Impact of Cardiovascular Comorbidity on Ovarian Cancer Mortality

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Abstract

Background: A retrospective cohort study utilizing prospectively collected data was conducted from August 2003 until March 2008 at M.D. Anderson Cancer Center. It is unknown whether cardiovascular comorbidity and chronic stress impact ovarian cancer outcome, which remains poor despite advances in therapy. The purpose of this study was to determine whether cardiovascular disease and markers that may be associated with stress are also associated with survival in patients with ovarian cancer.

Methods: Participants with newly diagnosed epithelial ovarian cancer were followed until time of death or truncation of study period (median follow-up = 4.2 years; n = 271). Tumor characteristics (stage, tumor grade, histology, debulking status), demographic variables, and cardiovascular comorbidity were documented and compared to overall survival.

Results: Of the nine cardiovascular events tracked during follow-up, venous thromboembolism [VTE; HR, 3.2; 95% confidence interval (CI), 1.8–5.5] and pulmonary hypertension (HR, 8.5; 95% CI, 3.9–18.7) were associated with shorter survival in multivariate analysis. In addition, high tumor grade, suboptimal cytoreduction, and baseline heart rate (HR, 1.02; 95% CI, 1.01–1.04) were related to decreased survival.

Conclusion: Careful management of certain cardiovascular comorbidities may extend survival in patients with ovarian cancer. Our findings suggest that increased baseline heart rate and the development of VTE and pulmonary hypertension after cancer diagnosis may be significant predictors of survival in women with ovarian cancer.

Impact: Our study emphasizes the importance of identifying and optimally treating tachycardia, VTE, and pulmonary hypertension in conjunction with cancer therapy.

Introduction

Ovarian cancer is the most lethal gynecologic cancer, for which 5-year survival rate is 15% to 30% (1, 2). Despite advances in therapy over the past 20 years, life expectancy has increased just 1.9 years, with overall median survival approximating 35 months (3, 4). As a less direct avenue toward extending survival, managing cardiovascular comorbidities may prove to be fruitful as cardiovascular comorbidities affect up to 60% of patients with ovarian cancer (5). A prospective study of 5,213 patients with ovarian cancer found that severe comorbidities were associated with increased mortality at 1 and 5 years (6). However, other population-based studies found no association (7–9). Beyond this potentially contradictory result, there is a lack of information on the effects of specific cardiovascular comorbidities as previous studies analyzed aggregate indices of comorbid severity rather than individual comorbidity diseases. It is unclear whether patients with comorbid cardiovascular disease are treated less aggressively as has been suggested for large retrospective studies in breast cancer (10). Thus, a detailed study of cardiovascular comorbidities that controls for tumor and treatment indices could clarify if cardiovascular disease has a significant impact on ovarian cancer outcome.

Furthermore, chronic psychological stress may be a significant factor in cancer progression (11, 12). Two recent meta-analyses have reported independent effects for chronic stress and depression on survival after adjustment for tumor characteristics in patients with breast, lung, head and neck, hepatobiliary cancers, and leukemia (13, 14). As an initial step to identifying a link between cancer and stress, our study was designed to examine whether cardiovascular comorbidities and chronic stress are associated with ovarian cancer outcome.
psychological stress and ovarian cancer outcomes, we examined whether sympathetically driven cardiovascular markers that have previously been linked with chronic stress, that is, elevated heart rate and hypertension, were associated with decreased survival in ovarian cancer (15–17). Therefore, we examined the effect of heart rate and hypertension recorded at cancer diagnosis, as well as cardiovascular disease events occurring after cancer diagnosis, on patient survival.

Materials and Methods

Patients

Following Institutional Review Board (IRB) approval, we retrospectively evaluated the electronic medical records of 271 newly diagnosed histologically confirmed patients with epithelial ovarian cancer receiving treatment at the University of Texas MD Anderson Cancer Center; complete data were available for 246 (or 91%) participants. All participants had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Participants who had provided informed consent and enrolled into a larger prospective psychosocial study between August 2003 and December 2006 were eligible. Women with recurrent ovarian cancer or with a primary cancer of nonepithelial ovarian or nonovarian origin were ineligible.

