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Differences in Risk Factors for Epithelial Ovarian Cancer by Histologic Type

Results of a Case-Control Study

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A case-control study of associations between dietary and reproductive factors and cancer of the ovary was conducted during 1989–1992 in metropolitan Toronto and nearby areas of southern Ontario, Canada. In total, 450 women aged 35–79 years with histologically verified new primary epithelial ovarian cancers were interviewed concerning their reproductive history and dietary practices. Over the same time period, 564 randomly selected population controls, frequency-matched to the cases according to three 15-year age groups, were also interviewed. Continuous unconditional logistic regression methods were used for analysis. It was found that childbearing and use of oral contraceptives were associated with significant decreasing trends in the risk of epithelial ovarian cancer of all principal histologic types except mucinous tumors. For each full-term pregnancy, the odds ratio was 0.76 (95% confidence interval (CI) 0.69–0.85) for nonmucinous tumors and 1.03 (95% CI 0.88–1.21) for mucinous tumors; for each year of oral contraceptive use, the odds ratio was 0.89 (95% CI 0.85–0.93) for nonmucinous tumors and 0.98 (95% CI 0.93–1.04) for mucinous tumors (p = 0.00051 and p = 0.0040, respectively, for the difference in odds ratios between mucinous and nonmucinous tumors). Saturated fat intake also appeared to convey greater increased risk for women with mucinous tumors than for women with neoplasms of other histologic types (p = 0.029). Among women with nonmucinous tumors, increasing trends in risk of invasive serous cancer (p = 0.018), and particularly endometrioid cancer (p = 0.0041), were seen with use of noncontraceptive estrogens. Otherwise, borderline-malignant neoplasms seemed to have a similar spectrum of risk factor associations as invasive cancers. On the basis of this study and a number of others, the authors suggest that mucinous ovarian tumors may be etiologically unrelated to other types of epithelial tumors, and thus should be considered separately in studies of ovarian cancer. *Am J Epidemiol* 1996;144:363–72.

contraception; diet; histology; ovarian neoplasms; parity; pregnancy; retrospective studies

Most epidemiologic studies of epithelial ovarian cancer group together the variety of different histologic types that occur under this designation. Epithelial ovarian neoplasms are classified as either borderline (of low malignant potential but capable of metastasis) or invasive; a second axis of classification is based on the histologic (cell) type giving rise to the tumor (1). Recent work summarizing a number of studies suggests that borderline-malignant tumors may have etiologic factors in common with invasive tumors (2). Such factors include parity and oral contraceptive use, the best-established and most protective factors for ovarian cancer (3). However, compared with women with invasive tumors, women with borderline tumors are generally younger (4), have more localized tumors at diagnosis (4), less frequently have a mutation of the tumor p53 gene and loss of its heterozygosity (5), and have better prognoses (4). In addition, in three ovarian cancer studies that evaluated risk associations with parity and oral contraceptive use according to specific histologic subtypes, protective associations were seen for serous and endometrioid tumors but not for mucinous tumors (6–8).

Thus, it is unclear whether the particular varieties of epithelial ovarian tumors have differing etiologies. We report here the results of a case-control exploration of ovarian cancer risk factors according to histology. We consider associations with reproductive, dietary, and other factors that have previously been examined

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within a single case group comprising all histologic types (9, 10).

MATERIALS AND METHODS

Subject selection and collection of data have been described elsewhere (9, 10) and will be briefly summarized here. All histologically confirmed primary, malignant, or borderline-malignant epithelial ovarian tumors first diagnosed from November 1989 through October 1992 among Ontario, Canada, residents aged 35–79 years were identified through review of the province-wide pathology reports received by the Ontario Cancer Registry. Case subjects living at the time of diagnosis in a defined geographic region that included metropolitan Toronto and other areas surrounding the western end of Lake Ontario were eligible for entry into the study. The small number of identified patients with a cytologic diagnosis only (no pathology report), or for whom the primary site was the oviduct or round ligament or was ultimately uncertain (including a few who had multiple, possibly independent primary tumors involving organs other than the ovaries), were considered ineligible and were excluded. In total, we identified 631 eligible cases and interviewed 450 (71.3 percent). Of the others, 55 had died (8.7 percent), 29 had physicians who refused consent (4.6 percent), 30 were too ill to be interviewed (4.8 percent), 17 were lost to follow-up (2.7 percent), and 50 refused to participate (7.9 percent).

