Risk prediction models for endometrial cancer: development and validation in an international consortium

Supplementary Materials

Table of Contents

Supplementary Methods

Data for model development: data collection and case definition

Risk factors considered for inclusion in the prediction model included those previously identified to be strongly associated with endometrial cancer risk: education level (high school or below; some college/associate's degree/vocation or technical school; college or above), smoking status (never smoker; former smoker; current smoker), body mass index (BMI, kg/m^2: <18.5; 18.5 to <25; 25 to <30; 30 to <35; ≥ 35), parity (0; 1; 2; 3; ≥ 4), age at first birth (years: <20; 20 to <25; 25 to <30; 30 to <35; ≥35; never given birth), age at menarche (years: ≤9; 10-11; 12-13; 14-15; ≥16), any hormone therapy (HT) use (yes; no), any estrogen-only (E-only) HT use (yes; no), duration of E-only HT use (years: 0; >0 to 5; >5 to 10; >10), any combination estrogen and progestin (E+P) HT use (yes; no), duration of E+P HT use (years: 0; >0 to 5; >5 to 10; >10), any oral conceptive (OC) use (yes; no), duration of OC use (years: 0; >0 to 5; >5 to 10; >10), history of diabetes (yes; no), and history of hypertension (yes; no).

Education was considered a proxy for socioeconomic status. We included BMI as a major risk factor for endometrial cancer, acknowledging that while many biologic mechanisms have been attributed to this relationship,[1,2] BMI measures may also act as a proxy for perceived weight discrimination, which can, in turn, cause increased experiences of stress and physiological dysregulation.[3–5] Availability of data for these risk factors varied by study site (Supplementary Table 2).

Data for model validation: study populations, data collection and case identification

For NHS and NHS II, women were included in the analysis once they reached menopause and were 45 years of age or older. Due to the lack of racial diversity, the analysis was restricted to white women. Participants were excluded from the study if they died, had a previous history of cancer (other than non-melanoma skin cancer) or had a previous hysterectomy prior to meeting the inclusion criteria. Participants were followed for 10 years, or until they were lost to follow-up. In sensitivity analyses, we censored participants upon a competing event (other cancers, hysterectomy, or death). For PLCO, similar inclusion and exclusion criteria were applied. However, start of follow-up began upon completion of the baseline questionnaire, and participants who did not allow themselves to be actively followed were excluded from the analysis. In PLCO, age at hysterectomy was reported in 5-year intervals—we assumed that hysterectomy occurred midway in the age interval reported.

Statistical analysis: model development and validation

To build a model for the log relative risks parameters for the predictors included in the model, we applied group least absolute shrinkage and selection operator (LASSO) penalized logistic regression to pooled data from E2C2 on endometrial cancer risk factors. LASSO penalized logistic regression was selected as the modelling approach for its ability to simultaneously regularize and select variables. Variables were parameterized as described above. We also included product terms (i.e., statistical interactions) for previously reported interactions between BMI and OC use, BMI and any HT use, BMI and E-only HT use, and BMI and E+P HT use.[6,7] For all interactions, BMI was categorized as <25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2 and <35 kg/m^2, and ≥35 kg/m^2. Since most studies included in the pooled analysis matched controls to cases based on age, we also included age at diagnosis for cases or age at interview or reference date for controls (in 5-year age groups) in the model. We additionally adjusted for study site. To address missing data, if one study did not collect data on a given risk factor, all participants of that study were assigned a missing indicator (Supplementary Table 2); if the study did collect data on a given risk factor, any participants of that study with missing data on that risk factor were dropped from the analysis

(Supplementary Figure 1A). Age, study site, and the missing indicator variables were forced into the models (i.e., a penalty factor of 0 was used) since these variables represented design features of the individual studies or of the analysis. We used leave-one-study-out cross-validation to select the tuning parameter λ which generated the most parsimonious model within one standard error of the minimum cross validation error. The model which included only the epidemiologic questionnaire data was referred to as the epidemiologic model. For the epidemiologic plus genetic model, we additionally included 18 previously identified genome-wide significant single nucleotide polymorphisms (SNPs) for endometrial cancer (Supplementary Table 7).[8] Since genetic data were available for only a subset of the participants included as part of the E2C2 consortium, we used estimates (i.e., the log of the allelic odds ratios) and allele frequencies reported in a previously published GWAS meta-analysis for our model.[8]

We used U.S. Surveillance Epidemiology and End Results (SEER) data to estimate the marginal age-specific incidence rates for endometrial cancer among white women. SEER rates from 1989 to 1993 were used for NHS and PLCO, while rates from 2003 to 2007 were used for NHS II (Supplementary Table 4). Since SEER incidence rates for endometrial cancer are calculated among all women in a given age group, incidence rates among women with an intact uterus are underestimated. As such, we divided the incidence rates from SEER by the age-specific prevalence for hysterectomy among white women, which were estimated using data from the Behavioral Risk Factor Surveillance System (BRFSS) survey for the same areas included in SEER.[9] We used the prevalence estimates from the 1988 BRFSS survey for NHS and PLCO, and averaged the prevalence estimates in the 2006 and 2008 BRFSS surveys for NHS II since BRFSS only asks about hysterectomy every other year. For competing risks, we obtained age-specific mortality rates in 1988 (for NHS and PLCO) and in 2004 (for NHS II) from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database, and age-specific incidence rates for cancers other than endometrial cancer from 1989 to 1993 (for NHS and PLCO) and from 2003 to 2007 (for NHS II) from SEER (Supplementary Table 4). We estimated age-specific incidence of hysterectomy using age-specific prevalence from BRFSS.[10] The age-specific incidences rates for mortality, cancers other than endometrial cancer and hysterectomy were summed to estimate the overall incidence rate of competing risks.

To estimate the underlying risk factor distribution in the population, we used data from the National Health and Nutrition Examination Survey (NHANES). We restricted the sample to white women, and estimated distributions in the 1999 to 2000 cycle for NHS and PLCO and in the 2007 to 2008 cycle for NHS II. To account for missing data in NHANES, we used multiple imputation by chained equations (MICE) to fit a series of conditional distributions to generate 10 fully imputed datasets. Weights were applied to account for the complex survey design.

Missing data in the validation cohorts was handled in the iCARE package by using a type of "hot deck" imputation approach.[11] The iCARE package estimates absolute risks by assuming a Cox proportional hazard model for the age-specific incidence rates, λ_0, and risk factors, Z, included into the model:

$$\Pr(T \in [t, t+\Delta t) | T \geq t, Z) = \lambda(t|Z) = \lambda_0(t)\exp(\beta_T Z)$$

where T represents the time to onset for endometrial cancer. The absolute risk of endometrial cancer for an individual aged a over the time interval $a+\tau$ is estimated according to:

$$\int_a^{a+\tau} \lambda_0(t)\exp(\beta^t Z)\exp\left(-\int_a^t [\lambda_0(u)\exp(\beta^T Z) + m(u)]\,du\right) dt$$

where competing risks are accounted for through the function $m(t)$. All statistical analyses were performed using R 4.0.2. Variable selection and regularization using group LASSO models were completed using the gglasso package 1.5, and model development and validation were completed using the iCARE package 1.16.0.

Statistical analysis: estimating absolute risks among the general U.S. population

To estimate absolute risks of endometrial cancer among a more current general U.S. population of white women, we developed a prediction model by combining the log relative risks from the LASSO penalized logistic regression model with (1) endometrial cancer incidence rates among white women, estimated using SEER data from 2013 to 2017 and hysterectomy prevalence rates from the 2016 and 2018 BRFSS surveys; (2) incidence rates for competing risks, estimated using CDC WONDER data from 2017 for mortality, SEER data from 2013 to 2017 for other cancers, and BRFSS data for hysterectomy; and (3) marginal risk factor distributions, estimating using NHANES data from the 2017-2018 cycle. We assessed 10-year and cumulative absolute risks by categories of risk percentiles among the 2017 to 2018 NHANES participants.

Supplementary References

1 Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol biomarkers Prev a Publ Am Assoc Cancer Res cosponsored by Am Soc Prev Oncol* 2002; **11**: 1531–43.

2 Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: Epidemiology, biomarkers, prevention and survivorship. Gynecol. Oncol. 2009; **114**: 121–7.

3 Vadiveloo M, Mattei J. Perceived Weight Discrimination and 10-Year Risk of Allostatic Load Among US Adults. *Ann Behav Med* 2017; **51**: 94–104.

