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Hormonal Risk Factors for Ovarian Cancer in Premenopausal and Postmenopausal Women

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Abstract

Ovarian cancer is most frequently diagnosed in postmenopausal women; however, the strongest risk predictors, pregnancy and oral contraceptive use, occur in most women in their twenties and thirties. Relatively few studies have examined how reproductive risk factors vary between pre- and postmenopausal ovarian cancer. The authors used data from a population-based, case-control study of ovarian cancer (896 cases, 967 controls) conducted in North Carolina from 1999 to 2006. Odds ratios and 95% confidence intervals were calculated by using unconditional logistic regression. Inverse associations with ovarian cancer were observed with duration of oral contraceptive use, later age at last use, and more recent use among premenopausal women; no significant associations were found for postmenopausal women. Analyses limited to oral contraceptive users showed that duration was a more significant predictor of risk than was timing of use. Parity was inversely associated with premenopausal but not postmenopausal ovarian cancer. Later age at pregnancy was associated with reduced risk for both pre- and postmenopausal women. Analyses among parous women showed that pregnancy timing was a stronger risk predictor than number of pregnancies. Findings suggest that associations between ovarian cancer and reproductive characteristics vary by menopausal status. Additional research is needed to further elucidate risk factors for postmenopausal disease.

Keywords

case-control studies; contraceptives; oral; menopause; ovarian neoplasms; pregnancy

More than 23,000 cases of epithelial ovarian cancer are diagnosed in the United States annually, with a median age at diagnosis of 63 years (1). Although more than two thirds of ovarian cancer cases are diagnosed among postmenopausal women (1), most known risk factors are characteristics related to reproduction that occur primarily when women are in their twenties

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or thirties. The most consistently reported ovarian cancer risk factors are nulliparity or low parity and no oral contraceptive (OC) use (2).

A leading hypothesis linking these risk factors is the “incessant ovulation” hypothesis, which posits that the rupture and subsequent rapid proliferation of the ovarian surface epithelium with ovulation may lead to malignant transformation of ovarian epithelium (3,4). Pregnancy and OC use should reduce ovarian cancer risk by reducing the number of ovulatory cycles. However, this hypothesis is not entirely consistent with epidemiologic observations because the risk reduction associated with one pregnancy or short-term OC use is greater than what would be expected based on months of ovulation suppression (5,6).

An alternative theory suggests that exposure to high progestin levels, whether through pregnancy or exogenous hormones, reduces ovarian cancer risk (7,8). Experimental studies in animals or human cell lines have shown that administration of progestins up-regulates expression of the p53 tumor suppressor gene (9,10) and induces apoptosis (10,11). These data suggest that apoptosis resulting from high progesterone levels during pregnancy or from exogenous hormones could “clear” transformed cells in the ovarian epithelium. If true, it would imply that both timing and duration of exposure are important determinants of ovarian cancer risk.

Although the preponderance of factors that influence ovarian cancer occurs during the premenopausal years, relatively few studies have reported how ovarian cancer risk factors vary by menopausal status or age at diagnosis. Most studies have included fairly small numbers of premenopausal cases, and many have not performed analyses stratified by menopausal status. Nonetheless, several case-control and cohort studies suggest that certain hormone-related risk factors, including OCs, pregnancies, and body mass index, have stronger associations with premenopausal than postmenopausal ovarian cancer (12–19). In this paper, we report data from a case-control study of ovarian cancer in North Carolina to evaluate whether associations with pregnancy and OCs differ by menopausal status.

MATERIALS AND METHODS

The North Carolina Ovarian Cancer Study is a population-based, case-control study conducted in central and eastern North Carolina. Cases were identified through the North Carolina Central Cancer Registry by using rapid case ascertainment. Pathology reports for ovarian cancer cases were forwarded to the Central Cancer Registry and then to the study office within 2 months of diagnosis. Eligible cases were diagnosed with epithelial ovarian cancer between 1999 and 2006, were aged 20–74 years, had no prior history of ovarian cancer, and resided in the 48-county study area. They were required to be mentally competent to give informed consent and complete an interview in English. All cases of disease underwent standardized histopathologic review by the study pathologist (R. C. B.) to confirm diagnosis. Nonparticipation among eligible cases was due to death (4 percent), debilitating illness (2 percent), physician refusal (4 percent), patient refusal (7 percent), and inability to locate (9 percent), for an overall response rate of 74 percent.

Controls from the same 48-county region were identified by using random digit dialing and were frequency matched to cases by age (5-year categories) and race (African American/non–African American). As with the cases, controls had to be English speaking and mentally competent to complete the interview. Controls had at least one intact ovary and no history of ovarian cancer. Screening for eligibility could not be completed for 14 percent of phone numbers. Seventy-three percent of potential controls who passed the eligibility screening agreed to be sent additional study information. Among those sent information, the response rate was 64 percent. Nonresponse was due to refusal (27 percent) and inability to contact (9

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percent). The protocol was approved by the Duke University Medical Center Institutional Review Board and human subjects committees at the Central Cancer Registry and each hospital where cases were identified.

