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Risk Factors for Invasive Epithelial Ovarian Cancer by Histologic Subtype

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Abstract:
It is unclear whether the different histologic subtypes of epithelial ovarian carcinoma have different risk factors. We investigated the relationships between selected epidemiologic variables (i.e., parity, family history of ovarian cancer, oral contraceptive use, a history of tubal ligation and noncontraceptive estrogen use) and the major histologic subtypes of epithelial ovarian cancer in a hospital-based case-control study of adult women at Roswell Park Cancer Institute in Buffalo, NY, USA. Multivariate unconditional logistic regression models were used for statistical analysis. We observed a pattern of increased risk associated with family history and a pattern of risk reduction associated with parity, noncontraceptive estrogen use and tubal ligation across all histologic subtype groups. However, we did not observe a consistent pattern of risk associated with oral contraceptive use. These results provide some additional support for the hypothesis that the effects of various ovarian cancer risk factors may differ according to the histologic subtype.

Key words: Epithelial ovarian cancer, Histology, Epidemiology, Case-control study

Introduction

Ovarian cancer is a devastating gynecological malignancy, with an estimated 100,000 deaths and 165,000 new cases occurring every year worldwide.(1) The ovarian surface is covered by a single layer of epithelial cells commonly referred to as the surface epithelium, and

approximately 80% of all malignant ovarian tumors are thought to derive from the surface epithelium and its inclusion glands and cysts.(2,3) Epithelial ovarian carcinomas are histologically classified into several subtypes according to their predominant pattern of differentiation, and the most frequently observed subtypes include serous, endometrioid, mucinous, and clear cell carcinomas. It is uncertain whether the different epithelial histologic subtypes are epidemiologically heterogeneous.(4,5) Some recent epidemiologic case-control investigations have reported various differences among histologic subtypes (6-11), while other studies have not.(12,13) In an effort to provide more data on this important issue, we conducted a hospital-based case-control study that assessed whether selected ovarian cancer risk factors differed according to histologic subtype.

Methods and Statistics

This study was approved by the Institutional Review Board of Roswell Park Cancer Institute (RPCI) in Buffalo, New York, U.S.A., and informed consent was properly obtained from all participants. Study subjects included adult women patients admitted to RPCI between 1982 and 1998 who volunteered to complete a self-administered epidemiologic questionnaire. The details of this hospital-based data collection system have been previously described.(14,15) Cases (n = 418) included patients diagnosed with primary invasive epithelial ovarian cancer of the following major histologic subtypes: serous carcinomas (n = 284; ICD-O (16) codes 8441, 8460, and 8461), endometrioid carcinomas (n = 65; ICD-O code 8380), mucinous carcinomas (n = 34; ICD-O codes 8470, 8471, and 8480), and clear cell carcinomas (n = 35; ICD-O code 8310). Cases were predominately Caucasian (99.3%) and ranged in age from 19 to 86 years (mean age 55.9 ± 13.1 years). Nearly seventy percent (290/418) of cases were 50 years of age and older. Controls (n = 836) included patients seen at RPCI who were discharged without a diagnosis of malignancy. Among a pool of 5,695 eligible patients, controls were randomly selected and frequency-matched to cases by five-year age intervals for a final case to control ratio of 1:2. Similar to cases, controls were predominately Caucasian (91.9%) and ranged in age from 18 to 89 years (mean age 55.9 ± 13.2 years).

Epidemiologic information for study subjects was extracted from a database compiled from the self-administered questionnaires. For the entire epithelial ovarian cancer case group and for each separate histologic subtype group, multivariate unconditional logistic regression models (17,18) were used to calculate odds ratio (OR) and 95% confidence interval (CI) estimates associated with the following risk factors: parity (live births), a family history of ovarian cancer in a first-, second-, or third-degree relative, oral contraceptive use, a history of tubal ligation, and noncontraceptive estrogen use. Models were adjusted for age (continuous), parity (0, 1), family history of ovarian cancer (no, yes), oral contraceptive use (never, ever), history of tubal ligation (never, ever), and noncontraceptive estrogen use (never, ever). Further adjustment for potential confounders such as education, income, cigarette smoking, and geographic area of residence failed to notably alter point estimates. All data analyses were performed using SPSS for Windows version 10.0 (SPSS Inc., Chicago, IL).

Results

The results from the logistic regression analyses are presented in Table 1.

