



## Reproductive Factors and Epithelial Ovarian Cancer Risk by Histologic Type: A Multiethnic Case-Control Study

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Associations of reproductive factors with ovarian cancer may differ by histologic type. Data from a multiethnic, population-based, case-control study, conducted in Hawaii and Los Angeles, California, between 1993 and 1999, were used to assess this hypothesis. A structured questionnaire was administered to 558 histologically confirmed epithelial ovarian cancer cases and 607 population controls. Factors suppressing ovulation, including pregnancy and oral contraceptive use, were inversely associated with the risk of all histologic types. Nonmucinous but not mucinous tumors were significantly associated with menstruation years (odds ratio = 1.5 for the highest vs. the lowest quartile) and lifetime ovulatory cycles (odds ratio = 2.8 for the highest vs. the lowest quartile). Duration of breastfeeding (odds ratio = 0.4 for the highest vs. the lowest quartile) was significantly and inversely related to nonmucinous tumors but not to mucinous tumors. Among all tumor types, endometrioid tumors were the most strongly related to pregnancy and tubal ligation, while clear cell tumors were the only type that was associated with noncontraceptive hormone use. The risk factors were similar for borderline and invasive tumors, except for age at diagnosis. Mucinous tumors, both borderline and invasive, were more common in Asian women than in Caucasian and other women. Our data suggest that histologic types of epithelial ovarian cancer are etiologically distinct.

breast feeding; case-control studies; contraceptives, oral; histology; ovarian neoplasms; ovulation; parity; pregnancy

Factors related to reproduction, such as pregnancy and oral contraceptive pill use, have been consistently associated with ovarian cancer (1). However, the underlying mechanisms for the influence of reproductive factors on the development of ovarian cancer remain unclear. Histologic differences in ovarian cancer contribute further to difficulties in understanding its etiology.

Epithelial ovarian cancers derive from the ovarian surface epithelium or its inclusion cysts, and they account for approximately 90 percent of all ovarian cancers. In spite of the simple biologic features of the epithelium, epithelial ovarian cancer is probably among the most histopathologically complex of human malignancies. One unique characteristic of this cancer is the müllerian differentiation

accompanied by neoplastic progression (2). This aberrant differentiation changes the original stromal characteristics to müllerian duct-derived epithelia, including oviduct, endometrium, and uterine cervix. Serous, endometrioid/clear cell, and mucinous tumors resemble the phenotypes of the fallopian tube, endometrium, and endocervix/gastrointestinal tract, respectively (3). Compared with nonmucinous types, mucinous tumors exhibit unique histologic characteristics, including more common occurrences of benign and borderline tumors than invasive tumors, and a greater likelihood of *K-ras* than *p53* mutations (4, 5). It is biologically plausible that the unique morphologic and immunohistochemical features of the ovary may reflect diverse histo-

pathogenesis pathways in the development of ovarian cancer.

Most previous epidemiologic studies have examined the relation between ovarian cancer and risk factors without considering the potential differences in invasiveness or histologic subtypes. Comparisons between borderline tumors and invasive tumors in some studies suggest common risk factors, in particular oral contraceptive use and parity (6, 7). Risch et al. (8) were the first to propose that mucinous tumors are etiologically distinct from nonmucinous tumors, and this contention has been supported by others (9, 10). Some studies suggested that parity, oral contraceptive use, and noncontraceptive estrogen use are associated with the risk of nonmucinous, but not mucinous, tumors (8, 9, 11), while others reported similar associations of oral contraceptive use (10, 12) and other reproductive factors among the subtypes (13). These results are inconsistent, and the comparisons focused primarily on mucinous and nonmucinous tumors rather than on specific histologic subtypes.

We conducted a population-based, case-control study to examine risk factors for ovarian cancer by major histologic subtypes. In this paper, we emphasize histologic-specific differences in the association of reproductive factors with the risk of epithelial ovarian cancer.

## MATERIALS AND METHODS

The details of this population-based, case-control study, conducted in Hawaii and Los Angeles, California, have been described elsewhere (14). Briefly, eligibility criteria for participation in this investigation included 1) residence in Hawaii or in Los Angeles County for at least 1 year prior to diagnosis for cases or the interview date for controls, 2) being 18 or more years of age, 3) having no prior history of ovarian cancer, and 4) having at least one intact ovary for controls.

All eligible cases diagnosed with primary histologically confirmed, epithelial ovarian cancer between 1993 and 1999 were identified through two population-based cancer registries, the Hawaii Tumor Registry and the Los Angeles County Cancer Surveillance Program. Interview information was obtained from 603 (62 percent) of the 972 ovarian cancer cases eligible for participation in the study. The reasons for nonparticipation included physician refusal ( $n = 69$ ), patient refusal ( $n = 222$ ), and inability to locate the patient ( $n = 78$ ). The response rates among eligible cases did not differ substantially by study location (65 percent in Hawaii, 61 percent in Los Angeles) or by ethnic group (63 percent among Asian Americans, 65 percent among Pacific Islanders, 60 percent among Caucasians). Thirty-nine cases were excluded from this analysis because of equivocal histologic classification. Consistent with our previous analysis (15), six additional cases were also excluded because of unreliable dietary information. Of the 558 ovarian cancer cases included in this analysis, 200 were from Hawaii and 358 were from Los Angeles.

A standardized classification and coding for histologic types were based on the second edition of *International Classification of Diseases for Oncology* (16). Four major histologic categories of epithelial ovarian cancer were

considered, based upon the *Histological Typing of Ovarian Tumours* by the World Health Organization (17): mucinous tumors, serous tumors, endometrioid tumors, and clear cell tumors. A fifth "other" category included less common undifferentiated tumors, squamous tumors, and transitional tumors. Mucinous and serous tumors were further divided into two subtypes, borderline and invasive, based upon their histologic characteristics.

