

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

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Running title: comorbidities and ovarian cancer prognosis

Keywords: chronic diseases, comorbidities, ovarian cancer, survival, prognosis

Financial support:

A.N. Minlikeeva was supported by National Cancer Institute (NCI) Interdisciplinary Training Grant in Cancer Epidemiology R25CA113951; J. L. Freudenheim was supported by National Institute of Health (NIH)/NCI (2R25CA113951); G. Friel was supported by NIH/NCI (R01CA095023 and R01CA126841); K.H.Eng was supported by NIH/NLM (K01LM012100) and the Roswell Park Alliance Foundation; J.B. Szender was supported by 5T32CA108456; B.H. Segal was supported by NIH (R01CA188900); K.B. Moysich was supported by NIH/NCI (2R25CA113951, R01CA095023, R01CA126841, P50CA159981) and the Roswell Park Alliance Foundation;

AOV was supported by the Canadian Institutes for Health Research (MOP-86727); AUS was supported by U.S. Army Medical Research and Materiel Command (DAMD17-01-1-0729), National Health & Medical Research Council of Australia (199600 and 400281), Cancer Councils of New South Wales, Victoria, Queensland, South Australia and Tasmania, Cancer Foundation of Western Australia; BAV was supported by ELAN Funds of the University of Erlangen-Nuremberg; CON was supported by NIH (R01-CA074850 and R01-CA080742); DOV was supported by NIH (R01-CA112523 and R01-CA87538); GER was supported by German Federal Ministry of Education and Research, Program of Clinical Biomedical Research (01GB9401) and German Cancer Research Center; HAW was supported by NIH (R01-CA58598, N01-CN-55424 and N01-PC-67001); HJO was supported by Funding: Intramural funding; Rudolf-Bartling Foundation; HOP was supported by Department of Defense (DOD): DAMD17-02-1-0669 and NIH/NCI (K07-CA080668, R01-CA95023, P50-CA159981, and R01-CA126841); JPN was supported by Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare; LAX was supported by American Cancer Society Early Detection Professorship (SIOP-06-258-01-COUN) and the National Center for Advancing Translational Sciences (NCATS), Grant UL1TR000124; MAC and MAY were supported by NIH (R01-CA122443, P30-CA15083, P50-CA136393), Mayo Foundation, Minnesota Ovarian Cancer Alliance, and Fred C. and Katherine B; MAL was supported by NIH/NCI (R01-CA61107), Danish Cancer Society (research grant 94 222 52), and the Mermaid I project; NCO was supported by NIH (R01-CA76016) and the DOD (DAMD17-02-1-0666); NEC was supported by NIH (R01-CA54419 and P50-CA105009) and DOD (W81XWH-10-1-02802); NJO was supported by NIH/NCI (K07 CA095666, K22-CA138563, and P30-CA072720) and the Cancer Institute of New Jersey; NTH was supported by Radboud University Medical Centre; TBO was supported by NIH (R01-CA106414-A2), American Cancer Society (CRTG-00-196-01-CCE), DOD (DAMD17-98-1-8659), and Celma Mastery Ovarian Cancer Foundation; UCI was supported by NIH R01-CA058860, and the Lon V Smith Foundation grant LVS-39420; UKO was funded by The Eve Appeal (The Oak Foundation) and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre; USC was supported by P01CA17054, P30CA14089, R01CA61132, N01PC67010, R03CA113148, R03CA115195, N01CN025403, and California Cancer Research Program (00-01389V-20170, 2II0200); WOC was supported by Polish Ministry of Science and Higher Education (4 PO5C 028 14, 2 PO5A 068 27), The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland.

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Conflict of interest: No potential conflicts of interest were disclosed.

Word count:...

Total number of tables: 2

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 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 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 ($18.5 \text{ kg/m}^2 < \text{body mass index (BMI)} < 25.0 \text{ kg/m}^2$ vs. $\text{BMI} \geq 25.0 \text{ kg/m}^2$), 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.