A random sample of population controls, frequency-matched to the cases in three 15-year age groups, was obtained from the Enumeration Composite Record listing of individuals compiled by the Ontario Ministry of Finance. Potential control women who reported having had both (or an unknown number of) ovaries removed 1 year or more previously were considered ineligible for the study and were omitted ($n = 103$). In total, 873 eligible controls were identified and 564 (64.6 percent) were interviewed. The remainder either refused to participate (30.2 percent), were too ill to participate (1.9 percent), or were lost to follow-up (3.2 percent).

An in-person questionnaire interview was used for the ascertainment of dietary, reproductive, and medical history. Detailed information was sought regarding pregnancies, hormone and contraceptive usage, and infertility factors. Usual dietary practices were determined using the complete diet history questionnaire created by the National Cancer Institute of Canada Epidemiology Unit (11, 12), with quantitative portion sizes estimated via food models. Nutrient intakes were calculated from the questionnaire data by means of a database for Canadian foods that has been described elsewhere (10, 11).

For classification of histologic types, pathology reports were reviewed (by H. A. R.) for each case. The review was based on standardized diagnostic criteria applied to the microscopy descriptions and the pathologist's impressions; *International Classification of Diseases for Oncology* (field trial edition (13)) codes were assigned. In many cases, where the original pathologist was uncertain of the histologic diagnosis, pathology materials were sent to a regional reference pathologist in southern Ontario as part of the regular clinical workup, and his reports were also included in our review. We did not perform a separate review of pathology slides for this study.

For data analysis, we used multivariate unconditional logistic regression methods, which allow simultaneous examination of multiple exposure factors. The GLIM computer program (14) was employed. Both trends in risk odds with exposure (parameter estimates of slope) and odds ratio categories were examined. Tests of statistical significance were based on differences in log-likelihood, and all p values given are two-sided. For the histologic type-specific associations, we analyzed each case subtype with respect to the entire group of controls. Such models contained indicator terms for the age categories of the frequency matching (35–49, 50–64, and 65–79 years); age as a continuous variable was also included to adjust for residual age effects. To evaluate the statistical significance of the difference in magnitude of a risk factor's odds ratio between two case subtypes (e.g., mucinous vs. nonmucinous tumors), we used regression analyses with one of the subtypes entered as the "cases" and the other as the "controls" (15). These models contained age as a continuous term. Where not otherwise examined as variables of interest, total duration of oral contraceptive use and number of full-term pregnancies were included in the models as well.

RESULTS

Table 1 shows descriptive and risk factor data for the controls, and for the cases according to the principal histologic groups. Slightly more than half of the case tumors were classified as serous, including papillary serous neoplasms and papillary neoplasms not otherwise specified. Mucinous tumors comprised about 18 percent of the cases, split equally between borderline and invasive types. For the present work, we included the 28 malignant clear-cell tumors found in this study in the "other" category of invasive cancers, along with undifferentiated ($n = 5$) and mixed ($n = 8$) epithelial tumors and a malignant Brenner tumor. Sixteen percent of the cases had endometrioid tumors.

TABLE 1. Descriptive and risk factor data among epithelial ovarian-cancer cases and controls, southern Ontario, Canada, 1989–1992

