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PREGNANCY, BREAST FEEDING, AND ORAL CONTRACEPTIVES AND THE RISK OF EPITHELIAL OVARIAN CANCER

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Abstract—To quantify the effects of cumulative months of pregnancy, breast feeding, and oral contraceptive use on the risk of developing epithelial ovarian cancer, the authors used data collected for the Cancer and Steroid Hormone Study—a multicenter, population-based, case–control study. Detailed reproductive histories were obtained from 436 women aged 20–54 with epithelial ovarian cancer newly diagnosed between December 1980 and December 1982, and from 3833 women aged 20–54 selected at random from the same geographic areas. Estimated relative risks of epithelial ovarian cancer were 0.6 (95% confidence interval (CI) 0.5–0.8) for women who had ever been pregnant, 0.6 (95% CI 0.5–0.8) for women who had ever breast fed, and 0.5 (95% CI 0.5–0.7) for women who had ever used oral contraceptives. Logistic regression analysis revealed a strong trend in decreasing risk of epithelial ovarian cancer with increasing cumulative months of pregnancy; this effect was less pronounced in women aged 50–54 than in younger women. In contrast, a marked reduction in risk was associated with ever having breast fed or used oral contraceptives, while the decrease in risk from additional months of either of these exposures was less than that for pregnancy.

Ovarian neoplasms Pregnancy Breast feeding Oral contraceptives
Retrospective studies Epidemiology

INTRODUCTION

Despite improved understanding of the natural history of epithelial ovarian cancer and advances in its medical and surgical treatment, the prognosis remains poor for the nearly 60% of patients diagnosed beyond the early stages of disease. A review of recent progress in diagnosis and therapy of ovarian cancer concluded that current prospects for new therapies are so limited that the most important new development would be "discovery of a means of prevention" [1, 2].

Epidemiologic studies of ovarian cancer have attempted to identify risk factors that might help define groups of women at unusually high risk of disease or suggest etiologic hypotheses. Among case–control studies of ovarian cancer, the most consistent finding has been a relative deficit of pregnancies among cases [3–9]. These results have provided the main epidemiologic support for the "incessant ovulation" hypothesis, which holds that factors that suppress ovulation reduce the risk of developing ovarian cancer [10, 11]. The observation that two other common exposures that cause anovulation—lactation and oral contraceptive use—are also less prevalent among cases in some studies tends to support this hypothesis. However, other epidemiologic and biologic evidence indicates that the protective effects of pregnancy,

lactation, and oral contraceptive use may depend on mechanisms other than suppression of ovulation alone [7, 12, 13]. To further explore the relationships between each of these three exposures and the risk of epithelial ovarian cancer in women less than 55 years of age, we examined data from the Centers for Disease Control's Cancer and Steroid Hormone Study.

METHODS

The design and goals of the study have been described in detail previously [14, 15]. In brief, the Cancer and Steroid Hormone Study is a population-based case–control study coordinated by the Division of Reproductive Health, Centers for Disease Control. The study was designed primarily to investigate the relationship between oral contraceptive use and breast, endometrial, and ovarian cancers. It was limited to women under age 55, because older women would have been unlikely ever to have used oral contraceptives, which were not widely available in this country until the 1960s. Study participants were enrolled between December 1980 and December 1982 by collaborating Surveillance, Epidemiology, and End Results (SEER) Centers of the National Cancer Institute in eight areas of the U.S. (Atlanta, Detroit, San Francisco, Seattle, Connecticut, Iowa, New Mexico, and Utah).

Cases

The study attempted to identify all women 20–54 years of age who had histologically confirmed ovarian cancer diagnosed during the study period, and who lived in one of the eight study areas at the time of diagnosis. Of the 816 women identified who met our case definition, 579 (71.0%) were interviewed. Reasons that cases were not interviewed included death (3.1%), debilitating illness (5.1%), patient refusal (5.2%), physician refusal (2.9%), and the inability to locate the woman or conduct an interview within 6 months of diagnosis (12.7%). Of those interviewed, 494 cases (85.3%) had a final diagnosis of epithelial ovarian cancer [15]. Additional information on histologic type was available from the six centres that enrolled the majority of cases. These included 324 cases classified as malignant, 123 as borderline, and 2 as carcinoma *in situ*.

