	1.18, 1.33	1.18	1.13, 1.23	0.10
Glucose, nmol/L	1	4.41	4.28, 4.54	4.24	4.15, 4.33	0.06
HDL cholesterol, nmol/L	1	1.24	1.19, 1.28	1.34	1.30, 1.38	0.0004
LDL cholesterol, nmol/L	1	3.20	3.09, 3.32	3.17	3.09, 3.25	0.59
Adiponectin, ng/mL	1	8,428	7,938, 8,948	9,983	9,560, 10,424	<0.0001
C-peptide, ng/mL	0	2.73	2.55, 2.92	2.35	2.24, 2.47	0.0002
IGFBP-1, ng/mL	0	12.4	11.0, 14.0	13.9	12.8, 15.2	0.09
IGFBP-2, ng/mL	1	335	307, 364	392	369, 417	0.0008
SHBG, nmol/L	2	43.6	40.9, 46.4	48.7	46.5, 50.9	0.002
Testosterone, ng/mL	5	0.38	0.36, 0.41	0.35	0.34, 0.37	0.05
Androstenedione, ng/mL	1	1.15	1.08, 1.21	1.14	1.09, 1.18	0.76
DHEAS, μg/dL	3	73.3	66.8, 80.4	74.1	69.3, 79.2	0.78
Estrone, pg/mL	7	44.0	40.8, 47.3	39.9	37.8, 42.1	0.005
Postmenopausal estradiol, pg/mL	0	27.4	25.8, 29.1	24.2	23.2, 25.3	0.0001

Abbreviations: CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; HDL, high-density lipoprotein; IGFBP, insulin-like growth factor-binding protein; LDL, low-density lipoprotein; SHBG, sex hormone-binding globulin; TNF, tumor necrosis factor.

[a] Paired *t* test.

(Web Table 2). In postmenopausal women only, the factor loadings for androgens were slightly weaker and the contribution of this factor (now renamed the "androgen" factor) to the total variance explained was lower (6.9%) in comparison with the variance explained by the "steroids" factor (13.7%).

Associations between factor scores and endometrial cancer risk are presented in Table 4. In postmenopausal women, significant associations with endometrial cancer risk were observed for the highest tertiles of the "IR/MS" factor (odds ratio (OR) = 2.50, 95% confidence interval (CI): 1.55, 4.02; $P_{trend} = 0.0001$), the "steroids" factor (OR = 1.68, 95% CI: 1.06, 2.66; $P_{trend} = 0.03$), and the "inflammation" factor (OR = 1.62, 95% CI: 1.06, 2.49; $P_{trend} = 0.02$). No statistically significant associations were observed in premenopausal women. The "lipids" factor was not significantly associated with endometrial cancer risk, although a nonsignificant increased risk was observed in premenopausal women. Adjustment for BMI attenuated risk estimates slightly in premenopausal women and more markedly in postmenopausal women. Generally, adjustment for waist circumference gave results very similar to those for BMI adjustment (data not shown).

When factor scores were computed on estrogen-adjusted residuals, only slightly weaker risk estimates were observed for most of the factors (Table 5). The highest tertile of the "androgen" (i.e., "steroids") factor was associated with a significant decrease in risk (OR = 0.55, 95% CI: 0.35, 0.86; $P_{trend} = 0.008$), an association that became borderline significant after adjustment for BMI.

We observed a significantly increased risk of endometrial cancer among obese women compared with normal-weight women (Table 6). This risk was strongly attenuated (−40% for postmenopausal women and −30% for premenopausal women) after adjustment for the "IR/MS" factor but not after adjustment for the other 3 factors (<7% attenuation). Only the adjustment for the "lipids" factor in premenopausal women resulted in a 19% attenuation of the estimate.

DISCUSSION

In this prospective study, we identified 4 dimensions that could be defined as "IR/MS," "steroids," "inflammation," and "lipids," explaining about 40% of the overall biomarker variance. Three of these components ("IR/MS," "steroids,"

Table 3. Loadings From Factor Analysis of Hormonal, Metabolic, and Inflammatory Variables in Endometrial Cancer Cases and Matched Controls, by Menopausal Status, European Prospective Investigation Into Cancer and Nutrition, 1992–2000