Nurse-interviewers obtained written informed consent from study participants, administered the questionnaire, drew a blood sample, and performed anthropometric measurements (height, weight, and waist and hip circumferences). The questionnaire included information on ovarian cancer risk factors, including family history of cancer, menstrual characteristics, reproductive history, infertility, hormone use, and lifestyle characteristics such as smoking, alcohol consumption, and physical activity. A life-events calendar, which marked milestones such as marriages and births, was used to improve recall of reproductive history and hormone use. Pictorial displays of OCs, menopausal hormones, and certain other medications also were used to aid recall.

Self-reported history of menstrual status, surgeries, and hormone use was used to categorize women as pre- or postmenopausal at diagnosis (cases) or interview (controls). Premenopausal women were those who reported still having menstrual periods or were currently pregnant or breastfeeding. Postmenopausal women were those who reported that their menstrual periods had stopped naturally 12 or more months prior to the date of diagnosis/interview or as a result of bilateral oophorectomy, radiation, or chemotherapy. Additional information was used to categorize women who reported hysterectomies without bilateral oophorectomies or those who began using hormones before their periods stopped. Women who had had a premenopausal hysterectomy without bilateral oophorectomy were classified as postmenopausal if they were 51 years of age or older at diagnosis/interview or, if they were younger than age 51 years, at least 4 years had passed since they thought they had started going through menopause. Women who started hormone therapy before their periods stopped were classified as postmenopausal if they had been using hormones for at least 2 years or thought that they began menopause at least 4 years prior to diagnosis/interview. Lifetime ovulatory cycles were calculated by using a method previously described (20).

Comparisons of clinical characteristics between pre- and postmenopausal cases, and case-control comparisons of risk factors, were performed by using χ^2 analyses. Case-control differences in continuous variables were evaluated with *t* tests and analysis of covariance. Unconditional logistic regression modeling was used to calculate odds ratios and 95 percent confidence intervals associated with pregnancy or OC use, controlling for the matching variables age and race and other potential confounders. Tests for trend in duration of OC use, number of pregnancies, age at first and last pregnancy or OC use, and recency of pregnancy or OC use were performed by assigning an ordinal value to each pregnancy or OC category and testing for linear trends. Trend tests were restricted to ever users of OCs or to ever pregnant women.

RESULTS

These analyses were based on 896 cases (314 premenopausal, 582 postmenopausal) and 967 controls (360 premenopausal, 607 postmenopausal). Table 1 shows comparisons of clinical characteristics of ovarian cancers diagnosed in premenopausal and postmenopausal women. Premenopausal women were more likely to have tumors of low malignant potential (39 percent vs. 13 percent, $p < 0.0001$). Serous and endometrioid histologic types were observed in similar proportions of pre- and postmenopausal cases, but mucinous histology was more common in premenopausal cases. Premenopausal cases were more likely to have stage I tumors and, among invasive cases, to have lower-grade tumors.

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Table 2 shows selected characteristics of premenopausal and postmenopausal cases compared with controls. Young age at menarche was statistically significantly associated with premenopausal but not postmenopausal ovarian cancer. Tubal ligation was a statistically significant protective factor for both pre- and postmenopausal ovarian cancer. Family history of ovarian or breast cancer, high body mass index, and history of infertility were more common among cases than controls, but differences were not statistically significant.

Detailed characteristics of OC use in relation to ovarian cancer are presented in table 3. An inverse dose-response relation with years of OC use was observed for premenopausal women (odds ratio = 0.3, 95 percent confidence interval: 0.2, 0.6 for women with >10 years of use (*p*-trend = 0.008)). There was no trend with age at first use among premenopausal women, whereas a significant inverse relation was observed for age at last use, with the strongest association among women who last used OCs after age 35 years. A similar trend was noted for years since last OC use, which would be expected given the high correlation between these variables. A composite variable combining duration and years since last use showed the strongest inverse association for 5 or more years of use with last use within the past 10 years and a nonsignificant association for short-term use that ended 10 or more years earlier. Among postmenopausal women, no significant associations were observed for duration or age at first or last use of OCs. Because the vast majority of postmenopausal OC users reported that their last use occurred more than 20 years ago, no odds ratios were calculated to assess effects of recency of use. Interaction by menopausal status was assessed in models that included both pre- and postmenopausal women and had a product term for menopausal status and characteristics of OC use. Significant interactions by menopausal status were found for ever use of OCs ($p = 0.022$) and duration of use ($p = 0.03$).

