

Timing of Pregnancy and the Risk of Epithelial Ovarian Cancer

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Abstract

Recent animal studies suggest that progestagen-induced apoptosis of transformed ovarian surface epithelial cells may underlie the observed protective effect of pregnancy on the risk of ovarian cancer. Assuming that increasing numbers of cells are transformed with advancing age, we postulated that the benefits of pregnancy would be greater for older than younger women and tested this hypothesis in a population-based case-control study. We conducted interviews with 620 parous women, ages 18–79 years, with histologically confirmed incident ovarian cancer and 723 parous controls of the same age. Detailed information was collected on reproductive history, as well as hormonal exposures, smoking, medical history, and other factors. We estimated the relative risk of ovarian cancer associated with births at different ages through multiple logistic regression models. After adjusting for parity, older age at first and last births, and shorter time since last birth were all associated with significantly reduced risks of ovarian cancer. Age at first birth and time since last birth were not associated with ovarian cancer when adjusted for each other, whereas age at last birth remained strongly protective [odds ratio (OR), 0.57; 95% confidence interval (CI), 0.36–0.90] among women >35 years *versus* women less than 25 years. The effect was independent of total parity (per year of age among women with one birth: OR, 0.93; 95%CI, 0.87–1.01; among women with four or more births: OR, 0.96; 95%CI, 0.90–1.02). Our finding that ovarian cancer risk is reduced by pregnancy at older ages is further evidence that pregnancy confers a benefit beyond anovulation and is consistent with the theory that ovarian surface epithelial cell apoptosis induced by pregnancy hormones may be the underlying protective mechanism.

Introduction

The accumulated evidence from epidemiological studies suggests that the risk of epithelial cancer of the ovary is strongly related to the number of ovulations throughout a woman's reproductive life (1, 2). Factors that suppress ovulation, such as

pregnancy or use of hormonal contraceptives, have been widely observed to reduce a woman's risk of ovarian cancer. Insight into the biological mechanisms involved is lacking, yet is central to an understanding of the causal pathways leading to cancer of the ovary.

Historically, there have been two main theories about the origins of ovarian cancer. The "incessant ovulation" hypothesis proposed that the monthly cycle of epithelial trauma and subsequent repair provide an ideal environment for the initiation of cancer (3). The "gonadotropin" hypothesis asserted that ovarian cancer is principally caused by high levels of gonadotropins that increase estrogen production and ovarian surface epithelial proliferation (4). Whereas both hypotheses are compatible with many of the findings from epidemiological studies, several anomalies remain.

The apparent discrepancy between the magnitude of protection against ovarian cancer conferred by 9 months of pregnancy and 9 months of anovulation due to other causes (2) suggests that certain factors associated with pregnancy, such as the hormonal milieu, provide additional protection to the ovarian epithelium, over and above the respite from ovulatory trauma. Moreover, a pregnancy resulting in the birth of two or more offspring reduces a woman's risk of ovarian cancer more than a singleton pregnancy (5). Given that levels of pregnancy hormones are higher in multiple than singleton pregnancies (6), these findings are consistent with the notion that pregnancy hormones provide specific benefits to the ovary.

Adami *et al.* (7) proposed that the protective effect of pregnancy is mediated, at least in part, by "clearance" of precancerous cells from the epithelial lining of the ovary and speculated that such an effect might be mediated by placental or ovarian hormones. Experimental studies in animals provide some support for this theory, with the recent finding that macaques receiving synthetic progestagens have higher frequencies of apoptotic ovarian epithelial cells than control animals, or those receiving estrogen alone (8).

Older women would be more likely to have accumulated a greater number of transformed ovarian surface epithelial cells than younger women. If a certain proportion of epithelial cells is eliminated during each pregnancy, then pregnancy at older ages should, in theory, provide a greater benefit than pregnancy at younger ages in reducing risk of ovarian cancer. We sought to test this hypothesis in a population-based case-control study.

Materials and Methods

We ascertained all histologically confirmed incident cases of primary epithelial ovarian cancer registered in the major gynecological-oncology treatment centers in three Australian states. Women diagnosed in 1991 and 1992 were recruited in Queensland, New South Wales, and Victoria; in Queensland, where the cancer registry was an additional source, women diagnosed in 1993 and the latter part of 1990 were also eligible for enrollment. A specialist gynecological pathologist in each state conducted an independent histological review of all diagnostic specimens. A detailed description of the study has been

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Table 1 Relative risk of ovarian cancer by age at first birth, age at last birth, and time since last birth among all parous women

