Influence of Reproductive Factors on Mortality after Epithelial Ovarian Cancer Diagnosis

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Abstract

Introduction: **Although many studies have examined the influence of reproductive factors on ovarian cancer risk, few have investigated their effect on ovarian cancer survival. We examined the prognostic influence of reproductive factors on survival after ovarian cancer diagnosis.**

Methods: **We conducted a longitudinal analysis of 410 women, ages 20 to 54 years, who participated in the 1980 to 1982 Cancer and Steroid Hormone study as incident ovarian cancer cases. We obtained their vital status by linking Cancer and Steroid Hormone records with Surveillance, Epidemiology, and End Results data. We used the Kaplan-Meier approach to estimate survival probabilities and Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (95% CI).**

Results: **During a median follow-up of 9.2 years, 212 women died. Of the reproductive factors examined, only age at menarche and number of lifetime ovulatory cycles (LOC) relative to age significantly predicted ovarian cancer survival. Risk for death was higher among women with highest number of LOC compared with those having fewest LOC (HR, 1.67; 95% CI, 1.20-2.33). Women with fewest LOC had the highest 15-year survival (56.7%; 95% CI, 47.8-64.6%), and women with the highest LOC had the poorest (33.3%; 95% CI, 25.3-41.5%). Women whose age at menarche was <12 years had a higher risk of death compared with women whose menses began at ≥14 years (HR, 1.51; 95% CI, 1.02-2.24).**

Conclusions: **We found that high LOC and early age at menarche were associated with decreased survival after ovarian cancer.** (Cancer Epidemiol Biomarkers Prev 2009;18(7):2035–41)

Introduction

Ovarian cancer, the fifth leading cause of cancer mortality in women and fourth leading cause of cancer mortality in white women, accounts for more deaths than any other gynecologic cancer (1). Because of diagnostic challenges, only one fifth of ovarian cancer cases are detected at the localized stage, when relative survival rates are highest. In the vast majority of cases, by the time the cancer is detected, regional or distant metastasis has seriously compromised 5-year survival, which is only 30% when diagnosed at the distant stage.[4] Beyond age at diagnosis and stage of disease, relatively little is known about factors that may influence survival after ovarian cancer diagnosis.

Several studies have examined the influence of reproductive factors on the risk of developing ovarian cancer. Consistent evidence suggests that fewer lifetime ovulatory cycles (LOC), higher parity, oral contraceptive use, hysterectomy, and tubal ligation are associated with decreased risk of ovarian cancer (2-10). Results are inconsistent concerning any association between ovarian cancer risk and breast-feeding, age at menarche, menopausal status, and age at first birth (3, 6, 9, 10). In contrast with ovarian cancer occurrence, studies examining ovarian cancer survival have found few significant independent reproductive predictors (11-17). Although some studies report that improved survival is associated with having breast-fed (11), being older at menarche (12), not having a history of sterilization (18), and having lower numbers of LOC (12), findings across studies are inconsistent (11, 12, 14, 15, 17).

To examine the influence of reproductive factors on ovarian cancer survival, we linked records from women who participated as incident ovarian cancer cases in the Cancer and Steroid Hormone (CASH) study with survival data from the Surveillance, Epidemiology, and End Results (SEER) Program. A previous analysis from the CASH study examined numerous prognostic factors, including use of oral contraception and menopausal status, in a subset of ovarian cancer cases and found no association between these reproductive factors and ovarian cancer survival (13). In this report, we extend

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[4] http://www.cancer.org/downloads/STT/caff2007PWSecured.pdf

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those analyses by examining a broader set of reproductive factors in a larger group of CASH ovarian cancer cases with an additional 5 years of follow-up.

Materials and Methods

The CASH study was a population-based, case-control, multicenter study conducted in eight areas of the United States (Atlanta, Detroit, San Francisco, Seattle, Connecticut, Iowa, and New Mexico, and four urban counties of Utah). It was designed to examine the association between oral contraceptive use and breast, endometrial, and ovarian cancer. Women with primary ovarian cancer diagnosed between December 1, 1980 and December 31, 1982 who had no history of ovarian cancer before the index diagnosis were eligible for the CASH study. Cases were identified through the population-based cancer registries that participate in the SEER Program; these registries routinely collect data on patient demographics, tumor characteristics, first course of treatment, and follow-up for vital status. Of the 816 women identified through SEER who met the case definition criteria for ovarian cancer, 575 (70%) participated in the CASH study (18). Only 5.2% of the eligible women refused to participate. Other reasons for nonparticipation included inability to conduct an interview within 6 months of selection (12.7%), illness (5.1%), death (3.1%), and refusal by physician (2.9%).

