Plasma Adiponectin Levels and Endometrial Cancer Risk in Pre- and Postmenopausal Women

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Background: Adiponectin, an adipocytokine secreted by adipose tissue, is decreased in obesity, insulin resistance, type 2 diabetes, and polycystic ovary syndrome, all of which are well-established risk factors for endometrial cancer.

Methods: We conducted a case-control study nested within the European Prospective Investigation into Cancer and Nutrition to examine the relation between prediagnostic plasma adiponectin levels and endometrial cancer risk. Among pre- and postmenopausal women who were not currently using exogenous hormones, 284 women developed incident endometrial cancer during an average of 5.1 yr of follow-up. Using risk set sampling, 548 control subjects were selected, matched on center, age, menopausal status, phase of menstrual cycle, time of blood draw, and fasting status. Conditional logistic regression models were used to estimate relative risks and 95% confidence intervals.

Results: Adiponectin levels were inversely associated with endometrial cancer risk [body mass index-adjusted relative risk for the top *vs.* bottom quartile = 0.56 (95% confidence interval 0.36–0.86), P_{trend} = 0.006]. There was evidence of a stronger inverse association among obese women than among nonobese women ($P_{heterogeneity}$ = 0.03). The inverse association also appeared stronger for women who were postmenopausal or perimenopausal than premenopausal at baseline, but this was not statistically significantly heterogeneous ($P_{heterogeneity}$ = 0.51). The association remained statistically significant after separate adjustment for other obesity-related physiological risk factors such as C-peptide, IGF binding protein-1, IGF binding protein-2, SHBG, estrone, or free testosterone but only marginally statistically significant after simultaneous adjustment for these factors.

Conclusions: High circulating adiponectin levels are associated with reduced endometrial cancer risk, largely independent of other obesity-related risk factors. (*J Clin Endocrinol Metab* 92: 255–263, 2007)

ADIPOSE TISSUE IS an active endocrine organ that re-
leases a number of cytokines and hormones, collec-
tively termed adipocytokines, including adiponectin, leptin,
resistin, and TNF-α (1). Adiponectin is the most abundant
circulating adipocytokine and is decreased in obesity, insulin
resistance, type 2 diabetes, and polycystic ovary syndrome,
all of which are independent and well-established risk fac-
tors for endometrial cancer (2). Polymorphisms in the gene
encoding adiponectin have also been associated with these
risk factors (1, 3, 4). Thus, adiponectin may have a role in
endometrial carcinogenesis.

A major metabolic pathway through which adiponectin
could influence risk is by decreasing blood insulin and glu-
cose levels, through increased fatty acid oxidation, inhibition
of hepatic glucose production, improved insulin signal trans-
duction, and increased peripheral tissue sensitivity to insulin
(1, 5–7). Animal models and human studies suggest that
adiponectin may have strong antiinflammatory properties
that could counteract the proinflammatory and neoplastic
effects of TNF-α, IL-6, and C-reactive protein (7–13). These
cytokines are implicated in endometrial cancer development
through their effects on nuclear factor-κB activity (10, 14),
estrogen (14, 15), and insulin levels (7, 9, 16).

Initial, more direct evidence linking adiponectin with en-
dometrial cancer comes from the results of three relatively
small (<120 cases) hospital-based case-control studies (17–
19). High adiponectin levels were associated with a 20–90%
reduction in risk of endometrial cancer, independently of
body mass index (BMI), and particularly strongly among
younger or premenopausal women.

To address the hypothesis that prediagnostic adiponectin
levels are inversely associated with risk of endometrial can-
cer, we designed a case-control study among 284 incident
cases of endometrial cancer in pre- and postmenopausal
women and 548 matched controls, nested within the Euro-
pean Prospective Investigation into Cancer and Nutrition
(EPIC) cohort study. Furthermore, to investigate whether
other obesity-related biological markers may mediate this
association, we also examined the relations between plasma
adiponectin concentrations, measures of adiposity, and cir-
culating levels of C-peptide (a marker of pancreatic insulin
production), IGF binding proteins (IGFBP)-1 and IGFBP-2
and endogenous sex steroid hormones.

Subjects and Methods

Study population

EPIC recruitment and follow-up procedures and collection of ques-
tionnaire data, anthropometric measurements, and blood samples have
been described in detail elsewhere (20). Briefly, approximately 366,500
women and 153,500 men in 10 western European countries joined the
study between 1992 and 1998, and of these, about 386,000 also provided
a blood sample. The present study includes subjects from eight of the 10
participating countries: Denmark, France, Germany, Greece, Italy, The
Netherlands, Spain, and the United Kingdom. Norway was not included
in the present study because blood samples had been collected only
recently, and very few cases of endometrial cancer had been diagnosed
when the present study was initiated. Sweden was not included because
a separate study within their cohort had already been planned.