Acknowledgements:

The AOV group thanks Jennifer Koziak, Mie Konno, Michelle Darago, Faye Chambers and the Tom Baker Cancer Centre Translational Laboratories. The Australian Ovarian Cancer Study Management Group (D. Bowtell, G. Chenevix-Trench, A. deFazio, D. Gertig, A. Green, P. Webb) and ACS Investigators (A. Green, P. Parsons, N. Hayward, P. Webb, D. Whiteman) thank all the clinical and scientific collaborators (see <http://www.aocstudy.org/>) and the women for their contribution. The cooperation of the 32 Connecticut hospitals, including Stamford Hospital, in allowing patient access, is gratefully acknowledged (CON). This study was approved by the State of Connecticut Department of Public Health Human Investigation Committee. Certain data used in this study were obtained from the Connecticut Tumor Registry in the Connecticut Department of Public Health. The authors assume full responsibility for analyses and interpretation of these data. The German Ovarian Cancer Study (GER) thanks Ursula Eilber for competent technical assistance. The Hannover-Jena Ovarian Cancer Study (HJO) thanks Rüdiger Klapdor for his help in collecting comorbidity data. UKO study group thanks I. Jacobs, M. Widschwendter, E. Wozniak, A. Ryan, J. Ford and N. Balogun for their contribution to the study.

References

1. Maas HA, Kruitwagen RF, Lemmens VE, Goey SH, Janssen-Heijnen ML. The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: a population-based study. *Gynecol Oncol. United States* 2005. p. 104-9.
2. Sperling C, Noer MC, Christensen IJ, Nielsen ML, Lidegaard O, Hogdall C. Comorbidity is an independent prognostic factor for the survival of ovarian cancer: a Danish register-based cohort study from a clinical database. *Gynecol Oncol.* 2013;129:97-102.
3. Tetsche MS, Dethlefsen C, Pedersen L, Sorensen HT, Norgaard M. The impact of comorbidity and stage on ovarian cancer mortality: a nationwide Danish cohort study. *BMC Cancer.* 2008;8:31.
4. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol.* 2005;55:231-40.
5. O'Malley CD, Cress RD, Campleman SL, Leiserowitz GS. Survival of Californian women with epithelial ovarian cancer, 1994-1996: a population-based study. *Gynecol Oncol.* 2003;91:608-15.
6. Tingulstad S, Skjeldestad FE, Halvorsen TB, Hagen B. Survival and prognostic factors in patients with ovarian cancer. *Obstet Gynecol.* 2003;101:885-91.
7. Minlikeeva AN, Freudenheim JL, Cannioto RA, Szender JB, Eng KH, Modugno F, et al. History of hypertension, heart disease, and diabetes and ovarian cancer patient survival: evidence from the ovarian cancer association consortium. *Cancer Causes Control.* 2017.
8. Hemminki K, Liu X, Ji J, Försti A, Sundquist J, Sundquist K. Effect of autoimmune diseases on risk and survival in female cancers. *Gynecol Oncol.* 2012;127:180-5.

Table 1. Characteristics of studies included in the analysis: Ovarian Cancer Association Consortium¹.												
Study acronym	Study name	Study location, year of diagnosis	Data collection method	Endometriosis	Asthma	Auto immune	Depression	Osteoporosis	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	Hospital-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

AOV: Kelemen LE, Köbel M, Chan A, Taghaddos S, Dinu I. Differentially methylated loci distinguish ovarian carcinoma histological types: Evaluation of a DNA methylation assay in FFPE tissue. *Biomed Res Int Pathol* 2013;2013:815894.

AUS: Merritt MA, Green AC, Nagle CM, Webb PM, Australian Cancer Study, Australian Ovarian Cancer Study Group. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer*, 2008; 122: 170-6. (PMID 17721999)

BAV, HJO: Song H, Ramus SJ, Tyrer J, Bolton KL, Gentry-Maharaj A, Wozniak E, Anton-Culver H, Chang-Claude J, Cramer DW, DiCiccio R, Dörk T, Goode EL, Goodman MT, Schildkraut JM, Sellers T, Baglietto L, Beckmann MW, Beesley J, Blaakaer J, Carney ME, Chanock S, Chen Z, Cunningham JM, Dicks E, Doherty JA, Dürst M, Ekici AB, Fenstermacher D, Fridley BL, Giles G, Gore ME, De Vivo I, Hillemanns P, Hogdall C, Hogdall E, Iversen ES, Jacobs IJ, Jakubowska A, Li D, Lissowska J, Lubiński J, Lurie G, McGuire V, McLaughlin J, Medrek K, Moorman PG, Moysich K, Narod S, Phelan C, Pye C, Risch H, Runnebaum IB, Severi G, Southey M, Stram DO, Thiel FC, Terry KL, Tsai YY, Tworoger SS, Van Den Berg DJ, Vierkant RA, Wang-Gohrke S, Webb PM, Wilkens LR, Wu AH, Yang H, Brewster W, Ziogas A; Australian Cancer (Ovarian) Study; Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium, Houlston R, Tomlinson I, Whittemore AS, Rossing MA, Ponder BA, Pearce CL, Ness RB, Menon U, Kjaer SK, Gronwald J, Garcia-Closas M, Fasching PA, Easton DF, Chenevix-Trench G, Berchuck A, Pharoah PD, Gayther SA. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. *Nat Genet.* 2009 Sep;41(9):996-1000. Epub 2009 Aug 2. (PMID 19648919)

