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Pregnancy history and risk of endometrial cancer

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Abstract

Background—Epidemiologic studies are consistent in finding that women who have had at least one birth are less likely to develop endometrial cancer. Less clear is whether timing of pregnancies during reproductive life influences risk, and the degree to which incomplete pregnancies are associated with a reduced risk.

Methods—We evaluated pregnancy history in relation to endometrial cancer risk using data from a series of four population-based endometrial cancer case-control studies of women 45–74 years of age (1,712 cases and 2,134 controls) during 1985–2005 in western Washington State. Pregnancy history and information on other potential risk factors were collected by in-person interviews.

Results—Older age at first birth was associated with a reduced risk of endometrial cancer after adjustment for number of births and age at last birth (test for trend $P = 0.004$). The odds ratio comparing women at least 35 years of age at their first birth with those younger than 20 years was 0.34 (95% confidence interval = 0.14–0.84). Age at last birth was not associated with risk after adjustment for number of births and age at first birth (test for trend $P = 0.830$). Overall, a history of incomplete pregnancies was not associated with endometrial cancer risk to any appreciable degree.

Conclusions—In this study, older age at first birth was more strongly associated with endometrial cancer risk than was older age at last birth. To date, there remains some uncertainty in the literature on this issue.

Epidemiologic studies have consistently found that women with endometrial cancer are more likely than other women to be nulliparous.¹ Among parous women, risk tends to be lower for those who have had more births compared with those who have had fewer births.¹ Less clear is the impact on risk of the timing of pregnancies during reproductive life, and the

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degree to which incomplete pregnancies are associated with a reduced risk.¹ Using detailed reproductive history information collected in our series of population-based endometrial cancer case-control studies, we evaluated the association between endometrial cancer risk and pregnancy history.

Methods

Data were pooled from four population-based case-control studies^{2–5} of endometrial cancer conducted over a 20-year period in western Washington State.^{2–5} All four studies used similar data collection protocols and study questionnaires. Each study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and informed consent was obtained in writing from each participant.

Case ascertainment

Cases were women with histologically confirmed endometrial adenocarcinoma, diagnosed between 45–74 years of age in King, Pierce or Snohomish Counties during 1985–1991,² 1994–1995,³ 1997–1999,⁴ or 2003–2005.⁵ All cases were identified through the Cancer Surveillance System, a population-based cancer registry in western Washington State that is affiliated with the National Cancer Institute's Surveillance, Epidemiology and End Results Program. Of a total of 2,324 women who were eligible to be included as a case in one of the four studies, 1,716 (74%) were interviewed, 162 died before they could be interviewed and 446 either declined to be interviewed or their physician instructed us not to contact them. Of the 1,716 women who were interviewed, one was excluded because of poor-quality interview data, one was excluded because she was later found to not have endometrial cancer, one was excluded because her interview data were lost, and one was excluded because we did not have information on her parity. A total of 1,712 cases remained for analysis.

Control ascertainment

For the four time periods of case ascertainment, control women were identified as follows. For reference years 1985–1991 (ages 45–74 years), 1994–1995 (ages 50–64 years) and 1997–1999 (ages 50–65 years) eligible controls were identified by random-digit dialing⁶ and included only women with no history of endometrial cancer who also had an intact uterus. Across these three time periods, the screening response was 95% and the interview response was 77%, for an overall random-digit dialing response (screening response × interview response) of 73% (1,411 women interviewed). In addition, for time periods 1994–1995 and 1997–1999, Health Care Financing Administration files were used to identify eligible controls 65–69 years of age. Of the eligible women identified from these files, 66% (116 women) were interviewed. The controls identified by either process were frequency-matched to cases by 5-year age group and county of residence. Controls were assigned a reference date (year and month); the year was assigned so as to approximate the distribution of the year of diagnosis of the cases, and the month was assigned randomly.