Methods for the collection of data and blood samples and ascertainment of follow-up

Data on nondietary lifestyle and health factors were collected via
standardized questionnaires that included menstrual and reproductive
history, current and previous use of oral contraceptives (OCs) and post-
menopausal hormone replacement therapy (HRT), health history, smok-
ing and alcohol consumption, past-year physical activity, level of edu-
cation, and brief occupational history. Height, weight, and waist and hip
circumferences were measured according to standardized protocols, in
light dressing, except for part of the Oxford cohort, in which height and
weight were self-reported (21). A summary measure of physical activity,
combining recreational and household activity in metabolic equivalent
(MET)-hours/week, and the definition of menopausal status have been
previously described (22, 23). All baseline questionnaire and follow-up
data were entered into a central database at the International Agency for
Research on Cancer (IARC) in Lyon, France. Blood samples were col-
lected and stored according to standardized protocols (20, 23). Methods
for the follow-up for cancer incidence and vital status in each EPIC
country are described elsewhere (20). Vital status was known for 98.4%
of all EPIC participants as of April 2004. For each EPIC study center,
closure dates of the study period were defined as the date of the last
complete follow-up for both cancer incidence and vital status (between
June 1999 and December 2003, depending on the center). The average
duration of follow-up for this analysis was 5.1 yr.

Selection of case and control subjects

Case subjects were women who were diagnosed with endometrial
cancer after the initial blood donation and before the end of the study
follow-up period in each study center. Women were excluded from
being a case or control for this study if, at the time of blood donation,
they had a previous diagnosis of cancer (except nonmelanoma skin
cancer), had had a hysterectomy, or were presently using exogenous
hormones (OCs or HRT) because these can alter circulating hormone
levels (24). We further excluded endometrial tumors of known nonepi-
thelial or nonmalignant morphology (25). A total of 135,953 women from
the eight participating countries met these eligibility criteria, of whom
300 women were diagnosed with endometrial cancer during the fol-
low-up period. After further exclusion of 16 cases with insufficient blood
sample volume, there were 284 cases included in this study, comprising
67 cases in Denmark, 61 in Italy, 41 in Spain, 36 in The Netherlands, 34
in the United Kingdom, 19 in Germany, 17 in France, and nine in Greece.
The cancer diagnosis was confirmed by histology (92%), clinical exam-
ination (7%), self-report, tomography scan, surgery, or autopsy (1%).
Detailed tumor morphology was specified for 142 cases (50%), of which
133 cases (94%) were classified as type I (generally estrogen dependent
endometrioid adenocarcinomas) and nine cases (6%) as type II (mostly
nonestrogen dependent, serous papillary, clear cell, or squamous ade-
nocarcinomas) (25, 26).

Control subjects were chosen at random among risk sets consisting
of all eligible cohort members alive and free of cancer (except nonmela-
noma skin cancer) at the time of diagnosis of the index case. An incidence
density sampling protocol for control selection was used, such that
controls could include subjects who became a case later in time, whereas
each control could also be sampled more than once. Matching criteria
included: study center, menopausal status (premenopausal, postmeno-
pausal, perimenopausal/unknown), age at blood collection (±6
months), time of the day of blood collection (±1 h), time between blood
draw and last consumption of foods or drinks (<3, 3–6, >6 h, unknown),
and for premenopausal women phase of menstrual cycle [estimated
from the reported start date of the menses preceding or subsequent to
the blood donation, reported in detail elsewhere (27)]. Two matched
controls were identified for 264 cases, and one matched control for 20
cases (total of 548 controls).

All participants gave written consent for future analyses of their
blood samples, and the study was approved by the local ethics com-
mittees in the participating countries and the Internal Review Board of
the IARC.

Hormone assays

All hormone assays were performed at the IARC, France, by labo-
ratory staff blinded to the case-control status of the study subjects. The

plasma samples of each matched case-control set were analyzed with sets from the same center, within the same batch (*i.e.* using the same assay kit) on the same day. Adiponectin concentrations were measured by ELISA (R&D Systems Europe, Abingdon, UK). Three additional samples were inserted randomly in each batch as a quality control measure. The intrabatch coefficients of variation were 8.2, 5.6, and 5.1%, and the interbatch coefficients of variation were 7.7, 7.9, and 7.6% for adiponectin concentrations of 4.3, 4.9, and 14.7 μg/ml, respectively.

Serum levels of C-peptide, IGFBP-1, IGFBP-2, and endogenous sex steroid hormones (testosterone, androstenedione, dehydroepiandrosterone sulfate, estrone, SHBG, free testosterone, and, in postmenopausal women, total and free estradiol) had been previously analyzed and will be examined in separate papers.

Statistical analyses

Circulating levels of adiponectin and other hormones were log transformed to normalize their distributions. Differences in baseline characteristics and the geometric mean adiponectin levels between cases and controls (using the average of the two matched controls) were compared using paired *t* tests for continuous variables and χ^2 tests for categorical variables. Analysis of covariance, adjusting for age and laboratory batch, was used to examine the contribution of different factors on the between-subject variation in adiponectin levels. Pearson's partial correlation coefficients, adjusted for age at blood collection, laboratory batch, and case-control status, were estimated to assess the correlations between adiponectin levels, anthropometric measures, physical activity, and levels of circulating hormones.

Conditional logistic regression models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the associations between plasma adiponectin levels and endometrial cancer risk. For stratification by BMI categories, we used unconditional logistic regression adjusted for laboratory batch and all matching factors, to retain all subjects in the model. The prospective design and use of incidence density sampling for selecting controls in this study permitted the direct estimation of the relative risk rather than the odds ratio (28). Quartile cut-points (or tertile cut-points for subgroup analyses) were based on the distribution of adiponectin concentration in control subjects in the full study group; these same cut-points were also used for the subgroup analyses. Likelihood ratio tests using medians for each quantile category were used to assess linear trends in RRs.