Factor	Controls	Cases										
		Invasive histologies					Borderline histologies			All histologies		
		Serous	Mucinous	Endometrioid	Other*	All	Serous	Mucinous	All	Serous	Mucinous	All
No. of subjects	564	212	40	73	42	367	42	40	83	254	80	450
Mean age (years) at diagnosis/interview	57.5	59.5	55.3	57.2	57.4	58.3	52.1	52.7	52.3	58.3	54.0	57.2
% born in Canada or the United States	64.7	57.1	70.0	49.3	54.8	56.7	64.3	75.0	69.9	58.3	72.5	59.1
% white	96.3	97.2	100.0	95.9	95.2	97.0	95.2	97.5	96.4	96.9	98.9	96.9
Mean years of schooling	12.5	11.9	12.4	11.9	13.5	12.1	13.0	13.1	13.1	12.1	12.7	12.3
% parous	88.8	75.5	82.5	75.3	76.2	76.3	73.8	85.0	78.3	75.2	83.8	76.7
Mean parity (among parous women)	2.76	2.59	3.06	2.22	2.06	2.51	2.03	2.59	2.32	2.50	2.82	2.48
% who had ever used oral contraceptives	49.6	34.0	42.5	31.5	31.0	34.1	50.0	67.5	59.0	36.6	55.0	38.7
Mean years of oral contraceptive use (among ever users)	5.53	3.64	5.65	4.07	3.39	3.96	3.71	5.11	4.71	3.65	5.32	4.17
Mean months of lactation/pregnancy (among parous women)	2.72	2.09	3.51	2.01	3.05	2.35	1.89	1.67	1.77	2.06	2.58	2.24
% who had had tubal ligation	24.3	15.1	17.5	12.3	21.4	15.5	33.3	25.0	28.9	18.1	21.2	18.0
% who had had hysterectomy	24.8	11.8	10.0	20.5	14.3	13.6	4.76	25.0	14.5	10.6	17.5	13.8
% who had ever used noncontraceptive estrogens	17.9	21.7	10.0	27.4	11.9	20.4	2.4	15.0	8.4	18.5	12.5	18.2
Mean years of noncontraceptive estrogen use (among ever users)	5.23	6.16	1.96	7.82	1.47	6.06	5.00	4.15	4.27	6.13	3.28	5.91
% who had a mother or sister with breast cancer	7.98	16.5	7.50	12.3	9.52	13.9	7.14	10.0	8.43	15.0	8.75	12.9
Mean height at age 21 years (cm)	162.9	162.6	163.3	163.6	162.6	162.8	164.5	164.4	164.4	162.9	163.8	163.1
Mean weight at age 21 years (kg)	55.3	55.2	52.9	55.7	52.7	54.8	56.3	55.2	55.7	55.4	54.0	55.0
Mean total daily calorie intake	2,096	2,309	2,328	2,233	2,347	2,301	2,487	2,247	2,366	2,339	2,288	2,313
Mean % of saturated fat intake/total fat intake	33.9	34.4	35.7	35.1	33.5	34.6	35.0	37.0	35.9	34.5	36.4	34.8
Mean daily vegetable fiber intake (g)	10.1	9.73	10.4	8.63	9.36	9.54	9.72	8.55	9.20	9.73	9.45	9.48

* Includes 28 clear-cell tumors.

Virtually all of the cases and controls were white, and as expected from the frequency matching, the mean ages overall were close: 57.2 and 57.5 years (table 1). Case women with borderline tumors were about 6 years younger at diagnosis than those with invasive tumors. Women with mucinous tumors were also slightly younger than women with other tumor types. Mean numbers of years of education were similar across the various groups. Average reported height and weight at age 21 were slightly greater for the borderline cases than for the invasive cases, but both measures were comparable to those of the controls; thus, mean body mass indices (weight/height^2) were all similar. Consistent with many other studies of ovarian cancer, smaller percentages of cases than of controls were parous or had ever used oral contraceptives. Likewise, among parous subjects or those who had used oral contraceptives, cases had had fewer full-term pregnancies than controls and had used oral contraceptives for shorter amounts of time. However, women with mucinous tumors did not differ appreciably from controls with respect to parity or oral contraceptive usage.

