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Oral Contraceptive Use and Reproductive Characteristics Affect Survival in Patients With Epithelial Ovarian Cancer:

A Cohort Study

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Abstract

Objectives—Prognostic risk factors influencing survival in patients with epithelial ovarian cancer (EOC) include tumor stage, grade, histologic subtype, debulking, and platinum status. Little is known about the impact of hormonal milieu and reproductive factors before cancer diagnosis on clinical outcome. We sought to evaluate whether oral contraceptive (OC) use carries any prognostic significance on overall survival (OS) in patients with EOC.

Methods—Newly diagnosed patients with EOC, fallopian tube, and primary peritoneal cancers between 1982 and 1998 were prospectively evaluated with a comprehensive epidemiologic questionnaire. A retrospective chart review was performed to abstract clinicopathologic data, including OS. A Kaplan-Meier analysis was performed to compare survival across various exposures. A Cox regression model was used to compute adjusted hazards ratios (aHRs) and 95% confidence intervals (CIs).

Results—We identified 387 newly diagnosed cancers with evaluable information in this cohort. Decreased risk of death was observed in women who reported prior use of OC (aHR, 0.79; 95% CI, 0.58–1.09), previous pregnancy (aHR, 0.77; 95% CI, 0.57–1.04), or a live birth (aHR, 0.81; 95% CI, 0.60–1.08) after adjusting for age at diagnosis, stage, and histologic subtype. Oral contraceptive use was associated with a crude reduced risk of death (HR, 0.55; 95% CI, 0.42–0.72), with reported median OS of 81 months in OC users versus 46 months in nonusers. Patients who reported a single live birth experienced the largest potential survival advantage (aHR, 0.61; 95% CI, 0.39–0.94). Oral contraceptive use and prior pregnancy were associated with improved survival across all strata.

Conclusions—Oral contraceptive use may have lasting effects on epithelial ovarian tumor characteristics conferring favorable prognosis. Putative mechanisms that affect tumor biology include complex interactions between ovarian cells, host immune cells, and hormonal

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microenvironment during carcinogenesis. Future efforts should be directed to determine the role of reproductive factors in antitumor immunity.

Keywords

Reproductive characteristics; Oral contraceptives; Parity; Ovarian cancer survival

Epithelial ovarian cancer is the fifth leading cause of cancer death in women. Despite scientific advances aimed at earlier detection and targeted therapeutic strategies, most patients are still diagnosed at an advanced stage, frequently require multiple lines of chemotherapy, and ultimately succumb to the disease. Approximately 22,000 US women are diagnosed with epithelial ovarian cancer (EOC), annually resulting in 14,000 deaths.[1,2]

Prognostic factors associated with clinical outcomes in women with ovarian cancer include age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor grade, histology, and debulking status.[3–5] An accumulating body of evidence suggests the hormonal milieu has a role in EOC carcinogenesis, which leads to the question, “What etiologic factors and host reproductive characteristics affect disease course and survival?” Although large observational studies consistently demonstrate that use of oral contraceptives (OCs), childbearing, previous hysterectomy, and tubal ligation are known to decrease the risk of ovarian cancer, little is known about their impact on survival in ovarian cancer patients.[6–9]

Insight into the role of hormonal and behavioral characteristics of patients was subsequently diagnosed with ovarian cancer to inform development of strategies for prevention of this disease. In this study, we aimed to evaluate the relationship between established reproductive risk factors, including prior OC use and parity, and overall survival (OS) in patients with EOC. We extrapolated this information and hypothesized that reproductive characteristics and hormonal milieu can favorably modify tumor microenvironment and host defense mechanisms to improve OS in patients with EOC.

