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Racial differences in stage IV colorectal cancer survival in younger and older patients

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Abstract

Introduction—African Americans (AA) compared to European Americans (EA) have poorer stage specific survival from colorectal cancer (CRC). Recent reports have indicated that the racial difference in survival has worsened over time, especially among younger patients. To better characterize this association, we used population-based SEER registry data to evaluate the impact of race on stage IV CRC survival in patients < 50 and ≥ 50.

Patients and Methods—The population was comprised of 16,782 patients diagnosed with stage IV colon and rectal adenocarcinoma between 01 January 2004 and 31 December 2011. Cox proportional hazards regression was used to evaluate the association between race and other prognostic factors and the risk of death in each age group.

Results—Younger AAs compared to EAs had a higher prevalence of proximal CRC at diagnosis, a factor associated with significantly higher risk of death in both races. Among patients < 50 years of age, AAs had a higher risk of death compared to EAs (HR 1.35, 95% CI 1.20 to 1.51), which was attenuated in patients ≥ 50 years of age (HR 1.10, 95% CI 1.04 to 1.16); p for interaction 0.01.

Conclusion—The results revealed poor overall survival in AA compared to EA, especially in those < 50 years of age. The higher prevalence of proximal CRC at diagnosis among younger aged

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AA (vs. EA) may contribute to the racial difference in survival. Future studies will be needed to understand how colonic location impacts the efficacy of treatment regimens.

Keywords

race; survival; metastatic; colon cancer; early onset

Introduction

African Americans (AA) compared to European Americans (EA) have higher colorectal cancer (CRC) incidence and poorer stage-specific survival (1, 2). For most Americans, survival has improved significantly over the past twenty years, but for AAs the rates have improved more slowly, especially among those with advanced disease stages (3, 4). Unfortunately, younger AAs appear to be more vulnerable to CRC as the relative difference in survival by race is more pronounced in younger compared to older patients (5–7).

A primary reason for improvement in stage IV colorectal cancer survival is due to better treatment options. Since the introduction of combination chemotherapy and biologic agents in 2004, median survival for stage IV CRC has increased from approximately 10 months in the mid-1990s to 20 months in 2008 (8, 9). In our previous study (5), we found that the racial disparity in advanced CRC had worsened over time, especially among younger age AAs compared to EAs diagnosed post 2003. One of the reasons for the poorer survival in AAs compared to EAs may be due to the higher prevalence of proximal neoplasia in AAs (10–15), which is often associated with worse survival (16–19), especially in the context of metastatic disease. A recent investigation has found that treatment with biologic agents appears to be less effective in patients with proximal CRC compared to distal or rectal cancer (20).

In our previous study, we had a limited number of cases younger than 50 years of age and only two years of CRC case data after the introduction of the biologic therapies. Therefore, in the present analysis we took advantage of the population-based SEER registry data to investigate racial differences in CRC survival in younger (< 50 years) and older (≥ 50 years) cases diagnosed with stage IV CRC after 2003. Our analysis focused on stage IV cases from 2004–2011 for several reasons, including: similar standard recommended treatment guidelines, a large relative difference in survival by race in stage IV CRC and a high proportion of cases dying from CRC rather than competing causes. We also investigated whether clinical or pathologic factors at diagnosis (colonic location, histology, grade, elevated CEA) differ by race and help to explain differences observed in survival.

Materials and Methods

Study population

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is a population-based data system that collects cancer incidence in 18 regions within the USA. The mortality data reported by SEER are provided by the National Center for Health Statistics. For our analysis, the study population was comprised of adults (≥ 18

years of age) with pathologically documented colon and rectal adenocarcinoma cases in the SEER registry diagnosed between 01 January 2004 and 31 December 2011 with positive follow-up time (> 0 days). SEER codes cancer stage using SEER staging criteria defined as local, regional, or distant disease, and we further limited the study population to include only cases who presented with distant disease (equivalent to TNM stage IV), which includes disease detected at lymph nodes or other distant sites. We used the following additional case selection criteria to further define the study population: single primary tumor only; AA or EA race; tumor histology reported as adenocarcinoma not otherwise specified (NOS), mucinous adenocarcinoma, or signet ring cell adenocarcinoma; tumor grade reported as well-differentiated, moderately differentiated, poorly differentiated, or undifferentiated (grades I, II, III or IV, respectively); colonic location proximal (cecum, ascending colon, or hepatic flexure transverse colon); distal (splenic flexure, descending colon, or sigmoid colon); or rectal (recto-sigmoid, or rectum); and carcinoembryonic antigen (CEA) serum level at diagnosis, either normal or elevated. Cases with variable values other than those specified (including missing or unknown values) were excluded from the final analysis set (Figure 1).