CASH study data sources included histology reports, specimen slides, and in-depth patient interviews that encompassed sociodemographics, reproductive and contraceptive histories, personal and family medical histories, health care information, and health risk behaviors. The original CASH study protocol was approved by the Centers for Disease Control and Prevention Institutional Review Board.

In the CASH study, which has been described in detail elsewhere (18-20), trained interviewers administered a 1-hour standardized questionnaire to study participants in their homes within approximately 6 months of their ovarian cancer diagnoses. The average time between diagnosis and interview was 3 months. Using life calendars to enhance recall of major life events occurring before cancer diagnosis, interviewers elicited in-depth information about participants' medical and reproductive histories, including pregnancies, oral contraceptive use, and breast-feeding.

To ascertain survival through December 31, 1997 for the CASH ovarian cancer cases, we attempted to link CASH data with SEER public access data files.[5] We successfully linked 494 (86%) CASH records to a SEER incident ovarian cancer case record using the following match criteria: sex, cancer site, geographic location of SEER registry, SEER identification number, birth year, and date of diagnosis (within 2 mo). Reasons why the linkage was not 100% successful included lack of valid SEER identification number, borderline cancer pathology designation, records matched on SEER identification did not match birth year and date of diagnosis, and multiple SEER identification numbers. Survival time was defined as the number of months between date of diagnosis and death, or as the number of months between date of diagnosis and date last known to be alive. In analyses, we excluded cases with ovarian cancer types other than epithelial (n = 41), missing data on cancer type (n = 15), unknown or *in situ* stage (n = 9 and 1, respectively), and cases with missing data on reproductive variables of interest (n = 18); 410 cases were available for analysis.

We explored the influence of the following reproductive factors on ovarian cancer survival: parity, use of oral contraceptives, breast-feeding history, age at menarche, menopausal status, age at first birth, and history of hysterectomy and tubal sterilization. Parity included pregnancies lasting more than 6 months that resulted in single, multiple, or still births. Oral contraceptive use was defined as any lifetime use for ≥3 consecutive months. All reproductive factors were defined as occurring before the ovarian cancer diagnosis. In addition to independent reproductive factors, we considered the influence of a composite variable, LOC.

In the CASH study, the number of LOC was estimated by calculating each woman's maximum ovulatory time as the total months from self-reported age at menarche to age at last menstrual period. From this total time, the months of anovulatory events from pregnancy, use of oral contraceptives, and breast-feeding were subtracted. Each woman was assumed to have an average cycle length of 28 days, or 13 cycles per year. Women who underwent hysterectomy and had at least one intact ovary remaining were assumed to still be ovulating if they were under age 49; if they were older than 49, they were assumed to have stopped ovulating at age 49. To separate the effects of LOC from age, we created tertiles of LOC within each of three age groups (20-40 years, 41-50 years, and 51-54 years) and then combined LOC groupings from each age stratum. For example, the total low LOC group included the lowest tertile of LOC among women 20 to 40 years, 41 to 50 years, and 51 to 54 years.

We used several cancer-specific factors in these analyses: age at diagnosis, stage of disease, and histology. Cancer stage was based on SEER historic stage A.[5] We created a dichotomous variable to indicate localized versus regional (n = 26) or distant (n = 225) stage cancer. CASH histology classifications were based on a review of cancer specimens by a panel of three pathologists. Specimen slides were available for 90% of the cases and were classified as mucinous, serous, endometriod, clear cell, and other. The remaining cases (n = 41) were known to have epithelial tumors based on SEER data, but their histologic type was unknown. For analyses, we combined cases with unknown histologic type, clear cell tumors (n = 35), and other epithelial tumors (n = 8) into a single category (''other'').