METHODS

Patient Selection

This protocol was reviewed by the institutional review board at the Roswell Park Cancer Institute (Buffalo, NY). Women aged 18 to 99 years with newly diagnosed EOC, fallopian tube, or primary peritoneal carcinoma seeking care at our institution were eligible to participate in this study. After informed consent was obtained, subjects were asked to complete a comprehensive epidemiologic questionnaire upon entry into the study; these data were prospectively entered into a research database. Details about data collection and the study population have been described elsewhere.[10–12] As part of this 16-page questionnaire, patients were asked about presence or absence of specific medical comorbidities, as well as reproductive factors including the use of hormonal medications. Individual subject information on treatment and survival, tumor stage, grade, and histologic type was obtained from the Roswell Park Cancer Institute (RPCI) tumor registry and matched to questionnaire information. Medical records were also reviewed to collect additional clinicopathologic

data, including presence of diabetes mellitus, hypertension, thyroid disorder, arthritis, and gastroesophageal reflux disease. Subjects were excluded from the current analysis if there were incomplete data with regard to the use of Oral Contraceptive Pill (OCPs), pregnancy history, or survival.

Statistical Analysis

The number of incident ovarian, fallopian tube, and primary peritoneal cancer cases presented at the Roswell Park Cancer Institute for treatment during the study period determined the sample size. Overall survival time was calculated in months from the date of diagnosis until the date of death or of last follow-up. Patients alive at last contact were censored at the date of last contact. The Kaplan-Meier technique was used to compare survival across various exposures. Categorical exposures were tested using the log-rank test, whereas continuous variables were analyzed with Cox regression. A threshold of $P < 0.20$ was used to identify candidate variables for final models. Final models were selected using a forward selection process; for consistency, covariates identified for any model were included in all adjusted models. Cox regression was used to compute crude hazards ratios (HRs) and adjusted HRs (aHRs), as well as 95% confidence intervals (95% CIs). Linearity of associations between continuous variables and survival were confirmed using linear spline models. The proportional hazards assumption was verified for each factor of interest.

RESULTS

We identified 409 women with newly diagnosed ovarian, fallopian tube, or primary peritoneal carcinoma seeking care at the Roswell Park Cancer Institute from January 1, 1982 to December 31, 1998. We excluded 22 women from analysis based on incomplete epidemiologic survey information or incomplete covariate information. Thus, 387 subjects were included for the remainder of the analysis. The characteristics of the cohort are described in Table 1. We identified differences between those with and without history of OC use in terms of histologic subtype (P= 0.0004), history of Hypertension (HTN) (P = 0.0093), and multiple reproductive factors. Survival was also significantly different, where those with a history of OC use had a 45% lower risk of death from ovarian cancer (crude HR, 0.55; 95% CI, 0.42–0.72) that remained significant after adjustment for stage, grade, histology, and age at diagnosis (aHR, 0.66; 95% CI, 0.46–0.94). In this cohort, the odds of reporting a history of irregular menses was 73%lower in non-OC users versus those who took OCs (odds ratio [OR], 0.27; 95% CI, 0.15–0.5). Furthermore, the odds of prior Bilateral Tubal Ligation (BTL) were 63% higher in never users versus those with a history of OC use (OR, 0.37; 95% CI, 0.19–0.7). Other reproductive factors such as age at menarche, parity, and duration of breast feeding were not associated with history of OC use. Crude HR and aHR of death in relation to reproductive variables are presented in Table 2. History of OC use was associated with a 35-month improvement in median OS (81 vs 46 months; HR, 0.51; 95% CI, 0.39–0.66), although this association was attenuated when analyses were adjusted for age at diagnosis, stage, and histologic subtype (aHR, 0.71; 95% CI, 0.53–0.97). Improved survival approached statistical significance was noted for women who reported previous pregnancy (aHR, 0.76; 95% CI, 0.57–1.01) or a live birth (aHR, 0.80; 95% CI, 0.60–1.06). Patients who reported a single live birth experienced the largest potential

survival advantage (aHR, 0.72; 95% CI, 0.48–1.08) although this did not reach statistical significance.