Duration of use and age at last use are correlated; thus, it is important to take into account each variable when considering the other. It is inappropriate, however, to have both duration and timing of use in models that include never OC users because it is not possible to adjust the odds ratios associated with one characteristic of exposure for another characteristic when unexposed women are the referent category (21). Therefore, we examined the joint effects of these variables in models restricted to OC users. Table 4 shows results of models examining the timing of OC use with duration of OC use included as a continuous variable. No association was noted for age at first or last use once duration of OC use was taken into account. There still was a suggestion of reduced risk for more recent use, but the estimates were not statistically significant. Duration of use was statistically significantly associated with ovarian cancer, with reductions of 20–30 percent for each 5 years of use, controlling for timing of use. In analyses restricted to postmenopausal OC users, no associations were found with longer duration of use or age at first or last use.

Table 5 presents results of analyses examining pregnancy characteristics. Parous women were at reduced risk of premenopausal ovarian cancer, although there was no clear relation with number of pregnancies. Controls were more likely than cases to report older age at first and last pregnancy, with a significant trend for only age at last pregnancy. There was a strong inverse effect for pregnancy recency (odds ratio = 0.3, 95 percent confidence interval: 0.1, 0.5 for women who had been pregnant within the past 5 years). A composite variable looking at number of pregnancies and years since last pregnancy showed the strongest inverse relation for women with three or more full-term pregnancies, with the last pregnancy within the last 10 years (odds ratio = 0.2, 95 percent confidence interval: 0.1, 0.5). Breastfeeding also showed a significant inverse relation with premenopausal ovarian cancer. Among postmenopausal women, there was no association with number of pregnancies but a significant trend showing reduced risk for older age at last pregnancy. The associations with age at last pregnancy were weaker among postmenopausal than premenopausal women, but the test for interaction was

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not statistically significant. Because most postmenopausal women's last pregnancy occurred at least 20 years ago, no odds ratios were calculated for pregnancy recency.

Similar to analyses performed for OC users, we analyzed the joint effect of number of pregnancies and timing of pregnancies restricted to parous women (table 6). Among premenopausal women, recency of pregnancy was strongly associated with ovarian cancer risk when we controlled for number of pregnancies, with statistically significant inverse trends for age at last pregnancy, years since first pregnancy, and years since last pregnancy. Odds ratios for each additional birth were not statistically significant when controlling for timing of pregnancy. The inverse association with breastfeeding duration remained significant when we controlled for number of births. Among postmenopausal women, inverse associations were observed for older age at first pregnancy and older age at last pregnancy, controlling for number of pregnancies. Additional births were not associated with a reduction in risk once age at pregnancy was considered.

Analyses involving pregnancy and OC variables were repeated stratifying by tumor behavior (invasive and low malignant potential). The observed patterns were substantively the same as those seen in the entire group, with long-term OC use, recent OC use, and recent pregnancies being associated with the largest risk reductions among premenopausal women, whether considering invasive or lowmalignant-potential disease. Pregnancy and OC use showed much weaker associations with postmenopausal ovarian cancer, whether invasive or of low malignant potential. The only suggestion of a difference was a more pronounced inverse association with age at last pregnancy among postmenopausal women with invasive cancer (data not shown).

We also examined the number of lifetime ovulatory cycles in pre- and postmenopausal cases and controls. Premenopausal cases had significantly more ovulatory cycles than controls did (271 vs. 251, $p = 0.012$; adjusted for age, race, and history of tubal ligation), whereas the number of ovulatory cycles was nearly identical in postmenopausal cases and controls (355 vs. 354, $p = 0.35$).

DISCUSSION

Our analyses found that reproductive risk factors are more strongly associated with premenopausal than postmenopausal ovarian cancer. Pregnancies and OC use are consistently reported as protective factors for ovarian cancer; however, our data suggest that the associations differ between younger and older women and are dependent on duration and timing of the exposures.

Our observations that reproductive factors are more strongly associated with premenopausal than postmenopausal cancer are not surprising since cancer is typically considered to have a latency period of 10–20 years between an initiating event and clinically apparent disease. In our study population, age at last use was 35 years or younger for more than 75 percent of OC users and age at last birth was less than 35 years for more than 80 percent of parous women. Therefore, it is very plausible that these factors' effects on ovarian cancer would be observed predominantly among premenopausal women.

Examination of the joint effects of total exposure (defined as duration of OC use or number of pregnancies) and timing of exposure suggested different effects for pregnancy and OCs. Among parous premenopausal women, timing of pregnancy was a stronger predictor of ovarian cancer risk than total number of pregnancies. Stronger inverse associations were observed with more recent pregnancies, and additional pregnancies were not associated with further risk reduction once timing of pregnancy was considered. In contrast, among OC users, there was a significant inverse association with duration of OC use, but associations with recency of use were not statistically significant when controlling for duration.

