Published in final edited form as:
Obstet Gynecol. 2013 November ; 122(5): . doi:10.1097/AOG.0b013e3182a92011.

Racial Disparities in the Treatment of Advanced Epithelial Ovarian Cancer

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Abstract

OBJECTIVE—To examine whether treatment with guideline-recommended care (surgery and chemotherapy) is associated with mortality differences between black and white women with advanced epithelial ovarian cancer.

METHODS—We conducted an observational cohort study using the Surveillance, Epidemiology, and End Results (SEER) linked to Medicare claims for 1995-2007. We evaluated long-term survival for 4,695 black and white women with stage III or IV epithelial ovarian cancer with Kaplan-Meier analysis and Cox regression, and then in patients matched by propensity score to create two similar cohorts for comparison. We investigated the association between race, stage, and survival among women who were treated with guideline-recommended care and those who received incomplete treatment.

RESULTS—Black women with advanced epithelial ovarian cancer were more likely to die than white women; unadjusted hazard ratio (HR):1.27 (95% confidence interval [CI]: 1.10-1.46). Black women were less likely than white women to receive guideline-recommended care (54% vs. 68%, $p<0.001$) and women who did not receive recommended treatment had lower survival than women who received recommended care. Cox proportional hazards models demonstrated no black versus white differences in mortality among women who were treated with guideline-recommended care; adjusted HR:1.04 (95% CI: 0.85-1.26) or among women who received incomplete treatment; adjusted HR:1.09 (95% CI: 0.89-1.34). The survival analysis of patients matched by propensity score confirmed these analyses.

Conclusions—Differences in rates of treatment with guideline-recommended care are associated with black–white mortality disparities among women with advanced epithelial ovarian cancer.

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Financial Disclosure: Dr. Wisnivesky is a member of the research board of EHE International, he has received consulting honorarium from Merck Pharmaceutical, UBS, and IMS Health and a research grant from GlaxoSmithKline. The other authors did not report any potential conflicts of interest.

Introduction

Epithelial ovarian cancer is the 5th leading cause of cancer deaths among women in the United States and significant racial and ethnic disparities exist in ovarian cancer mortality.[1] Black women are more likely to die from ovarian cancer than white women in this country. Between 1975 and 2005, the 5-year survival rate for U.S. white women with advanced ovarian cancer improved from 37% to 45% but declined for black women from 43% to 38%.[2] This discrepancy is particularly striking because the overall improvement in survival is largely attributed to the introduction of platinum-based chemotherapy.[3]

The higher mortality experienced by black women with ovarian cancer in this country is thought to be due to the fact that black women are more likely to present with advanced disease.[4] Using Surveillance, Epidemiology, and End Results (SEER) data, investigators found that blacks are more likely to be diagnosed at a later stage and this difference is most pronounced for stage IV disease which accounts for 41% of black compared with 34% of white women with ovarian cancer ($p<.0001$).[4] Survival is directly related to stage of disease at the time of diagnosis with a 5-year survival rate of 89% for women with Stage I disease and declining to 11% for women with the most advanced disease, Stage IV.[5] Black–white mortality disparities may also be explained by differences in the receipt of treatment, with blacks less likely to undergo ovarian cancer specific procedures (i.e., hysterectomy, colon resection, and lymphadenectomy), and less likely to be operated on by high-volume surgeons.[6]

Many of the studies investigating racial disparities in ovarian cancer mortality have used data from single institutions, case studies, and voluntary registries.[7,8] The few research studies using population based samples such as Surveillance, Epidemiology, and End Results (SEER) database are limited because these data do not contain information on chemotherapy or comorbidities.[5] Studies using SEER-Medicare linked data that contain reliable information on both surgery and chemotherapy have found that blacks, those with higher comorbidity scores, and older age are less likely to receive surgery and chemotherapy.[9,10] None of these studies, however, examined whether differences in rates of treatment with guideline-recommended care was associated with black–white mortality disparities in advanced ovarian cancer survival using propensity score matching methods.

