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A prospective clinical cohort study of women at increased risk for endometrial cancer

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Abstract

Objective: To evaluate endometrial cancer (EC) risk assessment and early detection strategies in high-risk populations, we designed a large, prospective cohort study of women undergoing endometrial biopsy to assess risk factors and collect novel biospecimens for future testing of emerging EC biomarkers. Here we report on the baseline findings of this study.

Methods: Women aged ≥45 years were enrolled at the Mayo Clinic from February 2013 – June 2018. Risk factors included age, body mass index (BMI), smoking, oral contraceptive and hormone therapy use, and parity. We collected vaginal tampons, endometrial biopsies, and Tao brush samples. We estimated mutually-adjusted odds ratios (OR) and 95% confidence intervals (CI) using multinomial logistic regression; outcomes included EC, atypical hyperplasia, hyperplasia without atypia, disordered proliferative endometrium, and polyps, versus normal endometrium.

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Conflicts of Interest: The authors have no conflicts of interest to disclose.

Results: Subjects included 1,205 women with a mean age of 55 years; 55% were postmenopausal, and 90% had abnormal uterine bleeding. The prevalence of EC was 4.1% (n=49), predominantly diagnosed in postmenopausal women (85.7%). Tampons and Tao brushings were obtained from 99% and 68% of women, respectively. Age (OR 1.14, 95% CI 1.1– 1.2) and BMI (OR 1.39, 95% CI 1.1–1.7) were positively associated with EC; atypical hyperplasia (OR 1.07, 95% CI 1.0–1.1; OR 2.00, 95% CI 1.5–2.6, respectively), and polyps (OR 1.06, 95% CI 1.0–1.1; OR 1.17, 95% CI 1.0–1.3, respectively); hormone therapy use and smoking were inversely associated with EC (OR 0.42, 95%, 0.2–0.9; OR 0.43, 95% CI, 0.2–0.9, respectively). Parity and past oral contraception use were not associated with EC.

Conclusions: Well-established EC risk factors may have less discriminatory accuracy in high-risk populations. Future analyses will integrate risk factor assessment with biomarker testing for EC detection.

Keywords

Endometrial cancer; endometrial hyperplasia; postmenopausal bleeding; risk factors; prospective cohort

Introduction

Endometrial cancer (EC) is the most common gynecologic cancer diagnosed in the U.S., with approximately 61,880 new cases and 12,160 deaths estimated for 2019.[1] Unlike most cancers, EC incidence and mortality rates have been increasing worldwide[2, 3], and these trends are projected to continue over the next decade.[4] EC is most commonly diagnosed in postmenopausal women, with peak incidence rates occurring among those aged 60 to 70 years. Obesity is by far the strongest risk factor for EC; other major risk factors for EC are those presumptively related to cumulative lifetime estrogen exposure, including early age at menarche, older age at menopause, and nulliparity.[5–7] Diabetes and metabolic syndrome, tamoxifen exposure, and family history of EC (particularly Lynch Syndrome) are also associated with increased risk of EC, whereas a history of oral contraceptive use and smoking have been shown to be protective against EC.[6, 8–12]

Most ECs are diagnosed at an early, localized stage, with a 5-year survival of approximately 95%. In contrast, the 5-year survival among women diagnosed with regional and distant stage EC is 70% and 18%, respectively.[3, 13–15] The development of invasive EC is preceded by precancerous lesions which can manifest with abnormal uterine bleeding in premenopausal or perimenopausal women (AUB) or postmenopausal bleeding (PMB). Because PMB occurs in approximately 90% of postmenopausal EC, including early stages amenable to cure, a diagnostic and/or therapeutic window of opportunity exists for the early detection and treatment of pre-invasive or early invasive lesions[16, 17] However, AUB and PMB are also common symptoms of benign uterine conditions, and only 5% of postmenopausal women undergoing initial diagnostic evaluation for PMB are diagnosed with endometrial cancer in the U.S.[16]

The increasing burden of EC underscores the need for improved risk assessment and minimally invasive and cost-effective diagnostic options in order to improve early detection

without causing undue morbidity and cost in patients without cancer or pre-cancerous conditions.[18] While epidemiologic risk prediction models for EC have been validated in population-based studies[19, 20], it is not clear how they would perform in high-risk populations such as women with AUB or PMB. Similarly, promising molecular markers for early detection of EC measured from novel, non-invasive sampling devices such as vaginal tampons and Pap tests, require validation in clinically-relevant target populations. [21–23]

To address this important gap, we designed a large, prospective clinical cohort study of women who present for diagnostic evaluation secondary to signs/symptoms common in EC. The study includes the collection of a novel biospecimen, the vaginal pool [21, 24], through the placement of an intravaginal tampon, as well as collection of material from the uterine lining using a Tao brush. Here we describe the design, methods, and baseline findings from this study, with emphasis on evaluating associations of epidemiologic risk factors among women with pre- or perimenopausal AUB and PMB and EC.

Materials and Methods

Study Population

Women presenting to the Mayo Clinic's Division of Gynecology with a clinical indication for endometrial biopsy were prospectively enrolled from February 21, 2013 through June 25, 2018, with passive follow-up every 6 to 12 months. The current analysis includes data from the baseline visit only. Women who were eligible included those aged 45 years or older presenting with clinical signs and/or symptoms common in EC including, pre- or perimenopausal AUB, PMB, and/or abnormal pelvic ultrasound findings. AUB was defined as AUB occurring at age 45 years or older in women who were not in menopause. Women were also eligible if they had a diagnosis of Lynch syndrome and had not undergone risk reducing hysterectomy. Exclusion criteria included prior hysterectomy, prior pelvic radiation, endometrial sampling within the past 3 months, and current pregnancy. The majority of patients were non-Hispanic white (96%); very few identified as non-Hispanic black or Hispanic (1% respectively). This study was approved by the Mayo Clinic and National Cancer Institute Institutional Review Boards; written informed consent was obtained from all participants prior to study enrollment.