Reproductive and familial factors

Table 2 gives odds ratios of ovarian cancer for a number of exposure factors, according to specific histologic groups. Each line in the table constitutes a separate model comparing that particular subset of cases to the entire set of controls. Significant protective trends in risk with number of full-term pregnancies and with years of oral contraceptive use were present for the invasive serous, endometrioid, and other nonmucinous tumors and for the borderline serous tumors, but not for the mucinous tumors, either invasive or borderline. Tubal ligation conveyed a lower risk for invasive tumors but not for borderline tumors, whereas hysterectomy was associated with decreased risk for all but borderline mucinous tumors. Use of noncontraceptive estrogen was associated with increasing trends in risk for invasive serous tumors, and particularly for endometrioid tumors ($p = 0.018$ and $p = 0.0041$, respectively). Compared with never use, women who had used noncontraceptive estrogens for 5 years or more had an odds ratio of 2.78 (95 percent confidence interval 1.13–6.83) for endometrioid carcinoma. A reported history of breast cancer in a mother or sister also appeared to convey increased risk among women with invasive serous or endometrioid cancers, but this was less so for cases with other tumor types. We did not examine reported family history of ovarian cancer, because of potential reporting bias among the cases.

We also examined age at first full-term pregnancy and a reported history of infertility. Age at first full-term pregnancy was not associated with risk of ovarian cancer, and this finding held without heterogeneity for all of the case groups. Among nulliparous subjects, a history of at least 2 years of trying to conceive without success ("infertility") was reported by seven controls and 18 cases. While these numbers were too small to provide meaningful comparisons between the specific case subtypes, all of the invasive tumor groups but mucinous had nonsignificant odds ratios ranging from 1.4 to 1.8 among the nulliparous women. None of the seven nulliparous cases with invasive mucinous tumors reported a history of infertility, and elevated risk was not seen for infertility among nulliparous women with borderline tumors (of any kind). No increase in risk of ovarian cancer of any histologic type was observed for parous women who reported a history of infertility.

Dietary factors

Table 3 presents histologic type-specific odds ratios for total daily caloric intake and for two nutrient indices that were found in an earlier report (10) to be related to risk of ovarian cancer. Positive associations were seen with increasing caloric intake for all of the case subtypes; these associations were significant for all tumors except mucinous tumors. The saturated fat/total fat index, defined as daily saturated fat intake (g) divided by daily total fat intake (g), was associated with appreciable increases in risk among cases with mucinous tumors, both borderline and malignant. This index was less associated with risk of tumors of the other types, although the overall association was significant. Daily consumption of vegetable fiber, which was seen in our previous report to convey decreased risk of ovarian cancer (10), here showed odds ratios less than 1 for all of the case subtypes, with little variation between them.

In addition, we considered risks related to daily intake of lactose and free galactose and to reported history of lactose intolerance. No associations were seen for any of these factors, either among the cases as a whole or for any of the specific histologic groups.

Mucinous versus nonmucinous tumors

Because of three previous studies that reported protective associations between parity and oral contraceptive use and the risk of ovarian cancer specifically of histologic types other than mucinous (6–8), we compared the effects of various risk factors presented in tables 2 and 3 in women with mucinous tumors versus those with nonmucinous tumors (table 4). Mucinous

TABLE 2. Histologic type-specific odds ratios for epithelial ovarian cancer according to reproductive and familial risk factors, southern Ontario, Canada, 1989–1992*