Controls

The control group consisted of women 20–54 years of age, identified by an established method of randomly selecting telephone numbers of households in the geographic areas where women in the case group lived [16]. We selected a proportion of controls in each 5-year age group to match the expected age distribution of women with breast cancer enrolled in the study. Of the 5698 women selected as controls, 83.4% agreed to participate, while 11.9% refused and 4.7% could not be located or interviewed within 6 months of selection. We excluded 516 women without ovaries or with an unknown number of ovaries from the control group for this analysis.

Interview

Trained interviewers administered a standard questionnaire to both cases and controls in the women's homes. Questions focused on reproductive, contraceptive, and medical histories, medical care utilization, and personal characteristics and habits. The interviews used a month-by-month calendar to record major life events from menarche to menopause, including marriages, divorces, and deaths of family members. With these usually well-remembered events as a framework, all pregnancies of any length, as well as periods of breast feeding and contraceptive use, were entered on the calendar. Months of oral contraceptive use were not recorded if a woman reported never having used them for at least 3 consecutive months.

Analysis

Because this analysis focused on the relationship between epithelial ovarian cancer and total months of pregnancy, breast feeding, and oral contraceptive use, we excluded the 58 cases and 405 controls for whom any of this information was incomplete. Among those excluded were the 42 cases and 249 controls who reported never having used oral contraceptives for at least 3 consecutive months. These women could potentially have used oral contraceptives for any number of brief periods; however, since these were not recorded, their total cumulative exposure could not be calculated.

For the remaining 436 cases and 3833 controls, information from the interview questionnaire and calendar enabled us to calculate the cumulative numbers of months that a woman had been pregnant, had breast fed, or had

used oral contraceptives. These exposures were examined first in stratified tables. Categorical and continuous variables for each exposure in months were then used in a logistic regression analysis. The continuous pregnancy variable included all months of all pregnancies, regardless of outcome. The continuous breast feeding variable included all months that a woman reported she had breast fed, regardless of pattern. Finally, the continuous variable for oral contraceptive use was the sum of all months of exposure, regardless of the length or number of episodes of use, or of the oral contraceptive formulations used.

To identify factors that might distort the effects of the main exposures under study, we looked for associations in our data between several demographic and personal characteristics and risk of epithelial ovarian cancer. We found no associations for study center (eight centers), education (<12 years, $\geqslant 12$ years), income ($<\$20{,}000$, \$20,000–\$39,000, $\geqslant \$40{,}000$, refused/unknown), or history of thyroid disease (none, hypothyroid, hyperthyroid). On the other hand, race (white, black, other), adiposity (weight (g)/height (cm) squared; <2.5, $\geqslant 2.5$), frequency of pelvic examinations (less often than once every 5 years, more often), and family history of ovarian cancer (yes, no, unknown) all appeared to be associated with ovarian cancer risk; these findings have been presented previously [15, 17]. We also examined the effects on ovarian cancer risk of several reproductive characteristics (including infertility and age at first birth), which are described below. However, controlling for the potentially confounding effects of these demographic, personal, and reproductive characteristics did not alter the associations we found between pregnancy, breast feeding, and oral contraceptive use and risk of epithelial ovarian cancer.

We performed stratified analyses to assess these associations among women of different ages. Observed age-specific differences were examined in terms of age-related characteristics, including menopausal status and time since last pregnancy, as described below. The study employed a frequency-matched design because the incidence of ovarian cancer (as well as breast and endometrial cancer) increases markedly with age, and many hypothesized risk factors are likewise highly age-dependent. However, because controls had been selected to match the expected age distribution of breast (not epithelial ovarian) cancer cases, slightly more cases than controls in our study population were in the younger age groups [15]. Controlling for age using either one continuous or several categorical variables had little effect on the main associations. The results presented have been adjusted for age using categories (20–29, 30–39, 40–49, 50–54 years) collapsed from the 5-year age groups employed in the design.