Clinical Evaluation

Women enrolled underwent clinical evaluation of the endometrium as determined by their care provider. Clinical testing could include any combination of the following: transvaginal ultrasound, office hysteroscopy, and office endometrial biopsy. If complete workup in the clinic was not feasible, women underwent assessment under anesthesia via hysteroscopy and dilation and curettage (D&C). If clinical indications existed, hysterectomy was performed.

Transvaginal Ultrasound.—Ultrasound was performed as clinically indicated and the interpretation performed by radiologists specialized in pelvic ultrasound interpretation. Abnormal ultrasound findings were defined as any of the following: the presence of an endometrial mass with or without evidence of myometrial invasion, papillary endometrial projections, suspected blood in the uterine cavity, cystic endometrial lesions, or endometrial

debris among postmenopausal women. Endometrial stripe thickness was measured by the interpreting clinical radiologist and reported in millimeters (mm).

Hysteroscopy.—Office hysteroscopy using a flexible 3.1 mm diagnostic scope was performed as per the treating clinician's discretion according to patient age, imaging findings, and clinical feasibility. If an endometrial polyp was found, polyps were resected using an intrauterine morcellator either in the office or under anesthesia in the operating room. If a hysteroscopy was indicated and not feasible to perform in the clinic, women underwent a hysteroscopy under anesthesia.

Endometrial Sampling.—All women enrolled in this study were anticipated to undergo diagnostic evaluation via endometrial sampling. This was performed as a clinic endometrial biopsy with a Pipelle (Pipelle® CooperSurgical, Turnbull, CT) or Endosampler device (MedGyn, Addison, IL) or as a D&C if clinic biopsy was not feasible. Pathology diagnoses were made clinically by gynecologic pathologists. Final pathology from the baseline visit on endometrial sampling was the criterion standard for endometrial pathology diagnosis among those who did not require a hysterectomy. Among women who underwent hysterectomy, the most severe pathology diagnosis on either the endometrial sampling or hysterectomy specimen from the baseline visit was considered the final study diagnosis.

Study Biospecimen Sampling Methods

An intravaginal tampon to collect the vaginal pool, the vaginal effluent from the female reproductive tract [21, 24], was obtained from each woman prior to their clinically indicated office procedures. After providing informed consent, women self-inserted a regular sized polyester-cotton blend tampon into the vagina until the time of clinical exam (approximately 30 minutes). The intravaginal tampon dwell time was recorded. After removal, the tampon was placed in a 50mL conical tube containing a sterile buffer and processed in the research laboratory as previously described [21].

An endometrial brushing was performed using a Tao brush (Cook® Medical, Bloomington, IN) either prior to or following endometrial biopsy. The brush end was removed and placed into a vial containing PreservCyt solution and transferred to the research laboratory where they were processed as previously described.[25, 26]

Outcome Definitions

Final baseline endometrial pathology diagnoses were classified as: Normal endometrium, endometrial polyp, disordered proliferative endometrium (DPEM), hyperplasia without atypia, hyperplasia with atypia, EC, or other benign histologic findings (e.g., endometritis, fibroids). If an endometrial biopsy was not clinically indicated or performed, the indication was recorded and final pathology was determined from the surgical specimen at baseline, if applicable. Inadequate or non-diagnostic biopsies were also recorded.

Endometrial Cancer Risk Factors and Clinical Characteristics

Baseline information on relevant clinical risk factors for EC including the indication for endometrial sampling, bleeding description, age, body mass index (BMI), hypertension,

type II diabetes, and smoking history were abstracted from electronic medical records. Other epidemiologic risk factors including, tamoxifen exposure, current and former hormone replacement therapy (HRT) use, past oral contraception (OC) use, parity, and family history of EC were ascertained via patient interview. Among postmenopausal women, PMB was characterized as either initial episode of or recurrent bleeding. Among premenopausal women, AUB pattern was characterized as one of the following: Heavy menstrual bleeding, intermenstrual bleeding, menometrorrhagia, irregular menses, or other AUB.

Statistical Analysis

We summarized baseline characteristics for the study cohort, overall and by worst diagnosis, using descriptive statistics with Pearson's chi-square test for categorical variables and one-way ANOVA tests for continuous variables. Among women diagnosed with EC, we summarized method of diagnosis (endometrial sampling and/or hysterectomy), FIGO stage, grade, histology, myometrial invasion, and tumor size, using descriptive statistics, stratified by menopausal status.

We evaluated epidemiologic EC risk factors using multinomial logistic regression analyses, mutually adjusted for age (continuous per 1-year increase), BMI (continuous, per 5kg/m^2 increase), ever HRT use, past OC use, parity (parous vs. nulliparous), type II diabetes, hypertension, ever smoking, and family history of EC. We estimated adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association of these risk factors with the full range of histologic outcomes including uterine polyps, DPEM, hyperplasia without atypia, atypical hyperplasia, and EC. For these analyses our reference group included women with normal or other benign histology findings as well as those without an indication for biopsy. We also evaluated associations of EC risk factors with combined endpoints of DPEM and hyperplasia without atypia as well as atypical hyperplasia and EC with the reference group including normal or other benign histology findings, no indication for biopsy, and uterine polyps. Women with inadequate biopsy results were excluded from all models. Results are presented for all women and separately for women with PMB. All analyses were performed in Stata (version 14). All statistical tests were two-sided with $p<0.05$ considered significant.

Results

Study Population

A total of 2,274 eligible patients presented for evaluation for EC at the Mayo Clinic between February 21, 2013 and June 25, 2018 (Table 1), of these, 1,210 women agreed and consented to participate, and 1,205 aged 45–86 years (mean 55.3 years) were included in the current study (Figure 1). A majority of women presented with PMB (47.1%) or AUB (42.7%), with most postmenopausal women reporting recurrent PMB (59.5%) and most pre- and perimenopausal women reporting menometrorrhagia (38.1%). Among the full cohort, the mean BMI was 30.2 kg/m^2 (range 17.2 kg/m^2 – 68.6 kg/m^2) and the prevalence of hypertension and type II diabetes was 24.3% and 7%, respectively. Most women reported never using HRT (67.3%), never smoking (68.8%) and having one or more live births (83.5%).

