

A Prospective Study of the Transient Decrease in Ovarian Cancer Risk Following Childbirth

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Abstract

Epidemiologic evidence shows that the risk of ovarian cancer is decreased following childbirth. We examined the time points when the decreased risk of postpartum maternal ovarian cancer reaches the lowest point and whether the protective effect diminishes over time. A case-control study nested within the Swedish Fertility Register included 10,086 cases of epithelial ovarian cancer recorded in the Swedish Cancer Register from 1961 to 2001. From the Fertility Register, 49,249 eligible subjects matched to the cases by age were selected as controls. The analysis contrasted risk between adjacent parities through logistic regression models that included indicator variables representing each year of age, age at delivery, and time since delivery. Compared with nulliparous women, uniparous women had a transient decrease in maternal

ovarian cancer risk at 2 years after delivery (spline-derived odds ratio, 0.71; 95% confidence interval, 0.53-0.95, for those delivered at age 25 years) and maintained a lower risk for 4 years postpartum. Similar transient decreases were observed in biparous women compared with uniparous women and in women with three parities compared with biparous women. The protective effect of childbearing seemed to diminish with time. The transient decrease in postpartum ovarian cancer risk may define the latent period required for pregnancy hormones in clearing out ovarian cells that have undergone early stages of malignant transformation. The period before the risk increases again could indicate the period required for ovarian cancer induction. (Cancer Epidemiol Biomarkers Prev 2006;15(12):2508-13)

Introduction

Increasing parity has consistently been shown to reduce risk of ovarian cancer (1-8). There is also epidemiologic evidence that the risk of ovarian cancer is lower in women who have an older age at first birth (8-10). With conflicting results, several investigators have examined the association between time since last birth and the risk of ovarian cancer (8, 9, 11). Two studies (8, 9) found evidence of a significantly increased risk of ovarian cancer along with longer time since last birth, whereas others have failed to detect such a temporal trend (11). Whiteman et al. (9) reported a lower risk of ovarian cancer in the category of <10 years since last birth. However, due to sample size limitations and linear extrapolation from models using continuous (1) or wide intervals for time-related variables (8-11) in previous studies, it remains unclear whether there are specific time points following birth when the risk of ovarian cancer is at the lowest.

A recent hypothesis suggests that a pregnancy clears from the ovaries cells that have already undergone malignant transformation (1). The likelihood that such transformed cells exist should increase with age, as does the incidence of clinical disease. The effect associated with pregnancy clearance may be mediated by placental or ovarian hormones associated with childbirth (3). The mechanism of clearance would accommodate the observation that a pregnancy at older age seems to provide a greater reduction in risk than a pregnancy at

younger age. Elimination of the initiated cells itself should have an effect that diminishes with increased time since a delivery. To examine this hypothesis in more details, we applied a single-year categorical modeling approach (12) in a nested case-control study based on information from Swedish nationwide population registers.

Materials and Methods

Members of the study cohort were identified in the nationwide Swedish Fertility Register, which includes all female resident citizens of Sweden born from 1925 and thereafter. The database contains fertility information on number (including nulliparity), gender, and dates of live births, if any, for >3.4 million women. Information on dates of birth for biological and adopted children born between 1943 and 1960 was collected retrospectively at the 1960 Census. From 1961, only biological children were included, with all new births added annually from vital statistics records. The quality of information on reproductive history (i.e., number and dates of births) is generally high, with the exception of the oldest cohorts (mainly women born on 1925-1929) for whom individual fertility levels may be both underestimated and overestimated. Use of the unique national registration number assigned to all individuals at birth or time of first residency permits record linkage and retrieval of information from other population-based registers (13). Vital statistics for women in the Fertility Register is updated annually based on information obtained from the National Population Register.

Since 1958, the Swedish National Cancer Register receives reports about all newly diagnosed malignant tumors from both the physician who made the diagnosis and the pathologist/cytologist who confirmed the diagnosis (14). Each histopathologically confirmed cancer case is assigned a pathologic code. The Cancer Register also contains

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information about residence at the time of diagnosis as well as the hospital and pathology department where the diagnosis was made. The completeness of cancer registration is considered to be close to 100% (14).