Multivariate logistic regression was used to examine the effects of potential confounders other than those controlled for by matching, including BMI (kilograms per square meter; continuous), waist circumference (centimeters; continuous), waist-hip ratio (continuous), age at menarche (<12, 12, 13, 14 yr, ≥15, missing), age at menopause (<44, 44–47, 48–50, 51–52, 53–54, ≥55 yr, missing), parity (nulliparous, one or more, missing), age at birth of last child (nulliparous, <25, 25–29, 30–34, ≥35 yr, missing), OC use (never, past, missing), HRT use (never, past, missing), smoking (never, past, current, missing), physical activity level (MET-hours/week in quartiles: <61.5, 61.5–96.9, 97.0–141.9, ≥142.0), and education level (completed secondary school: yes, no, missing). Other than BMI and waist circumference, none of these variables changed the beta coefficients for the association between adiponectin (as a log continuous variable) and endometrial cancer risk by more than 10%; therefore, we present only the crude (adjustment for matching variables only) and adiposity-adjusted values in this paper.

In addition, we examined whether circulating levels of C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free estradiol, and free testosterone mediated the association between adiponectin and endometrial cancer risk by including these variables as continuous variables in the regression models.

χ^2 tests were used to examine heterogeneity of endometrial cancer risk estimates associated with a doubling of adiponectin levels among the following subgroups: country, menopausal status, age at cancer diagnosis (<55, ≥55 yr), BMI (<25, 25–29.9, ≥30 kg/m^2), fasting status (≤6 h, >6 h since last food or drink), physical activity level (above and below the median MET-hours/week), and lag time between blood donation and diagnosis (<2, ≥2 yr). All statistical tests were two tailed, and *P* < 0.05 was considered statistically significant. All statistical analyses were performed using the SAS software package, version 9.1 (SAS Institute, Cary, NC).

Results

Baseline characteristics and geometric mean plasma adiponectin levels of the study participants are shown in Table 1. Overall, the mean prediagnostic plasma adiponectin concentration was 15% lower for cases, compared with control subjects. The mean adiponectin concentration remained consistently lower among cases, compared with controls, when stratified by menopausal status, BMI, or fasting status, although the differences were not always statistically significant.

Differences in adiponectin levels according to baseline characteristics were evaluated after adjustment for age at blood collection, case-control status, and laboratory batch (data not shown). Increasing BMI, waist circumference, and waist to hip ratio were associated with lower adiponectin levels ($P_{\text{trend}} < 0.0001$). Adiponectin levels were also lower in women who reported having diabetes (*P* = 0.03), never using OCs (*P* = 0.05), or having less education (*P* = 0.03). There were no significant differences in adiponectin levels according to fasting status, menopausal status, previous HRT use, reproductive factors, phase of menstrual cycle, or level of physical activity. Similarly, analysis of covariance showed that menopausal status, fasting status, physical activity level, and country of recruitment each predicted less than 1% of the between-subject variation in levels.

Pearson partial correlation coefficients, adjusted for age, case-control status, and laboratory batch, showed that plasma adiponectin levels were negatively correlated with measures of adiposity (Table 2). In addition, adiponectin levels were negatively correlated with levels of C-peptide and estrogens and positively correlated with SHBG, IGFBP-1, and IGFBP-2 levels. Adiponectin levels were negatively correlated with free testosterone but not other serum androgen levels or physical activity. The correlations were somewhat weakened but remained statistically significant after additional adjustment for BMI (Table 2).

Conditional logistic regression analyses showed a strong inverse association between adiponectin concentration and risk [RR for the top *vs.* bottom quartile = 0.47 (95% CI 0.31–0.72), P_{trend} = 0.0002] (Table 3).

When stratified by menopausal status at the time of blood donation, there was a strong inverse association between adiponectin levels and risk among postmenopausal women [RR for the top *vs.* the bottom tertile = 0.44 (95% CI 0.28–0.69), P_{trend} = 0.0003] and perimenopausal/unknown women [RR for the top *vs.* the bottom tertile = 0.41 (95% CI 0.16–1.01), P_{trend} = 0.03] but not among premenopausal women [RR for the top *vs.* the bottom tertile = 1.05 (95% CI 0.49–2.25), P_{trend} =0.84] (Table 4). Formal tests for heterogeneity of the effect of menopausal status on the association between adiponectin and endometrial cancer risk were not statistically significant ($P_{\text{heterogeneity}}$ = 0.51). There was some evidence of a stronger inverse association between adiponectin levels and endometrial cancer risk among obese women than among nonobese women (Table 4) ($P_{\text{heterogeneity}}$ = 0.03), even after additional adjustment for BMI and other obesity-related biological factors within each BMI category. A similar effect was observed when postmenopausal women were analyzed separately (Table 4). There was no evidence that the associations between adiponectin and endometrial cancer

TABLE 1. Baseline characteristics and geometric mean prediagnostic plasma adiponectin levels for women who developed endometrial cancer during follow-up (cases) and control subjects