Histologic subgroup	Full-term pregnancy†		Oral contraceptive use‡		Lactation/ pregnancy§		Tubal ligation‖		Hysterectomy‖		Noncontraceptive estrogen use‡		Mother or sister with breast cancer‖	
	Odds ratio	95% CI¶	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Invasive tumors														
Serous	0.83	0.74–0.94	0.89	0.84–0.94	0.93	0.87–0.99	0.60	0.38–0.97	0.33	0.20–0.54	1.06	1.01–1.11	2.63	1.57–4.41
Mucinous	1.06	0.86–1.31	0.97	0.89–1.05	1.02	0.93–1.11	0.48	0.20–1.16	0.36	0.12–1.04	0.84	0.62–1.13	1.05	0.30–3.63
Endometrioid	0.70	0.57–0.86	0.86	0.79–0.95	0.93	0.85–1.02	0.49	0.23–1.07	0.64	0.33–1.23	1.09	1.03–1.16	1.93	0.86–4.36
Other	0.59	0.44–0.78	0.85	0.74–0.98	1.04	0.94–1.15	0.85	0.36–1.99	0.50	0.20–1.28	0.77	0.52–1.14	1.23	0.38–3.97
All	0.82	0.74–0.90	0.90	0.86–0.94	0.96	0.91–1.00	0.58	0.39–0.85	0.41	0.28–0.61	1.04	1.00–1.09	2.09	1.32–3.29
Borderline tumors														
Serous	0.62	0.46–0.83	0.86	0.77–0.96	0.93	0.81–1.05	1.58	0.74–3.39	0.19	0.05–0.83	0.76	0.48–1.20	1.22	0.34–4.42
Mucinous	1.00	0.80–1.26	1.00	0.93–1.07	0.89	0.78–1.02	0.86	0.39–1.90	1.18	0.53–2.60	0.97	0.84–1.12	1.53	0.51–4.60
All	0.81	0.67–0.98	0.95	0.90–1.01	0.90	0.82–0.99	1.12	0.64–1.95	0.63	0.32–1.24	0.94	0.82–1.08	1.27	0.53–3.02
All tumors														
Serous	0.80	0.72–0.90	0.88	0.84–0.93	0.93	0.88–0.98	0.75	0.49–1.14	0.31	0.19–0.51	1.05	1.00–1.10	2.47	1.49–4.08
Mucinous	1.03	0.88–1.21	0.98	0.93–1.04	0.97	0.90–1.04	0.64	0.35–1.17	0.71	0.37–1.33	0.93	0.82–1.06	1.30	0.55–3.03
All	0.82	0.75–0.90	0.91	0.88–0.95	0.95	0.91–0.99	0.67	0.47–0.94	0.45	0.32–0.65	1.03	1.00–1.08	1.93	1.25–2.99

* Each line constitutes a separate model, adjusted for age (three categories and continuous term), and contains number of full-term pregnancies, total years of oral contraceptive use, average lactation/pregnancy, and total years of noncontraceptive estrogen use as continuous terms and tubal ligation, hysterectomy, and mother or sister with breast cancer as dichotomous terms.
† Odds ratio for each full-term pregnancy.
‡ Odds ratio for each year of use.
§ Odds ratio for each month of average lactation per pregnancy.
‖ Odds ratio for having had the specified condition or history.
¶ CI, confidence interval.

TABLE 3. Histologic type-specific odds ratios for epithelial ovarian cancer according to dietary risk factors, southern Ontario, Canada, 1989–1992*

Histologic subgroup	Total daily calories†		Saturated fat/total fat‡		Vegetable fiber§	
	Odds ratio	95% CI‖	Odds ratio	95% CI	Odds ratio	95% CI
Invasive tumors						
Serous	1.69	1.31–2.17	1.16	0.87–1.55	0.73	0.53–1.00
Mucinous	1.49	0.94–2.37	1.74	0.97–3.12	0.90	0.51–1.60
Endometrioid	1.59	1.10–2.29	1.56	0.97–2.51	0.46	0.26–0.84
Other	2.05	1.26–3.32	0.97	0.53–1.78	0.52	0.25–1.06
All	1.65	1.34–2.02	1.23	0.97–1.58	0.68	0.52–0.90
Borderline tumors						
Serous	1.87	1.20–2.89	1.44	0.79–2.61	0.58	0.29–1.13
Mucinous	1.37	0.85–2.21	2.40	1.29–4.44	0.48	0.22–1.06
All	1.58	1.13–2.21	1.66	1.07–2.57	0.55	0.32–0.93
All tumors						
Serous	1.73	1.37–2.19	1.18	0.90–1.56	0.70	0.51–0.95
Mucinous	1.41	0.99–1.99	2.03	1.30–3.17	0.72	0.44–1.18
All	1.62	1.33–1.97	1.28	1.02–1.62	0.66	0.51–0.86

* Each line constitutes a separate model, adjusted for age group (three categories) and for the continuous terms age, number of full-term pregnancies, and total duration of oral contraceptive use, and contains total daily calories, saturated fat/total fat, and vegetable fiber as continuous terms.
† Odds ratio for each 1,000 calories/day.
‡ Odds ratio for each 10% increase in this ratio.
§ Odds ratio for each 10 g/day of vegetable fiber.
‖ CI, confidence interval.

cases differed significantly from nonmucinous cases in number of full-term pregnancies, and this relation appeared for both invasive and borderline-malignant tumors. A similar difference between mucinous and nonmucinous tumors was present for duration of oral contraceptive use. However, no consistent differences were seen for average length of lactation per pregnancy, tubal ligation, or hysterectomy. Having a mother or sister with breast cancer was associated with appreciably elevated risks of invasive serous and endometrioid cancers (table 2), although, because of the small number of women with mucinous tumors who reported such a history (three invasive and four borderline), the difference in table 4 was not significant. Women with invasive serous and endometrioid tumors also differed from women with mucinous ones in terms of their past usage of noncontraceptive estrogens.

