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ORIGINAL REPORT

Type I and II Endometrial Cancers: Have They Different Risk Factors?

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ABSTRACT

Purpose
Endometrial cancers have long been divided into estrogen-dependent type I and the less common clinically aggressive estrogen-independent type II. Little is known about risk factors for type II tumors because most studies lack sufficient cases to study these much less common tumors separately. We examined whether so-called classical endometrial cancer risk factors also influence the risk of type II tumors.

Patients and Methods
Individual-level data from 10 cohort and 14 case-control studies from the Epidemiology of Endometrial Cancer Consortium were pooled. A total of 14,069 endometrial cancer cases and 35,312 controls were included. We classified endometrioid (n = 7,246), adenocarcinoma not otherwise specified (n = 4,830), and adenocarcinoma with squamous differentiation (n = 777) as type I tumors and serous (n = 508) and mixed cell (n = 346) as type II tumors.

Results
Parity, oral contraceptive use, cigarette smoking, age at menarche, and diabetes were associated with type I and type II tumors to similar extents. Body mass index, however, had a greater effect on type I tumors than on type II tumors: odds ratio (OR) per 2 kg/m^2 increase was 1.20 (95% CI, 1.19 to 1.21) for type I and 1.12 (95% CI, 1.09 to 1.14) for type II tumors ($P_{heterogeneity} < .0001$). Risk factor patterns for high-grade endometrioid tumors and type II tumors were similar.

Conclusion
The results of this pooled analysis suggest that the two endometrial cancer types share many common etiologic factors. The etiology of type II tumors may, therefore, not be completely estrogen independent, as previously believed.

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INTRODUCTION

On the basis of differences in histology and clinical outcomes, endometrial cancers have long been divided into two types.[1-4] Type I tumors comprise the large majority of endometrial cancers, are mostly endometrioid adenocarcinomas, are associated with unopposed estrogen stimulation, and are often preceded by endometrial hyperplasia. Type II tumors are predominantly serous carcinomas and are commonly described as estrogen independent, arising in atrophic endometrium and deriving from intraepithelial carcinoma, a precancerous lesion. Type II tumors generally are less well differentiated and have poorer prognoses than type I tumors, and they account for a disproportionate number of endometrial cancer deaths (40% of deaths, whereas they only account for 10% to 20% of cases).[5] The disparate genetic alterations found in type I and type II tumors suggest that these subtypes may have distinct etiologies.[1,3,6]

Many established risk factors for type I endometrial cancers are related to an imbalance between estrogen and progesterone exposures, including obesity and the use of unopposed estrogen therapy. Use of combined oral contraceptives (OCs), which is associated with progesterone-dominant states, reduces the risk of endometrial cancer. Other risk factors include nulliparity, early menarche, and late menopause, whereas smoking is associated with reduced risk. Little is known about risk factors for type II tumors, mainly because most epidemiologic studies[7-12] have lacked enough cases to study these less common tumors separately.

In this study, we combined individual-level data from 24 epidemiologic studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2)[13] and performed a pooled analysis with 854 type II and 12,853 type I cases and 35,312 controls. The E2C2 is an international consortium established to pool data in an effort to identify endometrial cancer genetic and environmental risk factors that are not addressable in a single study. The large number of cases and controls in E2C2 allowed us to evaluate risk factors for type II tumors as well as the associations for specific histologic subtypes.

PATIENTS AND METHODS

Participating Studies

Twenty-four studies (10 cohort and 14 case-control) in the E2C2 with available type II cases were included in the pooled analysis (Table 1). Cohort studies were analyzed as nested case-control studies, with up to four controls randomly selected from the risk set (women with intact uteri and without endometrial cancer before the index case diagnosis) for each case based on exact year of birth, date of cohort entry (± 6 months), and other criteria as appropriate for each individual study (eg, race/ethnicity, study area). The majority of participants were non-Hispanic white, and the populations were from the United States, Canada, Europe, and Australia. Three studies (Multiethnic Cohort [MEC], Hawaii Endometrial Cancer Study [HAW], and Shanghai Endometrial Cancer Study [SECS]) included mainly or exclusively nonwhite populations from the United States or China. Informed consent was obtained from all study participants as part of the original studies in accordance with the requirements of each study's institutional review board.

Data Collection

Data, with personal identifiers removed, from individual studies were received at the E2C2 data coordinating center at Memorial Sloan-Kettering Cancer Center. Each study provided information regarding tumor characteristics, demographic variables (age at diagnosis for cases and at interview or reference date for controls, and race/ethnicity), and risk factors (body weight, height, age at menarche, parity, menopausal hormone use, OC use, smoking history, and history of diabetes). These variables were defined and uniformly recoded in accordance with the E2C2 data dictionary. Risk factor data were obtained from the baseline questionnaire for all cohort studies except one (Nurses' Health Study [NHS]) that used information from follow-up cycles in which index cases were diagnosed. In case-control studies, risk factor data were based on a specific reference date (usually 6 to 12 months before date of diagnosis for cases and date of interview for controls). Body mass index (BMI, in kilograms per square meter) in cohort studies was calculated using self-reported weight and height at baseline, except for Canadian National Breast Screening Study (NBSS), which used direct measurement of weight and height during interview. Weight and height in case-control studies was either ascertained by direct measurement during interview (Alberta, HAW, SECS, Turin, and University of Southern California, Los Angeles, Case-Control [USC]) or was self-reported as of the reference date (Australian National Endometrial Cancer Study [ANECS], Bay Area Women's Health Study [BAWHS], Connecticut Endometrial Cancer Study [CECS], Estrogen, Diet, Genetics, and Endometrial Cancer [EDGE], Fred Hutchinson Cancer Research Center [FHCRC], Polish Endometrial Cancer Study [PECS], Patient Epidemiologic Data System [PEDS], US Endometrial Cancer Study [US], and Women's Insight and Shared Experience [WISE]).

Data Availability

Data on age, race/ethnicity, BMI, age at menarche, parity, menopausal hormone use (any type), and OC use were provided by all 24 studies. Data specifically on menopausal estrogen use were not available in five studies (Alberta, Iowa Women's Health Study [IWHS], NBSS, Swedish Mammography Cohort [SMC], and Turin), and data on menopausal estrogen-progestin use were not available in seven studies (Alberta, Breast Cancer Detection Demonstration Project [BCDDP], CECS, IWHS, NBBS, Netherlands Cohort Study [NCLS], and Turin). Duration and recency of estrogen or estrogen-progestin use were not provided by the majority of studies. Thus we were unable to quantify the association of specific types of menopausal hormone use with tumor subtypes. For purposes of analysis, we classified women age ≥ 55 years whose menopausal status was not available (FHCRC) as postmenopausal. Smoking history was not available in BAWHS, and information regarding pack-years of smoking was not available in six studies (Alberta, CECS, FHCRC, National Institutes of Health America Association of Retired Persons Diet and Health Study [NIH-AARP], Turin, and WISE). A history of diabetes was not available in five studies (ANECS, BAWHS, NBSS, PEDS, and SMC).

