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Impact of cardiovascular comorbidity on ovarian cancer mortality

Eileen H. Shinn, Ph.D.¹, Daniel J. Lenihan, M.D.², Diana L. Urbauer, M.S.¹, Karen M. Basen-Engquist, Ph.D.¹, Alan Valentine, M.D.¹, Laura Palmero, M.P.H.³, Myrshia L. Woods, M.H.S., PA-C¹, Pooja Patel, B.A.³, Alpa M. Nick, M.D.¹, Mian M. K. Shahzad, M.D.⁴, Rebecca L. Stone, M.D.¹, Antoinette Golden, B.S.⁵, Emma Atkinson, B.A.¹, Susan K. Lutgendorf, Ph.D.⁶, and Anil K. Sood, M.D.¹

¹University of Texas M. D. Anderson Cancer Center

²Vanderbilt University Medical Center

³Baylor College of Medicine

⁴University of Wisconsin School of Medicine and Public Health

⁵Rush University Medical Center

⁶University of Iowa

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 ovarian cancer patients.

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 9 cardiovascular events tracked during follow-up, venous thrombo embolism (VTE; Hazard Ratio= 3.2; 95%CI =1.8–5.5) and pulmonary hypertension (Hazard Ratio=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 (Hazard Ratio=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.

Corresponding Author and Reprint Requests: Anil K. Sood, M.D., Departments of Gynecologic Oncology and Cancer Biology, University of Texas M.D. Anderson Cancer Center, Unit 1362, P.O. Box 301439, Houston, TX 77230-1439, Phone: (713) 745-5266; Fax: (713) 792-7586, asood@mdanderson.org.

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Keywords

Ovarian cancer; tachycardia; VTE; survival

Introduction

Ovarian cancer is the most lethal gynecologic cancer, for which 5-year survival is 15–30%. (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 (CV) comorbidities may prove to be fruitful since CV comorbidities affect up to 60% of patients with ovarian cancer. (5) A prospective study of 5,213 ovarian cancer patients 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 CV comorbidities since previous studies analyzed aggregate indices of comorbid severity rather than individual comorbid diseases. It is unclear whether patients with comorbid CV disease are treated less aggressively as has been suggested for large retrospective studies in breast cancer. (10) Thus, a detailed study of CV comorbidities that controls for tumor and treatment indices could clarify if CV 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 breast, lung, head and neck, hepatobiliary, and leukemia cancer patients. (13, 14) As an initial step to identifying a link between psychological stress and ovarian cancer outcomes, we examined whether sympathetically-driven cardiovascular markers that have previously been linked with chronic stress, i.e., 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 CV disease events occurring after cancer diagnosis, on patient survival.

Materials and Methods

Patients

Following IRB approval, we retrospectively evaluated the electronic medical records of 271 newly-diagnosed histologically-confirmed epithelial ovarian cancer patients receiving treatment at the University of Texas MD Anderson Cancer Center; complete data was available for 246 (or 91%) participants. All participants had an ECOG performance status of 0–1. 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 non-epithelial ovarian or non-ovarian origin were ineligible.

Pre- and post-surgery care—Shortly after diagnosis, all patients in the sample received a pre-operative work-up prior to surgery. As part of this work-up, cardiovascular comorbidities and CVD risks (heart rate, blood pressure, cardiovascular family disease history, BMI, smoking status, diabetes mellitus (DM) or hyperlipidemia), were assessed and recorded in the medical record for each participant. Patients who did not meet ECOG0-1 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 grade versus high grade; *Debulking status* categorized into two levels: a) optimal (between 0–1 cm of residual disease, which was the surgical standard during the study period), and b) suboptimal (>1 cm of residual disease). *Stage* was dichotomized into early stage (I–II) vs 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 versus high grade). *Marital/ Partner Status* information was collected from the parent study using de-identified questionnaires and dichotomized into either living with a spouse or significant other versus living alone.