Current guidelines from the National Comprehensive Cancer Network recommend that primary treatment for most patients with advanced ovarian cancer should include cytoreductive surgery and at least six cycles of systemic chemotherapy.[11] We sought to examine whether treatment with guideline-recommended care is associated with mortality differences between U.S. white and black women with advanced epithelial ovarian cancer.

METHODS

We used the Surveillance, Epidemiology, and End Results (SEER) linked to Medicare claims (Medicare Enrollment Database) for 1995-2007. The SEER database includes cancer registries representing approximately 15% to 25% of the United States population during this study period.[2] Validity and reliability of the combined SEER-Medicare database have been studied extensively.[12-16] The Mount Sinai School of Medicine Institutional Review Board (Program for the Protection of Human Subjects) approved this study.

Using the linked SEER-Medicare database, we identified women diagnosed with ovarian cancer from January 1, 1996 - December 31, 2007 (N=35,995). Among them, there were 32,934 white and blacks. We excluded women with more than one primary cancer and women with nonepithelial ovarian cancer, as well as women diagnosed on autopsy or death certificate and women with stage I or II ovarian cancer as classified by the American Joint

Commission on Cancer. We excluded women not enrolled in Medicare parts A and B and women enrolled in an HMO who do not have Medicare fee for service claims. We excluded women less than 66, to provide one year of data on comorbidities that can influence treatment decisions. Treatment information was obtained from Medicare parts A and B claims. All steps of study population selection are shown in Figure 1.

To identify treatment, we searched Medicare claims from 30 days prior to diagnosis and up to 120 days after the date of diagnosis. Since SEER reports only month and year of the diagnoses, the diagnosis date was assigned the 15th day of the month of diagnosis. We identified primary surgical treatment in MEDPAR files using ICD-9 procedure and HCPCS codes. Surgical resection codes were determined based on literature review and expert gynecologic oncologic and biller's opinion. [17] We identified treatment with chemotherapy using inpatient, outpatient, physician claims, and DME (Durable Medical Equipment) files. We classified chemotherapy treatment in Medicare claims as the 1st chemotherapy that occurred within 180 days prior to surgery and 90 days after surgical treatment. The chemotherapy claims from all sources within three days were grouped into one. The number of chemotherapy cycles were identified from the initial chemotherapy date and by counting number of cycles.

We classified treatment into two categories: complete versus incomplete. All women who were treated with guideline-recommended care (cytoreductive surgery and six or more cycles of chemotherapy) were classified as receiving complete treatment. Incomplete treatment included women who did not receive treatment and those who received suboptimal treatment. Suboptimal treatment included surgery only, chemotherapy only, and surgery plus 5 or less cycles of chemotherapy. We conducted additional analyses varying the definition of complete treatment as surgery plus 4 or more cycles of chemotherapy; as findings are similar, we report the standard six cycles as complete.

Sociodemographic and clinical variables of age, SEER geographic region, year of diagnosis, tumor grade, and histology were derived from SEER. Data on race for these analyses was ascertained from the Medicare Enrollment Database an accurate source to assess race.[18-20] Comorbidity score was determined using Medicare claims for the 12 months prior to ovarian cancer diagnosis to calculate the Charlson comorbidity index.[21,22] Bivariate analyses were performed using chi-square tests for categorical variable and t-test for continuous variables. Multivariable logistic regression was performed to investigate the association between treatment with guideline-recommended care and race. Kaplan-Meier survival analysis methods were used to compare the overall survival of black versus white women with advanced epithelial ovarian cancer and to compare the overall survival of women who received complete treatment versus women who received incomplete treatment. Adjustment for multiple comparisons for the logrank test was done with Sidak test. Cox proportional hazard regression models assessed the association between overall survival and race, and overall survival and treatment group after controlling for sociodemographics, tumor characteristics, and comorbidity. We used the Martingale methods to check the proportional hazard assumption.