Biospecimen Collection

Overall, a total of 1,041 women had a histologically-confirmed diagnosis (Table 1). A total of 1,080 women had an endometrial biopsy performed, and in 1,022 of these sampling was adequate (Figure 1). Among the 58 women with inadequate biopsies, 12 underwent other surgical procedures in which a diagnostic tissue specimen was obtained. Of the 125 women without endometrial biopsy, 7 underwent surgery and in the remaining 118, biopsy was not clinically indicated based on age, ultrasound, and/or hysteroscopy results. Intravaginal tampon samples were obtained from 1,197 women (99.3%) prior to biopsy. Tao brush samples were obtained from 826 women (68.5%); the majority of women who did not have a Tao brush sample (n=371) had either a benign endometrial sampling (n=172, 46%) or inadequate/no sampling performed (n=140, 38%).

Histologic Outcomes

The overall prevalence of EC in the study cohort was 4.1% (n=49), with 7 cases occurring in pre- or perimenopausal women (14.3%) and 42 occurring in postmenopausal women (85.7%). Of the 42 cases in postmenopausal women, 40 had PMB (95.2%) and of the 7 cases in pre-or perimenopausal women, 6 had AUB (85.7%). A total of 36 cancers were diagnosed on both biopsy and hysterectomy specimens and 11 cases were diagnosed on hysterectomy only, with two women having benign and 9 having atypical hyperplasia diagnoses on the biopsy specimen. One woman had a biopsy diagnosis of EC and benign endometrium diagnosed from the hysterectomy specimen and one has not undergone hysterectomy (Table 2). Overall, most ECs were endometrioid histology (81.6%), low grade (84%; Grade 1 or 2) and diagnosed at an early stage (85.7%; Stage I). All 7 cases with non-endometrioid histology were diagnosed in postmenopausal women (Table 2). Other pathology diagnoses included normal endometrium (54.1%), polyps (13.1%), DPEM (9.1%), hyperplasia without atypia (2.5%), and atypical hyperplasia (1.7%) (Table 1).

Risk Factor Associations with EC, Atypical Hyperplasia, and Benign Histology Diagnoses

Among the whole cohort, older age (per each 1-year increase) and increasing BMI (per each 5kg/m^2 increase) were associated with atypical hyperplasia (OR, 1.07, 95% CI, 1.0–1.1 and OR 2.00, 95% CI, 1.5–2.6, respectively) and EC (OR, 1.14, 95% CI, 1.1–1.2 and OR 1.39, 95% CI, 1.1–1.7, respectively) (Table 3). Ever HRT use and ever smoking were both associated with significantly decreased odds of EC compared to never HRT use and never smoking, respectively (OR 0.42, 95% CI, 0.2–0.9 and OR 0.43, 95% CI, 0.2–0.9, respectively), but not with atypical hyperplasia, although smoking showed a similar, but non-significant protective effect (OR, 0.57, 95% CI, 0.2–1.7). Other factors, such as past OC use, parity, type II diabetes, hypertension, and family history of EC were not significantly associated with EC or atypical hyperplasia in this cohort (Table 3; Figure 2A). We observed similar associations in analyses evaluating combined endpoints atypical hyperplasia and EC, although the protective effect of ever HRT use on the odds of EC and atypical hyperplasia was slightly attenuated compared to the association with EC alone (OR 0.55, 95% CI, 0.3–1.0; Supplemental Table 1).

With respect to benign endometrial histologic diagnoses, older age was significantly associated with increased odds of endometrial polyps (OR 1.06 per 1-year increase in

age, 95% CI 1.0–1.1), and with decreased odds of DPEM (OR 0.95 per 1-year increase in age, 95% CI 0.9–1.0). Elevated BMI was significantly associated with increased odds of endometrial polyps (OR 1.17 per each 5kg/m^2 increase, 95% CI 1.0–1.3), whereas parity was associated with decreased odds of endometrial polyps compared to nulliparity (OR 0.58, 95% CI, 0.4–0.9) (Table 3; Figure 2A). We observed similar associations in analyses evaluating combined endpoints of DPEM and hyperplasia without atypia (Supplemental Table 1).

Risk factor patterns among women with PMB were generally similar to those observed in the overall cohort (Table 4; Figure 2B). Of note, BMI became significantly associated with increased odds of hyperplasia without atypia (OR 1.48, 95% CI 1.0–2.1) and older age (OR, 1.06, 95% CI, 1.0–1.1) and ever HRT use (OR, 3.20, 95% CI, 0.9–11.4) became marginally significantly associated with increased odds of hyperplasia without atypia in women with PMB. Patterns were similar in analyses of combined endpoints, with the exception of type II diabetes becoming significantly associated with increased odds of atypical hyperplasia and EC (OR 2.64, 95% CI, 1.1–6.2) compared to not having diabetes. The effects of age, BMI, and ever HRT use were not significantly associated with odds of DPEM and hyperplasia without atypia combined (Supplemental Table 2).

Discussion

The growing burden of EC and the impact of early diagnosis on improved cancer-specific survival underscore the imperative for developing effective early detection approaches. Currently population-based screening for EC does not exist, and the most common presenting symptoms, pre- or perimenopausal AUB or PMB, lack specificity for EC.[16] This study was designed to evaluate clinical and epidemiologic risk factors for EC, and to collect novel biospecimens for future testing of emerging molecular markers of EC in a clinical cohort of women at elevated risk. [21, 26] Importantly, as opposed to most previous efforts, our study design enables the evaluation of EC risk assessment and early-detection approaches in a target population of women in whom these strategies would ultimately be applied; women presenting for evaluation prior to biopsy.