Baseline Heart Rate, Hypertension: *Heart Rate* (pulse) was defined as continuous, but dichotomized into *tachycardia* for the univariate model using a cutoff of 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 less than 25), overweight (BMI at least 25 but less than 30) and obese/ morbidly obese (BMI greater or equal to 30), but it was found to have a linear risk, so it was included in the final model without categorization. *Diabetes Mellitus (DM)* was present if a previously established diagnosis required therapy. *Smoking* was categorized into three levels: a) *current* smoker, b) *ever smoked* if the patient had smoked more than 100 cigarettes in her lifetime, and c) *never smoked* (100 cigarettes or less). *Hyperlipidemia* was present if LDL was 100 mg/dl or higher or the patient was on therapy.

CV Disease 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 performed. *Coronary artery disease (CAD)* was defined with established CAD present on angiography or cardiac ischemia confirmed by symptoms and electrocardiographic (ECG) changes on at least two 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, depression, demographics, tumor characteristics, CV baseline factors and CV disease 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 CV 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 of that were thought to be related to outcome (tumor characteristics, demographics, depression, all CV risk factors) and CV disease events that were significant in univariate analyses at $p < 0.2$. CV disease 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 backwards selection to keep only those variables that were statistically significant at $p < .10$ for inclusion in the reduced model. For the reduced model, significance was tested using two-sided alpha = 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, CHF, PE/DVT, MI, 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 CV disease events).

Univariate Analyses

Age, high-grade tumor, high stage disease, suboptimal cytoreduction, and baseline tachycardia were significantly associated with shortened survival (Table 3 and Figure 1: A–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, depression, baseline diabetes status, nor hyperlipidemia were significantly associated with survival.

Regarding the 9 CV disease endpoints tracked during study follow-up, VTE, pulmonary hypertension, and pericardial disease/tamponade were associated with shorter survival times (Table 3 and Figure 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 CV events, less than 15% of the patients died within 1 month of the respective CV event.

Multivariate Proportional Hazards Model for Survival using Time-Dependent Cardiac Disease Covariates

Backwards elimination resulted in the following reduced model with terms significant at $p < .10$: 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 for each beat per minute increase; 95% 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 HTN (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.

Independent Predictors for Pulmonary Hypertension and VTE

Since the incidence of pulmonary hypertension and VTE were related to survival, follow-up analyses were conducted to understand these results obtained in the initial analysis. Two separate regression analyses were run to determine baseline predictors for pulmonary hypertension and for VTE. Demographics (age, education, marital/ partnered status), CV risk factors (BMI, smoking status, hyperlipidemia, family history of CV disease) and the variable of interest, depression, were entered into the model using backwards selection to select only those variables that were statistically significant at $p < .10$ for inclusion in the reduced model. For the reduced model, significance was tested using two-sided alpha = 5%. For pulmonary hypertension, age (OR = 1.06, $p = 0.0211$), marital status (OR = 0.30, $p = 0.0136$), and family history of cardiovascular disease (OR = 3.29, $p = 0.0151$) were 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 CV 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 CV comorbidities are common in cancer patients, ranging from 12 to 60% incidence.(18) While several population-based studies of lung, breast, and colorectal cancer patients 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 ovarian cancer patients 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 course marked by multiple recurrences and chemotherapy regimens, resulting in increased risk for developing CV 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 cancer patients 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.(28)(25) However, our data show that 8 of the 39 patients developed VTE within the first three 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 breast and prostate cancer patients, heart rate and blood pressure were positively associated with patient-reported levels of stress, elevated cortisol levels and decreased immune function at all three timepoints of a mindfulness-based stress intervention study (baseline, 6 and 12 month follow-up).(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)(33)(34)

Our findings may have several important clinical implications. Most women with ovarian cancer are post-menopausal at the time of diagnosis and others become menopausal due to surgical removal of ovaries. The post-menopausal 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 post-menopausal women undergoing chemotherapy can have an important effect on outcomes, (35)(36)Heart rate is routinely measured in oncological settings and can be used to identify at-risk patients who may benefit from pharmacological and behavioral strategies during cancer treatment. Similarly, a thrombotic event or pulmonary hypertension during cancer treatment points toward poor outcome in cancer patients. 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 beta-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 was collected prospectively. Because we relied on electronic medical record data, it is possible that some CV 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 since ovarian cancer patients 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 ovarian cancer patients. The pattern of findings with elevated heart rate could be due to decreased physical conditioning or possibly to nor adrenergically-mediated sympathetic activation. These results set the stage for further research examining CV risk factors and events in conjunction with direct measurement of chronic stress and its effect on tumor growth and metastasis.

