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Timing of births and endometrial cancer risk in Swedish women

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Abstract

While a protective long-term effect of parity on endometrial cancer risk is well established, the impact of timing of births is not fully understood. We examined the relationship between endometrial cancer risk and reproductive characteristics in a population-based cohort of 2,674,465 Swedish women, 20–72 years of age. During follow-up from 1973 through 2004, 7,386 endometrial cancers were observed. Compared to uniparous women, nulliparous women had a significantly elevated endometrial cancer risk (hazard ratio [HR] = 1.32, 95% confidence interval [CI], 1.22–1.42). Endometrial cancer risk decreased with increasing parity; compared to uniparous women, women with ≥ 4 births had a HR=0.66 (95% CI, 0.59–0.74); p-trend < 0.001. Among multiparous women, we observed no relationship of risk with age at first birth after adjustment for other reproductive factors. While we initially observed a decreased risk with later ages at last birth, this appeared to reflect a stronger relationship with time since last birth, with women with shorter times being at lowest risk. In models for multiparous women that included number of births, age at first and last birth, and time since last birth, age at last birth was not associated with endometrial cancer risk, while shorter time since last birth and increased parity were associated with statistically significantly reduced endometrial cancer risks. The HR was 3.95 (95% CI; 2.17–7.20; p-trend=<0.0001) for women with ≥ 25 years since a last birth compared to women having given birth within 4 years. Our findings support that clearance of initiated cells during delivery may be important in endometrial carcinogenesis.

Keywords

endometrial carcinoma; parity; registry; reproductive factors

INTRODUCTION

Endometrial cancer is strongly influenced by a woman's reproductive history. Much like breast (1–4) and ovarian (5–7) cancers, increased parity is known to lower a woman's overall risk of

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endometrial cancer (8–17). For breast cancer, parity shows a dual effect with a transient increase in risk, roughly up to 5 years following pregnancy, and a long-term decline in risk thereafter (1–3). Age at first birth also influences breast cancer risk with older ages being associated with increased risk (2).

Although a protective long-term effect of increased parity is also observed in endometrial cancer, the influence of timing of births is less well established. Some studies have shown older ages at first birth to lower the risk of developing endometrial cancer (12–15), while other studies have not found such an association (11,16–22). Similarly inconclusive is the relationship between age at last birth and risk of endometrial cancer. While some studies show a lower risk among women who complete their family at an older age (8,12,14,15,18), others have not found this association (11,19). Several studies showing a reduced risk associated with later ages at last birth have attributed the association to short time intervals since the last birth, prompting the suggestion that the association might reflect the clearance of premalignant or initiated endometrial cells.

Disentangling the independent effects of ages at births and time since completion of a woman's reproductive history on endometrial cancer risk is complicated by the perfect correlation between these variables. This may explain some of the contradictory findings of previous small studies. In addition, many of the previous investigations involved restricted age ranges or had limited information on the exact timing of births. We therefore investigated the association of parity and the timing of births with endometrial cancer risk in a cohort comprised of roughly 2.6 million Swedish women with follow-up data from 1973 through 2004, the largest study to date on reproductive factors and endometrial cancer risk.

MATERIALS AND METHOD

Study population

The Swedish cohort was created by merging several Swedish registries, the Medical Birth, the Multi-Generation Registry and the Cancer Registries, based on a unique national registration number assigned to every Swedish resident alive in 1947 or born after 1947. Since 1947, immigrants have also been assigned a national registration number when they first immigrate to Sweden. The Medical Birth Registry contains reproductive information on women born after 1925 who have given birth (including live and still births) in Sweden in 1973 or later. The Multi-Generation Registry consists of individuals born in 1932 or later who were alive in 1961, with links to their parents, siblings and offspring. The Swedish Cancer Registry was started in 1958 and contains information on all newly diagnosed tumors for every resident. We excluded women who were not born in Sweden because information on parity for them was incomplete, and women younger than 20 years at the end of follow up, as only a single endometrial cancer was diagnosed in our cohort before age 20. Our final dataset included 2,674,465 women, on whom detailed cancer and birth-related (number and dates of live births) information up to the 6th live birth was available. Each woman's date variables were recorded by month and year of occurrence.