Thus, members of the study cohort were all women who were born on and after 1925 and listed in the Fertility Register. We adopted a nested case-control sampling design to allow more efficient analyses. Case subjects were cohort members diagnosed from 1961 to 2001 with incident invasive epithelial ovarian cancer (ICD-7: 175.0 with a pathology code of 096 for adenocarcinoma, 196 for undifferentiated carcinoma, or 146 for squamous cell cancer; ref. 1), as ascertained from the records of the Swedish National Cancer Register. For each woman with ovarian cancer, five comparison control subjects were randomly selected from cohort members listed in the Fertility Register. These women were individually matched by birth year with the index case, were residents of Sweden at the time when the case was diagnosed, were alive at least to the date of the diagnosis for the index case, and had not been previously diagnosed with ovarian cancer. For both cases and controls, only live births before the index case's date of diagnosis were included in the analyses.

Statistical Analysis. To detect whether the relative rate of ovarian cancer varies over time after a delivery and whether there is a nadir in ovarian cancer risk after giving birth, our analyses focused on the exposure contrast between adjacent parities, assuming that, without childbirth and with comparable other risk factors, uniparous women would have the same age-specific rates of ovarian cancer as nulliparous women (15). Similarly, biparous women, given the same age at first birth but without the second birth, would have had the same age-specific rates as uniparous women, and so on. Odds ratio (OR) was used as an estimate of relative risk in our study. To obtain OR estimates associated with single-year time variables, we further refined the logistic regression model with categorical predictor variables as suggested by Heuch et al. (16). We generated indicator variables for each individual year of subject's age (attained age, i.e., case subject's age at diagnosis or control subject's age at identification), age at each delivery, and time since last delivery (12). Age was a matching variable and was adjusted for in the analyses using single-year indicator variable representation. For time since delivery, the first category (<1 year since delivery) served as the reference category. For age at first, second, and third delivery, the category with the largest number of subjects was chosen as the reference category for stability of effect estimate. Conceptually, our model can be partitioned into two parts: the first is a model with age (baseline effect) using the data of women with one

less parity (e.g., nulliparous); the second is a model with age and age at delivery for women with one additional parity (e.g., uniparous). Assuming that, without childbirth, uniparous women would have the same baseline age effect as nulliparous women, relative risk comparing uniparous with nulliparous women could be estimated by subtracting the first from the second model. The residual effect of age (after removing the baseline effect of age) for uniparous women could then be further decomposed into age at delivery and year since delivery (12). For the purpose of graphic presentation, we first fit a six-degree polynomial function to the categorical-specific relative risk point estimates to identify inflexion points in trend over years since delivery (17). We then fit a power (quadratic or cubic) spline model to the original data using as knots the corresponding inflexion points identified from the fitted polynomial functions (18). Usually, a quadratic spline is flexible enough for modeling a nonlinear trend for epidemiologic purposes (18), whereas a cubic model will be used if likelihood ratio test shows that the cubic spline model is significantly better than the quadratic spline model. The graph presents the relative risk since last delivery for women who gave last birth at a particular year compared with women with one less parity, at the same age.

Results

This nested case-control study included subjects who were 13 years or older and consisted of a total of 10,086 epithelial ovarian cancer patients that had matching information in the Fertility Register and 49,249 control subjects.

The first analysis focused on the comparison between uniparous and nulliparous women; 2,534 cases and 10,675 controls were nulliparous, whereas 2,103 cases and 8,796 controls were uniparous. Table 1 shows the distribution of these subjects according to age at diagnosis and age at delivery. Most cases were in the age range 40 to 59 years (55% for nulliparous and 59% for uniparous). Table 2 shows relative risk estimates and 95% confidence intervals (95% CI) associated with each year of age at delivery and each postpartum year since delivery, adjusting for attained age, from the categorical model using single-year indicator variable representation for all three variables. Compared with <1 year since delivery, relative risk estimates were the lowest around 2 years after delivery, and were generally increased from 5 years postpartum and onward (Table 2). However, none of these estimates were significantly different from unity.