We estimated 5-, 10-, and 15-year probabilities of ovarian cancer survival using the Kaplan-Meier method (21). The log-rank test for equality of survivor functions was used to determine whether survival curves differed statistically by reproductive factor. Using Cox proportional hazards models (22), we estimated hazard ratios (HR) and 95% confidence intervals (95% CI) for any-cause death associated with reproductive factors. We also examined the HR of ovarian cancer death (International Classification of Disease, 9th Revision, codes 183.0-183.9) associated with

[5] http://seer.cancer.gov/manuals/CD2.SEERDic.pdf

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Table 1. Selected characteristics of 410 women with primary epithelial ovarian cancer

Characteristic	*n* (%)
Age at diagnosis (y)	
20-30	46 (11.2)
31-40	84 (20.5)
41-50	175 (42.7)
51-54	105 (25.6)
Stage of disease	
Localized	159 (38.8)
Regional/distant	251 (61.2)
Histology	
Serous	193 (47.1)
Mucinous	56 (13.7)
Endometriod	77 (18.8)
Other*	84 (20.5)
Parity	
Nulliparous	104 (25.4)
1-2	169 (41.2)
≥3	137 (33.4)
Use of oral contraceptives †	
Yes	169 (41.2)
No	241 (58.8)
Breast-feeding history (mo)	
Nulliparous	104 (25.4)
Never breast-fed	178 (43.4)
1-3	55 (13.4)
≥4	73 (17.8)
Age at menarche (y)	
<12	77 (18.8)
12-13	228 (55.6)
≥14	105 (25.6)
Menopause status	
Postmenopausal	132 (32.2)
Premenopausal	258 (62.9)
Age at first birth (y)	
Nulliparous	104 (25.4)
≤19	73 (17.8)
20-24	147 (35.9)
25-29	69 (16.8)
≥30	17 (4.2)
Hysterectomy	
Yes	39 (9.5)
No	369 (90.0)
Tubal sterilization	
Yes	42 (10.2)
No	365 (89.0)
Race	
White	389 (94.9)
Black	15 (3.7)
Other	6 (1.5)
Education level attained (y)	
<12	68 (16.6)
12	155 (37.8)
13-15	94 (22.9)
≥16	93 (22.7)
Smoking status	
Never	190 (46.3)
Former	62 (15.1)
Current	158 (38.5)
Body mass index	
<18.50	17 (4.2)
18.5-24.99	297 (72.4)
25.0-29.99	69 (16.8)
≥30.0	26 (6.3)
Family history of breast cancer	
Yes	91 (22.2)
No	283 (69.0)
Family history of ovarian cancer	
Yes	32 (7.8)
No	340 (82.9)

NOTE: Women were participants in the CASH study, 1980 to 1982. Due to missing data and rounding, values may not add to 410 or 100%, respectively.
*Other includes other epithelial (n = 8), clear cell tumors (n = 35), and tumors for which no review was done by the CASH panel (n = 41).
† Yes = ≥3 consecutive mo; no = never used or used <3 consecutive mo.

reproductive factors by censoring cases where death was attributed to underlying causes other than ovarian cancer. Analyses were adjusted a priori for two cancer-specific factors (age at diagnosis and stage of disease) due to their established influence on ovarian cancer survival (11, 13, 23-25). We considered other potential confounders, including smoking, race, education, body mass index, and family history of breast or ovarian cancer, but none of these altered the HR estimates. We also examined whether the influence of reproductive factors on ovarian cancer survival varied by age at diagnosis, stage of cancer, histologic type, or menopausal status, as previous reports have identified these as independent predictors of ovarian cancer survival (24, 26-28). We used the log likelihood ratio test of a full model containing the relevant interaction terms and a reduced model without the interaction terms. Our models did not violate the proportional hazards assumption as verified by visual inspection of log-log survival plots and the absence of any statistically significant interactions between the covariates and time. Stata version 9.2 was used to carry out all analyses.

Results

In this study population of 410 women, 130 (31.7%) were diagnosed with epithelial ovarian cancer at ages 20 to 40 years, 175 (42.7%) were diagnosed at ages 41 to 50, and 105 (25.6%) were diagnosed at ages 51 to 54 (Table 1). The majority of cases were diagnosed at the regional or distant stage (61.2%), and 193 (47.1%) were serous type tumors. Nearly one third of the women were postmenopausal at the time of diagnosis (32.2%), fewer than half had ever used oral contraceptives for ≥3 consecutive months (41.2%), one quarter were nulliparous (25.4%), and 18% breast-fed for ≥3 months. The study population was racially homogenous, with 94.9% being white.