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Two major etiologic hypotheses have been put forth to explain the observed inverse associations with OC use and pregnancies. The incessant ovulation hypothesis suggests that these factors reduce ovarian cancer risk by preventing the rupture of the ovarian epithelium that occurs with the monthly release of an ovarian follicle. Inhibition of ovulation, by either pregnancy or OC use, should reduce a woman's risk of ovarian cancer, and longer duration of OC use or more pregnancies should result in greater reductions in risk. Our findings that duration of OC use had stronger associations with ovarian cancer than timing of use are consistent with this hypothesis, but our findings related to number of pregnancies are not.

A second major hypothesis is that the hormonal changes during pregnancy lead to a "clearing" of transformed cells in the ovarian epithelium. In particular, high progesterone levels during pregnancy may have an apoptotic effect on transformed cells. Our findings that older age at last pregnancy has a strong inverse effect on ovarian cancer risk, with stronger effects noted among premenopausal than postmenopausal women, are consistent with this hypothesis. Our results are also consistent with an alternative hypothesis that recent pregnancy per se does not protect against ovarian cancer. Instead, the ability to have become pregnant in the recent past is an indication of "healthy" ovaries, and women who are unable to become pregnant may have an ovarian pathology that places them at higher risk of cancer. It was not possible with our data to determine which mechanism is the more plausible explanation for the effect of pregnancy.

Although our analyses were stratified by menopausal status, it must be acknowledged that the effects may be due to age rather than the endogenous hormonal environment. Pregnancy and OCs are exposures that occur only in premenopausal women (with rare exceptions). Therefore, by definition, postmenopausal women would have experienced these exposures in the more distant past than premenopausal women. The stronger associations we found for premenopausal women may simply reflect time since exposure rather than differences in risk associated with the hormonal milieu. When we analyzed our data stratified by age (<50 vs. ≥50 years), results were virtually identical to those stratified by menopausal status. Although our data set was not large enough to determine whether the effects of exposures occurring at a given age depend upon a woman's menopausal status, the Cancer and Steroid Hormone study analyzed the relation between pregnancy and ovarian cancer among women aged 40–54 years stratifying by menopausal status (6). Stronger associations with pregnancy were noted for premenopausal than postmenopausal women in the same age range, which at first glance suggests that the effects of pregnancy are dependent on the hormonal environment. However, the authors' analyses did not take into account time since last pregnancy, and, because pregnancies on average would have occurred more recently in premenopausal women, their results could have been confounded. Analyses of much larger data sets may provide insight into whether the effects of these exposures are more strongly related to age or to menopausal status. Pooled analyses also might help determine whether risk-factor differences are related to histologic subtypes, which we were unable to examine because of sample size limitations within specific histologies.

To date, relatively few published studies have stratified by menopausal status when examining risk factors for ovarian cancer, perhaps reflecting relatively small numbers of premenopausal cases in most studies. The report that most closely parallels our analyses described stronger inverse associations with pregnancy and OC use among premenopausal women but did not present results on recency of exposure (12). Other reports on timing of pregnancy in relation to ovarian cancer are consistent with our results and suggest that more recent pregnancies confer a stronger protective effect (14–17). A combined analysis of four case-control studies found a significant trend of higher risk of ovarian cancer among women with longer time since last pregnancy, with a somewhat stronger association noted for women younger than age 50 years (17). In contrast to these studies, one report suggested increased risk for more recent pregnancies, with similar increases for younger and older women (22).

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With regard to OC use, only a few studies have examined associations stratified by age or menopausal status. A combined analysis of 12 case-control studies published in 1992 found OCs to be associated with a larger percentage reduction in ovarian cancer risk for older women (aged ≥55 years) than younger women (23), which contrasts with our findings as well as those of other investigators (12,24,25). Patterns of use and OC dosages in the studies in the combined analysis undoubtedly differed from more contemporary studies because of temporal trends, which may partially explain the different findings.

Possible sources of bias in our study are related to the case-control design and to lower response rates among controls. All study participants were asked to recall details of reproduction and contraception over their lifetime; therefore, postmenopausal women were being asked about events that occurred much longer ago for them than for premenopausal women. Although pregnancies are likely to be recalled accurately regardless of age, there may have been more misclassification of OC use among postmenopausal women. If we assume that this misclassification was non-differential between cases and controls, the odds ratios may have been attenuated, resulting in weaker associations with OC use.

Differences in response rates between cases and controls could have introduced bias if nonrespondents differed from respondents on key exposures. Although we had no information on pregnancy or contraceptive use among nonrespondents, other studies have reported that nonrespondents tend to be of lower socioeconomic status and are less likely to report hormone use (26). If participants in our study reported more OC use or experienced pregnancy later than women from the underlying population, the bias may have led to an overestimate of the true effect of OCs or age at last pregnancy since response rates were lower among controls than cases.

