Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Predictors of Long-Term Survival among High-Grade Serous Ovarian Cancer Patients

Christina L. Clarke[1], Lawrence H. Kushi[2], Jessica Chubak[3], Pamala A. Pawloski[4], Joanna E. Bulkley[5], Mara M. Epstein[6,7], Andrea N. Burnett-Hartman[1], Bethan Powell[8], Celeste L. Pearce[9], and Heather Spencer Feigelson[1]

Abstract

Background: Relatively little is known about factors associated with long-term survival (LTS) following a diagnosis of ovarian cancer.

Methods: We conducted a retrospective study of high-grade serous ovarian cancer (HGSOC) to explore predictors of LTS (defined as $\geq$7 years of survival) using electronic medical record data from a network of integrated health care systems. Multivariable logistic regression with forward selection was used to compare characteristics of women who survived $\geq$7 years after diagnosis ($n = 148$) to those who died within 7 years of diagnosis ($n = 494$).

Results: Our final model included study site, age, stage at diagnosis, CA-125, comorbidity score, receipt of chemotherapy, BMI, and four separate comorbid conditions: weight loss, depression, hypothyroidism, and liver disease. Of these, only younger age, lower stage, and depression were statistically significantly associated with LTS.

Conclusions: We did not identify any new characteristics associated with HGSOC survival.

Impact: Prognosis of ovarian cancer generally remains poor. Large, pooled studies of ovarian cancer are needed to identify characteristics that may improve survival.

Introduction

Despite intense study, relatively little is known about factors associated with long-term survival (LTS) from ovarian cancer (1). Ovarian cancer is rare and survival is poor (47% 5-year survival; ref. 2). These characteristics make it difficult to study in a single institution or cohort. We conducted a retrospective observational study of high-grade serous ovarian cancer (HGSOC) to explore predictors of LTS, using data from five integrated health systems in the Cancer Research Network (CRN, https://crn.cancer.gov; ref. 3).

Materials and Methods

All data for this analysis were derived from the Virtual Data Warehouse (VDW), a common data model that includes standardized, individual-level data extracted from the electronic medical record from the participating sites (4). We identified all incident cases of ovarian cancer diagnosed between 2000 and 2008 at five integrated health systems affiliated with the CRN: Health Partners (Minnesota), and four Kaiser Permanente regions: Colorado, Northern California, Northwest, and Washington state. This study received Institutional Review Board approval and a waiver of informed consent.

We limited this analysis to cases of incident high-grade (grade 3 or 4) serous (morphology codes between 8440 and 8490) ovarian cancer, stages I–IV. We defined LTS as survival $\geq$7 years and used the VDW to follow patients through December 31, 2015 for death, disenrollment, or end of follow-up. Cases were included if they were age 18 years or older at diagnosis and enrolled continuously with a drug coverage in their health care plan for at least 1 year prior to diagnosis. Cases were excluded if they were known to be alive but disenrolled before 7 years of follow-up.

Logistic regression was employed to model associations between covariates and the outcome of LTS. All covariates were assessed in the year prior to diagnosis. We used forward-selection to build the model and retained all variables with a $P < 0.3$. We decided *a priori* that age, stage, and CA-125 level at diagnosis would be in the final model as these factors have been previously reported to be associated with survival among ovarian cancer cases (5, 6). We computed the Elixhauser comorbidity score (7) for each case and included individual components of the score in the model-building process if at least 20 patients had the condition. All analyses were conducted using SAS/STAT software, Version 9.4 (SAS Institute Inc.). We conducted a *post hoc* power calculation for our study. We had 80% power, using a two-sided test with an $\alpha = 0.05$, to

[1]Institute for Health Research, Kaiser Permanente Colorado, Denver, Colorado. [2]Division of Research, Kaiser Permanente Northern California, Oakland, California. [3]Health Research Institute, Kaiser Permanente Washington, Seattle, Washington. [4]HealthPartners Institute, Bloomington, Minnesota. [5]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon. [6]Meyers Primary Care Institute, Worcester, Massachusetts. [7]Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts. [8]Gynecologic Oncology Program, Kaiser Permanente Northern California, San Francisco, California. [9]School of Public Health, University of Michigan, Ann Arbor, Michigan.