Figure 1 displays relative risk estimates associated with each postpartum year since delivery comparing uniparous women

Table 1. Distribution of nulliparous and uniparous epithelial ovarian cancer cases and controls by age at delivery and age at diagnosis

Age at diagnosis (y)	Group	Nulliparous	Uniparous, age at delivery (y)					
			15-19	20-24	25-29	30-34	35-39	40-48
13-19	Cases	49	2	0	0	0	0	0
	Controls	244	6	0	0	0	0	0
20-29	Cases	233	19	38	30	0	0	0
	Controls	1,000	72	216	137	0	0	0
30-39	Cases	343	34	96	72	39	6	0
	Controls	1,283	97	276	350	205	40	0
40-49	Cases	653	75	193	156	86	43	7
	Controls	2,680	221	738	642	379	192	40
50-59	Cases	737	81	205	207	124	54	9
	Controls	3,148	295	905	891	516	222	64
60-69	Cases	424	47	144	113	79	30	6
	Controls	1,912	184	564	548	364	159	36
70-76	Cases	95	9	33	32	15	15	4
	Controls	408	42	134	140	89	24	8

Table 2. ORs and 95% CIs of developing epithelial ovarian cancer in uniparous women, based on single-year categorical model with separate terms for age at first delivery and time since delivery

Variables	Cases (n)	Controls (n)	OR (95% CI)
Parity			
Nulliparous	2,534	10,675	1.00 (Reference)
Uniparous	2,103	8,796	0.82* (0.45-1.51)
Age at delivery (y)			
15	0	14	0.00 (0.00-∞)
16	19	58	1.36 (0.78-2.39)
17	41	160	1.07 (0.72-1.59)
18	80	282	1.17 (0.86-1.60)
19	127	403	1.35 (1.03-1.78)
20	115	529	0.92 (0.70-1.21)
21	167	526	1.33 (1.03-1.72)
22	124	582	0.89 (0.68-1.16)
23	154	579	1.11 (0.86-1.43)
24	149	617	1.00 (Reference)
25	134	583	0.94 (0.73-1.22)
26	140	584	0.99 (0.77-1.29)
27	135	571	0.97 (0.75-1.26)
28	113	510	0.91 (0.69-1.19)
29	88	460	0.79 (0.59-1.05)
30	83	413	0.82 (0.61-1.10)
31	84	324	1.06 (0.78-1.44)
32	63	302	0.86 (0.62-1.19)
33	55	263	0.86 (0.61-1.21)
34	58	251	0.94 (0.67-1.33)
35	43	215	0.83 (0.57-1.22)
36	37	139	1.12 (0.74-1.69)
37	28	130	0.92 (0.59-1.45)
38	21	82	1.09 (0.65-1.84)
39	19	71	1.15 (0.67-1.98)
40	12	53	0.98 (0.51-1.89)
Years since delivery			
<1	14	74	1.00 (Reference)
1	30	165	0.92 (0.46-1.85)
2	22	149	0.75 (0.36-1.56)
3	24	118	0.99 (0.48-2.05)
4	23	115	0.99 (0.48-2.06)
5	23	97	1.12 (0.54-2.34)
6	27	100	1.36 (0.66-2.78)
7	24	98	1.21 (0.58-2.52)
8	24	129	0.92 (0.44-1.89)
9	32	119	1.38 (0.68-2.77)
10	24	107	1.13 (0.54-2.34)
11	28	140	1.00 (0.49-2.03)
12	33	132	1.24 (0.62-2.49)
13	37	150	1.26 (0.63-2.50)
14	50	141	1.83 (0.94-3.56)
15	35	141	1.27 (0.64-2.54)
16	48	180	1.37 (0.71-2.67)
17	56	211	1.38 (0.72-2.65)
18	51	204	1.31 (0.67-2.52)
19	55	201	1.42 (0.73-2.73)
20	56	234	1.25 (0.65-2.41)

NOTE: For brevity, results were not shown for age at delivery from 41 to 48 years and for year since delivery from 21 to 58 years.

*Estimated effect of uniparity with age at delivery and year since delivery at the reference level (i.e., age at delivery of 24 years and time since delivery <1 year) relative to nulliparity, adjusting for age in single-year-indicator representation.