Statistical considerations

Data analysis was performed using SAS (version 9.4) and R (version 3.1.2) (21). All analyses were performed using data stratified by age at diagnosis (<50 versus ≥ 50 years of age) and gender, with primary comparisons within strata being those between EA and AA cases. Univariate associations of demographic and clinical characteristics with race were evaluated using Wilcoxon rank-sum tests for continuous variables and chi square tests for categorical variables.

Overall survival was calculated as the time (in months) from diagnosis with distant stage CRC to death from any cause. Survival times for cases alive as of 31 December 2011 were censored at the end of follow-up. Kaplan-Meier methods were used to estimate median survival time, five year survival probabilities, and corresponding 95% confidence intervals (CIs). Comparisons between survival curves were performed using log-rank tests.

Factors' associations with survival were evaluated by fitting Cox proportional hazards (CPH) regression models. Because of the significant interaction between age category and race, we fit separate CPH regression models for the two age groups. The p for interaction for both univariate and multivariable CPH models was 0.01. We first fit univariate CPH models investigating unadjusted associations between demographic and clinical characteristics and survival. We then fit multivariable CPH models with independent variables of age (as a continuous variable), race and gender (model 1); and additionally, colonic location, tumor grade, histologic type, and CEA elevation status (model 2). Finally, we further stratified by gender, and fit all univariate and multivariable CPH models described (with gender removed as an independent variable). Associations were summarized using hazard ratios (HRs) and corresponding 95% CIs.

Results

The population was comprised of 85% EAs (n= 14182) and 15% AAs (n=2600), resulting in 16,782 cases available for analysis. Among the 2735 cases under the age of 50, 82% were EA and 18% AA, and among the 14047 cases fifty years of age or older, 85% were EA and 15% AA. Also, of the 8932 males, 86% were EA and 14% AA, and of the 7750 females, 83% were EA and 17% AA. Overall, survival was better in younger compared to older cases irrespective of race. Among the AA group, those under the age of 50 had a median survival of 20 months (18 to 22 months) compared to 13 months (12 to 14 months) for those 50 years of age and older. Similarly, in the EA group, the median survival for the younger group was 25 months (24 to 26 months) compared to 14 months (14 to 15 months) for the older group.

Under age 50

Overall, 19% of AA cases diagnosed with CRC were under the age of 50 compared to 16% of EAs (Table 1). In this age group, several pathologic features differed significantly at diagnosis by race. These include tumor location, tumor grade, and CEA level. Specifically, the prevalence of proximal CRC was 17% higher in AAs women than EA women and 9% higher in AA men than EA men. In contrast, rectal cancer was 10% lower in AA women than EA women and 9% lower in AA men than their EA counterparts. CEA positivity was 6% higher in both AA men and women than their EA counterparts. The prevalence of high-grade tumors in AA and EA males was 24% and 33%, respectively. No significant differences were observed in histologic types.

Median survival was lower in AAs compared to EA (Table 2, Figure 1). Relative to EA women, AA women had significantly worse survival (18 months versus 25 months) and lower 5 year survival rates (0.12 versus 0.18; log rank $p < 0.0001$). For both AA and EA women, median survival was lowest among those with proximal neoplasia (Table 2). AA women with distal and rectal disease experienced worse survival than EA women (21 versus 27 months, distal; 17 versus 29 months, rectal). Based on stratified Cox regression analysis (Table 3), AA women compared to EA women had significantly higher risk of death (HR= 1.48, 95% CI=1.25 to 1.75). Adjustment for clinicopathologic covariates slightly attenuated the risk (HR= 1.39, 95% CI=1.17 to 1.65).