Population controls were randomly selected from a neighborhood walk procedure in Los Angeles and from lists of participants in a Department of Health statewide annual survey in Hawaii. The selection was performed so that controls were frequency matched to cases with an approximate 1:1 ratio based upon specific ethnicity (e.g., Japanese), age (year of birth  $\pm 5$  years), and study site. A total of 907 women meeting eligibility criteria were contacted to participate in the study. Complete demographic and nutrient information was obtained for 607 (67 percent) of these women. Of the 607 controls included in this analysis, 283 were from Hawaii and 324 were from Los Angeles.

The questionnaire included information regarding menstrual, reproductive, and gynecologic histories; birth control and hormone use; and other lifestyle practices. We used monthly calendars to collect detailed information on specific reproductive events, such as ages at menarche and menopause, all pregnancies, hysterectomy, and birth control. Menstrual history included age at menarche, menstrual length, menstrual pain, menstrual irregularity (periods varying from cycle length by 2 or more days), amenorrhea, and menopausal information. Reproductive history included all pregnancy outcomes (full term, stillbirth, abortion, miscarriage), lactation for each live birth, and fertility problems. Birth control included detailed information on oral contraceptive use, tubal ligation, and hysterectomy. Hormone use included any noncontraceptive hormones (pills, cream, shots) taken for reasons such as period regulation, menopausal symptoms, or painful menstrual periods. The majority of subjects (>95 percent) were interviewed in their homes. All interviews were administered by trained interviewers according to a standard protocol and took approximately 2.5 hours to complete.

The premenopausal group included women who were under age 40 years or still having menstrual periods at diagnosis for cases or interview for controls. The postmenopausal group included women whose periods had stopped naturally or because of surgery or medical treatment or who were more than 55 years of age.

We calculated total years of menstruation as the difference between the age at menarche and the age at menopause for postmenopausal women or the age at interview for premenopausal women. A total of 8.7 percent of women have an unknown age at menopause because of the use of hormone or oral contraceptive pills. An age was assigned as 1) the age at the very last menstrual period, 2) the age at surgery or other medical treatment, or 3) the age of 55 years for women more than 55 years; otherwise, the age at menopause remained missing. Lifetime ovulatory cycles were calculated by subtracting any anovulatory periods due to pregnancies, lactation, use of oral contraceptives, and amenorrhea from total menstrual years. This quantity was then multiplied by

**TABLE 1. Frequency distributions and means of selected demographic variables for ovarian cancer cases and controls, Hawaii and Los Angeles, California, 1993–1999**

Demographic variables	Controls (n = 607)	Cases								
		All (n = 558)		Invasive (n = 431)					Borderline (n = 127)	
		Mucinous (n = 109)	Nonmucinous (n = 449)	Mucinous (n = 48)	Serous (n = 220)	Endometrioid (n = 72)	Clear cell (n = 48)	Other (n = 43)	Mucinous (n = 61)	Serous (n = 66)
<b>Age (years)</b>										
≤43	149 (25)*	42 (39)	80 (18)	16 (33)	21 (9)	14 (19)	10 (21)	5 (12)	26 (43)	30 (45)
44–54	171 (28)	24 (22)	144 (32)	12 (25)	64 (29)	30 (42)	15 (31)	10 (23)	12 (20)	25 (38)
55–64	98 (16)	24 (22)	93 (21)	8 (17)	54 (25)	12 (11)	10 (21)	14 (33)	16 (26)	3 (4)
>64	189 (31)	19 (17)	132 (29)	12 (25)	81 (37)	16 (22)	13 (27)	14 (33)	7 (11)	8 (12)
Mean†	55.8	50	55.2	52.6	57.6	53.6	57.4	54.2	48.0	48.0
<b>Race</b>										
Caucasian	266 (44)	33 (30)	225 (50)	12 (25)	119 (54)	39 (54)	12 (25)	21 (49)	21 (34)	34 (52)
Asian	254 (42)	55 (51)	151 (34)	24 (50)	72 (33)	23 (32)	28 (58)	16 (37)	31 (51)	12 (18)
Other	87 (14)	21 (19)	73 (16)	12 (25)	29 (13)	10 (14)	8 (17)	6 (14)	9 (15)	20 (30)
<b>Education (years)</b>										
≤12	163 (27)	41 (38)	148 (33)	19 (40)	76 (34)	18 (25)	16 (33)	16 (37)	22 (36)	22 (33)
13–14	214 (35)	35 (32)	159 (35)	16 (33)	75 (34)	29 (40)	15 (31)	16 (37)	19 (31)	24 (36)
15–16	150 (25)	27 (25)	86 (19)	11 (23)	41 (19)	10 (14)	12 (25)	10 (23)	16 (26)	13 (20)
>16	80 (13)	6 (5)	56 (13)	2 (4)	28 (13)	15 (21)	5 (10)	1 (2)	4 (7)	7 (11)
Mean	13.4	12.2	13.2	12.2	13.3	13.1	13.8	13.4	12.2	12.7

\* Numbers in parentheses, percent.

† Means were adjusted by analysis of covariance for study site, oral contraceptive pill use, pregnancy status, tubal ligation, age, race, and education, where appropriate.

the number of estimated cycles per year on the basis of a woman's cycle length.