4 Daly M, Sutin AR, Robinson E. Perceived Weight Discrimination Mediates the Prospective Association Between Obesity and Physiological Dysregulation: Evidence From a Population-Based Cohort. *Psychol Sci* 2019; **30**: 1030–9.

5 Jackson SE, Kirschbaum C, Steptoe A. Perceived weight discrimination and chronic biochemical stress: A population-based study using cortisol in scalp hair. *Obesity* 2016; **24**: 2515–21.

6 Pfeiffer RM, Park Y, Kreimer AR, *et al.* Risk Prediction for Breast, Endometrial, and Ovarian Cancer in White Women Aged 50 y or Older: Derivation and Validation from Population-Based Cohort Studies. *PLoS Med* 2013; **10**: e1001492.

7 Hüsing A, Dossus L, Ferrari P, *et al.* An epidemiological model for prediction of endometrial cancer risk in Europe. *Eur J Epidemiol* 2016; **31**: 51–60.

8 O'Mara TA, Glubb DM, Amant F, *et al.* Identification of nine new susceptibility loci for endometrial cancer. *Nat Commun* 2018; **9**. DOI:10.1038/s41467-018-05427-7.

9 CDC. Behavioral Risk Factor Surveillance System Survey Data. Atlanta, Georgia.

10 Leske MC, Ederer F, Podgor M. Estimating incidence from age-specific prevalence in glaucoma. *Am J Epidemiol* 1981; **113**: 606–13.

11 Pal Choudhury P, Maas P, Wilcox A, *et al.* iCARE: An R package to build, validate and apply absolute risk models. *PLoS One* 2020; **15**: e0228198.

Supplementary Table 1. Characteristics of the 19 studies and their participants included in the pooled analysis for model training

Study	Location	Recruitment period	Matching factors	Age (years), mean ± SD	Number of cases	Number of controls
Estrogen, Diet, Genetics, and Endometrial Cancer (EDGE)	New Jersey	2001-2005	Age (5-year group)	65.1 ± 8.7	345	343
Fred Hutchinson Cancer Research Study (FHCRC)	Washington	1994-2005	Age (5-year group)	59.5 ± 5.9	751	640
Women's Insights and Shared Experiences (WISE)	Philadelphia	1999-2002	Age (±5 years), race	64.6 ± 7.9	300	587
Hawaii Endometrial Cancer Case-Control Study (HAWAII)	Hawaii	1988-1993	Age (5-year group)	66.4 ± 6.9	29	22
Polish Case Control Study (POL)	Poland	2000-2003	Age (±5 years), site	61.4 ± 7.3	491	1201
Connecticut Endometrial Cancer Study (CONN)	Connecticut	2004-2009	Age (5-year group)	63.9 ± 8.1	504	506
US Endometrial Case-Control Study (USEC)	5 US clinics	1987-1990	Age (±5 years), race, telephone exchange	62.3 ± 6.8	168	150
Alberta Endometrial Cancer and Physical Activity Study (ALBERTA)	Canada	2002-2006	Age (±5 years)	62.6 ± 7.2	399	720
Bay Area Women's Health Study (BAWHS)	California	1996-1999	Age (5-year group), ethnicity	65.0 ± 8.3	327	288
University of Southern California Los Angeles Study (USC)	Los Angeles	1987-1993	Age (±5 years)	63.1 ± 5.4	833	791
Australian National Endometrial Cancer Study (ANECS)	Australia	2005-2007	Age (5-year group), state	64.4 ± 7.3	859	410
Patient Epidemiological Data System (PEDS)	New York	1982-1998	Age (±5 years)	66.0 ± 9.6	47	39
Switzerland Vaud (VAUD)	Switzerland	1988-1992	Study center	65.1 ± 6.2	206	400
Western New York Diet Study (WNYDS)	New York	1986-1991	Age, county of residence	64.7 ± 7.5	184	350
Milano Endometrial Cancer Case Control Study 1 (ML1)	Italy	1979-1988	Age (5-year group)	61.6 ± 7.1	415	1399
Milano Endometrial Cancer Case Control Study 2 (ML2)	Italy	1988-1991	Age, study center	62.4 ± 6.6	174	181
Turin Case Control Study (TURIN)	Italy	1988-1999	None	62.5 ± 6.4	213	227
Italian Mulitcenter Study (IMS)	Italy	1992-2006	Age (5-year group), study center	63.3 ± 7.3	367	722
Molecular signatures for early detection of endometrial and ovarian cancers (Screenwide)	Spain	2017-2019	Age (5-year group)	62.8 ± 8.8	53	86

Supplementary Table 2. Availability of data on endometrial cancer predictors by study site

	EDGE	FHCRC	WISE	HAWAII	POL	CONN	USEC	ALBERTA	BAWHS	USC	ANECS	PEDS	VAUD	WNYDS	ML1	ML2	TURIN	IMS	Screenwide	**Total**
Demographic factors																				
Education	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	19
Lifestyle factors																				
Smoking status	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18
Pack-years of smoking	✓			✓	✓		✓			✓	✓	✓		✓				✓		9
Alcohol (drinks/week)	✓			✓	✓		✓	✓	✓			✓		✓			✓			9
Body mass index (kg/m^2)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	19
Reproductive and hormonal factors																				
Parity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	19
Age at first birth	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓		✓			✓		✓	13
Age at last birth		✓		✓		✓											✓			4
Age at menarche	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	19
Any HT use																				
All	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	19
E+P HT	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓		✓					✓	12
E-only HT	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓					✓	13
Duration of HT use (years)																				
E+P HT	✓		✓		✓		✓		✓	✓	✓									7
E-only HT	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓								10
Any OC use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	19
Duration of OC use (years)	✓	✓	✓	✓	✓		✓		✓	✓	✓							✓	✓	11
Clinical factors																				
History of diabetes	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	17
History of endometriosis	✓			✓	✓		✓	✓		✓	✓								✓	8
History of hypertension	✓	✓		✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	16
Family history of endometrial cancer	✓						✓		✓	✓	✓	✓							✓	7
Total	19	15	13	18	18	12	19	11	13	17	18	16	9	14	9	9	12	11	15	

Supplementary Table 3. SNPs included in epidemiologic plus genetic risk prediction models for endometrial cancer [a]

Chr	Position	rsID	Reference allele	Alternate allele	Alternate allele frequency	Allelic OR (95% CI)
1	38073356	rs113998067	T	C	0.03963	1.23 (1.14, 1.32)
2	60897579	rs148261157	G	A	0.0352	1.26 (1.16, 1.36)
6	21649085	rs1740828	A	G	0.50414	1.15 (1.11, 1.19)
6	126008372	rs2747716	G	A	0.56507	1.10 (1.07, 1.14)
8	129599278	rs4733613	G	C	0.13481	1.18 (1.13, 1.24)
8	129623902	rs139584729	G	C	0.98667	1.40 (1.25, 1.58)
9	22207037	rs1679014	C	T	0.06005	1.18 (1.12, 1.25)
11	32489664	rs10835920	C	T	0.35016	1.09 (1.06, 1.13)
12	26426338	rs9668337	G	A	0.73881	1.11 (1.08, 1.15)
12	111884608	rs3184504	T	C	0.526228	1.10 (1.07, 1.14)
12	115214548	rs10850382	C	T	0.30124	1.10 (1.07, 1.14)
13	73812141	rs7981863	T	C	0.75081	1.16 (1.12, 1.20)
14	105243220	rs2498796	G	A	0.31578	1.07 (1.03, 1.11)
15	40322124	rs937213	T	C	0.42647	1.09 (1.06, 1.13)
15	51553909	rs17601876	A	G	0.50159	1.12 (1.09, 1.16)
17	29646032	rs1129506	A	G	0.3629	1.10 (1.06, 1.13)
17	36097775	rs11263761	G	A	0.5328	1.15 (1.12, 1.19)
17	46294236	rs882380	C	A	0.59978	1.10 (1.06, 1.13)

[a] Obtained from O'Mara et al.[8]

Supplementary Table 4. Estimated marginal risks for endometrial cancer and competing causes