Baseline characteristic	Cases	Controls	P for difference[a]
Total no. of women	284	548	
Menopausal status			
Premenopausal (n; 19%)	54	105	
Postmenopausal (n; 68%)	192	371	
Perimenopausal/unknown (n; 13%)	38	72	
Age at blood collection (yr)	56.9 (45.4–67.9)	56.9 (45.0–68.0)	
Age at diagnosis (yr)	59.9 (47.0–71.0)		
Years between blood collection and diagnosis	3.0 (0.0–6.0)		
Anthropometric measures			
Weight (kg)	72.1 (52.8–97.9)	68.1 (51.5–88.6)	<0.0001
Height (cm)	160.4 (149.7–171.0)	160.5 (149.5–171.7)	0.82
BMI (kg/m^2)	28.1 (20.9–37.6)	26.5 (20.2–34.8)	<0.0001
Waist circumference (cm)	86.5 (67.2–111.5)	83.0 (67.7–104.0)	<0.0001
Hip (cm)	105.7 (90.3–124.5)	102.6 (90.0–120.0)	<0.0001
Waist to hip ratio	0.82 (0.72–0.93)	0.81 (0.70–0.93)	0.04
Obese (%, BMI $\geq$ 30 kg/m^2)	32.4	18.3	<0.0001
Age at menarche (yr)	13.0 (11.0–15.0)	13.3 (11.0–16.0)	0.03
Nulliparous (%)	19.8	9.9	0.0002
Age at first pregnancy in parous women (yr)	24.5 (18.0–31.0)	25.3 (19.0–34.0)	0.08
Age at birth of last child in parous women (yr)	29.5 (21.0–37.0)	30.3 (23.0–38.0)	0.09
No. of pregnancies in parous women	2.3 (1.0–4.0)	2.4 (1.0–5.0)	0.30
Age at menopause in postmenopausal women (yr)	51.3 (45.0–56.0)	49.7 (41.0–55.0)	0.0002
Previous OC use (%)	32.3	41.9	0.01
Previous HRT use (%)	18.6	14.4	0.15
Self-reported diabetes (%)	3.6	3.9	0.79
Completed secondary school or equivalent (%)	60.5	54.8	0.12
Smoking status (%)			
Never smoker	66.1	59.8	0.21
Ex-smoker	18.4	22.1	
Current smoker	15.6	18.1	
Household and recreational physical activity[b]	97.7 (24.5–190.6)	106.2 (30.0–197.1)	0.01
Geometric mean (95% CIs) of plasma adiponectin levels (μg/ml)			
All women	8.4 (8.0–8.9)	9.9 (9.5–10.3)	<0.0001
Premenopausal	8.2 (7.3–9.2)	9.0 (8.3–9.8)	0.32
Postmenopausal	8.5 (8.0–9.1)	10.1 (9.6–10.6)	0.0001
Normal weight (BMI < 25 kg/m^2)	10.4 (9.6–11.3)	11.0 (10.4–11.5)	0.13
Overweight (BMI 25 < 30 kg/m^2)	8.6 (7.8–9.5)	9.6 (9.0–10.3)	0.49
Obese (BMI $\geq$ 30 kg/m^2)	6.6 (6.0–7.3)	8.2 (7.5–9.0)	0.007
Fasting (>6 h since last food or drink)[c]	7.7 (7.0–8.5)	9.3 (8.7–9.9)	0.006
Nonfasting ($\leq$6 h since last food or drink)[c]	8.9 (8.3–9.6)	10.3 (9.8–10.8)	0.003

Data are presented as means (fifth to 95th percentiles) or percentages for the baseline demographic and lifestyle characteristics and as geometric means (95% CIs) for the plasma adiponectin levels. Missing values are excluded from percentage calculations.
[a] Calculated using two-sided paired *t*-tests for continuous variables and χ^2 tests for categorical variables.
[b] Estimated as MET-hours/week
[c] There were 266 fasting subjects, 522 nonfasting subjects, and 44 subjects with unknown fasting status.

risk significantly differed by age at cancer diagnosis (Table 4), time to diagnosis, fasting status, physical activity, or country ($P_{\text{heterogeneity}}$ all > 0.10).

Adjustment for BMI, or both BMI and waist circumference, mildly attenuated the RRs for the association between adiponectin and endometrial cancer risk, but the associations remained statistically significant both overall (Table 3) and among postmenopausal women (Table 4). Conversely, the association between BMI and risk was moderately attenuated after adjustment for adiponectin, such that the RR for obese subjects (BMI $\geq$ 30 kg/m^2), compared with normal-weight subjects (BMI < 25 kg/m^2) was reduced by 30% from 2.42 (95% CI 1.63–3.58) to 1.99 (95% CI 1.32–3.01), but the association remained statistically significant (P_{trend} = 0.001).

The overall adiponectin-endometrial cancer risk association was further attenuated but remained statistically significant when we included C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, or free testosterone as separate factors in the model in addition to BMI but only marginally statistically significant after simultaneous adjustment for these factors (Table 3). Similarly, the association was partly attenuated after full adjustment for these factors among postmenopausal and perimenopausal/unknown women at baseline and women 55 yr or older at diagnosis but became stronger among younger or premenopausal women (Table 4). Women diagnosed at 50 to 60 yr also had a slightly stronger association in the fully adjusted model than the BMI-adjusted model [RR for the top *vs.* the bottom tertile = 0.46 (95% CI 0.21–0.99), P_{trend} = 0.02 and 0.57 (95% CI 0.32–1.02), P_{trend} = 0.03], respectively (data not shown). Adjustment for other lifestyle risk factors did not appreciably alter the risk estimates and thus were not included in the models.