Corresponding Author: Christina L. Clarke, Kaiser Permanente, Institute for Health Research, 2550 S. Parker Rd., Suite 200, Aurora, CO 80014. Phone: 303-636-2439; E-mail: Christina.L.Clarke@kp.org

doi: 10.1158/1055-9965.EPI-18-1324

Table 1. Characteristics of ovarian cancer cases at five Cancer Research Network sites stratified by survival time

Characteristic	All ($n = 642$)	Survived < 7 years ($n = 494$)	Survived ≥7 years ($n = 148$)	P^a
CRN Site				
Site 1	7 (1.1%)	5 (1%)	2 (1.4%)	0.070
Site 2	54 (8.4%)	48 (9.7%)	6 (4.1%)	
Site 3	68 (10.6%)	47 (9.5%)	21 (14.2%)	
Site 4	442 (68.8%)	335 (67.8%)	107 (72.3%)	
Site 5	71 (11.1%)	59 (11.9%)	12 (8.1%)	
Race/Ethnicity				
Non-Hispanic white	504 (78.5%)	391 (81.1%)	113 (76.9%)	0.392
Hispanic	62 (9.7%)	46 (9.5%)	16 (10.9%)	
Non-Hispanic Asian	36 (5.6%)	27 (5.6%)	9 (6.1%)	
Non-Hispanic black	24 (3.7%)	15 (3.1%)	9 (6.1%)	
Other/multi, non-Hispanic	3 (0.5%)	3 (0.6%)	0 (0%)	
Missing[b]	13 (2%)			
Age at diagnosis (years)				
18–49	73 (11.4%)	48 (9.7%)	25 (16.9%)	<0.001
50–59	182 (28.3%)	129 (26.1%)	53 (35.8%)	
60–69	190 (29.6%)	145 (29.4%)	45 (30.4%)	
≥70	197 (30.7%)	172 (34.8%)	25 (16.9%)	
Smoking Status				
Current	44 (6.9%)	33 (16%)	11 (15.5%)	0.410
Former	66 (10.3%)	53 (25.7%)	13 (18.3%)	
Never/Passive	167 (26%)	120 (58.3%)	47 (66.2%)	
Missing[b]	365 (56.9%)			
BMI Group (kg/m^2)				
Underweight/Normal (BMI = 13.0–24.9)	129 (20.1%)	93 (38.9%)	36 (47.4%)	0.289
Overweight (BMI = 25.0–29.9)	91 (14.2%)	74 (31%)	17 (22.4%)	
Obese (BMI≥30.0)	95 (14.8%)	72 (30.1%)	23 (30.3%)	
Missing[b]	327 (50.9%)			
AJCC Stage at diagnosis				
Stage I	45 (7.0%)	15 (3.0%)	30 (20.3%)	<0.001
Stage II	38 (5.9%)	20 (4.0%)	18 (12.2%)	
Stage III	363 (56.5%)	276 (55.9%)	87 (58.8%)	
Stage IV	196 (30.5%)	183 (37%)	13 (8.8%)	
Grade				
3	516 (80.4%)	402 (81.4%)	114 (77%)	0.243
4	126 (19.6%)	92 (18.6%)	34 (23%)	
Received chemotherapy treatment				
Yes	573 (89.3%)	434 (89.1%)	139 (93.9%)	
No	62 (9.7%)	53 (10.9%)	9 (6.1%)	0.085
Missing[b]	7 (1.1%)			
CA-125 Prior to treatment				
CA 125 < 35 (U/mL)	58 (9%)	34 (8.1%)	24 (17.8%)	0.001
CA 125 ≥ 35 (U/mL)	499 (77.7%)	388 (91.9%)	111 (82.2%)	
Missing[b]	85 (13.2%)			
Estrogen use				
≥2 pharmacy fills for systemic Estrogen in year prior to diagnosis	173 (26.9%)	135 (27.3%)	38 (25.7%)	0.691
≥2 pharmacy fills for non-systemic vaginal estrogen in year prior to diagnosis	27 (4.2%)	22 (4.5%)	5 (3.4%)	0.568
Private pay insurance plan				
Yes	166 (25.9%)	136 (27.8%)	30 (20.5%)	
No	469 (73.1%)	353 (72.2%)	116 (79.5%)	0.080
Missing[b]	7 (1.1%)			
Commercial insurance plan				
Yes	550 (85.7%)	415 (84.3%)	135 (91.8%)	
No	89 (13.9%)	77 (15.7%)	12 (8.2%)	0.021
Missing[b]	3 (0.5%)			

(Continued on the following column)

detect an OR >1.6 with one primary predictor. Power calculations were performed in PASS.