Only cases classified as primary invasive endometrial cancer (ICD 7th Revision, 172) were considered. We did not impose any restrictions on the histologic type. A total of 7,386 women were diagnosed with endometrial cancer during follow-up.

Approval was obtained from the Karolinska Institutional Review Board (IRB) for this study. Informed consent was waived because we had no contact with study subjects. An exemption from IRB review was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

Statistical Analysis

Cox proportional hazard models (PROC PHREG, SAS version 9.1; SAS Institute, Cary, NC) were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Age was used as the underlying time-metric in all analyses (23). Follow-up for a woman started at her age at entry into the cohort and ended at cancer diagnosis or censoring. The age of cohort entry was defined as the woman's age on January 1st 1973 if she was born before January 1st 1973, and her age at birth, i.e. 0, if she was born on January 1st 1973 or later. Censoring events were death, the diagnosis of cancers other than endometrial cancer, emigration from Sweden, or end of follow up, defined as December 31, 2004. We also repeated all analyses starting follow-up at age 20 years for those who entered the cohort before age 20. The proportional hazards assumption was visually checked by plotting hazard curves for reproductive factors and all other adjustment variables (PROC LIFETEST, SAS version 9.1; SAS Institute, Cary, NC) for all women combined, and for women ages 20–49 years and ≥ 50 years. Age 50 was chosen to approximate age at menopause. The proportional hazards assumption was met for all covariates. Reproductive risk factors were used in the models in the following categorizations: number of births: 0, 1, 2, 3, and ≥ 4 births; age at first birth: ≤ 19 , 20–24, 25–29, 30–34 and ≥ 35 years of age; age at last birth: ≤ 24 , 25–29, 30–34, 35–39 and ≥ 40 . For analyses restricted to women ages 20–49, time since last birth was used in the categories 0–4, 5–9, 10–14 and ≥ 15 years, for analyses restricted to women ages 50 years or older, in the categories 0–14, 15–19, 20–24 and ≥ 25 years, and for all women combined in the categories 0–4, 5–9, 10–14, 15–19, 20–24 and ≥ 25 years. For analyses based on all women combined as well as those restricted to women ages 20–49, year of birth was categorized as ≤ 1939 , 1940–1949 and ≥ 1950 . In analysis restricted to women ages 50 years or older, year of birth was categorized as ≤ 1936 , 1937–1941, 1942–1946 and ≥ 1947 . We tested hypotheses of linear trend across categories by assigning increasing integer values to the categories and treating the variable as a continuous covariate.

For analyses including all women, or restricted to women ages 20–49 years, we modeled the number of births and ages at first and last birth as time-dependent categorical variables, represented by indicator variables in the models. A woman changed exposure category whenever she gave birth to a child. In analyses restricted to the 20–49 year age group, we included all women but censored them at age 50. For analyses restricted to parous women ages 20–49 years or all ages combined, follow-up started at the later of age at cohort entry or age at first pregnancy. For analyses restricted to women ages 50 or older, we fit Cox proportional hazards models in which the number of births and ages at first and last births were constant covariates and started follow-up at age 50.

In addition to age at last birth, we also investigated time since last birth, defined as (age – age at last birth), which increases as women get older, but was reset to 0 at the occurrence of another birth. Time since last childbirth was modeled as a time dependent covariate for women of all ages. Wald type chi-square tests were used to compute p-values for heterogeneity of HR estimates.

RESULTS

Table 1 shows the distributions of reproductive characteristics among women in the Swedish cohort at the end of follow up. Overall, 70.27% of the women were parous, and among these women 21.1%, 48.0%, 22.5% and 8.5% had one, two, three and four or more births, respectively. The majority of nulliparous women, 82.0%, were younger than 50 years at the end of follow-up. The median ages of women at their first, second, third and fourth birth were 24 (inter quartile range (IQR) = 21–27), 27 (IQR = 24–30), 30 (IQR = 27–32), and 31 (IQR = 28–35) years, respectively. The median follow-up time in the cohort was 18.5 years.