The relative risk estimates did not appreciably change when we restricted the analysis to the 133 cases (and their matched controls) with known type I histology or when we excluded cases diagnosed less than 2 yr after study entry (n =

TABLE 2. Pearson partial correlation coefficients and 95% CIs of baseline plasma adiponectin levels with anthropometric measures, C-peptide, sex steroid hormones, and physical activity

	Adiponectin[a]	Adiponectin[b]
BMI	−0.31 (−0.37, −0.25)	
Waist circumference	−0.37 (−0.43, −0.31)	−0.22 (−0.29, −0.16)
Waist to hip ratio	−0.35 (−0.41, −0.29)	−0.28 (−0.34, −0.21)
Physical activity[c]	0.03 (−0.04, 0.10)	0.03 (−0.04, 0.10)
C-peptide	−0.35 (−0.40, −0.28)	−0.27 (−0.33, −0.21)
IGFBP-1	0.39 (0.33, 0.44)	0.32 (0.26, 0.38)
IGFBP-2	0.43 (0.37, 0.48)	0.35 (0.29, 0.41)
SHBG	0.38 (0.32, 0.44)	0.30 (0.24, 0.36)
Androstenedione	−0.06 (−0.13, 0.01)	−0.07 (−0.13, 0.00)
DHEAS	−0.05 (−0.12, 0.02)	−0.07 (−0.14, 0.00)
Testosterone	−0.07 (−0.14, 0.00)	−0.07 (−0.14, 0.00)
Free testosterone	−0.24 (−0.31, −0.18)	−0.19 (−0.26, −0.12)
Estrone	−0.15 (−0.22, −0.08)	−0.10 (−0.17, −0.03)
Total estradiol[d]	−0.26 (−0.33, −0.18)	−0.19 (−0.27, −0.11)
Free estradiol[d]	−0.37 (−0.44, −0.29)	−0.28 (−0.36, −0.20)

[a] Pearson partial correlation coefficients were adjusted for age, case-control status, and laboratory batch. DHEAS, Dehydroepiandrosterone sulfate.

[b] Adjusted for BMI, age, case-control status, and laboratory batch.

[c] MET-hours/week of household and recreational physical activity.

[d] Serum estradiol level was measured only in postmenopausal women because of its considerable intraindividual variation during the menstrual cycle among premenopausal women.

85 cases) or women with self-reported diabetes (n = 31). Results were also similar when adiponectin cut-points were country-specific rather than calculated for all countries combined.

Discussion

In this prospective study, women in the highest quartile of adiponectin levels had a 50% reduced risk of endometrial cancer, compared with women in the lowest quartile. This strong inverse association persisted after adjustment for BMI, suggesting that adiponectin is a predictor of endometrial cancer risk, independent of obesity.

A major strength of this study is its prospective design, which minimizes recall bias and selection bias arising from inappropriate selection of control subjects. Blood samples were collected at baseline, before endometrial cancer diagnosis, avoiding reverse causation bias that could occur if the presence, diagnosis, or treatment of a tumor influences circulating adiponectin and hormone levels or lifestyle changes such as weight loss. Laboratory variability was minimized by using one laboratory for adiponectin and hormone measurements, with blood samples from cases and their matched control subjects collected under similar conditions and assayed in the same batch. Furthermore, the protocols for the collection of questionnaire data and blood samples were standardized to a large extent across study centers.

A limitation of our study was the use of a single adiponectin measurement from one baseline blood sample, which does not fully characterize long-term adiponectin levels. Nevertheless, two other prospective studies that analyzed repeated adiponectin measurements donated on average 1 yr apart reported intraclass correlations of 0.71 (29) and 0.84 (30), indicating high reproducibility. The inclusion of both fasting and nonfasting blood samples in our study were unlikely to bias the results because we were able to match case and control subjects according to fasting status and because circulating adiponectin levels are not acutely influenced by meals (31). As such, the risk estimates for the association between adiponectin and endometrial cancer did not differ appreciably between fasting and nonfasting samples. In this study we measured only plasma total adiponectin levels; however, recent evidence suggests that the high-molecular-weight form of adiponectin, rather than the lower-molecular-weight form, may be the bioactive form of the protein (32).

