



Aggregation of Ovarian Cancer with Breast, Ovarian, Colorectal, and Prostate Cancer in First-degree Relatives

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Epidemiologic studies have demonstrated a tendency for common cancers to aggregate in families. The authors investigated the effects of family history of cancer at multiple sites, including the breast, ovary, colorectum, and prostate, on ovarian cancer risk among 607 controls and 558 ovarian cases in Hawaii and Los Angeles, California, in 1993–1999. A family history of cancer of the breast, ovary, colorectum, or prostate in first-degree relatives was associated with an increased risk of ovarian cancer (odds ratio (OR) = 1.7, 95% confidence interval (CI): 1.1, 2.6; OR = 3.2, 95% CI: 1.3, 7.9; OR = 1.5, 95% CI: 0.9, 2.5; and OR = 1.6, 95% CI: 1.0, 2.8, respectively). A greater risk of ovarian cancer was observed for women with parents rather than siblings with a history of breast or prostate cancer and for women with parental colorectal cancer diagnosed at an early age, suggesting a genetic predisposition among these women. The risk of nonmucinous tumors, but not mucinous tumors, was positively associated with a family history of cancer. No significant interaction effects on risk existed between oral contraceptive pill use or pregnancy and family history of breast and/or ovarian cancer. Study findings suggest that ovarian cancer aggregates with several common cancers in family members.

breast neoplasms; colorectal neoplasms; neoplastic syndromes, hereditary; ovarian neoplasms; prostatic neoplasms

Abbreviations: CI, confidence interval; OR, odds ratio.

Hereditary ovarian cancer is a well-established entity, and epidemiologic studies have estimated that it accounts for approximately 5–10 percent of epithelial ovarian cancer. A history of ovarian cancer in first-degree relatives doubles the risk of ovarian cancer, and a history of breast and/or ovarian cancer in first-degree relatives increases ovarian cancer risk by 50 percent (1). In addition to hereditary breast-ovarian cancer syndrome (2), the incidence of ovarian cancer in families has also been linked to prostate cancer (3, 4) as well as to hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome II) (5). Hereditary nonpolyposis colorectal cancer is an inherited disorder characterized by early-onset colorectal cancer and is associated with an increased risk of several extracolonic cancers, including ovarian, in families (6).

Inherited germline mutations of the breast cancer susceptibility genes, *BRCA1* and *BRCA2* (7), as well as the colorectal

mismatch repair genes *hMLH1* (8) and *hMSH2* (9), have been found to confer predisposition to cancer in families with hereditary breast-ovarian cancer and hereditary nonpolyposis colorectal cancer, respectively. *BRCA1* and *BRCA2* mutations have also been linked to prostate cancer (10). These inherited mutations may have a role in DNA repair and genome integrity. The tumorigenicity of hereditary susceptibility genes may be mediated through a multi-stage DNA repair pathway (11, 12). Therefore, each mutation may involve several cancer sites.

In an earlier analysis of these data, we found that a family history of ovarian or breast cancer was significantly more common among ovarian cancer cases than among controls (13). The objective of this analysis was to examine the relation of familial cancer with ovarian cancer risk in greater detail. Previous case-control studies of ovarian cancer have examined family history of breast and/or ovarian cancer in

first- or second-degree relatives, without considering other cancer sites. In this analysis, we investigated the ovarian cancer risk associated with a family history of cancer at the four most common hereditary cancer sites: breast, ovary, colorectum, and prostate. In particular, we were interested in how these relations were modified by age at diagnosis or histologic type of ovarian cancer. Because family history represents shared environmental risk factors in addition to genetic predisposition within families, we also examined the interactions between established reproductive factors, including parity and oral contraceptive use, and family history of breast and/or ovarian cancer to determine whether a history of familial cancer modified the association of these exposures with the risk of 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 (13). Briefly, eligibility criteria for participation in this investigation included 1) residency in Hawaii or Los Angeles County for at least 1 year prior to diagnosis for cases or interview date for controls; 2) being 18 years of age or older; 3) having no prior history of ovarian cancer; and 4) for controls, having at least one intact ovary.

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 ovarian cancer cases eligible for participation in the study. Response rates among eligible cases did not differ substantially by study location (65 percent in Hawaii, 61 percent in Los Angeles) or ethnic group (63 percent among Asian Americans, 65 percent among Pacific Islanders, 60 percent among Whites). Thirty-nine cases were excluded from this analysis because of equivocal histologic classification. Consistent with our previous analysis (13), 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.