The control population for reference years 1994–1995 and 1997–1998 additionally included a subset of control women from a population-based case-control study of breast cancer (Women's Contraceptive and Reproductive Experiences Study).⁷ Participants in the breast cancer study were asked questions about pregnancy history and other exposures relevant to endometrial cancer risk (similar to those asked of participants in the endometrial cancer studies described here). Control women in the breast cancer study were identified by random-digit dialing; the screening response was 84% and the interview response was 88%, for an overall random-digit dialing response of 74%. We restricted the controls from the breast cancer study to women who at the time of their reference date, 1994–1995 or 1997–

1998, had an intact uterus, were residents of King County and were 50–64 years of age (252 women).

For reference years 2003–2005, controls were a subset of control women from a population-based case-control study of ovarian cancer.⁸ Women in this study were also asked questions about pregnancy history and other exposures similar to those asked of participants in the endometrial cancer studies described here. Control women in the ovarian cancer study were identified by random-digit dialing; the screening response was 82% and the interview response was 84%, for an overall random-digit dialing response of 69%. We restricted the control women to those who, at the time of their reference date, 2003–2005, had an intact uterus, were residents of King, Pierce, or Snohomish Counties and were 50–74 years of age (356 women). In total, across all reference periods, 2,135 controls were interviewed; one control was later found to be ineligible and was excluded, leaving a total of 2,134 controls for analysis.

Exposure ascertainment

In each of the four studies,^{2–5} most participants were interviewed in person by trained personnel; a small proportion were interviewed by telephone. Questions were asked about events that occurred before the diagnosis of endometrial cancer in the cases, or before the assigned and comparable reference date in the controls. Information was collected about demographic and lifestyle characteristics, medical history, and reproductive history – including menstrual, pregnancy, and contraceptive history and use of noncontraceptive hormones. To enhance participants' recall of prior exposures and events, a life-events calendar and photographs of contraceptive and noncontraceptive hormones were used during the interview; photographs had been mailed to participants who were interviewed by telephone.

The pregnancy-history variables that we examined were defined as follows. A woman was classified as parous if she had ever given birth (single or multiple birth) to at least one infant that showed signs of life after separation from the mother (a live birth), or if she had ever had a single or multiple birth at 20 weeks or greater gestation that did not result in a live birth (a stillbirth). Each live birth or stillbirth was counted as a “birth” (a multiple birth was counted as one birth). A woman was classified as nulliparous if she had not had at least one birth. An incomplete pregnancy was defined as either a miscarriage (less than 20 weeks' gestation) or an induced abortion. Parous women were also queried about their age at their first birth and, if they were multiparous, their age at their last birth.

Statistical analysis

Unconditional logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CI) of endometrial cancer associated with each pregnancy history variable. All odds ratios were adjusted for the variables on which cases and controls had been frequency-matched: reference age, reference year, and county of residence. We also adjusted all odds ratios for factors that consistently have been shown to be related to endometrial cancer incidence: body mass index (BMI; weight [kg]/ height [m]²), use of certain estrogen therapy regimens (defined below), and duration of use of oral contraceptives. After adjustment for the factors listed above, we additionally adjusted for variables that changed the risk estimate by at least 10% among the following: race, education, and cigarette smoking. Only cigarette smoking met this criterion for confounding, and only in the analysis of age at first birth. In order to have comparability in adjustment factors across the risk estimates for age at first birth and age at last birth, we also adjusted for cigarette smoking in the analysis of age at last birth. All adjustment factors were categorized as shown in Table 1 except for race, which was categorized as white, black,

Native American, Asian, and other. On the basis of data collected in these studies, categories of estrogen therapy were defined as follows: (1) never-users: women who had never used unopposed estrogen or an estrogen plus progestin with fewer than 10 days of progestin per month for ≥ 6 months; (2) medium-risk: women who had used unopposed estrogen for 6 months to 4 years, regardless of their recency of use, or who had used unopposed estrogen for 4 to 8 years and quit at least 2 years previously, or women who had used a sequential estrogen and progestin regimen with <10 days per month of progestin for up to 12 years regardless of their recency of use; and (3) high-risk: women who had used unopposed estrogen for >4 to 8 years and quit within the last 2 years, or women who used unopposed estrogen for >8 years, regardless of recency, or used a sequential estrogen and progestin regimen with <10 days per month of progestin for >12 years, regardless of recency.