Among all women, 7,386 developed endometrial cancer during follow up. The majority of women were diagnosed at ages 50 years or older ($N=5912$), while only 1474 women were diagnosed at ages 20–49 (Table 2). Compared to uniparous women, nulliparous women had a higher risk of developing endometrial cancer overall, $HR = 1.32$ (95% CI, 1.22–1.42). The risk was significantly higher for women aged 20–49, $HR = 1.69$ (95% CI, 1.46–1.96), than among women aged ≥ 50 , $HR = 1.20$ (95% CI, 1.10–1.31); p -heterogeneity <0.0001 . Compared to uniparous women, the risk of endometrial cancer decreased as the number of births increased. For example, the risk was $HR=0.83$ for 2 births, $HR=0.69$ for 3 births and $HR=0.63$ for ≥ 4 births (p -trend <0.001). The inverse association with number of births was slightly stronger for younger than older women, with HR s for ≥ 4 births vs. 1 birth being 0.49 (95% CI, 0.38–0.63) for women 20–49 and 0.66 (95% CI, 0.59–0.74) for those ≥ 50 (Table 2).

Among uniparous women, no significant association with age at first (and only) birth was observed for women ages ≥ 50 (p -trend=0.55). However, among women 20–49 years of age, there was a significant reduction in risk with age at first birth (p -trend=0.008; Table 2; p -heterogeneity=0.07). Among those who gave birth at ages ≥ 35 , compared to 20–24, the HR was 0.52 (95% CI, 0.31–0.85). Among multiparous women, there was no association of age at first birth and endometrial cancer risk in Cox models that were adjusted for birth cohort, parity, and age at last birth. Later ages at last birth were associated with statistically significantly lowered risks of endometrial cancer in multiparous women overall, as well as in analyses restricted to those aged 20–49 and ≥ 50 . For example, the hazard ratio for women who had their last birth at ages ≥ 40 compared to ages 25–29 was 0.45 (95% CI, 0.35–0.58; p -trend <0.001). The relationship was slightly enhanced among younger than older women, with $HR=0.22$ (95% CI, 0.090–0.55), p -trend <0.001 , for those <50 years of age and 0.60 (95% CI, 0.46–0.80), p -trend = 0.003, for those aged ≥ 50 years (Table 2). Hazard ratios for parity did not change in models for multiparous women that also included age at first and last birth and birth cohort.

Among parous women, longer periods of time since a last birth were associated with a statistically significant increase in endometrial cancer risk for all women combined, and for women in the age groups 20–49 and 50 years or older (Table 3) in models that also included number of births and ages at first birth. Among parous women aged 20–49 years, the hazard ratios for times since last birth were 1.87 (95% CI, 1.25–2.81), 2.33 (95% CI, 1.58–3.46) and 2.66 (95% CI, 1.76–4.00) for 5–9, 10–14, and ≥ 15 years, respectively, compared to the baseline of 0–4 years since last birth (p -trend = 0.01, Table 3). Among parous women aged >50 years, the hazard ratios for times since last birth were 1.06 (95% CI, 0.98–1.51), 1.21 (95% CI, 1.05–1.40) and 1.37 (95% CI, 1.19–1.58) for 15–19, 20–24 and ≥ 25 years, respectively, compared to the baseline of 0–14 years since last birth (p -trend=0.0013). The association was also seen when the ≥ 50 age group was additionally stratified on age at last pregnancy <35 years or ≥ 35 years, with somewhat stronger effects in the latter group. Women with two, three and four or more births respectively had a progressively lower endometrial cancer risk compared to uniparous women, and age at first birth was not significantly associated with endometrial cancer risk (Table 3). Effects of parity did not differ significantly between the two age at last pregnancy strata for women in the ≥ 50 age group (p -heterogeneity=0.099), but increased parity was significantly more protective among women ages 20–49 than among women in the ≥ 50 age group (p -heterogeneity <0.0001).