Results

We identified 2,388 incident stage I to IV ovarian cancers. Of these, we excluded 298 patients who were not enrolled at least 1 year prior to diagnosis with a drug coverage benefit, and 160 who did not have a record of death and were not continuously enrolled at least 7 years post diagnosis. There were an additional 1,288 cancers that were not high-grade serous tumors, of those, 62% ($n = 578$) were missing information to classify the tumor grade. This left a total of 642 high-grade serous ovarian cancers for analysis.

Table 1 shows the characteristics that were considered for inclusion in the logistic regression model. The median survival time was 38 months [95% confidence interval (CI): 35–42 months]; 148 (23%) survived at least 7 years and were considered LTSs, while the remainder ($N = 494$, 77%) survived fewer than 7 years. Our final logistic regression model included study site, age, stage at diagnosis, CA-125 (categorized as <35 or ≥35 U/mL), comorbidity score (categorized as 0, 1, 2, or ≥3), receipt of chemotherapy, body mass index (BMI, in categories), and four separate comorbid conditions: weight loss, depression, hypothyroidism, and liver disease (see Fig. 1 for ORs and 95% CIs). Information on BMI and smoking status were missing in approximately half of the population. Patients diagnosed at an earlier stage had statistically significantly higher odds of LTS than patients diagnosed at a later stage ($P < 0.0001$). Younger patients were statistically more likely to survive than older patients ($P = 0.009$), and a diagnosis of depression within the year prior to a cancer diagnosis was inversely associated with LTS ($P = 0.011$). Our final model had a c-statistic of 0.806 suggesting a strong model fit.

Table 1. Characteristics of ovarian cancer cases at five Cancer Research Network sites stratified by survival time (Cont'd)

Characteristic	All ($n = 642$)	Survived < 7 years ($n = 494$)	Survived ≥7 years ($n = 148$)	P^a
Elixhauser score in the year prior to diagnosis				
0	150 (23.4%)	113 (22.9%)	37 (25%)	0.054
1	175 (27.3%)	125 (25.3%)	50 (33.8%)	
2	130 (20.2%)	100 (20.2%)	30 (20.3%)	
≥3	187 (29.1%)	156 (31.6%)	31 (20.9%)	
Individual Elixhauser-scored conditions where $n \geq 20$				
Arrhythmia	55 (8.6%)	47 (9.5%)	8 (5.4%)	0.117
Congestive heart failure	24 (3.7%)	22 (4.5%)	2 (1.4%)	0.081
Chronic pulmonary disease	109 (17%)	84 (17%)	25 (16.9%)	0.975
Depression	91 (14.2%)	76 (15.4%)	15 (10.1%)	0.108
Diabetes	72 (11.2%)	61 (12.3%)	11 (7.4%)	0.096
Drug abuse	25 (3.9%)	19 (3.8%)	6 (4.1%)	0.909
Fluid and electrolyte disorders	57 (8.9%)	50 (10.1%)	7 (4.7%)	0.043
Hypertension	265 (41.3%)	207 (41.9%)	58 (39.2%)	0.556
Hypothyroidism	96 (15%)	83 (16.8%)	13 (8.8%)	0.016
Liver disease	22 (3.4%)	21 (4.3%)	1 (0.7%)	0.036
Weight loss	39 (6.1%)	36 (7.3%)	3 (2.0%)	0.019

[a]χ^2 P value.
[b]Missing values not included in statistical calculations of χ^2 tests. All categories include missing for "all" group only.