To investigate the risk of ovarian cancer by specific histologic types, we used a polytomous logistic model (18), comparing cases having a specific histology with all eligible controls. Two such models were used to estimate the risk of combined histologic subgroups: 1) borderline and invasive tumors and 2) mucinous and nonmucinous tumors. Global and pairwise comparisons among histologic-specific ovarian cancer risks were based on Wald tests. Cutpoints for the quartiles and the tertiles of exposures were based on the combined distributions of the cases and controls. Adjustment variables included age (continuous), race (indicator variables for Caucasian, Asian, other), study site (indicator variables for Hawaii, Los Angeles), education (continuous), oral contraceptive use (ever vs. never), pregnancy (ever vs. never), and tubal ligation (yes vs. no). We also considered other potential risk factors as adjustment variables, such as menopausal status, family history of breast and/or ovarian cancer, years of oral contraceptive use, numbers of pregnancies, and body mass index, but these did not materially alter the fit of the models or the estimates of odds ratios. The number of full-term pregnancies and the total months of breastfeeding were included in the same models to serve as adjustment variables for each other. A test for linear trend in the logit of risk was performed by comparing twice the difference in log likelihoods for models with and without a trend variable, assigned the median values for the appro-

priate quartile or tertile. Covariate-adjusted means were computed by analysis of covariance.

## RESULTS

Table 1 shows the distribution of cases and controls by selected demographic variables. Of the 558 ovarian cancer cases, 431 (77 percent) had invasive tumors, and 127 (23 percent) had borderline tumors. Serous tumors were the most common histologic type among women with invasive tumors (51 percent), followed by endometrioid (17 percent), clear cell (11 percent), mucinous (11 percent), and other tumors (10 percent). The frequency of serous and mucinous tumors was similar among borderline tumors.

The age at diagnosis varied by the histologic subtype of ovarian cancer (table 1). The mean age at diagnosis for women with borderline tumors (48 years of age) was younger than the mean age for women with invasive tumors (56 years of age). The mean age for women with mucinous tumors was also younger than the mean age for women with nonmucinous histologic types ( $p < 0.01$ ). Asian women were more commonly diagnosed with both mucinous and clear cell tumors than serous tumors when compared with Caucasian women (table 1). Women with mucinous tumors were less educated than were controls and cases with nonmucinous histologic subtypes of tumors.

Tables 2, 3, and 4 present the estimated risks for the associations between the reproductive factors of interest and

**TABLE 2. Odds ratios\* and 95% confidence intervals for the association of menstruation variables with the risk of ovarian cancer, Hawaii and Los Angeles, California, 1993–1999**

	All										Invasive					Borderline						
	All			Mucinous			Nonmucinous			All			Serous			Mucinous			Serous			
	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p	
<b>Menopausal status</b>																						
Premenopausal	1†			1			1			1			1			1			1			1
Postmenopausal	2.3 (1.6, 3.3)	1.8 (1.0, 3.4)	2.4 (1.6, 3.6)	2.6 (1.7, 4.0)	1.8 (0.7, 4.4)	3.0 (1.8, 5.0)	3.1 (1.4, 6.8)	2.0 (0.8, 5.1)	3.0 (1.0, 8.5)	1.7 (0.9, 3.0)	1.9 (0.9, 4.2)	1.6 (0.7, 3.4)										
<b>Menstrual irregularity</b>																						
Regular	1			1			1			1			1			1			1			1
Irregular	0.7 (0.5, 0.9)	0.9 (0.6, 1.4)	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)	0.9 (0.5, 1.8)	0.7 (0.5, 1.1)	0.6 (0.3, 1.1)	0.3 (0.1, 0.7)	0.9 (0.4, 1.9)	0.8 (0.5, 1.3)	0.9 (0.5, 1.6)	0.8 (0.4, 1.4)										
<b>Menstruation years</b>																						
≤27	1			1			1			1			1			1			1			1
28–34	1.2 (0.9, 1.7)	0.6 (0.3, 1.0)	1.6 (1.1, 2.3)	1.5 (1.0, 2.1)	0.4 (0.2, 0.9)	1.8 (1.1, 3.0)	1.6 (0.8, 3.4)	3.0 (1.0, 8.2)	1.5 (0.5, 4.3)	0.9 (0.5, 1.6)	0.7 (0.4, 1.5)	1.1 (0.5, 2.4)										
35–38	1.5 (1.0, 2.2)	0.8 (0.4, 1.5)	1.8 (1.2, 2.7)	1.7 (1.2, 2.6)	0.7 (0.3, 1.7)	2.0 (1.2, 3.4)	2.2 (1.0, 4.8)	1.7 (0.5, 5.8)	2.8 (1.0, 8.0)	1.1 (0.6, 2.1)	0.9 (0.4, 2.0)	1.4 (0.5, 3.6)										
>38	1.2 (0.8, 1.8)	0.5 (0.2, 1.0)	1.5 (1.0, 2.4)	1.4 (0.9, 2.2)	0.5 (0.2, 1.5)	1.6 (0.9, 2.7)	1.1 (0.4, 2.8)	3.6 (1.2, 11)	2.2 (0.7, 6.8)	0.9 (0.4, 1.9)	0.4 (0.1, 1.3)	1.8 (0.6, 4.8)										
p† for trend	0.16	0.06	0.02	0.04	0.15	0.05	0.34	0.05	0.07	0.88	0.21	0.32										
<b>Ovulatory cycles</b>																						
≤266.4	1			1			1			1			1			1			1			1
266.5–363.9	1.6 (1.1, 2.3)	0.7 (0.4, 1.3)	2.0 (1.4, 3.0)	1.9 (1.2, 2.8)	0.6 (0.2, 1.6)	2.2 (1.3, 3.7)	1.1 (0.5, 2.5)	26 (3.3, 208)	2.5 (0.7, 9.1)	1.3 (0.7, 2.2)	0.8 (0.4, 1.7)	2.0 (0.9, 4.2)										
364.0–436.7	2.1 (1.5, 3.1)	1.2 (0.6, 2.2)	2.7 (1.8, 4.0)	2.6 (1.7, 3.8)	1.4 (0.6, 3.1)	2.8 (1.6, 4.7)	1.5 (0.7, 3.4)	32 (3.9, 258)	5.0 (1.5, 17)	1.7 (0.9, 3.1)	1.1 (0.5, 2.4)	2.6 (1.1, 6.2)										
≥436.8	2.3 (1.5, 3.4)	1.0 (0.5, 2.1)	2.8 (1.9, 4.4)	2.7 (1.7, 3.8)	1.1 (0.4, 2.9)	2.6 (1.5, 4.5)	2.4 (1.1, 5.2)	27 (3.1, 230)	7.4 (2.1, 26)	1.6 (0.8, 3.2)	1.0 (0.4, 2.7)	2.5 (0.9, 7.0)										
p† for trend	<0.0001	0.80	<0.0001	<0.0001	0.67	0.0003	0.03	0.0005	0.0005	0.13	0.96	0.03										