The data from our study add to a growing body of literature suggesting that the established protective factors for ovarian cancer, pregnancy and OC use, are much more strongly associated with premenopausal than postmenopausal disease. Analyses of the duration and timing of these exposures imply that total duration of OC use may be the more critical factor (consistent with the incessant ovulation hypothesis), whereas recency is a stronger predictor of the effects of pregnancy (consistent with the clearance of transformed cells hypothesis). It is notable that associations with postmenopausal cases, which constitute the majority of ovarian cancers, were markedly weaker than for premenopausal cases. Similar results found in other populations would suggest the need for additional work to identify factors that contribute to later-onset ovarian cancer.

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Abbreviation

OC oral contraceptive

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TABLE 1

Tumor characteristics of pre- and postmenopausal ovarian cancer cases, the North Carolina Ovarian Cancer Study, 1999–2006

	Premenopausal (*N* = 314)		Postmenopausal (*N* = 582)		*p* value
	No.	%	No.	%	
Behavior					
Invasive	192	61	504	87	<0.001
Low malignant potential	122	39	75	13	
Missing	0		3		
Histology					
Serous	191	61	354	61	<0.001
Endometrioid	39	12	68	12	
Mucinous	52	17	39	7	
Clear cell	13	4	56	10	
Other	19	6	64	11	
Missing	0		1		
Stage					
I	137	44	167	29	<0.001
II	18	6	47	8	
III	151	49	349	61	
IV	2	1	8	1	
Missing	6		11		
Grade (invasive tumors only)					
1	35	19	53	11	0.002
2	62	34	136	28	
3 or 4	87	47	298	61	
Missing	8		20		

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TABLE 2

Characteristics of ovarian cancer cases and controls, stratified by menopausal status, the North Carolina Ovarian Cancer Study, 1999–2006

	Premenopausal					Postmenopausal				
	Cases (*N* = 314)		Controls (*N* = 360)		*p* value	Cases (*N* = 582)		Controls (*N* = 607)		*p* value
	No.	%	No.	%		No.	%	No.	%	
Age (years)										
20–29	21	7	24	7		0	0	0	0	
30–39	69	22	77	21		1	0	1	0	
40–49	167	53	185	51		33	6	19	3	
50–59	57	18	74	21		221	38	232	38	
60–69	0	0	0	0		230	40	241	40	
70–74	0	0	0	0		97	17	114	19	
Race										
White	252	80	281	78		508	87	497	82	
African-American	44	14	70	19		69	12	93	15	
Other	18	6	9	3		5	1	17	3	
Education										
<High school	26	8	19	5	0.366	68	12	85	14	0.611
High school graduate	174	55	206	57		375	64	375	62	
College graduate	70	22	90	25		88	15	89	15	
Postgraduate	44	14	45	13		51	9	58	10	
Family history of breast or ovarian cancer (first degree)										
No	266	85	322	90	0.052	442	76	482	80	0.136
Yes	48	15	37	10		139	24	123	20	
Don’t know	0		1			1		2		
Age at menarche (years)										
<12	91	29	80	22	0.047	129	22	114	19	0.391
12–13	165	53	199	55		306	53	342	56	
>13	57	18	81	23		147	25	150	25	
Don’t know	1		0			0		1		

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	Premenopausal					Postmenopausal				
	Cases (*N* = 314)		Controls (*N* = 360)		*p* value	Cases (*N* = 582)		Controls (*N* = 607)		*p* value
	No.	%	No.	%		No.	%	No.	%	
Age at menopause (years)										
<45						79	14	93	15	0.635
45–49						178	31	190	31	
50–54						259	45	260	43	
>54						62	11	63	10	
Missing						4		1		
Tubal ligation										
No	230	73	220	61	0.001	436	75	400	66	0.001
Yes	84	27	140	39		146	25	207	34	
Physician-diagnosed female infertility										
No	267	85	323	90	0.066	516	89	557	92	0.072
Yes	47	15	37	10		66	11	50	8	
Body mass index (kg/m^2) 1 year prior to diagnosis/interview										
<25	121	40	151	43	0.061	218	39	220	37	0.587
25–29.99	70	23	96	28		164	29	196	33	
≥30	114	37	101	29		183	32	173	29	
Missing	9		12			17		18		

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TABLE 3

Odds ratios and 95% confidence intervals for associations between patterns of oral contraceptive use and ovarian cancer, stratified by menopausal status, the North Carolina Ovarian Cancer Study, 1999–2006