Crude HR and aHR for OS by OC use based on histologic subtype, FIGO stage, or tumor grade are reported in Table 3. Oral contraceptive use imparted a survival advantage across all histologic subtypes, although after adjustment for age and stage, chance cannot be excluded as the reason for the observed observation. The magnitude of association was greatest for mucinous, endometrioid, and clear cell cancers. Oral contraceptive use was also protective for all FIGO stages, although this association is attenuated after adjustment for age and histology. Prior OC use had a consistent protective effect for poorly differentiated cancers (crude HR, 0.57; 95% CI, 0.41–0.8; aHR, 0.65; 95% CI, 0.44–0.96).

DISCUSSION

Parity and OC use are established protective factors for ovarian cancer. In this study, we found that a history of OC use and parity are associated with improved survival in patients diagnosed with ovarian cancer. After adjustment for differences in histology, stage, and grade, the trends in differences lost statistical significance, but CIs remained close to 1.0. Emerging data point to the long-term effects of reproductive events and OC use on tumor biology and host immune function.[13–16]

Poole et al[17] evaluated the role of reproductive risk factors and OC use on disease aggressiveness. They demonstrated that less aggressive cases of ovarian cancer were associated with shorter duration of OC use. In addition, the authors observed an inverse association with OC use and rapidly fatal disease; whereas OC use 20 years preceding the diagnosis resulted in decreased risk of rapidly fatal disease.[17] The greatest benefit was associated with OC use for more than 5 years within 20 years before diagnosis ($P < 0.0001$).[17] Similarly, they found an association between less aggressive disease and parity, each birth resulted in a 13% decreased risk (95% CI, 0.81–0.93) of aggressive disease.[17] In addition, the authors demonstrated that duration of breastfeeding and previous tubal ligation had no impact on disease aggressiveness. These results are consistent with the findings of the present study.

The traditional theory of incessant ovulation as a contributor to ovarian carcinogenesis may support the hypothesis that hormonal changes associated with ovarian suppression due to OC use and parity may have long-term effects on tumor biology and host defense mechanisms. Assessment of reproductive characteristics in patients with stage III ovarian cancer confirmed that increasing number of lifetime ovulatory events may adversely impact ovarian cancer survival (aHR, 1.53 per 10 ovulatory years; 95% CI, 1.09–2.14).[18,19] Along the same lines, others have observed that older age at menarche was associated with improved survival (HR, 0.91; 95% CI, 0.84–0.99 per year).[18,19] Interestingly, ovulation may not be the only hormone-driven event triggering neoplastic transformation of ovarian surface epithelium. Previous research evaluating the role of hormone replacement therapy use by patients with EOC before diagnosis also demonstrated significant improvement in survival (aHR, 0.69; 95% CI, 0.48–0.98).[19,20] Merritt et al[21] reported the strongest protective role of parity in type I tumors that increased with the number of children (≥3 vs 0 children; OR,

0.15; 95% CI, 0.11–0.21). The same authors also showed that higher number of ovulatory cycles (>431 vs ≤ 272 cycles) was associated with development of both type I and II tumors, respectively (OR, 1.83; 95% CI, 1.28–2.62; OR, 5.88; 95% CI, 4.33–7.99).[21] We observed beneficial effect of OC use in patients with endometrioid tumors (aHR, 0.67; 95% CI, 0.18–2.52) although given small numbers of patients chance cannot be excluded as the reason for the observed association in this study.

One potential mechanism for OCs or pregnancy to affect ovarian cancer prognosis may be through systemic and local effects of the immune system, also known as the Tissue Control System theory.[22] Substantial evidence indicates that the immune system plays an important role at every level of the hypothalamic-pituitary-ovarian axis through complex, interdependent interactions of immune cells, ovarian cells, sex hormones, and the autonomic nervous system.[22] These interactions, occurring at the level of ovarian tissue, have been proposed to affect tissue regeneration and senescence and alter immune surveillance mechanisms, potentially affecting ovarian tumorigenesis.