\* Data, including menopausal status, menstrual irregularity, and menstruation years, were adjusted by a polytomous logistic regression model for age, ethnicity, study site, education, oral contraceptive pill use, parity, and tubal ligation. Oral contraceptive pill use and parity were excluded from the model for the data analysis of ovulatory cycles.  
 † Reference group.  
 ‡ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

**TABLE 3. Odds ratios\* and 95% confidence intervals for the association of pregnancy and lactation with the risk of ovarian cancer, Hawaii and Los Angeles, California, 1993–1999**

	All					Invasive					Borderline			
	All	Mucinous	Nonmucinous	All		All	Mucinous	Serous	Endometrioid	Clear cell	Other	All	Mucinous	Serous
<b>Pregnancy</b>														
Never	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ever	0.6 (0.4, 0.8)	0.6 (0.4, 1.1)	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)	0.5 (0.2, 1.1)	0.7 (0.5, 1.1)	0.3 (0.2, 0.6)	0.4 (0.2, 0.9)	0.9 (0.4, 2.1)	0.7 (0.4, 1.2)	0.8 (0.4, 1.6)	0.6 (0.3, 1.3)	
<b>Full-term pregnancies</b>														
0	1	1	1	1	1	1	1	1	1	1	1	1	1	
1	0.6 (0.4, 0.9)	0.6 (0.3, 1.3)	0.6 (0.4, 1.0)	0.6 (0.4, 0.9)	0.7 (0.3, 1.8)	0.7 (0.4, 1.2)	0.5 (0.2, 1.2)	0.3 (0.1, 0.8)	0.6 (0.2, 1.9)	0.8 (0.4, 1.4)	0.6 (0.3, 1.5)	0.9 (0.4, 2.0)		
2	0.6 (0.4, 0.9)	0.6 (0.3, 1.0)	0.6 (0.4, 0.9)	0.5 (0.4, 0.9)	0.6 (0.3, 1.6)	0.9 (0.5, 1.4)	0.5 (0.2, 1.0)	0.5 (0.2, 1.1)	0.4 (0.1, 1.1)	0.5 (0.3, 0.9)	0.5 (0.2, 1.1)	0.5 (0.2, 1.1)		
>2	0.6 (0.4, 0.8)	0.5 (0.2, 0.9)	0.6 (0.4, 0.9)	0.6 (0.3, 0.9)	0.5 (0.2, 1.2)	0.8 (0.5, 1.3)	0.3 (0.1, 0.7)	0.4 (0.2, 1.1)	0.8 (0.3, 1.9)	0.5 (0.2, 0.9)	0.5 (0.2, 1.1)	0.5 (0.2, 1.2)		
p† for trend	0.011	0.05	0.03	0.03	0.16	0.49	0.008	0.17	0.89	0.02	0.14	0.10		
<b>Age at last birth§ (years)</b>														
<28	1	1	1	1	1	1	1	1	1	1	1	1	1	
28–30	1.1 (0.7, 1.6)	1.3 (0.7, 2.5)	1.0 (0.7, 1.5)	1.2 (0.8, 1.8)	1.9 (0.8, 4.7)	1.5 (0.9, 2.4)	1.4 (0.6, 3.3)	0.5 (0.1, 1.7)	0.3 (0.1, 1.3)	0.7 (0.4, 1.4)	1.0 (0.4, 2.2)	0.6 (0.2, 1.4)		