	Premenopausal						Postmenopausal					
	Cases (*N* = 314)		Controls (*N* = 360)		OR*,†	95% CI*	Cases (*N* = 582)		Controls (*N* = 607)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
OC* use												
Nonuser‡	69	22	42	12	1.0	Referent	234	40	238	39	1.0	Referent
User	245	78	318	88	0.5	0.3, 0.8	347	60	369	61	0.8	0.6, 1.1
Unknown							1					
Years of OC use												
<1	32	10	24	7	0.8	0.4, 1.7	69	12	61	10	1.1	0.7, 1.6
1–<5	98	32	115	32	0.6	0.4, 1.0	119	21	147	25	0.7	0.5, 1.0
5–10	71	23	99	28	0.5	0.3, 0.9	88	16	94	16	0.8	0.6, 1.2
>10	37	12	78	22	0.3	0.2, 0.6	50	9	48	8	0.9	0.6, 1.5
Unknown duration	7		2				22		19			
p-trend					0.008						0.799	
Age at first OC use (years)												
<20	144	46	187	52	0.5	0.3, 0.8	75	13	74	12	0.9	0.5, 1.3
20–24	82	26	106	30	0.5	0.3, 0.9	144	25	146	25	0.8	0.6, 1.1
25–29	11	4	20	6	0.4	0.2, 1.0	63	11	75	13	0.8	0.5, 1.2
>29	8	3	4	1	1.2	0.3, 4.4	51	9	61	10	0.9	0.6, 1.4
Unknown	0		1				15		13			
p-trend					0.514						0.850	
Age at last OC use (years)												
<20	34	11	30	8	0.8	0.4, 1.5	15	3	19	3	0.7	0.3, 1.5
20–24	71	23	80	22	0.6	0.3, 1.0	76	14	63	11	1.1	0.7, 1.6
25–29	53	17	72	20	0.6	0.3, 1.0	94	17	92	16	0.9	0.6, 1.3
30–35	36	12	50	14	0.6	0.3, 1.1	62	11	90	15	0.7	0.5, 1.0
>35	45	15	84	23	0.3	0.2, 0.6	79	14	90	15	0.8	0.6, 1.2
Unknown	6		2				22		15			

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	Premenopausal						Postmenopausal					
	Cases (*N* = 314)		Controls (*N* = 360)		OR*,†	95% CI*	Cases (*N* = 582)		Controls (*N* = 607)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
p-trend					0.021						0.345	
Years since first use												
>20	171	54	210	58	0.6	0.4, 0.9	327	58	351	59		
10–20	58	18	86	24	0.5	0.3, 0.9	5	1	3	1		
<10	16	5	21	6	0.4	0.2, 0.9	1	0	2	0		
Unknown	0		1				15		13			
p-trend					0.540							
Years since last use												
>20	95	31	94	26	0.8	0.5, 1.4	279	50	313	53		
10–20	67	22	91	25	0.6	0.3, 1.0	35	6	26	4		
≥5–<10	18	6	28	8	0.4	0.2, 0.9	3	1	2	0		
<5	59	19	103	29	0.3	0.2, 0.6	9	2	13	2		
Unknown	6		2				22		15			
p-trend					0.009							
Duration of use, years since last use												
<5 years, ≥10 years	109	36	104	29	0.8	0.5, 1.3	185	33	204	35		
<5 years, <10 years	21	7	35	10	0.4	0.2, 0.8	3	1	4	1		
≥5 years, ≥10 years	53	17	81	23	0.5	0.3, 0.9	129	23	132	22		
≥5years, <10 years	55	18	96	27	0.3	0.2, 0.6	9	2	10	2		
Unknown	7		2				22		19			

*OR, odds ratio; CI, confidence interval; OC, oral contraceptive.

†Adjusted for age (cubic spline), race (African American, non–African American), family history of breast or ovarian cancer, age at menarche, tubal ligation, infertility, body mass index, number of full-term pregnancies, and age at last pregnancy.

‡Nonusers are the referent group for all comparisons.

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TABLE 4

Odds ratios and 95% confidence intervals for associations between patterns of oral contraceptive use and ovarian cancer among oral contraceptive users, stratified by menopausal status, the North Carolina Ovarian Cancer Study, 1999–2006

	Premenopausal						Postmenopausal					
	Cases (*N* = 245)		Controls (*N* = 318)		OR*,†	95% CI*	Cases (*N* = 348)		Controls (*N* = 369)		OR †	95% CI
	No.	%	No.	%			No.	%	No.	%		
Age at first OC* use (years)												
<20	144	59	187	59	1.0	Referent	75	23	74	21	1.0	Referent
20–24	82	33	106	33	1.0	0.7, 1.6	144	43	146	41	1.0	0.7, 1.6
25–29	11	4	20	6	0.7	0.3, 1.8	63	19	75	21	1.0	0.5, 1.7
>29	8	3	4	1	2.0	0.6, 7.7	51	15	61	17	1.1	0.6, 2.2
Unknown	0		1				15		13			
p-trend					0.693						0.888	
OR for 5-year duration of OC use					0.8	0.6, 0.9					1.0	0.9, 1.2
Age at last OC use (years)												
<20	34	14	30	9	1.0	Referent	15	5	19	5	1.0	Referent
20–24	71	30	80	25	0.8	0.4, 1.6	76	23	63	18	1.5	0.7, 3.3
25–29	53	22	72	23	0.9	0.5, 1.9	94	29	92	26	1.2	0.5, 2.7
30–35	36	15	50	16	1.1	0.5, 2.5	62	19	90	25	0.9	0.4, 2.0
>35	45	19	84	27	0.7	0.3, 1.5	79	24	90	25	0.9	0.4, 2.3
Unknown	6		2				22		15			
p-trend					0.530						0.174	
OR for 5-year duration of OC use					0.8	0.6, 1.0					1.1	0.9, 1.4
Years since first use												
>20	171	70	210	66	1.0	Referent	327	98	351	99		
10–20	58	24	86	27	0.9	0.5, 1.6	5	2	3	1		
<10	16	7	21	7	0.6	0.2, 1.4	1	0	2	1		
Unknown	0		1				15		13			
p-trend					0.296							