The statistically significant increase in endometrial cancer risk associated with longer time since last birth persisted for women ages 20–49 years and 50 years or older in models that also included number of births, and ages at first and last births (Table 4). For parous women ages 20–49, the hazard ratio was 2.49 (95%CI: 1.37–4.53) for those in the ≥ 15 years since last birth category compared to the baseline of 0–4 years since last birth (p -trend=0.0056), and $HR=2.12$ (95%CI:1.04–4.33) when models were restricted to multiparous (2+ births) women ages 20–49 (p -trend=0.0098). Among women 50 years or older the relation with increased time since

last birth was slightly stronger in models restricted to multiparous women, HR=1.51 (95%CI: 1.06–2.15; p-trend=0.042), than for all parous women, HR=1.44 (95%CI: 1.06–1.96; p-trend<0.0001), for the ≥ 25 years since last birth category compared to the baseline of 0–14 years since birth. Age at last birth was not associated with endometrial cancer risk, except for parous women ages 20–49 years, where the hazard ratio for women who had their last birth at ages 40 or later compared to women who had their last birth at ages 25 to 29 years was 0.35 (95% CI, 0.14–0.88; p-trend=0.0862). With the exception of multiparous women ages 20–49, increased parity was associated with a statistically significantly reduced endometrial cancer risk. When all women were analyzed jointly, the HR estimates for the time since last birth categories 0–4, 5–9, 10–14, 15–19, 20–24 and ≥ 25 years were 2.25, 3.26, 3.97, 4.34 and 4.99 (p-trend<0.0001) for parous women, and 1.84, 2.68, 3.25, 3.69 and 3.95 (p-trend<0.0001) for multiparous women, respectively. Age at first and age at last birth were not statistically significantly associated with endometrial cancer risk in the two models.

Sensitivity analyses in multiparous women confirmed the associations reported in Table 4. When age at last pregnancy was used as a continuous variable in a Cox model that also included time since last birth, birth cohort, age at first birth and parity, the HR estimates for the time since last birth categories for multiparous women ages 20–49 years were 1.63 (95%CI: 0.94–2.84), 2.09 (95%CI: 1.15–3.80) and 2.23 (95%CI: 1.10–4.50) for 5–9, 10–14 and ≥ 15 years, respectively (p-trend=0.0492). For multiparous women ages 50 or older, the HR estimates for the time since last birth categories 15–19 years, 20–24 years or ≥ 25 years for the same model were 1.40 (95%CI: 1.02–1.90), 1.53 (95%CI: 1.12–2.081) and 1.65 (95%CI: 1.18–2.31) respectively (p-trend=0.0076). When time since last birth was used as a continuous variable in a Cox model that included all other reproductive factors for multiparous women, the HR estimates for age since last birth for the categories ≤ 24 years, 30–34 years, 35–39 years and ≥ 40 years compared to the baseline of 25–29 years were 0.94 (95%CI: 0.69–1.29), 1.15 (95%CI: 0.86–1.54), 0.80 (95%CI: 0.46–1.41) and 0.50 (95%CI: 0.16–1.60), respectively, for women ages 20–49 (p-trend=0.9655) and 0.89 (95%CI: 0.80–0.99), 0.94 (95%CI: 0.86–1.03), 0.85 (95%CI: 0.73–0.98) and 0.70 (95%CI: 0.52–0.96), respectively, for multiparous women ages 50 or older (p-trend=0.4284). Age at first birth was not significantly associated with endometrial cancer risk in any of the sensitivity analyses, while the hazard ratio estimates for parity did not change noticeably.

We also fitted the model presented in Table 4 that included time since last birth, age at first and last birth, parity and birth cohort separately to women with 2 births, and 3 or more births for women ages 20–49 and ≥ 50 years. The effects of time since last birth appeared more pronounced for women with 2 births than for women with 3 or more births, for both age strata, albeit estimates were not statistically significantly different (p-heterogeneity=0.8365 for women ages 20–49 and p-heterogeneity=0.244 for women ages 50 or older), while the effects of age at last birth or age at first birth did not differ (data not shown).

When analyses were repeated with follow-up starting at 20 years of age, results (data not shown) were very similar to those presented.

DISCUSSION

We comprehensively analyzed the impact of parity and timing of childbearing on endometrial cancer risk in a large cohort of roughly 2.6 million Swedish women with detailed cancer and birth-related (number and dates of live and still births) information. The very large sample size and thirty year follow-up allowed us to disentangle the independent effects of the highly correlated age related reproductive factors, including number of births, age at first and last birth, and time since last birth in relation to age at diagnosis of endometrial cancer using time-dependent survival analyses.