31–34	1.0 (0.7, 1.4)	0.9 (0.4, 1.7)	1.0 (0.7, 1.5)	1.1 (0.8, 1.7)	1.4 (0.5, 3.6)	1.0 (0.6, 1.6)	1.9 (0.8, 4.2)	1.3 (0.5, 3.1)	0.8 (0.3, 2.2)	0.7 (0.4, 1.3)	0.6 (0.2, 1.5)	0.8 (0.4, 1.8)		
>34	0.9 (0.6, 1.3)	0.7 (0.3, 1.3)	1.0 (0.7, 1.5)	1.1 (0.5, 1.1)	0.7 (0.2, 2.2)	1.2 (0.7, 1.9)	1.1 (0.4, 2.7)	0.8 (0.3, 2.0)	1.2 (0.5, 2.8)	0.6 (0.4, 1.2)	0.6 (0.2, 1.5)	0.5 (0.2, 1.3)		
p† for trend	0.65	0.18	1.00	0.82	0.55	0.88	0.68	0.92	0.45	0.08	0.18	0.21		
<b>Years since last pregnancy§</b>														
<14	1	1	1	1	1	1	1	1	1	1	1	1	1	
14–25	1.8 (1.2, 2.8)	1.6 (0.8, 3.4)	1.9 (1.2, 3.1)	1.6 (1.0, 2.6)	1.1 (0.4, 3.1)	1.6 (0.8, 2.9)	1.5 (0.6, 4.0)	2.5 (0.7, 8.3)	3.9 (1.1, 14)	3.0 (1.5, 6.0)	2.5 (1.0, 6.5)	3.6 (1.5, 8.8)		
26–36	1.6 (0.9, 2.9)	1.6 (0.6, 4.9)	1.6 (0.9, 3.0)	1.3 (0.7, 2.5)	0.7 (0.1, 3.2)	1.6 (0.7, 3.5)	0.9 (0.2, 3.6)	1.7 (0.3, 9.1)	1.2 (0.2, 6.5)	3.3 (1.2, 9.0)	3.7 (0.9, 15)	3.1 (0.8, 12)		
>36	1.4 (0.6, 3.2)	3.5 (0.8, 15)	1.2 (0.5, 2.7)	0.9 (0.4, 2.1)	0.8 (0.1, 6.1)	1.1 (0.4, 3.1)	0.6 (0.1, 3.9)	1.9 (0.2, 17)	0.4 (0.04, 3.6)	6.8 (1.6, 28)	14 (2.1, 98)	3.1 (0.4, 22)		
p† for trend	0.35	0.14	0.64	0.88	0.71	0.77	0.63	0.62	0.34	0.009	0.01	0.13		
<b>Breastfeeding</b>														
Never	1	1	1	1	1	1	1	1	1	1	1	1	1	
Ever	0.6 (0.4, 0.7)	0.8 (0.5, 1.4)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	1.2 (0.6, 2.7)	0.5 (0.3, 0.7)	0.5 (0.3, 0.9)	0.5 (0.2, 1.0)	0.5 (0.3, 1.1)	0.6 (0.4, 1.0)	0.7 (0.4, 1.2)	0.6 (0.3, 1.0)		
<b>Months of breastfeeding</b>														
Never	1	1	1	1	1	1	1	1	1	1	1	1	1	
≤5	0.6 (0.4, 0.9)	0.6 (0.4, 1.4)	0.7 (0.4, 0.9)	0.6 (0.4, 0.9)	0.7 (0.3, 1.8)	0.6 (0.4, 0.9)	0.6 (0.3, 1.2)	0.6 (0.3, 1.5)	0.7 (0.3, 1.8)	0.7 (0.4, 1.2)	0.7 (0.3, 1.6)	0.7 (0.3, 1.5)		
6–16	0.6 (0.4, 0.9)	0.7 (0.3, 1.3)	0.5 (0.3, 0.7)	0.5 (0.4, 0.8)	1.1 (0.5, 2.6)	0.5 (0.3, 0.8)	0.6 (0.3, 1.3)	0.5 (0.2, 1.4)	0.2 (0.1, 0.8)	0.5 (0.4, 0.9)	0.4 (0.1, 1.0)	0.6 (0.3, 1.5)		
>16	0.6 (0.4, 0.8)	0.9 (0.8, 1.8)	0.4 (0.3, 0.7)	0.5 (0.3, 0.7)	1.2 (0.5, 3.0)	0.4 (0.2, 0.7)	0.3 (0.1, 1.0)	0.3 (0.1, 1.1)	0.6 (0.2, 1.8)	0.6 (0.3, 1.2)	0.8 (0.3, 1.8)	0.5 (0.2, 1.3)		
p† for trend	0.011	0.99	0.0005	0.002	0.30	0.96	0.10	0.40	0.92	0.23	0.96	0.52		