Overall, young AA men experienced worse survival compared to EAs (log-rank $p = 0.006$), with lower median survival (22 versus 25 months) and five-year survival probabilities (0.07 versus 0.18) (Table 2). Similar to women, young men of both races with proximal CRC had the lowest survival. In young men, the greatest difference in survival was observed with rectal cancer when comparing AAs to their EA counterparts (21 versus 26 months). Stratified Cox regression analysis revealed that AA men had a higher risk of mortality than EA men (HR= 1.25, 95% CI= 1.06 to 1.47) (Table 3), even after adjustment for clinical covariates (HR= 1.29, 95% CI = 1.10 to 1.52).

50 years of age and older

Personal characteristics along with clinical and pathologic features assessed at diagnosis differed by race in cases of populations of 50 years of age and older (Table 1). Average age

at diagnosis was 3 years earlier in AA men and 4 years earlier in AA women than their EA counterparts. Similar to observations observed in cases < 50 years, AA men and women were more likely to have proximal tumors and higher CEA positivity, but less likely to have high-grade lesions. Older AA women had a 5% higher prevalence of proximal tumors than EA women. However, this difference was appreciably lower compared to the 17% difference observed in the younger cohort.

Overall, median survival was slightly higher in older EA compared to AA cases (Table 2; Figure 1). Most of the racial difference in survival in cases over the age of 50 years was confined to men. For example, median survival did not differ by race in women over 50 (13 months in EAs versus 14 months in AAs). The 5-year survival probability was only slightly higher in older EA women relative to AA (0.10 versus 0.07). Furthermore, the risk of death did not differ significantly by race in older women (HR 1.03, 95% CI 0.95 to 1.11) (Table 3). Adjustment for the multiple prognostic factors at diagnosis increased the risk by 6% (HR= 1.09, 95% CI= 1.01 to 1.18).

In contrast, median survival in older AA men was poorer than in EA (13 months versus 16 months). Likewise, the 5-year survival probability was lower in older AA men compared to EA men (0.07 versus 0.10). Based on stratified CPH regression models, the univariate analysis revealed a higher risk of death for older AA men compared to EA men (HR= 1.18, 95% CI = 1.09 to 1.27) (Table 3). Adjustment for covariates led to an increase in this racial difference (HR= 1.24, 95% CI=1.15 to 1.34).

Discussion

Our analysis using the population-based SEER registry data revealed poorer stage-specific survival in AA compared to EA, especially in less than 50 years of age. Overall we observed that 19% of AA cases were diagnosed with CRC under the age of 50 compared to 16% of EA. Significantly worse survival was observed for AA men in both younger and older age groups but the largest racial difference in survival occurred among AA women < 50 years who had 48% higher risk of death than younger EA women. In contrast, survival was poor for all women ≥ 50 years of age. The prevalence of several poor prognostic factors at diagnosis differed by race, age, and sex and appears to explain some of the reasons for differences in survival by race and age. AAs of all ages had a higher prevalence of proximal tumors, higher CEA level compared to EAs but a lower prevalence of high-grade tumors. Much of the difference in CRC survival by race in younger women appears to be due to the difference in the prevalence of the proximal neoplasia at diagnosis. In summary, our findings highlight the importance of considering patient's age, sex, and colonic location on assessing the differences by race in stage IV CRC outcomes.

CRC is the second leading cause of cancer related death yet is one of the most preventable and treatable cancers when identified in the early stages with upwards of 90% survival at five years compared to less than 20% for stage IV cases. Despite recommendations by some physician organizations to begin screening earlier in AA (22, 23), others have argued that efforts should be directed toward increasing screening rates in those age 50 and over (24) because of the scarcities of resources and the much higher prevalence of disease in older

patients. In the cases of this SEER cohort with stage IV CRC, approximately one-sixth of the cases were diagnosed before 50 years of age. Moreover, the average age of diagnosis in the younger cases was 45 years in AA men, 44 years in EA men and 44 years in both AA and EA women. From a public health perspective, screening younger aged AAs should be considered, regardless of the underlying etiology, given the poor survival and high prevalence of poor prognostic factors such proximal location.

