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Risk factors for endometrial cancer in Black women

Todd R. Sponholtz[1], **Julie R. Palmer**[2], **Lynn Rosenberg**[2], **Chu Chen**[3], **Yu Chen**[4], **Megan A. Clarke**[5], **Tess Clendenen**[4], **Mengmeng Du**[6], **Lisa Johnson**[3], **Linda M. Liao**[5], **Kara A. Michels**[5], **Kelli O'Connell**[6], **Sara H. Olson**[6], **Stacey Petruzella**[6], **Timothy R. Rebbeck**[7,8], **Veronica Wendy Setiawan**[9], **Britton Trabert**[5,10], **Noel S. Weiss**[11], **Nicholas Wentzensen**[5], **Lynne Wilkens**[12], **Lauren A. Wise**[13]

[1]Section of Preventive Medicine and Epidemiology, Boston University School of Medicine, Boston, MA

[2]Slone Epidemiology Center at Boston University, Boston, MA

[3]Fred Hutchinson Cancer Research Center, Seattle, WA

[4]Division of Epidemiology, Department of Population Health, New York University Grossman School of Medicine, New York, NY, USA

[5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

[6]Memorial Sloan Kettering Cancer Center, New York, NY

[7]Division of Population Science, Dana-Farber Cancer Institute, Boston, MA

[8]Harvard TH Chan School of Public Health, Boston, MA

[9]Keck School of Medicine, University of Southern California, Los Angeles, CA

[10]Department of Obstetrics and Gynecology, University of Utah, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

[11]University of Washington, Seattle, WA

[12]University of Hawaii Cancer Center, Honolulu, HI

[13]Department of Epidemiology, Boston University School of Public Health, Boston, MA

Abstract

Purpose: The incidence of endometrial cancer (EC) has been increasing faster among Black women than among other racial/ethnic groups in the United States. Although the mortality rate is nearly twice as high among Black than White women, there is a paucity of literature on risk

Corresponding Author: Todd R. Sponholtz, spnhltz@bu.edu.

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factors for EC among Black women, particularly regarding menopausal hormone use and severe obesity.

Methods: We pooled questionnaire data on 811 EC cases and 3,124 controls from eight studies with data on self-identified Black women (4 case-control and 4 cohort studies). We analyzed cohort studies as nested case-control studies with up to 4 controls selected per case. We used logistic regression to estimate multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: We observed a positive association between BMI and EC incidence (P_{trend} <0.0001) The OR comparing BMI ≥40 vs. <25 kg/m^2 was 3.92 (95% CI 2.91, 5.27). Abdominal obesity among those with BMI <30 kg/m^2 was not appreciably associated with EC risk (OR=1.21, 95% CI 0.74, 1.99). Associations of reproductive history with EC were similar to those observed in studies of White women. Long-term use of estrogen-only menopausal hormones was associated with an increased risk of EC (≥5 years vs. never use: OR=2.08, 95% CI: 1.06, 4.06).

Conclusions: Our results suggest that the associations of established risk factors with EC are similar between Black and White women. Other explanations, such as differences in the prevalence of known risk factors or previously-unidentified risk factors likely underlie the recent increases in EC incidence among Black women.

Keywords

Black Women; Endometrial Cancer; Obesity; Reproductive History; Exogenous Hormones

Introduction

Endometrial cancer (EC) is the fourth most common cancer among women in the United States (US); an estimated 66,500 new cases and 12,900 deaths were expected in the US in 2021 [1]. The risk of EC varies by self-identified race; Black women have higher risk of rarer, more aggressive subtypes and higher EC mortality than White women [2, 3]. In addition, while EC incidence increased by 1.1% annually from 2003–2015 among US women overall, a higher annual percentage increase has been observed among Black women compared with White women (2.1% annual change from 2000–2015 vs. 0.2%) [4]. This increase was primarily driven by an increase in the rate of the more aggressive non-endometrioid subtypes, which were increasing among all US women, but constituted a greater proportion of incident EC cases among Black women than among other races [4]. The reasons for these differences are unclear. The few studies of EC risk factors among Black women have found similar associations of established EC risk factors as in White women, including obesity, reproductive history, and use of exogenous hormones [5–8]. A previous pooled analysis that directly compared associations among Black (516 cases) and White women (5,693 cases), based on data from 11 studies (including 5 contributing to the current analysis), reported similar associations in the two populations [5], but did not present data on menopausal hormone use. In addition, the prior pooled analysis only investigated the association of obesity (BMI ≥ 30 kg/m^2) with EC risk, while some other studies have indicated that risk continues to increase at levels of BMI exceeding 35 kg/m^2 [9–11].