\* Data, including pregnancy, age at last birth, years since last birth, and breastfeeding, were adjusted by a polytomous logistic regression model for age, ethnicity, study site, education, oral contraceptive pill use, and tubal ligation. The number of full-term pregnancies and total months of breastfeeding were additional adjustment variables for each other.  
 † Reference group.  
 ‡ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.  
 § Among women who were ever pregnant.

**TABLE 4. Odds ratios\* and 95% confidence intervals for the association of birth control and noncontraceptive hormone use with the risk of ovarian cancer, Hawaii and Los Angeles, California, 1993–1999**

	All				Invasive				Borderline			
	All	Mucinous	Nonmucinous	All	Mucinous	Serous	Endometrioid	Clear cell	Other	All	Mucinous	Serous
Oral contraceptives use												
Never	1†	1	1	1	1	1	1	1	1	1	1	1
Ever	0.6 (0.4, 0.8)	0.50 (0.3, 0.9)	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)	0.6 (0.3, 1.3)	0.7 (0.4, 1.0)	0.5 (0.3, 1.0)	0.7 (0.3, 1.4)	0.2 (0.1, 0.5)	0.6 (0.4, 1.0)	0.5 (0.3, 0.9)	0.7 (0.4, 1.3)
Years of oral contraceptive use												
Never	1	1	1	1	1	1	1	1	1	1	1	1
≤1.5	0.8 (0.5, 1.1)	0.7 (0.4, 1.4)	0.8 (0.5, 1.2)	0.8 (0.5, 1.1)	1.0 (0.4, 2.5)	0.8 (0.5, 1.4)	0.7 (0.3, 1.5)	1.1 (0.4, 2.7)	0.3 (0.1, 0.9)	0.9 (0.5, 0.7)	0.6 (0.2, 1.3)	1.3 (0.6, 2.6)
1.6–5	0.6 (0.4, 0.8)	0.4 (0.2, 0.8)	0.6 (0.4, 0.9)	0.6 (0.4, 1.0)	0.7 (0.2, 1.7)	0.8 (0.5, 1.3)	0.5 (0.2, 1.2)	0.7 (0.3, 1.9)	0.3 (0.1, 0.9)	0.4 (0.2, 0.7)	0.2 (0.1, 0.7)	0.5 (0.2, 1.2)
>5	0.4 (0.3, 0.6)	0.5 (0.3, 1.0)	0.4 (0.2, 0.5)	0.3 (0.2, 0.5)	0.3 (0.1, 1.0)	0.4 (0.2, 0.7)	0.4 (0.2, 0.9)	0.4 (0.1, 1.2)		0.6 (0.3, 1.0)	0.7 (0.3, 1.4)	0.5 (0.2, 1.1)
p‡ for trend	0.002	0.10	<0.0001	<0.0001	0.03	0.003	0.05	0.08	0.02	0.06	0.65	0.02
Years since last use of oral contraceptives§												
≤10.7	1	1	1	1	1	1	1	1	1	1	1	1
10.8–19.7	2.4 (1.3, 4.3)	1.9 (0.8, 5.1)	2.8 (1.5, 5.5)	3.0 (1.5, 6.3)	3.5 (0.7, 17)	4.9 (1.5, 16)	2.2 (0.7, 7.4)	5.5 (0.8, 37)		2.4 (1.0, 5.4)	1.6 (0.5, 4.8)	3.3 (1.1, 9.6)
19.8–24.9	2.9 (1.5, 5.4)	1.9 (0.6, 5.7)	3.6 (1.8, 7.3)	4.3 (2.0, 9.1)	5.1 (0.8, 34)	7.2 (2.1, 24)	1.1 (0.3, 4.6)	9.1 (1.2, 70)		1.8 (0.7, 4.7)	1.2 (0.3, 4.4)	2.6 (0.7, 9.2)
>24.9	3.4 (1.6, 7.0)	2.0 (0.5, 7.9)	4.2 (1.9, 9.4)	4.9 (2.1, 11)	15 (1.8, 122)	7.1 (1.9, 26)	2.0 (0.5, 8.9)	9.1 (0.9, 91)	27 (0.8, 854)	2.0 (0.6, 6.4)	0.3 (0.03, 2.9)	5.2 (1.2, 22)
p‡ for trend	0.0005	0.23	0.0002	<0.0001	0.02	0.001	0.51	0.04		0.16	0.83	0.03
Tubal ligation												
Never	1	1	1	1	1	1	1	1	1	1	1	1
Ever	0.7 (0.5, 1.0)	1.0 (0.6, 1.8)	0.6 (0.4, 0.9)	0.7 (0.5, 1.0)	0.9 (0.4, 2.1)	0.8 (0.5, 1.2)	0.2 (0.1, 0.6)	0.5 (0.2, 1.4)	1.2 (0.5, 2.9)	0.9 (0.5, 1.5)	1.1 (0.5, 2.3)	0.6 (0.3, 1.4)
Fertility problem												
No	1	1	1	1	1	1	1	1	1	1	1	1
Yes	1.4 (0.8, 1.6)	0.9 (0.5, 1.6)	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)	1.3 (0.6, 2.8)	1.2 (0.8, 1.9)	0.6 (0.3, 1.3)	1.4 (0.6, 3.0)	2.3 (1.1, 4.9)	0.9 (0.5, 1.6)	0.6 (0.2, 1.5)	1.2 (0.6, 2.4)
Noncontraceptive hormone use												
Never	1	1	1	1	1	1	1	1	1	1	1	1
Ever	0.8 (0.6, 1.1)	0.6 (0.4, 1.0)	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)	0.8 (0.4, 1.5)	1.0 (0.7, 1.4)	0.8 (0.5, 1.4)	2.0 (1.0, 3.8)	0.6 (0.3, 1.1)	0.6 (0.4, 0.9)	0.5 (0.3, 1.0)	0.6 (0.3, 1.2)

\* Data related to oral contraceptive use were adjusted by a polytomous logistic regression model for age, ethnicity, study site, education, pregnancy status, and tubal ligation. Oral contraceptive pill use was additional adjustment variable for the rest of data analysis.

† Reference group.

‡ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned median values for the categories.

§ Among women who ever used oral contraceptives.

ovarian cancer by histologic subtype. Postmenopausal women had about a twofold increased risk of ovarian cancer compared with premenopausal women (table 2). This association was somewhat stronger among women with invasive nonmucinous tumors, most particularly serous and endometrioid types. Menstrual irregularity was associated with a decreased risk of nonmucinous tumors, especially clear cell types. The total years of menstruation were significantly associated with an increased risk of nonmucinous tumors but not with mucinous tumors ( $p$  for difference = 0.001), and the risk of invasive clear cell, "other," and serous types was significantly higher than that of the mucinous tumors. We found significant, strong positive trends in the risk of nonmucinous, but not mucinous, tumors, with increasing lifetime ovulatory cycles ( $p$  for difference = 0.005). Neither age at menarche, age at menopause, nor other menstrual patterns (cycle length, pain) were associated with the risk of any histologic subtypes of ovarian cancer (data not shown).