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References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics 2010. *CA-Cancer Journal for Clinicians*. 2010; 60:277–300.
2. Jemal A, et al. Cancer statistics, 2006. *CA-Cancer Journal for Clinicians*. 2006; 56:106–130.
3. Terplan M, Temkin S, Tergas A, Lengyel E. Does equal treatment yield equal outcomes? The impact of race on survival in epithelial ovarian cancer. *Gynecologic Oncology*. 2008; 111:173–178. [PubMed: 18823649]
4. Huang L, Cronin K, Johnson K, Mariotto A, Feuer E. Improved survival time: What can survival cure models tell us about population-based survival improvements in late-stage colorectal, ovarian and testicular cancer? *Cancer*. 2008; 112:2289–2300. [PubMed: 18393325]
5. Barnholtz-Sloan J, Schwartz A, Qureshi F, et al. Ovarian cancer: Changes in patterns at diagnosis and relative survival over the last three decades. *American Journal of Obstetrics and Gynecology*. 2003; 189:1120–1127. [PubMed: 14586365]
6. Tetshe M, Dethlefsen C, Pedersen L, Sorenson H, Norgaard M. The impact of comorbidity and stage on ovarian cancer mortality: A nationwide Danish cohort study. *BMC Cancer*. 2008; 8:31. [PubMed: 18230177]
7. Maas H, Kruitwagen R, Lemmens V, Goey S, Janssen-Heijnen M. The influence of age and comorbidity on treatment and prognosis in ovarian cancer: a population-based study. *Gynecologic Oncology*. 2005; 97:104–109. [PubMed: 15790445]
8. DiSilvestro P, Peipert J, Hogan J, Granai C. Prognostic value of clinical variables in ovarian cancer. *Journal of Clinical Epidemiology*. 1997; 50:501–505. [PubMed: 9180642]
9. Tingulstad S, Skjeldestad F, Halvorsen T, Hagen B. Survival and prognostic factors in patients with ovarian cancer. *Obstetrics & Gynecology*. 2003; 101:885–891. [PubMed: 12738145]
10. Doyle J, Neugut A, Jacobson J, Grann V, Hershman D. Chemotherapy and cardiotoxicity in older breast cancer patients: A population-based study. *Journal of Clinical Oncology*. 2005; 23:8597–8605. [PubMed: 16314622]
11. Armaiz-Pena G, Lutgendorf S, Cole S, Sood A. Neuroendocrine modulation of cancer progression. *Brain, Behavior and Immunity*. 2009; 23:10–15.
12. Lutgendorf S, Sood AK, Antoni M. Host factors and cancer progression: Biobehavioral signaling pathways and interventions. *Journal of Clinical Oncology*. 2010; 28:4094–4099. [PubMed: 20644093]
13. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nature Reviews Clinical Oncology*. 2008; 5:466–475.
14. Satin J, Linden W, Phillips M. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer*. 2009; 115:5349–5361. [PubMed: 19753617]