Pre- and post-surgery care. Shortly after diagnosis, all patients in the sample received a preoperative work-up before surgery. As part of this work-up, cardiovascular comorbidities and cardiovascular disease (CVD) risks [heart rate, blood pressure, cardiovascular family disease history, body mass index (BMI), smoking status, diabetes mellitus, or hyperlipidemia], were assessed and recorded in the medical record for each participant. Patients who did not meet ECOG 0–1 performance status were not eligible for debulking surgery. Following surgery, patients were on anticoagulation therapy from time of surgery to discharge (average 5–7 days); length of anticoagulation therapy did not change during the study period. Post-surgery, all patients received at least six cycles of adjuvant paclitaxel and platinum chemotherapy. Cancer treatment was individualized for each participant on the basis of the extent of her ovarian cancer. All comorbid cardiovascular conditions and incident events were managed with a multidisciplinary approach utilizing MD Anderson’s cardiology and internal medicine services throughout follow-up.

Definition of demographics and tumor characteristics. The following information was abstracted at the time of first diagnosis of epithelial ovarian cancer: Age (years); Tumor grade dichotomized into low versus high grade; Debulking status categorized into 2 levels: (i) optimal (between 0 and 1 cm of residual disease, which was the surgical standard during the study period) and (ii) suboptimal (0–1 cm of residual disease). Stage was dichotomized into early stage (I–II) versus late stage (III–IV) according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines (staged I, II, III, or IV). Tumor grade was assessed by pathology reports (low vs. high grade). Marital/partner status information was collected from the parent study using deidentified questionnaires and dichotomized into either living with a spouse or significant other versus living alone.

Baseline heart rate and hypertension. Heart rate (pulse) was defined as continuous, but dichotomized into tachycardia for the univariate model using a cutoff of \( \geq 100 \) heart beats per minute. Hypertension was defined as having a recorded blood pressure of at least 140 mm/Hg systolic and 90 mm/Hg diastolic pressure on at least three occasions within the first month after cancer diagnosis, or a previously established diagnosis requiring antihypertensive therapy.

Baseline control risk factors. BMI was initially categorized into underweight/normal weight (BMI < 25), overweight (BMI at least 25 but less than 30), and obese/morbidly obese (BMI \( \geq 30 \)), but it was found to have a linear risk, so it was included in the final model without categorization. Diabetes mellitus was present if a previously established diagnosis required therapy. Smoking was categorized into three levels: (i) current smoker, (ii) ever smoked if the patient had smoked more than 100 cigarettes in her lifetime, and (iii) never smoked (100 cigarettes or less). Hyperlipidemia was present if LDL was 100 mg/dl or higher or the patient was on therapy.

CVD incidents occurring after initial cancer diagnosis. The following information was abstracted from each patient’s medical record during her follow-up period. All cardiology, laboratory, radiology, emergency center, and gynecologic oncology records (including all scanned documents from outside healthcare institutions) were evaluated. Pulmonary embolus/deep venous thrombosis (VTE) was confirmed by any standard imaging modality such as ultrasound, computed tomography (CT), or high probability V/Q scan. Myocardial infarction was defined by standard criteria with cardiac biomarker elevation or electrocardiogram findings and/or regional wall motion abnormalities noted on echocardiography. Transient ischemic attack (TIA) or cerebral vascular accident (CVA) was documented if any transcribed dictation from any service confirmed its occurrence. Pericardial disease/cardiac tamponade was documented if an echocardiogram noted “tamponade,” “pericardial disease,” “significant pericardial effusion” or if a pericardiocentesis was conducted. Coronary artery disease (CAD) was defined with established CAD present on angiography or cardiac ischemia confirmed by symptoms and electrocardiographic (EKG) changes on at least 2 separate occasions. Cardiomyopathy was defined with a reduction in left ventricular ejection fraction (LVEF) by echocardiography to <0.50. Pulmonary hypertension was documented if elevated pressures were noted on echocardiography with an estimated pulmonary artery pressure \( >45 \) mmHg. Heart failure was documented as present if right or left "congestive heart failure" was documented by clinical findings, laboratory tests, and/or X-ray abnormalities. Valvular
disease was defined as at least moderate valvular disease noted on echocardiography.