For the dietary factors, mucinous cases had a slightly lower magnitude of association with total

TABLE 4. Comparison of women with mucinous tumors versus those with nonmucinous tumors according to reproductive, familial, and dietary ovarian cancer risk factors, southern Ontario, Canada, 1989–1992

Model	Factor	*p* value for difference in odds ratio between mucinous and nonmucinous cases		
		Invasive tumors	Borderline tumors	All tumors
1	Age at diagnosis	0.079	0.91	0.013
	No. of full-term pregnancies	0.0063	0.0080	0.00051
	Duration of oral contraceptive use	0.096	0.075	0.0040
2*	Average lactation per pregnancy	0.11	0.90	0.37
	Had tubal ligation	0.58	0.15	0.56
	Had hysterectomy	0.55	0.073	0.22
	Duration of noncontraceptive estrogen use	0.049	0.76	0.052
	Had mother or sister with breast cancer	0.21	0.31	0.43
3*	Total daily calorie intake	0.52	0.47	0.31
	Saturated fat/total fat	0.22	0.12	0.026
	Vegetable fiber intake	0.38	0.99	0.61

* Adjusted for age at diagnosis, number of full-term pregnancies, and duration of oral contraceptive use (continuous terms).

daily caloric intake than did nonmucinous cases (table 3). On the other hand, the association with the fat index, saturated fat as a percentage of total fat, was appreciably and significantly stronger for mucinous cases than for nonmucinous ones. Finally, vegetable-fiber consumption appeared to convey similarly decreased risks for all tumor types; no significant differences were present.

DISCUSSION

This study was designed to investigate a number of dietary and reproduction-related factors among ovarian cancer cases and controls. A detailed discussion of many of these factors, as well as of the representativeness of our case and control samples, has been published elsewhere (9, 10). With respect to the histologic distinctions, two potential limitations should be considered before drawing conclusions from the present work. First, some errors in histologic classification could have occurred, because the tumor slides were not reviewed by the same pathologist for all of the cases. As we noted above, a regional reference pathologist did review the slides of many of the cases when the original pathologist was unsure of the histologic type. Additionally, we reviewed all of the pathology reports, and in some cases (<5 percent) we contacted the pathologist for clarification or the attending physician for clinical confirmation of the ovary as the primary site.

Nevertheless, complete slide review by a single pathologist might have provided a slightly more consistent histologic classification. Distinguishing between invasive and borderline malignancy is usually easy to do for serous tumors but may be difficult for some mucinous ones (16, 17). The borderline tumor as a distinct classifiable entity was not well recognized by pathologists in the 1960s, but by the late 1970s most of these neoplasms were being correctly identified (18). A study involving slide review of cases occurring between 1980 and 1985 showed that 94 percent of tumors initially described as borderline were diagnosed correctly (19). Our fraction of borderline tumors (18.4 percent) was similar to that observed by others (15–21 percent) (4, 17, 18, 20, 21), and this suggests that relatively few truly borderline cases were misdiagnosed as invasive in the present study. The distinction between serous and mucinous neoplasms is also fairly straightforward for all but the most undifferentiated tumors, but distinguishing between serous and endometrioid cancers can be problematic (1, 18). A study that included slide reviews of cases diagnosed between 1976 and 1979 found that 77 percent of epithelial tumors originally considered endometrioid and 85 percent of those considered nonendometrioid had been classified correctly (22). The overall distribution of histologic types in our study (serous, 56.4 percent; mucinous, 17.8 percent; endometrioid, 16.4 percent; clear-cell, 6.2 percent; other, mixed, and undifferentiated, 3.1 percent) was consistent with that seen elsewhere (serous, 34–58 percent; mucinous, 7–25 percent; endometrioid, 9–31 percent; clear-cell, 5–9 percent) (4, 8, 18, 23–27). Thus, the histologic categories considered in this report are likely to have been reasonably accurate, especially for the comparisons of borderline and nonborderline tumors and mucinous and nonmucinous tumors.