We used two approaches to examine the effects of the main exposures on risk of epithelial ovarian cancer. First, we constructed a logistic regression model [18, pp. 235–263] *a priori* to test the "incessant ovulation" hypothesis, comparing the effects of cumulative months of pregnancy, breast feeding, and oral contraceptive use on the risk of developing epithelial ovarian cancer. Second, we examined these exposures more closely for clues to the differences in their effects. Because the three main exposures were interrelated, we used logistic regression methods to examine each exposure in the context of the other two. Pregnancy and oral contraceptive use each occurred in some women in the absence of the other exposures; however, all women who breast fed had also been pregnant. The effects we report for pregnancy and breast feeding reflect the following comparisons: women who had been pregnant but never breast fed were compared with women who were never pregnant; women who had breast fed were compared with women who had been pregnant but never breast fed.

Maximum-likelihood estimates were obtained using the SAS PROC LOGIST computer program [19]. Odds ratios and 95% confidence intervals for the various exposures were calculated from the estimated β coefficients and their standard errors. For ease of interpretation, we refer to odds ratios as relative risk estimates.

Tests for trend within the exposed groups were performed using continuous exposure variables. To assess interactions among the main exposures and age, we used likelihood ratio tests [18, pp. 259–263] to compare logistic regression models with and without the relevant interaction terms. When not otherwise specified, tests of statistical significance were performed at the $\alpha = 0.5$ level.

We assessed the goodness of fit of logistic regression models using the likelihood ratio test and a statistic based on observed and expected numbers of cases and controls within groups defined by deciles of risk [18, pp. 263–265; 20]. In conjunction with these statistical tests, we

used graphic plots of predicted values of relative risk to compare several continuous models with simple categorical models for each of the main exposures.

RESULTS

Pregnancy, breast feeding, and oral contraceptive use were all less prevalent among cases than among controls in our study (Table 1). These relationships remained consistent when we considered borderline and malignant, or serous and mucinous, cases separately. All three exposures were associated with reduced risk of epithelial ovarian cancer, even when we controlled for the effects of the other two and for age; this is indicated in Table 2, Model I by the negative β estimates, which correspond to relative risk estimates <1.0. Estimated relative risks of ovarian cancer were 0.6 (95% CI 0.5–0.8) for women who had ever been pregnant, 0.6 (95% CI 0.5–0.8) for women who had ever breast fed, and 0.5 (95% CI 0.5–0.7) for women who had ever used oral contraceptives, in comparison with women without the relevant exposures. There were no statistically significant two-way interactions among the dichotomous main exposure variables, or between any of them and age.

Table 1. Pregnancy, breast feeding, and oral contraceptive use in epithelial ovarian cancer cases and controls, Cancer and Steroid Hormone Study, 1980–1982

	Unexposed		Exposed		Cumulative exposure (months)*	
	N	(%)	*N*	(%)	Median	25th–75th percentiles
Pregnancy						
Cases	92	(21)	344	(79)	20	17–29
Controls	390	(10)	3443	(90)	27	18–36
Breast feeding						
Cases	299	(69)	137	(31)	5	2–11
Controls	2037	(53)	1796	(47)	6	2–13
Oral contraceptive use						
Cases	240	(55)	196	(45)	32	12–61
Controls	1517	(40)	2316	(60)	43	15–87

*Among exposed.