The overall prevalence of EC in our study population was 4.1% and varied by menopausal and bleeding status, with the highest prevalence among women with PMB (7.1%). Among pre- and perimenopausal women with AUB the most common abnormal finding was DPEM, whereas among women with PMB, the most common abnormal finding was uterine polyps. Interestingly, the prevalence of atypical hyperplasia was much lower than the prevalence of EC in our cohort. Approximately 30% of women with atypical hyperplasia are expected to progress to EC over 25 years, suggesting that the prevalence of atypical hyperplasia in the population should be higher than EC.[27] It is conceivable that a subset of atypical hyperplasia does not present with abnormal bleeding, while almost all women with EC have abnormal bleeding. It is also plausible that a subset of atypical hyperplasias regress spontaneously or in response to pharmacologic therapy.[28]

Women with abnormal bleeding are an ideal group for EC early detection strategies, given their increased risk of being diagnosed with EC and the fact that most ECs occur in women

with abnormal bleeding, including early-stage ECs.[16] However, most epidemiologic risk prediction models[19, 20] and molecular biomarkers for EC detection[22, 23] have not been evaluated in this population. Unlike population-based studies, our study was enriched for women with pre- and perimenopausal AUB and PMB, including those with benign uterine conditions. Importantly, not all established EC risk factors showed associations with EC in our population. While some risk factors including older age, increasing BMI, and smoking (protective), were associated with EC as expected, the established strong protective risk factor OC use was not significantly associated with reduced risk of EC in our study cohort, but instead showed an increased odds ratio. While the association between OC use and EC is strong and undisputed[11,12], approximately 70% of women in our study, including those with a pathologically unremarkable appearing endometrium, reported past OC use compared with 40–50% of women in other population-based cohort studies.[29–31] Thus, the lack of an association between past OC use and EC in our study is likely secondary to higher OC use in our reference group compared to the general population. Further, we found that age, BMI, and nulliparity, were significantly associated with benign endometrial polyps, suggesting that shared associations between benign endometrial conditions and EC may limit the performance of established risk factors for prediction of EC in women with AUB/PMB. In the future, molecular markers may allow to better distinguish polyps, and other benign conditions, from EC among women presenting with AUB or PMB.

We observed a strong inverse relationship between ever HRT use and decreased odds of EC. This observation could have several explanations: In the general population, studies have shown that certain combined formulations of estrogen plus progestin hormone therapy are protective against EC.[32] Further, HRT can cause irregular uterine bleeding, particularly within the first 6 months of use, which likely leads to an enrichment of our population for women with HRT-related uterine bleeding not related to EC. In support of that, in a recent review of the literature, we found that among women with PMB, the risk of EC was significantly lower in studies of women using HRT compared to studies that excluded these women, in line with our results.[16]

Strengths of this study include a large clinical population of women undergoing diagnostic evaluation for perimenopausal AUB and PMB, symptoms that are present in 90% of women diagnosed with EC, which allows us to evaluate current clinical practice and inform evidence-based clinical decision making. Follow-up of this study cohort is ongoing and will enable prospective evaluation of clinical gynecologic outcomes following the baseline endometrial pathology diagnoses at the time of enrollment. Currently, our understanding of the longitudinal sensitivity of endometrial biopsy and other diagnostic and sampling approaches is limited. The assessment of longitudinal associations of epidemiologic and clinical risk factors, long-term performance of diagnostic and management approaches at enrollment and in subsequent encounters, as well as testing of emerging molecular EC biomarkers will lead to further understanding of diagnostic procedures and early intervention and prevention opportunities. The limitations of this study include the fact that, despite a large sample size, the prevalence of EC and precursor lesions in this population was still relatively low, therefore, our power to detect statistically significant associations for some EC risk factors with smaller effect sizes was limited. However, we were adequately powered to detect associations with key risk factors like BMI and OC use. As enrollment

is still ongoing, and follow-up of this population continues, the opportunity to accrue additional cases and study prospective outcomes and biomarkers exists. Additionally, while our study cohort reflects real-world clinical practice, the population was predominantly white, we did not have data on factors such as socioeconomic status, and results may not be generalizable to other, racially-diverse populations and/or clinical settings (e.g., primary care or Women's Health clinics).

Conclusions

The growing incidence of EC supports the need to develop clinically-useful risk prediction models and early detection strategies. Findings from the present study suggest that models based on classic epidemiologic risk factors for EC may have more limited discriminatory accuracy in elevated risk populations with the ambiguous symptom of AUB or PMB, given the shared risk factors between EC and benign etiologies of AUB/PMB. Our prospective cohort study establishes a rich resource that will integrate clinical, epidemiologic, and biomarker data in a population of women at elevated risk for EC. Going forward, it will be important to evaluate the performance of established epidemiologic[19, 20] and clinical EC risk prediction models[33], as well as novel candidate EC biomarkers, in our study population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- This large clinical prospective cohort study evaluates risk factors for endometrial cancer and its precursors
- Vaginal tampons, endometrial biopsies, and Tao brushes were collected for future testing of emerging biomarkers
- Of the 1,205 participants, 90% had abnormal uterine bleeding and the prevalence of endometrial cancer was 4.1% (n=49)
- Endometrial cancer and benign uterine conditions (e.g., polyps) shared risk factors such as age and body mass index
- Parity and oral contraception use were not associated with endometrial cancer risk in this high-risk population