The second limitation of the present study concerns the small numbers of cases in some of the histologic categories. Because of these small numbers, only the most significant risk associations, such as those with parity and oral contraceptive use, were strong enough to be statistically distinguishable between the specific groups. The problem was magnified for relatively infrequent exposures such as infertility or family history of cancer. There was more power for analysis of the combined histologic groups—e.g., all borderline tumors (n = 83) or all mucinous tumors (n = 80)—although it may still have been somewhat limited.

Considering the above limitations, we find our results to be generally consistent with those of other studies of ovarian cancer risk factors. Similar to the combined analysis of Harris et al. (2) and others (8), the present work shows that childbearing and oral contraceptive use are associated with significant and appreciable reductions in the risk of borderline malignancy. In addition, lactation and hysterectomy both appear to convey some protection against these tumors, supporting the results of the combined analysis (2). Our study showed a negative association between tubal ligation and risk of invasive carcinoma but not risk of borderline tumors, either altogether or for nonmucinous borderline tumors. The dietary factors seen in our previous report (10) to be associated with risk of ovarian cancer were more strongly associated with the borderline tumors: We found increasing trends in risk with total daily calories and with saturated fat as a percentage of total fat, and a decreasing trend with daily intake of vegetable fiber.

In addition, this study confirms the lack of association seen elsewhere between parity and oral contraceptive use and risk of mucinous tumors. A prospective ovarian cancer study observed decreasing trends in risk with increasing parity among serous, endometrioid, and other epithelial tumors but not among mucinous tumors (7). Two case-control studies (6, 8) found odds ratios associated with ever use of oral contraceptives in the range of 0.53–0.57 for serous tumors, 0.38–0.45 for endometrioid or clear-cell tu-

mors, and 0.17–0.62 for other (nonmucinous) epithelial tumors, but 0.94–1.41 for mucinous tumors. Including the current study, the four studies have generally had at least as many cases with mucinous tumors as cases with endometrioid, clear-cell, or other types of tumors, so small numbers of subjects do not appear to account for the lack of association with mucinous tumors. However, older studies have reported a general similarity among all of the principal histologic types in the relative infrequency of oral contraceptive use among cases (28) and in the percentage of cases who had ever been married (which may be related to parity) (29). Nevertheless, the present work does show mucinous and nonmucinous cases to differ statistically significantly in ovarian cancer risk according to parity and oral contraceptive use.

Perhaps because of small numbers of subjects or lesser strengths of association, we did not see consistent differences between mucinous and nonmucinous cases with regard to other reproduction-related factors. However, compared with case women who had invasive serous and endometrioid tumors, case women with mucinous tumors had fewer mothers or sisters with breast cancer. In a follow-up project, we identified cases in our study who had reported sufficient numbers of first- or second-degree relatives with breast or ovarian cancer to suggest a familial component, and reinterviewed 48 of them (and/or their family members) to obtain corroborated pedigree information (30). Analysis of these 48 women showed that only one of the 31 cases considered to have familial or hereditary ovarian cancer had a tumor of mucinous histology; in contrast, 79 of the 419 "sporadic" cases were of the mucinous type ($p = 0.01$) (30). Other studies of familial ovarian cancer have also shown exceedingly few patients with mucinous tumors among all of the ovarian cancers occurring in probands and family members (31–34).