Four major histologic categories of epithelial ovarian cancer were considered based on the classification scheme of the World Health Organization (14): mucinous, serous, endometrioid, and clear cell. 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 on their histologic characteristics.

Population controls were randomly selected from a neighborhood walk procedure in Los Angeles (15) and from lists of participants in a Department of Health statewide annual survey in Hawaii (16). The controls were frequency matched to cases with an approximate 1:1 ratio based on specific ethnicity (e.g., Japanese), age (year of birth ± 5 years), and study site. A total of 907 women meeting the eligibility criteria were contacted to participate in the study. Complete demographic and nutrient information was obtained from 609 (67 percent) of these women. We excluded two controls

from the analysis because of unreliable dietary information. Of the 607 controls, 283 were from Hawaii and 324 were from Los Angeles. Although the control selection procedures were somewhat different in the two locations, we found similar frequency distributions for most risk factors at the two geographic locations.

The questionnaire included information regarding menstrual, reproductive, and gynecologic histories; birth control methods; use of exogenous hormones; and other lifestyle practices. Family history of cancer included detailed information on all cancer sites as well as age at diagnosis for first-degree relatives (mother, father, brothers and sisters). The majority (>95 percent) of subjects were interviewed in their homes. All interviews were administered by trained interviewers according to a standard protocol and took approximately 2.5 hours.

An unconditional logistic regression model (17) was used to estimate the risk of ovarian cancer associated with a family history of cancers of the breast, ovary, colorectum, prostate, and all sites combined. A positive family history of cancer was defined as at least one cancer in a first-degree relative. We separately examined the associations of cancers in parents and siblings with ovarian cancer risk. Women with no family history of cancer at any site were considered the reference group when estimating risk related to cancer in any family member and in parents. We considered only those women with at least one sibling as the reference group when estimating the association of ovarian cancer risk with family history of cancer in siblings. For sex-specific cancers, such as ovarian and prostate cancers, the reference group was further reduced to include women with at least one sibling of the appropriate gender. In addition to age (continuous), race (indicator variable for White, Asian, other), and study site (indicator variable for Hawaii, Los Angeles), adjustment variables included education (continuous), oral contraceptive use (ever vs. never), pregnancy (ever vs. never), and tubal ligation (yes vs. no) because they were significant risk factors for ovarian cancer according to our previous analysis (13). We also considered other potential adjustment variables, such as menopausal status, body mass index, and sibship size, but these variables did not materially alter the fit of the models or the estimates of the odds ratios.

To investigate risk of ovarian cancer by specific histologic types, a polytomous logistic model (17) was run comparing cases with a specific histology with all eligible controls. Two such models were used to compare the risk of combined histologic subgroups: 1) borderline and invasive tumors and 2) mucinous and nonmucinous tumors. The groups were compared statistically by using a Wald test. Lastly, risk of early- and late-onset ovarian cancer was estimated in a polytomous logistic model comparing all controls with cases diagnosed when they were either age 50 years or younger or older than age 50 years. The risk for early- and late-onset cancer was compared statistically by using a Wald test.

The likelihood ratio test was used to evaluate the interaction between family history and reproductive factors on the risk of ovarian cancer. This test compared a no-interaction model containing main-effect terms with a fully parameterized model containing all possible interaction terms for the variables of interest. All data were analyzed by using SAS

version 8.2 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The distribution of subject demographic and risk factor information is shown in table 1. Cases and controls were similar in age (mean, 54.8 years), and the majority were of European or Asian ancestry. Controls were better educated than cases, had had a greater number of full-term pregnancies, were more likely to have used oral contraceptives, and had a higher frequency of tubal ligation. These risk factors were used as adjustment variables in subsequent analyses. The numbers of family members with any cancer were similar between cases (mean, 1.53) and controls (mean, 1.48). Number of siblings was also similar between cases (mean, 3.35) and controls (mean, 3.19). The majority of tumors were invasive and of nonmucinous histology.