Under the "incessant ovulation" hypothesis, each month of anovulation should produce the same reduction in risk of ovarian cancer, regardless of the cause of anovulation or the cumulative number of previous anovulatory months. To test this hypothesis, we compared the respective effects of months of pregnancy, breast feeding, and oral contraceptive use, modeled as continuous variables and controlled for age (Table 2, Model II). This model suggested that each month of pregnancy was associated with a 2.6% reduction in the estimated relative risk of ovarian cancer; each month of breast feeding reduced risk by 2.4%, while each month of oral contraceptive use reduced it by 0.8%.

We next examined a model including dichotomous and continuous variables for each of the three main exposures (Table 2, Model III). This model permitted statistical testing for dose–response effects among women with the relevant exposures, and for a "threshold" effect associated with ever having been exposed. For pregnancy, only the continuous variable contributed significantly to the model, and there was a strong trend in decreasing risk with increasing total exposure. For both breast feeding and oral contraceptive use, a consider-

Table 2. Results of logistic regression models for pregnancy, breast feeding, oral contraceptive use, and risk of epithelial ovarian cancer, Cancer and Steroid Hormone Study, 1980–1982

	Model*				
	I	II	III		
Variable	β	β	β	χ^2 for removal	One-tailed p for trend
Pregnancy					
Dichotomous	−0.490		0.050	0.09	
Continuous		−0.026	−0.025	28.91	4×10^{-8}
Breast feeding					
Dichotomous	−0.514		−0.251	3.20	
Continuous		−0.024	−0.014	2.16	0.07
Oral contraceptives					
Dichotomous	−0.570		−0.314	4.94	
Continuous		−0.008	−0.005	9.44	0.002

*Models include variables for all three main exposures as indicated, and categorical variable for age; β coefficients are the logarithms of odds ratios (relative risk estimates).

able reduction in risk was associated with ever having been exposed, while the decrease in risk with subsequent months of exposure was less than that for pregnancy. These relationships remained unchanged if we redefined the exposures as suggested by Risch *et al.* [7], attributing an additional 1.5 months of anovulation to each term pregnancy and a total of 0.55 months of anovulation to each month of breast feeding.

To characterize further the effects of pregnancy, breast feeding, and oral contraceptive use on ovarian cancer risk, we investigated each of the main exposures in more detail. As a framework for this part of the analysis, we used a model including dichotomous and continuous variables as in Table 2, Model III, omitting the dichotomous variable for pregnancy. This model fit the data adequately (goodness-of-fit $\chi^2 = 6.01$, $8\,df$, $p = 0.65$), significantly better than the model including only continuous variables for the main exposures ($\chi^2 = 8.56$, $p = 0.01$). Further modifications of the model suggested by the data are described below.

Compared with nulligravidas, women who had ever been pregnant had a similarly reduced risk of ovarian cancer, regardless of age. In all age groups, full-term pregnancies accounted for most months of pregnancy. Although women aged 50–54 tended to have the highest parity, they experienced less reduction in risk with each full-term pregnancy than did younger women (Table 3). A term for interaction between age (<50, $\geqslant 50$) and total months of pregnancy contributed significantly ($\chi^2 = 12.81$, $p = 3 \times 10^{-4}$) to the basic logistic regression model.

We examined this age–pregnancy interaction among women aged 40–54 to see whether the difference in the effect of pregnancy was a function of menopausal stratus. Women were considered menopausal if they reported that their menstrual periods had ceased naturally, if they had not menstruated in the previous 6 months and were experiencing menopausal symptoms, or if they had had a hysterectomy and were more than 49 years of age. The protective effect of parity was more pronounced in premenopausal women (Table 4); however, even when we added terms for menopausal status and its interaction with age (<50, $\geqslant 50$) to the logistic regression model, the interaction between age and months of pregnancy remained statistically significant. Results were similar when we restricted the analysis to women who had ever been pregnant and controlled for the effect of number of months since the end of the last pregnancy (data not shown). The effects of age, menopausal status, and months since the end of the last pregnancy were difficult to separate, since menopausal status and time since last pregnancy are correlated with age. We retained only the interaction term for age and months of pregnancy in the subsequent analysis.