During a median follow-up of 9.2 years, 212 women died (Table 2). Of the 212 deaths, 169 (79.7%) were recorded as deaths due to ovarian cancer. Of the 43 deaths in the study population not coded as due to ovarian cancer, 52% (n = 22) were coded as other neoplasms and 19% (n = 8) did not have cause of death available. The remaining causes of death may be classified as circulatory system (n = 8), injury (n = 2), kidney disease (n = 1), diabetes (n = 1), and HIV (n = 1). Analyses with all-cause mortality and ovarian cancer mortality yielded similar results; only those with all-cause mortality are shown in tables. Overall survival from any cause of death at 5, 10, and 15 years was 61% (95% CI, 56.16-65.64), 52% (95% CI, 46.89-56.66), and 48% (95% CI, 42.85-52.67), respectively (Table 2). In these unadjusted analyses, poorer survival was observed among the following groups (P < 0.05, log-rank test): women with high LOC, compared with medium or low LOC; women who never used oral contraceptives, compared with women who ever used oral contraceptives; postmenopausal women, compared with premenopausal and perimenopausal women; and those having a history of tubal sterilization, compared with those with none.

In multivariate analyses, the only reproductive factors associated with survival from any cause of death were higher number of LOC and earlier age at menarche (Table 3). Survival also significantly differed by age at

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diagnosis, stage of disease, and histology. Women in the high LOC group had a higher risk of death than women in the low LOC group (HR, 1.67; 95% CI, 1.20-2.33; Table 3). Across all survival times, the survival disadvantage was most pronounced for women in the high LOC group compared with either the medium or low LOC groups (Fig. 1). Survival for women in the medium and low LOC groups did not differ significantly. These associations were essentially unchanged when considering only ovarian cancer deaths (HR comparing high with low LOC, 1.56; 95% CI, 1.07-2.26 and HR comparing medium with low LOC, 1.09; 95% CI, 0.73-1.62). Younger age at menarche adversely affected survival in adjusted analyses; women who began menstruating before age 12 years had an increased risk of death compared with women who reached menarche at ≥ age 14 years (HR, 1.51; 95% CI, 1.02-2.24). Although women who had their first birth at age 30 years or later had a higher risk of death compared with nulliparous women, there was no indication of a trend. No other reproductive factors were

Table 2. Kaplan-Meier estimates of survival among 410 women with epithelial ovarian cancer

