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Pre-diagnostic circulating inflammation markers and endometrial cancer risk in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial

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Abstract

Inflammation is proposed to increase risk of developing endometrial cancer, but few prospective epidemiologic studies have investigated the relationship between circulating inflammation markers and endometrial cancer risk. In a nested case-control study within the PLCO Screening Trial we measured serum levels of 64 inflammation-related biomarkers in 284 incident endometrial cancer cases and 284 matched controls. Using multivariable logistic regression inflammation markers were evaluated individually and combined into a cross-validated inflammation score. Of 64 markers, 22 were associated with endometrial cancer risk at $p < 0.05$ and 17 of 22 markers remained associated after multiple testing corrections. After adjusting for BMI and estradiol, SERPINE1 [quartile(Q)4 vs. Q1 odds ratio (OR) (95% confidence interval (CI)), p -trend = 2.43 (0.94–6.29), 0.03] and VEGFA [2.56 (1.52–4.30), 0.0002] were positively associated with endometrial cancer risk, while CCL3 [0.46 (0.27–0.77), 0.01], IL13 [0.55 (0.33–0.93), 0.01], IL21 [0.52 (0.31–0.87), 0.01], IL1B [0.51 (0.30–0.86), 0.01], and IL23 [0.60 (0.35–1.03), 0.02] were inversely associated with risk. We observed large differences in ORs across BMI-inflammation score categories. Endometrial cancer risk was most pronounced among obese women with the highest inflammation score tertile (T) [10.25 (3.56–29.55) vs. normal BMI/T1]. Several inflammation markers were prospectively associated with endometrial cancer, including adipokines, pro- and anti-inflammatory cytokines, angiogenic factors, and acute phase proteins. Inverse associations with anti-inflammatory markers (IL13, IL21), other inflammation markers/mediators (CCL3, IL1B, IL23), and a robust positive association between VEGFA and

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endometrial cancer risk were independent of BMI and estradiol, suggesting that these factors may influence risk through other mechanisms.

Keywords

Endometrial cancer; circulating inflammation markers; pre-diagnostic; nested case-control

INTRODUCTION

Endometrial cancer incidence is projected to surpass colorectal cancer incidence and become the third leading type of cancer in U.S. women by 2030¹. It has been suggested this increase is in part due to increasing prevalence of obesity and decreasing prevalence of hysterectomy¹. Chronic inflammation is postulated to contribute to endometrial carcinogenesis, but evidence is limited compared with data supporting hormonal and metabolic factors^{2, 3}. Throughout childbearing years, the endometrium undergoes rapid growth, remodeling, differentiation, and angiogenesis that involves synthesis and release of inflammatory cytokines by the epithelial, stromal, and vascular cells of the endometrium^{3, 4}.

However, few epidemiologic studies have evaluated effects of pre-diagnostic circulating inflammation markers on endometrial cancer risk. Studies focusing on pro-inflammatory cytokines have demonstrated a consistent association with the biomarker C-reactive protein (CRP), and possible associations with interleukin (IL) 6, IL1 receptor antagonist (IL1RN), and tumor necrosis factor alpha (TNF)⁵⁻⁷. In contrast, reports on associations of adipokines and endometrial cancer risk have been inconsistent suggesting inverse^{8, 9} and no association^{10, 11}. Adipose tissue expresses several inflammatory and anti-inflammatory cytokines (e.g. CRP, IL1A, IL6, IL10, chemokine (C-X-C motif) ligand (CXCL) 8 (also known as IL8), TNF, leptin, chemokine (C-C motif) ligand (CCL)2, and CCL3) and obesity was found to be associated with elevated serum levels of CRP, IL6, TNF, and leptin¹². Laboratory studies have shown tumorigenic effects of pro-inflammatory cytokines via cell proliferation, cell survival, and angiogenesis. Better understanding the role of inflammation in endometrial carcinogenesis can help further elucidate how obesity and hormones cause endometrial cancer and could identify novel disease mechanisms that could have relevance for cancer prevention.

We conducted a nested case-control study within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial to assess the association of endometrial cancer risk with 64 inflammation-related biomarkers. We further evaluated whether associations remained after adjustment for robust endometrial cancer risk factors, i.e., obesity and increased levels of circulating estradiol.

MATERIALS AND METHODS

Study Design

We conducted a nested case-control study within the screening arm of the PLCO Cancer Screening Trial, details of which have been reported previously¹³. Between 1993 and 2001, approximately 155 000 subjects (78 216 women) 55–74 years of age were recruited from ten

cities and randomized to the screening or non-screening arm of the study. Screening-arm subjects provided blood samples at baseline and five subsequent annual medical examinations¹⁴. In addition to trial outcomes detected by annual screening, individuals were followed by annual mailed questionnaires for cancer diagnoses, which were confirmed through pathology reports. All participants provided written informed consent and the study was approved by the institutional review board of the National Cancer Institute.