The relative balance of exposure to estrogens and progestogens over the lifecourse is thought to be a key determinant of EC risk [12]. Estrogens stimulate cellular proliferation within the endometrium, while progestogens inhibit the effects of estrogen [12]. Thus, many of the identified risk factors for EC, including obesity, reproductive history, and exogenous hormone use are thought to act, at least in part, by influencing estrogen and/or progestogen levels [12, 13]. Both obesity [14] and the use of estrogen-only menopausal hormones [15] are among the most strongly associated risk factors for EC. The association between estrogen-only menopausal hormones use and EC incidence among Black women has been little studied. Obesity is more prevalent among Black women compared with White women, and the prevalence of severe obesity (BMI ≥40 kg/m^2) is nearly 80% higher among Black women [16]. The greater increase in obesity prevalence in the decades prior to the observed increase in EC incidence has been suggested as a possible cause of the increase in incidence among all women, although it is not likely to be the sole explanation [17].

The aims of this analysis were to expand research into the etiology of EC in Black women by assembling the largest case group to date and evaluating associations with menopausal hormone use and obesity ≥35 kg/m^2, as well as reproductive history and use of oral contraceptives. To this end, we pooled data from eight US studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2).

Methods

Data Collection

The E2C2 is a collaboration of 37 epidemiologic studies worldwide with the goal of investigating the etiology of endometrial cancer (EC) by pooling resources among participating studies. The current analysis is based on data from eight studies (four cohort, four case-control) that included at least 10 Black women who developed any histologic type of incident invasive EC [18–26]. Details of the included studies are shown in Table 1. Data collection methods varied by study. Data from cohort studies were self-reported via questionnaires specific to each study. Participants from the included case-control studies provided information via interview with study personnel. All participants self-identified as Black women.

For the included cohort studies, up to four women without cancer were matched to each woman who developed cancer on year of birth and year of diagnosis; women without cancer were required to have an intact uterus during the year of diagnosis of her matched case. Covariate data from each study, except the Case-Control Surveillance Study (CCS), were sent to a common data coordinating center at Memorial Sloan Kettering Cancer Center (MSK). Briefly, we harmonized a core set of 55 clinical and epidemiologic variables across all current studies in E2C2. Within each study, a basic set of clinical data (stage, grade, histology) were collected from medical records, pathology reports, and/or linkages to SEER or state cancer registries. Epidemiologic data were collected within each study by self-report (in-person interview or structured questionnaires). Each study provided sociodemographic variables (e.g., age, race/ethnicity, education), comorbid conditions (e.g., obesity, hypertension, diabetes), and other known/potential EC risk factors (e.g., body mass index, menstrual and reproductive history, postmenopausal hormone use, oral contraceptive

use, smoking history). Clinical and epidemiologic data from participating studies were transferred securely to the MSK E2C2 data coordinating center where we carried out a systematic multi-step data harmonization procedure to QC variables, identify common data elements across studies, and uniformly recode each variable in accordance with the core data dictionary. Data from studies agreeing to participate in the current analysis were de-identified, pooled, and delivered to Boston University, where CCS data were also cleaned and harmonized, and then combined with the E2C2 data for analysis. Informed consent was obtained from all participants in each of the studies, and each study was approved by its institutional review board.