Variable	*n**	Deaths	Survival probability (95% CI)			*P* †
			5 y	10 y	15 y	
Overall	410	212	0.61 (0.56-0.66)	0.52 (0.47-0.57)	0.48 (0.43-0.53)	
LOC ‡						
Low	138	58	0.66 (0.57-0.73)	0.62 (0.53-0.69)	0.57 (0.48-0.65)	
Medium	136	64	0.66 (0.57-0.73)	0.56 (0.48-0.64)	0.53 (0.44-0.61)	0.0001
High	136	90	0.51 (0.42-0.59)	0.37 (0.29-0.46)	0.33 (0.25-0.42)	
Parity						
Nulliparous	104	49	0.65 (0.55-0.73)	0.58 (0.48-0.67)	0.54 (0.44-0.63)	
1-2 births	169	82	0.64 (0.56-0.71)	0.53 (0.45-0.60)	0.51 (0.43-0.58)	0.1063
≥3 births	137	81	0.55 (0.46-0.63)	0.46 (0.37-0.54)	0.40 (0.31-0.48)	
Use of oral contraceptives §						
Yes	169	71	0.70 (0.62-0.76)	0.61 (0.53-0.68)	0.57 (0.49-0.64)	0.0012
No	241	141	0.55 (0.49-0.61)	0.46 (0.39-0.52)	0.42 (0.35-0.48)	
Breast-feeding history (mo)						
Nulliparous	104	49	0.65 (0.55-0.73)	0.58 (0.48-0.67)	0.54 (0.44-0.63)	
Never breast-fed	178	96	0.58 (0.50-0.65)	0.48 (0.41-0.56)	0.45 (0.38-0.52)	0.6214
1-3	55	31	0.58 (0.44-0.70)	0.47 (0.34-0.60)	0.43 (0.30-0.56)	
≥4	73	36	0.65 (0.53-0.75)	0.56 (0.43-0.66)	0.50 (0.38-0.61)	
Age at menarche (y)						
<12	77	46	0.52 (0.40-0.62)	0.43 (0.32-0.54)	0.41 (0.29-0.51)	
12-13	228	110	0.64 (0.57-0.70)	0.54 (0.48-0.61)	0.51 (0.44-0.57)	0.1880
≥14	105	56	0.63 (0.53-0.71)	0.53 (0.43-0.62)	0.46 (0.37-0.56)	
Menopause status						
Premenopausal	258	112	0.70 (0.64-0.75)	0.59 (0.53-0.65)	0.56 (0.50-0.62)	<0.0001
Postmenopausal	132	92	0.43 (0.34-0.51)	0.36 (0.28-0.44)	0.30 (0.22-0.38)	
Age at first birth (y)						
Nulliparous	104	49	0.65 (0.55-0.73)	0.58 (0.48-0.67)	0.54 (0.44-0.63)	
≤19	73	33	0.65 (0.53-0.75)	0.56 (0.44-0.67)	0.53 (0.41-0.64)	
20-24	147	80	0.60 (0.52-0.68)	0.50 (0.41-0.58)	0.45 (0.37-0.53)	0.1756
25-29	69	38	0.56 (0.44-0.67)	0.49 (0.37-0.60)	0.44 (0.32-0.56)	
≥30	17	12	0.47 (0.23-0.68)	0.28 (0.10-0.51)	0.28 (0.10-0.51)	
Hysterectomy						
Yes	39	22	0.51 (0.35-0.66)	0.46 (0.30-0.61)	0.44 (0.28-0.58)	0.5143
No	369	189	0.62 (0.57-0.67)	0.52 (0.47-0.57)	0.48 (0.43-0.53)	
Tubal sterilization						
Yes	42	28	0.49 (0.33-0.63)	0.39 (0.24-0.53)	0.31 (0.17-0.45)	0.0332
No	365	183	0.62 (0.57-0.67)	0.53 (0.48-0.58)	0.50 (0.44-0.55)	
Age at diagnosis (y)						
20-40	130	40	0.79 (0.71-0.85)	0.70 (0.61-0.77)	0.68 (0.59-0.75)	
41-50	175	99	0.59 (0.51-0.66)	0.48 (0.41-0.56)	0.43 (0.35-0.50)	<0.0001
51-54	105	73	0.44 (0.34-0.53)	0.36 (0.27-0.45)	0.32 (0.23-0.41)	
Stage of disease						
Localized	159	39	0.85 (0.78-0.90)	0.79 (0.71-0.84)	0.75 (0.67-0.81)	<0.0001
Regional/distant	251	173	0.46 (0.40-0.52)	0.35 (0.29-0.41)	0.31 (0.25-0.37)	
Histology						
Serous	193	104	0.59 (0.51-0.65)	0.50 (0.42-0.56)	0.46 (0.39-0.53)	
Mucinous	56	13	0.89 (0.77-0.95)	0.83 (0.70-0.91)	0.75 (0.60-0.84)	0.0002
Endometriod	77	50	0.53 (0.41-0.63)	0.39 (0.28-0.50)	0.35 (0.24-0.46)	
Other ‖	84	45	0.57 (0.46-0.67)	0.49 (0.38-0.59)	0.46 (0.35-0.57)	

NOTE: Survival = from any cause of death after ovarian cancer diagnosis, through December 31, 1997; women were participants in the CASH study, 1980 to 1982.
*Due to missing data, values may not add to 410.
† Log-rank test for equality of survivor functions.
‡ Age-specific cut points for low, medium, and high LOC (respectively) were as follows: ages 20 to 40: ≤174, 175 to 247, and 248+; ages 41 to 50: ≤377, 378 to 419, and 420+; ages 51 to 54: ≤424, 425 to 451, and 452+.
§Yes = ≥3 consecutive mo; no = never used or used <3 consecutive mo.
‖Other includes other epithelial (n = 8), clear cell tumors (n = 35), and tumors for which no review was done by the CASH panel (n = 41).

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Table 3. Cox proportional hazards regression models of the effect of reproductive and cancer-specific prognostic factors on risk of death after epithelial ovarian cancer diagnosis