To separate the independent effects of the pregnancy history variables, some analyses were also adjusted for other pregnancy history variables. Analyses were restricted to multiparous women in order to evaluate the impact of number of births independent of both age at first birth and age at last birth; women with one birth had to be excluded because they have no variation in age at last birth within stratum of age at first birth. For the same reason the analysis of age at first birth, controlling for age at last birth (and vice versa), was restricted to multiparous women.

The statistical significance of each pregnancy history variable was tested using a likelihood ratio test for trend, with the variable categorized in ordinal form. Because this test assumes a log-linear relationship between the odds ratio of endometrial cancer and the levels of the pregnancy history variable, we first tested for nonlinearity in this relation. To do so, we compared the model with the pregnancy history variable categorized as dummy variables to the model with the variable in ordinal form; if the models differed at a P value of 0.05 or less, the test for trend was not reported. All analyses were conducted in STATA/SE 10.1 (College Station, Texas).

Results

Women with endometrial cancer tended to have higher BMI and less education than control women (Table 1). They were also more likely than controls to have used estrogen therapy, and were less likely than controls to have ever used oral contraceptives or to have ever smoked cigarettes (Table 1).

Nulliparity was more common in cases (18%) than in controls (12%). Ever having a birth was associated with a 35% reduced risk of endometrial cancer (OR = 0.65 [95% CI = 0.53–0.79]). When we compared women with one birth to nulliparous women, risk of endometrial cancer was lower in the women for whom that birth was at age 30 years or older (OR = 0.49; 95% CI = [0.31–0.78]); there was little altered risk in women for whom the only birth had occurred before age 30 (Table 2).

Among parous women, there tended to be a greater reduction in risk as the number of births increased, up to and including five or more births (test for trend $P = 0.002$; Table 3). This pattern was also present after adjustment for age at first birth (test for trend $P < 0.001$; Table 3) and after adjustment for ages at first and last birth in women with at least two births (test for trend $P = 0.006$; Table 4).

A history of having an incomplete pregnancy was not associated to any appreciable degree with endometrial cancer risk (Table 2) except among nulliparous women, for whom there was a suggestion of a decreased risk associated with two or more incomplete pregnancies. Compared with nulliparous women who had no incomplete pregnancies, the odds ratio was 0.95 (95% CI = 0.54–1.67) in nulliparous women with one incomplete pregnancy and 0.55

(95% CI = 0.27–1.08) in nulliparous women with 2 or more incomplete pregnancies. Among parous women, the corresponding odds ratios were 1.02 (95% CI = 0.84–1.22) and 0.90 (95% CI = 0.70–1.16) after adjustment for number of births and age at first birth (data not shown).

Among women with at least one birth, older age at first birth was inversely related with endometrial cancer risk after adjusting for number of births (test for trend $P < 0.001$; Table 3). An inverse association persisted in women with at least two births after additionally adjusting for age at last birth (test for trend $P = 0.004$; Table 4).

Because parity can be influenced by age at first birth (i.e. women with an older age at their first birth have fewer reproductive years remaining compared with women who were younger at their first birth), we also evaluated the association between age at first birth and endometrial cancer risk without adjustment for parity. In this analysis the decreased risk associated with older age at first birth was weaker than in the analysis where we adjusted for parity (Table 3).

Older age at last birth was inversely related to endometrial cancer risk in women with at least one birth after adjusting for number of births (test for trend $P = 0.004$; Table 3). However, among women with at least two births, an association was not present after additionally adjusting for age at first birth (Table 5).

The associations with parity and age at first birth were not evident in women who had taken a high-risk form of estrogen therapy. The odds ratio comparing parous with nulliparous women was 0.69 (0.54–0.87) in never-users of estrogen therapy and 0.86 (0.45–1.66) in women who had taken a high-risk form of estrogen therapy. The odds ratio comparing women who had their first birth at 30 years of age or older versus before 20 years of age was 0.44 (0.30–0.64) in never-users of estrogen therapy and 0.90 (0.32–2.55) in women who had taken a high-risk form of estrogen therapy. In obese women ($\text{BMI} \geq 30 \text{ kg/m}^2$), who are another high-risk group, the results were similar to those overall.