Tumor Histology

Only incident cases of endometrial cancer (primary site codes: C54 and C55.9) were included in this analysis. Histology data were obtained either from cancer registry information, pathology report/medical chart review, or slide review (Table 1). Nineteen studies (Alberta, ANECS, BAWHS, BCDDP, CECS, Cancer Prevention Study II [CPS-II], CTS, EDGE, FHCRC, HAW, IWHS, MEC, NBSS, NCLS, NIH-AARP, PEDS, SMC, US, and USC) provided the International Classification of Diseases for Oncology (ICD-O-3) histology codes for each case. Four studies (PECS, SECS, Turin, and WISE) provided summary histologic type. One study, NHS, collapsed endometrioid, adenocarcinoma not otherwise specified (NOS), and mucinous adenocarcinoma into one group. Fourteen studies (ANECS, BCDDP, FHCRC, HAW, IWHS, MEC, NLCS, NIH-AARP, SECS, PECS, PEDS, US, USC, and WISE) provided tumor grade. Seven major tumor subtypes were analyzed separately: endometrioid adenocarcinoma (ICD-O-3 code: 8380, 8381, 8382, 8383; n = 7,246), adenocarcinoma NOS (8140; n = 4,830), adenocarcinoma with squamous differentiation (8560, 8570; n = 777), serous/papillary serous (8441, 8460, 8461; n = 508), mixed cell adenocarcinoma (8323; n = 346), clear cell (8310; n = 196), and mucinous adenocarcinoma (8480, 8481, 8482; n = 166). Tumors of other histologies were excluded from the present analysis owing to small numbers of each specific type. We classified endometrioid carcinoma, adenocarcinoma NOS, and adenocarcinoma with squamous differentiation (n = 12,853) as type I tumors. We classified serous/papillary serous and mixed cell adenocarcinoma (n = 854) as type II tumors. We also incorporated tumor grade in the endometrioid cancer analysis for studies with available grade information because previous reports have shown that high-grade endometrioid tumors (grade 3+) behave similarly to type II cancers.[14,15]

Exclusion Criteria

Women were excluded from the analysis for extreme BMI values (≤ 15 or ≥ 50 kg/m^2) because of concerns regarding the reliability of these data or for missing data on BMI, parity, age at menarche, OC use, or use of menopausal hormones (n = 3,987). With the exception of the BAWHS, which did not collect data on smoking, women in the other studies who had missing smoking data were excluded from the analyses (n = 797). After these exclusions, 854 type II and 12,853 type I cases and 35,312 controls remained for analysis.

Statistical Methods

We created categories for BMI (< 25, 25 to <30, 30 to < 35, 35 to < 40, ≥ 40 kg/m^2), age at menarche (< 11, 11 to 12, 13 to 14, ≥ 15 years), parity (0, 1, 2, 3, ≥ 4), OC use (never, ever), menopausal status (pre-, postmenopausal), menopausal hormone use (never, ever), smoking status (never, past, current, missing [for BAWHS]), pack-years of smoking (never smokers, < 20, ≥ 20), and a history of diabetes mellitus (no, yes). The associations between risk factors and tumor subtypes were estimated by odds ratios (ORs) and 95% CIs using conditional logistic regression stratified jointly by study, age (< 50,

Table 1. Characteristics* of the 24 Studies Participating in the Pooled Analysis

Study	Location	Recruitment Period	Matching Factors	Histology Source†	White Race, %	Mean Age, Years‡	No. of Cases: Endometrioid	Adenocarcinoma NOS	Adenocarcinoma With Squamous Differentiation	Serous	Mixed Cell	Clear Cell	Mucinous	No. of Controls
Cohort studies														
Breast Cancer Detection Demonstration Project (BCDDP)	29 US clinics	1979-1980	Birth year, cohort entry, race, clinic	Path	92.6	65.2	48	276	27	10		1	4	1,858
Cancer Prevention Study II (CPS-II) Nutrition Cohort	21 US states	1992	Birth year, cohort entry, race, area	Path/registry	98.7	68.9	205	270	18	30	2	9	16	2,431
Canadian National Breast Screening Study (NBSS)	Canada	1980-1985	Birth year, cohort entry, race, area	Registry	96.9	59.9	149	396	49	23	1	9	12	2,953
California Teachers Study (CTS)	California	1995-1996	Birth year, cohort entry, race, area	Registry	91.9	64.7	367	173	27	19	23	6	16	2,539
Iowa Women's Health Study (IWHS)	Iowa	1986	Birth year, cohort entry, race, area	Registry	98.7	71.6	99	316	26	26	2	6	3	2,120
Multiethnic Cohort (MEC)	Hawaii, California	1993-1996	Birth year, cohort entry, race, area	Registry	28.1	65.6	235	187	26	29	10	13	6	2,341
Nurses' Health Study (NHS)	11 US states	1976	Birth year, race	Path	94.8	62.4	430§		23	4		9		1,271
NIH-AARP Diet and Health Study (NIH-AARP)	8 US areas	1995-1996	birth year, cohort entry, race, area	Registry	93.9	67.5	809	495	39	71	23	19	29	6,831
Netherlands Cohort Study (NLCS)	Netherlands	1986	birth year, cohort entry	Path/registry	100.0	69.6	98	182	43	5		14	3	766
Swedish Mammography Cohort (SMC)	Sweden	1987-1990	Birth year, cohort entry	Registry	100.0	70.5		293	3	10		4	1	1,283
All cohort studies					61.0	66.4	2,440	2,588	281	227	61	90	90	24,393
Case-control studies														
Alberta	Canada	2002-2006	Age (± 5 years)	Path/registry	94.8	58.3	424	15	8	18	15	10	4	1,026
Australian National Endometrial Cancer Study (ANECS)	Australia	2005-2007	Age (5-year group), state	Path	88.6	61.2	861	1	164	49	132	21	3	703
Bay Area Women's Health Study (BAWHS)	California	1996-1999	Age (5-year group), ethnicity	Registry	90.3	61.8	178	199	10	15		11	20	445
Connecticut Endometrial Cancer Study (CECS)	Connecticut	2004-2009	Age (5-year group)	Path	93.2	61.5	502	22	5	35	23	9	9	627

(continued on following page)

Table 1. Characteristics* of the 24 Studies Participating in the Pooled Analysis (continued)