Through February 28, 2012 284 screening-arm participants developed first-primary endometrial cancer after baseline blood collection and were eligible for study inclusion given the availability of an unfrozen serum sample, consent to biochemical studies, completion of the baseline questionnaire, and no history of cancer (other than non-melanoma skin cancer). Serum samples were selected from baseline blood draw if available (90.1% baseline, 6.7% year 1, 3.2% year 2+). Controls (n=284) were frequency matched to cases on blood collection age (five-year categories), race (white, non-white), blood draw study year, and study year of randomization. Cases and controls were postmenopausal at blood draw. Controls were restricted to women with no history of hysterectomy and alive at diagnosis of their matched case. (Table 1 here)

Laboratory Methods

In a single laboratory, we measured serum levels of 70 immune and inflammation markers (Supplemental Table 1), assays which have previously demonstrated satisfactory performance and reproducibility¹⁵. Sixty-nine markers were measured on five Luminex bead-based commercial assay panels (Millipore Inc., Billerica, MA). TGF-beta1, was measured using a quantitative sandwich enzyme immunoassay (R&D Systems, Minneapolis, MN). Marker concentrations were calculated using a four- or five-parameter logistic curve (Bioplex Manager 6.1, BioRad, Hercules, CA). The same manufacturer lot was used for measurement of the high-sensitivity panel cytokines. The remaining marker panels were purchased across two lots (adipokine panel: seven batches lot 1/37 batches lot 2, cytokine panel 1: 34/10, cytokine panel 2: 31/13, chemokine panel 32/12, soluble receptor: 33/11, acute phase proteins: 37/7). Unconjugated estradiol was measured via gas chromatography tandem mass spectrometry in serum samples from the same study year as the serum samples used to measure the inflammatory markers (Pharmacogenomics Laboratory, CHUQ, Laval University, Quebec, Canada).

For all assays, cases and matched controls were included in the same analytic batch. To evaluate assay performance, we included a blinded duplicate sample from a quality control (QC) pool in each batch. Percent above the lower limit of detection (LLOD) of all samples, as well as coefficients of variation (CVs) and intraclass correlation coefficients (ICCs) for the QC samples are summarized in Supplemental Table 1. We excluded six markers with greater than 65% of values below the LLOD (IL3, IFNL1, IL33, SCF, LTA, TSLP). We further excluded all data from one batch (n=10) for the adipokine panel and two batches (n=34) from the soluble receptor panel, because the within batch CVs were greater than 50%. We similarly excluded seven batches of data for the acute phase protein SAA1 (serum amyloid A1) because the values for this marker were noticeably disparate across the two panel lots (n=78). After exclusions, 64 markers were included in statistical analyses.

Inflammation markers were grouped into categories according to the proportion below the LLOD: <25% (quartiles), 25–49% (undetectable, tertiles categories of detectable values), 50–65% (undetectable, median split of detectable values).

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for associations between the serum inflammation markers and endometrial cancer risk were calculated using logistic regression models. All models were adjusted for matching factors and *a priori* potential confounding factors cigarette smoking status (never, former, current), parity (nulliparous, parous), duration of oral contraceptive use (never, 1–5 years, 6+ years), and duration of menopausal hormone therapy (MHT) use (never, 1–5 years, 6+ years). Additional adjustment by assay batch, diabetes, aspirin/ibuprofen use, or history of tubal ligation did not substantially change the observed effect estimates. *P*-trends across categories of marker level were calculated using the Wald test for the ordinal variable.

Given that CRP levels among MHT users are artificially elevated due to a first-pass hepatic effect¹⁶ associations for CRP were evaluated stratified by MHT use. There is limited information on other circulating inflammation markers and their levels among current MHT users, thus we explored associations stratified by current/non-current (never/former) MHT use, and report stratified results if there was evidence for effect modification (*p*-interaction<0.05 and/or substantially different (effect vs. no effect) associations across MHT use categories). To assess if inflammation marker associations were confounded by BMI and estradiol, we evaluated markers with a nominal *p*-value<0.05 (in any of the MHT groups or overall) in models further adjusted for BMI (per 5 kg/m²), estradiol (log-2 transformed), and both BMI and estradiol.

To explore effect modification by obesity¹⁷ we stratified models by BMI category (<25, 25–29.99, 30 kg/m²). Tests for multiplicative interaction (MHT use, BMI) were conducted using the cross-product terms.

To account for multiple comparisons we applied the false discovery rate (FDR) in two stages: 1) for the primary marker associations (without adjustment for BMI or estradiol), FDR was applied to account for testing 64 markers separately for the following groups: never/former MHT users, current MHT users, overall; 2) for the subset of markers *p*<0.05, FDR was applied to models additionally adjusted for BMI, estradiol, or BMI and estradiol which included 42 tests (14 markers by 3 adjusted models) among never/former MHT users and 24 tests (8 markers by 3 adjusted models) overall. All other analyses were considered exploratory and not corrected for multiple comparisons.

In secondary analyses, we evaluated associations by histologic subtype [Type I (77 adenocarcinomas, 162 endometrioid, 8 mucinous) vs. Type II (13 serous, 1 clear cell)], grade of tumor among the endometrioid and adenocarcinomas [201 grades 1–2 vs. 24 grades 3–4], and time between blood collection and diagnosis [<2 years/ 2 years and <5 years/ 5 years].