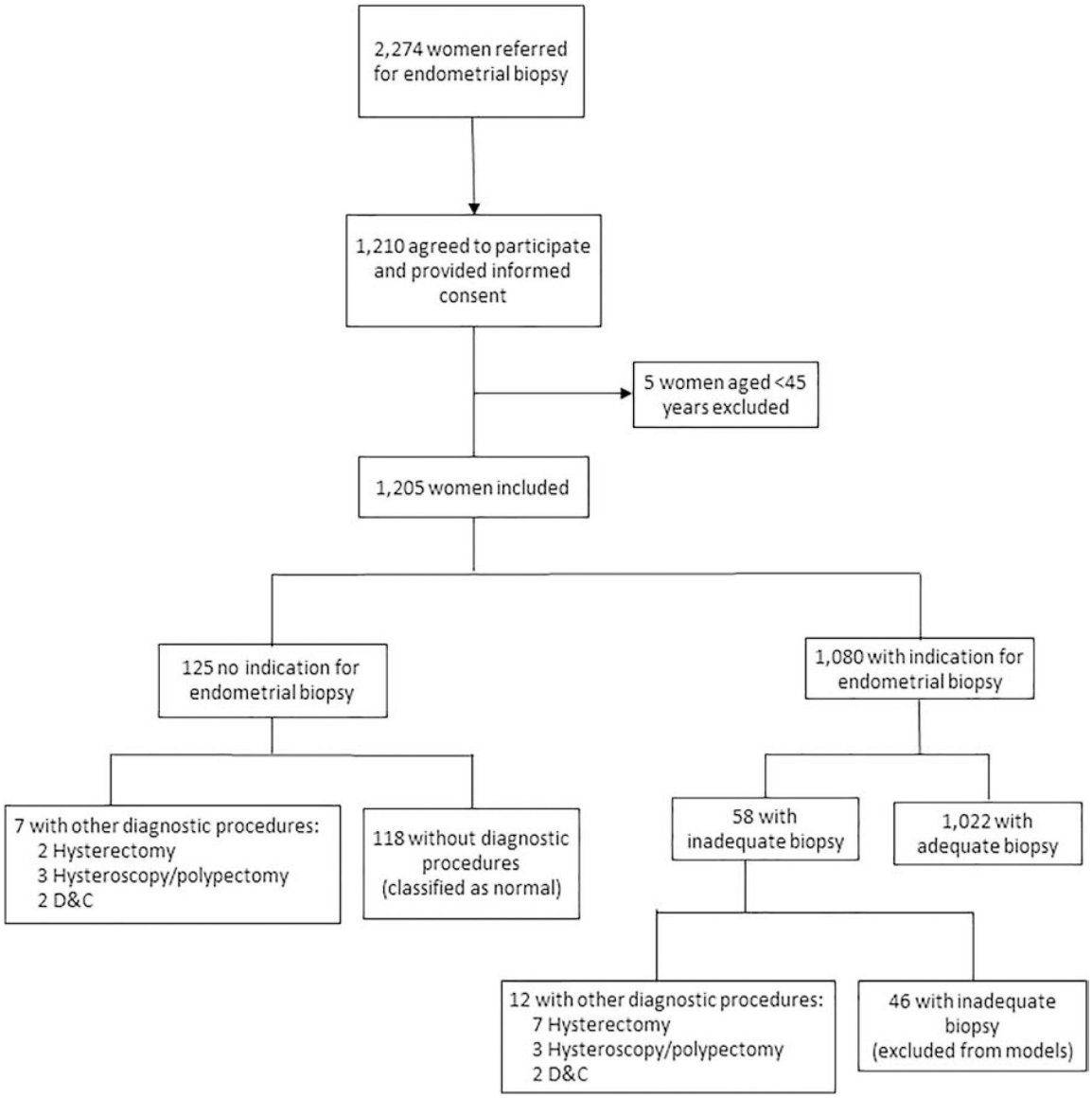

Figure 1.
Flow-Diagram of Study Population.

Figure 2A. All Women

	Polyps	DPEM	Hyperplasia, no atypia	Atypical Hyperplasia	EC
Age	1.06	0.95	1.03	1.07	1.14
BMI	1.17	1.12	1.10	2.00	1.39
HRT Use	0.81	0.75	1.45	1.00	0.42
Past OC Use	0.94	1.30	1.01	0.88	0.82
Parity	0.58	1.13	0.87	0.86	0.60
Type II Diabetes	1.14	0.88	2.09	1.63	2.11
Hypertension	0.79	1.18	1.55	1.59	0.94
Smoking	1.27	1.12	0.63	0.57	0.43
Family History	0.70	0.74	N/A	N/A	0.71

Figure 2B. Women with PMB

	Polyps	DPEM	Hyperplasia, no atypia	Atypical Hyperplasia	EC
Age	1.07	0.96	1.06	1.07	1.14
BMI	1.22	1.19	1.48	2.20	1.21
HRT Use	0.77	1.27	3.20	0.92	0.39
Past OC Use	1.42	2.16	2.27	0.90	1.22
Parity	0.70	0.64	1.33	2.99	0.73
Type II Diabetes	0.51	1.47	2.05	2.83	2.13
Hypertension	0.85	1.93	2.30	1.23	1.17
Smoking	1.53	0.64	0.46	0.49	0.44
Family History	0.93	0.52	N/A	N/A	0.75

Increased risk, CI's do not cross 1.0
Increased risk, CI's cross 1.0
Decreased risk, CI's do not cross 1.0
Decreased risk, CI's cross 1.0

Figure 2. Effect estimates for associations of endometrial cancer risk factors with histologic outcomes.

Figure 2A shows associations among all women and Figure 2B shows associations among women with postmenopausal bleeding. Red indicates positive associations for which the confidence intervals do not cross 1.0, whereas pink indicates positive associations for which the confidence intervals cross 1.0. Likewise, blue indicates inverse associations for which the confidence intervals do not cross 1.0, whereas light blue indicates inverse associations for which the confidence intervals cross 1.0. Abbreviations: DPEM, disordered proliferative endometrium; EC, endometrial cancer; BMI, body mass index; HRT, hormone replacement therapy; OC, oral contraceptive

Table 1.

Characteristics of 1,205 Women Enrolled in the Mayo Baseline Study by Worst Outcome *