who had an age at first delivery of 25, 30, or 35 years with nulliparous women. The solid lines were cubic spline-smoothed lines (compared with quadratic spline model, likelihood ratio test: $\chi^2 = 12.62$ with 1 degrees of freedom, $P = 0.0004$) to summarize general trends of postpartum risk of ovarian cancer. The spline model fit closely to the model using single-year indicator variables (likelihood ratio test: $\chi^2 = 50.43$ with 53 degrees of freedom, $P = 0.57$). The spline model had a significantly better fit comparing with the model using year since delivery as a continuous variable (likelihood ratio test: $\chi^2 = 10.22$ with 4 degrees of freedom, $P = 0.04$), indicating departure from linearity. Relative risks of developing ovarian

cancer for uniparous women who gave birth at an older age were generally lower than those who gave birth at younger ages (Table 2). Interaction between age at delivery (as a continuous variable) and the terms for year since delivery in cubic spline regression was not statistically significant ($P = 0.52$). Figure 1 shows that the relative risk of developing ovarian cancer for uniparous women was the lowest around 2 years after delivery: spline model-derived OR (95% CI) was 0.71 (0.53-0.95) for those with an age of 25 years at delivery, 0.62 (0.45-0.85) for age 30 years at delivery, and 0.63 (0.43-0.93) for age 35 years at delivery. Uniparous women who gave birth at 30 or 35 years of age had a relative risk of ovarian cancer that was always lower than nulliparous women. For those who gave birth at 25 years of age, the OR was >1.0 during the 13 to 28 years postpartum (spline model-derived OR, 1.01; 95% CI, 0.47-2.16, for 13 years postpartum; Fig. 1).

We next compared biparous (3,373 cases and 16,880 controls) with uniparous women (2,103 cases and 8,796 controls) to estimate relative risk associated with each year since the second delivery. Age at second delivery was not associated with ovarian cancer risk among biparous women after adjusting for age, age at first delivery, and year since the second delivery. Figure 2 displays graphically the findings on time since the last delivery from quadratic spline regression. Biparous women had a transient decrease in risk with a nadir at 3 years after the second delivery: spline model-derived OR (95% CI) was 0.58 (0.45-0.74) for those with an age of 25 years at the second delivery, 0.60 (0.48-0.76) for age 30 years at delivery, and 0.65 (0.49-0.86) for age 35 years at delivery, and the risk gradually increased after that.

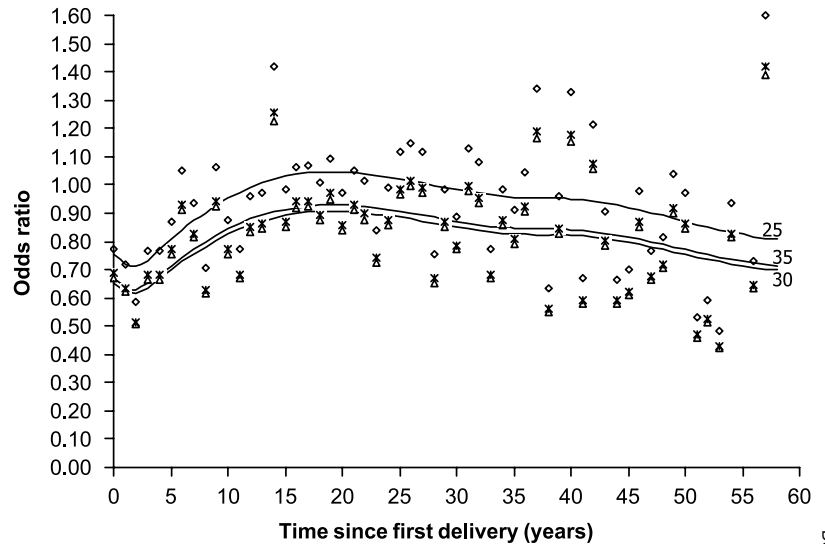
Finally, we compared women with three parities (1,455 cases and 8,658 controls) with biparous women (3,373 cases and 16,880 controls) to estimate relative risk associated with each year since the third delivery. Age at the third delivery was not associated with ovarian cancer risk among women with three parities after adjusting for age, age at the first and the second delivery, and year since the third delivery. Relative risk estimates associated with time since delivery from the spline model indicated that, compared with <1 year since delivery, statistically significant transient decrease in risk at 3 years after the third delivery was observed for women with age 30 years at the third delivery (OR, 0.58; 95% CI, 0.41-0.83), whereas a borderline statistically significant transient decrease in risk at 3 years after the third delivery was observed for those with ages 25 years (OR, 0.66; 95% CI, 0.44-1.00) and 35 years (OR, 0.74; 95% CI, 0.51-1.06) at the third delivery. The relative risk then gradually increased toward unity until 13 years after giving the third birth (Fig. 3).

