Published in final edited form as:

Cancer Causes Control. 2017 June ; 28(6): 579–588. doi:10.1007/s10552-017-0880-4.

Reproductive Factors and Incidence of Endometrial Cancer in U.S. Black Women

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Abstract

Purpose—Previous studies have shown that reproductive history is a strong determinant of endometrial cancer risk among white women. Less is known about how reproductive history affects endometrial cancer risk among black women, whose incidence and mortality differ from white women. We investigated the associations of age at menarche, parity, timing of births, and menopausal age with endometrial cancer in the Black Women’s Health Study, a prospective cohort study.

Methods—Every 2 years from 1995 to 2013, 47,555 participants with intact uteri at baseline in 1995 completed questionnaires on reproductive and medical history, and lifestyle factors. Self-reported cases of endometrial cancer were confirmed by medical record, cancer registry, or death certificate when available. Cox proportional hazards regression was used to estimate multivariable incidence rate ratios (IRR) and 95% confidence intervals (CI).

Results—During 689,501 person-years of follow-up, we identified 300 incident cases of endometrial cancer. The strongest associations with endometrial cancer were found for early age at menarche (<11 vs. 12–13 years: IRR: 1.82, 95% CI: 1.31, 2.52), and later age at first birth (≥30 vs. <20 years: IRR: 0.26, 95% CI: 0.13, 0.50). Parous women were less likely than nulliparous women

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants in the study.

to develop endometrial cancer (IRR: 0.77, 95% CI: 0.57, 1.05), but there was little evidence of a dose-response relation for number of births.

Conclusion—Associations between reproductive factors and endometrial cancer among black women were generally consistent with those in studies of white women.

Keywords

Black women; Endometrial cancer; Reproduction; Prospective studies

Introduction

Given the central role of estrogen and progesterone in the etiology of endometrial cancer [1], one would expect reproductive history to substantially influence risk of the cancer.

Reproductive factors consistently associated with increased risk of endometrial cancer include early age at menarche [2–6], late age at menopause [2–8], greater number of lifetime menstrual cycles [5,6,9], nulliparity [2–7,9–14], early age at last birth [3,4,12,14,15], and a greater number of years since last birth [2,13,14]. Associations between endometrial cancer and factors such as age at first birth [2–6,9,10,12,14–16], breastfeeding [2,6,9,10], and history of infertility [5,10,17–19] have been inconsistent across studies.

The majority of studies of reproductive history and endometrial cancer have been conducted among white women [20]. The generalizability of these findings to other racial and ethnic groups is unclear. The prevalence of several reproductive factors differs appreciably between black and white women: e.g., parity and early births are more common [21,22], and breast feeding is less common [23,24], among black women. We therefore evaluated the association between reproductive factors and risk of endometrial cancer in a U.S. prospective cohort study of black women.

Methods

Data Source

The Black Women's Health Study (BWHS) is a cohort of 59,000 self-identified U.S. black women.[25] In 1995, women aged 21–69 were recruited from the subscription list of *Essence* magazine, black professional organizations, and friends and relatives of study participants. Data on demographic factors, reproductive history, smoking, alcohol consumption, anthropometric measurements, health history, and medication use were collected via postal questionnaire at baseline and updated on biennial follow-up questionnaires. Follow-up is complete for 87% of potential person-years through 2013. The study was approved by the institutional review board of Boston University Medical Center, Boston, Massachusetts and all participants provided informed consent.

At baseline, we excluded women with a history of uterine cancer (n=258), cervical cancer (n=82), or hysterectomy (n=10,659) or who did not return at least 1 questionnaire after baseline (n=447). We followed the remaining 47,555 women for incident endometrial cancer from 1995 through 2013.