CON: Risch HA, Bale AE, Beck PA, Zheng W. PGR +331A/G and increased risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15:1738-41. (PMID 16985038)

DOV: Bodelon C, Cushing-Haugen KL, Wicklund KG, Doherty JA, Rossing MA. Sun exposure and risk of epithelial ovarian cancer. *Cancer Causes Control*.2012 Dec;23(12):1985-94. Epub 2012 Oct 12. (PMID: 23065074)

GER: Royar J, Becher H, Chang-Claude J. Low-dose oral contraceptives: protective effect on ovarian cancer risk. *Int J Cancer.* 2001 Nov 20;95(6):370-4. (PMID 11668519)

HAW: Goodman MT, Lurie G, Thompson PJ, McDuffie KE, Carney ME. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. *Endocr Relat Cancer.* Dec2008; 15(4):1055-1066. (PMID 18667686)

HOP: Lo-Ciganic WH, Zgibor JC, Bunker CH, Moysich KB, Edwards RP, Ness RB. Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology.* 2012 Mar;23(2):311-9. doi:10.1097/EDE.0b013e3182456ad3. (PMID: 22252409)

JPN: Hamajima N, Matsuo K, Saito T, Hirose K, Inoue M, Takezaki T, Kuroishi T, Tajima K. Gene-environment Interactions and Polymorphism Studies of Cancer Risk in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center II (HERPACC-II). *Asian Pac J Cancer Prev.* 2001, 2(2):99-107. (PMID 12718640)

MAY: Goode EL, Chenevix-Trench G, Hartmann LC, Fridley BL, Kalli KR, Vierkant RA, Larson MC, White KL, Keeney GL, Oberg TN, Cunningham JM, Beesley J, Johnatty SE, Chen X, Goodman KE, Armasu SM, Rider DN, Sicotte H, Schmidt MM, Elliott EA, Høgdall E, Kjaer SK, Fasching PA, Ekici AB, Lambrechts D, Despierre E, Høgdall C, Lundvall L, Karlan BY, Gross J, Brown R, Chien J, Duggan DJ, Tsai YY, Phelan CM, Kelemen LE, Peethambaram PP, Schildkraut JM, Shridhar V, Sutphen R, Couch FJ, Sellers TA; Ovarian Cancer Association Consortium. Assessment of hepatocyte growth factor in ovarian cancer mortality. *Cancer Epidemiol Biomarkers Prev.* 2011 Aug; 20(8):1638-48. (PMID 21724856)

MAL: Glud E, Kjaer SK, Thomasen BL, Hogdall C, Christensen L, Hogdall E, Bock JE, Blaakaer J. Hormone Therapy and the Impact of Estrogen Intake on the Risk of Ovarian Cancer. *Arch Intern Med* 2004; 164(29): 2253-2259. (PMID 15534163)

MAY: Kelemen LE, Sellers TA, Schildkraut JM, Cunningham JM, Vierkant RA, Pankratz VS, Fredericksen ZS, Gadre MK, Rider DN, Liebow M, Goode EL. Genetic variation in the one-carbon transfer pathway and ovarian cancer risk. *Cancer Res.* 2008 Apr 1;68(7):2498-506. (PMID 18381459)

NCO: Schildkraut JM, Iversen ES, Wilson MA, Clyde MA, Moorman PG, Palmieri RT, Whitaker R, Bentley RC, Marks JR and Berchuck A. Association between DNA damage response and repair genes and risk of invasive serous ovarian cancer. *PLoS One.* 2010 Apr 8;5(4):e10061. (PMID 20386703)

NEC: Terry KL, De Vivo I, Titus-Ernstoff L, Shih MC, Cramer DW. Androgen receptor cytosine, adenine, guanine repeats, and haplotypes in relation to ovarian cancer risk. *Cancer Res.* 2005;65:5974-81.(PMID 15994977)