	Premenopausal Women					Postmenopausal Women				
	Loading				Com[a]	Loading				Com[a]
	Factor 1: "IR/MS"	Factor 2: "Steroids"	Factor 3: "Inflammation"	Factor 4: "Lipids"		Factor 1: "IR/MS"	Factor 2: "Steroids"	Factor 3: "Inflammation"	Factor 4: "Lipids"	
IGFBP-2	0.76[b]	−0.18	0.21	0.02	0.66	0.72[b]	−0.07	0.06	−0.07	0.54
SHBG	0.63[b]	−0.12	−0.11	−0.14	0.45	0.70[b]	−0.06	−0.01	−0.07	0.49
IGFBP-1	0.64[b]	−0.06	−0.04	−0.19	0.46	0.61[b]	0.03	0.13	−0.12	0.40
Adiponectin	0.63[b]	0.03	−0.13	−0.05	0.42	0.58[b]	−0.12	−0.09	−0.14	0.38
C-peptide	−0.74[b]	−0.01	−0.02	0.00	0.55	−0.63[b]	−0.03	0.21	0.12	0.45
Glucose	−0.03	0.07	−0.13	0.18	0.05	−0.30	0.08	0.13	0.09	0.12
Testosterone	−0.04	0.83[b]	−0.04	0.13	0.71	−0.03	0.78[b]	0.01	0.02	0.60
DHEAS	−0.17	0.76[b]	0.03	0.10	0.61	0.01	0.79[b]	−0.04	−0.05	0.63
Androstenedione	0.12	0.75[b]	−0.01	−0.06	0.58	0.07	0.74[b]	−0.08	0.06	0.57
Estrone	−0.14	0.26	0.04	−0.11	0.10	−0.18	0.75[b]	0.07	0.02	0.60
Estradiol						−0.30	0.58[b]	0.07	−0.02	0.44
TNFR2	0.19	0.05	0.68[b]	0.12	0.51	−0.02	−0.01	0.81[b]	−0.04	0.65
TNFR1	−0.19	0.06	0.66[b]	−0.15	0.49	−0.04	−0.01	0.81[b]	−0.03	0.66
Interleukin-6	−0.26	−0.06	0.51[b]	0.22	0.38	−0.39	0.05	0.43[b]	−0.03	0.34
C-reactive protein	−0.27	−0.09	0.26	0.43[b]	0.33	−0.46[b]	0.11	0.40[b]	−0.08	0.39
IL-1Ra	−0.39	0.06	0.10	0.23	0.22	−0.28	0.09	0.21	0.15	0.15
TNF-α	0.03	−0.16	0.06	0.25	0.09	−0.01	−0.04	0.36	0.15	0.15
Triglycerides	−0.40[b]	0.09	0.06	0.58[b]	0.51	−0.39	0.01	0.07	0.64[b]	0.56
LDL cholesterol	−0.12	0.02	−0.01	0.57[b]	0.34	−0.04	−0.01	−0.03	0.53[b]	0.28
HDL cholesterol	0.53[b]	−0.03	−0.09	−0.34	0.40	0.43[b]	−0.05	−0.22	−0.46[b]	0.45
Total variance, %	17.0	10.6	7.0	6.8		15.5	13.7	10.0	5.1	
Cumulative total variance, %	17.0	27.6	34.6	41.4		15.5	29.2	39.2	44.3	

Abbreviations: Com, communalities; DHEAS, dehydroepiandrosterone sulfate; HDL, high-density lipoprotein; IGFBP, insulin-like growth factor-binding protein; IL-1Ra, interleukin-1 receptor antagonist; IR/MS, insulin resistance/metabolic syndrome; LDL, low-density lipoprotein; SHBG, sex hormone-binding globulin; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor.

[a] Proportion of the variance of the specific biomarker explained by the 4 factors.

[b] Loading ≥ |0.40|.

and "inflammation") were associated with endometrial cancer risk. The "lipids" component, apart from its contribution to the metabolic syndrome, was not significantly associated with endometrial cancer risk.

The use of factor analysis allowed us to reduce a high number of correlated parameters to a relatively small number of meaningful physiological profiles. It assumes the existence of unmeasured latent variables (or "constructs") among a larger set of measured (observed) variables which depend on these latent variables but which may also experience random variation. One main advantage of this technique is that it allows us to consider simultaneously variables that have shown individual associations with endometrial cancer but also present strong correlations between themselves. However, although it follows standard methodology, exploratory factor analysis is subject to arbitrary decisions from the investigators regarding the choice and interpretation of the factors, and confirmatory analyses are needed to reproduce our findings in other populations.