**Statistical methods**

For the univariate analyses, demographics, tumor characteristics, cardiovascular baseline factors, and CVD events were each analyzed to determine if they were related to survival. Kaplan–Meier survival curves were plotted to examine time to death for significant cardiovascular risk factors and other potential risk factors. Median survival times, log-rank tests, and univariate proportional hazards models were also calculated.

Next, a multivariate proportional hazards model was created to examine the effect of potential risk factors on time to death. A model was created containing all variables that were thought to be related to outcome (tumor characteristics, demographics, all cardiovascular risk factors) and CVD events that were significant in univariate analyses at \( P < 0.2 \). CVD incidents occurring during the study follow-up period were entered into the multivariate survival analysis. Given the large number of covariates in the model in proportion to the number of events, we were concerned we would not have enough power to detect important predictors of survival and therefore employed backward selection to keep only those variables that were statistically significant at \( P < 0.10 \) for inclusion in the reduced model. For the reduced model, significance was tested using two-sided alpha \( \leq 5\% \).

**Results**

Fifty-three percent of patients were alive at the end of the study period and were censored for all survival time analyses \((n = 144)\). For the remaining 47% \((n = 127)\), cause of death was persistent or recurrent ovarian cancer or complications associated with cancer disease and treatment. Forty-nine percent of patients \((n = 133)\) experienced a comorbid CVD during the study period (TIA/CVA, congestive heart failure, PE/DVT, myocardial infarction, pericardial disease/tamponade, CAD, cardiomyopathy, pulmonary hypertension, valvular disease). The mean follow-up time was 4.24 years (median survival time was 3.5 years). The median age of the sample was 57, ranging from 24 to 85 years (see Table 1 for sample characteristics and Table 2 for the prevalence of incident CVD events).

**Univariate analyses**

Age, high-grade tumor, high-stage disease, suboptimal cytoreduction, and baseline tachycardia were significantly associated with shortened survival (Table 3 and Fig. 1A and B). Patients with tachycardia at cancer diagnosis had a median survival of 4.0 years compared with 5.9 years for patients without tachycardia (32% reduction). Neither BMI, education, smoking status, baseline diabetes status, nor hyperlipidemia were significantly associated with survival.

Regarding the 9 CVD endpoints tracked during study follow-up, VTE, pulmonary hypertension, and pericardial disease/tamponade were associated with shorter survival times (Table 3 and Fig. 1). Patients with VTE after cancer diagnosis had a mean survival of 4.1 years compared to 6.4 years for patients without VTE (36% reduction in length of survival). Patients with pulmonary hypertension experienced similar reductions in survival time (Table 4). Contrary to the expectation that patients died shortly after experiencing these cardiovascular events,
less than 15% of the patients died within 1 month of the respective cardiovascular event.

**Multivariate proportional hazards model for survival using time-dependent cardiac disease covariates**

Backward elimination resulted in the following reduced model with terms significant at \( P < 0.10 \): tumor grade, tumor stage, suboptimal cytoreduction, BMI, heart rate, smoking status, VTE, and pulmonary hypertension. In the reduced model, baseline heart rate \([HR, 1.02 \text{ for each beat per minute increase}; 95\% \text{ confidence interval (CI), 1.01–1.04}] \) remained significantly associated with survival (Table 5), as did VTE (HR, 3.2; 95% CI, 1.8–5.5), pulmonary hypertension (HR, 8.5; 95% CI, 3.9–18.7), high-grade disease (HR, 2.1; 95% CI, 1.1–4.1), and suboptimal cytoreduction (HR, 1.9; 95% CI, 1.3–2.9); tumor stage, BMI, and smoking status dropped from significance.