Variable	Cases		Controls		Single terms	
	n	%	n	%	OR	95% CI
Age at first birth (yr)						
<20	97	15.6	98	13.5	1.00	
20–24	285	46.0	349	48.3	1.02	0.70–1.49
25–29	183	29.5	217	30.0	0.94	0.63–1.42
30+	55	8.9	59	8.2	0.58	0.34–0.97
Continuous					0.97	0.94–0.99
Age at last birth (yr)						
<25	117	18.9	88	12.2	1.0	
25–29	212	34.2	241	33.3	0.70	0.48–1.02
30–34	171	27.5	231	32.0	0.51	0.34–0.77
35+	120	19.4	163	22.5	0.50	0.32–0.78
Continuous					0.96	0.93–0.99
Time since last birth (yr)						
<10	43	6.9	76	10.5	0.21	0.09–0.50
10–14	38	6.2	56	7.7	0.50	0.27–0.92
15–19	63	10.1	85	11.8	0.64	0.40–1.02
20+	476	76.8	506	70.0	1.0	
Continuous					1.04	1.01–1.07

published (9). Briefly, with the consent of the attending doctor, all eligible cases between 18 and 79 years of age who were competent to complete a questionnaire, were invited to participate in the study with their written consent. Twenty-eight cases not on the electoral roll were excluded.

Controls were selected from the electoral roll by a random procedure designed to yield an age and regional distribution similar to that anticipated in the cases; enrollment to vote is compulsory in Australia. Women with a history of ovarian cancer or bilateral oophorectomy, or who were incapable of completing the questionnaire, were ineligible for inclusion in the control series. Ethical approval for the study was obtained from all participating hospitals and institutions.

Trained interviewers administered a standard questionnaire in person either in the clinic (cases) or in the woman's home (some cases, all controls). Topics covered included personal details such as age, place of birth, medical and surgical history, and family history of cancer. We collected details of each woman's reproductive history by a pregnancy and lactation calendar, including time to return of menses after each pregnancy, and a month-by-month calendar of contraceptive practice and attempts to become pregnant until menopause.

Analysis. Primary factors of interest were age at first birth, age at last birth, and time since last birth. These variates are all intercorrelated, and it was of interest to determine which of them had most influence on ovarian cancer risk. We defined parity in terms of full-term pregnancies (including stillbirths and live births, hereafter referred to as "births") rather than other pregnancy outcomes of shorter duration (such as miscarriage), because we were specifically testing the *a priori* hypothesis that exposure to pregnancy-associated progesterone reduces the risk of epithelial ovarian cancer by depleting the ovary of transformed epithelial cells. Progesterone levels climb steeply after the 20th week of pregnancy and are maximal in the third trimester (10).

To weaken the nexus of age, age at last birth, and time since last birth, we included nulliparous women when estimating the joint effect of the latter two variables, as recommended by Heuch *et al.* (11), thereby providing an estimate of the impact of age free of these effects. However, when analyzing the relationship between age at first birth and age at last birth,

only women who had at least two full-term births were included. For this analysis we used a conditional multiple logistic regression model with strata of age, in single years to allay concerns over residual confounding by age (especially for duration of use of oral contraceptives and time since first or last birth).

All analyses were adjusted for number of births, duration of oral contraceptive use, tubal sterilization, hysterectomy, smoking, and alcohol use. Separate analyses of the joint effects of age at and time since last birth were conducted for mucinous and nonmucinous ovarian tumors, invasive *versus* borderline tumors (12, 13), and across strata of number of births, including nulliparous women in each instance as before. We express all findings as relative risks, estimated by ORs with their 95% CIs.

Results

There were 791 cases of epithelial ovarian cancer and 853 controls with data suitable for analysis, reflecting response rates of 90% and 73%, respectively. Of these, there were 620 cases and 723 controls who had given birth to at least one child.

Each of the three factors—age at first birth, age at last birth, and time since last birth—was individually strongly associated with risk of ovarian cancer after adjustment for other covariates (Table 1). Women who were 30 years of age or older at the time of their first birth had a risk of ovarian cancer about one-third lower than women who were less than 20 years of age at first birth. Similarly, women who were 30 years of age or older at the time of their last birth had approximately half the risk of women who completed childbearing before age 25 years. There was also a strong inverse trend between time since last birth and risk of ovarian cancer, with women who gave birth in the last 10 years having an almost 80% reduced risk of ovarian cancer compared with age-matched women whose last birth was 20 or more years previously.