Outcome

New diagnoses of “uterine cancer” were reported on follow-up questionnaires from 1997 to 2013. Participants were not asked specifically about uterine cancer but were asked to report any “other serious illness” in 1995 and 2011. Potential cases were also identified through records from state cancer registries in 24 states where 95% of participants lived and death certificate data obtained from the National Death Index (NDI). There were 354 potential cases from all sources. When we contacted women for permission to release their medical records, eighteen reported that they had a condition other than uterine cancer. Of the remaining 336 potential cases, we obtained medical records, cancer registry data, and/or death certificate data for 249 (74%). Of these, 231 (93%) were confirmed as either endometrial cancer (n=213) or uterine sarcoma (n=18); 18 (7%) were disconfirmed. Because the confirmation rate was high, we accepted the remaining unverified cases as cases of incident endometrial cancer. Thus, after the exclusion of uterine sarcomas, there were a total of 300 cases of endometrial cancer (213 confirmed and 87 unverified) available for analysis. Among the 182 cancers for which we had data to classify subtypes, 131 were classified as type I (ICD-O codes 8010, 8020, 8140, 8210, 8255, 8260, 8262, 8263, 8380, 8382, 8383, 8440, 8480, 8481, 8570), 30 as type II (ICD-O codes 8041, 8050, 8070, 8071, 8072, 8310, 8323, 8441, 8460, 8461, 8560), and 21 were type III (ICD-O codes 8950, 8951, 8980).

Exposures

Women reported their age at menarche on the baseline questionnaire in 1995. Data on age at first birth, parity, gynecologic surgeries (hysterectomy, bilateral oophorectomy, unilateral oophorectomy), menopausal status, type of menopause (natural, surgical, and medical), and age at menopause were collected at baseline and updated on subsequent follow-up questionnaires. Women who reported cessation of menstrual cycles for 12 months, reported bilateral oophorectomy, or who were 57 years of age and whose menopausal status was obscured due to hormone use were considered postmenopausal. Women who did not report cessation of menstrual cycles for 12 months or bilateral oophorectomy, or who were <43 years of age and whose menopausal status was obscured by hormone use, were considered premenopausal. Women aged 43–56 years whose status was obscured due to hormone use were classified as unknown menopausal status. Participants reported the total duration of lactation from all births at baseline and updated duration of lactation on the 1997–2005 and 2011 questionnaires. Infertility was reported in 1995, 2007, and 2011 as “ever tried to become pregnant for more than one year without success,” along with the participant’s age at that time. In 1999 and 2001, women reported whether they had ever been diagnosed with polycystic ovary syndrome (PCOS) and year of first diagnosis. In 2003, women reported the usual length of their menstrual cycles. The lifetime number of menstrual cycles for premenopausal women was calculated as $[\text{current age} - \text{age at menarche}] * [365.25 / \text{usual length of menstrual cycle}] - [\text{parity} * 9] - [\text{total months of breastfeeding}] - [\text{total duration of oral contraceptive use}]$. For the 47% of women for whom menstrual cycle length was missing, we assumed a cycle length of 28 days. For postmenopausal women, age at menopause was substituted for current age.

Covariates

Participants reported their height and weight (with which we computed body mass index [BMI], kg/m²) and diagnosis of diabetes, diagnosis of uterine leiomyomata, oral contraceptive use, female menopausal hormone use, alcohol use, smoking status, and state of residence at baseline and on the follow-up questionnaires. Weight at age 18 was assessed at baseline and used to calculate BMI at age 18. Data on vigorous exercise (hours/week) was ascertained on all questionnaires with the exception of 2003 and 2005. Marital status was reported in 1995, 1997, 1999 and 2003. Participants reported their education level at baseline, household income in 2003, and parental and partner/spouse education in 2009.

Data Analysis

The analysis included 300 incident cases of endometrial cancer identified between 1995 and 2013. Participants contributed person-time from baseline until the diagnosis of endometrial cancer or one of the following censoring events: diagnosis of non-epithelial uterine cancer (n=52), hysterectomy (n=7,564), loss-to-follow-up (n=13,108), or the end of follow-up in 2013, whichever came first. Crude incidence rates and incidence rate ratios (IRRs) were calculated for all categories of exposure compared with the reference category. We estimated adjusted IRRs and 95% confidence intervals (CI) using Cox proportional hazards regression models [26] stratified by age and questionnaire cycle. The Andersen-Gill data structure [27] was used to accommodate time-varying covariates. All covariates with the exception of age at menarche and menopause were treated as time varying. Missing values were imputed by carrying forward the last observation. We modeled the median value of each exposure category as a continuous variable and calculated a Wald test statistic to test for linear trend. Departures from proportional hazards were assessed by comparing models with and without interaction terms between exposures and each of the time scales (age and questionnaire cycle) using the likelihood ratio test.