Finally, we estimated endometrial cancer risk (for the overall study population and never/former MHT users) using a cross-validated inflammation score. The 284 case-control pairs were randomly divided into 5 equal groups. Using data from 4 of the 5 groups, we used backwards stepwise conditional logistic regression to identify markers that retained statistical significance ($p < 0.05$) from a model that included the 22 markers individually associated with endometrial cancer. An inflammation score was calculated for individuals in the fifth group (sum of the product of marker regression coefficient with the respective marker level) and classified into tertiles based on the control distribution. We estimated ORs of endometrial cancer for categories defined by BMI and inflammation score tertile using conditional logistic regression. We compared inflammation score associations with and without adjustment for BMI, to estimate the extent to which the inflammation score explained the association between BMI and endometrial cancer among women not currently using MHT.

All tests of statistical significance were two-sided. Analyses were conducted using SAS version 9.3 (SAS Inc, Cary, NC).

RESULTS

The distribution of selected characteristics of the cases and controls are summarized in Table 1. Participants were on average 62.6 years old at enrollment and were predominately white (91.6%). The median length of follow-up from blood collection to case diagnosis was 5.3 years (interquartile range (IQR): 2.1–9.1 years). As expected the prevalence of obese BMI was higher in cases than controls [41.2% in cases vs. 20.8% in controls].

Twenty-two of 64 markers evaluated were associated with endometrial cancer risk (Table 2). Seventeen of these 22 markers were associated with endometrial cancer risk at 5% FDR, including adipokines (adiponectin, SERPINE1), chemokines (CCL19, CXCL10), anti-inflammatory cytokines (IL13, IL21), pro-inflammatory cytokines and their regulators (IL6, TNF, TNFRSF1A, IL1B, IL1R2, CSF3), angiogenic factors (VEGFA and its regulator FLT4), and acute phase proteins (CRP, SAA1, APCS). The remaining 42 markers evaluated were not associated with risk (Supplemental Table 2). (Table 2 here)

In models further adjusted for BMI and estradiol, seven markers remained associated with endometrial cancer risk. SERPINE1 [quartile (Q)4 vs. Q1 OR (95% CI), p -trend = 2.43 (0.94–6.29), 0.03] and VEGFA [2.56 (1.52–4.30), 0.0002] were associated with increased risk. Three markers that are generally classified as pro-inflammatory or inflammation mediators were associated with a decreased endometrial cancer risk, CCL3 [0.46 (0.27–0.77), 0.01], IL1B [0.51 (0.30–0.86), 0.01], and IL23 [0.60 (0.35–1.03), 0.02], as were two anti-inflammatory cytokines, IL13 [0.55 (0.33–0.93), 0.01] and IL21 [0.52 (0.31–0.87), 0.01].

There was some evidence for effect modification of the risk estimates by BMI (Table 3). Associations were typically observed in the highest BMI category (≥ 30 kg/m²), even after adjustment for continuous BMI within each category. Among obese women, SERPINE1 [32.5 (4.15–254), 0.003, $p_{\text{intx}}=0.03$] and CSF3 [17.7 (3.81–82.4), 0.001, $p_{\text{intx}}=0.02$] were

positively associated with increased risk, while IL13 [0.28 (0.11–0.76), 0.003, $p_{\text{intx}}=0.03$], IL21 [0.29 (0.11–0.74), 0.01, $p_{\text{intx}}=0.03$], and IL1B [0.23 (0.09–0.64), 0.001, $p_{\text{intx}}=0.02$] were inversely associated with risk. We also observed associations with TNF [15.5 (1.74–139), 0.02, $p_{\text{intx}}=0.54$], CRP [64.5 (1.35–999), 0.005, $p_{\text{intx}}=0.48$], and SAA1 [14.9 (2.27–97.7), 0.03, $p_{\text{intx}}=0.34$] and endometrial cancer among women with normal BMI, although the p -interaction was not statistically significant. In contrast, increased VEGFA levels were associated with increased risk of endometrial cancer ($\text{OR}>2.0$) across all BMI categories. (Table 3 here)

There was no evidence of heterogeneity of effect estimates between Type I/Type II endometrial cancers or tumor grade (Supplemental Table 3). There was no evidence of heterogeneity in analyses stratified by time between blood draw and diagnosis (Supplemental Table 4), the increased endometrial cancer risk with VEGFA persisted in analyses restricted to specimens collected five or more years prior to diagnosis [3.05 (1.57–5.94), 0.001, $p_{\text{-het}} = 0.59$].

Using the cross-validated inflammation score, we observed large differences in ORs across BMI-inflammation score categories. Compared to women with normal BMI and the lowest tertile inflammation score, obese women with the highest tertile score were at substantially elevated endometrial cancer risk [overall: 7.12 (3.27–15.48); non-current MHT users: 10.25 (3.56–29.55)] (Figure 1). Among non-current MHT users, obese BMI was strongly associated with endometrial cancer risk [adjusted OR (95% CI) 30 vs. <25 kg/m²: 6.39 (3.16–12.92)], the association was slightly attenuated after adjusting for inflammation score [4.72 (2.26–9.88)] (Table 4). (Figure 1 and Table 4 here)

DISCUSSION

In a large prospective study, we evaluated circulating inflammation markers and endometrial cancer risk accounting for known associations with BMI and estradiol. Twenty-two markers were associated with endometrial cancer risk representing several components of the inflammation process, including adipokines, chemokines, pro- and anti-inflammatory cytokines, angiogenic factors, and acute phase proteins. Our study represents the most comprehensive evaluation of pro- and anti-inflammatory markers in endometrial carcinogenesis to date, highlighting the important role of inflammation in endometrial cancer.