15. Esler M, Eikelis N, Schlaich M, et al. Chronic mental stress is a cause of essential hypertension: presence of biological markers of stress. *Clinical and Experimental Pharmacology and Physiology*. 2008; 35:498–502. [PubMed: 18307749]
16. Johansson M, Rundqvist B, Eisenhofer G, Friberg P. Cardioresenal epinephrine kinetics: Evidence for release in the human heart. *American Journal of Physiology*. 1997; 273:H2178–2185. [PubMed: 9374751]
17. Wilkinson D, Thompson J, Lambert G, et al. Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. *Archives General Psychiatry*. 1998; 55:511–520.
18. Ogle K, Swanson G, Woods N, Azzouz F. Cancer and comorbidity: Redefining chronic diseases. *Cancer*. 2000; 88:653–663. [PubMed: 10649261]
19. Houterman S, Janssen-Heijnen M, Verheij C, et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. *British Journal of Cancer*. 2004; 90:2332–2337. [PubMed: 15162155]
20. Janssen-Heijnen M, Houterman S, Lemmens V, et al. Prognostic impact of increasing age and comorbidity in cancer patients: A population-based approach. *Critical Reviews in Oncology/Hematology*. 2005; 55:231–240. [PubMed: 15979890]
21. Du Bois A, Rochon J, Lamparter C, Pfisterer J, AGO OOP. Pattern of care and impact of participation in clinical studies on the outcome of ovarian cancer. *International Journal of Gynecologic Cancer*. 2005; 15:183–191.
22. Le T, Alshaikh G, Hopkins L, Fraught W, Fung M. Prognostic significance of postoperative morbidities in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy and delayed primary surgical debulking. *Annals of Surgical Oncology*. 2006; 13:1711–1716. [PubMed: 17009146]
23. van de Poll-Franse L, Houterman S, Janssen-Heijnen M, et al. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population-based analysis. *International Journal of Cancer*. 2007; 120:1986–1992.
24. Rodriguez A, Wun T, Chew H, et al. Venous thromboembolism in ovarian cancer. *Gynecologic Oncology*. 2007; 105:784–790. [PubMed: 17408726]
25. Kuderer N, Ortel T, Francis C. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. *Journal of Clinical Oncology*. 2009; 27:4902–4911. [PubMed: 19738120]
26. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery. *Annals of Surgery*. 2006; 243:89–95. [PubMed: 16371741]
27. Lyman G, Khorana A. Cancer, clots and consensus: New understanding of an old problem. *Journal of Clinical Oncology*. 2009; 27:4821–4826. [PubMed: 19752337]
28. Chew H, Wun T, Harvey D, Zhou H, White R. Incidence of venous thromboembolism and the impact on survival in breast cancer patients. *Journal of Clinical Oncology*. 2007; 25:70–76. [PubMed: 17194906]
29. Theorell T, Perski A, Akersted T, et al. Changes in job strain in relation to changes in physiologic state. *Scandinavian Journal of Work and Environmental Health*. 1988; 15:189–196.
30. Cobb S. Physiologic changes in men whose jobs were abolished. *Journal of Psychosomatic Research*. 1974; 18:245–258. [PubMed: 4459457]
31. Carlson L, Specia M, Faris P, Patel K. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain, Behavior and Immunity*. 2007; 21:1038–1049.
32. Lutgendorf SK, Costanzo ES, Bradley S, et al. Stress-related mediators stimulate vascular endothelial growth factor secretion by two ovarian cancer cell lines. *Clinical Cancer Research*. 2003; 9:4514–4521. [PubMed: 14555525]
33. Thaker P, Han L, Kamat A, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nature Medicine*. 2006; 12:939–944.
34. Lutgendorf S, Lamkin D, Jennings N, et al. Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma. *Human Cancer Biology*. 2008; 14

35. Seicean S, Seicean A, Plana J, Budd T, Marwick T. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: An observational clinical cohort study. *Journal of the American College of Cardiology*. 2012; 60:2384–2390. [PubMed: 23141499]
36. Lenihan D. Statins in preparation for chemotherapy: “Do these medications help your fitness for battle?”. *Journal of the American College of Cardiology*. 2012; 60:2391–2392. [PubMed: 23141498]
37. Perez E, Suman V, Davidson N. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 Adjuvant Breast Cancer Trial. *Journal of Clinical Oncology*. 2008; 26:1231–1238. [PubMed: 18250349]
38. Healey Bird B, Swain S. Cardiac toxicity in breast cancer survivors: Review of potential cardiac problems. *Clinical Cancer Research*. 2008; 14:14–24. [PubMed: 18172247]