We found a significant association between endometrial cancer risk and the number of births and time since last birth. Consistent with other studies (8–18), women who had experienced more births had lower endometrial cancer risk. The association was stronger in pre-menopausal than in postmenopausal women, also seen previously (8,22). Among uniparous women, later ages at birth lowered risk in women ages 20–49, but older age at last birth was not associated with risk of endometrial cancer in the ≥ 50 age group. Among multiparous women, no significant association with age at first birth was observed, which is in agreement with most studies (11,16–22) but contradictory to others (12–15). Older age at last birth, adjusted for parity and age at first birth was associated with significant decreases in risk of endometrial cancer among multiparous women. We observed an increase in endometrial cancer risk with increasing time since last birth in models adjusted for parity and age at first birth that persisted when models were additionally adjusted for age at last birth. In models adjusted for time since last birth, age at last birth showed no significant association with endometrial cancer risk. This finding has to be interpreted with caution, however, as we attempted to avoid the problem of complete collinearity of age, age at last birth and time since last birth by assuming that risks associated with age at last birth and time since last birth were constant over pre-specified intervals, i.e. by categorizing those two variables. Sensitivity analyses that used either age at last birth or time since last birth as continuous variables in a Cox model that included all reproductive factors confirmed the importance of time since last birth as the major endometrial cancer risk predictor.

The effects of infertility on endometrial cancer are well recognized (24), and the inverse association of parity with risk could be explained by a shift in the hormonal balance towards more progesterone and less estrogen which stimulates endometrial mitotic activity (25). The lower risk of endometrial cancer associated with shorter time since last birth could be due to the shedding of endometrial tissue during delivery that may result in elimination of initiated or precancerous cells (10). However, it could also reflect beneficial hormonal changes that dissipate with the time since the last birth.

While it is well accepted that increased parity lowers endometrial cancer risk, the impact of age at pregnancy on endometrial cancer risk is less well understood, and published results provide contradicting evidence. However, with a few exceptions (10,11), most published studies did not simultaneously analyze ages at first and last birth as well as time since last birth. In a Danish case-control study (12) and in a Polish population-based case-control study (11) endometrial cancer risk decreased with increasing age at first birth. Brinton et al (11) did not observe an association of endometrial cancer risk with time since last birth or with age at last birth. In a hospital based case-control study in Italy (20), age at first birth was not associated with endometrial cancer risk, but time since last birth was. In a prospective cohort study of women in Iowa, aged 55–69 years, McPherson et al.(19) found no association of endometrial cancer incidence with age at first or last pregnancy based on 167 endometrial cancer cases. In a prospective Norwegian cohort Albrektsen et al.(10) found a protective effect of increasing age at last birth for endometrial sarcoma, based on 112 cases, but did not see this association for endometrial carcinoma, based on 554 cases. In this study, time since last birth was associated with risk of endometrial carcinoma but not sarcoma among multiparous women. However, in addition to low power due to the small sample sizes, the study was restricted to women aged 30–56 years, which limits the interpretability of the findings, since endometrial cancer is most commonly diagnosed between ages 50 and 65 years (9). In a prior Swedish study that included data between 1960 and 1992, Lambe et al.(8) observed a significant decrease in risk with later ages at first birth. In addition, among women with two or more births, older ages (≥ 35 years) at last birth were associated with reduced risk after adjustment for parity, ages at first births and ages at interim births. This study was a nested case-control study based on data from matching the Swedish Fertility Registry and Swedish Cancer Registry. The oldest woman in the study was 67 years of age and 90% of the women were born before 1940.

Our dataset also used endometrial cancer cases identified through the Swedish cancer registry. However, the women in our cohort were born and diagnosed more recently, covered a wider age range (the oldest woman in our cohort was 72 years of age), and included 50% more cases (n=7386). We also obtained information on timing and number of pregnancies from different sources, the multigenerational registry and the medical birth registry. All these differences may have contributed to discrepant findings on the effects of age at first pregnancy between our study and that of Lambe (8).