After adjusting for BMI and estradiol, a number of known anti-inflammatory markers (IL13, IL21), as well as other inflammation markers/mediators (CCL3, IL1B, IL23), were indicative of a reduced endometrial cancer risk. We observed a robust association between increased VEGFA levels and endometrial cancer risk. The BMI-endometrial cancer association was explained, to a modest extent, by the inflammation score, suggesting that obesity partially acts through inflammation in endometrial carcinogenesis. We also observed strong relative risk increases (ORs up to 10) with higher inflammation scores among obese women, supporting further evaluation of inflammation markers for endometrial cancer risk prediction.

Few studies have investigated the role of pre-diagnostic inflammation markers and endometrial cancer risk and none have evaluated as diverse a set of inflammation-related markers as in our study. In a nested case-control study in European Prospective Investigation into Cancer (EPIC), increased endometrial cancer risk was associated with elevated levels of TNF, TNFRSF1A, TNFRSF1B⁶, CRP, IL-6, and IL1RN⁵, however associations did not remain after adjustment for BMI. In a nested study in the Women's Health Initiative Observational Cohort, IL6 and TNF were not associated with endometrial cancer risk, while the increased risk with CRP did not persist after BMI and estradiol adjustment⁷. A prior study in PLCO reported decreased endometrial cancer risk with adiponectin even after adjusting for BMI and estradiol⁹. However, in the current study (with almost double the number of cases, and a different set of controls), the adiponectin-endometrial cancer association did not remain after adjustment for BMI and estradiol. The lack of an independent association with adiponectin is consistent with three prior studies^{8, 10, 11}. Our results are generally consistent with prior studies; however, since we measured a larger set of markers, we identified a number of novel associations. In addition to associations for CRP, IL6, TNF, TNFRSF1A, and adiponectin, we report increased endometrial cancer risks with select adipokines (resistin and SERPINE1), chemokines (CCL19, CXCL10), pro-inflammatory cytokines and their regulators (IL1R2, CSF3), angiogenic factors (VEGFA, FLT4), and acute phase proteins (SAA1, APCS) and inverse associations with anti-inflammatory cytokines (IL10, IL13, IL21), and other inflammation markers/mediators (CCL3, IL1B, IL23, CSF2).

Prior studies were restricted to postmenopausal^{7, 11}, or mostly postmenopausal^{5, 6, 10} women not using MHT. All of our study subjects were postmenopausal and 44% reported MHT use at baseline. We found that inclusion of current MHT users modified associations for some circulating inflammation markers. This has been demonstrated previously for CRP¹⁶ and adiponectin⁹, but not for other inflammation markers. Importantly, inclusion of MHT users did not modify associations with VEGFA or markers associated with reduced endometrial cancer risk.

To our knowledge, prior studies have not prospectively evaluated associations between circulating levels of anti-inflammatory markers (IL10, IL13, IL21) or angiogenic markers (VEGFA) and endometrial cancer risk. VEGFA plays a crucial role in the initiation of physiological and pathological angiogenesis, lymphangiogenesis, and vasculogenesis¹⁸. Angiogenesis plays an important role in the endometrium during the menstrual cycle, but also in the growth of endometrial cancers¹⁸. Findings from the current study suggest that VEGFA is important early in the carcinogenic process, given the persistence of the increased endometrial cancer risk in samples collected more than five years prior to diagnosis.

The association between chronic inflammation and cancer is well accepted^{19–21}; however, the specific role inflammation plays in cancer is complex and likely tumor specific. Inflammation may occur early or late in tumor development and/or progression via numerous mechanisms, such as increased proliferation, enhanced survival, angiogenesis, and/or tumor invasion¹⁹. Serum samples in the current study were collected on average 5.3 years prior to cancer diagnosis and we did not observe substantial heterogeneity in associations with time since serum collection, suggesting that these markers may be acting

at different stages in the endometrial cancer continuum (e.g., endometrial hyperplasia to cancer).

Importantly, not all chronic inflammation is associated with increased cancer risk. Notably, we observed inverse associations between the ‘pro-inflammatory’ markers CCL3, IL1B, IL23 and endometrial cancer. Data suggests that CCL3 is indicative of enhanced local cytokine production with low levels being correlated with ineffective control of infection/inflammation²². IL1B, IL23, and IL21 either induce or are produced by CD4+ T helper 17 (Th17) cells²³. The role of Th17 cells in carcinogenesis is unclear, with recent data demonstrating both protective and pathogenic effects²⁴.

Strengths of our study include the prospective design (reducing concern regarding reverse causation), comprehensive evaluation of inflammation-related markers using a validated technology, and careful control for confounding. Similar to other prospective studies, we had limited power to investigate associations stratified by endometrial cancer subtypes other than Type I or high-grade endometrioid/adenocarcinomas. Our assessments were made on a single sample at one time point which may not accurately reflect long-term exposure, although prior studies evaluating inflammation markers in blood samples taken over a two year period showed moderate to good reliability (ICCs ranged from 0.52–0.92 for markers included in the current study)^{25–28}. Lastly, while internally cross-validated, the inflammation score requires independent validation.