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	Premenopausal						Postmenopausal					
	Cases (*N* = 245)		Controls (*N* = 318)		OR*,†	95% CI*	Cases (*N* = 348)		Controls (*N* = 369)		OR †	95% CI
	No.	%	No.	%			No.	%	No.	%		
OR for 5-year duration of OC use					0.7	0.6, 0.9						
Years since last use												
>20	95	40	94	30	1.0	Referent	279	86	313	88		
10–20	67	28	91	29	0.9	0.5, 1.6	35	11	26	7		
≥5–<10	18	8	28	9	0.6	0.3, 1.3	3	1	2	1		
<5	59	25	103	33	0.6	0.3, 1.3	9	3	13	4		
Unknown	6		2				22		15			
p-trend					0.163							
OR for 5-year duration of OC use					0.8	0.7, 1.0						

*OR, odds ratio; CI, confidence interval; OC, oral contraceptive.

†Models included terms for age or timing of OC use (age at first use, age at last use, years since first use, or years since last use), duration of OC use, age (cubic spline), race (African American, non–African American), family history of breast or ovarian cancer, age at menarche, tubal ligation, infertility, body mass index, number of full-term pregnancies, and age at last pregnancy.

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TABLE 5

Odds ratios and 95% confidence intervals for associations between pregnancy characteristics and ovarian cancer, stratified by menopausal status, the North Carolina Ovarian Cancer Study, 1999–2006

	Premenopausal						Postmenopausal					
	Cases (*N* = 314)		Controls (*N* = 360)		OR[*,†]	95% CI[*]	Cases (*N* = 582)		Controls (*N* = 607)		OR[†]	95% CI
	No.	%	No.	%			No.	%	No.	%		
Pregnant												
Never[‡]	102	32	65	18	1.0	Referent	83	14	64	11	1.0	Referent
Ever	212	68	295	82	0.5	0.3, 0.7	499	86	543	89	0.9	0.6, 1.3
No. of full-term pregnancies												
1	63	20	75	21	0.5	0.3, 0.8	93	16	90	15	0.9	0.6, 1.5
2	96	31	135	38	0.5	0.3, 0.8	190	33	216	36	0.8	0.5, 1.2
3	35	11	65	18	0.3	0.2, 0.6	112	19	128	21	0.8	0.5, 1.3
>3	18	6	20	6	0.4	0.2, 0.9	104	18	109	18	1.0	0.6, 1.7
p-trend					0.292						0.498	
Age at first pregnancy (years)												
<20	71	23	84	23	0.5	0.3, 0.9	163	28	172	28	1.0	0.6, 1.5
20–24	65	21	91	25	0.5	0.3, 0.8	232	40	247	41	0.9	0.6, 1.4
25–29	56	18	73	20	0.5	0.3, 0.9	83	14	81	13	1.0	0.6, 1.6
>29	20	6	46	13	0.3	0.1, 0.6	21	4	43	7	0.4	0.2, 0.7
p-trend					0.148						0.039	
Age at last pregnancy (years)												
<25	59	19	52	14	0.7	0.4, 1.1	131	23	124	20	1.0	0.6, 1.6
25–29	65	21	85	24	0.5	0.3, 0.8	183	32	184	30	0.9	0.6, 1.4
30–34	64	20	102	28	0.4	0.3, 0.7	126	22	151	25	0.8	0.5, 1.2
>34	23	7	55	15	0.2	0.1, 0.5	56	10	83	14	0.6	0.4, 1.1
p-trend					0.004						0.031	
Years since first pregnancy												
>20	125	40	142	40	0.5	0.3, 0.9	491	84	535	88		
10–20	66	21	119	33	0.4	0.2, 0.6	8	1	8	1		
<10	21	7	33	9	0.4	0.2, 0.9	0	0	0	0		