One possible limitation of our approach is the apparently low percentage of variance explained by the 4 factors (approximately 40%). Although this might seem low compared with what is usually recommended (60%–80%), this is higher than what is generally observed—in dietary pattern analyses (approximately 30%), for instance.

A minor limitation of our study is the fact that some biomarkers had missing values that had to be imputed. However, the proportion of missing values for each biomarker was relatively low (<6%) and did not generally tend to cumulate in subsets of individuals (98% of the subjects had fewer than 2 biomarkers missing). Missing data can lead to underestimation of the covariances in the factor analysis

Table 4. Odds Ratios for Endometrial Cancer According to Menopausal Status and Tertile of Factor Score, European Prospective Investigation into Cancer and Nutrition, 1992–2000

Menopausal Status and Factor Score Tertile	No. of Cases	No. of Controls	Crude Results		BMI-Adjusted Results	
			OR	95% CI	OR	95% CI
–Factor 1 ("IR/MS")[a]						
Premenopausal women						
1	12	31	1.00	Referent	1.00	Referent
2	13	31	1.07	0.43, 2.67	1.14	0.45, 2.88
3	25	32	1.85	0.81, 4.21	2.20	0.81, 5.98
P_{trend}			0.13		0.12	
Postmenopausal women						
1	39	116	1.00	Referent	1.00	Referent
2	49	116	1.43	0.85, 2.39	1.19	0.70, 2.04
3	95	120	2.50	1.55, 4.02	1.70	0.99, 2.91
P_{trend}			0.0001		0.04	
Factor 2 ("Steroids")						
Premenopausal women						
1	17	32	1.00	Referent	1.00	Referent
2	19	30	1.20	0.54, 2.66	1.22	0.55, 2.70
3	14	32	0.80	0.36, 1.79	0.79	0.35, 1.78
P_{trend}			0.64		0.62	
Postmenopausal women						
1	47	117	1.00	Referent	1.00	Referent
2	58	116	1.27	0.80, 2.00	1.25	0.78, 2.00
3	78	119	1.68	1.06, 2.66	1.64	1.01, 2.66
P_{trend}			0.03		0.04	
Factor 3 ("Inflammation")						
Premenopausal women						
1	12	32	1.00	Referent	1.00	Referent
2	17	30	1.40	0.57, 3.40	1.42	0.58, 3.49
3	21	32	1.72	0.73, 4.07	1.70	0.72, 4.03
P_{trend}			0.22		0.23	
Postmenopausal women						
1	49	117	1.00	Referent	1.00	Referent
2	49	115	0.99	0.61, 1.61	0.89	0.54, 1.45
3	85	120	1.62	1.06, 2.49	1.24	0.79, 1.95
P_{trend}			0.02		0.31	
Factor 4 ("Lipids")						
Premenopausal women						
1	13	31	1.00	Referent	1.00	Referent
2	16	32	1.27	0.53, 3.02	1.27	0.53, 3.01
3	21	31	1.74	0.73, 4.15	1.71	0.70, 4.15
P_{trend}			0.21		0.23	
Postmenopausal women						
1	50	117	1.00	Referent	1.00	Referent
2	71	116	1.44	0.93, 2.24	1.42	0.90, 2.25
3	62	119	1.21	0.78, 1.89	1.15	0.73, 1.82
P_{trend}			0.41		0.59	

Abbreviations: BMI, body mass index; CI, confidence interval; IR/MS, insulin resistance/metabolic syndrome; OR, odds ratio.

[a] Opposite of factor 1.

Table 5. Odds Ratios for Endometrial Cancer According to Menopausal Status and Tertiles of Estrogen Level and Estrogen-adjusted Factor Scores, European Prospective Investigation into Cancer and Nutrition, 1992–2000