Age group	Hysterectomy prevalence	Endometrial cancer risk (per 100,000)		Competing causes	
		Original	Corrected for hysterectomy	Mortality (per 100,000)	Other cancers (per 100,000)
NHS	**BRFSS 1988**	**SEER 1989-1993**		**CDC WONDER 1988**	**SEER 1989-1993**
45-49	0.304	24.2	34.8	320.4	422.1
50-54	0.350	43.9	67.6	320.4	590.9
55-59	0.366	63.5	100.2	858.7	809.1
60-64	0.375	88.4	141.4	858.7	1089.0
65-69	0.312	106.0	154.1	1995.8	1391.7
70-74	0.370	119.2	189.1	1995.8	1674.0
75-79	0.387	113.3	184.7	5040.4	1899.3
80-84	0.294	88.9	126.0	5040.4	2001.9
NHS II	**BRFSS 2006-2008**	**SEER 2003-2007**		**CDC WONDER 2004**	**SEER 2003-2007**
45-49	0.174	23.9	28.9	239.0	425.1
50-54	0.226	47.3	61.1	337.8	583.3
55-59	0.298	73.9	105.2	525.0	785.6
60-64	0.351	88.2	136.0	851.1	1069.1
65-69	0.416	93.8	160.6	1327.6	1392.6
70-74	0.448	88.0	159.3	2141.8	1649.3
75-79	0.463	83.1	154.7	3447.3	1910.8
80-84	0.441	79.2	141.6	5845.5	2026.9
PLCO	**BRFSS 1996-1998**	**SEER 1996-2000**		**CDC WONDER 1997**	**SEER 1996-2000**
45-49	0.226	24.3	31.4	281.6	422.1
50-54	0.294	51.3	72.7	281.6	590.9
55-59	0.375	73.2	117.1	758.7	809.1
60-64	0.415	91.9	157.1	758.7	1089.0
65-69	0.424	100.5	174.6	1880.4	1391.7
70-74	0.426	108.1	188.3	1880.4	1674.0
75-79	0.418	105.0	180.5	4705.8	1899.3
80-84	0.388	100.6	164.3	4705.8	2001.9

Supplementary Table 5. Distribution of endometrial cancer risk factors in reference data sets and estimated relative risks from pooled E2C2 case-control studies

	Weighted summary statistics		RRs from LASSO model [a]
	NHANES 1999-2000	NHANES 2007-2008	E2C2
Demographic factors			
Education, %			
High school or below	52.2	43.2	(ref)
Some college or equivalent	27.3	29.5	0.97
College or above	20.6	27.3	0.96
Lifestyle factors			
Smoking status, %			
Never smoker	50.7	54.1	(ref)
Former smoker	29.9	26.9	0.80
Current smoker	19.4	19	0.64
Body mass index (kg/m^2), %			
<18.5	1.9	2	0.74
18.5 to <25	33.5	32.2	(ref)
25 to <30	28.1	30.4	1.41
30 to <35	19.7	17.5	2.49
≥35	16.7	17.9	5.57
Reproductive and hormonal factors			
Parity, %			
0	9.4	9.8	(ref)
1	7.8	13.3	1.10
2	21.4	26.7	0.91
3	23.6	22.8	0.77
≥4	37.7	27.4	0.60
Age at first birth, %			
<20	31.8	25.8	(ref)
20 to <25	39.9	40.1	0.96
25 to <30	13.9	16.8	0.85
30 to <35	4.4	6	0.83
≥35	0.5	1.4	0.84
Never given birth	9.4	9.8	1.28
Age at menarche, %			
≤9	1.1	2.6	(ref)
10-11	17.1	17.6	1.04
12-13	60.4	49.2	1.04
14-15	15.7	23.4	0.92
≥16	5.6	7.2	0.89
Any HT use, %	53.2	42.2	1.61
Any E-only HT use, %	43.9	29.1	1.06
Duration of E-only HT use (years), %			
0	56.2	70.8	(ref)
>0 to 5	18.8	15	0.84
>5 to 10	10.1	4.4	1.42
>10	14.9	9.9	2.55
Any E+P HT use, %	13.8	14.6	0.82
Duration of E+P HT use (years), %			
0	86.2	85.4	(ref)
>0 to 5	11.9	9.8	1.00

>5 to 10	1.6	3.3	1.00
>10	0.4	1.5	1.00
Any OC use, %	64.7	77.7	0.79
Duration of OC use (years), %			
0	35.3	22.2	(ref)
>0 to 5	42.2	46.3	1.05
>5 to 10	15.9	16.8	0.94
>10	6.5	14.6	0.69
Clinical factors			
History of diabetes, n (%)	7.3	9.8	1.39
History of hypertension, n (%)	35.7	41.2	1.22
Product terms between OC use and BMI			
(Any OC use) × (BMI of 25 to <30 kg/m^2)			1.00
(Any OC use) × (BMI of 30 to <35 kg/m^2)			1.00
(Any OC use) × (BMI ≥35 kg/m^2)			1.00
(Duration of OC use >0 to 5 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of OC use >0 to 5 years) × (BMI of 30 to <35 kg/m^2)			1.00
(Duration of OC use >0 to 5 years) × (BMI ≥35 kg/m^2)			1.00
(Duration of OC use >5 to 10 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of OC use >5 to 10 years) × (BMI of 30 to <35 kg/m^2)			1.00
(Duration of OC use >5 to 10 years) × (BMI ≥35 kg/m^2)			1.00
(Duration of OC use >10 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of OC use >10 years) × (BMI of 30 to <35 kg/m^2)			1.00
(Duration of OC use >10 years) × (BMI ≥35 kg/m^2)			1.00
Product terms between any HT use and BMI			
(Any HT use) × (BMI of 25 to <30 kg/m^2)			0.87
(Any HT use) × (BMI of 30 to <35 kg/m^2)			0.64
(Any HT use) × (BMI ≥35 kg/m^2)			0.60
Product terms between E-only HT use and BMI			
(Any E-only HT use) × (BMI of 25 to <30 kg/m^2)			1.00
(Any E-only HT use) × (BMI of 30 to <35 kg/m^2)			1.00
(Any E-only HT use) × (BMI ≥35 kg/m^2)			1.00
(Duration of E-only HT use >0 to 5 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of E-only HT use >0 to 5 years) × (BMI ≥30 kg/m^2)			1.00
(Duration of E-only HT use >5 to 10 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of E-only HT use >5 to 10 years) × (BMI ≥30 kg/m^2)			1.00
(Duration of E-only HT use >10 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of E-only HT use >10 years) × (BMI ≥30 kg/m^2)			1.00
Product terms between E+P HT use and BMI			
(Any E+P HT use) × (BMI of 25 to <30 kg/m^2)			1.00
(Any E+P HT use) × (BMI of 30 to <35 kg/m^2)			1.00
(Any E+P HT use) × (BMI ≥35 kg/m^2)			1.00
(Duration of E+P HT use >0 to 5 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of E+P HT use >0 to 5 years) × (BMI ≥30 kg/m^2)			1.00
(Duration of E+P HT use >5 to 10 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of E+P HT use >5 to 10 years) × (BMI ≥30 kg/m^2)			1.00
(Duration of E+P HT use >10 years) × (BMI of 25 to <30 kg/m^2)			1.00
(Duration of E+P HT use >10 years) × (BMI ≥30 kg/m^2)			1.00

[a] RR of 1.00 indicates the variable was selected out of the final model

Supplementary Table 6. Characteristics of study participants from the E2C2 case-control studies