Study	Location	Recruitment Period	Matching Factors	Histology Source†	White Race, %	Mean Age, Years‡	No. of Cases: Endometrioid	Adenocarcinoma NOS	Adenocarcinoma With Squamous Differentiation	Serous	Mixed Cell	Clear Cell	Mucinous	No. of Controls
Estrogen, Diet, Genetics, and Endometrial Cancer (EDGE)	New Jersey	2001-2005	Age (5-year group)	Registry	90.1	62.8	292	96	9	26	6	4	3	464
Fred Hutchinson Cancer Research Center (FHCRC)	Washington	1994-2005	Age (5-year group)	Registry	95.5	59.7	463	260	35	35	20	3	6	847
Hawaii Endometrial Cancer Study (HAW)	Hawaii	1988-1993	Age (± 2.5 years), ethnicity	Path/registry	29.1	62.5	93	192	19	4	3	2	3	335
Polish Endometrial Cancer Study (PECS)	Poland	2000-2003	Age (± 5 years), site	Path/slide	100.0	57.2	312		110	10	68	5	4	1,829
Patient Epidemiologic Data System (PEDS)	New York	1982-1998	Age (± 5 years)	Registry	97.4	62.9	72	327	33	19	5	8	2	504
Shanghai Endometrial Cancer Study (SECS)	China	1997-2004	Age (± 5 years)	Path/slide	0.0	54.6	997	60	7	15	3	8	2	1,205
Turin Case Control Study (TURIN)	Italy	1998-2008	—	Path	100.0	60.9	180	12	4	9	3	10	2	266
US Endometrial Cancer Study (US)	5 US clinics	1987-1990	Age (± 5 years), race, telephone exchange	Path	93.1	58.8	18	224	47	11	1	7	10	303
USC LA case-control (USC)	Los Angeles	1987-1993	Age (± 5 years)	Path	100.0	63.1	38	666	45	7		1	8	791
Women's Insight and Shared Experience (WISE)	Philadelphia	1999-2002	Age (± 5 years), race	Path	78.9	61.7	376	168		28	6	7		1,574
All case-control studies					79.7	60.0	4,806	2,242	496	281	285	106	76	10,919
Pooled studies					85.4	63.9	7,246	4,830	777	508	346	196	166	35,312

Abbreviations: AARP, American Association of Retired Persons; NIH, National Institutes of Health; NOS, not otherwise specified.
*Based on women included in the pooled analysis (ie, after excluding women with missing risk factor data).
†Path = review of pathology report; slide = review of pathology slides; registry = histologic type/code as reported to a cancer registry.
‡Age at diagnosis for cases and age at interview/reference date for controls.
§NHS grouped endometrioid, adenocarcinoma NOS, and mucinous tumors in one category.

50 to < 55, 55 to < 60, 60 to < 65, 65 to < 70, ≥ 70 years), and race/ethnicity (non-Hispanic white, African American/black, Asian, Hawaiian/Pacific Islander, and other) and adjusted for BMI, age at menarche, parity, OC use, menopausal status, menopausal hormone use, and smoking status. Tests for trend were performed by entering the ordinal values representing categories of BMI, age at menarche, parity, and pack-years of smoking as continuous variables in the models. Differences in ORs between tumor types were tested using case-only logistic regression models. To minimize residual confounding owing to menopausal hormone use, we repeated analyses restricted to postmenopausal women who had never used menopausal hormones. We also evaluated the risk factor associations by selected elements of study design (ie, cohort *v* case-control study and source of histologic data [pathologic review *v* registry-based]). All *P* values were two-sided. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Characteristics of endometrial cancer cases, by histologic type, and of controls are shown in Table 2. The majority of women were white (> 77% for each group) and postmenopausal (> 79% for each group). The mean age at diagnosis was highest among patients with serous tumors and lowest among those diagnosed with endometrioid cancer or adenocarcinoma with squamous differentiation. Cases with these seven histologic types all had higher average BMI than controls; among cases, the lowest BMI was observed among patients with serous disease. Compared with controls, cases were less likely to be parous or to have ever smoked.

We examined the association of each risk factor with the seven histologic types (Table 3). All factors were associated with endometrioid tumors and adenocarcinoma NOS in the direction expected based on the results of previous research; that is, increasing BMI and diabetes were positively associated with risk, whereas increasing age at menarche, number of children, use of OCs, smoking, and pack-years of smoking were inversely associated with risk. The ORs for a 2 kg/m^2 increase in BMI for serous, mixed cell, clear-cell, and mucinous adenocarcinomas (ORs ranged from 1.10 to 1.16) were smaller than those seen for endometrioid adenocarcinoma or the other type I tumors (ORs ranged from 1.20 to 1.21). The associations of age at menarche, parity, OC use, smoking, and diabetes with serous, mixed cell, and mucinous adenocarcinoma were generally similar to those for the endometrioid tumors. Clear-cell tumors, however, were similar only with regard to reduced risk associated with OC use. Unlike for other histologies, increasing age at menarche and number of children were not significantly associated with reduced risk of clear-cell tumors, although numbers were small.

Table 4 shows the associations of endometrial cancer risk factors with risk of type I and type II tumors. Risk factors for both types were similar. The OR per 2 kg/m^2 increase in BMI was 1.12 (95% CI, 1.09 to 1.14) for type II tumors, weaker than that for type I tumors (OR = 1.20; 95% CI, 1.19 to 1.21; $P_{heterogeneity} < .0001$). Increasing parity, age at menarche, and pack-years of smoking were associated with reduced risk of both type II and type I tumors to a similar degree and with significant trends ($P_{trend} \leq .0006$). Prior OC use and past and current smoking were inversely associated with both type II and type I tumors as well. A history of diabetes was positively associated with both tumor types (OR = 1.53; 95% CI, 1.19 to 1.95 for type II tumors and OR = 1.27; 95% CI, 1.17 to 1.38 for type I tumors). An analysis restricted to postmenopausal women who never used menopausal hormones yielded similar results (Appendix Table A1, online only).

We further examined risk factor associations for endometrioid tumors by tumor grade (Table 5). Compared with low-grade endometrioid tumors (grade ≤ 2, n = 3,630), risk factor associations for high-grade tumors (grade ≥ 3, n = 519) were different only with respect to BMI, with a stronger association for low-grade tumors (OR per 2 kg/m^2 = 1.23; 95% CI, 1.21 to 1.25) than for high-grade tumors (OR = 1.16; 95% CI, 1.12 to 1.20; $P_{heterogeneity} < .0001$). Risk factor associations for high-grade endometrioid and type II tumors were not different ($P_{heterogeneity} \geq 0.08$).