### Table 2. Prevalence of incident cardiovascular events during follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Total n (%)</th>
<th>Within 1 y n (%)</th>
<th>After 1 y n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attack/cerebral vascular accident</td>
<td>18 (7)</td>
<td>0 (0)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>13 (5)</td>
<td>1 (17)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Diastolic heart failure</td>
<td>8 (3)</td>
<td>1 (0)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Systolic heart failure</td>
<td>4 (1)</td>
<td>1 (0)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>20 (7)</td>
<td>1 (17)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (4)</td>
<td>0 (0)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Pericardial disease/tamponade or pericardiocentesis procedure</td>
<td>22 (8)</td>
<td>0 (0)</td>
<td>22 (8)</td>
</tr>
<tr>
<td>VTE</td>
<td>39 (14)</td>
<td>1 (17)</td>
<td>38 (14)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>8 (3)</td>
<td>0 (0)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>21 (8)</td>
<td>2 (33)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>22 (8)</td>
<td>1 (17)</td>
<td>21 (8)</td>
</tr>
</tbody>
</table>

### Table 3. Univariate HRs for survival time

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of patients</th>
<th>No. of deaths</th>
<th>HR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>32</td>
<td>12</td>
<td>1.9 (1.02–3.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>High grade</td>
<td>239</td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonserous</td>
<td>50</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>221</td>
<td>104</td>
<td>0.8 (0.5–1.3)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Cytoreduction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic/optimal ((\leq 1 \text{ cm}))</td>
<td>187</td>
<td>77</td>
<td>2.0 (1.4–2.8)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Suboptimal ((&gt;1 \text{ cm}))</td>
<td>83</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate at cancer diagnosis</strong></td>
<td></td>
<td></td>
<td>1.02 (1.01–1.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>232</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>31</td>
<td>2.2 (1.4–3.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Pulmonary hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>250</td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>12</td>
<td>1.8 (0.98–3.2)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
significant. For the analyses examining VTE, increased heart rate (OR = 1.03, \( P = 0.0441 \)) was significant.

**Discussion**

The key findings of this study are that certain cardiovascular comorbidities (heart rate at diagnosis; VTE and pulmonary hypertension occurring after diagnosis) are independently related to reduced survival after controlling for tumor stage, grade, and extent of cytoreduction.

Important cardiovascular comorbidities are common in patients with cancer, ranging from 12% to 60% incidence (18). While several population-based studies of patients with lung, breast, and colorectal cancer have reported poorer prognoses for patients with comorbid disease after controlling for treatment complications and treatment strategy (19–23), there is paucity of information in women with ovarian cancer. A report from the Danish National Hospital Discharge Registry with 5,213 patients with ovarian cancer revealed that severity of comorbidity was associated with shortened survival after controlling for age, stage, treatment, and time (6). In contrast, three other population-based studies found no association with severity of comorbidity (7–9). It is essential to note that the negative studies measured established comorbidity at a single time point (i.e., cancer diagnosis). This is significant because ovarian cancer tends to have an eventful

**Table 4.** Median length of survival in years

<table>
<thead>
<tr>
<th>Cardiac comorbidity</th>
<th>No comorbidity median</th>
<th>Comorbidity median</th>
<th>Reduction in survival time (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia at cancer diagnosis</td>
<td>5.9</td>
<td>4.0</td>
<td>1.9 (32)</td>
</tr>
<tr>
<td>VTE</td>
<td>6.4</td>
<td>4.1</td>
<td>2.3 (36)</td>
</tr>
<tr>
<td>Pulmonary HTN</td>
<td>5.9</td>
<td>3.4</td>
<td>2.5 (42)</td>
</tr>
</tbody>
</table>
course marked by multiple recurrences and chemotherapy regimens, resulting in increased risk for developing cardiovascular morbidity during the course of their disease. The negative population-based studies also relied solely on aggregate measures of comorbidity, such as the Charlson index; whereas two of the positive studies analyzed associations of specific comorbid events, such as VTE and diabetes, with mortality (23, 24).