	Met eligibility criteria and included in the final analysis				Met eligibility criteria but were excluded from the final analysis due to missing data			
	Cases (n = 6,665)		Controls (n = 9,062)		Cases (n = 1,328)		Controls (n = 1,631)	
	n (% missing)	Summary statistic	n (% missing)	Summary statistic	n (% missing)	Summary statistic	n (% missing)	Summary statistic
Demographic factors								
Age (years), mean ± SD	6,665 (0.0)	63.1 ± 7.2	9,062 (0.0)	62.8 ± 7.4	1,328 (0.0)	63.7 ± 8.0	1,631 (0.0)	63.4 ± 7.9
Hispanic, n (%)	3,679 (44.8)	76 (2.1)	5,693 (37.2)	86 (1.5)	530 (60.1)	13 (2.5)	917 (43.8)	26 (2.8)
Education, n (%)	6,665 (0.0)		9,062 (0.0)		1,251 (5.8)		1,604 (1.7)	
High school or below		3,697 (55.5)		5,506 (60.8)		692 (55.3)		768 (47.9)
Some college or equivalent		1,700 (25.5)		1,989 (21.9)		294 (23.5)		392 (24.4)
College or above		1,268 (19.0)		1,567 (17.3)		265 (21.2)		444 (27.7)
Lifestyle factors								
Smoking status, n (%)	6,338 (4.9)		8,774 (3.2)		1,229 (7.5)		1,583 (2.9)	
Never smoker		3,932 (62.0)		4,949 (56.4)		749 (60.9)		799 (50.5)
Former smoker		1,704 (26.9)		2,187 (24.9)		381 (31.0)		534 (33.7)
Current smoker		702 (11.1)		1,638 (18.7)		99 (8.1)		250 (15.8)
Pack-years of smoking among ever smokers, median (IQR)	1,216 (49.5)	17.5 (5.5, 36.0)	1,757 (54.1)	16.5 (5.2, 35.0)	270 (43.8)	22.0 (8.0, 37.8)	323 (58.8)	20.7 (10.0, 35.0)
Alcohol (drinks/week), median (IQR)	1,564 (76.5)	0.9 (0.1, 3.0)	2,250 (75.2)	1.0 (0.2, 3.4)	687 (48.3)	0.5 (0.0, 3.0)	634 (61.1)	1.0 (0.0, 4.0)
Body mass index (kg/m^2), mean ± SD	6,665 (0.0)	29.5 ± 7.5	9,062 (0.0)	25.9 ± 5.0	1,205 (9.3)	28.6 ± 7.4	1,546 (5.2)	25.3 ± 5.2
Reproductive and hormonal factors								
Parity, median (IQR)	6,665 (0.0)	2.0 (1.0, 3.0)	9,062 (0.0)	2.0 (1.0, 3.0)	1,203 (9.4)	2.0 (1.0, 3.0)	1,594 (2.3)	2.0 (1.0, 3.0)
Age at first birth, mean ± SD	4,777 (28.3)	19.5 ± 10.1	5,352 (40.9)	21.5 ± 8.7	1,150 (13.4)	19.6 ± 10.3	1,527 (6.4)	21.0 ± 9.6
Age at last birth, mean ± SD	1,214 (81.8)	28.4 ± 5.0	1,225 (86.5)	29.7 ± 5.1	100 (92.5)	28.8 ± 4.6	209 (87.2)	30.3 ± 5.5
Age at menarche, mean ± SD	6,665 (0.0)	12.7 ± 1.6	9,062 (0.0)	13.0 ± 1.7	1,219 (8.2)	12.8 ± 1.6	1,551 (4.9)	12.9 ± 1.6
Any HT use, n (%)								
All	6,665 (0.0)	2,316 (34.7)	9,062 (0.0)	2,601 (28.7)	1,252 (5.7)	627 (50.1)	1,604 (1.7)	919 (57.3)
E+P HT	4,387 (34.2)	872 (19.9)	4,907 (45.9)	988 (20.1)	790 (40.5)	161 (20.4)	1,154 (29.2)	468 (40.6)
E-only HT	4,891 (26.6)	965 (19.7)	5,413 (40.3)	862 (15.9)	804 (39.5)	255 (31.7)	929 (43.0)	249 (26.8)
Duration of HT use among ever users (years), median (IQR)								
E+P HT	622 (28.7)	5.0 (2.0, 10.0)	652 (34.0)	4.7 (2.0, 9.0)	111 (31.1)	5.0 (2.0, 9.0)	335 (28.4)	5.0 (2.0, 9.0)
E-only HT	864 (10.5)	6.6 (2.0, 12.9)	706 (18.1)	2.0 (0.9, 6.0)	152 (40.4)	4.7 (1.0, 11.2)	169 (32.1)	1.9 (0.6, 5.0)
Any OC use, n (%)	6,665 (0.0)	2,393 (35.9)	9,062 (0.0)	2,796 (30.9)	1,250 (5.9)	405 (32.4)	1,592 (2.4)	739 (46.4)
Duration of OC use among ever users (years), median (IQR)	1,728 (27.8)	3.0 (1.0, 7.0)	1,784 (36.2)	4.0 (1.0, 9.0)	308 (24.0)	3.4 (1.0, 7.0)	628 (15.0)	4.0 (1.1, 9.0)

Clinical factors								
History of diabetes, n (%)	6,038 (9.4)	1,062 (17.6)	8,187 (9.7)	784 (9.6)	537 (59.6)	90 (16.8)	529 (67.6)	49 (9.3)
History of endometriosis, n (%)	3,124 (53.1)	654 (20.9)	3,699 (59.2)	100 (2.7)	437 (67.1)	22 (5.0)	447 (72.6)	8 (1.8)
History of hypertension, n (%)	5,205 (21.9)	2,352 (45.2)	7,396 (18.4)	2,459 (33.2)	509 (61.7)	213 (41.8)	485 (70.3)	180 (37.1)
Family history of endometrial cancer, n (%)	2,632 (60.5)	117 (4.4)	2,107 (76.7)	45 (2.1)	874 (34.2)	16 (1.8)	720 (55.9)	4 (0.6)

Supplementary Table 7. Characteristics of participants in validation cohorts at start of follow-up

	NHS		NHS II	PLCO	
	Full cohort	**With genetic data available**	**Full cohort**	**Full cohort**	**With genetic data available**
	(n = 68,150)	**(n = 11,365)**	**(n = 56,076)**	**(n = 39,996)**	**(n = 30,102)**
Calendar year, median (range)	1986 (1976, 2012)	1984 (1976, 2004)	2007 (1993, 2013)	1997 (1993, 2001)	1997 (1993, 2001)
Age (years), median (range)	52 (45, 75)	52 (45, 64)	52 (45, 66)	62 (52, 75)	61 (53, 75)
Demographic factors					
Education, n (%)					
High school or below	0 (0.0)	0 (0.0)	0 (0.0)	12,846 (32.2)	9,079 (30.2)
Some college or equivalent	0 (0.0)	0 (0.0)	0 (0.0)	13,892 (34.8)	10,459 (34.8)
College or above	68,150 (100.0)	11,365 (100.0)	56,076 (100.0)	13,189 (33.0)	10,520 (35.0)
Lifestyle factors					
Smoking status, n (%)					
Never smoker	28,262 (41.6)	4,998 (44.1)	34,854 (62.2)	21,816 (54.5)	16,874 (56.1)
Former smoker	21,744 (32.0)	3,926 (34.6)	16,168 (28.9)	14,314 (35.8)	10,772 (35.8)
Current smoker	18,005 (26.5)	2,411 (21.3)	4,990 (8.9)	3,863 (9.7)	2,456 (8.2)
Body mass index (kg/m^2), n (%)					
<18.5	871 (1.4)	113 (1.0)	617 (1.2)	453 (1.1)	299 (1.0)
18.5 to <25	34,223 (54.5)	6,144 (56.6)	23,112 (43.1)	16,654 (42.1)	12,594 (42.3)
25 to <30	17,790 (28.3)	2,951 (27.2)	15,572 (29.1)	13,473 (34.1)	10,191 (34.2)
30 to <35	6,651 (10.6)	1,112 (10.2)	7,839 (14.6)	5,738 (14.5)	4,340 (14.6)
≥35	3,311 (5.3)	538 (5.0)	6,462 (12.1)	3,209 (8.1)	2,368 (7.9)
Reproductive and hormonal factors					
Parity, n (%)					
0	3,924 (5.9)	648 (5.8)	10,408 (18.6)	4,165 (10.4)	3,020 (10.0)
1	4,854 (7.3)	728 (6.5)	7,995 (14.3)	2,920 (7.3)	2,126 (7.1)
2	18,239 (27.3)	2,917 (26.0)	21,663 (38.6)	9,446 (23.7)	7,238 (24.1)
3	18,494 (27.7)	3,133 (27.9)	11,639 (20.8)	9,764 (24.4)	7,466 (24.8)
≥4	21,282 (31.9)	3,814 (33.9)	4,371 (7.8)	13,642 (34.2)	10,215 (34.0)
Age at first birth, n (%)					
<20	335 (0.5)	53 (0.5)	2,187 (4.0)	5,083 (12.8)	3,735 (12.5)
20 to <25	30,327 (45.4)	5,228 (46.5)	12,439 (22.5)	18,473 (46.4)	14,021 (46.8)
25 to <30	24,983 (37.4)	4,135 (36.8)	18,489 (33.4)	8,845 (22.2)	6,792 (22.7)
30 to <35	5,629 (8.4)	926 (8.2)	8,344 (15.1)	2,378 (6.0)	1,781 (5.9)
≥35	1,588 (2.4)	248 (2.2)	3,419 (6.2)	826 (2.1)	609 (2.0)
Never given birth	3,924 (5.9)	648 (5.8)	10,408 (18.8)	4,165 (10.5)	3,020 (10.1)