In conclusion, our prospective investigation of 64 inflammation-related markers provides epidemiologic evidence for an association of diverse components of the inflammation process with endometrial cancer risk. The majority of the pro-inflammatory associations did not persist after accounting for BMI and/or circulating estradiol and only a modest proportion of the BMI-endometrial cancer risk association was explained by the inflammation score. Inverse associations with anti-inflammatory markers as well as a robust positive association between VEGFA levels and endometrial cancer risk were independent of both BMI and estradiol, suggesting that anti-inflammatory and angiogenic factors may influence risk through other mechanisms, which warrants further evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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NOVELTY & IMPACT STATEMENTS

Our study provides novel molecular data demonstrating that VEGFA levels were positively associated with endometrial cancer risk and several anti-inflammatory markers were inversely associated with risk; these associations were independent of known risk factor associations with BMI and circulating estradiol. The cross-validated inflammation score demonstrated that higher inflammation scores among obese women may have utility in risk prediction but that only a modest proportion of the BMI-endometrial cancer association was explained by the inflammation score.

Figure 1.

Odds Ratio (OR) of endometrial cancer by BMI category and inflammation score quartiles, nested case-control study in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Inflammation score was estimated through five-fold cross-validation and categorized in tertiles (T). BMI categories, normal: <25, overweight: 25–29.9, obese: 30 kg/m². ORs were estimated from conditional logistic regression models.

Table 1

Characteristics of endometrial cancer cases and matched controls, nested case-control study in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

	Cases (N=284)		Controls (N=284)	
	mean	(std.dev)	mean	(std.dev)
Age at baseline	62.6	(5.2)	62.6	(5.1)
Race	n	%	n	%
Non-Hispanic White	260	91.6	260	91.6
Non-Hispanic Black	11	3.9	20	7.0
Hispanic	11	3.9	3	1.1
Asian	2	0.7	1	0.4
Highest education level attained				
High school or less	74	26.1	78	27.5
Some post high school training	107	37.7	105	37.0
College graduate	103	36.3	101	35.6
Body Mass Index (BMI)				
< 25 kg/m ²	76	26.8	122	43.0
25–29.9 kg/m ²	90	31.7	100	35.2
30 kg/m ²	117	41.2	59	20.8
Missing	1	0.3	3	1.0
Cigarette smoking status				
Never	180	63.4	156	54.9
Former	90	31.7	105	37.0
Current	14	4.9	23	8.1
Parity				
Nulliparous	30	10.6	18	6.3
Parous	254	89.4	266	93.7
Duration of oral contraceptive use				
Never	167	58.8	127	44.7
1–5 years	85	29.9	92	32.4
6+ years	32	11.3	64	22.5
Missing	0	0.0	1	0.4
Menopausal hormone therapy (MHT) use at baseline				
Never/former	159	56.0	157	55.3
Current	125	44.0	127	44.7
Duration of MHT use				
Never	112	39.4	106	37.3
1–5 years	82	28.9	96	33.8
6+ years	88	31.0	81	28.5
Missing	2	0.7	1	0.4

Associations of selected circulating inflammation markers and endometrial cancer risk stratified by menopausal hormone therapy (MHT) use at baseline or overall, nested case-control study in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Table 2

<i>Adipokines</i>	Exogenous MHT use at baseline					
	Never/former (159 cases/157 controls)		Current (125 cases/127 controls)		Overall (284 cases/284 controls)	
	aOR* (95% CI)	P _{trend}	aOR* (95% CI)	P _{trend}	aOR* (95% CI)	P _{trend}
<i>ADIPOQ (Adiponectin)</i>						
Adjusted model	0.31 (0.15–0.68)	0.0002 [†]	0.97 (0.39–2.42)	0.79	0.64 (1.09–3.16)	0.01
+ BMI (per 5 kg/m ²)	0.64 (0.28–1.50)	0.12			1.45 (0.83–2.54)	0.14
+ Estradiol (doubling)	0.61 (0.26–1.41)	0.11			1.70 (0.99–2.93)	0.04
+ BMI and Estradiol	0.79 (0.33–1.89)	0.32			1.42 (0.81–2.48)	0.17
<i>RETN (Resistin)</i>						
Adjusted model					0.64 (1.09–3.16)	0.01
+ BMI (per 5 kg/m ²)					1.45 (0.83–2.54)	0.14
+ Estradiol (doubling)					1.70 (0.99–2.93)	0.04
+ BMI and Estradiol					1.42 (0.81–2.48)	0.17
<i>SERPINE1 (Plasminogen activator inhibitor-1 (PAI-1))</i>						
Adjusted model	4.50 (1.89–10.69)	<0.0001 [†]	1.06 (0.44–2.55)	0.66	0.03	
+ BMI (per 5 kg/m ²)	2.77 (1.09–7.02)	0.01				
+ Estradiol (doubling)	2.86 (1.12–7.28)	0.01				
+ BMI and Estradiol	2.43 (0.94–6.29)	0.03				
<i>Chemokines</i>						
<i>CCL19 (MIP-3b)</i>						
Adjusted model	7.26 (3.07–17.21)	<0.0001 [†]	0.56 (0.25–1.26)	0.06	0.0001	
+ BMI (per 5 kg/m ²)	2.57 (0.97–6.85)	0.11				
+ Estradiol (doubling)	3.86 (1.52–9.77)	0.01				
+ BMI and Estradiol	2.27 (0.84–6.14)	0.20				
<i>CXCL10 (IP-10)</i>						