Table 2 presents the relative risk estimates for each of these three variables after adjustment for each of the other two factors, in turn. When age at last birth was included in a model

² The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 Relative risk of ovarian cancer by age at first birth, age at last birth, and time since last birth among women, with simultaneous adjustment for other time-related variables

Variable	Adjusted for	Simultaneously adjusted ORs	
		OR	95% CI
Age at first birth (yr) ^a	Age last birth		
<20		1.00	
20–24		1.15	0.77–1.70
25–29		1.32	0.83–2.11
30+		0.96	0.50–1.85
Continuous		0.99	0.95–1.04
Age at last birth (yr) ^a	Age first birth		
<25		1.0	
25–29		0.65	0.43–0.98
30–34		0.48	0.29–0.78
35+		0.48	0.27–0.87
Continuous		0.97	0.93–1.01
Age at last birth (yr) ^a	Time since last birth		
<25		1.0	
25–29		0.75	0.52–1.10
30–34		0.56	0.37–0.84
35+		0.57	0.36–0.90
Continuous		0.97	0.94–0.99
Time since last birth ^b	Age last birth		
<10 yrs		0.65	0.36–1.18
10–14 yrs		0.87	0.50–1.51
15–19 yrs		0.86	0.56–1.34
20+ yrs		1.0	
Continuous		1.00	0.98–1.02

^a Analysis restricted to multiparous women (see text).

^b Nulliparous women included in this analysis (see text).

with terms for age at first birth, the risk estimates for all categories of age at first birth were essentially null. Because women with only one birth have the same age for first and last birth, these analyses were restricted to women with at least two births. Relative risks for time since last birth were similarly null after adjustment for age at last birth. In contrast, the trend of decreasing risks of ovarian cancer associated with increasing age at last birth persisted after separate adjustment for age at first birth and time since last birth. Overall, the relative risk of ovarian cancer was significantly reduced by 3% (95% CI, 1–6%) for each additional year of mother's age at the birth of her last child.

We investigated whether the observed effect of age at last birth was modified by the well documented protective effect of high parity, because women with greater numbers of births tended to be significantly older at the time of their last birth than women with fewer children (Kendall's tau-b, 0.36; $P = 0.03$). For women with one birth, the mean age at last birth among cases and controls was 26.3 years and 28.0 years respectively; for women with five or more births, 35.0 years and 35.6 years. The protective effect of age at last birth persisted regardless of the total number of births that a woman had (Table 3). Among women with only one birth, each additional year of maternal age reduced the relative risk of ovarian cancer by a similar factor (OR, 0.93; 95% CI, 0.87–1.01) to that observed among women with four or more births (OR, 0.96; 95% CI, 0.90–1.02). We also examined the effect of age at last birth separately for mucinous and nonmucinous histological subtypes, and for borderline and invasive tumors, but there were no discernible differences among them (data not shown).

Discussion

We found that women who were older than 30 years when their last child was born were at significantly lower risk of ovarian cancer than women whose last birth was at younger ages, and this was so after adjusting for other factors, including parity and use of hormonal contraceptives.

We considered the possibility that our findings might be explained by various sources of error. High parity is an established protective factor for ovarian cancer (9, 14, 15), and women with greater numbers of births were appreciably older at the birth of their last child than women with fewer children. Thus, it is possible that the observed protective effect of age at last birth may have been due to confounding by high parity. We controlled for this in two different ways, first by including a term for parity in the multiple regression models, and second by analyzing the relationship within strata of numbers of births. In both sets of analyses, we found that women who had their last birth at older ages had lower risks of ovarian cancer than women who had their last birth at younger ages.

Recall bias was not considered to be a major source of error because it was unlikely that healthy women or women with ovarian cancer would systematically mis-report the dates of birth of their children.

Our attempts to quantify the independent effects of age at last birth and time since last birth were complicated by the reciprocal relationship that exists between the two variables. This relationship can lead to problems of collinearity when fitting a statistical model incorporating an age adjustment and terms for both measures. We were able to address this issue, at least in part, by including nulliparous women in models to estimate the impact of age free of the effects of age at last birth and time since last birth (11). Overall, we found that a woman's age at the birth of her last child was a more important determinant of cancer risk than the time since the birth of her last child, and this was so regardless of her current age. Whereas age at last birth and age at first birth are also correlated, our analyses suggest that a woman's age at the birth of her first child has no independent effect on risk of ovarian cancer after accounting for her age at the birth of her last child and her number of children.

Of the few previous studies that have undertaken these types of analyses, most report similar associations. In a pooled analysis of four United States case-control studies, Cooper *et al.* (16) found high relative risks of ovarian cancer associated with young age at first pregnancy and young age at last pregnancy. Among a cohort of Norwegian women, ages 20–56 years, the risks of epithelial ovarian cancer were observed to increase with time since last birth (17), although this study was unable to control for confounding by hormonal and other environmental factors. Finally, Titus-Ernstoff *et al.* (18) reported a 60% increased risk of ovarian cancer among women who delivered their last birth before age 25 compared with women who delivered at an older age.