	Total	Not Done †	Inadequate	Normal	Other ‡	Polyps	DPEM	Hyperplasia without atypia	Atypical Hyperplasia	Endometrial Cancer
Total, n (%)	1,205 (100.0)	118 (9.8)	46 (3.8)	652 (54.1)	23 (1.9)	158 (13.1)	109 (9.1)	30 (2.5)	20 (1.7)	49 (4.1)
Mean Age ±SD	55.3 ± 8.0	55.6 ± 8.6	58.0 ± 7.0	54.2 ± 7.4	52.6 ± 7.1	58.1 ± 9.1	52.1 ± 5.0	57.0 ± 7.9	57.8 ± 7.8	63.4 ± 8.9
Race/Ethnicity										
Non-Hispanic White	1,125 (93.4)	112 (94.9)	43 (93.5)	610 (93.6)	22 (95.7)	147 (93.0)	101 (92.7)	27 (90.0)	19 (95.0)	44 (89.9)
Non-Hispanic Black	11 (0.9)	1 (0.9)	1 (2.2)	7 (1.1)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Hispanic	18 (1.5)	1 (0.9)	1 (2.2)	12 (1.8)	0 (0.0)	3 (1.9)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Asian/Hawaiian Pacific Islander	12 (1.0)	1 (0.9)	1 (2.2)	7 (1.1)	1 (4.3)	1 (0.6)	(0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Other/Unknown	39 (3.2)	2 (2.5)	0 (0.0)	16 (2.5)	0 (0.0)	6 (3.8)	8 (7.3)	3 (10.0)	0 (0.0)	3 (6.1)
Menopausal Status, n (%) §										
Pre-menopausal	544 (45.2)	52 (44.1)	3 (6.5)	314 (47.8)	16 (69.6)	50 (32.7)	81 (74.3)	15 (50.0)	6 (30.0)	7 (14.3)
Post-menopausal	661 (54.8)	66 (55.9)	43 (93.5)	343 (52.2)	7 (30.4)	103 (67.3)	28 (25.7)	15 (50.0)	14 (70.0)	42 (85.7)
Abnormal Bleeding, n (%) §										
None	123 (10.2)	13 (11.0)	11 (23.9)	67 (10.2)	1 (4.4)	23 (15.0)	4 (3.7)	0 (0.0)	1 (5.0)	3 (6.1)
Postmenopausal Bleeding	567 (47.1)	60 (50.9)	33 (71.7)	291 (44.3)	7 (30.4)	81 (52.9)	27 (24.8)	15 (50.0)	13 (65.0)	40 (81.6)
Abnormal Uterine Bleeding	515 (42.7)	45 (38.1)	2 (4.4)	299 (45.5)	15 (65.2)	49 (32.0)	78 (71.6)	15 (50.0)	6 (30.0)	6 (12.2)
Bleeding Episode (postmenopausal), n (%) *										
Recurrent	323 (59.5)	32 (54.2)	14 (46.7)	154 (56.0)	3 (42.9)	48 (60.8)	19 (73.1)	11 (73.3)	12 (100.0)	30 (75.0)
Initial	220 (40.5)	27 (45.8)	16 (53.3)	121 (44.0)	4 (57.1)	31 (39.2)	7 (26.9)	4 (26.7)	0 (0.0)	10 (25.0)
Abnormal Uterine Bleeding Type (premenopausal), n (%) //										
Menorrhagia	160 (31.1)	13 (28.9)	0 (0.0)	106 (35.5)	2 (13.3)	12 (24.5)	22 (28.2)	3 (20.0)	2 (33.3)	0 (0.0)
Metrorrhagia	110 (21.4)	15 (33.3)	1 (50.0)	61 (20.4)	4 (26.7)	12 (24.5)	11 (14.1)	4 (26.7)	0 (0.0)	2 (33.3)
Menometrorrhagia	196 (38.1)	9 (20.0)	1 (50.0)	106 (35.5)	6 (40.0)	20 (40.8)	39 (50.0)	7 (46.7)	4 (66.7)	4 (66.7)

	Total	Not Done†	Inadequate	Normal	Other ‡	Polyps	DPEM	Hyperplasia without atypia	Atypical Hyperplasia	Endometrial Cancer
Anovulatory Bleeding	25 (4.9)	1 (2.2)	0 (0.0)	15 (5.0)	0 (0.0)	3 (6.1)	5 (6.4)	1 (6.7)	0 (0.0)	0 (0.0)
Other	24 (4.7)	7 (15.6)	0 (0.0)	11 (3.7)	3 (20.0)	2 (4.1)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Current Tamoxifen Use, n (%)//										
No	1,148 (95.3)	118 (100.0)	41 (89.1)	619 (94.2)	21 (91.3)	145 (94.8)	105 (96.3)	30 (100.0)	20 (100.0)	49 (100.0)
Yes	57 (4.7)	0 (0.0)	5 (10.9)	38 (5.8)	2 (8.7)	8 (5.2)	4 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hormone Replacement Therapy Use, n (%)//										
Never	811 (67.3)	86 (72.9)	29 (63.0)	434 (66.1)	12 (52.2)	97 (63.4)	84 (77.1)	17 (56.7)	15 (75.0)	37 (75.5)
Former	144 (12.0)	11 (9.3)	5 (10.9)	75 (11.4)	1 (4.4)	29 (19.0)	8 (7.3)	4 (13.3)	3 (15.)	8 (16.3)
Current	250 (20.8)	21 (17.8)	12 (26.1)	148 (22.5)	10 (43.5)	27 (17.6)	17 (15.6)	9 (30.0)	2 (10.0)	4 (8.2)
Mean Body Mass Index ± SD§	30.2 ± 8.0	28.0 ± 6.4	30.3 ± 8.7	29.5 ± 7.7	28.9 ± 7.5	31.2 ± 8.1	30.8 ± 7.5	30.9 ± 8.0	41.9 ± 7.8	34.2 ± 10.4
Hypertension, n (%)§										
No	912 (75.7)	87 (73.7)	31 (67.4)	526 (80.1)	17 (73.9)	114 (74.5)	82 (75.2)	19 (63.3)	8 (40.0)	28 (57.1)
Yes	293 (24.3)	31 (26.3)	15 (32.6)	131 (19.9)	6 (26.1)	39 (25.5)	27 (24.8)	11 (36.7)	12 (60.0)	21 (42.9)
Type II Diabetes, n (%)//										
No	1,121 (93.0)	114 (96.6)	39 (84.8)	621 (94.5)	21 (91.3)	141 (92.2)	103 (94.5)	26 (86.7)	16 (80.0)	40 (81.6)
Yes	84 (7.0)	4 (3.4)	7 (15.2)	36 (5.5)	2 (8.7)	12 (7.8)	6 (5.5)	4 (13.3)	4 (20.0)	9 (18.4)
Smoking Status, n (%)										
Never	828 (68.8)	71 (60.2)	32 (71.1)	463 (70.5)	20 (87.0)	93 (60.8)	73 (67.6)	23 (76.7)	14 (70.0)	39 (79.6)
Current	81 (6.7)	7 (5.9)	4 (8.9)	47 (7.2)	0 (0.0)	12 (7.8)	8 (7.4)	0 (0.0)	1 (5.0)	2 (4.1)
Former	294 (24.4)	40 (33.9)	9 (20.0)	147 (22.4)	3 (13.0)	48 (31.4)	27 (25.0)	7 (23.3)	5 (25.0)	8 (16.3)
Past Oral Contraception Use, n (%)										
No	315 (27.2)	40 (34.8)	7 (16.3)	162 (25.5)	5 (22.7)	46 (30.7)	23 (22.6)	8 (28.6)	6 (31.6)	18 (40.9)