Exogenous MHT use at baseline									
<i>Adipokines</i>	Never/former (159 cases/157 controls)			Current (125 cases/127 controls)			Overall (284 cases/284 controls)		
	aOR*	(95% CI)	P _{trend}	aOR*	(95% CI)	P _{trend}	aOR*	(95% CI)	P _{trend}
Adjusted model	2.50	(1.16–5.41)	0.001 [‡]	0.31	(0.12–0.77)	0.01			0.003
+ BMI (per 5 kg/m ²)	1.41	(0.61–3.25)	0.09						
+ Estradiol (doubling)	1.86	(0.82–4.24)	0.02						
+ BMI and Estradiol	1.35	(0.58–3.16)	0.12						
CCL3 (MIP-1a)									
Adjusted model							0.90	(0.31–0.82)	0.03
+ BMI (per 5 kg/m ²)							0.45	(0.27–0.75)	0.01 [‡]
+ Estradiol (doubling)							0.52	(0.32–0.86)	0.05
+ BMI and Estradiol							0.46	(0.27–0.77)	0.01 [‡]
<i>Anti-inflammatory cytokines/mediators</i>									
IL10									
Adjusted model							0.36	(0.42–1.13)	0.04
+ BMI (per 5 kg/m ²)							0.69	(0.41–1.15)	0.06
+ Estradiol (doubling)							0.68	(0.41–1.12)	0.04
+ BMI and Estradiol							0.68	(0.41–1.15)	0.06
IL13									
Adjusted model							0.44	(0.32–0.87)	0.01 [‡]
+ BMI (per 5 kg/m ²)							0.54	(0.32–0.91)	0.01 [‡]
+ Estradiol (doubling)							0.55	(0.33–0.91)	0.01 [‡]
+ BMI and Estradiol							0.55	(0.33–0.93)	0.01 [‡]
IL21									
Adjusted model							0.88	(0.30–0.81)	0.003 [‡]
+ BMI (per 5 kg/m ²)							0.53	(0.32–0.88)	0.01 [‡]
+ Estradiol (doubling)							0.48	(0.29–0.80)	0.003 [‡]

Exogenous MHT use at baseline									
Adipokines	Never/former (159 cases/157 controls)			Current (125 cases/127 controls)			Overall (284 cases/284 controls)		
	aOR*	(95% CI)	P _{trend}	aOR*	(95% CI)	P _{trend}	aOR*	(95% CI)	P _{trend}
+ BMI and Estradiol							0.52	(0.31–0.87)	0.01 [†]
<i>Pro-inflammatory cytokines/regulators</i>									
IL6									
Adjusted model	3.18	(1.47–6.86)	0.01 [†]	1.24	(0.56–2.73)	0.45			0.15
+ BMI (per 5 kg/m ²)	1.69	(0.72–3.99)	0.51						
+ Estradiol (doubling)	1.84	(0.80–4.20)	0.45						
+ BMI and Estradiol	1.42	(0.59–3.42)	0.91						
TNF (TNF-alpha)									
Adjusted model	2.43	(1.17–5.04)	0.01 [†]	0.91	(0.41–2.01)	0.89			0.11
+ BMI (per 5 kg/m ²)	1.28	(0.58–2.86)	0.31						
+ Estradiol (doubling)	1.86	(0.85–4.08)	0.06						
+ BMI and Estradiol	1.29	(0.57–2.93)	0.30						
TNFRSF1A (sTNFRI)									
Adjusted model	2.45	(1.11–5.41)	0.002 [†]	1.16	(0.45–3.00)	0.50			0.14
+ BMI (per 5 kg/m ²)	1.06	(0.43–2.56)	0.70						
+ Estradiol (doubling)	2.00	(0.86–4.62)	0.03						
+ BMI and Estradiol	1.14	(0.47–2.78)	0.62						
IL1B									
Adjusted model							0.81	(0.30–0.83)	0.01 [†]
+ BMI (per 5 kg/m ²)							0.51	(0.30–0.86)	0.01 [†]
+ Estradiol (doubling)							0.50	(0.30–0.83)	0.01 [†]
+ BMI and Estradiol							0.51	(0.30–0.86)	0.01 [†]
IL1R2 (soluble interleukin 1 receptor, type II)									
Adjusted model	2.32	(1.08–4.99)	0.01 [†]	1.35	(0.59–3.08)	0.49			0.11