Discussion

Our results indicate that there is a time window of 2 to 3 years after giving birth when maternal ovarian cancer risk reaches its lowest. Models using continuous variable representations, which assume linearity of effect for time since delivery, are likely to miss this nadir in risk. The results of lower risk within 10 years since last birth are compatible with that observed by Titus-Ernstoff et al. (8) and Whiteman et al. (9). Biparous women and women with three parities in turn had a similarly lower risk of ovarian cancer than that in women with one less parity. Pike et al.'s study (10) has also shown that the additional births further reduce the risk of ovarian cancer.

This study is among the largest epidemiologic analyses of ovarian cancer. Selection and information biases are minimized since the case-control sampling was nested within a well-defined cohort and the exposure information was recorded independent of outcome. The Fertility Register contains no information on stillbirths, and recorded parity status is based on number of live births. However, stillbirths

Figure 1. OR estimates associated with each year since delivery for uniparous women with age at delivery of 25 years (\diamond), 30 years (\triangle), or 35 years (\times) compared with nulliparous women. *Solid lines*, fitted results from power spline logistic regression. The power spline logistic regression core model is $\beta_0 + \beta_p$ (parity) + β_a (age) + β_{aafd} (age at first delivery) + $\beta_1\chi_1 + \beta_2\chi_1^2 + \beta_3\chi_1^3 + \beta_4\chi_2^2 + \beta_5\chi_3^2$, where age and age at first delivery are one-year categorical time variables. χ_1 is the continuous variable of years since first delivery. $\chi_2 = \chi_1 - 3$ if $\chi_1 > 3$, otherwise $\chi_2 = 0$. $\chi_3 = \chi_1 - 38$ if $\chi_1 > 38$, otherwise $\chi_3 = 0$. $\beta_1 = -0.0706$, $\beta_2 = 0.0204$, $\beta_3 = 0.000032$, $\beta_4 = -0.0231$, $\beta_5 = -0.0021$.



represented only a small proportion of all births in Sweden with a decrease from 1.67% in 1955 to 0.39% in 1985 (19). Potential residual bias from excluding stillbirths and misclassification of parity from adopted children for a small number of subjects in the oldest birth cohorts are likely to be negligible and nondifferential.

We could not examine and control for confounding by age at menarche, age at menopause, oral-contraceptive use, and anthropometric factors. A study on mathematical models of ovarian cancer incidence showed that age at menarche and age at menopause were related to cumulative risk of ovarian cancer (20), whereas other studies observed that the association between risk of ovarian cancer and age at menarche or age at menopause was almost null (8, 10, 21). The magnitude of collective confounding by anthropometric factors is likely to be small (22-25). Inability to control for oral contraceptive use is a major limitation in our analysis, as oral contraceptive use has been found in most studies to be inversely associated with ovarian cancer risk and such use also leads to delayed childbirth. However, our results were essentially unaltered when the analyses were restricted to the oldest birth cohort (1925-1935) in which the likelihood of exposure to oral contraceptives or fertility drugs was considered to be small (data not shown). Confounding by age, parity, and age at first

delivery is potentially more substantial and was accounted for in the analyses.

Due to sample size limitation, most previous studies on the time-varying effects of childbirth on maternal ovarian cancer risk fit models using continuous forms or broad intervals for age, age at delivery, and year since last delivery (8-11, 20, 21). Consequently, effect estimates for extreme categories were derived from linearly extrapolated values in such models and yearly variations in postpartum risk could not be adequately examined. Thus far, no study has investigated change in ovarian cancer risk associated with time since last delivery while taking into account the effect of age and age at delivery.