We also examined risk factor associations for type II and type I tumors by study type and source of histologic data (Appendix Table A2, online only). The associations were consistent between case-control and cohort studies and between registry-based studies and those with review of pathology reports (or for PECS and SECS, review of pathology slides).

DISCUSSION

In this large pooled analysis, we observed that most of the classical endometrial cancer risk factors (ie, obesity, age at menarche, parity, OC use, smoking, and diabetes) were associated with the less common and more clinically aggressive type II tumors (serous and mixed cell). In addition, we observed that the risk factor pattern of high-grade endometrioid tumors and type II tumors were similar and that the risk factors for clear-cell tumors seemed to differ from other histologic types of endometrial cancer.

The first epidemiologic study examining risk factors for specific endometrial cancer histologic subtypes was a case-control study with 26 serous and 328 endometrioid cancer cases.[10] This study found that BMI, menopausal estrogen use, age at menarche, and parity were associated with endometrioid tumors but not with serous tumors. OC use and smoking were associated with a reduced risk of both tumor types. The study also found that the age- and BMI-adjusted serum levels of endogenous estrogen and sex-hormone-binding globulin (SHBG) were significantly different between patients with endometrioid tumors and patients with serous tumors. Although small in size, this study raised the possibility that risk factors for serous tumors might differ from those for endometrioid tumors. Data from this study coupled with other clinicopathologic and molecular data have led to the proposed dualistic model of endometrial carcinogenesis.[1]

Since the initial study, five epidemiologic studies examining risk factors for type II tumors have been reported,[7-9,11,12] with two of these studies focusing on BMI.[8,9] Similar to our findings, the largest study,[8] with 992 type II cases (including papillary, serous, clear cell, and some poorly differentiated carcinomas), found that BMI was associated with type II tumors as well as with type I tumors (including endometrioid and mucinous adenocarcinomas) and that the magnitude of risk was somewhat stronger for type I than type II tumors. However, the lack of control for potential confounders (ie, parity, exogenous hormone use, and smoking) in that study left open the possibility of bias and thus weakened the validity of its finding. The other BMI study[9] had limited statistical power with 70 type II cases, but they also found BMI to be associated with type II tumors.

The classical endometrial cancer risk factors have been generally thought to act via estrogenic mechanisms, either by increasing estrogen exposure or opposing the effects of estrogen.[16] Obesity is associated with higher levels of circulating estrogens in postmenopausal

Table 2. Characteristics of Women in the Pooled Analysis by Case-Control Status and Histology

	Cases														Controls	
	Endometrioid* (n = 7,246)		Adenocarcinoma NOS (n = 4,830)		Adenocarcinoma With Squamous Differentiation (n = 777)		Serous (n = 508)		Mixed Cell (n = 346)		Clear Cell (n = 196)		Mucinous (n = 166)		(n = 35,312)	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years																
Mean	61.9		64.1		61.8		66.5		62.4		65.6		64.6		64.3	
SD	9.5		8.4		8.8		8.0		9.5		8.6		8.6		9.1	
Race																
White	5,629	77.7	4,356	90.2	701	90.2	415	81.7	312	90.2	163	83.2	150	90.4	30,528	86.5
Black	154	2.1	103	2.1	13	1.7	44	8.7	10	2.9	9	4.6	5	3.0	1,360	3.9
Asian	1,165	16.1	256	5.3	28	3.6	25	4.9	9	2.6	11	5.6	9	5.4	2,270	6.4
Hawaiian/Pacific Islander	21	0.3	39	0.8	5	0.6					1	0.5			257	0.7
Other†	277	3.8	76	1.6	30	3.9	24	4.7	15	4.3	12	6.1	2	1.2	897	2.5
Postmenopausal	5,768	79.6	4,246	87.9	648	83.4	471	92.7	177	90.3	294	85.0	135	81.3	29,513	83.6
BMI, kg/m^2	28.9	6.7	28.1	6.7	29.0	6.9	27.6	6.1	28.5	6.3	27.7	5.8	28.1	6.6	25.7	4.9
Mean																
SD																
Parous	5,951	82.1	3,867	80.1	584	75.2	425	83.7	279	80.6	165	84.2	130	78.3	30,719	87.0
Ever used menopausal hormone‡	2,310	40.1	2,069	48.7	253	39.0	159	33.8	97	33.0	54	30.5	79	58.5	12,397	42.0
Ever smoked§	2,583	36.5	1,877	40.5	314	40.9	191	38.7	116	33.5	75	40.5	65	44.5	16,052	46.0

Abbreviations: BMI, body mass index; SD, standard deviation.
*Includes endometrioid carcinoma, mucinous and adenocarcinoma not otherwise specified for one study (Nurses' Health Study).
†Includes mixed, Hispanic, other, and unknown race/ethnicity.
‡Among postmenopausal women only.
§Based on 23 studies with smoking data (Bay Area Women's Health Study did not have smoking data).

Table 3. Association of Endometrial Cancer Risk Factors With Specific Endometrial Cancer Histology