Pregnancy was associated with a reduced risk of all histologic types of ovarian cancer (table 3). Ever-pregnant women had a significantly lower risk of invasive endometrioid or clear cell tumors than did nulliparous women. We also observed an inverse dose-response relation between the number of full-term pregnancies and the risk of mucinous and nonmucinous tumors, most notably endometrioid tumors, but the differences in risk among histologic types were not significant ( $p = 0.87$ ). Women who had their last birth after 34 years of age had a nonsignificant decreased risk of all mucinous tumors and borderline serous tumors. Conversely, a longer duration since the last birth significantly increased the risk of borderline mucinous tumors. The difference in risk was significant between borderline and invasive tumors ( $p = 0.009$ ) but not between mucinous and nonmucinous tumors ( $p = 0.24$ ). Except for invasive mucinous tumors, breastfeeding lowered the risk of all ovarian cancer types. A longer duration of breastfeeding was significantly and inversely associated with the risk of nonmucinous, but not mucinous, tumors ( $p$  for difference = 0.03).

Oral contraceptive use was associated with a reduced risk of all histologic types of ovarian cancer (table 4). Inverse relations were generally similar for borderline and invasive tumors ( $p = 0.73$ ) and by histologic type ( $p = 0.51$ ). A significant inverse gradient in risk with increasing years of oral contraceptive use was seen for invasive tumors, especially serous, mucinous, and "other" types. Except for borderline mucinous tumors, a longer duration since last oral contraceptive use was associated with an increased risk of ovarian cancer, particularly for invasive serous, mucinous, and clear cell tumors. The risk of nonmucinous tumors, but not mucinous tumors, was reduced among women who reported a history of tubal ligation, although the difference was not significant ( $p = 0.14$ ). The greatest reduction in risk was among women with endometrioid tumors. Self-reported infertility was associated with an elevated risk of "other" histologic types of invasive ovarian cancer. This observation, however, was based on a limited number of cases. The use of noncontraceptive hormones for any reason was inversely related to borderline, but not invasive, tumors

( $p$  for difference = 0.04). Its effect varied among invasive tumors by histologic type ( $p$  for difference = 0.004): The risk was either null or protective for all types other than clear cell tumors, where there was a significant increase in risk.

## DISCUSSION

Our analysis suggests that certain reproductive factors are more strongly associated with the risk of nonmucinous tumors than mucinous tumors. This difference by histologic type appears to be independent of tumor invasiveness. We found that women with borderline tumors shared common menstrual, pregnancy, and hormone risk factors with invasive cases, although women with borderline tumors were somewhat younger.

Homogeneous inverse associations of parity and oral contraceptive use with the risk of borderline and invasive mucinous and nonmucinous tumors were evident in these data. Similar to our results, those of Siskind et al. (12), Wittenberg et al. (10), and Modugno et al. (13) showed a comparable relation of oral contraceptive use or parity with ovarian cancer risk among the major histologic types. In contrast, heterogeneous associations, most particularly between mucinous and nonmucinous tumors, have also been reported. Risch et al. (8) observed that risk reductions associated with parity and oral contraceptive use were limited to nonmucinous tumors. Riman et al. (19) and Adami et al. (20) reported that the use of oral contraceptives was not associated with the risk of borderline tumors. In a pooled collaborative analysis of 12 US case-control studies, the association of oral contraceptive use was weaker and less consistent for borderline tumors than for malignant tumors. Kvale et al. (21) also found no significant reduction in the risk of mucinous tumors with increasing numbers of pregnancies in a cohort study.

In spite of the inconsistent relation among parity, oral contraceptive use, and ovarian cancer, epidemiologic studies generally support the hypothesis that the protective role of parity and oral contraceptive use on the risk of ovarian cancer is attributed mainly to suppression of ovulation, although the underlying mechanism for ovarian carcinogenesis remains unclear. Factors related to ovulation, such as age at menopause and age at menarche, had little effect on the risk of the major histologic types of ovarian cancer in this study and previous studies. Similar to Purdie et al. (9), we observed a significant positive dose-response relation between lifetime ovulatory cycles and the risk of nonmucinous tumors, while ovulatory cycles had much less influence on the risk of mucinous tumors. Although ovulation may play a role in the pathogenesis of ovarian cancer, it does not explain the homogenous relations of parity and oral contraceptive use among histologic types. Our findings support the notion that both oral contraceptive use and parity may have protective effects against ovarian cancer independent of ovulation suppression, as suggested by others (7, 12).

Elevation in circulating progestin levels during pregnancy or use of oral contraceptives has been hypothesized to protect against ovarian cancer by mediating apoptosis induction and increasing the clearance of transforming cells from the ovarian epithelium (20, 22–24). According to this theory,

more recent pregnancies and oral contraceptive use would provide more protection against ovarian cancer than events in the distant past. Several studies have demonstrated that older age at first birth/last birth or recent pregnancy was associated with a decreased risk of ovarian cancer and that these associations varied by histologic type (25–27). Similar to the study of Cramer et al. (28), our study found that older age at last birth was associated with a nonsignificant decreased risk of borderline and invasive mucinous tumors but not of nonmucinous tumors. In addition, increasing years since the last pregnancy (table 3) were positively associated with the risk of borderline mucinous tumors ( $p$  for trend = 0.01). Our findings provide evidence that pregnancy clearance effects on cancer risk may not be uniform among histologic types and appear to protect most against borderline mucinous tumors.

Along with pregnancy and oral contraceptive use, breastfeeding also suppresses ovulation and has been associated with a reduced risk of ovarian cancer (29). In agreement with previous studies (9, 25), our study found that longer periods of breastfeeding reduced the risk of nonmucinous ovarian cancers, particularly endometrioid and clear cell type tumors. Prolonged lactation was not related to the risk of mucinous tumors.

Menstrual irregularity was more strongly associated with a reduced risk of nonmucinous tumors than of mucinous tumors. A possible mechanism for this association is through anovulation, which may be modulated by hormones (30). Similar to a previous study (31), our study found that women with irregular menstrual periods also had a higher frequency (25 percent) of abnormal cycle length (either <25 days or  $\geq 37$  days) than did women with regular menstruation (7 percent). However, abnormal cycle length was homogeneously associated with a reduced risk of ovarian cancer among mucinous (odds ratio = 0.8) and nonmucinous (odds ratio = 0.7) tumors.