Age at menarche, n (%)					
≤9	591 (0.9)	91 (0.8)	856 (1.5)	513 (1.3)	383 (1.3)
10-11	13,927 (20.6)	2,342 (20.8)	12,240 (21.8)	7,010 (17.6)	5,250 (17.5)
12-13	39,276 (58.1)	6,576 (58.3)	32,803 (58.5)	21,852 (54.7)	16,531 (55.0)
14-15	11,456 (16.9)	1,899 (16.8)	8,248 (14.7)	8,808 (22.1)	6,611 (22.0)
≥16	2,398 (3.5)	378 (3.3)	1,929 (3.4)	1,738 (4.4)	1,270 (4.2)
Any HT use, n (%)	21,559 (33.9)	3,728 (35.2)	16,260 (31.6)	17,432 (65.5)	14,993 (66.8)
Any E-only HT use, n (%)	3,528 (5.6)	696 (6.6)	1,395 (2.6)	4,026 (17.3)	3,446 (17.6)
Duration of E-only HT use, n (%)					
Never user	59,611 (94.4)	9,870 (93.4)	51,670 (97.4)	19,180 (83.7)	16,120 (83.5)
>0 to 5 years	3,493 (5.5)	686 (6.5)	1,389 (2.6)	1,679 (7.3)	1,451 (7.5)
>5 to 10 years	27 (0.0)	9 (0.1)	5 (0.0)	1,150 (5.0)	986 (5.1)
>10 years	8 (0.0)	1 (0.0)	1 (0.0)	897 (3.9)	756 (3.9)
Any E+P HT use, n (%)	7,583 (11.8)	1,472 (13.6)	5,809 (11.1)	7,446 (32.1)	6,511 (33.3)
Duration of E+P HT use, n (%)					
Never user	56,794 (88.2)	9,368 (86.4)	46,736 (88.9)	15,767 (70.3)	13,051 (69.2)
>0 to 5 years	7,523 (11.7)	1,460 (13.5)	5,628 (10.7)	2,959 (13.2)	2,589 (13.7)
>5 to 10 years	60 (0.1)	12 (0.1)	160 (0.3)	2,190 (9.8)	1,918 (10.2)
>10 years	0 (0.0)	0 (0.0)	21 (0.0)	1,505 (6.7)	1,303 (6.9)
Any OC use, n (%)	31,692 (46.5)	5,394 (47.5)	48,211 (86.1)	21,596 (54.0)	16,861 (56.0)
Duration of OC use, n (%)					
Never user	37,626 (55.5)	6,160 (54.4)	7,800 (15.6)	18,368 (46.0)	13,225 (44.0)
>0 to 5 years	19,756 (29.1)	3,291 (29.1)	23,884 (47.9)	12,665 (31.7)	9,859 (32.8)
>5 to 10 years	7,144 (10.5)	1,264 (11.2)	10,935 (21.9)	3,664 (9.2)	2,907 (9.7)
>10 years	3,264 (4.8)	611 (5.4)	7,257 (14.6)	5,232 (13.1)	4,069 (13.5)
Clinical factors					
History of diabetes, n (%)	2,322 (3.4)	417 (3.7)	1,940 (3.5)	1,954 (4.9)	1,235 (4.1)
History of hypertension, n (%)	13,733 (20.2)	2,318 (20.4)	12,017 (21.4)	11,600 (29.2)	8,333 (27.8)

Supplementary Table 8. Age-specific AUCs of the epidemiologic and epidemiologic plus genetic (E+G) risk prediction models for endometrial cancer

Validation cohort	Prediction model	Baseline age	Number of participants	Number of events	Age-specific AUC (95% CI)
NHS Full cohort	Epidemiologic	All	68150	700	0.647 (0.626, 0.667)
		45 to <55	57251	539	0.644 (0.620, 0.667)
		55 to <65	10803	161	0.641 (0.597, 0.684)
		65 to <75	96	0	N/A
NHS II Full cohort	Epidemiologic	All	56076	304	0.693 (0.664, 0.723)
		45 to <55	46690	232	0.710 (0.677, 0.743)
		55 to <65	9382	72	0.632 (0.566, 0.699)
		65 to <75	4	0	N/A
PLCO Full cohort	Epidemiologic	All	39996	511	0.640 (0.615, 0.665)
		45 to <55	11	0	N/A
		55 to <65	26332	337	0.648 (0.618, 0.679)
		65 to <75	13625	174	0.625 (0.579, 0.670)
PLCO Genetic cohort	E+G	All	30102	401	0.665 (0.636, 0.693)
		45 to <55	7	0	N/A
		55 to <65	20633	272	0.665 (0.630, 0.700)
		65 to <75	9446	129	0.661 (0.613, 0.709)

Supplementary Table 9. Relative and absolute 10-year risk calibration of the epidemiologic risk prediction models for endometrial cancer in the NHS and NHS II

Study / Decile	N	Number of events	Relative 10-year risk		Absolute 10-year risk (%)		
			Observed (95% CI)	Expected	Observed (95% CI)	Expected	E/O ratio (95% CI)
NHS							
1	6,818	27	0.39 (0.27, 0.56)	0.32	0.40 (0.25, 0.55)	0.18	0.46 (0.31, 0.67)
2	6,816	33	0.47 (0.34, 0.66)	0.44	0.48 (0.32, 0.65)	0.25	0.51 (0.36, 0.72)
3	6,972	46	0.64 (0.49, 0.85)	0.54	0.66 (0.47, 0.85)	0.3	0.46 (0.34, 0.61)
4	6,654	34	0.50 (0.36, 0.69)	0.63	0.51 (0.34, 0.68)	0.35	0.69 (0.49, 0.96)
5	6,824	79	1.13 (0.92, 1.39)	0.72	1.16 (0.90, 1.41)	0.41	0.35 (0.28, 0.44)
6	6,824	63	0.90 (0.71, 1.14)	0.83	0.92 (0.70, 1.15)	0.47	0.50 (0.39, 0.64)
7	6,797	66	0.95 (0.75, 1.19)	0.97	0.97 (0.74, 1.20)	0.55	0.56 (0.44, 0.72)
8	6,815	83	1.19 (0.97, 1.45)	1.15	1.22 (0.96, 1.48)	0.65	0.53 (0.43, 0.66)
9	6,818	102	1.46 (1.22, 1.74)	1.48	1.50 (1.21, 1.78)	0.83	0.56 (0.46, 0.67)
10	6,812	167	2.39 (2.09, 2.72)	2.92	2.45 (2.08, 2.82)	1.65	0.67 (0.58, 0.78)
Overall	68,150	700					0.55 (0.51, 0.59)
NHS II							
1	5,609	8	0.26 (0.13, 0.52)	0.29	0.14 (0.04, 0.24)	0.17	1.20 (0.60, 2.40)
2	5,659	11	0.36 (0.20, 0.64)	0.39	0.19 (0.08, 0.31)	0.23	1.19 (0.66, 2.15)
3	5,557	14	0.46 (0.28, 0.77)	0.47	0.25 (0.12, 0.38)	0.28	1.11 (0.66, 1.88)
4	5,609	16	0.53 (0.33, 0.85)	0.57	0.29 (0.15, 0.42)	0.33	1.17 (0.72, 1.91)
5	5,609	33	1.09 (0.79, 1.50)	0.64	0.59 (0.39, 0.79)	0.38	0.64 (0.46, 0.90)
6	5,603	21	0.69 (0.46, 1.04)	0.73	0.37 (0.21, 0.53)	0.43	1.16 (0.75, 1.77)
7	5,607	23	0.76 (0.51, 1.12)	0.89	0.41 (0.24, 0.58)	0.53	1.29 (0.86, 1.94)
8	5,608	42	1.38 (1.04, 1.83)	1.11	0.75 (0.52, 0.97)	0.66	0.88 (0.65, 1.19)
9	5,607	45	1.48 (1.13, 1.94)	1.55	0.80 (0.57, 1.04)	0.92	1.14 (0.86, 1.53)
10	5,608	91	2.99 (2.52, 3.55)	3.35	1.62 (1.29, 1.95)	1.98	1.22 (1.00, 1.50)
Overall	56,076	304					1.09 (0.98, 1.22)