Our cohort was created by merging multiple registries, providing us with a large number of observations, and also allowing us to include information on stillbirths. However, a limitation includes lack of information on non-reproductive endometrial cancer risk factors, such as age at menarche and menopause, use of menopausal hormone therapy and body mass index. These factors have all been found to increase endometrial cancer risk, presumably by increasing levels of estrogen (9). However, in another investigation (10), additional adjustment for these factors had small effects on the risk estimates for age at first birth and last birth. We also did not have information on hysterectomies and thus could not truncate follow-up of women at the time their uteri were removed. The protective effect of parity may be overestimated if women with high parity have higher rates of hysterectomy. However, hysterectomy rates in Scandinavia are lower than those in the U.S. and most conditions leading to hysterectomy are at present not known to be related to parity (26,27).

In summary, our study is the largest study to date on reproductive factors and endometrial cancer risk. We confirmed that endometrial cancer risk increases as parity decreases. We also found that longer time intervals since a last birth in multiparous women significantly increased endometrial cancer. Age at first birth, and, after adjustment for time since last birth, age at last birth were not associated with endometrial cancer risk in our data. Our association with time since a last birth supports the hypothesis that endometrial cancer risk may be influenced by clearance of pre-initiated cells during delivery.

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Table 1

Distribution of reproductive characteristics in the Swedish women's cohort at the end of follow-up

Variable	N	%
Total number of women	2,674,465	
Parity		
0 births	795,027	29.73
≥1 births	1,879,438	70.27
Number of births among parous women		
1 birth	406,669	21.08
2 births	900,280	47.96
3 births	417,197	22.50
≥4 births	155,292	8.46
Age at first birth among parous women		
< 20	267,978	10.02
20–24	744,840	27.85
25–29	584,830	21.87
30–34	220,204	8.23
≥35	61,586	2.30
Age at last birth among parous women		
<25	347,472	12.99
25–30	675,417	25.25
30–34	583,145	21.80
35–39	232,856	8.71
≥40	40,548	1.52
Median age of women with N births (Inter Quartile Range)		
N = 0	30 (24–43)	
1	43 (32–57)	
2	48 (38–58)	
3	50 (41–60)	
≥4	52 (43–62)	
Median age (Inter Quartile Range)		
1 st birth	24 (21–27)	
2 nd birth	27 (24–30)	
3 rd birth	30 (27–32)	
4 th birth	31 (28–35)	

Table 2

Hazard ratios (95% CI) of endometrial cancer for three different models, for various reproductive characteristics

	Women ages 20–49		Women ages ≥50		All ages	
	# cases	HR (95%CI)s	# cases	HR (95%CI)s	# cases	HR (95%CI)s
Total	1474		5912		7386	
All women^o						
Number of births						
0	446	1.69 (1.46–1.96)	1023	1.20 (1.10–1.31)	1469	1.32 (1.22–1.42)
1	291	1.00	1030	1.00	1321	1.00
2	453	0.59 (0.51–0.68)	2384	0.90 (0.84–0.97)	2837	0.83 (0.78–0.89)
3	202	0.51 (0.42–0.60)	1044	0.74 (0.68–0.81)	1246	0.69 (0.64–0.74)
≥4	82	0.49 (0.38–0.63)	431	0.66 (0.59–0.74)	513	0.63 (0.57–0.69)
p-trend		< 0.001		< 0.001		< 0.001
Uniparous women^r						
Age at birth						
≤19	40	1.10 (0.76–1.59)	111	0.92 (0.74–1.14)	151	0.96 (0.80–1.15)
20–24	97	1.00	342	1.00	439	1.00
25–29	87	0.91 (0.68–1.22)	316	0.96 (0.82–1.12)	403	0.95 (0.83–1.09)
30–34	49	0.86 (0.61–1.21)	169	0.90 (0.75–1.09)	218	0.89 (0.76–1.05)
≥35	18	0.52 (0.31–0.85)	92	0.93 (0.74–1.17)	110	0.82 (0.67–1.02)
p-trend		0.008		0.549		0.051
Multiparous women²						
Age at first birth						
≤19	166	1.05 (0.86–1.28)	749	1.07 (0.97–1.17)	915	0.96 (0.90–1.04)
20–24	349	1.00	1747	1.00	2096	1.00
25–29	185	0.94 (0.77–1.15)	1140	1.12 (1.03–1.22)	1325	0.94 (0.88–0.99)
30–34	33	0.89 (0.60–1.33)	196	1.03 (0.87–1.21)	229	0.93 (0.83–1.05)
≥35	4	1.01 (0.35–2.87)	27	1.03 (0.69–1.55)	31	1.16 (0.95–1.42)
p-trend		0.394		0.511		0.016
Age at last birth						
≤24	142	1.17 (0.93–1.46)	558	0.90 (0.81–0.99)	700	0.88 (0.82–0.95)