Statistical Methods

We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. Exposures of interest included adult BMI (<25, 25–29, 30–34, 35–39, ≥40 kg/m^2), self-reported BMI in late adolescence or early adulthood (i.e. 18 or 20 years, depending on the study; <25, 25–29, ≥30 kg/m^2), BMI at ages 18–20 years cross-classified with adult obesity, waist circumference (quintiles [<73.7, 73.7–82.3, 82.4–89.4, 89.5–96.5, >96.5 cm), general obesity cross-classified with abdominal obesity (general obesity=BMI ≥30 kg/m^2, abdominal obesity= waist circumference ≥88 cm [27]), diabetes, age at menarche (<11, 11–12, 13–14, ≥15 years), parity (nulliparous, parous), number of births (0, 1, 2, 3, 4, ≥5), ages at first and last birth (age at first birth: <20, 20–24, 25–29, ≥30 years; all studies included; age at last birth <25, 25–29, 30–34]., history of tubal ligation, oral contraceptive use (0, 1–4, ≥5 years duration) and use of estrogen-only menopausal hormones (0, 1–4, ≥5 years duration). Exposures available for each included study are listed in Table 1. Analyses of number of births and ages at first and last birth were restricted to parous women; analyses of estrogen-only menopausal hormones were restricted to postmenopausal women. For each exposure, we estimated ORs from two models: a minimally-adjusted model that included terms indicating the study from which the participants were drawn, age, and menopausal status (premenopausal, postmenopausal); and a multivariable model that additionally included known and suspected risk factors for EC that were common to all eight studies, including adult BMI, (<25, 25–29, 30–34, 35–39, ≥40 kg/m^2), age at menarche (<10, 11, 12, 13, 14, ≥15 years), parity (0, 1, 2, 3, ≥4 births), ever use of OCs (yes, no), use of any menopausal hormones (yes, no), and smoking status (never, former, current). We modeled cross-product terms between exposure variables to perform Wald tests for multiplicative interaction were performed using a Wald test by modelling both exposures along with an interaction term. We conducted all analyses using SAS version 9.4 (Cary, North Carolina).

Results

We observed a positive monotonic association between adult BMI and EC risk in Black women (Table 2). In multivariable models, the ORs for BMI 25–29, 30–34, 35–39 and ≥40 kg/m^2 vs. <25 kg/m^2 were 1.31 (95% CI=1.02, 1.67), 1.94 (95% CI=1.50, 2.51), 2.35 (95% CI=1.74, 3.17), and 3.92 (95% CI=2.91, 5.27), respectively (p trend <0.0001). BMI at age 18 or 20 years (depending on study) was not associated with endometrial cancer risk after adjustment for adult BMI. When we cross-classified BMI at age 18–20 years with adult

BMI, women with BMI ≥25 kg/m^2 at both life stages had a higher EC risk than women with at ages 18–20 years or at adult BMI ≥25 kg/m^2 (OR=2.81, 95% CI=2.01, 3.92 and OR=1.86, 95% CI=1.42, 2.44, respectively; reference= BMI in both life stages <25 kg/m^2). Greater waist circumference was not associated with increased risk in models adjusted for BMI or when we cross-classified abdominal obesity (waist circumference >88 cm) with general obesity (BMI ≥30 kg/m^2) (OR for abdominal obesity in the absence of general obesity=1.21, 95% CI=0.74, 1.99). The BMI-adjusted OR for diabetes was 1.19 (95% CI 0.95–1.49).

EC risk was lower among women with ages at menarche ≥11 years (Table 3]. compared with those with age at menarche <11 years. However, there was no evidence of a monotonic association. The OR for nulliparous relative to parous women was 1.38 (95% CI=1.11, 1.72). Among parous women, the OR comparing age at first birth ≥30 vs. 18–20 years was 0.49 (95% CI=0.32, 0.74].. Neither age at last birth nor history of tubal ligation was materially associated with EC risk. Long-term use of OCs was strongly related to decreased EC risk; the OR for ≥5 years of OC use was 0.44 (95% CI=0.27, 0.70). Use of estrogen-only menopausal hormones for ≥5 years was associated with an increase in EC risk compared with never use (OR=2.08, 95% CI=1.06, 4.08]..

Of the 811 cases included in the study, we had histologic subtype data for 495 cases. The classification of study cases in shown in Supplemental Table 1. The distribution of risk factors of interest, along with the multivariable-adjusted associations of those risk factors with EC, are shown in Tables 2 and 3.