Exposures were categorized as follows: age at menarche (<11, 11, 12–13, 14 years), parity (nulliparous, parous), number of live- or still-births (1, 2, 3, 4 births), age at first birth (<20, 20–24, 25 years), age at last birth (<25, 25–29, 30–34, 35 years), years since last birth (<20, 20–29, 30–39, 40 years), breastfeeding (never, ever), lifetime duration of breastfeeding (0, 1–11, 12 months), estimated number of lifetime menstrual cycles (<300, 300–399, 400–499, 500), age at natural menopause (<45, 45–49, 50–54, 55 years), history of diagnosis of PCOS (no, yes), and history of infertility (no, yes).

To control for potential confounding, we adjusted for known or suspected risk factors for endometrial cancer. These covariates included participant education (less than high school, high school diploma, some college, college degree, postgraduate), marital status (single, married, separated/divorced/widowed), oral contraceptive use (never, former, current), use of estrogen-only and estrogen plus progesterone female menopausal hormones (never, former, current), smoking status (never, former, current), BMI (<25, 25–29, 30–34, 35–39, 40 kg/m²), vigorous physical activity (0, 1–4, 5 hours/week), as well as age at menarche (<11, 11, 12–13, 14 years), number of births (0, 1, 2, 3, 4), and menopausal status (premenopausal vs. postmenopausal). Analyses of exposures involving timing of births and breastfeeding

were restricted to parous women and adjusted for the above variables plus age at first birth (in the categories listed above).

Both obesity and menopause influence the hormonal environment of the endometrium [28] and thus may modify those associations of reproductive factors with endometrial cancer mediated by ovarian hormones. We therefore decided a priori to repeat analyses stratified by menopausal status (premenopausal vs. postmenopausal) and by current BMI (<30 vs. ≥30 kg/m²). We created interaction terms between exposures of interest and the stratification terms, comparing models with and without these terms using the likelihood ratio test. To evaluate the impact of including unverified cases on our results, we restricted the analysis to confirmed cases, censoring all other incident cases.

All analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics of the cohort are given in Table 1. Mean age was 36.6 years, 39% of women were nulliparous and 10% were postmenopausal. Mean length of follow-up was 14.5 years.

After control for other variables (Table 2), earlier age at menarche was associated with an increased risk of endometrial cancer: compared with women who experienced menarche at age 12–13 years, the IRR for women with age at menarche <11 years was 1.82 (95% CI: 1.31, 2.52). The IRR for parous women compared with nulliparous women was 0.77 (95% CI: 0.57, 1.05). The decrease in risk seen among parous women was only slightly diminished when history of infertility was added to the model (data not shown). There was little evidence of a dose-response relationship between number of births and endometrial cancer risk. Women who had their first birth at age ≥30 years had a reduced risk of endometrial cancer compared with women who had their first birth at less than 20 years (IRR=0.26, 95% CI: 0.13, 0.50, $p_{\text{trend}}=0.0004$). The inverse association with age at last birth and positive association with years since last birth were no longer apparent after control for age at first birth. Breastfeeding was not associated with endometrial cancer risk. There was a positive monotonic relationship between the number of menstrual cycles and endometrial cancer risk ($p_{\text{trend}}=0.004$); the IRR for ≥500 menstrual cycles compared with <300 menstrual cycles was 1.79 (95% CI: 1.10, 2.92). The IRR for age at natural menopause ≥55 years compared with <45 years was 1.45 (95% CI: 0.70, 3.02) but there was no clear trend with increasing age ($p_{\text{trend}}=0.47$). Additionally, risk was higher among women who reported a history of infertility (IRR=1.26, 95% CI: 0.90, 1.75) or diagnosis of PCOS (IRR=1.86, 95% CI: 0.76, 4.55), although the latter IRR was based on only 5 cases.