Risk Factor	No. of Controls	Endometrioid No. of Cases	Endometrioid OR*	Endometrioid 95% CI	Adenocarcinoma NOS No. of Cases	Adenocarcinoma NOS OR*	Adenocarcinoma NOS 95% CI	Adenocarcinoma With Squamous Differentiation No. of Cases	Adenocarcinoma With Squamous Differentiation OR*	Adenocarcinoma With Squamous Differentiation 95% CI	Serous No. of Cases	Serous OR*	Serous 95% CI	Mixed Cell No. of Cases	Mixed Cell OR*	Mixed Cell 95% CI	Clear Cell No. of Cases	Clear Cell OR*	Clear Cell 95% CI	Mucinous No. of Cases	Mucinous OR*	Mucinous 95% CI
Body mass index, kg/m^2																						
< 25	18,400	2,428	1.00		1,914	1.00		260	1.00		208	1.00		122	1.00		74	1.00		67	1.00	
25 to < 30	10,986	2,163	1.57	1.46 to 1.68	1,332	1.31	1.21 to 1.42	223	1.41	1.17 to 1.71	149	1.11	0.89 to 1.38	104	1.27	0.96 to 1.68	60	1.29	0.91 to 1.83	43	1.13	0.76 to 1.67
30 to < 35	4,078	1,319	2.56	2.35 to 2.80	830	2.41	2.19 to 2.67	145	2.32	1.86 to 2.89	94	1.73	1.34 to 2.25	65	1.71	1.23 to 2.37	42	2.46	1.65 to 3.68	31	2.10	1.35 to 3.28
35 to < 40	1,255	753	4.75	4.22 to 5.34	412	4.05	3.52 to 4.66	82	4.18	3.15 to 5.54	32	1.80	1.20 to 2.68	33	2.79	1.83 to 4.25	10	1.94	0.98 to 3.87	17	3.36	1.90 to 5.96
≥ 40	593	583	6.88	5.95 to 7.96	342	7.17	6.05 to 8.49	67	7.76	5.56 to 10.82	25	2.85	1.80 to 4.52	22	3.49	2.06 to 5.90	10	4.36	2.16 to 8.82	8	3.29	1.51 to 7.19
P trend			< .0001			< .0001			< .0001			< .0001			< .0001			< .0001			< .0001	
Body mass index, per 2 kg/m^2	35,312	7,246	1.21	1.20 to 1.22	4,830	1.20	1.18 to 1.21	777	1.20	1.17 to 1.23	508	1.10	1.07 to 1.14	346	1.13	1.09 to 1.18	196	1.14	1.08 to 1.20	166	1.16	1.10 to 1.22
Age at menarche, years																						
< 11	1,633	508	1.00		285	1.00		51	1.00		40	1.00		28	1.00		12	1.00		16	1.00	
11-12	7,332	1,740	0.87	0.76 to 0.99	926	0.94	0.80 to 1.10	166	0.74	0.53 to 1.05	134	0.74	0.51 to 1.08	86	0.57	0.36 to 0.91	41	0.76	0.39 to 1.47	34	0.53	0.28 to 0.97
13-14	21,563	3,963	0.83	0.73 to 0.94	3,104	0.90	0.77 to 1.04	461	0.71	0.52 to 0.98	283	0.66	0.47 to 0.95	183	0.57	0.37 to 0.89	113	0.76	0.41 to 1.41	105	0.57	0.33 to 0.99
≥ 15	4,784	1,035	0.67	0.58 to 0.78	515	0.77	0.65 to 0.92	99	0.59	0.41 to 0.86	51	0.48	0.31 to 0.75	49	0.50	0.30 to 0.84	30	0.83	0.41 to 1.69	11	0.32	0.14 to 0.70
P trend			< .0001			.002			.01			.001			.04			.81			.03	
Parity																						
0	4,593	1,295	1.00		963	1.00		193	1.00		83	1.00		67	1.00		31	1.00		36	1.00	
1	4,528	1,271	0.73	0.65 to 0.81	621	0.81	0.71 to 0.91	107	0.54	0.41 to 0.70	74	1.00	0.72, 1.40	47	0.63	0.42 to 0.95	25	0.81	0.46 to 1.42	26	0.82	0.48 to 1.40
2	10,147	2,159	0.68	0.62 to 0.75	1,347	0.71	0.64 to 0.78	222	0.48	0.38 to 0.59	142	0.75	0.57 to 1.00	108	0.55	0.39 to 0.77	48	0.70	0.44 to 1.13	46	0.63	0.40 to 0.99
3	12,119	1,970	0.56	0.51 to 0.62	1,519	0.60	0.54 to 0.66	197	0.39	0.32 to 0.49	150	0.60	0.45 to 0.80	81	0.51	0.35 to 0.72	62	0.71	0.45 to 1.11	49	0.53	0.34 to 0.83
≥ 4	3,925	551	0.42	0.37 to 0.47	380	0.41	0.36 to 0.48	58	0.25	0.18 to 0.35	59	0.55	0.38 to 0.78	43	0.54	0.35 to 0.84	30	0.73	0.43 to 1.24	9	0.30	0.14 to 0.65
P trend			< .0001			< .0001			< .0001			< .0001			.0007			.19			.0002	
Oral contraceptive use																						
Never	20,785	4,139	1.00		3,378	1.00		494	1.00		306	1.00		191	1.00		131	1.00		103	1.00	
Ever	14,527	3,107	0.78	0.73 to 0.84	1,452	0.67	0.62 to 0.73	283	0.64	0.53 to 0.78	202	0.87	0.70 to 1.07	155	0.54	0.40 to 0.72	65	0.66	0.46 to 0.94	63	0.65	0.44 to 0.95
Cigarette smoking†																						
Never	18,815	4,485	1.00		2,754	1.00		453	1.00		302	1.00		230	1.00		110	1.00		81	1.00	
Former	10,900	2,025	0.83	0.78 to 0.89	1,421	0.91	0.84 to 0.98	202	0.83	0.69 to 0.99	145	0.76	0.61, 0.94	82	0.62	0.47 to 0.81	47	0.78	0.54 to 1.11	57	1.14	0.80 to 1.62
Current	5,152	558	0.61	0.55 to 0.68	456	0.64	0.57 to 0.71	112	0.88	0.70 to 1.10	46	0.66	0.48 to 0.91	34	0.53	0.36 to 0.78	28	1.13	0.73 to 1.73	8	0.41	0.19 to 0.85
Pack-years of smoking‡																						
Never	13,693	2,988	1.00		2,246	1.00		412	1.00		190	1.00		177	1.00		76	1.00		58	1.00	
< 20	5,383	772	0.80	0.73 to 0.89	724	0.93	0.84 to 1.03	143	0.79	0.64 to 0.98	54	0.79	0.57 to 1.09	52	0.59	0.42 to 0.83	28	0.98	0.62 to 1.54	19	0.81	0.48 to 1.39
≥ 20	3,594	465	0.68	0.60 to 0.77	544	0.71	0.64 to 0.80	100	0.80	0.63 to 1.02	46	0.83	0.59 to 1.17	23	0.49	0.31 to 0.78	17	0.82	0.47 to 1.41	14	0.77	0.42 to 1.41
P trend			< .0001			< .0001			.02			.17			.0002			.50			.33	

(continued on following page)

Table 3. Association of Endometrial Cancer Risk Factors With Specific Endometrial Cancer Histology (continued)

		Cases																				
		Endometrioid			Adenocarcinoma NOS			Adenocarcinoma With Squamous Differentiation			Serous			Mixed Cell			Clear Cell			Mucinous		
Risk Factor	No. of Controls	No. of Cases	OR*	95% CI	No. of Cases	OR*	95% CI	No. of Cases	OR*	95% CI	No. of Cases	OR*	95% CI	No. of Cases	OR*	95% CI	No. of Cases	OR*	95% CI	No. of Cases	OR*	95% CI
Diabetes§																						
No	26,575	4,967	1.00		3,100	1.00		453	1.00		314	1.00		158	1.00		122	1.00		109	1.00	
Yes	2,077	929	1.28	1.16 to 1.42	417	1.25	1.10 to 1.43	56	1.04	0.76 to 1.41	63	1.33	0.98 to 1.81	41	1.93	1.30 to 2.85	19	1.23	0.73 to 2.09	13	1.37	0.73 to 2.55

Abbreviations: NOS, not otherwise specified; OR, odds ratio.
*Stratified by age, study, and race/ethnicity and mutually adjusted for body mass index, age at menarche, parity, oral contraceptive use, menopausal status, menopausal hormone use, and smoking status.
†Based on 23 studies with smoking data.
‡Based on 18 studies with pack-years of smoking data.
§Based on 19 studies with diabetes data.