Discussion

There are some limitations of this study, and our results should be interpreted in the context of these limitations. Across the four studies, about 25% of eligible cases and a slightly larger proportion of eligible controls did not participate. Cases who did not participate included some women who died before they could be interviewed or were too sick to be interviewed. If pregnancy history were related to severity of endometrial cancer at diagnosis, our odds ratios could be biased (over- or underestimated) as a result of not having interviewed these women. Our odds ratios may also be biased (over or under-estimated) if the eligible controls who did not participate had different distributions of the pregnancy history variables compared with the women who did participate. Additionally, a history of incomplete pregnancy was plausibly underreported, due to social desirability bias. Case women may have been more motivated than control women to report an incomplete pregnancy, and in this scenario any true decrease in risk due to an incomplete pregnancy would be lower than the estimate reported here. Lastly, although we adjusted for several factors strongly associated with endometrial cancer risk, uncontrolled confounding by unmeasured factors associated with both endometrial cancer risk and pregnancy history may have been present.

Ages at first and last birth tend to be correlated, yet only a small proportion of prior studies have evaluated the effect on endometrial cancer risk of age at first birth after controlling for age at last birth, and vice versa. In five^{9–13} studies that examined the association with age at first birth after adjusting for age at last birth (and parity), the risk estimates comparing the oldest category of age at first birth (≥ 30 or ≥ 35 years) to the youngest category (≤ 20 or < 25

years) ranged from 0.66 to 0.84. As well, a stratified analysis of data from a cohort study showed that risk of endometrial cancer decreased with increasing age at first birth in strata defined jointly by parity and age at last birth.¹⁴ In contrast, in another cohort study, the hazard ratio comparing women who were ≥ 35 to those 20–24 years at their first birth was 1.16.¹⁵ In that study,¹⁵ and in three mentioned above^{10,11,14} (two cohort studies^{11,14} and one case-control study¹⁰), pregnancy history was ascertained using data from geographically defined population-based registries, and so confounding by endometrial cancer risk factors such as BMI, oral contraceptive use, noncontraceptive hormone use, and smoking could not be assessed and, if needed, adjusted for.

In our data, age at first birth was an important confounder in the relationship between age at last birth and endometrial cancer risk. Findings from prior studies on the relation between age at last birth and endometrial cancer, after controlling for age at first birth (and parity), are mixed. All four^{10,11,14,15} of the registry-based studies found an inverse association between endometrial cancer risk and age at last birth; the risk estimates comparing women in the oldest age at last birth category (≥ 40) to those in a younger category (< 25 or 25–29 years) ranged from 0.56 to 0.85. Findings from a stratified analysis of data from a cohort study were also consistent with an inverse association between age at last birth and endometrial cancer risk in strata defined jointly by parity and age at first birth.¹⁴ Three studies^{9,12,13} were able to control for factors such as BMI, oral contraceptive use, noncontraceptive hormone therapy use, and smoking history (in addition to age at first birth and parity). In two of the studies, one a population-based case-control study⁹ and the other a cohort study,¹³ there was no association between age at last birth and endometrial cancer risk; risk estimates comparing women in the oldest age at last birth category (> 35 or > 30 years) with the youngest category (≤ 25 or < 25 years) were 1.06⁹ and 1.05.¹³ In the third study, also a cohort study, the hazard ratio comparing women ≥ 40 years at their last birth to those 25–29 years was 0.58.¹² If the comparison group had been the youngest category of age at last birth (< 25 years at last birth; HR = 0.73), the hazard ratios would be 1.36 ($=1.00/0.73$) for women 25–29, 1.16 ($=0.85/0.73$) for women 30–34, 1.05 ($=0.77/0.73$) for women 35–39, and 0.79 ($=0.58/0.73$) for women ≥ 40 years of age at their last birth.¹² At present, no firm conclusion can be drawn about the degree of the reduction in risk, if any, of an older age at last birth.