At present, the influence of reproductive factors on the clinical outcome of EOC is not fully understood, as most of the publications draw their conclusions based on a small number of patients and frequently lack detailed information on OC dosage and duration. While this study also lacks dosage and duration information, the prospective nature of follow-up after exposure ascertainment in a moderate sample size adds strength to the evidence provided here. Models were adjusted for established prognostic factors with the potential to confound the associations under investigation. The role of residual confounding and chance cannot be eliminated from observational studies such as this; however, the potential protective effects identified were consistent with prior published studies of similar biological mechanisms.[18–20] In addition, the effects were generally consistent across groups of women with different stages, grades, or histologies, suggesting a more global impact on tumor biology.

In addition to the single institution information available, the current study suffers from the inherent limitations to cohort studies such as recall and reporting biases because questionnaires were used to classify exposure status, rather than prescription or hospital records. However, we attempted to minimize this risk by collecting the information on entry to the study, rather than at the time of follow-up. Limited information is available on formulation, duration of use, and timing of OC use relative to pregnancies.

In summary, we examined the potential influence of reproductive factors on OS among patients diagnosed with EOC. Our findings reveal that both use of OCs and prior live birth may have long-term favorable effects on survival in women who subsequently go on to develop this gynecologic malignancy. Tissue Control System theory[22] may serve as the framework for understanding the intricate mechanisms by which reproductive and immunologic factors may influence ovarian tumorigenesis later in life; however, further studies are necessary.

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TABLE 1

Ovarian cancer demographics by history of contraceptive use

Characteristic	Never Used OCs		Used OCs		*P**
FIGO stage	n = 266	%	n = 121	%	0.2391
I	49	18.63	33	27.27	
II	26	9.89	12	9.92	
III	148	56.27	57	47.11	
IV	40	15.21	19	15.70	
Tumor grade					0.6328
1, well differentiated	42	16.34	23	20.18	
2, moderately differentiated	68	26.46	27	23.68	
3, poorly differentiated	147	57.20	64	56.14	
Histologic subtype					0.0004
Serous	183	70.38	83	69.75	
Mucinous	13	5.00	20	16.81	
Endometrioid	43	16.54	10	8.40	
Clear cell	21	8.08	6	5.04	
Non-Hispanic white race	247	92.86	119	98.35	0.0271
Comorbid conditions					
Diabetes mellitus	23	8.95	4	3.42	0.0554
Hypertension	66	25.68	16	13.68	0.0093
Thyroid disorder	13	5.06	7	5.98	0.7125
Arthritis	37	14.40	12	10.26	0.2712
Gastroesophageal reflux disease	5	1.95	3	2.56	0.7092
Age at menarche, y					0.7218
<12	41	15.59	19	15.97	
12	78	29.66	29	24.37	
13	71	27.00	37	31.09	
≥14	73	27.76	34	28.57	
Menstrual regularity					<.0001
Regular	245	92.45	93	76.86	

Characteristic	Never Used OCs		Used OCs		*P**
Irregular	20	7.55	28	23.14	
Ever pregnant					0.1303
No	62	23.31	20	16.53	
Yes	204	76.69	101	83.47	
Ever live birth					0.5964
No	63	24.14	26	21.67	
Yes	198	75.86	94	78.33	
No. live births					0.2566
None	63	24.14	26	21.67	
1	30	11.49	19	15.83	
2	51	19.54	32	26.67	
3	53	20.31	22	18.33	
4+	64	24.52	21	17.50	
Ever had tubal ligation					0.0017
No	21	7.92	22	18.97	
Yes	244	92.08	94	81.03	
Duration of breastfeeding					0.5148
None	156	62.65	75	65.79	
<1 y	64	25.70	25	21.93	
1–2 y	17	6.83	11	9.65	
≥2 y	12	4.82	3	2.63	

*χ^2 or Fisher exact test, as appropriate.