Table 1: Logistic regression results for selected ovarian cancer risk factors according to histologic subtype, Roswell Park Cancer Institute, 1982-1998[a]

	Controls (n=836)	All Cases (n=418)		Serous Cases (n=284)		Endometrioid Cases (n=65		Mucinous Cases (n=34)		Clear Cell Cases (n=35)	
	n	n	OR (95% CI)[b]	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Parous											
Never	139	100	1.0 (referent)	59	1.0 (referent)	19	1.0 (referent)	10	1.0 (referent)	12	1.0 (referent)
Ever	688	311	0.61 (0.53-0.96)	222	0.71 (0.49-1.02)	43	0.53 (0.28-0.99)	23	0.36 (0.15-0.86)	23	0.41 (0.19-0.90)
1-2 children	296	140	0.63 (0.45-0.90)	96	0.63 (0.45-0.90)	20	0.58 (0.29-1.18)	12	0.39 (0.15-1.01)	12	0.47 (0.20-1.15)
3-4 children	279	145	0.69 (0.48-0.98)	107	0.83 (0.56-1.25)	20	0.58 (0.28-1.20)	8	0.34 (0.12-0.97)	10	0.47 (0.19-1.16)
≥5 children	113	26	0.31 (0.19-0.53)	19	0.37 (0.20-0.67)	3	0.24 (0.07-0.85)	3	0.31 (0.08-1.27)	1	0.12 (0.01-0.92)
(Missing)	9	7		3		3		1		0	
Family History of Ovarian Cancer											
No	804	386	1.0 (referent)	264	1.0 (referent)	61	1.0 (referent)	29	1.0 (referent)	32	1.0 (referent)
Yes	32	32	2.08 (1.24-3.48)	20	2.00 (1.11-3.58)	4	1.83 (0.61-5.47)	5	3.41 (1.06-10.96)	3	2.95 (0.83-10.51)
Oral Contraceptive Use											
Never	575	281	1.0 (referent)	193	1.0 (referent)	48	1.0 (referent)	13	1.0 (referent)	27	1.0 (referent)
Ever	243	128	1.22 (0.88-1.68)	85	1.20 (0.84-1.74)	16	0.79 (0.38-1.65)	20	4.58 (1.75-12.00)	7	0.78 (0.27-2.20)
≤5 years	135	75	1.22 (0.84-1.79)	47	1.18 (0.76-1.82)	9	0.71 (0.28-1.75)	15	6.12 (2.20-17.02)	4	0.70 (0.19-2.61)
>5 years	108	53	1.18 (0.78-1.79)	38	1.20 (0.75-1.91)	7	0.91 (0.36-2.28)	5	2.78 (0.81-9.55)	3	0.88 (0.23-3.35)
(Missing)	18	9		6		1		1		1	
Noncontraceptive Estrogen Use											
Never	597	322	1.0 (referent)	212	1.0 (referent)	54	1.0 (referent)	29	1.0 (referent)	27	1.0 (referent)
Ever	217	86	0.72 (0.53-0.96)	66	0.84 (0.60-1.17)	9	0.40 (0.18-0.90)	4	0.30 (0.09-1.03)	7	0.70 (0.29-1.68)
(Missing)	22	10		6		2		1		1	
Tubal Ligation											
Never	696	357	1.0 (referent)	240	1.0 (referent)	57	1.0 (referent)	28	1.0 (referent)	32	1.0 (referent)
Ever	118	47	0.84 (0.57-1.24)	34	0.89 (0.57-1.37)	6	0.75 (0.30-1.91)	5	0.68 (0.24-1.96)	2	0.53 (0.12-2.39)
(Missing)	22	14		10		2		1		1	

[a]Odds ratios adjusted for age (continuous), parity (0, □ 1), family history (no, yes), oral contraceptive use (never, ever), tubal ligation (never, ever), and noncontraceptive estrogen use (never, ever)

[b]OR = odds ratio, CI = confidence interval

Compared to nulliparous women, women who had one or more children had a statistically significant reduced risk of ovarian cancer in the total case group and in the endometrioid, mucinous, and clear cell histologic subtype groups. Parous women in the serous histologic group also experienced a reduced risk, but this finding was not statistically significant (OR = 0.71; 95% CI = 0.49 - 1.02). Compared to women who did not have a reported family history of ovarian cancer, women with such a history had an apparent increased risk for ovarian cancer in all the case groups. The observed risk was not statistically significant, however, in either the endometrioid (OR = 1.83; 95% CI = 0.61 - 5.47) or clear cell (OR = 2.95; 95% CI = 0.83 - 10.51) histologic groups. Women who had reported ever using oral contraceptives had a nonsignificant reduced risk for ovarian cancer in the endometrioid (OR = 0.79; 95% CI = 0.38 - 1.65) and clear cell (OR = 0.78; 95% CI = 0.27 - 2.27) groups, and a nonsignificant increased risk in the total case (OR = 1.22; 95% CI = 0.88 - 1.68) and serous (OR = 1.20; 95% CI = 0.84 - 1.74) groups. Oral contraceptive users in the mucinous histologic group experienced a statistically significant increased risk for ovarian cancer in both the ever (OR = 4.58; 95% CI = 1.75 - 12.00) and □5 years of use (OR = 6.12; 95% CI = 2.20 - 17.02) categorizations. This risk was nonsignificantly elevated (OR = 2.78; 95% CI = 0.81 - 10.51) in the small number of mucinous cases who had used oral contraceptives for greater than 5 years. We observed nonsignificant risk reductions for ovarian cancer across all case groups for those women who had undergone tubal ligation operations, and found that noncontraceptive estrogen users also had a reduced risk in all case groups, although this observed risk was statistically significant in only the total case and endometrioid groups.