Table 3. Parity among epithelial ovarian cancer cases and controls, by age, Cancer and Steroid Hormone Study, 1980–1982

Age group		Nulligravid	Gravid, nulliparous	Parity 1	2	3	4	≥5
20–29	Cases	24	8	10	4	0	0	0
	Controls	95	34	61	42	21	4	0
	RR*	Ref.†	1.3	1.0	0.7	‡	‡	‡
30–39	Cases	21	7	19	26	12	3	0
	Controls	103	53	150	332	176	67	38
	RR*	Ref.	0.7	0.8	0.5	0.4	0.3	‡
40–49	Cases	31	4	20	37	37	14	8
	Controls	107	25	120	374	412	256	291
	RR*	Ref.	0.6	0.7	0.5	0.5	0.3	0.1
50–54	Cases	16	4	12	44	38	15	22
	Controls	85	19	85	222	249	182	230
	RR*	Ref.	1.2	0.9	1.4	1.1	0.6	0.7
Total	Cases	92	23	61	111	87	32	30
	Controls	390	131	416	970	858	509	559
	RR*	Ref.	0.9	0.8	0.6	0.6	0.3	0.3

*Relative risks (RR) estimated by odds ratios, adjusted by logistic regression methods for breast feeding and oral contraceptive use (dichotomous and continuous variables as in Table 2, Model III); within each stratum, women who were never pregnant (nulligravid) constitute the referent group.
†Ref. = referent group.
‡Adjusted relative risk estimates not calculated for cells containing no cases.

Table 4. Parity among epithelial ovarian cancer cases and controls 40–54 years of age by menopausal status*, Cancer and Steroid Hormone Study, 1980–1982

Menopausal status	Nulligravid	Gravid, nulliparous	Parity 1	2	3	4	⩾5
Premenopausal							
Cases	17	2	11	18	24	7	6
Controls	70	16	66	233	272	164	169
RR†	Ref.‡	0.6	0.9	0.5	0.6	0.2	0.2
Menopausal							
Cases	28	6	20	63	48	21	24
Controls	120	28	138	358	383	270	347
RR†	Ref.‡	1.0	0.7	1.0	0.7	0.5	0.4

*Excludes 7 cases and 23 controls with unknown menopausal status.
†Relative risks (RR) estimated by odds ratios, adjusted by logistic regression methods for pregnancy (continuous variable), breast feeding and oral contraceptive use (dichotomous and continuous variables as in Table 2, Model III), and age (<50, ⩾50); within each stratum, women who were never pregnant (nulligravid) constitute the referent group.
‡Ref. = referent group.

Among both cases and controls, a history of breast feeding was somewhat less prevalent than either a history of pregnancy or of oral contraceptive use. Among controls, only 6.4% of parous women had breast fed for 24 months or more. When we excluded nulliparous women, women who had breast fed only 1–2 months had a relative risk of ovarian cancer of 0.6 (95% CI 0.5–0.9), compared with women who have never breast fed (Table 5). Further reduction in risk was seen only in women who had breast fed for 24 months or more. These findings were similar for women in all age groups. When we considered the number of pregnancies followed by breast feeding, rather than the total number of months breast fed, we again found that most of the protection due to breast feeding occurred with the first exposure.

Similarly, a considerable reduction in ovarian cancer risk occurred with just a few months of oral contraceptive use. No information on total duration of use was collected from women who reported using oral contraceptives for fewer than 3 consecutive months, and these women were excluded from the current analysis. However, even women who had used oral contraceptives for as few as 3–5 months had a relative risk of ovarian cancer of 0.7 (95% CI 0.5–1.0), compared with women who had never used them. These effects did not vary among women of different ages.