Table 2 shows the findings for family history of cancer at specific sites in relation to ovarian cancer risk. The risk of ovarian cancer increased for all cancers combined and for each study cancer site individually occurring in any first-degree relative. The risks were statistically significant for breast, ovarian, or either cancer, and for all cancers combined, and were nearly significant for colorectal and prostate cancers. For breast or prostate cancer history, the increased ovarian cancer risk was significantly associated with cancer occurring in a parent but not in a sibling; for ovarian and colorectal cancer history, the opposite was true. In general, White women had a stronger familial ovarian cancer risk than non-White women did (data not shown). Regarding other common cancers occurring in families (i.e., skin, stomach, and lung), only those women with a family history of lung cancer in a first-degree relative had a significantly increased risk of ovarian cancer (odds ratio (OR) = 1.73, 95 percent confidence interval (CI): 1.07, 2.81).

We found little association of family history of cancer at any study site with age at diagnosis of ovarian cancer (table 3). The risk of early-onset ovarian cancer was more strongly associated with ovarian cancer in a sister (OR = 6.46, 95 percent CI: 1.16, 35.9) and with prostate cancer in a father (OR = 3.27, 95 percent CI: 1.45, 7.35) than was late-onset ovarian cancer (OR for sister's ovarian cancer = 3.15, 95 percent CI: 0.69, 14.4 and OR for father's prostate cancer = 1.93, 95 percent CI: 0.92, 4.05). Conversely, the risk of late-onset ovarian cancer was more strongly associated with maternal ovarian cancer (OR = 3.33, 95 percent CI: 0.80, 13.9) and with a sibling's colorectal cancer (OR = 2.87, 95 percent CI: 1.12, 7.34) than was early-onset ovarian cancer (OR for mother's ovarian cancer = 1.69, 95 percent CI: 0.25, 11.5 and OR for sibling's colorectal cancer = 0.92, 95 percent CI: 0.10, 8.07). However, none of the differences was significant.

We also examined the association of ovarian cancer risk with age at diagnosis for parental cancer. An early onset (at <50 years of age) for parental colorectal cancer was more strongly associated with an increased risk of ovarian cancer for the probands (OR = 2.29, 95 percent CI: 0.52, 9.98) compared with late onset of this cancer in parents (OR = 1.17, 95 percent CI: 0.65, 2.09). However, risk of ovarian

cancer in the probands did not differ according to the mother's age at diagnosis for breast and/or ovarian cancer. All of the fathers were diagnosed with prostate cancer after age 50 years. However, we did find that the three fathers diagnosed with prostate cancer before age 60 years all had daughters with ovarian cancer.

A family history of breast and/or ovarian (4.6 percent), colorectal (5.5 percent), and prostate (5.5 percent) cancer was infrequent among women with mucinous tumors (table 4). Except for clear-cell types, a family history of breast and/or ovarian cancer was positively and significantly associated with borderline and invasive nonmucinous tumors, but there was no evidence of an elevated risk of mucinous tumors. The difference in risk between mucinous and nonmucinous tumors was significant ($p = 0.005$). However, we found that the difference was much stronger for Whites (OR for mucinous = 0.55, 95 percent CI: 0.11, 2.61 and OR for nonmucinous = 2.93, 95 percent CI: 1.69, 5.09; p for difference = 0.03) than for non-Whites (OR for mucinous = 0.53, 95 percent CI: 0.15, 1.83 and OR for nonmucinous = 1.75, 95 percent CI: 0.96, 3.20; p for difference = 0.06). Association of a family history of colorectal or prostate cancer with the risk of mucinous tumors was generally weaker than for nonmucinous tumors, but the differences were not significant.

No significant interaction was found between family history of breast or ovarian cancer and reproductive factors, such as pregnancy and oral contraceptive pill use (table 5). That is, pregnancy had a similar effect on risk of ovarian cancer for women with a family history of breast or ovarian cancer (OR = 1.24/3.13 = 0.40) as for women without a family history of any cancer (OR = 0.72); similarly, the odds ratio for ever versus never use of oral contraceptive pills was similar between family history (OR = 1.08/1.68 = 0.64) and no family history (OR = 0.52).

DISCUSSION

Our results confirm previous reports that a family history of cancer is a risk factor for ovarian malignancy. In our study, not only was a family history of breast, ovarian, colorectal, and prostate cancer associated with an increased risk of ovarian cancer, but this association varied by family relationship, age at diagnosis, and histologic subtypes of ovarian cancer.