Table 4. Association of Endometrial Cancer Risk Factors With Type I and Type II Tumors

Risk Factor	No. of Controls	Cases						*P* heterogeneity
		Type I*			Type II†			
		No. of Cases	OR‡	95% CI	No. of Cases	OR‡	95% CI	
Mean age at diagnosis, years		12,853	62.7		854	64.8		< .0001
Body mass index, kg/m^2								
< 25	18,400	4,602	1.00		330	1.00		
25 to < 30	10,986	3,718	1.45	1.37 to 1.53	253	1.16	0.98 to 1.38	
30 to < 35	4,078	2,294	2.52	2.35 to 2.69	159	1.73	1.40 to 2.12	
35 to < 40	1,255	1,247	4.45	4.05 to 4.89	65	2.15	1.60 to 2.88	
≥ 40	593	992	7.14	6.33 to 8.06	47	3.11	2.19 to 4.44	
P trend			< .0001			< .0001		< .0001
Body mass index, per 2 kg/m^2	35,312	12,853	1.20	1.19 to 1.21	854	1.12	1.09 to 1.14	< .0001
Age at menarche, years								
< 11	1,633	844	1.00		68	1.00		
11-12	7,332	2,832	0.89	0.80 to 0.99	220	0.67	0.50 to 0.90	
13-14	21,563	7,528	0.85	0.77 to 0.94	466	0.62	0.47 to 0.82	
≥ 15	4,784	1,649	0.71	0.63 to 0.80	100	0.50	0.35 to 0.70	
P trend			< .0001			.0002		.11
Parity								
0	4,593	2,451	1.00		150	1.00		
1	4,528	1,999	0.74	0.68 to 0.81	121	0.84	0.65 to 1.09	
2	10,147	3,728	0.67	0.63 to 0.72	250	0.67	0.54 to 0.83	
3	12,119	3,686	0.56	0.52 to 0.60	231	0.56	0.45 to 0.70	
≥ 4	3925	989	0.40	0.36 to 0.44	102	0.54	0.41 to 0.72	
P trend			< .0001			< .0001		.31
Oral contraceptive use								
Never	20,785	8,011	1.00		497	1.00		
Ever	14,527	4,842	0.73	0.69 to 0.77	357	0.74	0.62 to 0.89	.17
Cigarette smoking§								
Never	18,815	7,692	1.00		532	1.00		
Former	10,900	3,648	0.87	0.82 to 0.91	227	0.70	0.59 to 0.83	.11
Current	5,152	1,126	0.64	0.60 to 0.70	80	0.60	0.46 to 0.77	.79
Pack-years of smoking‖								
Never	13,693	5,646	1.00		367	1.00		
< 20	5,383	1,639	0.86	0.80 to 0.92	106	0.69	0.55 to 0.87	
≥ 20	3,594	1,109	0.71	0.65 to 0.77	69	0.68	0.52 to 0.90	
P trend			< .0001			.0006		.44
Diabetes¶								
No	26,575	8,520	1.00		472	1.00		
Yes	2,077	1,402	1.27	1.17 to 1.38	104	1.53	1.19 to 1.95	.14

Abbreviation: OR, odds ratio.
*Type I included endometrioid adenocarcinoma, adenocarcinoma not otherwise specified, and adenocarcinoma with squamous differentiation.
†Type II included serous and mixed cell adenocarcinoma.
‡Stratified by age, study and race/ethnicity and mutually adjusted for BMI, age at menarche, parity, oral contraceptive use, menopausal status, menopausal hormone use, and smoking status.
§Based on 23 studies with smoking data.
‖Based on 18 studies with pack-years of smoking data.
¶Based on 19 studies with diabetes data.

women and with lower progesterone levels in premenopausal women. Obesity is also associated with lower levels of SHBG, a protein that binds and modulates the biologic activity of estrogens. OCs contain progestins, which directly oppose the effect of estrogen on the endometrium. Smoking reduces estrogen levels by lowering age at menopause and by altering estrogen metabolism.[17-20] Hyperinsulinemia, a common feature of type 2 diabetes, can increase levels of bioactive estrogens by decreasing SHBG levels.[21,22]

Type II tumors are commonly described as estrogen independent, and thus it might be anticipated that estrogenic and antiestrogenic exposures would not be related to their risk. However, our pooled analysis identified associations between both estrogenic and antiestrogenic factors and risk of type II tumors, suggesting either that risk factor–associated estrogen-driven proliferation is also important for type II tumors or that associated mechanisms other than those involving estrogens drive these associations. For example, mechanisms associated with BMI/obesity, such as hyperinsulinemia, chronic inflammation, or oxidative activity, may be important.[23-27] Hyperinsulinemia is also a hallmark of type 2 diabetes, which we found to be associated with type II tumors independent of BMI. Cigarette smoking has been shown to increase progesterone receptor (*PGR*) and homeobox A10 (*HOXA10*) expression in human endometrium and

Table 5. Association of Endometrial Cancer Risk Factors With Endometrioid Tumors by Grade*