In the statistical model using categorical variables as suggested by Heuch et al. (16), relative risk associated with different time periods since childbirth could be estimated while taking age and age at delivery into consideration. The validity of that model depends on the tenability of at least two assumptions: (a) the effects of age are the same between women of different parities (e.g., uniparous versus nulliparous; biparous versus uniparous) and (b) the effect of age at delivery was homogeneous over age (not modified by age; ref. 26). The two assumptions were, however, judged to impose no restriction on the interpretation of the effect of time since delivery (27). As originally proposed in the model of

Figure 2. OR estimates associated with each year since second delivery for biparous women with age at second delivery of 25 years (\diamond), 30 years (\triangle), or 35 years (\times) compared with uniparous women. *Solid lines*, fitted results from quadratic spline logistic regression. The quadratic spline logistic regression core model is $\beta_0 + \beta_p$ (parity) + β_a (age) + β_{aafd} (age at first delivery) + β_{aasd} (age at second delivery) + $\beta_1\chi_1 + \beta_2\chi_1^2 + \beta_3\chi_2^2 + \beta_4\chi_3^2$, where age, age at first delivery, and age at second delivery are one-year categorical time variables. χ_1 is the continuous variable of years since second delivery. $\chi_2 = \chi_1 - 4$ if $\chi_1 > 4$, otherwise $\chi_2 = 0$. $\chi_3 = \chi_1 - 25$ if $\chi_1 > 25$, otherwise $\chi_3 = 0$. $\beta_1 = -0.1520$, $\beta_2 = 0.0231$, $\beta_3 = -0.0237$, $\beta_4 = 0.0003$.

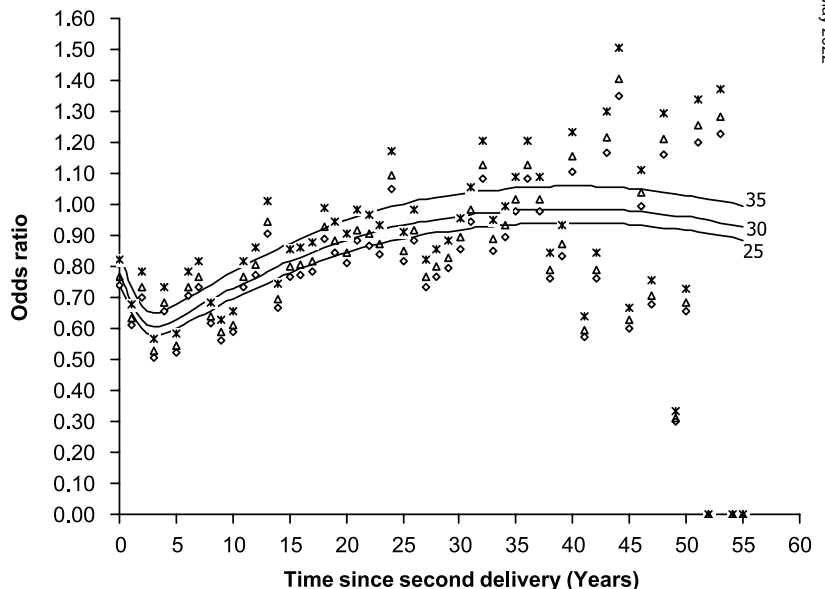




Figure 3. OR estimates associated with each year since third delivery for women who have three parities with age at third delivery of 25 years (\diamond), 30 years (\triangle), or 35 years (\times) compared with biparous women. *Solid lines*, fitted results from quadratic spline logistic regression. The quadratic spline logistic regression core model is $\beta_0 + \beta_p$ (parity) + β_a (age) + β_{aafd} (age at first delivery) + β_{aasd} (age at second delivery) + β_{aatd} (age at third delivery) + $\beta_1\chi_1 + \beta_2\chi_1^2 + \beta_3\chi_2^2 + \beta_4\chi_3^2$, where age, age at first delivery, and age at second delivery are one-year categorical time variables. χ_1 is the continuous variable of years since second delivery. $\chi_2 = \chi_1 - 3$ if $\chi_1 > 3$, otherwise $\chi_2 = 0$. $\chi_3 = \chi_1 - 14$ if $\chi_1 > 14$, otherwise $\chi_3 = 0$. $\beta_1 = -0.3159$, $\beta_2 = 0.0628$, $\beta_3 = -0.0660$, $\beta_4 = 0.0035$.

Heuch et al. (16), categories of age, time since delivery, and age at delivery were set in broad ranges, necessitating additional assumption of homogeneity in relative risk estimates within levels of each variable (26). With the use of single-year indicator representation for age, age at delivery, and years since delivery, the refined model in our analysis did not impose a functional form for the effect of year since delivery and allowed the estimation of nonlinear effects of time since delivery. With the large quantity of data, we were able to estimate relative risk associated with each individual year after delivery while controlling for current age and age at first birth also in single-year-indicator representation.