	Women ages 20–49		Women ages ≥50		All ages	
	# cases	HR (95%CI)s	# cases	HR (95%CI)s	# cases	HR (95%CI)s
25–29	299	1.00	1588	1.00	1887	1.00
30–34	237	0.92 (0.76–1.11)	1261	0.92 (0.84–0.99)	1498	0.86 (0.80–0.92)
35–39	54	0.50 (0.36–0.69)	394	0.78 (0.69–0.89)	448	0.68 (0.61–0.76)
≥40	5	0.22 (0.09–0.55)	58	0.60 (0.46–0.80)	63	0.45 (0.35–0.58)
p-trend		< 0.001		0.003		< 0.001

O model adjusted for birth cohort;
I model adjusted for birth cohort;
² Effects of age at first birth and age at last birth estimated jointly, model additionally adjusted for birth cohort, parity

Table 3

Hazard ratios (95% CI) of endometrial cancer among parous women by time since birth, age at first birth, and number of births adjusted for birth-cohort^a

		Ages 20–49 (# cases=1028)		All parous women ages ≥50		Ages ≥50 (# cases=4889)		Age at last birth <35 (# cases =4345)		Age at last birth ≥35 (# cases 544)		Overall (# cases=5917)	
		# cases ²	HR (95%CI)s	# cases ²	HR (95%CI)s	# cases ²	HR (95%CI)s	# cases ²	HR (95%CI)s	# cases ²	HR (95%CI)s	# cases ²	HR (95%CI)s
Time since last birth													
0–4		25	1.00										
5–9		100	1.87 (1.25–2.81)										
10–14		229	2.33 (1.58–3.46)										
≥15		674	2.66 (1.76–4.00)										
p-trend			0.01										
Time since last birth													
0–14				65	1.00								1.00
15–19				299	1.06 (0.98–1.51)								1.32 (1.14–1.53)
20–24				774	1.21 (1.05–1.40)								1.47 (1.26–1.70)
≥25				3751	1.37 (1.19–1.58)								1.65 (1.39–1.94)
p-trend					0.0013								0.0002
Age at first birth													
≤19		206	1.08 (0.91–1.27)	860	1.02 (0.94–1.11)								1.02 (0.95–1.09)
20–24		446	1.00	2089	1.00								1.00
25–29		272	0.92 (0.79–1.08)	1456	1.08 (1.01–1.16)								1.07 (1.00–1.14)
30–34		82	0.90 (0.69–1.17)	365	0.97 (0.85–1.10)								0.98 (0.88–1.10)
≥35		22	0.81 (0.50–1.31)	119	1.08 (0.88–1.33)								1.03 (0.86–1.25)
p-trend			0.68		0.25								0.53
Number of births													
1		291	1.00	1030	1.00								1.00
2		453	0.60 (0.52–0.70)	2384	0.91 (0.84–0.98)								0.86 (0.80–0.92)
3		202	0.53 (0.44–0.65)	1044	0.76 (0.69–0.84)								0.73 (0.67–0.79)
≥4		82	0.49 (0.35–0.70)	431	0.70 (0.62–0.80)								0.68 (0.60–0.77)
p-trend			<0.0001		<0.0001								<0.0001
													0.36

¹ Each model includes all variables listed in the respective column, in addition to birth cohort

² Numbers as observed at the end of follow up

Table 4
Hazard ratios (95% CI) of endometrial cancer among parous and multiparous women by time since birth, age at first birth, and number of births adjusted for birth-cohort