Supplementary Table 10. Relative and absolute 10-year risk calibration of the epidemiologic and epidemiologic plus genetic risk prediction models for endometrial cancer in the PLCO cohort

Study / Decile	N	Number of events	Relative 10-year risk		Absolute 10-year risk (%)		
			Observed (95% CI)	Expected	Observed (95% CI)	Expected	E/O ratio (95% CI)
Epidemiologic model							
1	4,002	23	0.45 (0.30, 0.67)	0.32	0.57 (0.34, 0.81)	0.42	0.74 (0.49, 1.11)
2	3,999	32	0.63 (0.45, 0.87)	0.44	0.80 (0.52, 1.08)	0.58	0.72 (0.51, 1.02)
3	3,998	36	0.70 (0.51, 0.96)	0.54	0.90 (0.61, 1.19)	0.71	0.79 (0.57, 1.10)
4	4,001	30	0.59 (0.41, 0.83)	0.63	0.75 (0.48, 1.02)	0.84	1.12 (0.78, 1.60)
5	4,014	44	0.86 (0.65, 1.13)	0.74	1.10 (0.77, 1.42)	0.98	0.90 (0.67, 1.21)
6	3,984	48	0.94 (0.72, 1.23)	0.88	1.20 (0.87, 1.54)	1.17	0.97 (0.73, 1.28)
7	3,999	35	0.68 (0.50, 0.94)	1.03	0.88 (0.59, 1.16)	1.36	1.55 (1.12, 2.16)
8	4,101	53	1.01 (0.78, 1.30)	1.2	1.29 (0.95, 1.64)	1.59	1.23 (0.94, 1.61)
9	3,898	80	1.60 (1.32, 1.96)	1.57	2.05 (1.61, 2.50)	2.09	1.02 (0.82, 1.26)
10	4,000	130	2.54 (2.19, 2.94)	2.65	3.25 (2.70, 3.80)	3.52	1.08 (0.92, 1.28)
Overall	39,996	511					1.04 (0.95, 1.13)
Epidemiologic plus genetic model							
1	3,023	12	0.30 (0.17, 0.52)	0.27	0.40 (0.17, 0.62)	0.33	0.84 (0.48, 1.48)
2	3,001	29	0.73 (0.51, 1.03)	0.4	0.97 (0.62, 1.32)	0.49	0.51 (0.36, 0.73)
3	3,021	18	0.45 (0.29, 0.70)	0.5	0.60 (0.32, 0.87)	0.62	1.04 (0.66, 1.65)
4	2,996	38	0.95 (0.70, 1.29)	0.6	1.27 (0.87, 1.67)	0.75	0.59 (0.43, 0.81)
5	3,010	25	0.62 (0.43, 0.91)	0.71	0.83 (0.51, 1.15)	0.89	1.07 (0.72, 1.58)
6	3,010	22	0.55 (0.37, 0.82)	0.85	0.73 (0.43, 1.04)	1.06	1.45 (0.96, 2.21)
7	3,016	32	0.80 (0.57, 1.11)	1.01	1.06 (0.70, 1.43)	1.26	1.19 (0.84, 1.68)
8	3,004	50	1.25 (0.97, 1.61)	1.24	1.66 (1.21, 2.12)	1.55	0.93 (0.71, 1.22)
9	3,010	61	1.52 (1.21, 1.91)	1.56	2.03 (1.52, 2.53)	1.94	0.96 (0.75, 1.23)
10	3,011	114	2.84 (2.44, 3.31)	2.87	3.79 (3.10, 4.47)	3.57	0.94 (0.79, 1.13)
Overall	30,102	401					0.94 (0.85, 1.03)

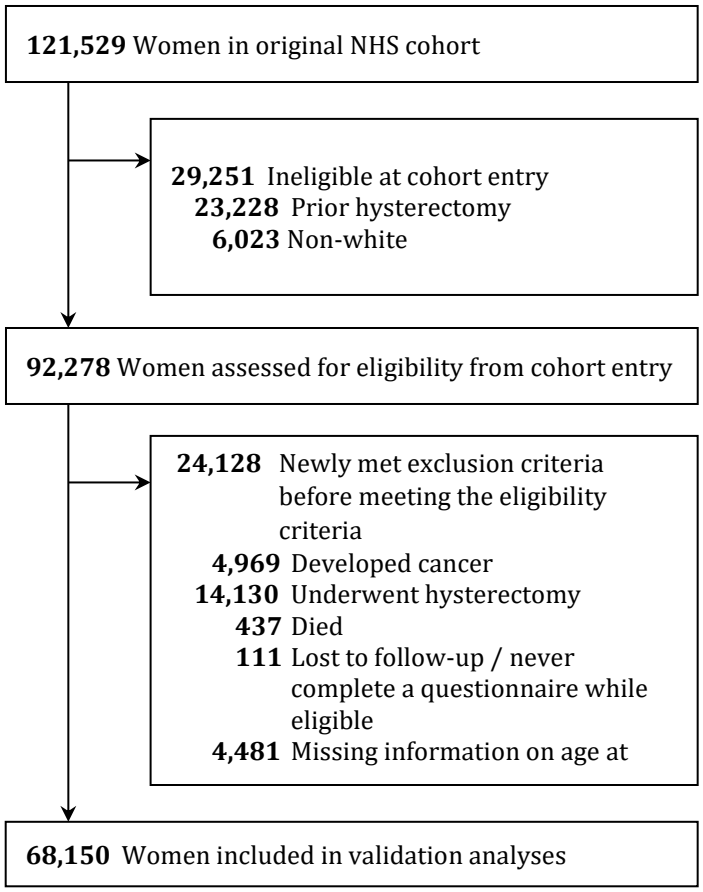
Supplementary Table 11. Relative and absolute 10-year risk calibration of the epidemiologic risk prediction models for endometrial cancer in the NHS and NHS II where participants were censored upon experiencing a competing event (other cancers, hysterectomy, or death)

Study / Decile	N	Number of events	Relative 10-year risk		Absolute 10-year risk (%)		
			Observed (95% CI)	Expected	Observed (95% CI)	Expected	E/O ratio (95% CI)
NHS							
1	6,818	25	0.39 (0.27, 0.58)	0.33	0.37 (0.22, 0.51)	0.17	0.47 (0.31, 0.69)
2	6,816	29	0.46 (0.32, 0.65)	0.45	0.43 (0.27, 0.58)	0.23	0.55 (0.38, 0.79)
3	6,972	38	0.58 (0.43, 0.79)	0.55	0.55 (0.37, 0.72)	0.28	0.52 (0.38, 0.71)
4	6,654	32	0.51 (0.37, 0.72)	0.64	0.48 (0.31, 0.65)	0.33	0.68 (0.48, 0.97)
5	6,824	71	1.11 (0.90, 1.38)	0.73	1.04 (0.80, 1.28)	0.38	0.36 (0.29, 0.46)
6	6,824	60	0.94 (0.74, 1.20)	0.82	0.88 (0.66, 1.10)	0.43	0.49 (0.38, 0.62)
7	6,797	63	0.99 (0.79, 1.25)	0.98	0.93 (0.70, 1.15)	0.50	0.54 (0.43, 0.70)
8	6,815	77	1.21 (0.98, 1.49)	1.14	1.13 (0.88, 1.38)	0.59	0.52 (0.42, 0.65)
9	6,818	96	1.51 (1.25, 1.81)	1.47	1.41 (1.13, 1.69)	0.76	0.54 (0.44, 0.66)
10	6,812	146	2.29 (1.99, 2.64)	2.90	2.14 (1.80, 2.49)	1.50	0.70 (0.60, 0.82)
Overall	68,150	637					0.55 (0.51, 0.60)
NHS II							
1	5,609	6	0.22 (0.10, 0.49)	0.29	0.11 (0.02, 0.19)	0.16	1.54 (0.69, 3.42)
2	5,659	11	0.41 (0.23, 0.72)	0.40	0.19 (0.08, 0.31)	0.22	1.14 (0.63, 2.06)
3	5,557	13	0.49 (0.29, 0.83)	0.48	0.23 (0.11, 0.36)	0.27	1.15 (0.67, 1.98)
4	5,609	15	0.56 (0.34, 0.91)	0.57	0.27 (0.13, 0.40)	0.32	1.19 (0.72, 1.98)
5	5,609	30	1.11 (0.80, 1.56)	0.64	0.53 (0.34, 0.73)	0.36	0.68 (0.47, 0.96)
6	5,603	21	0.78 (0.52, 1.18)	0.74	0.37 (0.21, 0.53)	0.41	1.10 (0.72, 1.69)
7	5,607	22	0.82 (0.55, 1.22)	0.89	0.39 (0.23, 0.56)	0.50	1.28 (0.84, 1.94)
8	5,608	38	1.41 (1.05, 1.89)	1.11	0.68 (0.46, 0.89)	0.62	0.92 (0.67, 1.26)
9	5,607	38	1.41 (1.05, 1.89)	1.54	0.68 (0.46, 0.89)	0.87	1.28 (0.93, 1.75)
10	5,608	75	2.79 (2.30, 3.37)	3.34	1.34 (1.04, 1.64)	1.87	1.40 (1.12, 1.75)
Overall	56,076	269					1.17 (1.04, 1.32)