How should our findings and those from previous epidemiological studies be interpreted? All findings suggest that the timing of childbearing plays an important role in determining a woman's future risk of epithelial ovarian cancer. The notion that the protective effect of full-term pregnancy is due solely to a 9-month respite from ovulatory trauma does not accord with these findings and suggests that a full-term pregnancy confers additional benefits on the ovarian epithelium to reduce the risk of neoplasia. On the basis of earlier observations, Adami *et al.* (7) speculated that high levels of circulating hormones during pregnancy may clear the ovary of precancerous cells. A possi-

Table 3 Relative risk of ovarian cancer by time since last birth and age at last birth among parous women, according to parity

Variable	Cases	Controls	OR	95% CI	OR	95% CI
			Without mutual adjustment		Mutually adjusted ^a	
Parity						
1	111	63	1.07	0.99–1.15	1.01	0.99–1.02
2	226	259	1.05	1.01–1.10	1.01	0.99–1.02
3	140	215	0.98	0.93–1.04	0.98	0.97–1.00
4+	143	186	1.04	0.98–1.11	1.00	0.98–1.02
Age at last birth						
Parity						
1	111	63	0.93	0.87–1.01	0.99	0.95–1.03
2	226	259	0.95	0.91–0.99	0.95	0.93–0.98
3	140	215	1.02	0.96–1.07	0.99	0.96–1.02
4+	143	186	0.96	0.90–1.02	0.97	0.94–1.00

^a Nulliparous women included in this analysis (see text).

ble explanation for this phenomenon at the cellular and molecular level has come from a recent experiment conducted on primates (8). In a randomized controlled trial of hormonal contraceptives in female macaques, the frequency of apoptotic cells in ovarian epithelium among the group randomized to levonorgestrel (a synthetic progestagen) was 24.9%. In comparison, apoptotic frequencies were substantially lower among controls (3.8%), and those receiving ethinyl estradiol (1.8%) or a combined preparation of ethinyl estradiol and levonorgestrel (14.5%). Because apoptosis is one of the principal protective mechanisms against neoplasia (whereby cells undergo programmed cell death in response to potentially cancerous damage), it is plausible that exposure to agents that promote apoptosis might reduce the risk of cancer.

Direct experimental evidence for protective effects of progestagens in humans is lacking, however, a reanalysis of case-control data, performed specifically to test the progestagen hypothesis, found that women taking oral contraceptives with high-potency progestagens had lower risks of ovarian cancer than women who took oral contraceptives with low progestagen potency (19). The recent observation that multiple births are more protective than singleton births for risk of ovarian cancer (5) also lends support to this theory, given that concentrations of progesterone in twin pregnancies are significantly higher than in singleton pregnancies (6, 20).

The role of sex hormones in the development of female reproductive cancers now seems far more complex than originally thought, having well recognized effects on tumor promotion, as well as tumor-inhibiting effects (21). Our principal finding that childbirth later in reproductive life reduces the risk of epithelial ovarian cancer is in keeping with the accumulating evidence for pregnancy hormones having some inhibitory role in the development of ovarian cancer. One possible explanation is that each pregnancy eliminates a certain proportion of transformed epithelial cells through apoptosis due to high concentrations of circulating progesterone (8).

Under a model of progesterone-induced apoptotic clearance, reductions in risk associated with time since last birth and age at last birth are seen to result from the same underlying phenomenon, namely, the protective benefit of pregnancy, viewed from two different perspectives. We have found after joint analysis that a woman's age at last birth dominates over time since last birth in determining the protective effect. Our data indicate that among a group of women of different ages who last gave birth, for example, 5 years ago, those who were older at the time of their last birth will derive a greater benefit than the younger women, after adjusting for differences in

age-specific ovarian cancer rates. We infer that because older women will have accumulated, on average, a greater number of transformed ovarian epithelial cells than younger women, they will, thus, derive a greater benefit from the pregnancy-induced apoptotic clearance of ovarian epithelial cells. For all women the benefits of pregnancy are maximal in the interval after pregnancy and then attenuate over time, presumably as increasing numbers of epithelial cells are progressively transformed (22).

Our findings need to be placed in context of the complex causal pathways leading to epithelial ovarian cancer. Clearly, ovulatory trauma remains an important mechanism for initiating ovarian carcinogenesis in many instances, and exogenous hormones, foreign bodies, infections, diet, and other factors will also play a role in the development of these tumors (2, 9, 23). We have found evidence supporting the notion that pregnancy hormones may ameliorate the damage incurred by exposure to these numerous causal factors. Discovering how various patterns of exposure to pregnancy hormones at different ages influence a woman's risk of cancer remains a challenge for epidemiologists.

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