	Total	Not Done[†]	Inadequate	Normal	Other [‡]	Polyps	DPEM	Hyperplasia without atypia	Atypical Hyperplasia	Endometrial Cancer
Yes	843 (72.8)	75 (65.2)	36 (83.7)	473 (74.5)	17 (77.3)	104 (69.3)	79 (77.4)	20 (71.4)	13 (68.4)	26 (59.1)
Parity, n (%)[//]										
Nulliparous	199 (16.5)	29 (24.6)	7 (15.2)	89 (13.6)	6 (26.1)	33 (21.6)	16 (14.8)	5 (16.7)	4 (20.0)	10 (20.4)
Parous	1,005 (83.5)	89 (75.4)	39 (84.8)	556 (86.4)	17 (73.9)	120 (78.4)	92 (85.2)	25 (83.3)	16 (80.0)	39 (79.6)
Family History of EC, n (%)										
No	1,097 (91.0)	105 (89.0)	40 (87.0)	595 (90.6)	20 (87.0)	141 (92.2)	101 (92.7)	30 (100.0)	20 (100.0)	45 (91.8)
Yes	108 (9.0)	13 (11.0)	6 (13.0)	62 (9.4)	3 (13.0)	12 (7.8)	8 (7.3)	0 (0.0)	0 (0.0)	4 (8.2)

[*] Worst outcome corresponds to the worst pathology of either the endometrial biopsy or hysterectomy specimen at baseline

[†] Not clinically indicated

[‡] Other benign uterine conditions such as endometriosis, fibroids

[§] $p<0.0001$

[//] $p<0.05$

Abbreviations: DPEM, Disordered proliferative endometrium; SD, standard deviation; EC, endometrial cancer

Note: Values may not sum to 100% due to rounding

Table 2.

Characteristics of Endometrial Cancers Overall and by Menopausal Status

	Total	Postmenopausal	Premenopausal
Total	49 (100.0)	42 (85.7)	7 (14.3)
Diagnostic Specimen			
Biopsy only *	2 (4.1)	2 (4.8)	0 (0.0)
Hysterectomy only †	11 (22.4)	8 (19.0)	3 (42.9)
Biopsy and Hysterectomy	36 (73.5)	32 (76.2)	4 (57.1)
Pathology Grade			
FIGO Grade 1	27 (55.1)	22 (52.4)	5 (71.4)
FIGO Grade 2	14 (28.6)	12 (28.6)	2 (28.6)
FIGO Grade 3	6 (12.2)	6 (14.3)	0 (0.0)
Missing	2 (4.1)	2 (4.8)	0 (0.0)
Pathology Stage			
FIGO Stage IA	35 (71.4)	29 (69.1)	6 (85.7)
FIGO Stage IB	7 (14.3)	7 (16.7)	0 (0.0)
FIGO Stage IIIA	1 (2.0)	1 (2.4)	0 (0.0)
FIGO Stage IIIC1/2	3 (6.1)	2 (4.8)	1 (14.3)
FIGO Stage IVB	1 (2.0)	1 (2.4)	0 (0.0)
Missing	2 (4.1)	2 (4.8)	0 (0.0)
Histology			
Endometrioid	40 (81.6)	33 (78.6)	7 (100.0)
Clear Cell	2 (4.1)	2 (4.8)	0 (0.0)
Serous ‡	3 (6.1)	3 (7.1)	0 (0.0)
Mixed Endometrioid/Mucinous	1 (2.0)	1 (2.4)	0 (0.0)
Carcinosarcoma (MMMT)	1 (2.0)	1 (2.4)	0 (0.0)
Missing	2 (4.1)	2 (4.8)	0 (0.0)
Myometrial Invasion			
No	10 (20.4)	7 (17.5)	3 (42.9)
Yes	36 (73.5)	33 (82.5)	3 (42.9)
Missing	3 (4.1)	2 (4.8)	1 (14.3)
Tumor Size, Mean ± SD	3.2 ± 1.6	3.3 ± 1.6	3.1 ± 1.6

* Of the two cases diagnosed on biopsy only, one woman has not yet undergone surgery

† Of the cases diagnosed by hysterectomy only, 2 had a normal biopsy and 9 had atypical hyperplasia diagnosed on biopsy

‡ Includes one mixed clear cell and serous

Abbreviations: MMMT, malignant mixed Mullerian tumor; SD, standard deviation

Gynecol Oncol. Author manuscript; available in PMC 2022 November 03.

Table 3.

Associations of Endometrial Cancer Risk Factors with Histologic Outcomes in all Women (n=1,159)*