NJO: Bandera EV, Williams-King MG, Chandran U, Paddock L, Rodriguez-Rodriguez L, Lu S-E, Faulkner S, Pulick K, Olson SH. Phytoestrogen consumption from food and supplements and ovarian cancer risk. *BMC Women's Health* 2011 Sept 23;11:40 . (PMID 21943063)

NTH : Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, Widschwendter M, Vierkant RA, Larson MC, Kjaer SK, Birrer MJ, Berchuck A, Schildkraut J, Tomlinson I, Kiemeny LA, Cook LS, Gronwald J, Garcia-Closas M, Gore ME, Campbell I, Whittemore AS, Sutphen R, Phelan C, Anton-Culver H, Pearce CL, Lambrechts D, Rossing MA, Chang-Claude J, Moysich KB, Goodman MT, Dörk T, Nevanlinna H, Ness RB, Rafnar T, Hogdall C, Hogdall E, Fridley BL, Cunningham JM, Sieh W, McGuire V, Godwin AK, Cramer DW, Hernandez D, Levine D, Lu K, Iversen ES, Palmieri RT, Houlston R, van Altena AM, Aben KK, Massuger LF, Brooks-Wilson A, Kelemen LE, Le ND, Jakubowska A, Lubinski J, Medrek K, Stafford A, Easton DF, Tyrer J, Bolton KL,

Harrington P, Eccles D, Chen A, Molina AN, Davila BN, Arango H, Tsai YY, Chen Z, Risch HA, McLaughlin J, Narod SA, Ziogas A, Brewster W, Gentry-Maharaj A, Menon U, Wu AH, Stram DO, Pike MC; Wellcome Trust Case-Control Consortium, Beesley J, Webb PM; Australian Cancer Study (Ovarian Cancer); Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium (OCAC), Chen X, Ekici AB, Thiel FC, Beckmann MW, Yang H, Wentzensen N, Lissowska J, Fasching PA, Despierre E, Amant F, Vergote I, Doherty J, Hein R, Wang-Gohrke S, Lurie G, Carney ME, Thompson PJ, Runnebaum I, Hillemanns P, Dürst M, Antonenkova N, Bogdanova N, Leminen A, Butzow R, Heikkinen T, Stefansson K, Sulem P, Besenbacher S, Sellers TA, Gayther SA, Pharoah PD; Ovarian Cancer Association Consortium (OCAC). A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. *Nat Genet.* 2010 Oct;42(10):874-9. Epub 2010 Sep 19. (PMID 20852632)

TBO: Pal T, Permuth-Wey J, Betts JA et al. (2005) BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer* 104:2807-2816 (PMID 16284991); Pal T, Permuth-Wey J, Kapoor R, Cantor A, Sutphen R. (2007) Improved survival in BRCA2 carriers with ovarian cancer. *Familial Cancer* 6:113-119 (PMID 17160431)

UCI: Ziogas A, Gildea M, Cohen P, Bringman D, Taylor TH, Seminara D, Barker D, Casey G, Haile R, Liao SY, Thomas D, Noble B, Kurosaki T, Anton-Culver H. Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2000 Jan;9(1):103-11. (PMID 10667470)

UKO: Balogun N, Gentry-Maharaj A, Wozniak EL, Lim A, Ryan A, Ramus SJ, Ford J, Burnell M, Widschwendter M, Gessler SF, Gayther SA, Jacobs IJ, Menon U. Recruitment of newly diagnosed ovarian cancer patients proved challenging in a multicentre biobanking study. *J Clin Epidemiol.* 2011 May;64(5):525-30. doi:10.1016/j.jclinepi.2010.07.008. Epub 2010 Nov 13. PubMed PMID: 21074968.

USC: Pike MC, Pearce CL, Peters R, Cozen W, Wan P, Wu AH. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study.

Infertility, Fertility Drugs, and Ovarian Cancer: A Pooled Analysis of Case-Control Studies. Roberta B. Ness, Daniel W. Cramer, Marc T. Goodman, Susanne Krüger Kjaer, Kathy Mallin, Berit Jul Mosgaard, David M. Purdie, Harvey A. Risch, Ronald Vergona, and Anna H. Wu. *Am J Epidemiol.* 2002 Feb 1;155(3):217-24. (PMID 11821246)

WOC: A novel germline PALB2 deletion in Polish breast and ovarian cancer patients. Dansonka-Mieszkowska A, Kluska A, Moes J, Dabrowska M, Nowakowska D, Niwinska A, Derlatka P, Cendrowski K, Kupryjanczyk J. *BMC Med Genet.* 2010 Feb 2;11:20. (PMID 20122277)

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