We created a sample of black and white patients with similar characteristics using propensity score matching.[23] All baseline sociodemographic and clinical factors including age, comorbidity, stage, histology, grade, year of diagnosis, and SEER region were included in a logistic model predicting black race. Once the model was fitted, we used a 1:2 scheme without replacement to match black and white patients by propensity scores. We used a paired t test or McNemar test, as appropriate to assess whether baseline characteristics of black and white patients were well-balanced in the matched cohort.(Appendix 1) In addition, standardized difference between blacks and white women prior and after the matching were

calculated. Rates of complete treatment were compared for the matched pairs of blacks and whites using McNemar chi square test. Survival of black and white patients were compared using a marginal Cox model with a robust sandwich variance. estimator.[24,25] All statistical analysis was performed using the SAS system software version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Our final sample included 4,695 women: 235 blacks and 4,460 whites. Of the 4,695 patients, 5% (n=235) were black and the remainder were white (Table 1). Black women were more likely to present with Stage IV disease (42.1% vs. 33.5%, p=.007), have higher mean Charlson comorbidity scores (0.93 vs. 0.56, p<.001), and one or more comorbidities (52.8% vs. 35.0%, p<.001). Blacks were more likely to come from the SEER geographic regions of the Midwest and the South and to have unknown tumor grade than whites.

Black women were less likely to receive complete treatment (surgery and six or more cycles of chemotherapy) as compared with white women (54% vs. 68%, p<.001). In a multivariable model predicting complete treatment that controlled for age, comorbidity, stage, and tumor characteristics, blacks were less likely than whites to be treated with guideline-recommended care (adjusted odds ratio 0.65; 95% CI: 0.48-0.88). Black women were more likely than whites to receive only surgery (28% vs. 18%), p<.001).

Overall, black women were more likely to die than white women, unadjusted hazard ratio (HR) of 1.27, 95% confidence interval (CI):1.10-1.46. Women who received complete treatment were less likely to die than women who received incomplete treatment, unadjusted HR 0.32, 95% CI: 0.30-0.34. Survival analyses stratified for treatment, revealed no racial mortality difference among women who received incomplete treatment: unadjusted HR of 1.13, 95% CI: 0.93-1.38 and among women who received complete treatment group: unadjusted HR of 1.11, 95% CI: 0.91-1.34, see Figure 2. In a Cox model adjusting for age, comorbidity, stage, and tumor characteristics, black women were more likely to die than white women (adjusted HR of 1.17; 95% CI:1.02-1.35). After adjusting for treatment, the hazard ratio for black women was no longer significantly elevated: adjusted HR of 1.10, 95% CI: 0.95-1.26, see Table 2.

Analyses using propensity matched cohorts confirmed these results. The standardized differences between whites and blacks in this matched cohort were less than 10% for the majority of variables.[26] (Appendix 1) The final propensity score model yielded good model discrimination (c-statistic was 0.75). The propensity score matching analyses demonstrated that blacks were less likely to receive complete treatment than whites (54% versus 66% respectively, p<.03). Similar to the analyses using the full data set, blacks were more likely to die than whites in survival analyses among the propensity matched cohorts: HR of 1.18, 95% CI: 1.00-1.38). However, there was no difference in mortality between black and white women in the survival analysis of propensity matched cohorts after adjustment for treatment; adjusted HR of 1.06, 95% CI: 0.84-1.34 (Table 2).

In the complete treatment group older age, later stage, increasing comorbidity, increasing or unknown grade were associated with higher mortality (Table 3). Among women in the incomplete treatment group, older age, later stage, increasing comorbidity, mucinous histology, and increasing or unknown grade increased risk of mortality.