Results were similar according to menopausal status except for two factors: age at menarche and age at first birth (Table 3). Among postmenopausal women, increasing age at menarche was inversely related with endometrial cancer risk ($p_{\text{trend}}=0.04$); in contrast, both early and late ages at menarche were associated with increased cancer risk in premenopausal women ($p_{\text{interaction}}=0.009$). The IRR for age at menarche <11 years compared with 12–13 years was

2.98 (95% CI: 1.69, 5.25), and for 14 years it was 2.79 (95% CI: 1.66, 4.69). Among premenopausal women, age at first birth at 25 years or later was associated with a lower risk of endometrial cancer relative to age at first birth earlier than 20 years (IRR=0.32, 95% CI: 0.15, 0.68), but there was little association in postmenopausal women ($p_{\text{interaction}}=0.008$). Associations with other reproductive factors did not appear to differ by menopausal status (Supplementary Table 1).

Results according to obesity status are given in Table 4. For women with BMI ≥ 30 kg/m², the IRR for age at menarche 11 years versus 12–13 years was 2.04 (95% CI: 1.38, 3.02); among women with BMI <30 kg/m², the IRR was 1.47 (95% CI: 0.79, 2.76) ($p_{\text{interaction}}=0.24$). Breastfeeding was associated with decreased risk of endometrial cancer among normal- or overweight women, but with increased risk among obese women ($p_{\text{interaction}}=0.002$): the IRR for ever versus never breastfeeding was 0.54 (95% CI: 0.33, 0.88) among non-obese women and 1.49 (95% CI: 1.03, 2.15) among obese women. Other associations with endometrial cancer risk did not vary by obesity status (Supplementary Table 2).

Most associations were similar when we limited analysis to confirmed cases (data not shown). The positive association between longer durations of breastfeeding and endometrial cancer remained, but was slightly weaker.

Discussion

The results of the present study suggest that early menarche, nulliparity, greater number of menstrual cycles, and later age at menopause are associated with an increased risk of endometrial cancer in black women. Among characteristics associated with childbearing, late age at first birth was strongly associated with decreased endometrial cancer risk, while number of births, age at last birth and years since last birth were weakly associated with risk. Age at menarche was strongly related to endometrial cancer risk among premenopausal women, with higher risks seen for both early and late menarche. Among postmenopausal women, there was an increased risk with earlier age at menarche but not late menarche. The association of age at menarche and breastfeeding with endometrial cancer risk appeared to vary by obesity status. Among non-obese women, similar increases in risk were seen with early and late ages at menarche, but risk was only clearly increased among women with early menarche among obese women. Breastfeeding appeared to be associated with decreased risk among non-obese women but increased risk among obese women. Since many comparisons were made, the novel results by menopausal- and obesity status may have occurred by chance.

The “unopposed estrogen hypothesis,” as summarized by Key and Pike [1], posits that endometrial cancers develop due to mutations that accumulate when endometrial tissue undergoes repeated cycles of proliferation. The number of menstrual cycles is proportional to the number of proliferative cycles, so a strong association with endometrial cancer risk would be expected. Factors that reduce the number of ovulatory cycles, such as late age at menarche and parity, may also be associated with lower levels of androgens and estrogens and/or higher levels of progesterone [29–33]. Several prior studies have reported that a

greater number of menstrual cycles is associated with greater risk of endometrial cancer [2,5,6,9,34,35]. However, a recent study by Yang et al. found that the association of the lifetime number of menstrual cycles with endometrial cancer risk varied greatly according to the specific algorithm used [36]. Our results were similar to those of prior studies. Unlike most of these studies [2,5,6,34,35], our results included premenopausal women, among whom the number of ovulatory cycles is closely related to age. In our stratified analysis, there was little evidence of a linear association between number of ovulatory cycles and endometrial cancer risk among postmenopausal women.