One major metabolic pathway through which adiponectin could influence endometrial cancer risk is by decreasing blood insulin and glucose levels, mainly through increased fatty acid oxidation in skeletal muscle, inhibition of hepatic

TABLE 3. RR estimates for the association between plasma adiponectin levels and endometrial cancer risk among all women

	RRs and 95% CIs for quartiles of plasma adiponectin[a]				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
Adiponectin cut-points (µg/ml)	<7.3	7.3–10.2	10.3–13.5	≥13.6	
Cases/controls[b]	107/137	67/137	57/137	53/137	
Crude[c]	1.00	0.61 (0.42–0.91)	0.51 (0.34–0.77)	0.47 (0.31–0.72)	0.0002
Adjusted for					
BMI	1.00	0.66 (0.44–0.99)	0.60 (0.39–0.92)	0.56 (0.36–0.86)	0.006
BMI, waist circumference	1.00	0.67 (0.45–1.00)	0.61 (0.40–0.94)	0.57 (0.37–0.89)	0.009
BMI, C-peptide	1.00	0.69 (0.46–1.04)	0.64 (0.41–0.99)	0.64 (0.40–1.01)	0.04
BMI, IGFBP-1, IGFBP-2	1.00	0.69 (0.46–1.04)	0.62 (0.39–0.96)	0.54 (0.34–0.87)	0.009
BMI, SHBG	1.00	0.71 (0.47–1.07)	0.62 (0.40–0.97)	0.59 (0.37–0.93)	0.02
BMI, estrone	1.00	0.75 (0.49–1.14)	0.62 (0.39–0.98)	0.56 (0.35–0.90)	0.01
BMI, free testosterone	1.00	0.75 (0.49–1.15)	0.66 (0.42–1.05)	0.63 (0.39–1.01)	0.04
BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.84 (0.53–1.34)	0.67 (0.41–1.11)	0.63 (0.36–1.10)	0.07

[a] RRs and 95% CIs for endometrial cancer risk, estimated by conditional logistic regression, for quartiles of plasma adiponectin (cut-points based on the distribution of control subjects).

[b] Some data for circulating levels of sex steroids were missing because of insufficient serum or failed analyses: for C-peptide (one case, 0 controls), IGFBP-1 (one case, 0 controls), IGFBP-2 (four cases, 10 controls), SHBG (eight cases, 12 controls), free testosterone (19 cases, 44 controls), estrone (16 cases, 34 controls), waist circumference (two cases, 0 controls), free estradiol among postmenopausal women (seven cases, 12 controls).

[c] Analysis matched on study center; baseline menopausal status; age at blood collection; time of day of blood collection; fasting status; and in premenopausal women, phase of menstrual cycle.

TABLE 4. RR estimates for the association between plasma adiponectin levels and endometrial cancer risk, stratified by baseline menopausal status, age at cancer diagnosis, and BMI

	RRs and 95% CIs for tertiles of plasma adiponectin[a]			
	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Adiponectin cut-points (μg/ml)[b]	<8.2	8.2 to <12	≥12.0	
Premenopausal at baseline				
Cases/controls[c]	27/46	12/33	15/26	
Crude[d]	1.00	0.67 (0.31–1.43)	1.05 (0.49–2.25)	0.84
Adjusted for BMI	1.00	0.69 (0.32–1.50)	1.13 (0.51–2.50)	0.98
Adjusted for BMI, C-peptide	1.00	0.74 (0.34–1.63)	1.47 (0.63–3.45)	0.61
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.55 (0.21–1.44)	0.94 (0.33–2.68)	0.64
Perimenopausal/unknown at baseline				
Cases/controls[c]	20/21	7/22	11/29	
Crude[d]	1.00	0.34 (0.11–1.03)	0.41 (0.16–1.01)	0.03
Adjusted for BMI	1.00	0.39 (0.12–1.22)	0.47 (0.18–1.20)	0.09
Adjusted for BMI, C-peptide	1.00	0.39 (0.12–1.24)	0.47 (0.18–1.25)	0.09
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.61 (0.12–3.07)	0.77 (0.20–2.98)	0.69
Postmenopausal at baseline				
Cases/controls[c]	88/114	57/126	47/131	
Crude[d]	1.00	0.56 (0.36–0.87)	0.44 (0.28–0.69)	0.0003
Adjusted for BMI	1.00	0.63 (0.41–0.99)	0.53 (0.33–0.85)	0.007
Adjusted for BMI, C-peptide	1.00	0.65 (0.41–1.03)	0.57 (0.34–0.94)	0.02
Adjusted for BMI, free estradiol[e]	1.00	0.73 (0.46–1.18)	0.63 (0.38–1.06)	0.08
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.67 (0.39–1.15)	0.61 (0.33–1.10)	0.08
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, free estradiol, free testosterone[e]	1.00	0.72 (0.44–1.19)	0.62 (0.35–1.11)	0.09
Younger than 55 yr at diagnosis				
Cases/controls[c]	33/42	12/43	14/30	
Crude[d]	1.00	0.39 (0.18–0.85)	0.60 (0.27–1.32)	0.08
Adjusted for BMI	1.00	0.44 (0.20–0.98)	0.69 (0.30–1.61)	0.21
Adjusted for BMI, C-peptide	1.00	0.47 (0.21–1.05)	0.74 (0.31–1.74)	0.28
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.35 (0.13–0.94)	0.40 (0.13–1.24)	0.06
Age 55 yr or more at diagnosis				
Cases/controls[c]	102/139	64/138	59/156	
Crude[d]	1.00	0.63 (0.42–0.94)	0.51 (0.34–0.76)	0.0007
Adjusted for BMI	1.00	0.69 (0.46–1.04)	0.60 (0.39–0.91)	0.01
Adjusted for BMI, C-peptide	1.00	0.71 (0.47–1.08)	0.66 (0.42–1.02)	0.05
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.85 (0.52–1.39)	0.81 (0.47–1.40)	0.43
BMI < 25 kg/m^2				
All women < 25 kg/m^2				
Cases/controls[c]	25/54	34/78	36/99	
Crude[d]	1.00	0.92 (0.43–1.96)	0.79 (0.38–1.64)	0.51
Adjusted for BMI	1.00	0.89 (0.42–1.90)	0.75 (0.36–1.57)	0.43
Adjusted for BMI, C-peptide	1.00	0.87 (0.40–1.90)	0.78 (0.39–1.68)	0.52
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	1.12 (0.46–2.71)	0.81 (0.34–1.93)	0.57
Postmenopausal women < 25 kg/m^2				
Cases/controls[c]	13/30	23/48	20/68	
Crude[d]	1.00	1.00 (0.38–2.69)	0.72 (0.26–2.00)	0.48
Adjusted for BMI	1.00	0.96 (0.36–2.60)	0.66 (0.24–1.85)	0.38
Adjusted for BMI, C-peptide	1.00	0.83 (0.29–2.31)	0.60 (0.21–1.76)	0.33
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	1.05 (0.30–3.62)	0.47 (0.12–1.90)	0.26
BMI 25 to < 30 kg/m^2				
All women 25 to < 30 kg/m^2				
Cases/controls[c]	48/77	23/73	26/67	
Crude[d]	1.00	0.37 (0.17–0.81)	0.52 (0.24–1.09)	0.05
Adjusted for BMI	1.00	0.39 (0.18–0.85)	0.55 (0.26–1.16)	0.08
Adjusted for BMI, C-peptide	1.00	0.46 (0.21–1.00)	0.71 (0.32–1.60)	0.32
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.40 (0.17–0.95)	0.58 (0.23–1.47)	0.18
Postmenopausal women 25 to < 30 kg/m^2				
Cases/controls[c]	29/49	20/53	20/49	
Crude[d]	1.00	0.55 (0.23–1.32)	0.59 (0.25–1.39)	0.20
Adjusted for BMI	1.00	0.58 (0.24–1.40)	0.61 (0.26–1.45)	0.24