	Women Ages 20–49		Women Ages ≥50		All women	
	Parous ¹ (# cases=1025)	Multiparous ² (# cases=736)	Parous ¹ (# cases=4889)	Multiparous ² (# cases=3859)	Parous ¹ (# cases=5914)	Multiparous ² (# cases=4595)
Time since last birth						
0–4	1.00	1.00			1.00	1.00
5–9	1.97 (1.21–3.19)	1.60 (0.91–2.81)			2.25 (1.40–3.62)	1.84 (1.07–3.17)
10–14	2.28 (1.35–3.86)	1.92 (1.03–3.58)			3.26 (2.03–5.25)	2.68 (1.543–4.64)
≥15	2.49 (1.37–4.53)	2.12 (1.04–4.33)				
p-trend	0.0056	0.0098				
Time since last birth						
0–14			1.00	1.00		
15–19			1.23 (0.92–1.64)	1.32 (0.95–1.82)	3.97 (2.44–6.45)	3.25 (1.85–5.71)
20–24			1.27 (0.95–1.70)	1.39 (1.00–1.94)	4.34 (2.64–7.14)	3.69 (2.01–6.42)
≥25			1.44 (1.06–1.96)	1.51 (1.06–2.15)	4.99 (2.98–8.34)	3.95 (2.17–7.20)
p-trend			<0.0001	0.042	<0.0001	<0.0001
Age at last birth						
≤24	1.11 (0.92–1.35)	1.14 (0.91–1.42)	0.94 (0.86–1.03)	0.89 (0.80–0.99)	0.96 (0.89–1.05)	0.92 (0.83–1.01)
25–29	1.00	1.00	1.00	1.00	1.00	1.00
30–34	0.98 (0.81–1.20)	1.00 (0.81–1.24)	0.97 (0.90–1.06)	0.94 (0.86–1.03)	0.99 (0.92–1.07)	0.96 (0.89–1.05)
35–39	0.62 (0.42–0.92)	0.65 (0.42–0.99)	0.88 (0.77–1.02)	0.85 (0.73–0.98)	0.89 (0.78–1.01)	0.85 (0.74–0.97)
40	0.35 (0.14–0.88)	0.41 (0.15–1.13)	0.70 (0.52–0.94)	0.73 (0.53–1.00)	0.72 (0.55–0.94)	0.74 (0.55–0.99)
p-trend	0.0862	0.1146	0.1143	0.0989	0.5922	0.4852
Age at first birth						
≤19	1.00	1.00	1.00	1.07 (0.97–1.17)	1.00	1.00
20–24	0.94 (0.79–1.12)	0.95 (0.78–1.17)	1.03 (0.95–1.12)	1.00	0.97 (0.90–1.05)	0.94 (0.87–1.02)
25–29	0.92 (0.73–1.16)	0.90 (0.69–1.17)	1.08 (1.00–1.17)	1.13 (1.03–1.22)	1.04 (0.94–1.15)	1.04 (0.93–1.15)
30–34	0.96 (0.68–1.37)	0.89 (0.57–1.39)	1.01 (0.88–1.16)	1.04 (0.88–1.22)	1.00 (0.86–1.16)	0.97 (0.82–1.15)
≥35	1.32 (0.73–2.36)	1.07 (0.37–3.12)	1.23 (0.97–1.55)	1.07 (0.71–1.60)	1.24 (0.98–1.55)	1.03 (0.70–1.51)
p-trend	0.9237	0.7290	0.4307	0.355	0.1170	0.2232
Number of births						

	Women Ages 20–49		Women Ages ≥50		All women	
	Parous ¹ (# cases=1025)	Multiparous ² (# cases=736)	Parous ¹ (# cases=4889)	Multiparous ² (# cases=3859)	Parous ¹ (# cases=5914)	Multiparous ² (# cases=4595)
1			1.00			
2	0.64 (0.54–0.75)	1.00	0.91 (0.84–0.99)	1.00	0.87 (0.81–0.94)	1.00
3	0.60 (0.48–0.76)	0.94 (0.79–1.13)	0.77 (0.69–0.86)	0.85 (0.78–0.92)	0.76 (0.69–0.83)	0.87 (0.81–0.93)
≥4	0.67 (0.49–0.93)	1.01 (0.76–1.34)	0.73 (0.63–0.84)	0.79 (0.71–0.90)	0.73 (0.64–0.84)	0.83 (0.74–0.93)
p-trend	0.0003	0.9769	<0.0001	<0.0001	<0.0001	<0.0001

¹ All women with ≥1 births

² All women with ≥2 births