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# 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.

## Keywords

chronic diseases; comorbidities; ovarian cancer; survival; prognosis

## Introduction

Preexisting chronic diseases among ovarian cancer patients can result 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

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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 are shown in Supplemental 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 (number 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 1. 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 survival (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 include 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

**OCAC**     Ovarian Cancer Association Consortium

**OS**       overall survival

**PFS**      progression-free survival

**BMI**      body mass index

**Table 1**

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 | 1.19(0.89-1.60) | 162 | 76 | 0.95(0.74-1.23) |
| Kidney disease | | | | | | |
| No | 1739 | 1317 | 1.00(ref) | 1004 | 516 | 1.00(ref) |
| Yes | 48 | 37 | 0.98(0.68-1.41) | 18 | 9 | 1.04(0.65-1.67) |
| Liver disease | | | | | | |
| No | 2186 | 1461 | 1.00(ref) | 1485 | 664 | 1.00(ref) |
| Yes | 31 | 15 | | 15 | 10 | 0.86(0.54-1.38) |
| Gallbladder disease | | | | | | |
| No | 2433 | 1626 | 1.00(ref) | 1483 | 645 | 1.00(ref) |

| Comorbidity | Deceased | | HR(95% CI)[1,2] | Progression | | HR(95% CI)[1,2] |
|---|---|---|---|---|---|---|
| | Yes | No | | Yes | No | |
| 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 Supplemental Table 1