Discussion

In this pooled analysis of 811 Black women with EC from 8 US studies, associations of previously identified risk factors with EC risk were similar to those observed in prior studies of primarily White populations [5, 14, 15, 28–30]. Our results suggested that the positive association with adult obesity becomes stronger with increasing levels of obesity, with nearly a four-fold increase in risk comparing BMIs ≥40 kg/m^2 with 18.5–24 kg/m^2. In addition, we observed that general obesity (measured by BMI) was more strongly associated with EC risk than abdominal obesity (measured by waist circumference). Long-term use of estrogen-only menopausal hormones was associated with an increased risk of EC.

EC is believed to develop largely as the result of the accumulation of mutations in endometrial cells after numerous repeated cycles of replication over the life course [12]. In the endometrium, exposure to estrogens is the principle driver of the proliferation of endometrial cells, with progestogens counter the effect of estrogens [12]. Therefore, the the relative balance of estrogens and progestogens to which the endometrium is exposed over time is thought to determine EC risk [12]. In support of this idea, established risk factors for EC such as obesity, reproductive history, and use of exogenous hormones influence levels of estrogens and/or progestagens [12, 13].

A prior meta-analysis of 28 studies including over 22,000 EC cases from the US, Europe, and Asia reported approximately 25%, 100%, 300%, and 900% increases in risk associated with a BMI of 25, 30, 35, and 40 kg/m^2, respectively, compared with a BMI of 20 kg/m^2

[14]. These estimates were somewhat stronger than those observed in the current analysis. This may be due, in part, to the different reference categories used. Differences in histologic type may also influence results, as there is evidence that the BMI association is weaker with the less common, more aggressive EC subtypes, which are more common in Black women [2, 3, 31]. We lacked sufficient data on histologic subtypes to meaningfully analyze subtype-specific associations.

In prior investigations [32–35], BMI in late adolescence and early adulthood was positively associated with EC incidence; in our analyses, this association was greatly attenuated by adjustment for adult BMI. When we cross-classified BMI at ages 18–20 years with adult BMI, EC risk was higher among women whose BMI at ages 18–20 and in adulthood were in the overweight/obese category, compared with women whose adult BMI, but not BMI at ages 18–20, was categorized as overweight/obese. This is consistent with a positive association between duration of overweight/obesity and EC risk. Studies have also reported a positive association between waist circumference and EC risk [32, 36, 37] We observed a substantial attenuation of the waist circumference association with further control for BMI, which was not included as a covariate in two of the three studies reporting an association [36, 37]. Further, in cross-classified analyses, general obesity, but not abdominal obesity, was associated with higher EC risk. Adipose tissue expresses aromatase, an enzyme which converts androgens to estrogen and is thought be one mechanism by which adiposity increases postmenopausal EC risk [13]. Although the visceral adipose tissue characteristic of abdominal adiposity is strongly tied to cardiovascular risk [38], limited evidence suggests that it is less efficient in producing estrogens among postmenopausal women [39] and represents a relatively small fraction of total adipose tissue [40]. This may explain why BMI-defined obesity, which may serve as a better proxy for total adiposity than waist circumference [41] was more strongly associated with EC risk. Since age-adjusted prevalence of abdominal obesity is higher than that for BMI-defined obesity for US women of all racial categories [42] it is important to understand the implications of abdominal obesity for EC risk.

Diabetes may increase EC risk through increased proliferation of endometrial cells as well as associated increases in bioavailable estrogen and IGF-I [13]. A recent meta-analysis of 13 studies reported a BMI-adjusted 62% greater risk of EC in predominantly White women with type 2 diabetes [43]. Similarly, a prior investigation among Black women reported a 40% increase in EC risk among women with diabetes compared with women without diabetes [5]. Our results are consistent with a moderate positive association between diabetes and EC after adjustment for BMI. Residual confounding by BMI may partially explain the stronger associations reported in prior studies. Although most of the included studies did not specifically ask participants to distinguish type 2 diabetes from type 1, estimates of the prevalence of type 2 diabetes indicate it is roughly 30 times that of type 1 diabetes [44]. We therefore expect any resulting misclassification to have little influence on our results.