Exogenous MHT use at baseline							
<i>Adipokines</i>	Never/former (159 cases/157 controls)			Current (125 cases/127 controls)			Overall (284 cases/284 controls)
	aOR [*]	(95% CI)	P _{trend}	aOR [*]	(95% CI)	P _{trend}	
+ BMI (per 5 kg/m ²)	1.89	(0.82–4.35)	0.09				
+ Estradiol (doubling)	1.53	(0.68–3.44)	0.15				
+ BMI and Estradiol	1.62	(0.70–3.75)	0.14				
IL23							
Adjusted model						0.80	0.60 (0.36–0.99) 0.02
+ BMI (per 5 kg/m ²)							0.59 (0.34–1.00) 0.01 [‡]
+ Estradiol (doubling)							0.62 (0.37–1.03) 0.03 [‡]
+ BMI and Estradiol							0.60 (0.35–1.03) 0.02 [‡]
CSF2 (GM-CSF)							
Adjusted model	0.40	(0.20–0.81)	0.03	0.82	(0.36–1.91)	0.85	0.41
+ BMI (per 5 kg/m ²)	0.42	(0.19–0.92)	0.08				
+ Estradiol (doubling)	0.36	(0.17–0.77)	0.03				
+ BMI and Estradiol	0.39	(0.18–0.88)	0.07				
CSF3 (G-CSF)							
Adjusted model	2.58	(1.34–4.96)	0.01 [‡]	1.37	(0.61–3.11)	0.26	0.17
+ BMI (per 5 kg/m ²)	1.42	(0.69–2.94)	0.42				
+ Estradiol (doubling)	1.52	(0.75–3.10)	0.26				
+ BMI and Estradiol	1.23	(0.59–2.59)	0.60				
Angiogenic factors/regulators							
VEGFA							
Adjusted model						0.38	2.56 (1.55–4.22) 0.0002 [‡]
+ BMI (per 5 kg/m ²)							2.54 (1.51–4.26) 0.0002 [‡]
+ Estradiol (doubling)							2.58 (1.56–4.28) 0.0002 [‡]
+ BMI and Estradiol							2.56 (1.52–4.30) 0.0002 [‡]

	Exogenous MHT use at baseline					
	Never/former (159 cases/157 controls)			Current (125 cases/127 controls)		
<i>Adipokines</i>	aOR [*]	(95% CI)	P _{trend}	aOR [*]	(95% CI)	P _{trend}
FLT4 (VEGFR3)						
Adjusted model	2.23	(1.07–4.64)	0.01 [†]	1.00	(0.44–2.27)	0.76
+ BMI (per 5 kg/m ²)	1.53	(0.68–3.45)	0.17			0.31
+ Estradiol (doubling)	1.95	(0.88–4.30)	0.05			
+ BMI and Estradiol	1.55	(0.68–3.55)	0.18			
<i>Acute phase proteins</i>						
CRP						
Adjusted model	6.33	(3.07–13.04)	<0.0001 [†]	0.87	(0.39–1.98)	0.89
+ BMI (per 5 kg/m ²)	1.99	(0.85–4.67)	0.20			0.001
+ Estradiol (doubling)	2.76	(1.21–6.26)	0.02			
+ BMI and Estradiol	1.44	(0.59–3.54)	0.62			
SAA1						
Adjusted model	5.05	(2.25–11.37)	<0.0001 [†]	1.69	(0.72–3.99)	0.14
+ BMI (per 5 kg/m ²)	2.18	(0.87–5.46)	0.11			0.03
+ Estradiol (doubling)	3.15	(1.30–7.60)	0.01			
+ BMI and Estradiol	2.00	(0.78–5.11)	0.18			
APCS (SAP)						
Adjusted model	4.50	(2.08–9.75)	<0.0001 [†]	1.22	(0.55–2.69)	0.68
+ BMI (per 5 kg/m ²)	1.87	(0.75–4.64)	0.18			0.01
+ Estradiol (doubling)	1.85	(0.79–4.32)	0.16			
+ BMI and Estradiol	1.33	(0.52–3.41)	0.63			

* Quartile 4 vs. quartile 1 OR estimate adjusted for matching factors (age at blood draw, study year of blood draw, race, fiscal year of randomization), smoking status, parity, duration of oral contraceptive use, and duration of menopausal hormone therapy use (never, 1–5 years 6+ years among never/former hormones users and overall, and 1–5 years, 6+ years among current hormone users) with additional adjustment for listed covariate(s).

[†]FDR 0.05.

Associations of selected circulating inflammation markers and endometrial cancer risk stratified by body mass index (BMI), nested case-control study in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Table 3