Risk Factor	Endometrioid Grade 1 and 2 No. of Cases	Endometrioid Grade 1 and 2 OR†	Endometrioid Grade 1 and 2 95% CI	Endometrioid Grade≥ 3 No. of Cases	Endometrioid Grade≥ 3 OR†	Endometrioid Grade≥ 3 95% CI	*P* heterogeneity	Type II No. of Cases	Type II OR†	Type II 95% CI	*P* heterogeneity‡
Body mass index, kg/m^2											
< 25	1,241	1.00		196	1.00			330	1.00		
25 to < 30	1,101	1.73	1.57 to 1.91	177	1.69	1.36 to 2.09		253	1.16	0.98 to 1.38	
30 to < 35	673	3.09	2.73 to 3.49	74	2.02	1.51 to 2.69		159	1.73	1.40 to 2.12	
35 to < 40	362	5.51	4.67 to 6.51	44	4.17	2.89 to 6.03		65	2.15	1.60 to 2.88	
≥ 40	253	7.77	6.30 to 9.58	28	4.51	2.81 to 7.26		47	3.11	2.19 to 4.44	
P trend		< .0001			< .0001		.0001		< .0001		.34
Body mass index, per 2 kg/m^2	3,630	1.23	1.21 to 1.25	519	1.16	1.12 to 1.20	< .0001	854	1.12	1.09 to 1.14	.89
Age at menarche, years											
< 11	219	1.00		40	1.00			68	1.00		
11-12	846	0.82	0.67 to 0.99	110	0.62	0.41 to 0.92		220	0.67	0.50 to 0.90	
13-14	1,853	0.77	0.64 to 0.93	276	0.67	0.46 to 0.97		466	0.62	0.47 to 0.82	
≥ 15	712	0.66	0.53 to 0.81	93	0.61	0.40 to 0.94		100	0.50	0.35 to 0.70	
P trend		< .0001			0.18		.75		.0002		.58
Parity											
0	624	1.00		87	1.00			150	1.00		
1	763	0.68	0.59 to 0.79	83	0.73	0.52 to 1.04		121	0.84	0.65 to 1.09	
2	1,026	0.65	0.57 to 0.74	136	0.69	0.52 to 0.93		250	0.67	0.54 to 0.83	
3	913	0.54	0.48 to 0.62	158	0.70	0.53 to 0.93		231	0.56	0.45 to 0.70	
≥ 4	304	0.42	0.35 to 0.50	55	0.57	0.40 to 0.83		102	0.54	0.41 to 0.72	
P trend		< .0001			.006		.06		< .0001		.39
Oral contraceptive use											
Never	2,247	1.00		329	1.00			497	1.00		
Ever	1,383	0.77	0.69 to 0.85	190	0.59	0.47 to 0.74	.11	357	0.74	0.62 to 0.89	.14
Cigarette smoking											
Never	2,494	1.00		322	1.00			532	1.00		
Former	886	0.82	0.74 to 0.91	146	0.93	0.75 to 1.16		227	0.70	0.59 to 0.83	
Current	250	0.55	0.47 to 0.64	51	0.84	0.61 to 1.15	.06	80	0.60	0.46 to 0.77	.08
Pack-years of smoking											
Never	1,822	1.00		196	1.00			367	1.00		
< 20	320	0.70	0.60 to 0.82	45	1.05	0.72 to 1.53		106	0.69	0.55 to 0.87	
≥ 20	184	0.66	0.54 to 0.81	25	0.83	0.52 to 1.32		69	0.68	0.52 to 0.90	
P trend		< .0001			0.56		.13		.0006		.47
Diabetes											
No	2,288	1.00		343	1.00			472	1.00		
Yes	465	1.46	1.28 to 1.67	72	1.26	0.94 to 1.69	.15	104	1.53	1.19 to 1.95	.30

Abbreviation: OR, odds ratio.
*Based on 14 studies with tumor grade information.
†Stratified by age, study and race/ethnicity and mutually adjusted for BMI, age at menarche, parity, oral contraceptive use, menopausal status, menopausal hormone use, and smoking status.
‡Comparing type II with endometrioid grade ≥ 3.

endometrial cells.[28] The role of other possible mechanisms needs to be considered further in endometrial cancer etiology.

The strengths of this study include a large sample size that provides greater statistical power than most previous studies have with regard to examining effects for specific histologic types; minimal, if any, publication bias as inclusion of an individual study in our analysis was not dependent on whether results had been previously published; and comparability across studies, in that we used individual-level data to standardize definitions and modeling approaches for the exposures and potential confounders, which is not possible in meta-analyses based on published estimates. Nonetheless, variation in exposure assessment in each study is a limitation of pooled analyses. The unavailability of detailed menopausal hormone data (recency and duration of use of specific hormone type) did not allow us to examine this important association and is a limitation of our analysis.

The source of histologic information did not seem to influence our results, but a certain amount of misclassification of tumor types is likely to be present. A central pathologic review that includes staining with such critical markers as p53 was not possible, and inclusion of some type I tumors within the type II group might, partly, account for the associations observed for type II tumors. Almost all of the common associations for type I and type II tumors are, however, equally strong. For our findings to be a result of misclassification of tumor type, almost all type II tumors would have to be type I tumors, and the BMI results would have been the same for the two tumor types. The BMI associations, however, were clearly statistically different, clearly supporting distinct classifications. Pathologists generally agree that the primary concern for misclassification is diagnosing low-grade endometrioid tumors at the expense of high-grade tumors[29] and that the misdiagnosis of tumors as serous is unlikely to be sufficiently common to have produced the necessary amount of misclassification to explain the results obtained here. However, it is clear that future studies need to use pathologic review and molecular diagnostics to accurately define tumor type.

In summary, this large pooled analysis provides epidemiologic evidence that in a number of respects, the risk factor profiles for type II and type I tumors are quite similar, suggesting that they share some common etiologic pathways. Thinking regarding aggressive histologic subtypes of endometrial cancer might be better served by moving away from the traditional type I versus type II distinction.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Association of Endometrial Cancer Risk Factors With Type I and Type II Tumors Among Postmenopausal Women Who Never Used Menopausal Hormones

Risk Factor	Type I*			Type II†			*P* heterogeneity
	No. of Cases	OR‡	95% CI	No. of Cases	OR‡	95% CI	
Body mass index, kg/m^2							
< 25	1,050	1.00		125	1.00		
25 to < 30	1,256	1.93	1.74 to 2.14	123	1.41	1.08 to 1.85	
30 to < 35	1,000	4.08	3.63 to 4.60	91	2.40	1.77 to 3.26	
35 to < 40	577	7.57	6.45 to 8.87	37	3.38	2.23 to 5.14	
≥ 40	460	10.64	8.80 to 12.87	26	3.93	2.37 to 6.49	
P trend		< .0001			< .0001		< .0001
Body mass index, per 2 kg/m^2	4,343	1.28	1.26 to 1.30	402	1.17	1.13 to 1.21	< .0001
Age at menarche, years							
< 11	323	1.00		29	1.00		
11-12	1,014	0.80	0.67 to 0.96	114	0.81	0.52 to 1.29	
13-14	2,342	0.79	0.66 to 0.94	205	0.69	0.45 to 1.07	
≥ 15	664	0.63	0.51 to 0.77	54	0.56	0.33 to 0.93	
P trend		< .0001			0.01		.30
Parity							
0	733	1.00		69	1.00		
1	596	0.74	0.63 to 0.86	51	0.77	0.51 to 1.15	
2	1,228	0.68	0.60 to 0.78	112	0.65	0.46 to 0.91	
3	1,334	0.57	0.50 to 0.64	110	0.53	0.38 to 0.75	
≥ 4	452	0.40	0.34 to 0.47	60	0.50	0.33 to 0.75	
P trend		< .0001			< .0001		.28
Oral contraceptive use							
Never	3,091	1.00		266	1.00		
Ever	1,252	0.70	0.63 to 0.78	136	0.69	0.52 to 0.92	.25
Cigarette smoking							
Never	2,751	1.00		267	1.00		
Former	1,144	0.82	0.75 to 0.91	89	0.58	0.45 to 0.76	
Current	342	0.60	0.52 to 0.69	39	0.55	0.38 to 0.80	.15
Pack-years of smoking							
Never	2,109	1.00		206	1.00		
< 20	499	0.81	0.70 to 0.93	45	0.55	0.38 to 0.79	
≥ 20	386	0.71	0.61 to 0.83	35	0.62	0.42 to 0.92	
P trend		< .0001			0.002		.33
Diabetes							
No	2,670	1.00		199	1.00		
Yes	637	1.44	1.27 to 1.64	56	1.63	1.16 to 2.30	.43

Abbreviation: OR, odds ratio.
*Type I included endometrioid adenocarcinoma, adenocarcinoma not otherwise specified, and adenocarcinoma with squamous differentiation.
†Type II included serous and mixed cell adenocarcinoma.
‡Stratified by age, study, and race/ethnicity and mutually adjusted for body mass index, age at menarche, parity, oral contraceptive use, and smoking status.