Most previous investigations of the association between age at menarche and EC have reported inverse monotonic associations [5, 6, 28]. We observed higher risk among women with early menarche (<11 years), but associations were of similar magnitude for all categories of menarcheal age above 10 years. EC risk was higher among nulliparous women,

as has been observed previously [29]. We did not find evidence of an inverse trend with increasing births, which has been observed by some, but not all, studies [29]. Late age at first birth was associated with lower EC risk, as has been reported in several prior studies [45–49] but not in others [7., 50–55]. In a prior E2C2 analysis of Black women (n=516 women with EC) [5], the association between age at first birth ≥30 versus <20 years was weaker than that observed in the present study.

In keeping with previous studies, our results suggest an inverse association between OC use for ≥5 years and EC risk [30]. We observed a doubling of EC risk with ≥5 years of estrogen-only menopausal hormones use for ≥5 years compared with never use. To our knowledge, this risk factor has not previously been examined among Black women. Although some of the eight studies on which our analyses are based provided data on use of estrogen plus progestin menopausal hormones, we lacked detailed data on the monthly duration of progestin use. Since the association of estrogen plus progestin menopausal hormoens with EC varies considerably according to the specific progestin regimen [15], we were unable to meaningfully analyze this exposure.

The present study includes the largest number of Black women with EC to date (811 vs. 516 in Cote et al. [5]). This allowed us to observe that EC risk continues to increase with increasing BMI in ranges above 40 kg/m^2. Seventy-five percent of cases were from prospective cohort studies, which are less prone to differential exposure misclassification. A limitation was the lack of adequate numbers of cases to examine histologic subtypes of EC, which may differ in their associations with known risk factors [36, 56]. In addition, adjustment for the different designs employed in the included studies via inclusion of study as a covariate may have been inadequate, and low numbers of participants in some studies precluded a meta-analysis. Despite the relatively large number of included cases, we had limited power to evaluate possible interactions between selected risk factors.

Our results are consistent with prior reports among both Black and White women regarding the associations between established EC risk factors and EC risk. Overall, our results indicate that associations between established EC risk factors and cancer risk among Black women do not differ from those previously observed in studies which primarily included White women. We also observed that higher BMIs, beyond class 2 obesity, were strongly associated with risk of EC in Black women. Overall obesity prevalence increased more rapidly among Black women, compared to White women, between 1988 and 2004 [58], although differences in more recent trends are less clear [59]. This finding may explain, in part, the rising incidence of EC observed in this population [4]. However, obesity and other estrogenic risk factors, are most strongly associated with endometrioid ECs [13] and a recent study demonstrated that the disproportionately increasing incidence of this disease among Black women is largely attributable to non-endometrioid cancers [4]. As such, there may be other yet-to-be-identified risk factors for these aggressive subtypes of EC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability:

Study participants did not give informed consent to share their data with external parties; however, the authors would be happy to share their analytic code upon request.

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Table 1.

Characteristics of included studies

Study	Mean Age at Diagnosis (years)	Cases	Controls	Exposure Data Available
Cohort Studies				
Black Women's Health Study (BWHS)	54.6	300	1200	Adult BMI, BMI at 18 to 20 years, waist circumference, diabetes, age at menarche, parity, number of births, age at first birth, age at last birth, oral contraceptive use, use of estrogen-only menopausal hormones
Multiethnic Cohort Study (MEC)	68.8	190	749	Adult BMI, BMI at 18 to 20 years, diabetes, age at menarche, parity, number of births, age at first birth, oral contraceptive use, use of estrogen-only menopausal hormones
New York University Women's Health Study (NYUWHS)	70.0	23	92	Adult BMI, BMI at 18 to 20 years, diabetes, age at menarche, parity, number of births, age at first birth, history of tubal ligation
NIH-AARP Diet and Health Study (AARP)	66.8	86	330	Adult BMI, BMI at 18 to 20 years, waist circumference, diabetes, age at menarche, parity, number of births, age at first birth, use of estrogen-only menopausal hormones
Case-control studies				
Case-Control Surveillance Study (CCS)	58.0	92	312	Adult BMI, BMI at 18 to 20 years, diabetes, age at menarche, parity, number of births, age at first birth, history of tubal ligation, oral contraceptive use, use of estrogen-only menopausal hormones
Estrogen, Diet, Genetics and Endometrial Cancer Study (EDGE)	61.2	39	23	Adult BMI, BMI at 18 to 20 years, waist circumference, diabetes, age at menarche, parity, number of births, age at first birth, age at last birth, history of tubal ligation, oral contraceptive use, use of estrogen-only menopausal hormones
Fred Hutchinson Cancer Research Center (FHCRC)	61.3	14	21	Adult BMI, BMI at 18 to 20 years, diabetes, age at menarche, parity, number of births, age at first birth, age at last birth, oral contraceptive use
Women's Insight and Shared Experience Study (WISE)	60.9	67	397	Adult BMI, age at menarche, parity, number of births, age at first birth, age at last birth, oral contraceptive use, use of estrogen-only menopausal hormones