Most previous epidemiologic studies have also reported a positive relation of ovarian cancer risk to a family history of ovarian cancer (18, 19) and breast cancer (19–21), but the results for breast cancer were inconsistent (18, 22). One other population-based study found a positive association of colorectal or prostate cancer with a familial risk of ovarian cancer (23). However, in a recent study, no association was reported between a family history of prostate cancer and ovarian cancer risk (24). As indirect evidence, breast and/or ovarian cancer was positively associated with the risk of familial prostate and colon cancers (25, 26). In addition to the potential for biased reporting of familial cancer by cases, inconsistent results of studies of breast cancer family history on ovarian cancer risk likely occur from differences in the relation of the familial cancer case to the study participant, age at diagnosis of ovarian cancer, age at diagnosis of cancer

TABLE 1. Odds ratios* and 95% confidence intervals for the association of selected demographic variables with the risk of ovarian cancer, Hawaii and Los Angeles, California, 1993–1999

Variable	Cases (n = 558)		Controls (n = 607)		OR†	95% CI‡
	No.	%	No.	%		
Study site						
Hawaii	200	35.8	283	46.2		
Los Angeles, California	358	64.2	324	53.4		
Age (years)‡						
<45	130	23.3	149	24.5		
45–54	160	28.7	171	28.2		
55–64	117	21.0	98	16.1		
≥65	151	27.1	189	31.1		
Ethnicity‡						
White	258	46.2	266	43.8		
Asian	206	37.2	254	41.8		
Other	94	16.6	87	14.3		
Education (years)						
<13	189	33.9	163	26.8	1§	
13–14	194	34.8	214	35.2	0.75	0.55, 1.02
15	113	20.2	150	24.7	0.63	0.41, 0.96
≥16	62	11.1	80	13.2	0.59	0.41, 0.83
No. of full-term pregnancies						
None	159	28.5	107	17.6	1§	
1	77	13.8	90	14.8	0.60	0.41, 0.89
2	139	24.9	179	29.5	0.60	0.42, 0.84
≥3	183	32.8	231	38.1	0.53	0.37, 0.75
Oral contraceptive pill use (years)						
Never	320	57.3	269	44.3	1§	
<1.9	93	16.7	99	16.3	0.74	0.51, 1.08
1.9–5.39	82	14.7	110	18.1	0.61	0.42, 0.88
≥5.4	63	11.3	129	21.2	0.36	0.24, 0.54
History of tubal ligation						
No	490	87.8	487	80.2	1§	
Yes	68	12.2	120	19.8	0.70	0.50, 0.99
Histology						
Mucinous	109	19.5				
Nonmucinous	449	80.5				
Invasiveness						
Borderline	127	22.7				
Invasive	431	77.2				

* After adjustment by unconditional multiple logistic regression for age, ethnicity, study site, education, oral contraceptive pill use, parity, and tubal ligation (where appropriate).

† OR, odds ratio; CI, confidence interval.

‡ Cases and controls were frequency matched on these variables.

§ Reference category.

in family members, number of family members affected with cancer, and histologic type of ovarian cancer.

We found that the risk of ovarian cancer was more strongly, positively associated with breast or prostate cancers occurring in parents than in siblings, whereas ovarian cancer was

more strongly associated with ovarian and colorectal cancer occurrence in siblings than in parents. Age at diagnosis of breast, ovarian, or prostate cancer in parents had little effect on the risk of ovarian cancer in daughters. However, in a Swedish cohort study, Anderson et al. (27) reported that

TABLE 2. Odd ratios* and 95% confidence intervals for the association of family history of cancer with ovarian cancer risk, Hawaii and Los Angeles, California, 1993–1999

Family-history cancer site	Any first-degree relative				Parent				Sibling			
	Cases (no.)	Controls (no.)	OR†	95% CI†	Cases (no.)	Controls (no.)	OR	95% CI	Cases (no.)	Controls (no.)	OR	95% CI
None	266	318	1‡		266	318	1‡		239	271	1§	
									196	198	1¶	
									198	227	1#	
Breast	69	53	1.71	1.13, 2.60	46	26	2.31	1.35, 3.94	24	28	1.13	0.65, 2.14
Ovary	18	7	3.15	1.26, 7.87	7	4	2.29	0.64, 8.17	11	3	3.92	1.02, 15.1
Breast and/or ovary	85	59	1.87	1.27, 2.77	53	30	2.27	1.38, 3.76	34	30	1.47	0.85, 2.55
Colorectum	48	40	1.52	0.94, 2.46	32	33	1.27	0.74, 2.19	17	8	2.57	1.05, 6.29
Prostate	39	32	1.64	0.97, 2.75	29	20	1.99	1.07, 3.70	11	13	1.21	0.51, 2.92
Any of the above	155	116	1.74	1.28, 2.38	107	81	1.69	1.19, 2.41	56	49	1.48	0.94, 2.33
All sites	292	289	1.32	1.03, 1.69	213	223	1.25	0.96, 1.63	132	116	1.53	1.09, 2.14