Findings from prior studies on the association between one or more incomplete pregnancies and endometrial cancer also are mixed. Five studies,^{13,16–19} including one cohort¹³ and four case-control studies,^{16–19} found no association between a history of one or more incomplete pregnancies (variously defined as spontaneous or induced abortions,¹³ spontaneous abortion,^{16–19} or induced abortion¹⁹) and endometrial cancer risk. Six studies,^{18,20–24} including two cohort^{20,23} and four case-control studies,^{18,21,22,24} found a decrease in risk; the risk estimates associated with a history of one or more incomplete pregnancies (defined as spontaneous or induced abortion^{20,21}) were 0.69²¹ and 0.85,²⁰ and the risk estimates associated with a history of two or more^{22–24} or three or more¹⁸ incomplete pregnancies (variously defined as spontaneous^{22,23} or induced abortions^{18,22,24}) ranged from 0.3 to 0.5. Adjustment factors varied across these studies; all adjusted for age, and some also adjusted for BMI (or weight),^{13,16,17,19,21,22,24} use of oral contraceptives,^{17,19,21,24} use of noncontraceptive hormones,^{16,17,19,22,24} smoking^{13,19,24} and parity.^{17–20,22,24} Some studies restricted their analysis to gravid women,^{18,20,21,23} but none stratified by nulliparity, as we did. Levels of progesterone, which arrests estrogen-induced endometrial cell proliferation and promotes endometrial cell differentiation,^{1,25,26} increase throughout pregnancy.²⁷ One possible explanation of our finding of a decreased risk in nulliparous but not parous women is that, among parous women, who have been exposed to the high levels of progesterone that occur late in pregnancy, any additional impact on risk of a comparatively small increase in progesterone levels from an incomplete pregnancy is small or nonexistent. In contrast, in

nulliparous women, the impact on risk could be greater because they had not previously been exposed to progesterone levels as great as those that occur during a term pregnancy.

In this study we observed that an older age at first birth was associated with a decreased risk of endometrial cancer; and, beyond the impact on risk of age at first birth, there was no additional impact of age at last birth. We also found no appreciable association overall between a history of incomplete pregnancies and endometrial cancer risk. While there was a suggestion of a decreased risk associated with 2 or more incomplete pregnancies in nulliparous women, no association was present in parous women.

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Table 1

Characteristics of nulliparous and parous women, by case-control status, western Washington state, 1985–2005

	Nulliparous				Parous			
	Cases (n = 308)		Controls (n = 254)		Cases (n = 1,404)		Controls (n = 1,880)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age at reference (years)								
45–49	19	(6)	16	(6)	52	(4)	120	(6)
50–54	77	(25)	84	(33)	225	(16)	394	(21)
55–59	67	(22)	66	(26)	309	(22)	455	(24)
60–64	63	(21)	43	(17)	353	(25)	453	(24)
65–59	52	(17)	30	(12)	326	(23)	337	(18)
70–74	30	(10)	15	(6)	139	(10)	121	(6)
Missing	0		0		0		0	
Reference year								
1985–1988	73	(24)	57	(22)	321	(23)	484	(26)
1989–1991	62	(20)	51	(20)	376	(27)	522	(28)
1994–1995	24	(8)	29	(11)	112	(8)	182	(10)
1997–1999	57	(19)	46	(18)	278	(20)	407	(22)
2003–2005	92	(30)	71	(28)	317	(23)	285	(15)
Missing	0		0		0		0	
County of residence								
King	207	(67)	196	(77)	883	(63)	1,359	(72)
Pierce	54	(18)	37	(15)	291	(21)	295	(16)
Snohomish	47	(15)	21	(8)	230	(16)	226	(12)
Missing	0		0		0		0	
Race								
White	300	(97)	240	(95)	1,344	(96)	1,794	(96)
Non-white	8	(3)	13	(5)	60	(4)	81	(4)
Missing	0		1		0		5	
Education (years)								