TABLE 4. *Continued*

| | RRs and 95% CIs for tertiles of plasma adiponectin[a] | | | |
	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Adjusted for BMI, C-peptide	1.00	0.63 (0.26–1.55)	0.71 (0.28–1.80)	0.44
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.62 (0.23–1.68)	0.75 (0.25–2.26)	0.54
BMI ≥ 30 kg/m²				
All women ≥ 30 kg/m²				
Cases/controls[c]	62/50	19/30	11/20	
Crude[d]	1.00	0.20 (0.07–0.58)	0.13 (0.03–0.49)	0.0005
Adjusted for BMI	1.00	0.21 (0.07–0.62)	0.14 (0.04–0.55)	0.001
Adjusted for BMI, C-peptide	1.00	0.21 (0.07–0.62)	0.14 (0.04–0.59)	0.002
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.03 (0.004–0.33)	0.12 (0.008–1.60)	0.01
Postmenopausal women ≥ 30 kg/m²				
Cases/controls[c]	46/35	14/25	7/14	
Crude[d]	1.00	0.23 (0.08–0.72)	0.27 (0.06–1.21)	0.02
Adjusted for BMI	1.00	0.24 (0.08–0.75)	0.28 (0.06–1.26)	0.02
Adjusted for BMI, C-peptide	1.00	0.24 (0.08–0.75)	0.28 (0.06–1.27)	0.02
Adjusted for BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone	1.00	0.09 (0.009–0.77)	0.18 (0.02–2.13)	0.04

[a] RRs and 95% CIs for endometrial cancer risk for tertiles of plasma adiponectin. Conditional logistic regression models were used for all models except for stratification by BMI categories, in which, to retain all subjects in the model, we used unconditional logistic regression adjusted for laboratory batch and all matching factors (see *d* below). The risk estimates by BMI strata were similar for both unconditional and conditional models.

[b] Cut-points are based on the distribution of adiponectin concentration among control subjects in the full study group.

[c] Some data for circulating levels of sex steroids were missing because of insufficient serum or failed analyses; see *b* in Table 3.

[d] Analysis matched on study center; baseline menopausal status; age at blood collection; time of the day of blood collection; fasting status; and in premenopausal women, phase of menstrual cycle.

[e] Free estradiol was measured only in postmenopausal women.

glucose production, improved insulin signal transduction, and increased peripheral tissue sensitivity to insulin (1, 5–7, 33). Circulating insulin and glucose levels are associated with increased endometrial cancer risk, through direct and indirect actions (2, 34–36). Insulin can down-regulate SHBG and IGFBPs and up-regulate ovarian sex steroid production, thus increasing total and bioavailable estrogen and androgen levels and IGF-I bioactivity (2, 34, 35).

Exposure to elevated estrogen levels that are insufficiently counterbalanced by progesterone is the predominant hypothesis for the etiology of endometrial cancer (2). However, factors that contribute to an imbalance of estrogens and progestogens also tend to increase the exposure of the endometrium to inflammation (14). Adiponectin may have strong antiinflammatory activity and could thereby potentially counteract the proinflammatory and neoplastic effects of cytokines TNF-α, IL-6, and C-reactive protein by inhibiting their production and action (7–13). These cytokines are implicated in the initiation and promotion of endometrial carcinogenesis through their effects on increasing nuclear factor-κB activity and up-regulating cyclooxygenase-2 expression and prostaglandin E_2 levels in the endometrium (1, 10, 14). IL-6 and TNF-α could also stimulate the synthesis of peripheral and tumor estrogens (13–15). In addition, TNF-α may mediate insulin resistance and chronic hyperinsulinemia (16).