* After adjustment by unconditional multiple logistic regression for age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, and tubal ligation.

† OR, odds ratio; CI, confidence interval.

‡ Reference category for the analysis of any first-degree relatives and parents.

§ Reference category includes women with at least one sibling considered in the analysis of family history of cancer of the breast, breast and/or ovary, colorectum, any of the above, and all sites.

¶ Reference category includes women with at least one sister considered in the analysis of family history of ovarian cancer.

Reference category includes women with at least one brother considered in analysis of family history of prostate cancer.

ovarian cancer risk was higher in offspring if the maternal ovarian cancer was diagnosed before age 50 years (standardized morbidity ratio = 3.70, 95 percent CI: 1.97, 6.33) than after age 50 years (standardized morbidity ratio = 2.12, 95 percent CI: 1.51, 2.90). The risk was even higher (standardized morbidity ratio = 7.67, 95 percent CI: 2.09, 19.65) if the mother's age at ovarian cancer diagnosis was less than 40 years. We did observe that ovarian cancer risk was more strongly associated with an early age at diagnosis for parental colorectal cancer. Genetic predisposition to *BRCA* mutations may provide a partial explanation for the variation in risk of

ovarian cancer associated with a family history of breast, colorectal, and possibly prostate cancer by type of relative. Ovarian cancer cases whose mothers have breast and/or ovary cancer are more likely to be *BRCA1* carriers than are cases for whom this cancer occurs in their siblings (28). *BRCA1* mutations may also be the genetic link between familial prostate cancer and a history of breast and/or ovarian cancer occurring in the mother but not the sister (25).

Our data suggest that ovarian cancer in a sister or prostate cancer in the father is associated with early age at diagnosis of ovarian cancer. Negri et al. (24) recently reported that

TABLE 3. Odd ratios* and 95% confidence intervals for the association of family history of cancer with ovarian cancer in first-degree relatives, by age at diagnosis, Hawaii and Los Angeles, California, 1993–1999

Family-history cancer site	Controls (no.)	Age (years) at diagnosis of ovarian cancer cases						<i>p</i> for difference†	
		≤50			>50				
		No.	OR‡	95% CI‡	No.	OR	95% CI		
None	318	128	1§				138	1§	
Breast	53	23	2.03	1.10, 3.77	46	1.73	1.08, 2.80	0.64	
Ovary	7	7	3.75	1.11, 12.6	11	3.25	1.14, 9.26	0.82	
Breast and/or ovary	59	29	2.25	1.26, 4.00	56	1.89	1.20, 2.96	0.59	
Colorectum	40	12	1.42	0.65, 3.10	36	1.63	0.95, 2.78	0.75	
Prostate	32	14	2.40	1.12, 5.13	25	1.60	0.88, 2.90	0.34	
Any of the above	116	52	2.21	1.37, 3.54	103	1.73	1.21, 2.49	0.37	
All sites	289	104	1.54	1.06, 2.23	188	1.35	1.00, 1.82	0.55	

* After adjustment by polytomous logistic regression for age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, and tubal ligation.

† *p* comparing odds ratios for early onset and late-onset disease based on a Wald test.

‡ OR, odds ratio; CI, confidence interval.

§ Reference category.