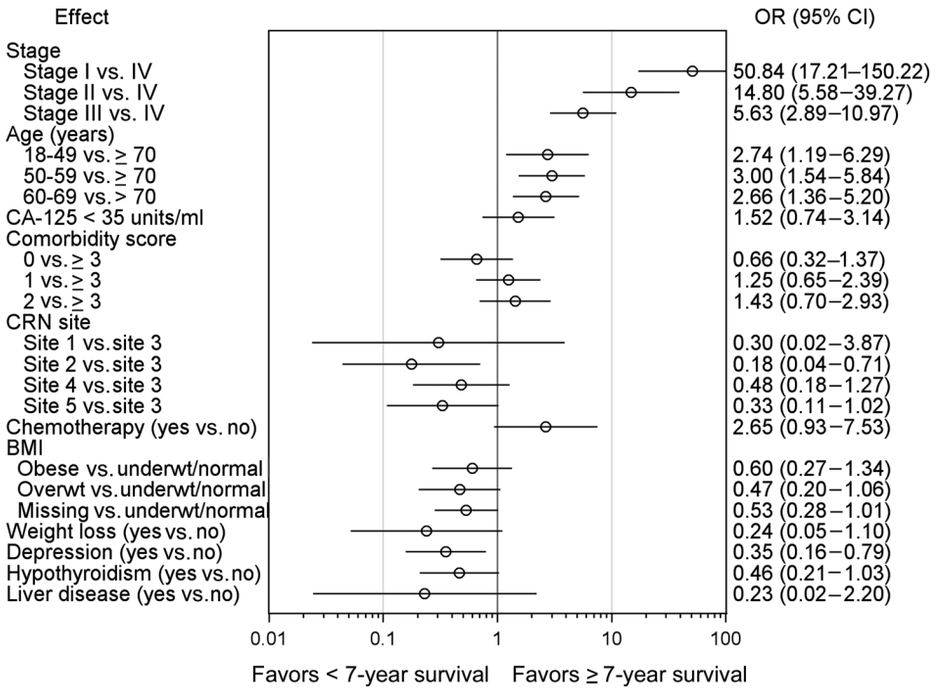

Figure 1.

Multivariable adjusted ORs and 95% confidence intervals for factors associated with LTS of incident high-grade serous ovarian cancer.

Discussion

In this exploratory analysis using electronic medical record data, we did not identify any new medical conditions or characteristics that may be associated with LTS of HGSOC. Others (8) have reported on comorbidities associated with ovarian cancer survival with mixed results. The strengths of this study include a rich data resource of an insured population that allows for detailed capture of comorbidities, treatment, and follow-up. However, we lacked information on BMI and smoking status on a large proportion of the study population. We had no data on family history or genetic susceptibility that would have strengthened our analysis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L.H. Kushi, P.A. Pawloski, B. Powell, C.L. Pearce, H.S. Feigelson

Development of methodology: C.L. Clarke, L.H. Kushi, P.A. Pawloski, J.E. Bulkley, A.N. Burnett-Hartman, B. Powell, H.S. Feigelson

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.L. Clarke, L.H. Kushi, J. Chubak, P.A. Pawloski, J.E. Bulkley, M.M. Epstein, B. Powell, H.S. Feigelson

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.L. Clarke, J. Chubak, P.A. Pawloski, J.E. Bulkley, M.M. Epstein, B. Powell, H.S. Feigelson

Writing, review, and/or revision of the manuscript: C.L. Clarke, L.H. Kushi, J. Chubak, P.A. Pawloski, J.E. Bulkley, M.M. Epstein, A.N. Burnett-Hartman, B. Powell, C.L. Pearce, H.S. Feigelson

Study supervision: H.S. Feigelson

Acknowledgments

This work was conducted in the Cancer Research Network (CRN) funded by the NCI (U24CA171524). M.M. Epstein received additional support by a grant from The University of Massachusetts Center for Clinical and Translational Science (KL2TR01455). C.L. Pearce received grant funding from the NCI (P30 CA046592).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received December 13, 2018; revised February 5, 2019; accepted February 15, 2019; published first April 9, 2019.

References

1. Hoppenot C, Eckert MA, Tienda SM, Lengyel E. Who are the long-term survivors of high grade serous ovarian cancer? Gynecol Oncol 2018;148:204–12.
2. American Cancer Society. Cancer Statistics Center. Available from: http://cancerstatisticscenter.cancer.org.
3. Chubak J, Ziebell R, Greenlee RT, Honda S, Hornbrook MC, Epstein M, et al. The Cancer Research Network: a platform for epidemiologic and health services research on cancer prevention, care, and outcomes in large, stable populations. Cancer Causes Control 2016;27:1315–23.

4. Ross TR, Ng D, Brown JS, Pardee R, Hornbrook MC, Hart G, et al. The HMO Research Network Virtual Data Warehouse: a public data model to support collaboration. EGEMS 2014;2:1049.
5. Cress RD, Chen YS, Morris CR, Petersen M, Leiserowitz GS. Characteristics of long-term survivors of epithelial ovarian cancer. Obstet Gynecol 2015;126: 491–7.
6. Hamilton CA, Miller A, Casablanca Y, Horowitz NS, Rungruang B, Krivak TC, et al. Clinicopathologic characteristics associated with long-term survival in advanced epithelial ovarian cancer: an NRG Oncology/Gynecologic Oncology Group ancillary data study. Gynecol Oncol 2018;148:275–80.
7. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8–27.
8. Minlikeeva AN, Freudenheim JL, Eng KH, Cannioto RA, Friel G, Szender JB, et al. History of comorbidities and survival of ovarian cancer patients, results from the Ovarian Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2017;26:1470–3.