	Nulliparous				Parous			
	Cases (n = 308)		Controls (n = 254)		Cases (n = 1,404)		Controls (n = 1,880)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Less than high school	16	(5)	9	(4)	125	(9)	172	(9)
High school graduate	65	(21)	49	(19)	464	(33)	516	(28)
Some college or technical school	95	(31)	68	(27)	472	(34)	644	(34)
College graduate	132	(43)	128	(50)	343	(24)	547	(29)
Missing	0		0		0		1	
Body Mass Index (kg/m ²) ^a								
<25	105	(34)	145	(58)	526	(38)	1,013	(54)
25–29	80	(26)	61	(24)	405	(29)	546	(29)
30–34	51	(17)	28	(11)	225	(16)	215	(11)
≥35	72	(23)	17	(7)	240	(17)	104	(6)
Missing	0		3		8		2	
Oral contraceptive use (years)								
Never	186	(61)	107	(43)	715	(51)	836	(45)
<5 years	87	(28)	75	(30)	438	(32)	573	(31)
≥5 years	34	(11)	70	(28)	238	(17)	459	(25)
Missing	1		2		13		12	
Estrogen therapy use ^b								
Never	196	(64)	201	(81)	873	(63)	1,464	(79)
Medium-risk	50	(16)	32	(13)	218	(16)	286	(16)
High-risk	60	(20)	15	(6)	291	(21)	95	(5)
Missing	2		6		22		35	
Cigarette smoking								
Never	175	(57)	126	(50)	788	(56)	865	(46)
Former	103	(33)	80	(32)	428	(31)	655	(35)
Current ^c	30	(10)	48	(19)	187	(13)	360	(19)
Missing	0		0		1		0	

^aWeight (kg)/height (m²)

^b See Methods section for a definition of each category of estrogen therapy.

^c Smoked cigarettes within one year of reference date

Table 2

Endometrial cancer risk in relation to characteristics of pregnancy history.

	Cases		Controls		Odds	
	No.	(%)	No.	(%)	Ratio	(95% CI)
Number of births ^a						
Nulliparous ^b	308	(18)	254	(12)	1.00	
1	205	(12)	221	(10)	0.78	(0.59–1.03)
2	485	(28)	639	(30)	0.70	(0.56–0.88)
3	373	(22)	525	(25)	0.60	(0.47–0.76)
4	210	(12)	275	(13)	0.63	(0.48–0.84)
≥5	131	(8)	220	(10)	0.46	(0.34–0.63)
Test for trend (parous women only)						<i>P</i> = 0.002
Age at first and only birth (years) ^c						
Nulliparous ^b	308	(60)	254	(54)	1.00	
<25	98	(19)	91	(19)	0.87	(0.60–1.28)
25–29	64	(13)	57	(12)	1.15	(0.74–1.79)
≥30	43	(8)	73	(15)	0.49	(0.31–0.78)
Test for trend						<i>N/A</i> ^d
Number of incomplete pregnancies ^e						
None ^b	1,173	(69)	1,419	(67)	1.00	
1	368	(22)	464	(22)	0.99	(0.83–1.18)
2	108	(6)	153	(7)	0.86	(0.65–1.14)
≥3	63	(4)	97	(5)	0.77	(0.54–1.12)
Test for trend						<i>P</i> = 0.138

N/A indicates not applicable

^a Odds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, and duration of use of oral contraceptives.

^b Reference category.

^c Odds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, duration of use of oral contraceptives, and cigarette smoking.

^d Not applicable (N/A) because the test for nonlinearity of the log-hazard ratio was significant at $\alpha = 0.05$.

^e An incomplete pregnancy was defined as a miscarriage at less than 20 weeks gestation or an induced abortion. We did not have information on number of incomplete pregnancies for one control. Odds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, duration of use of oral contraceptives, and number of births.

Table 3
Endometrial cancer risk in relation to characteristics of pregnancy history among parous women.