	Population	BMI Category									
		<25 kg/m ² n = 76 cases/122 controls (20/53 never/former MHT)			25–29.99 kg/m ² 90 cases/100 controls (46/63)			30 kg/m ² 117 cases/59 controls (92/40)			
		OR	(95% CI)	P _{trend}	OR	(95% CI)	P _{trend}	OR	(95% CI)	P _{trend}	P _{int}
Adipokines											
ADIPOQ	Never/former MHT	0.72	(0.10–5.34)	0.29	0.72	(0.20–2.64)	0.38	0.56	(0.12–2.70)	0.32	0.12
RETN	Overall	2.39	(0.89–6.39)	0.12	0.60	(0.24–1.49)	0.32	4.41	(1.37–14.2)	0.01	0.39
SERPINE1	Never/former MHT	0.94	(0.16–5.52)	0.83	2.32	(0.52–10.3)	0.08	32.5	(4.15–255)	0.003	0.03
Chemokines											
CCL19	Never/former MHT	2.76	(0.42–18.0)	0.25	3.53	(0.54–22.9)	0.41	2.35	(0.26–21.6)	0.95	0.64
CXCL10	Never/former MHT	3.11	(0.51–19.1)	0.17	0.83	(0.22–3.13)	0.87	2.12	(0.45–10.1)	0.07	0.75
CCL3	Overall	0.71	(0.28–1.82)	0.61	0.52	(0.22–1.26)	0.32	0.33	(0.12–0.95)	0.04	0.34
Anti-inflammatory cytokines/mediators											
IL10	Overall	1.61	(0.62–4.20)	0.60	0.52	(0.20–1.32)	0.09	0.54	(0.21–1.44)	0.21	0.32
IL13	Overall	0.88	(0.34–2.25)	0.92	0.75	(0.32–1.73)	0.37	0.28	(0.11–0.76)	0.003	0.03
IL21	Overall	0.81	(0.32–2.06)	0.64	0.66	(0.27–1.60)	0.52	0.29	(0.11–0.74)	0.01	0.03
Pro-inflammatory cytokines/regulators											
IL6	Never/former MHT	1.00	(0.11–9.37)	0.98	1.91	(0.50–7.25)	0.54	2.25	(0.46–11.2)	0.23	0.13
TNF	Never/former MHT	15.6	(1.74–139)	0.02	0.59	(0.17–2.07)	0.60	1.22	(0.26–5.79)	0.15	0.54
TNFRSF1A	Never/former MHT	1.71	(0.23–12.5)	0.92	0.68	(0.17–2.73)	0.95	4.87	(0.92–25.7)	0.19	0.23
IL1B	Overall	0.85	(0.34–2.17)	0.85	0.85	(0.34–2.14)	0.85	0.23	(0.09–0.64)	0.001	0.02
IL1R2	Never/former MHT	1.49	(0.17–13.4)	0.42	0.60	(0.17–2.21)	0.59	5.83	(1.21–28.0)	0.01	0.16
IL23	Overall	0.52	(0.20–1.39)	0.20	1.20	(0.48–2.98)	0.90	0.41	(0.15–1.11)	0.03	0.30
CSF2	Never/former MHT	0.54	(0.09–3.15)	0.60	0.89	(0.23–3.49)	0.57	0.42	(0.12–1.44)	0.15	0.31
CSF3	Never/former MHT	2.09	(0.35–12.4)	0.60	0.69	(0.23–2.10)	0.41	17.7	(3.81–82.4)	0.001	0.02
Angiogenic factors/regulators											
VEGFA	Overall	2.27	(0.87–5.90)	0.10	2.12	(0.88–5.14)	0.06	4.51	(1.53–13.3)	0.01	0.38
FLT4	Never/former MHT	0.98	(0.16–5.99)	0.76	1.08	(0.33–3.53)	0.79	3.00	(0.75–12.0)	0.16	0.57
Acute phase proteins											

BMI Category										
Adipokines	Population	<25 kg/m ² n = 76 cases/122 controls (20/53 never/former MHT)			25–29.99 kg/m ² 90 cases/100 controls (46/63)			30 kg/m ² 117 cases/59 controls (92/40)		
		OR	(95% CI)	P _{trend}	OR	(95% CI)	P _{trend}	OR	(95% CI)	P _{trend}
CRP	Never/former MHT	64.5	(1.35–999)	0.005	2.47	(0.71–8.64)	0.43	0.99	(0.14–6.88)	0.90
SAA1	Never/former MHT	14.9	(2.27–97.7)	0.03	0.47	(0.13–1.64)	0.23	0.90	(0.21–3.92)	0.99
APCS	Never/former MHT	9.49	(0.56–160)	0.02	0.99	(0.25–3.90)	0.61	1.21	(0.21–6.86)	0.54
										0.75

*. Quartile 4 vs. quartile 1 OR estimate adjusted for matching factors (age and study year of blood draw, race, and fiscal year of randomization), smoking status, parity, duration of oral contraceptive use, duration of menopausal hormone therapy (MHT) use, and continuous BMI (per 5 kg/m²).

Table 4

Odds ratios (OR) and 95% confidence intervals (CI) evaluating the effects of body mass index (BMI) and cross-validated inflammation score on endometrial cancer risk among never/former MHT users.

		OR [*]	95% CI
BMI (≥ 30 vs. <25kg/m ²)	[Not adjusted for inflammation score]	6.39	(3.16–12.92)
	[Adjusted for inflammation score]	4.72	(2.26–9.88)
Inflammation score (T3 vs. T1)	[Not adjusted for BMI]	3.58	(1.83–7.00)
	[Adjusted for BMI]	2.33	(1.14–4.75)

* OR estimate adjusted for matching factors (age at blood draw, study year of blood draw, race, fiscal year of randomization), smoking status, parity, duration of oral contraceptive use, and duration of menopausal hormone therapy use (never, 1–5 years 6+ years among never/former hormones users and overall, and 1–5 years, 6+ years among current hormone users). Additional adjustment for inflammation score or BMI as listed in 2nd column.