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	Premenopausal						Postmenopausal					
	Cases (*N* = 314)		Controls (*N* = 360)		OR*,†	95% CI*	Cases (*N* = 582)		Controls (*N* = 607)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
p-trend					0.066							
Years since last pregnancy												
>20	69	22	62	17	0.7	0.4, 1.3	462	80	511	84		
10–20	92	29	137	38	0.5	0.3, 0.8	31	5	29	5		
≥5–<10	31	10	48	13	0.4	0.2, 0.8	3	1	1	0		
<5	19	6	47	13	0.3	0.1, 0.6	0	0	1	0		
p-trend					0.002							
No. of pregnancies, years since last pregnancy												
<3, ≥10	115	37	140	39	0.5	0.3, 0.9	279	48	306	50		
<3, <10	43	14	69	19	0.4	0.2, 0.7	2	0	0	0		
≥3, ≥10	46	15	59	16	0.4	0.2, 0.8	214	37	234	39		
≥3, <10	7	2	26	7	0.2	0.1, 0.5	1	0	2	0		
Breastfeeding												
Never	226	72	212	59	1.0	Referent	418	72	426	70	1.0	Referent
<6 months	51	16	69	19	0.8	0.5, 1.2	99	17	101	17	1.0	0.7, 1.4
6–12 months	29	9	64	18	0.5	0.3, 0.8	45	8	61	10	0.7	0.5, 1.1
>12 months	9	3	15	4	0.3	0.1, 0.9	20	3	19	3	1.2	0.6, 2.4
p-trend					0.015						0.948	

*OR, odds ratio; CI, confidence interval.

†Adjusted for age, race, family history of breast or ovarian cancer, age at menarche, tubal ligation, infertility, body mass index, duration of oral contraceptive use, and age at last oral contraceptive use.

‡Never pregnant women are the referent category for all comparisons of the pregnancy variables.

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TABLE 6

Odds ratios and 95% confidence intervals for associations between pregnancy characteristics and ovarian cancer among parous women, stratified by menopausal status, the North Carolina Ovarian Cancer Study, 1999–2006

	Premenopausal						Postmenopausal					
	Cases (*N* = 212)		Controls (*N* = 295)		OR*,†	95% CI*	Cases (*N* = 501)		Controls (*N* = 543)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
Age at first pregnancy (years)												
<20	71	33	84	29	1.0	Referent	164	33	172	32	1.0	Referent
20–24	65	31	91	31	0.8	0.5, 1.4	232	46	247	45	0.9	0.7, 1.3
25–29	56	26	73	25	0.9	0.5, 1.6	83	17	81	15	1.0	0.7, 1.5
>29	20	9	46	16	0.5	0.2, 1.0	21	4	43	8	0.4	0.2, 0.7
p-trend					0.096						0.050	
OR for each additional birth					0.8	0.7, 1.1					1.0	0.9, 1.2
Age at last pregnancy (years)												
<25	59	28	52	18	1.0	Referent	131	26	124	23	1.0	Referent
25–29	65	31	85	29	0.8	0.4, 1.3	183	37	184	34	0.9	0.6, 1.2
30–34	64	30	102	35	0.6	0.4, 1.1	126	25	151	28	0.7	0.5, 1.0
>34	23	11	55	19	0.4	0.2, 0.8	56	11	83	15	0.6	0.4, 0.9
p-trend					0.006						0.013	
OR for each additional birth					1.0	0.8, 1.2					1.1	1.0, 1.3
Years since first pregnancy												
>20	125	59	142	48	1.0	Referent	491	98	535	99		
10–20	66	31	119	40	0.6	0.3, 1.0	8	2	8	1		
<10	21	10	33	11	0.5	0.2, 1.2	0	0	0	0		
p-trend					0.045							
OR for each additional birth					0.9	0.7, 1.1						
Years since last pregnancy												
>20	69	33	62	21	1.0	Referent	462	93	511	94		
10–20	92	44	137	47	0.5	0.3, 0.9	31	6	29	5		
≥5–<10	31	15	48	16	0.4	0.2, 0.9	3	1	1	0		

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	Premenopausal						Postmenopausal					
	Cases (*N* = 212)		Controls (*N* = 295)		OR*,†	95% CI*	Cases (*N* = 501)		Controls (*N* = 543)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
<5	19	9	47	16	0.2	0.1, 0.6	0	0	1	0		
p-trend					0.002							
OR for each additional birth					1.0	0.8, 1.2						
Breastfeeding												
<6 months	50	57	69	47	1.0	Referent	99	60	101	56	1.0	Referent
6–12 months	29	33	64	43	0.5	0.3, 1.1	45	27	61	34	0.7	0.4, 1.1
>12 months	9	10	15	10	0.3	0.1, 1.1	20	12	19	10	1.2	0.6, 2.7
p-trend					0.026						0.741	
OR for each additional birth					0.9	0.6, 1.3					1.6	0.5, 5.6

*OR, odds ratio; CI, confidence interval.

†Models included terms for pregnancy-related characteristics (i.e., age at first pregnancy, age at last pregnancy, years since first pregnancy, years since last pregnancy, or breastfeeding), parity, age, race, family history of breast or ovarian cancer, age at menarche, tubal ligation, infertility, body mass index, duration of oral contraceptive use, and age at last oral contraceptive use. Parity was 1 degree of freedom coded 1-2-3-4, with ≥4 included as 4).