Associations also would be expected for factors that influence the number of ovulatory cycles, such as age at menarche and menopause, parity, and breastfeeding. Previous studies [2–6] have found evidence for associations between age at menarche and endometrial cancer risk, with a trend for lower risk with later menarche. In addition to altered levels of endogenous hormones, low birth weight has been associated with early age at menarche [37], which, in turn, has been linked to adult obesity [38–40] and type 2 diabetes [41]. Age at menarche may therefore be a marker for early-life metabolic changes which increase subsequent endometrial cancer risk via some combination of increased levels of estrogens [29], decreased progesterone levels [42], menstrual cycle irregularities, and anovulation [43]. We found that the expected inverse trend for age at menarche held among postmenopausal women. However, among premenopausal women, endometrial cancer rates were elevated among those with early (<11 years) and late (>14 years) ages at menarche. Studies in French [44] and Japanese [45] populations found that, while overall age at menarche was decreasing over time in these populations, the interval between onset of menarche and the beginning of regular cycling was lengthening. In both populations, this interval was longer in women with later age at menarche. The reasons for this are unclear. However, if similar trends are occurring in U.S. black women, the positive association between late age at menarche and endometrial cancer we found in premenopausal women, if not a chance finding, may be because they experience a greater number of anovulatory cycles.

Monotonic inverse associations with endometrial cancer risk have been reported consistently for increasing number of births [2–6,9,10,12–15,46,47]. Most [3,4,9,12,14,15], but not all [5,10], prior studies have found inverse associations with age at last birth. While several studies have reported inverse associations with age at first birth [4,6,10,46,47], one reported a strong positive association [9] and many have found no association [5,12–15]. Three studies have found increasing risk with increasing time since last birth [2,13,14], with one finding no association [10]. Differentiating between the effects of childbearing factors is difficult because of the high degree of collinearity between variables; studies have varied in the extent to which they have tried to model these factors together. Multiple mechanisms have been suggested to explain the associations of endometrial cancer with the number and timing of births. Reported changes in ovarian hormone levels following the first birth [3,4,10,12,14], exposure to high levels of progesterone during pregnancy [3,6,12,13] and reduction in the overall number of ovulatory cycles by pregnancy [6,46] would be expected to reduce the rate of malignant transformation of endometrial cells. Precancerous or cancerous cells may be eliminated by mechanical shedding during parturition [2,3,12–14] or by apoptosis during involution [8]. Additionally, women who give birth later in life are less likely to experience anovulatory cycles as they approach menopause [3,10,12].

Some studies have found that a history of breastfeeding is protective against endometrial cancer [6,9], while others have found little association [2,10]. During lactation, levels of estrogen and progesterone are low [48], resulting in reduced exposure of the endometrium to unopposed estrogens. In our main analysis, there was little association. However, when we stratified by BMI, breastfeeding was associated with reduced risk among non-obese women but with increased risk in obese women. We are not aware of other studies that have examined the risk associated with breastfeeding stratified by BMI. One plausible mechanism for this finding is that adipose tissue may become an important source of estrogens during the period of lactational amenorrhea, similar to the situation in postmenopausal women. In the absence of adequate levels of progesterone, the endometria of obese women may continue to undergo proliferative cycles while those of non-obese women do not. This result must therefore be interpreted cautiously in the absence of confirmation by other studies.

A recent meta-analysis of five studies found that women diagnosed with PCOS had nearly three times the risk of endometrial cancer compared with women who had not been diagnosed [49]. Our results, based on only five cases, were consistent with a positive association. The high levels of unopposed estrogens, luteinizing hormone (LH), and insulin and low levels of sex hormone binding globulin (SHGB) found among women with PCOS may all contribute to increased risk [50]. Some prior studies have found a higher risk of endometrial cancer among women with a history of infertility [17,19], while others did not [5,10]. Our results agree with the latter studies. Escobedo and colleagues found that the increase in risk was restricted to women diagnosed with ovarian problems, and hypothesized that exposure to unopposed estrogens via anovulation was the cause [19].