Menopausal Status and Tertile	No. of Cases	No. of Controls	Crude Results		BMI-Adjusted Results	
			OR	95% CI	OR	95% CI
Estrogens[a]						
Premenopausal women						
1	19	32	1.00	Referent	1.00	Referent
2	19	30	1.03	0.43, 2.47	0.95	0.38, 2.37
3	12	32	0.64	0.25, 1.63	0.56	0.21, 1.54
P_{trend}			0.34		0.25	
Postmenopausal women						
1	40	117	1.00	Referent	1.00	Referent
2	58	115	1.72	1.01, 2.91	1.67	0.97, 2.86
3	85	120	2.53	1.50, 4.26	2.07	1.20, 3.57
P_{trend}			0.0004		0.01	
–Factor 1[b] *("IR/MS")*[c]						
Premenopausal women						
1	13	31	1.00	Referent	1.00	Referent
2	14	31	1.06	0.44, 2.55	1.08	0.44, 2.64
3	23	32	1.62	0.71, 3.68	1.73	0.66, 4.57
P_{trend}			0.25		0.28	
Postmenopausal women						
1	40	116	1.00	Referent	1.00	Referent
2	61	116	1.66	1.02, 2.71	1.39	0.84, 2.32
3	82	120	2.13	1.32, 3.44	1.46	0.86, 2.47
P_{trend}			0.002		0.19	
Factor 2/3 ("Steroids")[c]						
Premenopausal women						
1	16	31	1.00	Referent	1.00	Referent
2	19	31	1.23	0.54, 2.78	1.27	0.55, 2.91
3	15	32	0.90	0.41, 2.01	0.91	0.40, 2.03
P_{trend}			0.81		0.82	
Postmenopausal women						
1	80	116	1.00	Referent	1.00	Referent
2	58	117	0.75	0.49, 1.15	0.82	0.52, 1.28
3	45	119	0.55	0.35, 0.86	0.65	0.40, 1.03
P_{trend}			0.008		0.07	

Table continues

and therefore underestimation of the loadings. However, we do not expect that this would have strongly affected the relative contribution of each individual biomarker to the factors or the relative contribution of each factor to endometrial cancer risk.

Another possible limitation could be the range of biomarkers assessed. Although quite large and comprehensive, the list of biomarkers considered was nevertheless limited by sample volume and assay cost. Therefore, the biomarkers were chosen as the most representative and reliable among the full set of existing commercial assays, but they only partially capture the full spectrum of the 4 biological pathways. This is especially true for the inflammation pathway, where a rather limited list was chosen among the tens of existing cytokines. As a consequence, the factor analysis was limited by the biomarkers that were previously measured, and some associations might have been missed or underestimated.

Although statistically factor analysis produces constructs that are uncorrelated, this does not imply that the physiological pathways identified are not interrelated. Indeed, we observed that the factor that explains the higher percentage

Table 5. Continued

Menopausal Status and Tertile	No. of Cases	No. of Controls	Crude Results		BMI-Adjusted Results	
			OR	95% CI	OR	95% CI
Factor 2/3 ("Inflammation")[c]						
Premenopausal women						
1	14	32	1.00	Referent	1.00	Referent
2	17	30	1.24	0.49, 3.11	1.28	0.50, 3.25
3	19	32	1.33	0.56, 3.13	1.31	0.56, 3.10
P_{trend}			0.52		0.54	
Postmenopausal women						
1	52	116	1.00	Referent	1.00	Referent
2	49	117	0.91	0.56, 1.46	0.80	0.49, 1.30
3	82	119	1.50	0.98, 2.30	1.13	0.71, 1.78
P_{trend}			0.05		0.54	
Factor 4 ("Lipids")[c]						
Premenopausal women						
1	13	31	1.00	Referent	1.00	Referent
2	18	32	1.43	0.61, 3.38	1.41	0.59, 3.38
3	19	31	1.58	0.65, 3.82	1.55	0.61, 3.91
P_{trend}			0.32		0.37	
Postmenopausal women						
1	50	117	1.00	Referent	1.00	Referent
2	65	116	1.34	0.85, 2.11	1.36	0.85, 2.18
3	68	119	1.34	0.86, 2.09	1.25	0.79, 1.98
P_{trend}			0.21		0.37	

Abbreviations: BMI, body mass index; CI, confidence interval; IR/MS, insulin resistance/metabolic syndrome; OR, odds ratio.

[a] Estrone levels in premenopausal women; mean estrone and estradiol levels in postmenopausal women.

[b] Opposite of factor 1.