Table A2. Association of Endometrial Cancer Risk Factors With Type I and Type II Tumors by Aspects of Study Design

	Type I								Type II							
	Cohort		Case-Control		Path Review		Registry		Cohort		Case-Control		Path Review		Registry	
Risk Factor	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI
Body mass index, kg/m^2																
< 25	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
25 to < 30	1.32	1.23 to 1.43	1.60	1.48 to 1.73	1.53	1.40 to 1.66	1.40	1.31 to 1.50	1.14	0.86 to 1.52	1.19	0.95 to 1.48	1.08	0.84 to 1.40	1.24	0.98 to 1.57
30 to < 35	2.44	2.23 to 2.67	2.61	2.36 to 2.88	2.45	2.19 to 2.74	2.56	2.35 to 2.78	1.76	1.25 to 2.47	1.72	1.32 to 2.23	1.55	1.13 to 2.12	1.90	1.44 to 2.50
35 to < 40	4.15	3.65 to 4.72	4.84	4.20 to 5.58	4.45	3.76 to 5.26	4.46	3.98 to 5.00	2.22	1.37 to 3.61	2.15	1.48 to 3.11	2.21	1.42 to 3.45	2.12	1.43 to 3.16
≥ 40	6.66	5.66 to 7.83	7.86	6.54 to 9.44	8.45	6.69 to 10.67	6.73	5.83 to 7.75	3.08	1.69 to 5.61	3.29	2.11 to 5.12	4.20	2.44 to 7.23	2.64	1.63 to 4.30
P trend	< .0001		< .0001		< .0001		< .0001		< .0001		< .0001		< .0001		< .0001	
Body mass index, per 2 kg/m^2	1.20	1.18 to 1.21	1.22	1.20 to 1.23	1.21	1.19 to 1.23	1.20	1.19 to 1.22	1.12	1.08 to 1.17	1.12	1.08 to 1.15	1.13	1.08 to 1.17	1.11	1.08 to 1.15
Age at menarche, years																
< 11	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
11-12	0.90	0.78 to 1.04	0.88	0.75 to 1.03	0.90	0.74 to 1.09	0.88	0.77 to 1.00	0.62	0.40 to 0.97	0.72	0.48 to 1.07	0.67	0.40 to 1.11	0.67	0.46 to 0.96
13-14	0.87	0.75 to 0.99	0.83	0.71 to 0.96	0.82	0.68 to 0.97	0.86	0.76 to 0.97	0.52	0.34 to 0.79	0.71	0.49 to 1.03	0.68	0.42 to 1.10	0.58	0.41 to 0.81
≥ 15	0.72	0.61 to 0.86	0.69	0.59 to 0.82	0.68	0.56 to 0.83	0.73	0.63 to 0.84	0.52	0.31 to 0.90	0.52	0.33 to 0.81	0.45	0.26 to 0.78	0.58	0.37 to 0.90
P trend	.0002		< .0001		< .0001		.0001		0.01		.008		.008		.009	
Parity																
0	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
1	0.80	0.71 to 0.90	0.70	0.59 to 0.76	0.64	0.56 to 0.74	0.79	0.71 to 0.88	1.06	0.69 to 1.61	0.72	0.52 to 1.01	0.67	0.45 to 0.98	0.98	0.69 to 1.40
2	0.77	0.70 to 0.85	0.57	0.51 to 0.63	0.56	0.49 to 0.63	0.73	0.67 to 0.80	0.84	0.59 to 1.21	0.57	0.43 to 0.76	0.51	0.37 to 0.72	0.80	0.60 to 1.07
3	0.63	0.57 to 0.69	0.48	0.43 to 0.54	0.46	0.40 to 0.52	0.61	0.56 to 0.67	0.65	0.46 to 0.93	0.50	0.38 to 0.67	0.46	0.32 to 0.65	0.64	0.48 to 0.85
≥ 4	0.47	0.41 to 0.53	0.32	0.28 to 0.38	0.33	0.28 to 0.39	0.44	0.39 to 0.49	0.58	0.36 to 0.92	0.51	0.36 to 0.74	0.54	0.35 to 0.82	0.51	0.34 to 0.75
P trend	< .0001		< .0001		< .0001		< .0001		.001		< .0001		.0002		< .0001	
Oral contraceptive use																
Never	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Ever	0.76	0.71 to 0.82	0.68	0.62 to 0.73	0.68	0.62 to 0.74	0.75	0.70 to 0.81	0.81	0.62 to 1.07	0.68	0.54 to 0.86	0.59	0.44 to 0.79	0.86	0.68 to 1.08
Cigarette smoking†																
Never	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Former	0.88	0.83 to 0.95	0.84	0.78 to 0.91	0.84	0.77 to 0.92	0.88	0.82 to 0.94	0.87	0.67 to 1.12	0.62	0.49 to 0.77	0.60	0.47 to 0.79	0.79	0.63 to 0.98
Current	0.68	0.61 to 0.76	0.61	0.54 to 0.68	0.60	0.52 to 0.68	0.68	0.61 to 0.75	0.73	0.49 to 1.11	0.52	0.38 to 0.72	0.52	0.36 to 0.75	0.66	0.46 to 0.93
Diabetes‡																
No	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.21	1.06 to 1.38	1.31	1.18 to 1.47	1.34	1.18 to 1.52	1.24	1.10 to 1.39	1.15	0.73 to 1.82	1.76	1.31 to 2.37	1.53	1.05 to 2.24	1.55	1.13 to 2.14

Abbreviation: OR, odds ratio.
*Stratified by age, study, and race/ethnicity and mutually adjusted for body mass index, age at menarche, parity, oral contraceptive use, and smoking status.
†Based on 23 studies with smoking data.
‡Based on 19 studies with diabetes data.