DISCUSSION

Black–white mortality disparities in survival from advanced epithelial ovarian cancer among Medicare beneficiaries are associated with treatment differences. Black women are less

likely to receive recommended surgical and chemotherapy treatment for advanced epithelial ovarian cancer and women who receive incomplete treatment are more likely to die from this disease. Lower rates of surgery have been suggested to explain higher mortality of black women from advanced epithelial ovarian cancer.[6,7,27] While others have documented lower rates of chemotherapy among black women, these studies did not take into account potential selection bias inherent in observational data. This is a serious omission given racial differences in comorbidity, stage, and age at diagnosis, all factors that affect physician and patient decision making and also affect survival. Our data demonstrate that black women are more likely than white women to receive surgery only but are often not receiving recommended post surgical chemotherapy. This study advances current knowledge controlling for serious potential confounders of race's effect on receipt of cancer treatment and on mortality. We found no racial difference in mortality among women with equivalent risk factors and similar treatments.

Reasons as to why black women are less likely to receive postsurgical chemotherapy are unclear. Women with greater comorbidity were less likely to receive chemotherapy.[10] However, whether this association is driven by physician or patient preference or sound clinical judgment is uncertain. Our data sources do not allow us to determine the degree to which patient refusal versus providers not referring patients for chemotherapy explain this finding. Research studying causes of racial disparities in breast cancer found that both patient and system issues affect racially disparate treatment effects.[28,29] Black women were less likely to receive adjuvant chemotherapy post breast surgery. While surgeons referred patients at similar rates, system failures, cases in which patients were referred to oncologists, did not refuse treatment, yet care did not ensue, primarily accounted for the racial disparities in receipt of adjuvant chemotherapy. Black women were less likely to know the benefits of adjuvant treatment, were more mistrustful of the care delivery system, and less likely to receive adjuvant treatment. Whether system failures, physician recommendations, or patient preferences explain lower treatment rates in black women with advanced epithelial ovarian cancer is not known.

This study shares limitations posed by observational administrative data. Ascertainment of treatment and comorbidities is subject to the accuracy of coding. Although Medicare data and chart review have high level of agreement for surgery and chemotherapy, the accuracy is lower for diagnostic codes of comorbid illness and treatment complications.[14] Although there are not effective screening instruments for ovarian cancer detection, whites continue to be diagnosed at earlier stages than blacks. To reduce the potential effect of earlier detection we limited our study sample to women with later stage cancers. Given that Medicare starts at age 65 for the vast majority of people, we were unable to investigate outcomes among a younger age group of women. Because this is an observational study, there are potentially unmeasured characteristics associated with race that may have biased our results. However, our nearly identical findings of both Cox proportional hazards models and propensity scores analyses suggest that treatment differences do contribute to racial disparities in advanced epithelial ovarian cancer mortality among women older than 65 years.

Black women have higher mortality from a number of different types of cancer and ovarian cancer is no exception. While the mortality gap has been largely attributed to the fact that blacks are more likely to present at a later stage as compared with white women, our findings suggest that treatment differences account for a portion of the racial disparity in ovarian cancer mortality. There was no mortality gap between blacks and whites treated with guideline-recommended care nor between blacks and whites who received incomplete treatment. We found that a larger proportion of black than white women did not receive recommended care. Future research needs to investigate patient, provider, and system factors that may explain this finding. The silver lining of our disturbing findings lies in the

real possibility of remediating a significant racial disparity in cancer mortality by ensuring guideline concordant treatment is provided to all who can benefit from it.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Supported by the National Cancer Institute (1RO1CA157176-01).