Table 2.

Associations of anthropometric, metabolic, and lifestyle factors with endometrial cancer

	Cases	Controls	OR[1]	95% CI	OR[2]	95% CI
BMI, kg/m^2						
<25	126	852	1.00	Reference		
25–29	219	1061	1.31	1.02, 1.67		
30–34	191	617	1.94	1.50, 2.51		
35–39	111	295	2.35	1.74, 3.17		
≥40	144	225	3.92	2.91, 5.27		
Missing[3]	20	74				
P_{trend}				<0.0001		
Early adulthood BMI, kg/m^2 [3,4]						
<18.5	85	452			0.81	0.62, 1.06
18.5–24	405	1562			1.00	Reference
25–29	80	204			1.00	0.73, 1.35
≥30	45	84			1.18	0.78, 1.79
Missing[3]	129	425				
P_{trend}						0.19
Cross-classified early adulthood BMI × recent BMI, kg/m^2 [3,4,5]						
<25, <25	77	517	1.00	Reference		
<25, ≥25	412	1485	1.86	1.42, 2.44		
≥25, <25	4	21	1.33	0.44, 4.06		
≥25, ≥25[6]	120	261	2.81	2.01, 3.92		
Missing[3]	2	18				
Waist circumference, cm[7]						
<73.7	30	201			1.00	Reference
73.7–82.3	52	268			1.13	0.68, 1.86
82.4–89.4	50	174			1.30	0.78, 2.19
89.5–96.5	65	175			1.51	0.91, 2.52
>96.5	85	165			1.33	0.79, 2.22
Missing[3]	143	570				
P_{trend}						0.25
Cross-classified obesity with abdominal obesity[7]						
BMI<30 kg/m^2, WC≤88 cm	83	469	1.00	Reference		
BMI≥30 kg/m^2, WC≤88 cm	37	120	1.89	1.20, 2.96		
BMI<30 kg/m^2, WC>88 cm	29	119	1.21	0.74, 1.99		
BMI≥30 kg/m^2, WC>88 cm[8]	130	259	2.50	1.80, 3.49		
Missing[3]						

	Cases	Controls	OR[1]	95% CI	OR[2]	95% CI
Diabetes[9]						
No	587	2302			1.00	Reference
Yes	156	422			1.19	0.95, 1.49
Missing[3]	1	3				

BMI=body mass index, WC=waist circumference.

[1]Adjusted for age, study, menopausal status, ever use of menopausal hormones, age at menarche, parity, ever use of oral contraceptives, and smoking status.

[2]Adjusted for age, study, menopausal status, body mass index, ever use of menopausal hormones, age at menarche, parity, ever use of oral contraceptives, and smoking status.

[3]Number missing within studies included in the analysis

[4]Analysis of participants from AARP, BWHS, CCS, EDGE, FHCRC, MEC, and NYUWHS studies

[5]Correlation coefficient between BMI at age 18–20 and adult BMI=0.47

[6]$P_{interaction}=0.78$

[7]Analysis of participants from AARP, BWHS, and EDGE studies

[8]$P_{interaction}=0.73$

[9]Analysis of participants from AARP, BWHS, CCS, EDGE, FHCRC, MEC, and NYUWHS studies

Table 3.