Others have reported that VTE is associated with increased mortality in patients with cancer and that the coagulation cascade are linked with tumor growth (25–27). In particular, several studies have noted that VTE tended to occur within the first few months or the first year after cancer diagnosis (25, 28). However, our data show that 8 of the 39 patients developed VTE within the first 3 months after cancer diagnosis. Of those studies that reported the time interval from VTE diagnosis to death, most reported that death occurred within a few months of the VTE (28). In contrast, our study showed that patients tended to live an average of 22 months post-VTE diagnosis. Comorbidities generally influence how aggressively ovarian cancer may be treated (7). However, all patients in our study were treated with the preferred regimen of surgery plus platinum-based chemotherapy. This makes it unlikely that our results can be explained by patients with comorbidities receiving less aggressive treatment.

Possible explanations for the poorer outcome associated with higher heart rate at diagnosis might include decreased cardiorespiratory fitness or chronic biobehavioral stress. The direct impact of higher heart rate is consistent with other studies linking chronic stress and heart rate in both cancer and noncancer patient samples (29, 30). For example, in a prospective cohort study with 49 patients with breast and prostate cancer, heart rate and blood pressure were positively associated with patient-reported levels of stress, elevated cortisol levels, and decreased immune function at all 3 time points of a mindfulness-based stress intervention study (baseline, 6- and 12-month follow-up; ref. 31). Furthermore, molecular studies using both human ovarian cancer cells and animal models of ovarian carcinoma have shown that neuroendocrine stress factors can directly promote cancer growth via angiogenesis and increased invasion (32–34).

Our findings may have several important clinical implications. Most women with ovarian cancer are postmenopausal at the time of diagnosis and others become menopausal due to surgical removal of ovaries. The postmenopausal state could confer heightened cardiovascular risk. Therefore it is imperative to identify and optimally treat cardiovascular comorbidity in conjunction with cancer therapy, especially since many of these comorbidities are modifiable. For example, optimal treatment of hyperlipidemia in postmenopausal women undergoing chemotherapy can have an important effect on outcomes (35, 36). Heart rate is routinely measured in oncologic settings and can be used to identify at-risk patients who may benefit from pharmacologic and behavioral strategies during cancer treatment. Similarly, a thrombotic event or pulmonary hypertension during cancer treatment points toward poor outcome in patients with cancer. Current trends in ovarian cancer treatment (e.g., anti-VEGF therapy) exacerbate the very cardiovascular parameters (blood pressure, heart rate) that were found to be predictive of lowered survival in our study.
Therefore, as anti-angiogenic therapies increase in popularity, preventive medication strategies and watchful clinical management of cardiovascular comorbidity in at-risk patients should become paramount (37, 38). In addition, these findings suggest that prophylactic use of β-blocker therapy may be useful.

Limitations

While the design of the study was retrospective in that we looked up dates of death after patients had died, all baseline and cardiovascular incidence data were collected prospectively. Because we relied on electronic medical record data, it is possible that some cardiovascular risk factors and disease events were not captured in the analysis, which would have reduced statistical power and resulted in an overly conservative estimate of significant differences. However, this is unlikely as patients with ovarian cancer at MD Anderson tend to be followed very closely, due to the disease’s high recurrence rate. Because we did not measure chronic stress directly, our hypothesis that chronic stress may be mediating the relationship between higher heart rate and mortality will require further testing.

Conclusions

Our study shows that elevated heart rate at cancer diagnosis as well as the development of VTE and pulmonary hypertension after cancer diagnosis are predictive of shortened survival in patients with ovarian cancer. The pattern of findings with elevated heart rate could be due to decreased physical conditioning or possibly to noradrenergically mediated sympathetic activation. These results set the stage for further research examining cardiovascular risk factors and events in conjunction with direct measurement of chronic stress and its effect on tumor growth and metastasis.

Disclosure of Potential Conflicts of Interest

D.J. Lenihan is a consultant/advisory board member of Roche, AstraZeneca, and Oncomed. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.H. Shinn, D.J. Lenihan, M.L. Woods, P. Patel, A.M. Nick, M.M.K. Shahzad, A.K. Sood


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Palmero, M.L. Woods, A. Golden, E. Atkinson, A.K. Sood

Study supervision: E.H. Shinn, A.K. Sood

Collected data, cardiology reviewer of the data, and interpretation of the cardiology medical information: M.L. Woods

Reviewed cardiology notes and verified all cardiology events noted in this manuscript: D.J. Lenihan

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