Results of the present investigation mirror earlier reports showing survival differences were most pronounced by race in younger patients (5, 6, 25). In our earlier investigation, using South Carolina Central Cancer Registry data, we explored the associations between race, age and clinicopathologic features and stage IV CRC survival. In the multivariable proportional hazards regression, it was observed that AAs compared to EAs had a significantly higher risk of death after controlling for age, sex, year of diagnosis, and first-line chemotherapy use. As in the present analysis, we observed a significant interaction between race and age ($p=0.04$) on survival. Among AAs less than 50 years of age compared to EA, the adjusted HR was 1.34 (95% CI 1.06 to 1.71). The magnitude of the HR for cases < 50 years of age is similar to the adjusted HR found in the present study (HR 1.33 95% CI 1.18 to 1.49). The reason for the higher risk of death in younger cases is clearly complex, but at least partly due to the higher prevalence of proximal CRC in younger AAs compared to younger EA (Table 2). Similar to these results, many others (26–30) have reported a higher prevalence of proximal or advanced proximal neoplasia, especially microsatellite stable (MSS) CRC in AA compared to EA. Proximal colonic location outside of the context of MSI-High CRC is associated with greater mortality, especially among stage IV CRC patients (16, 31–33). Recent evidence has also documented a poorer response to treatment in patients with proximal CRC (20).

The racial difference in survival by race and sex differed in younger and older patients. In women, as reported above, there was marked difference in the prevalence of proximal CRC in women <50 (+17% AAs) but only a 5% difference by race among those ≥ 50 years. The reasons for the racial difference in survival among the younger women are not known but may reflect differences in the hormonal signatures by race. Younger EA women compared to AAs have higher estrogen levels (34–36), which could contribute to a lower prevalence of proximal neoplasia in younger women. Recently, a large prospective study reported a strong inverse association between endogenous estrogen levels and risk of CRC, especially for colon cancer compared to rectal (37). One possibility is that estrogen receptor expression loss results in more aggressive tumor behavior. In a murine model, the loss of estrogen receptor expression in the proximal colon leads to crypt fission and reduced wound healing (38), factors associated with increased tumor prevalence and growth. Moreover, poorer survival has been observed in younger aged AA women compared to EA women with breast cancer which may be explained by the higher proportion of poor prognostic ER– breast cancer tumors in AA (39). The poorer survival in younger aged AA women in the present study is similar to what we observed in our previous analysis (5).

Racial differences in initiation and adherence to standard treatment for CRC may contribute to the stage-specific survival differences. AA patients historically have been less likely to receive standard recommended therapy and refuse therapy at a higher rate (40). Although

systemic therapy use is not available in SEER dataset, the available agents (capecitabine, 5FU, irinotecan, oxaliplatin, bevacizumab, cetuximab) for the treatment of stage IV CRC remained consistent from 2004 to 2011, aside from the addition of panitumumab in 2006, and, more importantly, the restriction of EGFR-targeted therapies to KRAS wildtype tumors by 2008 (41). AA compared to EA are more likely to have KRAS mutant tumors (7, 30), and as a whole would be expected to derive less benefit from EGFR-targeted therapies. However, no notable differences in HRs for race were observed when we analyzed the time periods separately, i.e. in 2004–2007 vs. 2008–2011. AA compared to EA are less likely to undergo surgical interventions for non-metastatic colon and rectal cancer (40, 42, 43), raising the possibility that metastectomy rates may differ by race. To our knowledge, only one previous study has evaluated metastectomy rates by race and reported no differences (44). However, two large studies (44, 45) have found that AAs had significantly lower response rates to therapy, which could reduce the likelihood of undergoing resection.

We recognize strengths of our study, including the study of a large, racially diverse population of cases with advanced-stage colorectal cancer with careful characterization of demographic and pathologic characteristics as well as vital status. However, we also recognize its limitations. First, we had no data on patient-level factors (such as comorbid conditions or lifestyle and behaviors) or treatment regimen data, which could have confounded or modified the association between race and CRC survival. These results point to the need for detailed studies identifying risk factors for the poor prognostic signatures as well as patient-level, clinical, molecular, and treatment-related data to help advance understanding of the racial disparity in CRC survival.