TABLE 2

Ovarian cancer survival by reproductive characteristics

Characteristic	Survival, Median (Range), mo	Crude HR (95% CI)*	aHR (95% CI)*†
Age at menarche, y			
<12	56 (1–30)	Reference	Reference
12	52 (8–371)	0.98 (0.70–1.37)	1.04 (0.74–1.47)
13	50 (2–359)	0.86 (0.62–1.21)	1.01 (0.72–1.43)
≥14	67 (3–386)	0.77 (0.55–1.09)	0.95 (0.67–1.35)
Menstrual regularity			
Regular	56 (1–386)	Reference	Reference
Irregular	72 (3–346)	0.77 (0.54–1.10)	0.99 (0.69–1.42)
Ever used OCs			
No	46 (1–386)	Reference	Reference
Yes	81 (3–375)	0.51 (0.39–0.66)	0.71 (0.53–0.97)
Ever pregnant			
No	60 (7–386)	Reference	Reference
Yes	56 (1–375)	1.15 (0.87–1.51)	0.76 (0.57–1.01)
Ever live birth			
No	60 (7–386)	Reference	Reference
Yes	56 (1–375)	1.13 (0.86–1.47)	0.80 (0.60–1.06)
No. births			
None	60 (7–386)	Reference	Reference
1	89 (11–375)	0.83 (0.56–1.24)	0.72 (0.48–1.08)
2	60 (3–341)	1.05 (0.75–1.47)	0.78 (0.55–1.11)
3	44 (2–335)	1.30 (0.93–1.83)	0.88 (0.62–1.26)
4+	41 (1–371)	1.29 (0.93–1.80)	0.81 (0.57–1.14)
Ever had tubal ligation			
No	68 (1–375)	Reference	Reference
Yes	56 (3–386)	0.64 (0.43–0.93)	0.90 (0.60–1.34)
Lifetime duration of breastfeeding			
None	61 (1–386)	Reference	Reference
<1 y	50 (2–339)	1.31 (1.00–1.70)	1.00 (0.76–1.32)
1–2 y	76 (8–341)	0.75 (0.47–1.19)	0.68 (0.43–1.08)
≥2 y	29 (8–297)	1.48 (0.89–2.47)	0.92 (0.54–1.58)

*HRs and 95% CIs computed using Cox proportional hazards models.

†Adjusted for FIGO stage, age at diagnosis, and histology.

TABLE 3

Ovarian cancer survival by tumor characteristics

Prognostic Characteristic*	% Deceased (Nonusers)	% Deceased (Users)	Crude HR (95% CI) Users vs Nonusers	aHR (95% CI) Users vs Nonusers
Histologic subtype†				
Serous	94.0	78.3	0.64 (0.48–0.86)	0.85 (0.62–1.17)
Mucinous	100.0	25.0	0.16 (0.06–0.45)	0.16 (0.02–1.24)
Endometrioid	69.8	30.0	0.28 (0.08–0.91)	0.67 (0.18–2.52)
Clear cell	85.7	33.3	0.29 (0.07–1.26)	0.12 (0.01–1.12)
FIGO stage‡				
I	73.5	24.2	0.22 (0.10–0.49)	0.29 (0.11–0.80)
II	84.6	50.0	0.38 (0.14–1.01)	0.63 (0.21–1.86)
III	93.2	80.7	0.72 (0.51–1.01)	1.09 (0.74–1.60)
IV	100.0	89.5	0.48 (0.27–0.86)	0.51 (0.26–0.98)
Tumor grade§				
1, well differentiated	73.8	34.8	0.35 (0.16–0.75)	0.97 (0.28–3.39)
2, moderately differentiated	94.1	66.7	0.61 (0.36–1.03)	1.08 (0.60–1.97)
3, poorly differentiated	91.8	75.0	0.57 (0.41–0.80)	0.65 (0.44–0.96)

*HRs and CIs computed using Cox regression.

†Adjusted for age at diagnosis and FIGO stage.

‡Adjusted for age at diagnosis and histology.

§Adjusted for age at diagnosis, FIGO stage, and histology.