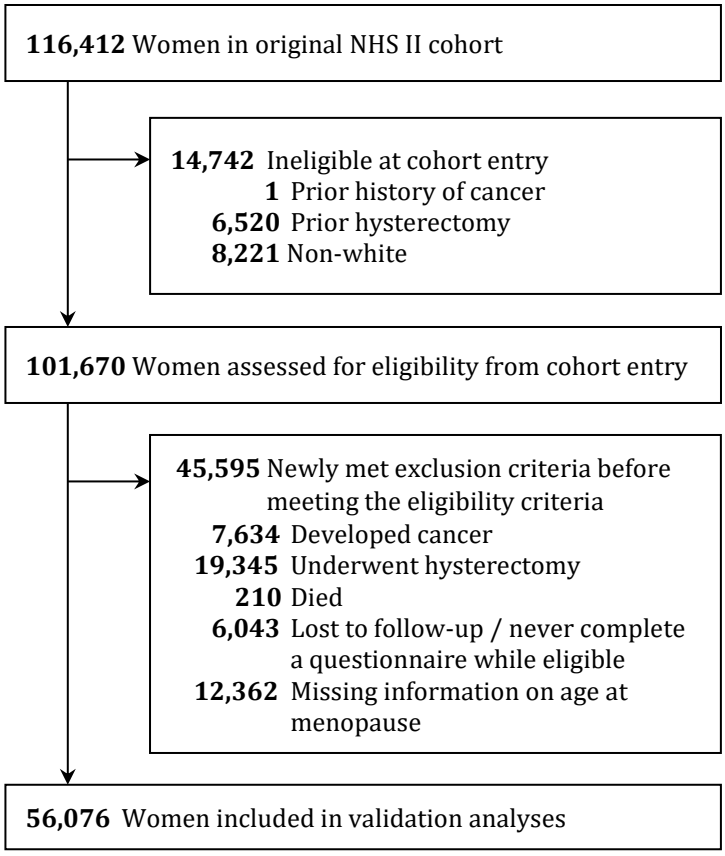
Supplementary Table 12. Relative and absolute 10-year risk calibration of the epidemiologic and epidemiologic plus genetic risk prediction models for endometrial cancer in the PLCO cohort where participants were censored upon experiencing a competing event (other cancers, hysterectomy, or death)

Study / Decile	N	Number of events	Relative 10-year risk		Absolute 10-year risk (%)		
			Observed (95% CI)	Expected	Observed (95% CI)	Expected	E/O ratio (95% CI)
Epidemiologic model							
1	4,002	23	0.45 (0.30, 0.67)	0.32	0.57 (0.34, 0.81)	0.39	0.68 (0.45, 1.03)
2	3,999	32	0.63 (0.45, 0.87)	0.44	0.80 (0.52, 1.08)	0.54	0.68 (0.48, 0.96)
3	3,998	36	0.70 (0.51, 0.96)	0.54	0.90 (0.61, 1.19)	0.66	0.73 (0.53, 1.01)
4	4,001	30	0.59 (0.41, 0.83)	0.64	0.75 (0.48, 1.02)	0.78	1.04 (0.73, 1.48)
5	4,014	44	0.86 (0.65, 1.13)	0.75	1.10 (0.77, 1.42)	0.91	0.83 (0.62, 1.12)
6	3,984	48	0.94 (0.72, 1.23)	0.88	1.20 (0.87, 1.54)	1.07	0.88 (0.67, 1.17)
7	3,999	35	0.68 (0.50, 0.94)	1.02	0.88 (0.59, 1.16)	1.24	1.42 (1.02, 1.97)
8	4,101	53	1.01 (0.78, 1.30)	1.19	1.29 (0.95, 1.64)	1.45	1.12 (0.86, 1.46)
9	3,898	80	1.60 (1.32, 1.96)	1.56	2.05 (1.61, 2.50)	1.90	0.93 (0.75, 1.15)
10	4,000	130	2.54 (2.19, 2.94)	2.66	3.25 (2.70, 3.80)	3.23	0.99 (0.84, 1.18)
Overall	39,996	511					0.95 (0.87, 1.04)
Epidemiologic plus genetic model							
1	3,011	13	0.32 (0.19, 0.55)	0.27	0.43 (0.20, 0.67)	0.32	0.73 (0.42, 1.26)
2	3,010	28	0.70 (0.49, 1.00)	0.40	0.93 (0.59, 1.27)	0.47	0.51 (0.35, 0.73)
3	3,010	19	0.47 (0.31, 0.73)	0.50	0.63 (0.35, 0.91)	0.59	0.93 (0.59, 1.45)
4	3,046	33	0.81 (0.59, 1.13)	0.60	1.08 (0.72, 1.45)	0.70	0.65 (0.46, 0.91)
5	2,981	30	0.76 (0.54, 1.06)	0.71	1.01 (0.65, 1.36)	0.83	0.83 (0.58, 1.18)
6	3,003	23	0.57 (0.39, 0.85)	0.85	0.77 (0.45, 1.08)	0.99	1.29 (0.86, 1.94)
7	3,010	30	0.75 (0.53, 1.05)	1.01	1.00 (0.64, 1.35)	1.18	1.18 (0.83, 1.68)
8	3,019	49	1.22 (0.94, 1.58)	1.24	1.62 (1.17, 2.07)	1.44	0.89 (0.67, 1.17)
9	3,001	62	1.55 (1.24, 1.94)	1.55	2.07 (1.56, 2.57)	1.80	0.87 (0.68, 1.12)
10	3,011	114	2.84 (2.44, 3.31)	2.87	3.79 (3.10, 4.47)	3.35	0.88 (0.74, 1.06)
Overall	30,102	401					0.88 (0.79, 0.97)

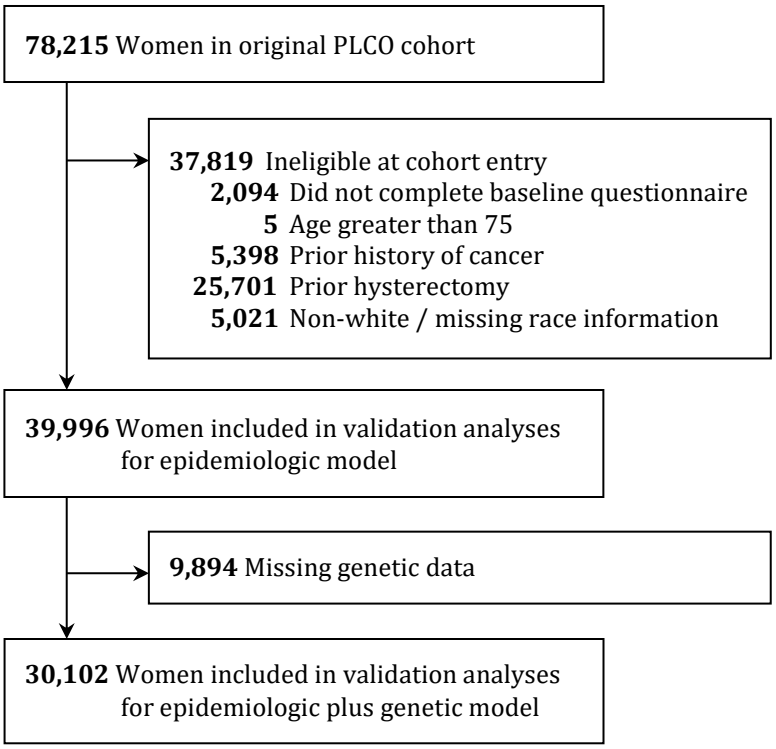
Supplementary Figure 1. Inclusion and exclusion of study participants from NHS