APPENDIX

Appendix 1

Patients' Characteristics Before and After Matching by Propensity Score

	Before Matching				After Matching			
	White (n=4,460)	**Black (n=235)**	***P***	**Standardized Difference**	**White (n=470)**	**Black (n=235)**	***P***	**Standardized Difference**
Mean age at diagnosis	74.9	74.4	0.252	13	74.7	74.4	0.144	0
Age 66-69	22.5%	26.8%	0.128	16	27.7%	26.8%	0.599	2
Age 70-74	28.1%	33.2%	0.093	6	36.4%	33.2%	0.541	7
Age 75-79	27.0%	18.7%	0.005	19	18.3%	18.7%	0.763	1
Age 80-84	15.3%	12.8%	0.285	7	10.9%	12.8%	0.758	6
Age 85 or greater	7.0%	8.5%	0.393	2	6.8%	8.5%	0.353	6
Stage III	66.5%	57.9%	0.007	15	62.1%	57.9%	0.094	9
Stage IV	33.5%	42.1%	0.007	15	37.9%	42.1%	0.094	9
Charlson Comorbidity Score	0.56	0.93	<.001	38	0.87	0.928	0.577	0
No comorbidity	65.0%	47.2%	<.001	39	49.4%	47.2%	0.354	4
1 comorbidity	22.3%	30.6%	0.003	20	27.7%	30.6%	0.225	7
2 comorbidities	7.7%	11.9%	0.021	12	14.3%	11.9%	0.206	7
3+ comorbidities	5.0%	10.2%	<0.001	25	8.7%	10.2%	0.384	5
Histology								
Serous	81.8%	81.3%	0.841	4	89.4%	81.3%	0.134	1
Clear cell	1.9%	≤4.7%	0.445	18	≤4.7%	≤4.7%	0.564	13
Endometroid	8.1%	7.7%	0.812	9	≤4.7%	7.7%	0.369	2
Mucinous	3.7%	6.0%	0.074	6	≤4.7%	6.0%	0.670	0
Other epithelial	4.6%	≤4.7%	0.189	0	≤4.7%	≤4.7%	0.317	0
Grade								
1	3.1%	≤4.7%	0.665	2	≤4.7%	≤4.7%	0.046	1
2	15.9%	17.0%	0.646	6	14.4%	17.0%	0.297	7
3	50.6%	44.7%	0.076	12	43.0%	44.7%	0.473	3
4	13.0%	11.5%	0.4934	5	14.3%	≤12.0%	0.047	8
9 *	17.4%	24.3%	0.007	15	26.0%	24.3%	0.606	4

	Before Matching				After Matching			
	White (n=4,460)	Black (n=235)	*P*	Standardized Difference	White (n=470)	Black (n=235)	*P*	Standardized Difference
Northeast	20.9%	16.2%	0.080	8	13.8%	16.2%	0.869	7
Midwest	19.5%	30.6%	<.001	23	34.0%	30.6%	0.249	7
South	15.2%	30.2%	<.001	37	28.5%	30.2%	0.599	4
West	44.5%	23.0%	<.001	48	23.6%	23.0%	0.414	2
Year of diagnoses	2002.3	2001.3	0.473	5	2001.7	2001.3	0.213	0
1995-1999	27.9%	31.1%	0.299	7	27.0%	31.1%	0.189	9
2000-2003	38.9%	37.9%	0.747	2	36.4%	37.9%	0.906	3
2004-2007	33.1%	31.1%	0.510	4	36.6%	31.1%	0.179	12
Probability	0.048	0.093	<.001	73	0.091	0.091	0.263	0

* Cell type not determined

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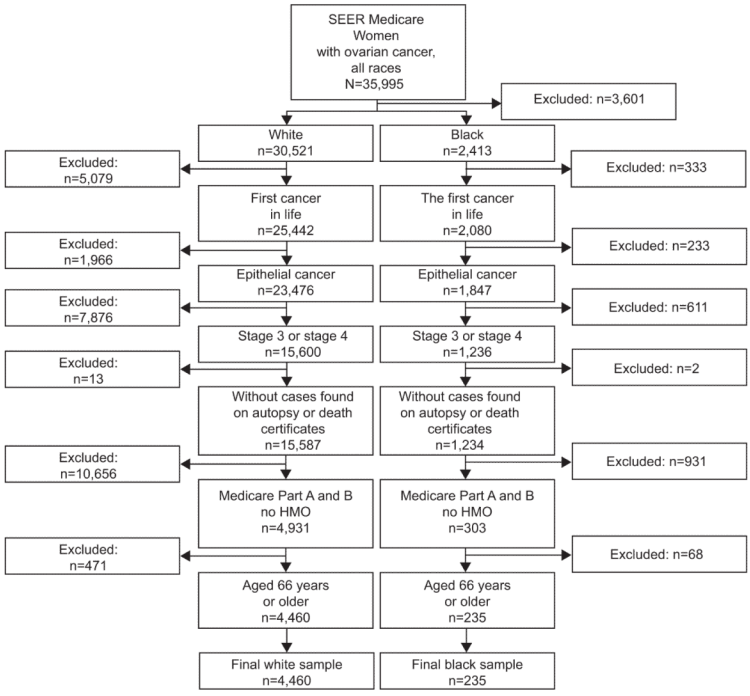