Characteristic	HR* (95% CI)
LOC [†]	
Low	1.00 (reference)
Medium	1.09 (0.76-1.56)
High	1.67 (1.20-2.33)
P trend	0.002
Parity	
Nulliparous	1.00 (reference)
1-2	0.87 (0.61-1.23)
≥3	0.92 (0.64-1.33)
P trend	0.733
Use of oral contraceptives [‡]	
Yes	0.87 (0.65-1.17)
No	1.00 (reference)
Breast-feeding history (mo)	
Nulliparous	1.00 (reference)
Never breast-fed	0.97 (0.68-1.37)
1-3	0.76 (0.48-1.19)
≥4	0.84 (0.54-1.30)
P trend[§]	0.336
Age at menarche (y)	
<12	1.51 (1.02-2.24)
12-13	1.18 (0.86-1.64)
≥14	1.00 (reference)
P trend	0.042
Menopause status	
Premenopausal	1.00 (reference)
Postmenopausal	1.17 (0.84-1.65)
Age at first birth (y)	
Nulliparous	1.00 (reference)
≤19	0.82 (0.53-1.29)
20-24	0.86 (0.60-1.24)
25-29	0.85 (0.55-1.31)
≥30	1.91 (1.01-3.61)
P trend[§]	0.163
Hysterectomy	
Yes	0.80 (0.51-1.25)
No	1.00 (reference)
Tubal sterilization	
Yes	1.35 (0.91-2.01)
No	1.00 (reference)
Age at diagnosis (y)	
20-40	1.00 (reference)
41-50	1.76 (1.22-2.55)
51-54	2.54 (1.72-3.75)
P trend	0.001
Stage of disease	
Localized	1.00 (reference)
Regional/distant	3.73 (2.63-5.29)
Histology	
Serous	1.00 (reference)
Mucinous	0.98 (0.52-1.81)
Endometriod	1.40 (1.00-1.97)
Other[¶]	1.34 (0.94-1.93)

NOTE: Risk of death is defined as death from any cause after ovarian cancer diagnosis, through December 31, 1997; data are from the CASH study, 1980 to 1982.

*Adjusted for age at diagnosis and stage of cancer.

[†]Age-specific cut points for low, medium, and high LOC (respectively) were as follows: ages 20 to 40: ≤174, 175 to 247, and 248+; ages 41 to 50: ≤377, 378 to 419, and 420+; ages 51 to 54: ≤424, 425 to 451, and 452+.

[‡]Yes = ≥3 consecutive mo; no = never used or used <3 consecutive mo.

[§]Among purous women.

[¶]Other includes other epithelial (n = 8), clear cell tumors (n = 35), and tumors for which no review was done by the CASH panel (n = 41).

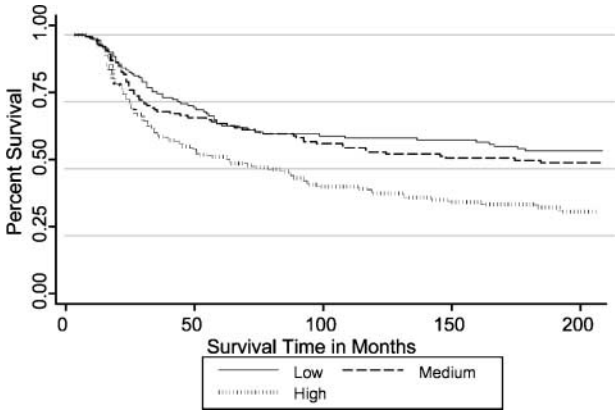

Figure 1. Kaplan-Meier estimates of survival by number of LOCs. As shown, the lower the number of LOC, the higher survival was.

statistically significant in multivariate analyses. Further analyses showed that HRs for LOC and age at menarche were consistent across subgroups defined by age, menopausal status, stage of cancer, and histologic type; all *P* values for interactions >0.4 (data not shown).

Discussion

Our findings suggest that high LOC is a predictor of poorer epithelial ovarian cancer survival in this relatively young population of women with ovarian cancer and that its influence on survival does not differ by age at diagnosis, stage of disease, menopausal status, or histology. Women in the high LOC group had an increased risk of death compared with women in the low LOC group. In addition, we found that women who reached menarche at <12 years of age had a higher risk of death compared with women who reached menarche at ≥14 years of age. No other reproductive factors were independent prognostic indicators.

Our findings are consistent with some previous studies in that we found parity, use of oral contraceptives, breast-feeding, menopausal status, age at first birth, hysterectomy, and tubal sterilization did not affect survival after an ovarian cancer diagnosis (11-16). Our findings that younger age at menarche and higher numbers of LOC were associated with increased risk of death after ovarian cancer are consistent with the Danish Malignant Ovarian Cancer study (12) but inconsistent with a population-based cohort study of Australian women that found no association (11).