Strengths of our study include its prospective design and high participation over 18 years of follow-up. We collected data on a large number of variables related to menstrual and reproductive history, and were able to control for a large number of potential confounders including obesity, use of oral contraceptives, and menopausal estrogen use. Although we included self-reported cases of endometrial cancer, we were able to verify approximately 71% through medical records and registry data.

Among the limitations of our study was the use of self-reported exposure data, which could have resulted in nondifferential misclassification of reproductive factors. The overall effect of nondifferential misclassification is expected to be towards the null for the extreme categories of exposure. We cannot exclude the possibility that BWHS participants differ from the general population of U.S. black women in ways that may limit the generalizability of these results.

In summary, the present study suggests that, consistent with previous results in white populations, factors that influence menstrual cycling and the endogenous hormonal milieu are associated with risk of endometrial cancer among black women. Novel findings of an association of late menarche with increased endometrial cancer risk among premenopausal women and breastfeeding with increased endometrial cancer risk among obese women require confirmation in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by National Cancer Institute grants R01-CA58420 (principal investigator: L.R.), UM1-CA164974 (principal investigator: L.R.), and R03-CA169888 (principal investigator: L.A.W.) and National Institute of Health grant 1T32HL125232-01A1 (principal investigator: Vasani S. Ramachandran).

We thank the participants and staff of the Black Women's Health Study as well as Drs. Sara Olson and Rie Adser Virkus for their feedback.

Data on endometrial cancer pathology were obtained from several state and district cancer registries (Arizona; California; Colorado; Connecticut; Delaware; Washington, DC; Florida; Georgia; Illinois; Indiana; Kentucky; Louisiana; Maryland; Massachusetts; Michigan; New Jersey; New York; North Carolina; Oklahoma; Pennsylvania; South Carolina; Tennessee; Texas; and Virginia). The study sponsors played no role in the study design, data collection, analyses, or interpretation of results, the preparation of the manuscript, or the decision to submit the manuscript for publication. The results reported here do not necessarily represent the views of the National Cancer Institute or the respective state cancer registries.

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Table 1Age-Standardized Baseline Characteristics^a of 47,555 Participants in the Black Women's Health Study, 1995

Age in 1995, years, mean (SD)	36.6 (9.8)
Education, years, mean (SD)	14.8 (1.8)
Marital status	
Single, %	38.8
Married/living together, %	38.4
Separated/Divorced/Widowed, %	21.8
Age at menarche, years, mean (SD)	12.3 (1.6)
Estimated number of menstrual cycles, mean (SD)	238.8 (118.4)
History of infertility, %	8.9
Parity	
Nulliparous, %	39.3
1–2, %	43.6
3, %	17.0
Ever breastfed, % ^b	42.5
Postmenopausal, %	9.8
Age at menopause, years, mean (SD)	47.8 (5.8)
Body mass index, kg/m ² (SD)	27.7 (6.7)
Vigorous physical activity, hours/week	
0, %	28.9
1–4, %	51.7
5, %	13.7
Ever use of oral contraceptives, %	85.5
Ever use of estrogen-only female hormones, %	1.4
Ever use of estrogen plus progestin female hormones, %	3.5

Abbreviations: SD, standard deviation.

^aValues are standardized to the age distribution of the study population.^bAmong women parous at baseline.