Figure 1.
Population selection. Surveillance, epidemiology,and end results (SEER).

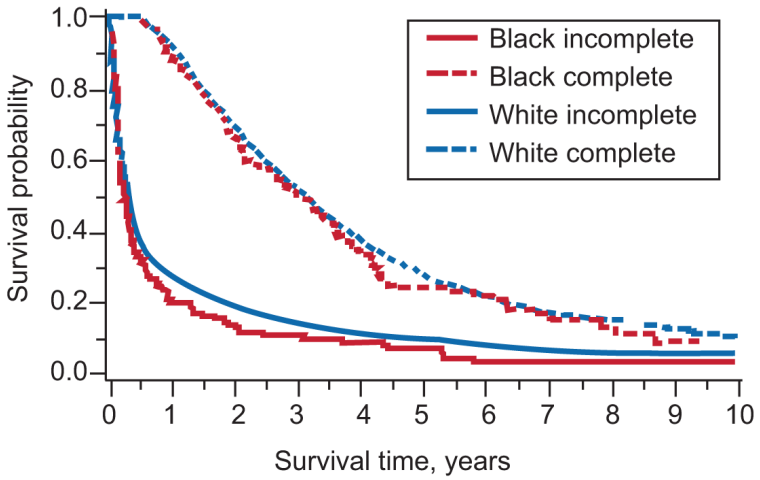

Figure 2.

Survival analysis for treatment by race (*P* value for race is 0.10; *P* value for treatment <0.001).

Number at risk: Complete treatment

White: 3,022, 2,094, 963, 438, 208, 85

Black: 127, 84, 38, 19, less than or equal to 11, less than or equal to 11.

Number at risk: Incomplete treatment

White: 1,438, 273, 147, 76, 53, 28

Black: 108, 15, less than or equal to 11, less than or equal to 11, less than or equal to 11, less than or equal to 11.

Table 1

Patient Baseline Characteristics

Demographics	Whites n=4,460	Blacks n=235	*P*
Mean age at diagnosis	74.9	74.4	NS
Age groups			0.025
Age 66-69	22.5%	26.8%	
Age 70-74	28.1%	33.2%	
Age 75-79	27.0%	18.7%	
Age 80-84	15.3%	12.8%	
Age 85 or greater	7.0%	8.5%	
Stage			0.007
Stage III	66.5%	57.9%	
Stage IV	33.5%	42.1%	
Comorbidities			
CHF	5.2%	9.4%	0.006
Diabetes	12.7%	29.9%	<.001
Diabetes with sequelae	2.1%	6.4%	<.001
Charlson Comorbidity Score	0.56	0.93	<.001
Comorbidity Groups			<.001
No Comorbidity	65.0%	47.2%	
1 Comorbidity	22.3%	30.6%	
2 Comorbidities	7.7%	11.9%	
3+ Comorbidities	5.0%	10.2%	
Histology			0.351
Adenocarcinoma	81.8%	81.3%	
Clear Cell	1.9%	≤4.7%	
Endometroid	8.1%	7.7%	
Mucinous	3.7%	6.0%	
Other Epithelian	4.6%	≤4.7%	
Treatment		<.0001	
Complete Treatment	67.8%	54.0%	
Incomplete Treatment	32.2%	46.0%	
- Surgery only	18.3%	28.1%	<0.001
- Surgery + 5 or less Chemotherapy cycles	13.9%	17.9%	NS
Debulking surgery (SEER code)	29.1%	26.7%	NS
Grade			NS
Grade 1	3.1%	≤4.7%	
Grade 2	15.9%	17.0%	
Grade 3	50.6%	44.7%	