In addition, our mucinous case women did not use noncontraceptive estrogens more frequently than controls, in contrast to the invasive serous cases, and particularly the endometrioid cases. Whether noncontraceptive estrogen use is associated with increased risk of ovarian cancer in general is uncertain; a number of studies have shown little relation (2, 3, 35–37). However, some studies have reported positive associations (22–24, 38), and one study that examined this association by histologic type also found an increased risk for invasive serous tumors, and especially endometrioid tumors (22). A more recent study that also explored histologic type did not observe the same relations (37), but that study, with appreciably younger women than the present work, had a shorter span of time between the age of menopause and the upper age limit (69 years) for inclusion in the study. Thus, the second study may have had insufficient power to detect an association between noncontraceptive estrogen use and a disease with a latency period of 20 years or more, and even less power within the histologic categories. For all histologic types combined, however, that study did show an odds ratio of 1.54 (95 percent confidence interval 1.02–2.32) for ever use starting at least 5 years before hospital admission (37).

Finally, dietary intake of saturated fat (as a percentage of total fat) differed significantly between our mucinous and nonmucinous cases, with the stronger risk association appearing among women with mucinous tumors. Data on other dietary factors (total daily caloric intake and vegetable fiber intake) were quite similarly distributed between the two case groups.

Because of the evidence distinguishing mucinous ovarian tumors from nonmucinous tumors with respect to parity, oral contraceptive use, breast/ovarian cancer familiality, and possibly dietary fat intake and use of noncontraceptive estrogens, we suggest that mucinous tumors be considered a distinct etiologic entity separate from the other types of epithelial neoplasms. The more frequently seen epithelial tumors (serous, mucinous, and endometrioid) are thought to share a common cellular ancestry with other structures of the reproductive tract. Adjacent to the developing fetal gonads, invaginations of the celomic epithelium form the müllerian ducts, from which the endosalpingeal, endometrial, and endocervical mucosa arise (1). The peritoneal cavity and the cortical surfaces of the ovaries and neighboring structures are also covered by a thin layer of germinal epithelial (mesothelial) cells derived from the same celomic epithelium (39). Repeatedly throughout life, the ovarian epithelium invaginates to produce surface cell-lined clefts recapitulating the formation of the fetal müllerian system (1). Inclusion cysts occur as the bases of these clefts close up (1), particularly during the increased mitotic activity accompanying ovulation and repair (40). Metaplasia of the cyst lining may give rise to growths of serous, mucinous, or endometrioid cells, and these resemble the mucosal epithelium of the fallopian tubes, cervix, and endometrium, respectively (1). Neoplastic transformation of cells lining the inclusion cysts produces serous, mucinous, or endometrioid tumors that are histologically and clinically similar to endosalpingeal, endocervical, and endometrial tumors, respectively (39). Thus, it is possible that etiologic features of the common epithelial ovarian cancers differ because of development from cells that are already histologically differentiated.

Perhaps mucinous ovarian neoplasms share some risk factors with adenocarcinomas of the uterine cer-

vix—for example, infection by human papilloma virus type 18 (or 16) (41, 42). Similarly to the risk of mucinous ovarian tumors, the risk of cervical adenocarcinoma is not reduced with oral contraceptive usage (43–45); neither type of tumor is associated with lowered risk according to parity (46–48). However, aside from the uncertain associations with obesity and use of noncontraceptive estrogens (49), there is little evidence to suggest that endometrioid ovarian tumors have risk factors in common with endometrial neoplasms.

An alternative explanation for the etiologic differences between mucinous and nonmucinous tumors may lie in a possible germ-cell teratoma origin of some mucinous neoplasms (16, 39). Mucinous tumors frequently show gastric or enteric differentiation (i.e., they resemble gastrointestinal mucosa) and contain goblet cells as well as gastrointestinal enzymes and polypeptides (1). It is not completely clear whether these enteric-type mucinous tumors occur as a result of intestinal metaplasia of the surface epithelium or are gastrointestinal teratomas of germ-cell origin (1). It is also possible that some mucinous ovarian neoplasms actually metastasize from occult primary adenocarcinomas of the large intestine (50) and thus mimic primary ovarian tumors.

In summary, nonmucinous borderline-malignant ovarian tumors appear to have a similar spectrum of risk factor associations as nonmucinous invasive tumors, whereas mucinous neoplasms differ significantly from nonmucinous ones with respect to the principal ovarian cancer risk factors. On the basis of this study and others, we suggest that mucinous tumors may be etiologically unrelated to the other epithelial tumors, and thus should be considered separately in studies of ovarian cancer.

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