These findings related to oral contraceptive use are illustrated in Fig. 1. In this figure, odds ratios (which estimate relative risks) are plotted on the y-axis, against months of oral contraceptive use on the x-axis. The horizontal line segments indicate the odds ratios associated with categorical variables for oral contraceptives use (3–11, 12–35, 36–59, 60–119, ⩾120 months). The vertical lines are positioned at the median months of oral contraceptive use among controls within each category; their endpoints on the y-axis indicate 95% confidence intervals around the odds ratio. The two broken lines correspond to continuous versions of the exposure variable (Table 2, Models II and III). The logistic regression procedure models the logarithm of the odds ratio as a linear function of exposure; thus, with a logarithmic scale on the y-axis, the continuous models are represented by straight lines. The dotted line passing through the origin represents Model II, which assumes the same decrease in risk with each month of oral contraceptive use. The dashed line represents an alternative model (Model III), which incorporates a dichotomous term in addition to the continuous variable for months of oral contraceptive use. This line has a y-intercept corresponding to the relative risk estimate associated with ever-use of oral contraceptives. Adding the dichotomous term resulted in a statistically significant improvement in fit.

Table 5. Breast feeding among epithelial ovarian cancer cases and controls, parous women only, Cancer and Steroid Hormone Study, 1980–1982

	Months of breast feeding 0	1–2	3–5	6–11	12–23	⩾24
Cases	184	40	32	33	25	7
Controls	1517	552	330	379	321	213
RR*	Ref.†	0.6	0.8	0.8	0.7	0.3

*Relative risks estimated by odds ratios, adjusted by logistic regression methods for pregnancy (continuous variable), oral contraceptive use (dichotomous and continuous variables as in Table 2, Model III), age (categorical variable) and age–pregnancy interaction; women who never breast fed constitute the referent group.
†Ref. = referent group.

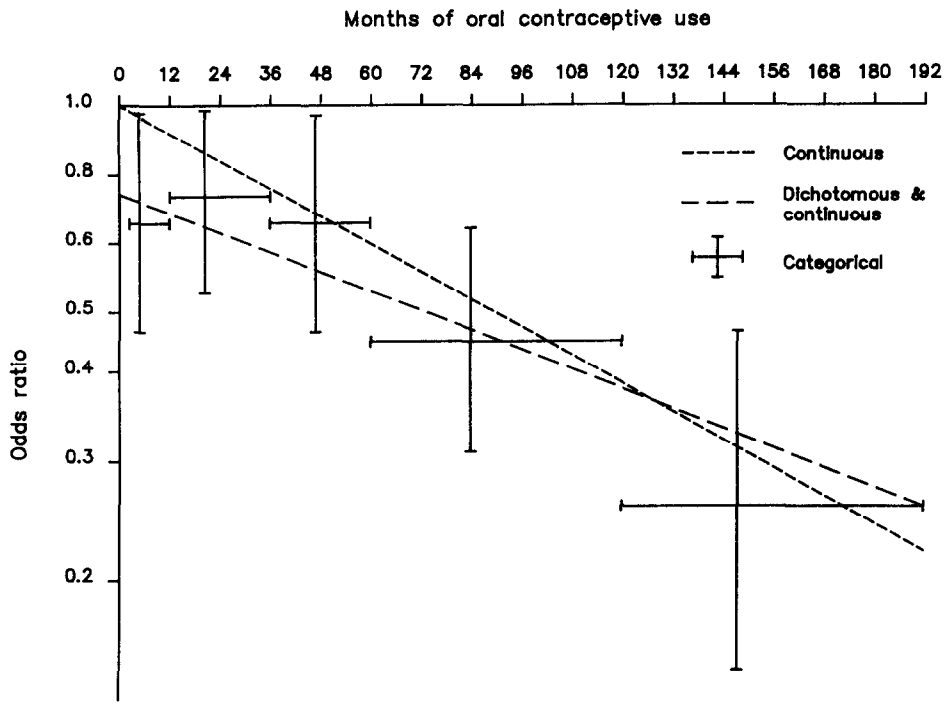

Fig. 1. Results of three different logistic regression models for oral contraceptive use and risk of epithelial ovarian cancer. Maximum exposure = 272 months among controls.