Discussion

Most prior epidemiologic studies of epithelial ovarian cancer have combined the various histologic subtypes in their analyses and have not assessed whether ovarian cancer risk factors differed according to histologic subtype.(6) Stratifying analyses by histologic subtype might enable researchers to identify clinically important subtype-specific risk factors, which ultimately could translate into improved prevention, detection, and treatment strategies for ovarian cancer. Although not all studies are in agreement (12,13), the results from recent case-control studies that have explored histologic subtype-specific associations suggest that the different subtypes are epidemiologically heterogeneous.(6-11) In particular, some data has been presented that supports the notion that ovarian cancer risk factors might differ for mucinous and nonmucinous tumors.(10)

In this hospital-based case-control study, we investigated the relationships between selected risk factors and the major histologic subtypes of invasive epithelial ovarian cancer. After statistically controlling for the effects of several potential confounders in the logistic regression analyses, we observed a pattern of risk reduction across all histologic groups associated with parity, noncontraceptive estrogen use, and a history of tubal ligation. A pattern of increased risk across all groups was observed for those women who had reported a family history of ovarian cancer. Interestingly, no consistent pattern of risk was associated with the use of oral contraceptives. Women who had reported ever using oral contraceptives had a nonsignificant reduced risk for ovarian cancer in the endometrioid and clear cell groups, but a nonsignificant increased risk in the total case and serous groups. These nonsignificant risk associations were maintained in both the □5 years of use and >5 years of use categorizations. In contrast to these observed associations, oral contraceptive users in the mucinous group experienced a statistically significant increase in risk in both the ever and □5 years of use categorizations. Although we observed only slight differences in subtype-specific associations related to parity, family history, noncontraceptive estrogen use, and tubal

ligation history, the epithelial histologic subtypes appear to be epidemiologically more heterogeneous in relation to oral contraceptive use.

Our findings with respect to the entire epithelial ovarian cancer case group are consistent with the results of previous epidemiologic studies that have reported reduced risk associations related to parity and a history of tubal ligation, and an increased risk association related to a family history of ovarian cancer. We observed a statistically significant reduced risk for ovarian cancer in those women who had reported using noncontraceptive estrogens, but most studies that have examined this risk factor have not provided clear evidence that any real association exists.(4,5,19,20) In contrast to the large majority of epidemiologic studies, we did not observe a statistically significant reduced risk for ovarian cancer in those women who had ever used oral contraceptives. Similar findings have been reported in the literature. For example, in a large prospective cohort study of U.S. registered nurses, Hankinson and colleagues (21) reported that the multivariate relative risk of ovarian cancer for ever users of oral contraceptives was 1.08 (95% CI = 0.83 - 1.43).

Two important limitations should be considered in the interpretation of the results from the present investigation. Since the histologic classification of epithelial ovarian carcinoma is beset by a number of complexities and difficulties for pathologists (2,22), we cannot exclude the possibility that potential errors in subtype classification may have occurred. On the other hand, all of the classification was performed in a specialized cancer hospital by highly qualified pathologists. Secondly, the small number of cases in the histologic subtype groups may account for the absence of statistical significance observed for some of the factors where risk was expected. We would like to emphasize, however, that our analyses are based on nearly twenty years of data collection at a regional cancer institution.

Conclusions

In conclusion, the results of this case-control investigation offer some additional support for the notion that the impact of different ovarian cancer risk factors, most notably oral contraceptive use, varies across the major epithelial histologic subtypes. Additional epidemiologic studies with large numbers of ovarian cancer cases are needed to further explore and resolve the important issue of whether a variety of risk factors (e.g., reproductive, dietary, behavioral, genetic) differ according to histologic subtype.

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Financial Conflicts of Interest: None

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