[c] Factor scores were computed on estrogen-adjusted residuals.

of variance in our data set is a constellation of markers related to the insulin, inflammation, and estrogen axes. In addition, some of the biomarkers had high factor loadings on more than 1 factor (e.g., estradiol, interleukin-6, and C-reactive protein), meaning that for those biomarkers the estimation of relationships with endometrial cancer risk would also be distributed over the corresponding factors. Nevertheless, the 4 factors identified did show a very clear pattern with respect to known physiological relationships between the individual biomarkers. For example, excess adiposity is known to be causally related to lower levels of adiponectin and higher levels of triglycerides (24, 25) and is also a well-established cause of insulin resistance and hyperinsulinemia (26). Furthermore, insulin is itself a strong negative regulator of the synthesis of IGFBP-1 and -2, as well as of SHBG (27, 28). These physiological relationships are each strongly reflected in factor 1. Likewise, the high loadings of factor 2 specifically with DHEAS, androstenedione, and testosterone, and in postmenopausal women with estrone and estradiol as well, reflect well-known pathways of steroidogenesis, plus the fact that in postmenopausal women circulating levels of androgens are a key determinant of estrogen levels (29). Factor 3 presented very high factor loadings specifically for TNF receptors, interleukin-6, and C-reactive protein, which are also known to be physiologically interrelated factors that are jointly involved in inflammatory response (30, 31). In addition, it is interesting to note that some biomarkers previously associated with endometrial cancer risk, such as glucose and TNF-α, were not well characterized by any of the 4 factors. Thus, more than a single exploratory analysis, the factors identified provide a synthetic way of describing interrelated physiological effects along well-known physiological axes, and this in turn allowed us to explore which of these major axes may independently contribute to increasing endometrial cancer risk.

Our results are in line with current knowledge regarding the etiology of endometrial cancer and the major role of obesity and obesity-related circulating markers in the development of this cancer (3, 8). The effect of the "IR/MS" factor on endometrial cancer risk seemed strongly related to obesity, as we observed a strong attenuation of its association with endometrial cancer after adjustment for BMI and a

Table 6. Odds Ratios for Endometrial Cancer According to Menopausal Status and World Health Organization Body Mass Index Category, With and Without Adjustment for Factor Scores, European Prospective Investigation into Cancer and Nutrition, 1992–2000

Menopausal Status and BMI[a] Category	No. of Cases	No. of Controls	Crude Results		Adjusted for Factor 1 ("IR/MS")		Adjusted for Factor 2 ("Steroids")		Adjusted for Factor 3 ("Inflammation")		Adjusted for Factor 4 ("Lipids")		Adjusted for All 4 Factors	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Premenopausal women														
<25	24	47	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25–29	15	33	0.92	0.37, 2.29	0.73	0.27, 1.98	0.92	0.37, 2.29	0.87	0.34, 2.21	0.84	0.33, 2.14	0.61	0.21, 1.74
≥30	11	14	1.54	0.58, 4.11	1.08	0.34, 3.44	1.53	0.57, 4.10	1.47	0.55, 3.95	1.24	0.43, 3.59	0.79	0.23, 2.78
P_{trend}			0.45		0.94		0.45		0.51		0.77		0.67	
Postmenopausal women														
<25	53	144	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25–29	67	140	1.36	0.87, 2.11	1.04	0.65, 1.68	1.36	0.87, 2.13	1.32	0.85, 2.06	1.35	0.87, 2.11	1.01	0.63, 1.64
≥30	63	168	2.73	1.66, 4.50	1.65	0.92, 2.98	2.72	1.65, 4.50	2.55	1.51, 4.29	>2.73	1.65, 4.50	1.50	0.81, 2.78
P_{trend}			0.0001		0.10		0.0001		0.0006		0.0001		0.22	

Abbreviations: BMI, body mass index; CI, confidence interval; IR/MS, insulin resistance/metabolic syndrome; OR, odds ratio.
[a] Weight (kg)/height (m)^2.

major reduction in the risk for obese women versus normal-weight women after adjustment for the "IR/MS" factor. Insulin can increase tumor growth by binding to the insulin receptor or the insulin-like growth factor 1 receptor, levels of which are both increased in endometrial tumors (32, 33). Insulin also down-regulates the most important IGFBP within the endometrium, IGFBP-1 (34), and thus increases bioavailability of insulin-like growth factor 1 within the tissue, stimulating further tumor development. Among postmenopausal women, an indirect mechanism of action of insulin on endometrial carcinogenesis is an increase in levels of bioavailable estrogens, through a decrease in the hepatic synthesis of SHBG. In premenopausal women, insulin can increase endometrial cancer risk by excessive stimulation of ovarian androgen synthesis, thereby causing chronic anovulation and progesterone deficiency (27), which in the presence of normal estradiol levels is a well-established risk factor for endometrial cancer (7, 8).