	Cases		Controls		Additionally adjusted ^e	
	No.	(%)	No.	(%)	OR	(95% CI)
Number of births ^b						
1 ^c	205	(15)	221	(12)	1.00	
2	485	(35)	639	(34)	0.90	(0.70–1.15)
3	373	(27)	525	(28)	0.78	(0.60–1.00)
4	210	(15)	275	(15)	0.82	(0.61–1.11)
≥5	131	(9)	220	(12)	0.61	(0.44–0.84)
Test for trend						<i>P</i> = 0.002
Age at first and only birth (years) ^d						
<25 ^c	98	(48)	91	(41)	1.00	
25–29	64	(31)	57	(26)	1.18	(0.69–2.00)
≥30	43	(21)	73	(33)	0.50	(0.29–0.87)
Test for trend						<i>N/A</i> ^e
Age at first birth (years) ^{d,f}						
<20 ^c	291	(21)	304	(16)	1.00	
20–24	664	(47)	884	(47)	0.83	(0.67–1.03)
25–29	335	(24)	480	(26)	0.84	(0.66–1.07)
30–34	85	(6)	154	(8)	0.62	(0.44–0.87)
≥35	28	(2)	58	(3)	0.52	(0.31–0.88)
Test for trend						<i>P</i> = 0.003
Age at last birth (years) ^{d,g}						
<25 ^c	323	(23)	342	(18)	1.00	
25–29	520	(37)	643	(34)	0.88	(0.71–1.09)
30–34	362	(26)	549	(29)	0.75	(0.60–0.94)
≥35	198	(14)	345	(18)	0.64	(0.49–0.82)
Test for trend						<i>P</i> = 0.004

^aOdds ratio for number of births additionally adjusted for age at first birth and age at last birth additionally adjusted for number of births.

^bOdds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, and duration of use of oral contraceptives.

^cReference category.

^dOdds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, duration of use of oral contraceptives, and cigarette smoking.

^eNot applicable (N/A) because the test for nonlinearity in the log-hazard ratio was significant at $\alpha = 0.05$.

^fWe did not have information on age at first birth for one case who had four births.

^gWe did not have information on age at last birth for one case and one control.

Table 4
Endometrial cancer risk in relation to characteristics of pregnancy history among women with at least 2 births.

	Cases		Controls		Additionally adjusted for age at last birth	
	No.	(%)	No.	(%)	OR	(95% CI)
Number of births ^a						
2 ^b	485	(41)	639	(39)	1.00	1.00
3	373	(31)	525	(32)	0.81	(0.66–1.00)
4	210	(18)	275	(17)	0.82	(0.64–1.05)
≥5	131	(11)	220	(13)	0.59	(0.44–0.78)
Test for trend					<i>P</i> = 0.001	<i>P</i> = 0.006
Age at first birth ^c						
<20 ^b	265	(22)	282	(17)	1.00	1.00
20–24	592	(49)	815	(49)	0.76	(0.61–0.95)
25–29	271	(23)	423	(26)	0.69	(0.53–0.90)
30–34	61	(5)	111	(7)	0.57	(0.38–0.85)
≥35	9	(<1)	28	(2)	0.33	(0.15–0.76)
Test for trend					<i>P</i> < 0.001	<i>P</i> = 0.004

^aOdds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, duration of use of oral contraceptives, and age at first birth.

^bReference category.

^cOdds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, duration of use of oral contraceptives, cigarette smoking, and number of births. We did not have information on age at first birth for one case who had four births.

Table 5
Endometrial cancer risk in relation to age at last birth among women with at least 2 births.

	Cases		Controls		OR		95% CI		OR		95% CI		Additionally adjusted for age at first birth
	No.	(%)	No.	(%)	No.	(%)	OR	95% CI	No.	(%)	OR	95% CI	
Age at last birth (years) ^a													
<25 ^b	225	(19)	251	(15)			1.00				1.00		
25–29	456	(38)	586	(35)			0.85	(0.67–1.09)			0.98	(0.75–1.28)	
30–34	338	(28)	506	(31)			0.81	(0.62–1.05)			1.01	(0.74–1.39)	
≥35	179	(15)	315	(19)			0.68	(0.50–0.92)			0.94	(0.64–1.37)	
Test for trend							<i>P</i> = 0.014				<i>P</i> = 0.830		

^aOdds ratio adjusted for age, reference year, county, body mass index, receipt of higher risk forms of estrogen therapy, duration of use of oral contraceptives, cigarette smoking status and number of births. We did not have information on age at last birth for one case and one control.

^bReference category.