Except for the “other” types of ovarian cancer, we failed to find a positive association of self-reported infertility with the risk of nonmucinous tumors, as reported in previous studies (7–9). In agreement with the finding of Purdie et al. (9), we observed no general association of fertility problems with either mucinous or nonmucinous tumors. Although Ness et al. (32) and Harris et al. (6) found that fertility problems were associated with increased risk of borderline tumors, we could not replicate their findings. Wittenberg et al. (10) reported a remarkably greater risk of mucinous tumors (odds ratio = 3.1) than nonmucinous tumors (odds ratio = 1.1) among infertile women. These inconsistent findings may result from the confounding effects of parity, use of oral contraceptives, use of fertility drugs, or endometriosis, since infertile or subfertile women tend to have lower parity, less frequent birth control use, more frequent use of fertility drugs, and a higher prevalence of endometriosis than more fertile women (33, 34).

We found that tubal ligation was associated with a reduced risk of nonmucinous tumors, particularly endometrioid and clear cell types, but not mucinous tumors. Similarly, Rosenblatt and Thomas (35) found that the inverse associations of tubal ligation were limited to endometrioid tumors and clear cell types. In contrast, other studies observed no differences

in risk reduction between mucinous and nonmucinous tumors for tubal ligation (9, 13). It is possible that some endometrioid and clear cell tumors are derived from malignant transformation of ovarian endometriosis lesions (36). Tubal ligation may protect against local inflammation in the pathogenesis of ovarian cancer risk by blocking passage of inflammatory agents from the genital tract to the ovarian epithelial cell (37). Therefore, the “inflammation” hypothesis would explain the distinct effects of tubal ligation in lowering the risk of endometrioid and clear cell types of ovarian cancer. Inflammation has also been linked to mutagenesis of the ovarian epithelium associated with ovulation, since ovulation is strongly associated with inflammatory reactions (38).

Our data strongly support the notion that mucinous tumors may be influenced to a lesser extent than nonmucinous tumors by factors directly linked to ovulation cycles. Diverse genetic patterns, that is, *p53* and *K-ras* (4, 39, 40), among histologic types may explain the differential associations of ovulatory-related factors such as lifetime ovulatory cycles, menstrual irregularity, and lactation. In addition, the *PTEN* tumor suppressor gene has been linked to the malignant transformation of endometriosis to endometrioid and clear cell types of ovarian cancer (41). Our results provide additional support for the hypothesis that distinct molecular pathways may be induced by specific underlying etiologic factors (42).

We found that ever use of noncontraceptive hormones or estrogens (odds ratio = 1.6) was associated with increased risk of clear cell tumors. It is uncertain whether this association is correlated with the absence of progesterin and/or estrogen  $\alpha$ -receptor expression among most clear cell types (43, 44). Hormone receptors of various histologic types may be modulated during müllerian differentiation or tumor progressions (45, 46). Thus, each histologic type of ovarian cancer may be mediated by distinct hormone carcinogenesis pathways according to the expression of receptors (46).

Consistent with previous studies (6, 13), our study showed that borderline tumors shared most common etiologic factors with invasive tumors, including parity, oral contraceptive use, lactation, and tubal ligation, suggesting that borderline tumors may be precursors for some invasive tumors (47) and, in particular, mucinous tumors (40). *K-ras* mutations may provide the most persuasive link between borderline and invasive tumors through the progressive spontaneous errors in DNA synthesis associated with cell proliferation (4, 48). We also found that women diagnosed with borderline tumors were generally younger than women diagnosed with invasive tumors. Similar to other reports (49), our study found that Asian women had a higher risk of mucinous and clear cell tumors while Caucasian women had a higher risk of serous tumors. Genetic predisposition may account for some of the racial differences in histologic patterns of ovarian cancer.

A major limitation of this study was the potential misclassification of histologic types of ovarian tumors. Histologic classification was based primarily upon histologic codes from hospital records and tumor registry review of pathology reports without central standardized pathology and slide review. Such review is especially important for mucinous

subtypes, because of the difficulties in distinguishing borderline from invasive tumors (50). It is reassuring that the frequency distributions for the major histologic types of ovarian cancer by race in our study were similar to those of reports that have undergone pathology review (8, 25, 51–54). One limitation of this study is the modest participation rates among eligible cases and controls, and that may lead to bias in the estimates of odds ratios. Madigan et al. (55) studied nonresponse in a case-control study of breast cancer and found that nonresponse had little effect on risk estimates, even though the response cases and controls were more likely to be educated or to use oral contraceptive pills than were nonrespondents (55). Therefore, we have no reason to suspect that nonresponse bias would be large in our study unless the characteristics associated with participation were different between cases and controls. Unfortunately, we have no ready means to investigate this possibility, as we do not have reproductive factors for the nonrespondents.

In summary, these data support the hypothesis that etiologic factors are heterogeneous among histologic types of ovarian cancer, especially between mucinous and nonmucinous tumors. Ovulatory factors, including lifetime ovulatory cycles and longer duration of breastfeeding, menstrual irregularity, and tubal ligation, were associated with the risk of nonmucinous tumors but not of mucinous tumors. There appears to be a histologic link between borderline and malignant tumors, since they share common risks factors. Ethnic differences in histologic patterns are intriguing and will be explored in our ongoing studies. Complex mechanisms in conjunction with ovulation, hormones, inflammation, and molecular pathways may all be involved in the pathogenesis of ovarian cancer.

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