Also expected is the association observed for the "steroids" factor in postmenopausal women. This relationship seems to be mostly driven by estrogens, as androgens alone did not show any increase in risk but rather pointed towards a negative association with endometrial cancer risk. Contrary to estrogens, androgens themselves do not seem to stimulate endometrial cell proliferation (35).

Besides the well-documented relationships of sex steroid and insulin-regulated pathways with endometrial cancer development, our results support an additional role for inflammation, albeit one not fully independent of BMI. Although less well established, this latter association is further supported by evidence that chronic inflammation could be involved in tumor initiation and progression (14, 30, 36). Inflammation is known to play a key role during the menstrual cycle, and cytokines are involved in the process of growth and shedding of the endometrial mucosa. Inflammatory markers could also influence endometrial carcinogenesis through indirect obesity-related effects such as the development of insulin resistance (37) or the modulation of aromatase activity by cytokines within adipose tissue (38, 39) or within the endometrium (40). However, there have been very few prospective studies on the association between inflammatory markers (cytokines) and endometrial cancer risk. EPIC was the first cohort study to find an increased risk of endometrial cancer with elevated levels of proinflammatory cytokines (19, 20). Since the publication of the EPIC results, only 1 other prospective cohort study, to our knowledge, has explored this association. In that study, Wang et al. (41) found that elevated C-reactive protein levels were associated with a more than 2-fold increased risk of endometrial cancer, independently of BMI.

By performing analyses both with and without adjustment for BMI, we can obtain some judgment on the portion of metabolic variability that is related to disease independently of adiposity. Conversely, by also performing analyses in which the relationship between endometrial cancer risk and BMI is examined both with and without adjustment for the metabolic factors as physiological mediators, we could also gauge the extent to which these markers may explain the relationship of BMI with risk. After adjustment for the 4 factors, the odds ratio for endometrial cancer among obese

women, although no longer statistically significant, was still 50% higher than that in lean women. This latter result suggests that part of the effects of adiposity may be mediated by physiological pathways not accounted for in our study. Alternatively, however, it is also possible that a single blood measurement of metabolic markers did not fully characterize subjects' longer-term metabolic profiles with 100% accuracy and that this led to a residual association of BMI with risk.

In conclusion, factor analysis identified 3 relatively independent and physiologically well-defined dimensions that each could be associated with endometrial cancer risk in postmenopausal women: the "IR/MS," "steroids," and "inflammation" pathways. Further experimental and clinical studies are needed to clarify whether inflammation has a direct causal biological role in endometrial carcinogenesis and to identify possible indirect effects through other related pathways such as insulin sensitivity.