Such a model might suggest a threshold effect associated with ever-use of oral contraceptives, as well as a further reduction in risk with additional months of use. However, the distinction between the two continuous models hardly seems conclusive if considered in the context of the figure, which illustrates the marked variability in the relative risk estimates at all levels of exposure.

Finally, we assessed possible relationships between selected additional reproductive variables (Table 6) and epithelial ovarian cancer risk. In general, these exposures were not associated with risk of ovarian cancer when we controlled for age, pregnancy, age–pregnancy interaction, breast feeding, and oral contraceptive use. The suggestion of a trend in decreasing risk with increasing age at first birth was limited in our data to women of parity one.

Table 6. Selected reproductive characteristics, epithelial ovarian cancer cases and controls, Cancer and Steroid Hormone Study, 1980–1982

	Cases		Controls			
	N	(%)	*N*	(%)	RR*	(95% CI)
Age at menarche						
<12	82	(19)	804	(21)	0.9	(0.7–1.2)
12–13	239	(55)	2040	(53)	1.0	Ref.‡
>13	111	(25)	974	(25)	1.0	(0.8–1.3)
Unknown	4	(1)	15	(<1)	—	—
Medically diagnosed infertility						
Yes	27	(6)	169	(4)	1.1	(0.7–1.7)
No	406	(93)	3652	(95)	1.0	Ref.
Unknown	3	(1)	12	(<1)	—	—
Possible subfecundity†						
Yes	138	(32)	1019	(27)	1.1	(0.8–1.3)
No	245	(56)	2270	(59)	1.0	Ref.
Unknown	53	(12)	544	(14)	0.9	(0.7–1.3)
Age at first birth (parous women)						
<20	78	(24)	809	(24)	1.0	Ref.
20–24	150	(47)	1580	(48)	0.8	(0.6–1.1)
25–29	71	(22)	681	(21)	0.7	(0.5–1.1)
⩾30	17	(5)	186	(6)	0.5	(0.3–1.0)
Unknown	5	(2)	56	(2)	—	—
Number of ovaries						
1	23	(5)	219	(6)	0.9	(0.6–1.5)
2	408	(94)	3614	(94)	1.0	Ref.
Unknown	5	(1)	0	(0)	—	—

*Relative risks estimated by odds ratios, adjusted by logistic regression methods for pregnancy (continuous variable), breast feeding and oral contraceptive use (dichotomous and continuous variables), age (categorical variable), and age–pregnancy interaction.

†24 months or more of sexual activity without contraception or conception (information derived from life-event calendar).

‡Ref. = referent group.

DISCUSSION

Although the causes of epithelial ovarian cancer remain unknown, animal studies and epidemiologic observations have suggested several etiologic hypotheses [12]. Among these is the "incessant ovulation" hypothesis, which holds that a key step in the pathogenesis of

ovarian cancer is the disruption of ovarian epithelium occurring at the time of the ovulation [10, 11]. Several case–control studies have found a decrease in risk of epithelial ovarian cancer associated with pregnancy, breast feeding [7], and oral contraceptive use [4, 6, 7, 21–23]—the three major causes of anovulation during normal reproductive life. Risch *et al.* [7] used logistic regression methods to test the hypothesis that equal periods of anovulation, regardless of cause, produce the same reduction in ovarian cancer risk; they found that the amounts of anovulatory time attributable to these three exposures did not completely account for their protective effects.