TABLE 4. Odd ratios* and 95% confidence intervals for the association of family history of cancer with ovarian cancer, by histologic type, Hawaii and Los Angeles, California, 1993–1999

	Family history of cancer in first-degree relatives												
	None (no.)	Breast and/or ovary			Colorectum			Prostate			Any of the above		
		No.	OR†	95% CI†	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Controls	318	59	1‡		40	1‡		32	1‡		116	1‡	
Cases													
Borderline	67	16	1.91	0.99, 3.69	9	1.74	0.76, 3.98	8	1.97	0.81, 4.77	31	1.92	1.13, 3.25
Serous	31	14	3.54	1.65, 7.61	5	2.27	0.76, 6.77	4	2.19	0.66, 7.27	21	2.78	1.43, 5.40
Mucinous	36	2	0.46	0.11, 2.02	4	1.43	0.46, 4.46	4	1.83	0.57, 5.83	10	1.21	0.56, 2.65
Invasive	199	69	1.91	1.26, 2.88	39	1.48	0.89, 2.44	31	1.60	0.92, 2.77	124	1.77	1.24, 2.39
Serous	93	41	2.22	1.37, 3.58	18	1.35	0.72, 2.54	19	1.98	1.05, 3.72	68	1.87	1.26, 2.78
Mucinous	33	3	0.66	0.19, 2.28	2	0.67	0.15, 3.01	2	0.85	0.19, 3.87	6	0.69	0.27, 1.75
Endometrioid	30	13	2.31	1.09, 4.90	7	1.83	0.70, 4.78	6	2.10	0.77, 5.69	26	2.44	1.32, 4.52
Clear	25	3	0.82	0.23, 2.95	6	1.97	0.72, 5.41	1	0.36	0.04, 2.93	9	1.09	0.47, 2.52
Other	18	9	2.86	1.16, 7.08	6	2.44	0.85, 6.98	3	1.62	0.43, 6.09	15	2.24	1.04, 4.79
Cases													
Mucinous	69	5	0.56	0.21, 1.48	6	1.03	0.41, 2.61	6	1.34	0.52, 3.47	16	0.94	0.51, 1.74
Nonmucinous	197	80	2.22	1.48, 3.31	42	1.63	0.99, 2.69	33	1.72	1.00, 2.96	139	1.95	1.41, 2.70
<i>p</i> for difference§			0.005			0.33			0.60			0.02	

* After adjustment by polytomous logistic regression for age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, and tubal ligation.

† OR, odds ratio; CI, confidence interval.

‡ Reference category.

§ *p* comparing odds ratios for mucinous and nonmucinous tumors based on a Wald test.

ovarian cancer risk associated with a family history of ovarian cancer was much stronger for younger women (aged <50 years; OR = 23, 95 percent CI: 2.6, 212) than for older women (aged ≥50 years; OR = 5.6, 95 percent CI: 2.2, 14). However, age at diagnosis of ovarian cancer was unaffected by a family history of colorectal cancer. Although early-onset ovarian cancer is more likely to be inherited (29, 30), *BRCA1/2*, *hMSH2*, and *hMLH1* gene mutations are rarely associated with ovarian cancer diagnosed before age 40 years (31). Case, as well as control, selection may account for some of the conflicting results associated with age at diagnosis. Cases in our study were population based and

were not selected specifically from high-risk families with multiple affected members. Thus, the majority of women in this study who had a family history of cancer had one affected relative (95 percent of women with familial breast and/or ovarian cancer had only one affected relative). A decreasing trend in age at diagnosis of ovarian cancer associated with increasing numbers of affected family members (32, 33) may be due to the presence of *BRCA* mutations in these high-risk families (34, 35).

We found a stronger positive association of nonmucinous tumors, especially borderline serous tumors, than mucinous tumors with a family history of breast and/or ovarian cancer

TABLE 5. Odd ratios* and 95% confidence intervals for the joint association of pregnancy status, oral contraceptive pill use, and family history of breast and/or ovarian cancer with the risk of ovarian cancer, Hawaii and Los Angeles, California, 1993–1999

	No family history of any cancer				Family history of breast and/or ovarian cancer				<i>p</i> for interaction†
	Cases (no.)	Controls (no.)	OR‡	95% CI‡	Cases (no.)	Controls (no.)	OR	95% CI	
Pregnancy									
Never	51	41	1§		21	6	3.13	1.13, 8.67	
Ever	215	277	0.72	0.45, 1.17	64	53	1.24	0.68, 2.24	0.27
OC‡ use									
Never	153	144	1§		47	27	1.68	0.97, 2.91	
Ever	113	174	0.52	0.35, 0.78	38	32	1.08	0.61, 1.90	0.59

* After adjustment by unconditional multiple logistic regression for age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, and tubal ligation (where appropriate).