Table 2

Incidence Rate Ratios for Endometrial Cancer According to Reproductive Factors

Exposure	Cases	Person-Years	Rate ^c	Age Adjusted ^a		Multivariable Adjusted ^b	
				IRR	95% CI	IRR	95% CI
Age at menarche, years							
<11	53	76,923	68.9	2.17	1.57, 2.99	1.82	1.31, 2.52
11	58	114,079	50.8	1.53	1.12, 2.10	1.41	1.03, 1.93
12–13	126	363,526	34.7	1.00	Referent	1.00	Referent
14	61	131,796	46.3	1.19	0.88, 1.62	1.23	0.90, 1.67
<i>P</i> _{trend}					0.002		0.04
Parity							
Nulliparous	74	212,512	34.8	1.00	Referent	1.00	Referent
Parous	225	473,064	47.6	0.72	0.55, 0.95	0.77	0.57, 1.05
Number of births ^{d,e}							
1	67	175,164	38.2	1.00	Referent	1.00	Referent
2	66	166,860	39.6	0.82	0.58, 1.15	0.71	0.50, 1.01
3	47	80,554	58.3	1.04	0.71, 1.53	0.81	0.54, 1.21
4	45	50,486	89.1	1.15	0.77, 1.71	0.74	0.48, 1.15
<i>P</i> _{trend}					0.36		0.27
Age at first birth, years ^d							
<20	88	127,552	69.0	1.00	Referent	1.00	Referent
20–24	79	146,001	54.1	0.78	0.57, 1.06	0.83	0.60, 1.15
25–29	47	106,160	44.3	0.78	0.54, 1.11	0.85	0.57, 1.26
30	11	87,845	12.5	0.25	0.13, 0.47	0.26	0.13, 0.50
<i>P</i> _{trend}					<0.0001		0.0004
Age at last birth, years ^{d,e}							
<25	73	126,071	57.9	1.00	Referent	1.00	Referent
25–29	78	134,031	58.2	1.00	0.73, 1.38	1.18	0.79, 1.74
30–34	42	12,096	33.6	0.60	0.41, 0.88	0.87	0.53, 1.43
35	25	77,444	32.3	0.51	0.32, 0.80	0.79	0.44, 1.42

Exposure	Cases	Person-Years	Rate ^c	Age Adjusted ^a		Multivariable Adjusted ^b	
				IRR	95% CI	IRR	95% CI
<i>p</i> _{trend}					0.0002		0.43
Years since last birth ^{d,e}							
<20	50	274,968	18.2	1.00	Referent	1.00	Referent
20–29	56	100,484	55.7	1.43	0.85, 2.40	0.98	0.57, 1.68
30–39	77	57,957	132.9	1.91	1.07, 3.41	1.03	0.53, 1.96
40	35	22,149	158.0	1.75	0.86, 3.57	0.75	0.32, 1.75
<i>p</i> _{trend}					0.04		0.46
Breastfeeding ^{d,e}							
No	139	253,648	54.8	1.00	Referent	1.00	Referent
Yes	86	219,416	39.2	0.85	0.65, 1.11	0.98	0.74, 1.31
<12 months	58	161,527	35.9	0.79	0.58, 1.08	0.92	0.67, 1.26
12 months	27	52,733	51.2	0.99	0.66, 1.51	1.17	0.75, 1.83
Lifetime number of menstrual cycles							
<300	52	328,728	15.8	1.00	Referent	1.00	Referent
300–399	64	178,784	35.8	1.26	0.82, 1.93	1.08	0.71, 1.64
400–499	114	133,651	85.3	1.86	1.21, 2.87	1.53	0.99, 2.35
500	67	43,992	152.3	2.62	1.64, 4.17	1.79	1.10, 2.92
<i>p</i> _{trend}					<0.0001		0.004
Age at natural menopause, years							
<45	12	22,960	52.3	1.00	Referent	1.00	Referent
45–49	38	46,155	82.3	1.44	0.72, 2.84	1.45	0.73, 2.89
50–54	64	64,053	99.9	1.32	0.68, 2.55	1.32	0.67, 2.56
55	28	19,161	146.1	1.65	0.80, 3.39	1.45	0.70, 3.02
<i>p</i> _{trend}					0.26		0.47
History of infertility							
No	254	626,155	40.6	1.00	Referent	1.00	Referent
Yes	46	36,385	72.6	1.19	0.87, 1.64	1.26	0.90, 1.75
Ever diagnosis of PCOS							
No	295	682,505	43.2	1.00	Referent	1.00	Referent

Exposure	Cases	Person-Years	Rate ^c	Age Adjusted ^a		Multivariable Adjusted ^b	
				IRR	95% CI	IRR	95% CI
Yes	5	6,996	71.5	2.33	0.96, 5.66	1.86	0.76, 4.55

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; PCOS, polycystic ovary syndrome.

