Null Findings in Brief

Title:

Reproductive factors do not influence survival with ovarian cancer

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Running title:

Reproductive factors not influence ovarian cancer survival

LIST OF ABBREVIATIONS

AUS	Australian Ovarian Cancer Study
CI	Confidence interval
COC	Combined oral contraceptive
CON	Connecticut Ovary Study
DOV	Diseases of the Ovary and their Evaluation
GER	German Ovarian Cancer Study
HAW	Hawaii Ovarian Cancer Case-Control Study
HOP	Hormones and Ovarian Cancer Prediction
HR	Hazard ratio
NCO	North Carolina Ovarian Cancer Study
NEC	New England Case Control Study
NJO	New Jersey Ovarian Cancer Study
OCAC	Ovarian Cancer Association Consortium
OPL	Ovarian Cancer Prognosis and Lifestyle Study
POL	Polish Ovarian Cancer Case-Control Study
SEA	Study of Epidemiology and Risk Factors in Cancer Heredity
STA	Genetic Epidemiology of Ovarian Cancer
U.S.	United States
UCI	University California Irvine Ovarian Study
UKO	United Kingdom Ovarian Cancer Population Study
USC	Study of Lifestyle and Women's Health

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Abstract

Background

Previous studies on the association between reproductive factors and ovarian cancer survival are equivocal, possibly due to small sample sizes.

Methods

Using data on 11,175 people diagnosed with primary invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer (ovarian cancer) from 16 studies in the Ovarian Cancer Association Consortium (OCAC), we examined the associations between survival and age at menarche, combined oral contraceptive use, parity, breastfeeding, age at last pregnancy, and menopausal status using Cox proportional hazard models. The models were adjusted for age at diagnosis, race/ethnicity, education level, and OCAC study and stratified on stage and histotype.

Results

During the mean follow-up of 6.34 years (SD=4.80), 6,418 patients passed away (57.4%). There was no evidence of associations between the reproductive factors and survival among ovarian cancer patients overall or by histotype.

Conclusions

This study found no association between reproductive factors and survival after an ovarian cancer diagnosis.

Impact

Reproductive factors are well-established risk factors for ovarian cancer, but they are not associated with survival after a diagnosis of ovarian cancer.

Introduction

Invasive epithelial ovarian cancer (ovarian cancer) has a five-year survival rate of less than 50%. Cigarette smoking[1] and higher body mass index[2] prior to diagnosis are both associated with poor survival, whereas menopausal hormone therapy use is a positive prognostic indicator[3]. However, the literature surrounding the association between reproductive factors and ovarian cancer survival is equivocal even though many are associated with risk of the disease. Older age at menarche has been associated with both poor[4] and longer survival[5], but three other studies have found no relationship[6-8]. Similarly, some[6, 7], but not all[4, 5, 8] studies have reported that parity is associated with better survival. One study reported a decreased death rate among those who used combined oral contraceptives (COCs)[8], but most studies did not observe an association[4-6]. A major concern with these studies is power; to our knowledge, the largest published study of reproductive factors and ovarian cancer survival included 1,698 patients[4]. Therefore, we have used data from 11,175 ovarian cancer patients in the Ovarian Cancer Association Consortium (OCAC) to clarify the associations between survival and age at menarche, COC use, parity, breastfeeding, age at last pregnancy, and menopausal status.

Materials and Methods

This analysis used self-reported data from 16 studies in the OCAC, including two studies from Australia, four from Europe, and ten from the United States (U.S.) (http://ocac.ccge.medschl.cam.ac.uk/; Table 1). All studies obtained institutional ethics committee approval and followed recognized ethnical guidelines, including the Declaration of Helsinki, the Belmont Report, and/or the U.S. Common Rule; and participants provided written informed consent. Participants who were diagnosed with primary invasive epithelial ovarian, fallopian tube, or primary peritoneal tumors (hereafter referred to as ovarian cancer) were included in the analysis. To be included, patients had to have been diagnosed with one of the five main histotypes (i.e., high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous) and

had follow-up time and vital status information available. Survival time was counted from date of diagnosis to either death or last follow-up. Follow-up is largely done via linkage with national death databases.

The six pre-diagnosis reproductive factors of interest were age at menarche, COC use, parity, breastfeeding, age at last pregnancy, and menopausal status. The covariates included age at diagnosis, race/ethnicity, education level, stage, histotype, and OCAC study. The percentage of patients missing data on any variables ranged from none for age to 5.9% for education level. Multiple imputation (*mice* package in R) was conducted to create 20 imputed datasets. All variables in the dataset with ≤70% missingness were included for imputation, including the six reproductive factors and those not used in the final models. Data were imputed separately by geographic region (i.e., Australia, Europe, and U.S.), and OCAC study was included as a predictor in all imputation models.

Cox proportional hazards models were fit for all-cause mortality among ovarian cancer patients overall and by histotype. All models included the six reproductive factors of interest (see above); were adjusted for age at diagnosis, race/ethnicity, education level, and OCAC study; and stratified on stage and histotype (see Table 2 for the coding schemes). Hazard ratios (HRs) and 95% confidence intervals (CIs) across the 20 imputed datasets were pooled using Rubin's rule to obtain a single point estimate and pooled standard error for each reproductive factor. The pooled standard error is derived from within and between imputation variances. Adjusting for cigarette smoking, menopausal hormone therapy, body mass index, and aspirin use did not change the results. Including only patients with complete information (N=9,422) yielded similar results. No evidence of heterogeneity between the OCAC studies for each factor-survival association was found using standard meta-analytic techniques.

Data availability

The data generated in this study are not publicly available due to limitations imposed by the original studies in which these data were collected. The corresponding author will facilitate access through existing data request processes for the Ovarian Cancer Association Consortium.

Results

Of the 11,175 ovarian cancer patients included in the analysis, there were 6,418 deaths (57.4%) during an average follow-up of 6.34 years (SD=4.80) (Table 1). There were no statistically significant reproductive factor-survival associations among ovarian cancer patients overall or by histotype (Table 2). There were two borderline significant associations with survival: breastfeeding for 24+ months (HR=1.11, 95% CI 0.99-1.24) and age at last pregnancy 30-34 years (HR=0.92, 95% CI 0.85-1.00, Table 2). However, there were no trends across the categories of these exposures suggesting that the associations were likely due to chance. Similarly, there were several borderline significant associations within each histotype, but they were likely due to chance for the same reasons (Table 2).

Discussion

Our study was the largest to date to investigate reproductive factors and survival among ovarian cancer patients, and found no statistically significant associations. Our sample size of more than 11,000 patients afforded us sufficient statistical power to detect potential associations. It further enabled histotype-specific analyses, which had not been evaluated previously. Our cohort's six-year survival of 43% is close to the Surveillance, Epidemiology, and End Results Program (SEER) five-year survival of 47%, suggesting that our cohort is well-representative of ovarian cancer patients. However, due to a large proportion of missing data for debulking status, treatment, and time to recurrence, we could not consider these factors in the analysis. Overall, our findings highlight that the pre-diagnosis reproductive factors included in this analysis have no significant impact on ovarian cancer survival regardless of their effects on the risk of developing ovarian cancer.

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Table 1: Description of the 16 OCAC studies included in the analysis.

Study Abbreviation	Study full name	Study Location	Recruitment Period	Data Collection Method	Participants	Number of deaths (%)	Mean years of follow-up (standard deviation)
AUS	Australian Ovarian Cancer Study	Australia	2001-2006	Self-completed questionnaire	1,329	947 (71.3%)	5.02 (3.44)
OPL	Ovarian Cancer Prognosis and Lifestyle Study	Australia	2012-2015	Self-completed questionnaire	793	314 (39.6%)	3.52 (1.24)
GER	German Ovarian Cancer Study	Baden-Württemberg and Rhineland-Palatinate, Germany	1993-1998	Self-completed questionnaire	152	100 (65.8%)	7.61 (5.82)
POL	Polish Ovarian Cancer Case-Control Study	Poland	2000-2004	In-person interview	152	82 (53.9%)	3.72 (1.97)
SEA	Study of Epidemiology and Risk Factors in Cancer Heredity	East Anglia and West Midlands, United Kingdom	1993-2013	Self-completed questionnaire	1,242	550 (44.3%)	7.31 (5.53)
UKO	United Kingdom Ovarian Cancer Population Study	United Kingdom	2006-2009	Self-completed questionnaire	631	323 (51.2%)	6.73 (4.17)
CON	Connecticut Ovary Study	Connecticut, US	1999-2003	In-person interview	329	180 (54.7%)	5.86 (2.92)
DOV	Diseases of the Ovary and their Evaluation	Washington, US	2002-2009	In-person interview	886	519 (58.6%)	7.34 (4.45)
HAW	Hawaii Ovarian Cancer Case-Control Study	Hawai'i, US	1994-2008	In-person interview	359	203 (56.5%)	7.86 (5.18)
HOP	Hormones and Ovarian Cancer Prediction	Western Pennsylvania, Northeast Ohio, Western New York, US	2003-2009	In-person interview	615	372 (60.5%)	5.29 (3.19)
NCO	North Carolina Ovarian Cancer Study	North Carolina, US	1999-2008	In-person interview	814	534 (65.6%)	6.15 (3.97)
NEC	New England Case Control Study	New Hampshire and Eastern Massachusetts, US	1992-2008	In-person interview	1,373	774 (56.4%)	5.17 (4.59)
NJO	New Jersey Ovarian Cancer Study	New Jersey, US	2005-2009	Telephone interview	195	118 (60.5%)	6.08 (2.95)
STA	Genetic Epidemiology of Ovarian Cancer	Greater Bay Area, California, US	1997-2002	In-person interview	407	236 (58.0%)	6.55 (4.20)
UCI	University California Irvine Ovarian Study	Orange County and San Diego County, California, US	1994-2004	Self-completed questionnaire	363	168 (46.3%)	7.47 (3.58)
USC	Study of Lifestyle and Women's Health	Los Angeles, California, US	1994-2010	In-person interview	1,535	998 (65.0%)	8.54 (6.84)
				Overall	**11,175**	**6,418 (57.4%)**	**6.34 (4.80)**

Table 2: Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between each reproductive factor and survival among ovarian cancer patients overall and by histotype

	All women			High-grade serous			Endometrioid			Clear cell			Mucinous			Low-grade serous		
	11,175 cases			6,582 cases			1,898 cases			1,013 cases			923 cases			759 cases		
Reproductive factors	**HR***	**95% CI**	**p-value**	**HR****	**95% CI**	**p-value**	**HR****	**95% CI**	**p-value**	**HR****	**95% CI**	**p-value**	**HR****	**95% CI**	**p-value**	**HR****	**95% CI**	**p-value**
Age at menarche (years)																		
<12	1.00	0.94-1.07	0.99	1.02	0.95-1.10	0.57	0.91	0.74-1.12	0.39	0.98	0.75-1.29	0.89	0.80	0.56-1.15	0.22	1.09	0.82-1.46	0.54
12-14	1.00			1.00			1.00			1.00			1.00			1.00		
15+	1.02	0.94-1.10	0.65	1.02	0.93-1.11	0.72	0.93	0.72-1.21	0.60	1.14	0.80-1.63	0.47	0.92	0.62-1.36	0.68	1.40	0.99-1.97	0.05
		p-trend= 0.63			p-trend=0.83			p-trend=0.72			p-trend=0.53			p-trend=0.50			p-trend=0.41	
Combined oral contraceptive use duration (years)																		
<1	1.00			1.00			1.00			1.00			1.00			1.00		
1-4.99	0.96	0.90-1.03	0.25	0.97	0.90-1.05	0.45	0.95	0.76-1.20	0.69	0.87	0.64-1.18	0.38	0.89	0.61-1.30	0.54	0.99	0.75-1.31	0.95
5-9.99	0.98	0.90-1.06	0.61	1.01	0.92-1.10	0.88	1.04	0.80-1.36	0.74	0.88	0.62-1.26	0.49	0.70	0.44-1.09	0.12	0.97	0.67-1.40	0.86
10+	0.96	0.88-1.05	0.39	0.97	0.88-1.08	0.61	0.93	0.69-1.27	0.67	0.82	0.54-1.24	0.35	1.10	0.72-1.69	0.66	0.91	0.63-1.30	0.60
		p-trend=0.29			p-trend=0.72			p-trend=0.84			p-trend=0.26			p-trend=0.76			p-trend=0.62	
Parity																		
0	1.00			1.00			1.00			1.00			1.00			1.00		
1	1.00	0.91-1.11	0.96	0.99	0.87-1.11	0.81	0.99	0.72-1.36	0.97	0.97	0.62-1.51	0.88	1.33	0.79-2.21	0.28	1.31	0.86-1.98	0.21
2	1.00	0.91-1.10	1.00	0.98	0.88-1.10	0.74	1.02	0.77-1.37	0.88	1.01	0.65-1.57	0.96	0.72	0.43-1.19	0.20	1.30	0.85-1.99	0.22
3+	0.98	0.89-1.09	0.75	0.99	0.88-1.12	0.93	1.02	0.75-1.40	0.89	0.67	0.40-1.12	0.12	1.09	0.64-1.87	0.75	0.92	0.59-1.45	0.73
		p-trend=0.83			p-trend=0.99			p-trend=0.84			p-trend=0.14			p-trend=0.90			p-trend=0.33	
Breastfeeding																		
Never breastfed	1.00			1.00			1.00			1.00			1.00			1.00		
<12 months	0.95	0.89-1.02	0.13	0.94	0.87-1.02	0.13	0.94	0.75-1.18	0.60	1.07	0.76-1.50	0.71	1.04	0.72-1.49	0.84	0.92	0.68-1.24	0.57
12-23 months	1.00	0.91-1.09	0.95	0.96	0.87-1.07	0.50	1.00	0.72-1.39	0.99	1.09	0.68-1.73	0.73	1.22	0.72-2.05	0.46	1.23	0.80-1.88	0.34
24+ months	1.11	0.99-1.24	0.07	1.12	0.99-1.27	0.08	0.77	0.49-1.19	0.24	1.13	0.65-1.99	0.66	1.44	0.83-2.48	0.19	1.05	0.66-1.67	0.84
		p-trend=0.37			p-trend=0.41			p-trend=0.38			p-trend=0.60			p-trend=0.18			p-trend=0.60	
Age at last pregnancy (years)																		
<25	1.00			1.00			1.00			1.00			1.00			1.00		
25-29	0.99	0.91-1.07	0.76	0.99	0.90-1.08	0.78	1.13	0.88-1.45	0.34	1.02	0.70-1.50	0.91	0.98	0.65-1.48	0.92	0.92	0.65-1.30	0.63
30-34	0.92	0.85-1.00	0.06	0.93	0.85-1.03	0.16	0.88	0.67-1.16	0.37	0.95	0.63-1.44	0.81	0.95	0.63-1.42	0.79	0.93	0.65-1.32	0.67
35+	0.94	0.86-1.03	0.17	0.97	0.88-1.08	0.61	0.82	0.60-1.10	0.19	0.88	0.56-1.40	0.59	0.65	0.40-1.05	0.08	0.92	0.63-1.35	0.68
		p-trend=0.055			p-trend=0.36			p-trend=0.07			p-trend=0.54			p-trend=0.10			p-trend=0.72	
Menopausal status																		
Pre-menopausal	1.04	0.96-1.13	0.32	1.07	0.97-1.18	0.19	0.86	0.67-1.10	0.23	1.18	0.85-1.65	0.33	1.22	0.80-1.85	0.35	1.02	0.70-1.50	0.91
Post-menopausal	1.00			1.00			1.00			1.00			1.00			1.00		

* Cox proportional hazards model including all reproductive factors, adjusted for age at diagnosis (continuous in years), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, other), education level (less than high school, high school, some college, college graduate or above), OCAC study (n=16), stratified on stage at diagnosis (local, regional, distant) and histotype (high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous).

** Cox proportional hazards models including all reproductive factors, adjusted for age at diagnosis (continuous in years), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, other), education level (less than high school, high school, some college, college graduate or above), OCAC study (n=16), stratified on stage at diagnosis (local, regional, distant).

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