Demographics	**Whites n=4,460**	**Blacks n=235**	***P***
Grade 4	13.0%	≤12.0%	
Unknown grade	17.4%	24.3%	
SEER Region			<.001
Northeast	20.9%	16.2%	
Midwest	19.5%	30.6%	
South	15.2%	30.2%	
West	44.5%	23.0%	

NS, not significant; SEER, Surveillance, Epidemiology, and End Results.

Table 2

Effect of Treatment on Black–White Mortality Differences in Advanced Ovarian Cancer

Type of Model	Hazard Ratio for Black (Compared With White Women) With Advanced Ovarian Cancer	95% Confidence Interval
Unadjusted	1.27	1.10-1.46
Adjusted for demographic, comorbidity, stage, and tumor characteristics	1.17	1.02-1.35
Adjusted for demographic, comorbidity, stage, tumor characteristics, and treatment	1.10	0.95-1.26
Confirmatory Analyses of Propensity Matched Cohorts		
Not adjusted for treatment	1.18	1.00-1.38
Adjusted for treatment	1.06	0.84-1.34

Table 3

Cox Model Predicting Mortality

	Hazards Ratio	95% CI	*P*
Received Complete Treatment			
Black vs. White	1.04	0.85-1.26	NS
Age at diagnosis	1.03	1.02-1.03	<.001
Stage IV vs. stage III	1.18	1.08-1.28	<.001
Charlson comorbidity score	1.14	1.09-1.19	<.001
Histology: mucinous vs. serous	1.14	0.87-1.50	NS
Clear cell vs. serous	0.86	0.62-1.20	NS
Endometroid vs. serous	0.82	0.71-0.95	0.001
Other epithelial vs. serous	0.79	0.64-0.97	0.024
Grade 2 vs. Grade 1	1.44	1.09-1.91	0.011
Grade 3 vs. Grade 1	1.36	1.04-1.78	0.027
Grade 4 vs. Grade 1	1.38	1.04-1.84	0.028
Unknown Grade* vs. Grade 1	1.71	1.29-2.27	<0.001
Midwest vs. Northeast	1.09	0.96-1.24	NS
South vs. Northeast	1.08	0.95-1.24	NS
West vs. Northeast	0.94	0.84-1.05	NS
Year of diagnoses	0.99	0.98-1.00	NS
Received Incomplete Treatment			
Black vs. White	1.09	0.89-1.34	NS
Age at diagnosis	1.02	1.01-1.03	<.001
Stage IV vs. stage III	1.49	1.33-1.66	<.001
Charlson comorbidity score	1.10	1.05-1.15	<.001
Histology: mucinous vs. serous	1.46	1.19-1.79	<.001
Clear cell vs. serous	0.71	0.49-1.05	NS
Endometroid vs. serous	0.92	0.75-1.12	NS
Other epithelial vs. serous	1.14	0.90-1.44	NS
Grade 1 vs. grade 3	1.40	1.02-1.90	0.035
Grade 2 vs. grade 3	1.63	1.2 -2.18	0.001
Grade 4 vs. grade 3	1.53	1.10-2.13	0.011
Unknown grade vs. grade 3	1.70	1.26-2.30	<0.001
Midwest vs. Northeast	0.95	0.81-1.12	NS
South vs. Northeast	0.98	0.82-1.16	NS
West vs. Northeast	0.89	0.78-1.03	NS
Year of diagnoses	1.01	1.00-1.03	NS

CI, confidence interval; NS, not significant.