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REFERENCES

1. Lee J, Demissie K, Lu SE, et al. Cancer incidence among Korean-American immigrants in the United States and native Koreans in South Korea. *Cancer Control*. 2007;14(1):78–85.
2. Liao CK, Rosenblatt KA, Schwartz SM, et al. Endometrial cancer in Asian migrants to the United States and their descendants. *Cancer Causes Control*. 2003;14(4):357–360.
3. Dossus L, Kaaks R. Nutrition, metabolic factors and cancer risk. *Best Pract Res Clin Endocrinol Metab*. 2008;22(4): 551–571.
4. Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. *Br J Cancer*. 1988;57(2):205–212.
5. Lukanova A, Lundin E, Micheli A, et al. Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. *Int J Cancer*. 2004;108(3):425–432.
6. Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I, et al. Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. *Br J Cancer*. 2001;84(7):975–981.
7. Henderson BE, Casagrande JT, Pike MC, et al. The epidemiology of endometrial cancer in young women. *Br J Cancer*. 1983;47(6):749–756.
8. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev*. 2002;11(12):1531–1543.
9. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP -1, -2 and -3 and risk of endometrial cancer. *Int J Cancer*. 2004;108(2): 262–268.
10. Bjorge T, Stocks T, Lukanova A, et al. Metabolic syndrome and endometrial carcinoma. *Am J Epidemiol*. 2010;171(8): 892–902.
11. Gunter MJ, Hoover DR, Yu H, et al. A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17(4):921–929.
12. Maybin JA, Critchley HO, Jabbour HN. Inflammatory pathways in endometrial disorders. *Mol Cell Endocrinol*. 2011;335(1):42–51.
13. Wallace AE, Gibson DA, Saunders PT, et al. Inflammatory events in endometrial adenocarcinoma. *J Endocrinol*. 2010;206(2):141–157.
14. Modugno F, Ness RB, Chen C, et al. Inflammation and endometrial cancer: a hypothesis. *Cancer Epidemiol Biomarkers Prev*. 2005;14(12):2840–2847.
15. Cust AE, Allen NE, Rinaldi S, et al. Serum levels of C-peptide, IGFBP-1 and IGFBP-2 and endometrial cancer risk; results from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2007;120(12): 2656–2664.
16. Allen NE, Key TJ, Dossus L, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer*. 2008;15(2):485–497.
17. Cust AE, Kaaks R, Friedenreich C, et al. Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer*. 2007; 14(3):755–767.
18. Cust AE, Kaaks R, Friedenreich C, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab*. 2007;92(1):255–263.
19. Dossus L, Rinaldi S, Becker S, et al. Obesity, inflammatory markers and endometrial cancer risk: a prospective case-control study. *Endocr Relat Cancer*. 2010;17(4): 1007–1019.
20. Dossus L, Becker S, Rinaldi S, et al. Tumor necrosis factor (TNF)-α, soluble TNF receptors and endometrial cancer risk: the EPIC study. *Int J Cancer*. 2010;129(8): 2032–2037.
21. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr*. 2002; 5(6B):1113–1124.
22. Kaaks R, Berrino F, Key T, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*. 2005;97(10):755–765.
23. Johnson RA, Wichern DW. *Applied Multivariate Statistical Analysis*. 6th ed. Upper Saddle River, NJ: Prentice-Hall; 2007.
24. Lihn AS, Pedersen SB, Richelsen B. Adiponectin: action, regulation and association to insulin sensitivity. *Obes Rev*. 2005;6(1):13–21.
25. Miller WM, Nori-Janosz KE, Lillystone M, et al. Obesity and lipids. *Curr Cardiol Rep*. 2005;7(6):465–470.
26. Gallagher EJ, Leroith D. Insulin, insulin resistance, obesity, and cancer. *Curr Diab Rep*. 2010;10(2):93–100.
27. Franks S, Kiddy DS, Hamilton-Fairley D, et al. The role of nutrition and insulin in the regulation of sex hormone binding globulin. *J Steroid Biochem Mol Biol*. 1991;39(5B): 835–838.
28. Lee PD, Giudice LC, Conover CA, et al. Insulin-like growth factor binding protein-1: recent findings and new directions. *Proc Soc Exp Biol Med.* 1997;216(3):319–357.
29. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab*. 2000;11(8):327–332.
30. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860–867.
31. Das UN. Is obesity an inflammatory condition? *Nutrition*. 2001;17(11-12):953–966.
32. Talavera F, Reynolds RK, Roberts JA, et al. Insulin-like growth factor I receptors in normal and neoplastic human endometrium. *Cancer Res*. 1990;50(10):3019–3024.
33. Roy RN, Gerulath AH, Cecutti A, et al. Discordant expression of insulin-like growth factors and their receptor messenger ribonucleic acids in endometrial carcinomas relative to normal endometrium. *Mol Cell Endocrinol*. 1999;153(1-2):19–27.
34. Bell SC. The insulin-like growth factor binding proteins—the endometrium and decidua. *Ann N Y Acad Sci*. 1991;622: 120–137.

35. Tuckerman EM, Okon MA, Li T, et al. Do androgens have a direct effect on endometrial function? An in vitro study. *Fertil Steril*. 2000;74(4):771–779.
36. Schottenfeld D, Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. *CA Cancer J Clin*. 2006;56(2):69–83.
37. Greenberg AS, McDaniel ML. Identifying the links between obesity, insulin resistance and beta-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. *Eur J Clin Invest*. 2002; 32(suppl 3):24–34.
38. Purohit A, Reed MJ. Regulation of estrogen synthesis in postmenopausal women. *Steroids*. 2002;67(12):979–983.
39. Zhao Y, Nichols JE, Bulun SE, et al. Aromatase P450 gene expression in human adipose tissue. Role of a Jak/STAT pathway in regulation of the adipose-specific promoter. *J Biol Chem*. 1995;270(27):16449–16457.
40. Salama SA, Kamel MW, az-Arrastia CR, et al. Effect of tumor necrosis factor-alpha on estrogen metabolism and endometrial cells: potential physiological and pathological relevance. *J Clin Endocrinol Metab*. 2009; 94(1):285–293.
41. Wang T, Rohan TE, Gunter MJ, et al. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):971–977.