Associations of reproductive history and exogenous hormone use with endometrial cancer

	Cases	Controls	OR[1]	95% CI	OR[2]	95% CI
Age at menarche, years						
<11	124	342	1.00	Reference	1.00	Reference
11–12	308	1184	0.67	0.51, 0.88	0.69	0.52, 0.92
13–14	271	1142	0.62	0.47, 0.80	0.68	0.52, 0.90
≥15	105	451	0.59	0.43, 0.81	0.66	0.38, 1.08
Missing[3]	3	5				
P_{trend}						0.03
Parity						
Parous	662	2685	1.00	Reference	1.00	Reference
Nulliparous	143	419	1.34	1.08, 1.66	1.38	1.11, 1.72
Missing[3]	6	20				
Number of births[4]						
1	146	598	1.00	Reference	1.00	Reference
2	154	743	0.86	0.67, 1.11	0.82	0.63, 1.07
3	152	543	1.14	0.88, 1.48	1.04	0.78, 1.37
4	103	343	1.23	0.92, 1.66	1.04	0.76, 1.43
≥5	107	458	0.93	0.69, 1.25	0.75	0.55, 1.04
P_{trend}						0.23
Age at first birth, years[4]						
<20	273	1082	1.00	Reference	1.00	Reference
20–24	234	875	1.08	0.89, 1.32	1.13	0.91, 1.40
25–29	113	418	1.08	0.84, 1.40	1.14	0.86, 1.50
≥30	34	283	0.48	0.33, 1.40	0.49	0.32, 0.74
Missing[3]	8	27				
P_{trend}						0.03
Age at last birth, years[4,5]						
<25	71	260	1.00	Reference	1.00	Reference
25–29	109	362	1.21	0.85, 1.71	1.34	0.91, 1.97
30–34	83	391	0.80	0.56, 1.15	1.12	0.73, 1.70
≥35	59	360	0.63	0.42, 0.92	0.87	0.55, 1.38
Missing[3]	3	15				
P_{trend}						0.40
Tubal ligation[6]						
No	89	203	1.00	Reference	1.00	Reference
Yes	31	101	0.68	0.41, 1.12	1.00	0.56, 1.77
Missing[3]	33	123				

	Cases	Controls	OR[1]	95% CI	OR[2]	95% CI
OC duration, years[7]						
Never use	207	685	1.00	Reference	1.00	Reference
<1	109	408	0.88	0.60, 1.29	0.86	0.58, 1.28
1–4	146	530	0.87	0.61, 1.23	0.85	0.59, 1.23
≥5	101	679	0.42	0.26, 0.67	0.44	0.27, 0.70
Missing[3]	139	400				
P_{trend}						0.04
Estrogen-only menopausal hormone use[8, 9, 10]						
Never	484	1831	1.00	Reference	1.00	Reference
Ever	63	275	0.90	0.67, 1.21	1.00	0.72, 1.39
Missing[3]	20	146				
Estrogen-only menopausal hormone duration of use, years[8, 9, 10]						
0	484	1831	1.00	Reference	1.00	Reference
1–4	48	252	0.76	0.55, 1.06	0.85	0.60, 1.22
≥5	15	31	1.77	0.93, 3.35	2.08	1.06, 4.06
Missing[3]	20	146				
P_{trend}						0.03

OC=oral contraceptives.

[1]Adjusted for age, study, menopausal status,

[2]Adjusted for age, study, menopausal status, body mass index, age at menarche, parity, ever use of oral contraceptives, and smoking status

[3]Number missing within studies included in the analysis

[4]Analysis restricted to parous women

[5]Analysis of participants from studies BWHS, EDGE, FHCRC, WISE studies

[6]Analysis of participants from CCS, EDGE, NYUWHS studies

[7]Analysis of participants from BWHS, CCS, EDGE, FHCRC, MEC, WISE studies

[8]Analysis restricted to postmenopausal women

[9]Analysis of participants from AARP, BWHS, CCS, EDGE, MEC, and WISE studies