Figure 1.
Univariate Survival for Cardiovascular Comorbidities

Table 1**Patient Characteristics at Cancer Diagnosis (n=271)**

Category	N (%)
Education	
No HS diploma	20 (7)
HS /GED or technical/vocational degree	78 (29)
Some college or 2-year college degree	70 (26)
College degree	103 (38)
Marital/ partner status	
Lives alone	76 (28)
Lives with significant other	193 (72)
FIGO Stage	
I	14 (5)
II	25 (9)
III	208 (7)
IV	24 (9)
Grade	
Low grade	32 (12)
High grade	239 (88)
Histology	
Non-serous	50 (19)
Serous	221 (82)
Cytoreduction	
Optimal (≤ 1 cm)	187 (69)
Suboptimal (> 1 cm)	83 (31)
Smoking History	
Never smoked	173 (64)
Past smoker	28 (10)
Current smoker	70 (26)
DM ¹	28 (10)
Lipid ²	66 (24)
Family history ³	87 (32)
Depression ⁴	14 (11)
BMI	
BMI ≤ lower quartile	65 (24)
Lower quartile < BMI ≤ middle quartile	70 (26)
Middle quartile < BMI ≤ upper quartile	68 (25)
BMI >upper quartile	67 (25)
Hypertension	160 (59)
Mean systolic BP (SD)	129 (17)
Mean diastolic BP (SD)	72 (11)
Mean heart rate (SD)	82 (14)

Category	N (%)
Range	50–122

¹DM= Diabetes mellitus

²Lipid= Hyperlipidemia

³Family history= Family history of cardiovascular disease

⁴Depression data was available for a subset of 125 participants.

Table 2

Prevalence of Incident Cardiovascular Events during Follow-up

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

Table 3

Univariate Hazard Ratios for Survival Time

	# of Patients	# of Deaths	HR	95% CI HR	P value
Grade					
Low grade	32	12			
High grade	239	114	1.9	1.02–3.4	.04
Histology					
Non-serous	50	22			
Serous	221	104	.8	.5–1.3	.4
Cytoreduction					
Microscopic/ optimal ($\leq$ 1cm)	187	77			
Suboptimal ($>$ 1cm)	83	49	2.0	1.4–2.8	.0003
Heart rate at cancer diagnosis			1.02	1.01–1.03	.003
VTE					
No	232	95			
Yes	39	31	2.2	1.4–3.2	.0002
Pulmonary HTN					
No	250	114			
Yes	21	12	1.8	0.98–3.2	.06

Table 4

Median Length of Survival in Years

Cardiac comorbidity	No Comorbidity Median	Comorbidity Median	Reduction in survival time (%)
Tachycardia at cancer diagnosis	5.9	4.0	1.9 (32)
VTE	6.4	4.1	2.3 (36)
Pulmonary HTN	5.9	3.4	2.5 (42)

Table 5

Time to Death Using Time-Dependent Covariates

	Full model			Reduced model		
	HR	p	95% CI	HR	p-Value	95% CI
Age at cancer diagnosis	1.00	0.95	0.98 – 1.02			
HS/GED/technical/vocational (Ref: No HS)*	0.96	0.93	0.4 – 2.3			
Some college/2-Year degree (Ref: No HS)*	0.9	0.80	0.4 – 2.2			
College degree (Ref: No HS)*	1.3	0.56	0.5 – 3.2			
Married/partner	0.9	0.55	0.5 – 1.4			
High grade	2.0	0.06	0.98 – 3.9	2.1	0.02	1.1 – 4.1
Stage III/IV	2.1	0.07	0.95 – 4.4	1.9	0.08	0.9 – 4.1
Serous histology	0.8	0.41	0.4 – 1.4			
Suboptimal cytoreduction	1.9	0.00	1.2 – 3.0	1.9	<0.01	1.3 – 2.9
Hypertension at cancer diagnosis	1.3	0.27	0.8 – 2.0			
BMI at cancer diagnosis	1.03	0.15	0.99 – 1.1	1.03	0.09	1.0 – 1.1
Heart rate at cancer diagnosis	1.02	0.05	1.00 – 1.03	1.02	0.01	1.01 – 1.04
Past smoker at cancer diagnosis (Ref: Never smoked)	1.4	0.34	0.7 – 2.7	1.6	0.17	0.8 – 3.0
Current smoker at cancer diagnosis (Ref: Never smoked)	0.7	0.18	0.4 – 1.2	0.7	0.11	0.4 – 1.1
Hyperlipidemia at cancer diagnosis	0.97	0.91	0.6 – 1.6			
VTE (Time Dependent)	2.7	<0.01	1.4 – 5.1	3.2	<0.01	1.8 – 5.5
Pericardial disease/tamponade (Time Dependent)	1.2	0.64	0.5 – 2.8			
Pulmonary hypertension (Time Dependent)	9.0	<0.01	4.1 – 20.2	8.5	<0.01	3.9 – 18.7