^a Adjusted for age and study period.

^b Adjusted for age, study period, education, marital status, age at menarche, number of births, menopausal status, oral contraceptive use, estrogen-only female menopausal hormone use, estrogen plus progestin female menopausal hormone use, smoking status, body mass index, and vigorous physical activity.

^c Crude incidence rate per 100,000 person-years.

^d Restricted to parous women.

^e Additionally adjusted for age at first birth.

Table 3
Incidence Rate Ratios for Endometrial Cancer According to Reproductive Factors, Stratified by Menopausal Status

Exposure	Premenopausal				Postmenopausal			
	Cases	Rate ^a	IRR ^b	95% CI	Cases	Rate ^a	IRR ^b	95% CI
Age at menarche, years								
<11	22	38.0	2.98	1.69, 5.25	25	152.6	1.34	0.86, 2.11
11	20	23.6	2.17	1.22, 3.86	34	133.5	1.25	0.84, 1.86
12–13	30	11.3	1.00	Referent	87	101.6	1.00	Referent
14	29	31.8	2.79	1.66, 4.69	30	83.6	0.83	0.55, 1.26
<i>P</i> _{trend}				0.83				0.04
Age at first birth, years ^c								
<20	31	39.2	1.00	Referent	51	117.7	1.00	Referent
20–24	24	26.1	0.79	0.45, 1.39	50	103.2	0.88	0.58, 1.33
25	12	8.3	0.32	0.15, 0.68	42	96.8	0.90	0.56, 1.46
<i>P</i> _{trend}				0.001				0.20

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

^aPer 100,000 person-years.

^bAdjusted for age, study period, education, marital status, age at menarche, number of births, oral contraceptive use, estrogen-only female menopausal hormone use, estrogen plus progestin female menopausal hormone use, smoking status, body mass index, and vigorous physical activity.

^cRestricted to parous women.

^dAdditionally adjusted for age at first birth.

Table 4
Incidence Rate Ratios for Endometrial Cancer According to Reproductive Factors, Stratified by Obesity

Exposure	BMI <30 kg/m ²				BMI ≥30 kg/m ²				<i>P</i> _{Interaction}
	Cases	Rate ^a	IRR ^b	95% CI	Cases	Rate ^a	IRR ^b	95% CI	
Age at menarche, years									
<11	12	33.0	1.47	0.79, 2.76	41	102.7	2.04	1.38, 3.02	
11	16	25.2	1.10	0.63, 1.91	41	82.7	1.61	1.09, 2.38	
12–13	56	24.0	1.00	Referent	68	53.8	1.00	Referent	
14	34	37.0	1.38	0.90, 2.12	27	70.0	1.16	0.74, 1.82	0.24
<i>P</i> _{trend}				0.62				0.005	
Age at first birth, years ^c									
<20	31	43.5	1.00	Referent	57	104.2	1.00	Referent	
20–24	33	37.6	1.00	0.59, 1.67	45	79.5	0.77	0.51, 1.16	
25	26	20.6	0.72	0.39, 1.34	30	45.3	0.58	0.35, 0.97	0.89
<i>P</i> _{trend}				0.19				0.03	
Breastfeeding ^{c,d}									
No	64	42.9	1.00	Referent	72	70.7	1.00	Referent	
Yes	26	18.6	0.54	0.33, 0.88	60	77.2	1.49	1.03, 2.15	0.002

Abbreviations: BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio.

^aPer 100,000 person-years.

^bAdjusted for age, study period, education, marital status, age at menarche, number of births, menopausal status, oral contraceptive use, estrogen-only female menopausal hormone use, estrogen plus progestin female menopausal hormone use, smoking status, body mass index (continuous), and vigorous physical activity.

^cRestricted to parous women.

^dAdditionally adjusted for age at first birth.