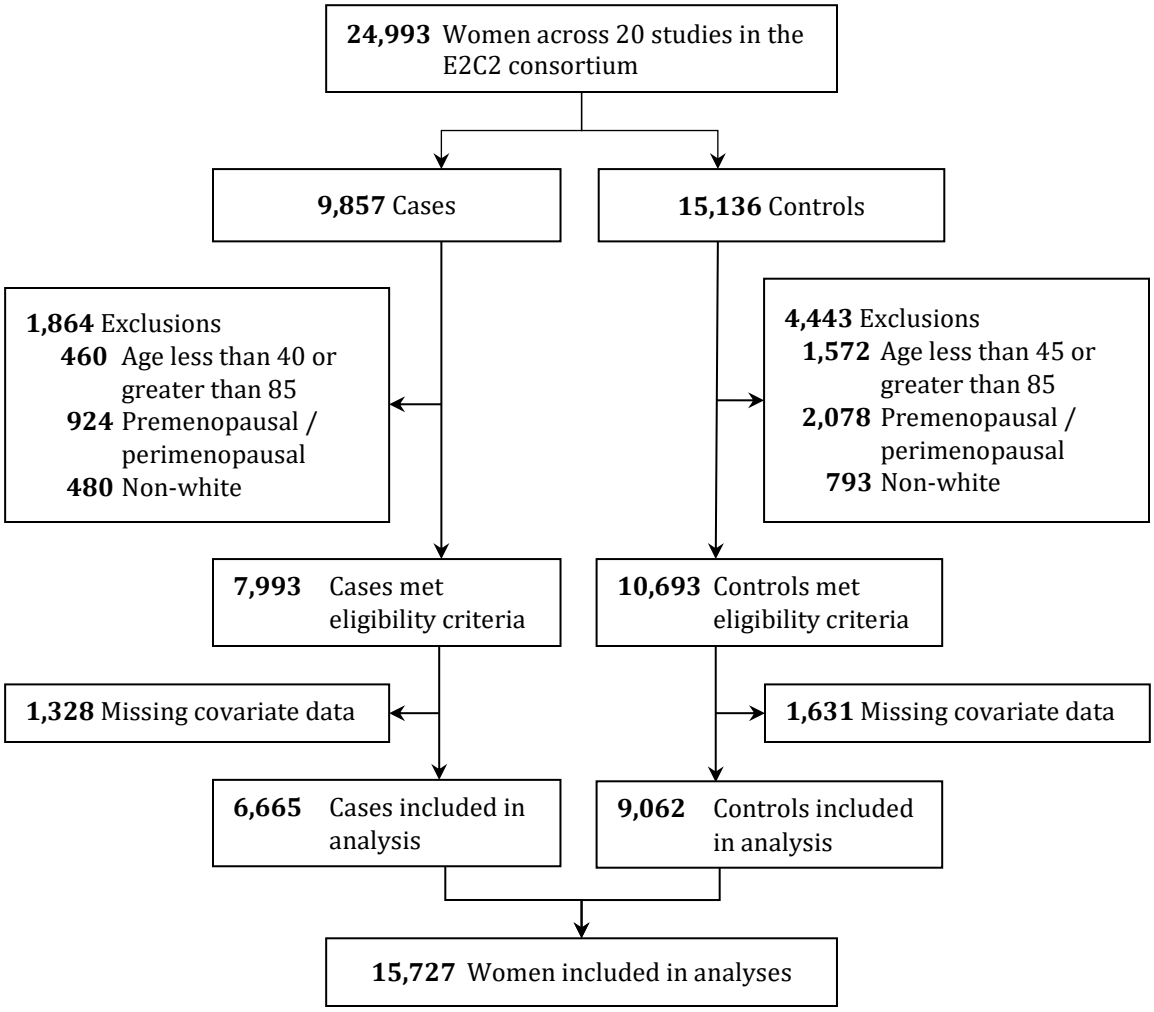
Supplementary Figure 2. Inclusion and exclusion of study participants from NHS II



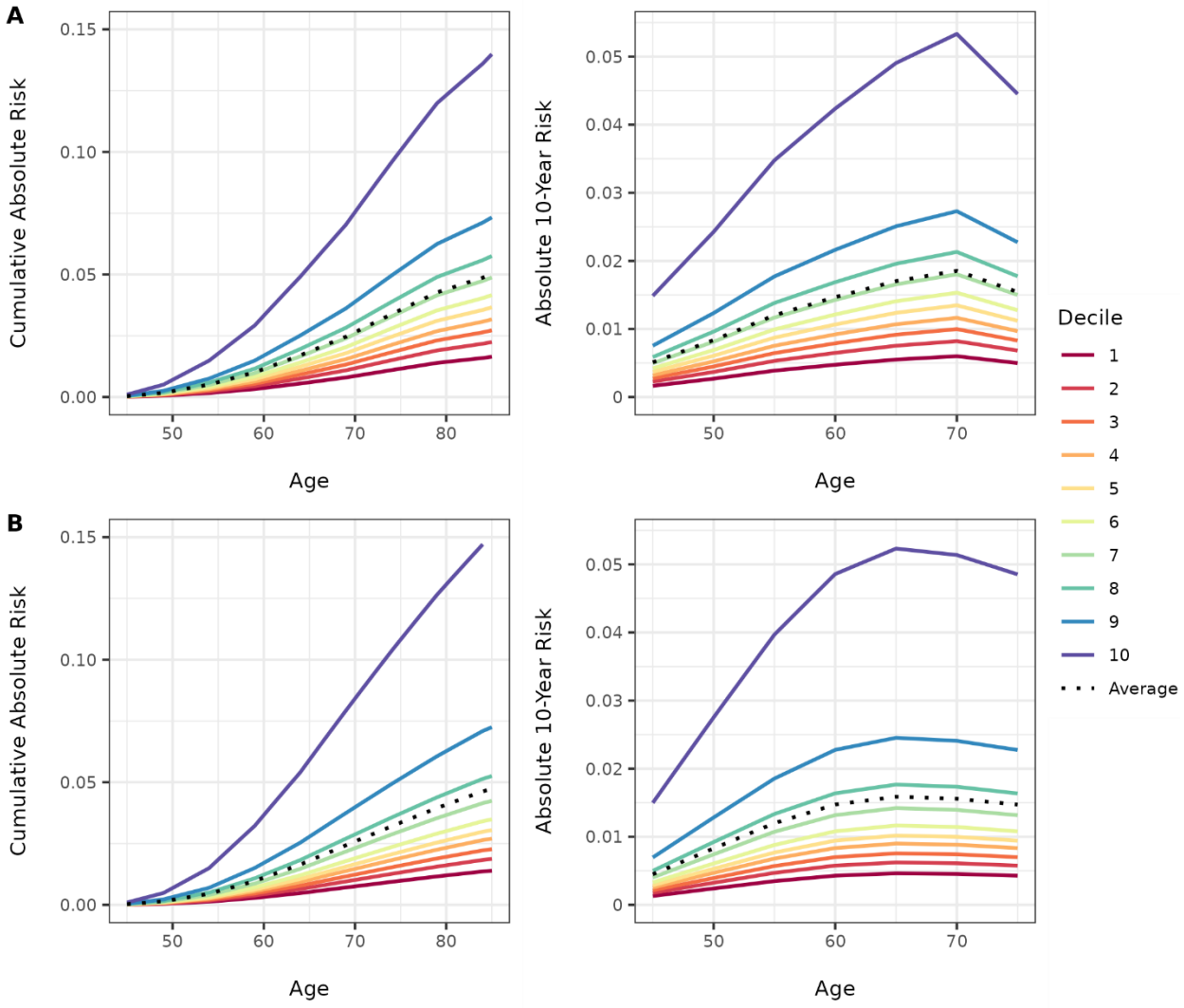
Supplementary Figure 3. Inclusion and exclusion of study participants from PLCO



Supplementary Figure 4. Inclusion and exclusion of study participants from E2C2 case-control studies



Supplementary Figure 5. Estimated cumulative absolute risk and absolute 10-year risk of endometrial cancer stratified by risk deciles using the epidemiologic model for (A) Nurses' Health Study, and (B) Nurses' Health Study II



Supplementary Figure 6. Estimated cumulative absolute risk and absolute 10-year risk of endometrial cancer stratified by risk deciles using the (A) epidemiologic model or (B) epidemiologic plus genetic model for the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial