History of comorbidities and survival of ovarian cancer patients, results from the Ovarian Cancer Association Consortium

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Abstract

Background: Comorbidities can affect survival of ovarian cancer patients by influencing treatment efficacy. However, little evidence exists on the association between individual concurrent comorbidities and prognosis in ovarian cancer patients.

Methods: Among patients diagnosed with invasive ovarian carcinoma who participated in 23 studies included in the Ovarian Cancer Association Consortium, we explored associations between histories of endometriosis, asthma, depression, osteoporosis, and autoimmune, gallbladder, kidney, liver and neurological diseases and overall and progression-free survival. Using Cox proportional hazards regression models adjusted for age at diagnosis, stage of disease, histology, and study site, we estimated pooled hazard ratios and 95% confidence intervals to assess associations between each comorbidity and ovarian cancer outcomes.

Results: None of the comorbidities were associated with ovarian cancer outcome in the overall sample nor in strata defined by histological subtype, weight status, age at diagnosis or stage of disease (local/regional vs. advanced).

Conclusions: Histories of endometriosis, asthma, depression, osteoporosis, and autoimmune, gallbladder, kidney, liver, or neurologic diseases were not associated with ovarian cancer overall or progression-free survival.

Impact: These previously diagnosed chronic diseases do not appear to affect ovarian cancer prognosis.

Introduction

Preexisting chronic diseases among ovarian cancer patients can results in the use of nonstandard treatment regimens (1) or intolerance to the standard treatments (2), therefore, limiting cancer therapy or affecting prognosis in these patients (3). Despite the likely role of comorbidities in ovarian cancer prognosis, detailed evidence regarding associations with particular comorbidities is limited, and results of earlier studies conducted to explore such associations are not consistent (1-6). These studies either did not distinguish among individual comorbidities or had insufficient statistical power to examine associations, particularly for histological subtypes.

Previously we reported on the association between histories of hypertension, heart disease, and diabetes in relation to overall survival (OS) and progression-free survival (PFS) among ovarian cancer patients (7). In this study, using a large multi-national sample of studies participating in the Ovarian Cancer Association Consortium (OCAC), we explore the relationship between other selected common comorbidities and OS and PFS among women diagnosed with ovarian cancer. We hypothesize that these comorbidities are associated with poor ovarian cancer prognosis.

Materials and methods

Our analyses use pooled data from 23 studies. Characteristics of the included studies included are shown in Table 1. Patient-related data were collected by either self- or interviewer-administered questionnaires and/or medical records reviews. These data were obtained from the participating study centers, cleaned, and harmonized. Comorbidities of interest comprise endometriosis, asthma, autoimmune diseases (dermatomyositis, polymyositis, rheumatoid

arthritis, Sjögren's syndrome, scleroderma, systemic lupus erythematosus, inflammatory bowel disease, Hashimoto's disease, Grave's disease, and Type I diabetes), depression/anxiety, osteoporosis, and any kidney, liver, gallbladder, and neurological diseases. For the analyses, the study sample was limited to women with invasive epithelial ovarian cancer and no missing information on vital status, length of follow up at the time of last contact or the comorbidity of interest (varies for each disease).

We used age-, stage-, histology-, and site-adjusted Cox proportional hazards models to explore associations between each comorbidity and ovarian cancer outcomes by calculating pooled hazards ratios (HRs) and their 95% confidence intervals (CIs). We were not able to assess heterogeneity among study-specific HRs due to limited numbers of cases in some studies. No other etiologically or prognostically important available factors appreciably changed observed estimates of age- and stage-adjusted study-specific or overall HRs; therefore, they were not included in any of the models.

In all the models, overall survival (OS) was defined as the time from the date of diagnosis to the date of death or end of follow up, whichever occurred first. Progression-free survival (PFS) was defined as the time from the date of diagnosis to the date when progression status (persistence, recurrence, or death) was determined, or the end of follow-up for cases without identified progression. Cases with no history of the comorbidity of interest were the referent.

We also examined whether or not associations differed according to the main histological subtypes (high-grade serous, low-grade serous, mucinous, endometrioid, and clear cell), overweight status (18.5 kg/m^2<body mass index (BMI)<25.0 kg/m^2 vs. BMI≥25.0 kg/m^2), age at diagnosis (<65 vs. ≥65 years), and stage of disease (local/regional vs. advanced). In addition, we examined possible multiplicative interactions by likelihood ratio statistics.

We had 80% power to detect the following risk estimates for OS and PFS respectively: 1.11 and 1.20 for endometriosis, 1.28 and 1.34 for asthma, 1.15 and 1.23 for depression, 1.26 and 1.41 for osteoporosis, 1.22 and 1.27 for autoimmune disease, 1.50 and 1.95 for kidney disease, 1.71 and 1.97 for liver disease, 1.16 and 1.21 for gallbladder disease, and 2.08 and 2.29 for neurological diseases.

Results

Results of the analyses are presented in Table 2. No significant associations were observed between histories of endometriosis, asthma, depression, osteoporosis, autoimmune, gallbladder, kidney, liver, and neurological diseases and OS or PFS. Results were also not significant and not different in strata defined by histological subtype, overweight status, age, and stage of disease. No evidence of multiplicative interaction was observed.

Discussion

In this large international sample of women diagnosed with invasive ovarian cancer, we did not observe associations between histories of endometriosis, asthma, depression, osteoporosis, and autoimmune, kidney, liver, gallbladder, and neurological diseases and OS and PFS. Results of our study are similar to others reporting no association between presence of comorbidity and survival among ovarian cancer patients (1, 4, 6). Our results are also consistent with those from Hemminki et al.(8) that showed no association between autoimmune disease and OS, HR=1.09 (95% CI:0.99-1.20). These results suggest that various comorbidities have little impact on survival for a disease that is already characterized by poor prognosis (4).

Strengths of our study include the large sample of patients with ovarian cancer, allowing for the assessment of associations within histological subtypes as well as potential effect modification. Limitations of this research includes the possibility of residual confounding, particularly due to the absence of information on treatment regimen and on comorbidities diagnosed after ovarian cancer diagnosis.

In conclusion, we did not observe evidence of the relationship between selected chronic diseases and OS and PFS among cases diagnosed with invasive epithelial ovarian carcinoma.

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Table 1. Characteristics of studies included in the analysis: Ovarian Cancer Association Consortium [1].												
Study acronym	**Study name**	**Study location, year of diagnosis**	**Data collection method**	**Endometriosis**	**Asthma**	**Auto immune**	**Depression**	**Osteo-porosis**	**Gallbladder disease**	**Kidney disease**	**Liver disease**	**Neurological disease**
AOV	Alberta Ovarian Tumor Types Study	Canada 1978-2010	MRR	MRR: reporting of disease	-	-	-	-	-	-	-	-
AUS[2]	Australian Ovarian Cancer Study	Australia 2002-2006	Self-completed questionnaire	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease
BAV[2]	Bavarian Ovarian Cancer Cases and Controls	Germany 2002-2006	In-person interview	Q: disease found during surgery	-	-	-	-	-	-	-	-
CON	Connecticut Ovarian Cancer Study	USA: CT 1998-2003	In-person interview	Q:Disease diagnosed by physician	-	-	-	-	-	-	-	-
DOV	Disease of the Ovary and their Evaluation Study	USA: WA 2002-2005 (DOV) 2006-2009 (DVE)	In-person interview	Q:Disease diagnosed by physician	-	Q:Disease diagnosed by physician	-	-	-	-	-	-
GER	German Ovarian Cancer Study	Germany 1993-1996	Self-administered questionnaire	Q:Disease diagnosed by physician	-	-	-	-	Q:Disease diagnosed by physician	-	-	-
HAW[2]	Hawaii Ovarian Cancer Study	USA: HI 1993-2008	In-person interview	Q:Disease diagnosed by physician	-	Q:Disease diagnosed by physician	Q:Disease diagnosed by physician	-	-	-	-	-
HJO[2]	Hannover-Jena Ovarian Cancer Study	Germany 2007-2011	MRR	MRR: reporting of disease		MRR: reporting of disease			MRR: reporting of disease			
HOP[2]	Hormones and Ovarian Cancer Prediction Study	USA: PA, OH, and NY 2003-2009	In-person interview, MRR	Q:Ever having disease; MRR: reporting of disease	Q:Disease diagnosed by physician MRR: reporting of disease	Q:Disease diagnosed by physician MRR: reporting of disease	MRR: reporting of disease	MRR: reporting of disease	MRR: reporting of disease	MRR: reporting of disease	MRR: reporting of disease	MRR: reporting of disease
JPN[2]	Hospial-based Research Program at Aichi Cancer Center	Japan 2001-2005	In-person interview	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease
LAX[2]	Women's Cancer Program at the Samuel Oschin Comprehensive	USA: CA 1989-present	MRR	MRR: reporting of disease	-	MRR: reporting of disease	-	-	MRR: reporting of disease	-	-	-

	Cancer Institute											
MAC[2]	Mayo Clinic Case-Only Ovarian Cancer Study	USA 2000-2011	Self-completed questionnaire	Q:Ever diagnosed with disease	-	-	-	-	-	-	-	-
MAL[2]	MALignant OVArian cancer	Denmark 1994-1999	In-person interview	Q:Disease diagnosed by physician	Q:Determined based on medication intake	Q:Disease diagnosed by physician	Q:Determined based on medication intake	Q:Disease diagnosed by physician	-	-	Q:Disease diagnosed by physician	-
MAY[2]	Mayo Clinic Ovarian Cancer Case-Control Study	USA: MN, SD, ND, IL, IA, WI 2003-2009	In-person interview	Q:Ever diagnosed with disease	-	-	-	-	-	-	-	-
NCO[2]	North Carolina Ovarian Cancer Study	USA: NC	Self-completed questionnaire	Q:Disease diagnosed by physician	-	Q:Disease diagnosed by physician	Q:Disease diagnosed by physician	Q:Disease diagnosed by physician	Q:Disease diagnosed by physician	-	-	-
NEC[2]	New England Case-Control Study of Ovarian Cancer	USA:NH and MA 1992-2003	In-person interview	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease	Q:Ever having disease
NJO	New Jersey Ovarian Cancer Study	USA: NJ 2002-2008	Phone interview	Q:Disease diagnosed by physician	-	Q:Disease diagnosed by physician	Q:Disease diagnosed by physician	Q:Disease diagnosed by physician	-	-	-	Q:Disease diagnosed by physician
NTH	Nijmegen Ovarian Cancer Study	Netherlands 1989-2006	Self-completed questionnaires MRR	Q:Disease diagnosed by physician MRR: reporting of disease	Q:Disease diagnosed by physician MRR: reporting of disease	Q: Disease diagnosed by physician	-	Q:Disease diagnosed by physician MRR: reporting of disease	-	Q:Disease diagnosed by physician MRR: reporting of disease	Q:Disease diagnosed by physician MRR: reporting of disease	Q:Disease diagnosed by physician MRR: reporting of disease
TBO	Tampa Bay Ovarian Cancer Study	USA:FL 2000-present	Self-completed questionnaires	Q:Disease diagnosed by physician	-	-	-	-	-	--	-	-
UCI	University of California, Irvine Ovarian Cancer Study	USA: CA 1995-2005	Self-completed questionnaires	Q:Disease diagnosed by physician	-	-	-	-	-	-	-	-
UKO	United Kingdom Ovarian Cancer Population Study	United Kingdom 2006-2010	Self-completed questionnaires	Q:Disease diagnosed by physician	-	-	-	-	-	-	-	-
USC	University of Southern California, Study of Lifestyle and Women's	USA: CA 1993-2005	In-person interview	Q:Diagnosed by physician	-	-	-	-	-	-	-	-

	Health OR Los Angeles County Case-Control Studies of Ovarian Cancer											
WOC	Warsaw Ovarian Cancer Study	Poland	Self-administered questionnaire	-	Ever having disease	Ever having disease	Ever having disease	Ever having disease	Ever having disease	Ever having disease	Ever having disease	Ever having disease

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[2] Studies that provided information on progression-free survival
Abbreviations used: MRR-medical records review, Q-question.

Table 2. Associations between history of selected comorbidities and overall and progression-free survival: Ovarian Cancer Association Consortium.

Comorbidity	Deceased		HR(95% CI)[1,2]	Progression		HR(95% CI)[1,2]
	Yes	No		Yes	No	
Endometriosis						
No	6356	4824	1.00(ref)	2554	1329	1.00(ref)
Yes	571	853	0.92(0.84-1.01)	203	184	1.06(0.91-1.24)
Asthma						
No	2117	1393	1.00(ref)	1446	640	1.00(ref)
Yes	125	101	1.00(0.84-1.20)	89	50	0.93(0.75-1.16)
Depression						
No	2731	1647	1.00(ref)	1669	741	1.00(ref)
Yes	439	308	0.97(0.87-1.08)	202	98	0.90(0.76-1.07)
Osteoporosis						
No	2043	1405	1.00(ref)	1093	445	1.00(ref)
Yes	170	85	0.95(0.81-1.12)	76	21	0.96(0.73-1.27)
Autoimmune disease						
No	907	579	1.00(ref)	784	386	1.00(ref)
Yes	242	178	0.94(0.73-1.22)	162	76	0.95(0.74-1.23)
Kidney disease						
No	1739	1317	1.00(ref)	1004	516	1.00(ref)
Yes	48	37	1.19(0.89-1.60)	18	9	1.04(0.65-1.67)
Liver disease						
No	2186	1461	1.00(ref)	1485	664	1.00(ref)
Yes	31	15	0.98(0.68-1.41)	15	10	0.86(0.54-1.38)
Gallbladder disease						
No	2433	1626	1.00(ref)	1483	645	1.00(ref)
Yes	438	205	1.06(0.96-1.18)	254	88	1.09(0.94-1.26)
Neurological disease						
No	1156	1031	1.00(ref)	547	250	1.00(ref)
Yes	17	11	1.32(0.79-2.21)	9	8	0.82(0.41-1.68)

[1] models adjusted for age (continuous), stage (localized, regional, or advanced), histology, and study site

[2] studies included for each comorbidity as presented in Table 1