Incessant ovulation (28) and high serum concentration of gonadotropins (29) have been the two major hypotheses for explaining the biological mechanism behind the development of ovarian cancer. Neither hypothesis, however, can fully explain the protective effect of pregnancy. The incessant ovulation hypothesis is consistent with the observed protective effect of interrupted ovulation due to childbearing or oral contraceptive use, but it cannot explain why oral contraceptive use for longer periods does not provide further protection (1, 2). Also, it cannot explain why the protective effect of interrupted ovulation seems unequal for different parities (1, 2). The effect of ovulation suppression from a pregnancy should be equal among women of different ages, but seems to be stronger in older parous women (1). The hypothesis would also predict a reduced risk with early age at menopause, which has not been convincingly shown (2). The gonadotropin hypothesis fits also with the established effects of parity and oral contraceptive use and would also accommodate a possible association with fertility drugs. However, owing to its effects on gonadotropin concentrations, early menopause should increase the risk, but no such effect has been documented (8). It has been suggested that gonadotropins, while involved in the feedback regulations of ovarian steroid hormones, may not in themselves be responsible for changes in ovarian cancer risk (3). Recently, studies that examined the association between twinning and maternal risk of epithelial ovarian cancer have yielded findings that are in direct conflict with the predictions of these two hypotheses. Mothers of dizygotic twins seem to be exposed to higher levels of follicle-stimulating hormone and may also double ovulate more frequently (30). Based on the two main hypotheses, risk of ovarian cancer in mothers of twins would be predicted to be elevated not only by excessive hormonal stimulation of ovarian cells, but also due to lifelong patterns of ovulation that predispose to malignant change. However, an excess risk

of ovarian cancer in mothers with multiple births has not been shown (8, 30-32). Thus, although many findings from epidemiologic studies are consistent with these two principal hypotheses, alternative hypotheses need to be proposed to accommodate observations that could not be readily inferred from them (1, 3). Findings based on the analyses of earlier experience of the present study cohort have prompted the formulation of a third hypothesis suggesting that the protective effect of childbearing can be explained by pregnancy-induced clearance of malignantly transformed cells from the ovaries (1). Such a mechanism would dictate that elimination of the initiated cells itself should have an effect that diminishes with increased time since a delivery. Study subjects in the previous analysis (1) had a maximum age at diagnosis of 59 years and thus had a limited power to evaluate whether the protective effect may diminish with increased time since pregnancy. In our study, compared with nulliparous women, uniparous women with older age at delivery had a more pronounced reduction in risk. The findings on pattern of relative risk for ages 25 and 35 years at delivery are consistent with the results in Pike et al.'s study (10). Increasing parity has consistently been shown to reduce ovarian cancer risk in epidemiologic studies (1-8), an association that was also confirmed in the current study (data not shown). More importantly, we were able to show that the risk of ovarian cancer is reduced soon after a birth and the protective effect diminished with time, consistent with the hypothesis of a pregnancy-induced clearance effect. Rostgaard et al.'s study (33) using a mathematical model based on the cell clearance hypothesis also showed that a decreased age-specific invasive ovarian cancer incidence rate ratios in the first few years after an pregnancy for women who have been pregnant only once in younger ages (20 or 25 years) compared with nulligravid women.

Our observations have given further support to the pregnancy clearance hypothesis (1). The effect associated with pregnancy clearance may be mediated by placental or ovarian hormones associated with childbirth and is supported by findings in both animal and human studies suggesting that elevated levels of progesterone increase apoptosis in macaque's ovarian epithelial cells (34, 35) and that the combination oral contraceptive formulations with high-progestin potency seem to be associated with a greater reduction in ovarian cancer risk than those with low progestin potency (36). In addition, the period of 12 or more years observed in our analysis before the protective effect of a childbirth diminishes might provide further etiologic insight into the latent period

for the induction of ovarian cancer. Assuming that pregnancy-dependent clearance effect clears from the ovaries the transformed cells, leading to the observed transient decrease in risk, the period that is required for the risk to return to the reference level can reasonably be considered as the time window required for a newly transformed cell to become clinically manifested. If the latency between ovarian cancer initiation and clinical manifestation can be determined, it may lead to development of effective strategies for early detection and intervention of ovarian cancer.

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