Through more direct mechanisms, adiponectin could impair the growth and survival of tumor cells by directly activating several signaling pathways in endometrial and other tissues (13). These signaling pathways, including 5′-AMP-activated protein kinase (8, 37), have been shown to exert direct effects on specific enzymes and transcriptional factors that regulate insulin resistance, cell proliferation, protein synthesis, apoptosis, and angiogenesis (13, 37, 38). Finally, adiponectin can inhibit the proliferative actions of several mitogenic growth factors by precluding their binding to the membrane receptors (13, 39).

Excess weight is a strong risk factor for endometrial cancer (2) and is also causally associated with insulin resistance (40). Although adiponectin is secreted almost exclusively by adipocytes, and is negatively correlated with BMI, adiponectin concentrations have been shown to be more closely inversely related to insulin resistance and insulin concentrations than to the degree of obesity (41). Our results, after mutual adjustment for adiponectin and BMI, suggest that both obesity and adiponectin each maintain independent associations with endometrial cancer risk. These findings are consistent with results from three hospital-based case-control studies in Greece (84 cases, 84 controls) (17), Italy (87 cases, 132 controls) (18), and the United States (Texas; 116 cases, 200 controls) (19), which examined the association between adiponectin and endometrial cancer risk after adjustment for BMI and other potential confounders. Petridou *et al.* (17) reported an odds ratio for endometrial cancer of 0.78 (0.56–1.10) with 1 SD increase in serum adiponectin levels, whereas Dal Maso *et al.* (18) reported odds ratios of 0.42 (95% CI 0.19–0.94) and 0.30 (95% CI 0.14–0.68) for the highest *vs.* lowest tertile of plasma and serum adiponectin levels, respectively. Recently Soliman *et al.* (19) reported an 11-fold (95% CI 4.2–26.4) increased risk among women in the lowest *vs.* highest tertile of serum adiponectin, although they had limited data on other potential confounders in their study. They noted that the association remained strong, even in the subset of normal-weight women (<25 kg/m²) (19). In our

study, the inverse association between adiponectin and endometrial cancer risk was stronger among obese women.

In contrast to previous studies (17, 18), we did not find a stronger association between adiponectin levels and risk among younger or premenopausal women. Rather, the effect appeared stronger for women who were postmenopausal or perimenopausal/unknown status at baseline. However, with only 54 cases that were premenopausal at baseline, we lacked power to examine this association precisely among these women, and hence, the confidence intervals were wide and the risk estimates were not statistically heterogeneous. Furthermore, in women under aged 55 or between 50 and 60 yr at the time of cancer diagnosis, there was an inverse trend between adiponectin levels and risk that was stronger than for older women when fully adjusted for other obesity-related biological markers. Increasing mean BMI with age and the onset of menopause in our cohort may explain the apparent stronger association observed from around the start of menopause.

On the basis of observational data alone, it is difficult to determine the extent to which low adiponectin levels contribute to the etiology of endometrial cancer, over and above other obesity-related physiological risk factors. Adjustments of the adiponectin-risk association for C-peptide or free estradiol suggest that the effects of adiponectin on cancer risk could be either partly mediated through, or confounded by, decreased insulin levels or levels of bioavailable estrogens that are strongly increased among postmenopausal women with elevated BMI (2). In addition, each of these obesity-related parameters is determined with some random measurement error (42), and BMI itself is an imperfect measure of adiposity (43). Thus, on the one hand, there could be residual confounding of the adiponectin-endometrial cancer association after adjustments for any of the other obesity-related physiological parameters. On the other hand, random measurement errors of adiponectin levels could have led to an underestimation of the association between adiponectin and risk. Physiologically, little is known about factors that regulate adiponectin production, secretion, and clearance. Insulin, hormones (*e.g.* testosterone), weight loss of 10% or greater, proinflammatory cytokines, certain medications, and possibly dietary factors and sustained physical activity are implicated as possible regulators of adiponectin levels (5, 7, 13, 33, 41, 44–47). Conversely, adiponectin itself has regulating effects on blood levels of glucose and insulin, proinflammatory cytokines, and possibly other hormones (1, 5, 10, 11, 13). Thus, a complex physiological relationship may exist between adiponectin levels and endometrial cancer risk.

In conclusion, prediagnostic, high levels of circulating adiponectin were associated with reduced risk of endometrial cancer, particularly among obese and peri-/postmenopausal women. Low adiponectin concentration is a marker for insulin resistance (41), and our results support the hypothesis that insulin resistance, independent of obesity, is a risk factor for endometrial cancer. The biological mechanisms linking adiponectin with a reduction in endometrial tumors remain unclear. Further experimental studies are needed to determine whether adiponectin has a direct causal biological effect on endometrial carcinogenesis separate from other known physiological risk factors and to elucidate possible indirect effects of adiponectin through insulin sensitivity, inflammation, and estrogen-related pathways.

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