In our study, interviewers recorded detailed information on periods of pregnancy, breast feeding, and oral contraceptive use for each woman, using a month-by-month calendar; this information enabled us to compute the total months of each exposure. We found that all three exposures were associated with decreased risk of epithelial ovarian cancer. Any month-by-month comparison of the effects of pregnancy, breast feeding, and oral contraceptive use on risk of ovarian cancer is complicated by the fact that equal months of these exposures do not necessarily result in equal periods of anovulation. The reduction in risk per month of breast feeding might be expected to be less than that for pregnancy, since ovulation tends to resume before the end of lactation; however, in our data the effects of these variables were quite similar, while that for months of oral contraceptive use was only one third as great. If suppression of ovulation were the single underlying protective mechanism, we would at least expect a given period of a particular exposure to produce the same reduction in risk, regardless of previous exposure. This was not the case in our data, since the initial months of breast feeding and oral contraceptive use had greater influence on risk than did later months.

We found a strong trend in decreasing risk of epithelial ovarian cancer with increasing cumulative months of pregnancy; this effect was considerably less pronounced in women 50–54 years of age than among younger women, a finding that could not be explained solely in terms of menopausal status or time since last pregnancy. A limitation of our study is that it was restricted to women less than 55 years of age; therefore, we were unable to investigate this relationship in older women—those at highest risk of developing epithelial ovarian cancer. A reduction after age 50 in the protective effect of pregnancy is consistent with a recently proposed model based on "cell-cycle time" [24], which is related to the "incessant ovulation" hypothesis. However, we found no analogous dependence on age of the protective effects of breast feeding and oral contraceptive use which would also be predicted by this model.

For breast feeding and oral contraceptive use, we found that a marked reduction in risk was associated with ever having been exposed, while the decrease in risk with additional months of exposure was less than that for pregnancy, even though women tend to be able to recall their oral contraceptive use in the context of a life-event calendar [25], they still may not remember periods of oral contraceptive use or breast feeding as accurately as their pregnancies. Random errors in the reported durations of either of these exposures might result in observed attenuation of their associated dose–response effects [26] in comparison with that for pregnancy. This situation might also result in an apparent "threshold" effect if women's recall for whether or not they had ever breast fed or used oral contraceptives was better than their recall for duration of exposure.

A threshold effect could also be due to an underlying difference between women who breast fed or used oral contraceptives and those who did not, which was not accounted for in our analysis. None of the potentially confounding demographic, personal, and reproductive characteristics considered in the analysis appreciably altered the results. In particular, the information on infertility provided by women in our study had no role in explaining the findings of this or of a previous, more detailed analysis of the data related to oral contraceptive use and risk of ovarian cancer [15]. A biological explanation of the threshold effects that we observed for breast feeding and oral contraceptive use would have to hypothesize a permanent change in at least one factor underlying ovarian carcinogenesis, such as function of the hypothalamo–pituitary–ovarian axis. Such effects might well differ for the two exposures. Our analysis provided no suggestion of a similar effect for pregnancy.

In general, our findings support a role for anovulation in protecting against epithelial ovarian cancer, but they suggest that the protective effects of pregnancy, breast feeding, and oral contraceptive use may involve other mechanisms as well. Although all three of

these exposures suppress ovulation, they have different effects on a woman's hormonal milieu. Investigations of these differences are needed to interpret the results of epidemiologic studies in ways that can reveal new clues to the pathogenesis and prevention of ovarian cancer. For example, investigators who studied plasma prolactin in relation to parity and age at first birth in a group of 4500 women found that levels depended not only on parity, but on time since last birth and on menopausal status [27]. Similar investigations of other hormonal factors could help to place epidemiologic findings—such as the interaction we observed between the effects of pregnancy and age on risk of ovarian cancer—in a useful context.

Several epidemiologic studies have found a reduction in risk of ovarian cancer associated with pregnancy, breast feeding, and oral contraceptive use. However, even in this relatively large study, we had limited ability to distinguish clearly among models with different etiologic implications. Although epidemiologic studies of cancer can suggest risk factors or test etiologic hypotheses, epidemiologic data and analytic techniques alone are generally too imprecise to distinguish subtle differences in the effects of risk factors or to choose among complex models. Studies that link additional biologic data with information available from epidemiologic studies such as this one may provide the best means to better understand the etiology of ovarian cancer.

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