† Based on the likelihood ratio test comparing a main-effects model and an interaction model (df = 1).

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

§ Reference category.

in first-degree relatives. This finding is consistent with those of Purdie et al. (36). However, Modugno et al. (37) reported a more pronounced association of a family history of ovarian cancer with invasive mucinous tumors (OR = 7.67, 95 percent CI: 2.64, 22.24). *BRCA1* mutations are linked to most familial nonmucinous invasive ovarian cancers in families with hereditary breast-ovarian cancer (38–40). These molecular patterns are in accord with the association of a family history of breast and/or ovarian cancer with specific histologies (40–42) except for borderline serous tumors. It is possible that ethnic differences in the study population may have contributed to the inconsistent results, since *BRCA1* mutations are more likely to occur in White women than in non-White women (43, 44). In our study, the majority of women with mucinous tumors were Asians, who are less likely to be *BRCA1* carriers, compared with other studies that included mainly White women. Our sample was too small to investigate whether the results for mucinous tumors varied by race, but we did find that the differences in risks between mucinous and nonmucinous tumors associated with breast and/or ovarian cancer history were limited to White women. Nonetheless, our finding of a possible familial aggregation of borderline serous ovarian cancer implies that non-*BRCA* mutations may be involved in the pathogenesis of ovarian cancer and support a polygenic model for this disease (45) or that family members share joint exposures.

In our study, a family history of colorectal cancer or prostate cancer appeared to be more strongly associated with an increased risk of nonmucinous tumors than with mucinous tumors, especially borderline serous tumors. An excess of endometrioid tumors has been observed in families with hereditary nonpolyposis colorectal cancer (30), suggesting that other mismatch repair genes may favor the development of this type of cancer because *BRCA1* mutations are less commonly present in endometrioid tumors than in serous tumors (46). There is a possibility that ovarian cancer cases with a family history of colorectal and prostate cancers were *BRCA2* carriers since a late age at diagnosis was suggested for borderline ovarian cancer cases who had a family history of colorectal cancer (28).

In agreement with the findings of Tavani et al. (47) and Godard et al. (48), we found no evidence that a family history of breast and/or ovarian cancer modified the association of pregnancy history or oral contraceptive pill use with ovarian cancer risk. Our results support the notion that the underlying pathogenetic mechanisms in ovarian cancer are similar between familial and sporadic ovarian cancer (49). In contrast, a recent study showed that nulliparity was a much stronger risk factor for women with a family history of ovarian or breast and/or ovarian cancer in their first- and second-degree relatives (22). Walker et al. (50) found that the reduction in ovarian cancer risk associated with oral contraceptive pill use was significantly greater for women with a family history of ovarian cancer than for women without such a history. Narod et al. (51) reported that oral contraceptive pill use reduced ovarian cancer risk for *BRCA* carriers, while Modan et al. (52) found that the risk reduction associated with oral contraceptive pill use was limited to noncarriers of the *BRCA* mutation.

A major weakness of this study was the use of a self-reported family history of cancer without any validation. However, self-reported family history of cancer in first-degree relatives was found to be reasonably accurate when compared with medical records (54, 55). Although recall bias in self-reported family history of malignancy is less likely between cases and controls for the most common cancer sites (56), we cannot exclude the possibility that women with extensive family histories of cancer were more likely than women with no such history to report an accurate family cancer history. It is possible that a family history of cancer may have had a positive influence on participation in this study, most particularly among controls. If so, then the association between a family history of cancer and ovarian cancer risk may have been stronger. Unfortunately, we did not have detailed information about the nonparticipants and could not evaluate the potential effects of differential selection bias. Nevertheless, selection bias in this study should be minor since the prevalence of a family history of breast and/or ovarian cancer in first-degree relatives among cases (15 percent) and controls (9.7 percent) was similar to that in the US population (57) as well as in other population-based studies with similar or higher response rates (23, 36). A further limitation was the small sample size in our subgroup analyses.

In summary, in this study, the risk of ovarian cancer was associated with the occurrence of breast, ovarian, colorectal, and prostate cancer in first-degree relatives, suggesting that familial ovarian cancer aggregates with several cancer sites. Several established reproductive risk factors, including oral contraceptive pill use and parity, appear to reduce the risk of familial and sporadic ovarian cancers to a similar extent. Our results provide indirect support for a polygenic etiology of familial ovarian cancer.

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