	Polyps (n=158)	p-value	DPEM (n=109)	p-value	Hyperplasia without atypia (n=30)	p-value	Atypical Hyperplasia (n=20)	p-value	Endometrial Cancer (n=49)	p-value
Age (per 1 year increase)	1.06 (1.0–1.1)	<0.0001	0.95 (0.9–1.0)	0.006	1.03 (1.0–1.1)	0.253	1.07 (1.0–1.1)	0.045	1.14 (1.1–1.2)	<0.0001
BMI (per 5kg/m^2 increase)	1.17 (1.0–1.3)	0.011	1.12 (1.0–1.3)	0.107	1.10 (0.9–1.4)	0.446	2.00 (1.5–2.6)	<0.0001	1.39 (1.1–1.7)	0.001
HRT Use										
Never (n=782)	Ref		Ref		Ref		Ref	Ref	Ref	
Ever (n=377)	0.81 (0.5–1.2)	0.320	0.75 (0.5–1.3)	0.276	1.45 (0.6–3.3)	0.369	1.00 (0.3–3.1)	0.987	0.42 (0.2–0.9)	0.022
Past Oral Contraception Use										
No (n=308)	Ref		Ref		Ref		Ref	Ref	Ref	
Yes (n=807)	0.94 (0.6–1.4)	0.773	1.30 (0.8–2.2)	0.312	1.01 (0.4–2.4)	0.980	0.88 (0.3–5.5)	0.819	0.82 (0.4–1.6)	0.573
Parity										
Nulliparous (n=192)	Ref		Ref		Ref		Ref	Ref	Ref	
Parous (n=966)	0.58 (0.4–0.9)	0.014	1.13 (0.6–2.0)	0.674	0.87 (0.3–2.4)	0.786	0.86 (0.3–2.9)	0.806	0.60 (0.3–1.3)	0.209
Type II Diabetes										
No (n=1,082)	Ref		Ref		Ref		Ref	Ref	Ref	
Yes (n=77)	1.14 (0.6–2.3)	0.713	0.88 (0.3–2.2)	0.787	2.09 (0.6–7.0)	0.235	1.63 (0.5–5.9)	0.457	2.11 (0.9–5.2)	0.107
Hypertension										
No (n=881)	Ref		Ref		Ref		Ref	Ref	Ref	
Yes (n=278)	0.79 (0.5–1.2)	0.303	1.18 (0.7–2.0)	0.529	1.55 (0.6–3.7)	0.328	1.59 (0.5–4.6)	0.394	0.94 (0.5–1.9)	0.870
Smoking Status										
Never (n=796)	Ref		Ref		Ref		Ref	Ref	Ref	
Ever (n=362)	1.27 (0.9–1.8)	0.196	1.12 (0.7–1.7)	0.613	0.63 (0.3–1.5)	0.301	0.57 (0.2–1.7)	0.311	0.43 (0.2–0.9)	0.030
Family History of EC										
No (n=1,057)	Ref		Ref		Ref		Ref	Ref	Ref	
Yes (n=102)	0.70 (0.4–1.3)	0.287	0.74 (0.3–1.6)	0.449	--	--	--	--	0.71 (0.2–2.2)	0.549

* The reference group includes normal or other benign histology or no indication for biopsy, women with inadequate biopsy results are excluded (n=46)

Note: Two dashes (--) indicate the odds ratio, confidence intervals, and corresponding p-value could not be estimated from the model.

Abbreviations: DPEM, Disordered proliferative endometrium; BMI, body mass index; HRT; hormone replacement therapy; EC, endometrial cancer

Table 4.

Associations of Endometrial Cancer Risk Factors with Histologic Outcomes in Women with Postmenopausal Bleeding, n=534 *

	Polyps (n=82)	p-value	DPEM (n=27)	p-value	Hyperplasia without atypia (n=15)	p-value	Atypical Hyperplasia (n=13)	p-value	Endometrial Cancer (n=40)	p-value
Age (per 1 year increase)	1.07 (1.0–1.1)	<0.0001	0.96(0.9–1.0)	0.293	1.06 (1.0–1.1)	0.093	1.07 (1.0–1.2)	0.149	1.14 (1.1–1.2)	<0.0001
BMI (per 5kg/m^2 increase)	1.22 (1.0–1.4)	0.020	1.19 (0.9–1.6)	0.183	1.48 (1.0–2.1)	0.030	2.20 (1.5–3.3)	<0.0001	1.21 (1.0–1.5)	0.110
HRT Use										
Never (n=278)	Ref		Ref		Ref		Ref		Ref	
Ever (n=256)	0.77 (0.5–1.3)	0.345	1.27 (0.5–3.0)	0.591	3.20 (0.9–11.4)	0.073	0.92 (0.2–4.2)	0.911	0.39(0.2–0.9)	0.022
Past Oral Contraception Use										
No (n=153)	Ref		Ref		Ref		Ref		Ref	
Yes (n=352)	1.42 (0.8–2.5)	0.234	2.16 (0.7–6.8)	0.188	2.27 (0.6–8.9)	0.239	0.90 (0.2–3.3)	0.872	1.22 (0.5–2.7)	0.625
Parity										
Nulliparous (n=91)	Ref		Ref		Ref		Ref		Ref	
Parous (n=443)	0.70 (0.4–1.3)	0.278	0.64 (0.2–1.7)	0.368	1.33 (0.3–6.6)	0.726	2.99 (0.3–27.0)	0.329	0.73 (0.3–1.8)	0.501
Type II Diabetes										
No (n=490)	Ref		Ref		Ref		Ref		Ref	
Yes (n=44)	0.51 (0.2–1.6)	0.250	1.47 (0.4–5.9)	0.589	2.05 (0.5–9.2)	0.352	2.83 (0.7–11.8)	0.153	2.13 (0.8–5.9)	0.150
Hypertension										
No (n=382)	Ref		Ref		Ref		Ref		Ref	
Yes (n=152)	0.85 (0.5–1.6)	0.616	1.93 (0.8–5.0)	0.176	2.30 (0.7–7.8)	0.181	1.23 (0.3–4.9)	0.764	1.17 (0.5–2.6)	0.691
Smoking Status										
Never (n=355)	Ref		Ref		Ref		Ref		Ref	
Ever (n=179)	1.53 (0.9–2.5)	0.102	0.64 (0.3–1.6)	0.353	0.46 (0.1–1.6)	0.226	0.49 (0.1–1.9)	0.302	0.44 (0.2–1.0)	0.059
Family History of EC										

	Polyps (n=82)	p-value	DPEM (n=27)	p-value	Hyperplasia without atypia (n=15)	p-value	Atypical Hyperplasia (n=13)	p-value	Endometrial Cancer (n=40)	p-value
No (n=479)	Ref		Ref		Ref		Ref		Ref	
Yes (n=55)	0.93 (0.4–2.1)	0.862	0.52 (0.1–2.4)	0.397	--	--	--	--	0.75 (0.2–2.5)	0.631

*The reference group includes normal or other benign histology or no indication for biopsy, women with inadequate biopsy results are excluded (n=33)

Note: Two dashes (--) indicate the odds ratio, confidence intervals, and corresponding p-value could not be estimated from the model.

Abbreviations: DPEM, Disordered proliferative endometrium; BMI, body mass index; HRT, hormone replacement therapy; EC, endometrial cancer