In light of our finding that LOC was an independent predictor of epithelial ovarian cancer survival, we considered why important components of LOC (i.e., parity, use of oral contraceptives, and breast-feeding) were not independent predictors in adjusted models that included age at diagnosis and stage of disease. We were particularly puzzled by the lack of associations with parity or use of oral contraceptive in adjusted analyses because they accounted for the majority of anovulatory cycles in our cases. However, in unadjusted Kaplan-Meier survival analyses, oral contraceptive use was associated with improved survival, and although not statistically significant, it is noteworthy that HRs for

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parity, oral contraceptive use, and breast-feeding were in the protective direction, as expected. It may be that power was limited to detect modest associations due to sample size. Alternatively, it is feasible that combined, the LOC component variables become statistically significant in the composite measure (12). Yet, another possibility is that age at menarche is driving the association between LOC and ovarian cancer survival, but because the HR of high LOC is greater than the HR of younger age at menarche, we find the synergistic explanation more compelling. Finally, we considered what effect additional survival data might have on the observed associations, and because of the lethality of this disease, we think it is unlikely that increasing follow-up would yield very different results from 15-year survival results.

The association between LOC and ovarian cancer incidence has been attributed to a variety of possible hormonal hypotheses, such as incessant ovulation (29), and influence of other hormones, such as gonadotropins, estrogens, androgens, and progesterones (30, 31). It is plausible that incessant ovulation or hormonal influences could not only explain pathogenesis but may also influence survival after ovarian cancer diagnosis. One study that used a subset of CASH study ovarian cancer incidence cases found that higher numbers of ovulatory cycles were associated with more aggressive tumors, namely, those with overexpression of mutant p53 protein (32). Schildkraut and colleagues (32) suggested that proliferation of ovarian epithelium from incessant ovulation leads to spontaneous errors during DNA replication, which causes p53 genetic mutations. In two additional reports that examine the prognostic significance of p53 expression in epithelial ovarian cancer, both find that p53 reactivity is associated with decreased survival in univariate analyses (13, 33). However, only one of these studies showed that p53 overexpression is an independent prognostic factor for survival in women with ovarian cancer (13). Alternatively, the influence of progesterone may explain the association between LOC and epithelial ovarian cancer survival because progesterone is known to inhibit ovulation (34) and ovarian cancer cell proliferation (31). Moreover, progesterone is known to have antitumor properties and may be useful in the treatment of ovarian cancer (35, 36). Two studies showed that progesterone inhibited growth of ovarian carcinoma cells and promoted apoptosis (31, 33); both of which may, theoretically, improve ovarian cancer survival.

We considered several limitations that may have influenced our findings. First, our results could be biased to some degree due to inaccurate recall of reproductive history and the elements of LOC. Although recall bias cannot be excluded, we would expect any misclassification to be nondifferential with respect to mortality. Additionally, our estimation of LOC may be somewhat imprecise, as it did not account for anovulation due to menstrual irregularities. Moorman and colleagues (5) compared the standard calculation of LOC (used in this study) with a more detailed method that accounted for menstrual irregularities, and both approaches showed that higher LOC was associated with increased risk of ovarian cancer, although the standard calculation produced higher estimates of ovarian cancer risk. Moreover, although breast-feeding is a conventional component of LOC estimation, it can be argued that lactational amenorrhea is an unreliable indicator of ovulation, particularly after 6 months (5). Because only 13% of the women in our study breast-fed more than 6 months, it is unlikely that this is a significant source of misclassification. Another potential limitation is that we could not assess whether the effect of LOC on survival may have been influenced by cancer treatment because minimal treatment data were available. Finally, our findings may not be generalizable to all women with ovarian cancer. As the CASH study was designed to investigate the association between oral contraceptives and reproductive cancers, the women in our study were relatively young (mean, 43 years), and in the general population, half of all ovarian cancer cases occur in women over age 63 years (37). If anything, the younger age distribution in our sample is likely to minimize recall bias related to LOC because older women would be more likely to have forgotten important details around their menstrual histories.

In addition to expanding the literature examining the association between reproductive factors and ovarian cancer survival, our study has several strengths, including its long follow-up period, population-based sample, and review of ovarian cancer diagnoses by a pathology panel. Additionally, cases were enrolled close to diagnosis, reducing the possibility that the cohort is biased toward healthier survivors. Finally, we took measures to separate the effects of LOC from age by creating a variable of LOC relative to age. Further research is needed to explore the associations between reproductive factors and ovarian cancer survival in other study populations, particularly those that include older women and contain more detailed menstrual cycle information and complete data on cancer treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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