In summary, using the large population based SEER dataset, we have shown that AAs with stage IV CRC have higher mortality than EAs, particularly in those < 50 years of age. These data suggest that CRC screening should have greater emphasis in younger AA cases and further raise the possibility that national guidelines for CRC screening should be modified especially for AA females.

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Clinical Practice Points

Several previous investigations have detailed a racial disparity in colorectal cancer survival yet the reasons for this remain incompletely understood. The higher rates of death in AAs compared to EAs persist despite adjustment for common confounding variables such as sex, age, and socioeconomic status. Our results suggest that the racial difference in survival may be influenced by differences in prevalence of proximal and rectal CRC at diagnosis; survival among both AAs and EAs with proximal CRC in stage IV disease is poor. Future research is needed to understand why AAs develop proximal neoplasia at a younger age. There was a 17% difference in the prevalence of proximal CRCs in younger female AAs compared to EAs yet only a 5% difference by race among female cases ≥ 50 years. We also need to have a better understanding of how to improve treatment response in patients with stage IV proximal CRC.

Figure 1.
Flowchart detailing exclusion criteria and number of cases dropped for each clinical or pathologic variable.

Figure 2. Survival distributions were analyzed, using survival probability in months from diagnosis, for (A) under 50 male, (B) under 50 female, (C) 50 & over male, (D) 50 & over female.

Table 1

Univariate associations of demographic and clinical characteristics with gender and race for younger (<50 years) and older (≥ 50 years) patients.

Characteristic ^a	Age < 50 years			
	Male (n=1467)	Female (n=1268)	<i>p</i> ^b	<i>p</i> ^b
	EA (n=1204)	EA (n=1033)	AA (n=263)	AA (n=235)
Age (years)	44(18–49)	44(18–49)	45(19–49)	44(21–49)
			0.51	0.14
Colonic Location			0.004	<0.0001
Distal	416(35)	432(42)	91(35)	83(35)
Proximal	281(23)	272(26)	85(32)	100(43)
Rectal	507(42)	329(32)	87(33)	52(22)
Tumor Grade			0.005	0.16
Low	808(67)	708(69)	200(76)	172(73)
High	396(33)	325(31)	63(24)	63(27)
Histologic Type			0.97	0.43
Adeno NOS	1073(89)	919(89)	235(89)	213(91)
Mucinous	86(7)	74(7)	19(7)	17(7)
Signet Cell	45(4)	40(4)	9(3)	5(2)
CEA Antigen			0.02	0.05
Normal	240(20)	216(21)	36(14)	36(15)
Elevated	964(80)	817(79)	227(86)	199(85)
			Age ≥ 50 years	
	Male (n=7565)	Female (n=6482)		
	EA (n=6534)	EA (n=5411)	AA (n=1031)	AA (n=1071)
Age (years)	65(50–98)	65(50–103)	62(50–94)	65(50–108)
			<0.0001	<0.0001
Colonic Location			<0.0001	<0.0001

Distal	2029(31)	333(32)	1535(28)	321(30)
Proximal	2499(38)	447(43)	2607(48)	572(53)
Rectal	2006(31)	251(24)	1269(23)	178(17)
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Tumor Grade			<0.0001	<0.0001
Low	4623(71)	793(77)	3649(67)	829(77)
High	1911(29)	238(23)	1762(33)	242(23)
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Histologic Type			<0.0001	0.10
Adeno NOS	5913(91)	977(95)	4852(90)	965(90)
Mucinous	477(7)	43(4)	453(8)	95(9)
Signet Cell	144(2)	11(1)	106(2)	11(1)
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CEA Antigen			<0.0001	<0.0001
Normal	1293(20)	136(13)	1024(19)	128(12)
Elevated	5241(80)	895(87)	4387(81)	943(88)

Column percents may not total 100 % due to rounding

^a Descriptive measures are median (range) for age, and frequency (%) for all others

^b *p* value is based on Wilcoxon's rank-sum test for age-race association and a chi-square test for all others

Table 2

Kaplan-Meier median survival time and survival probability estimates by age, gender, colonic location and race.

Age	Gender	Colonic Location	Race	n	*n _e	Prevalence (%)	[†] M (mos)	[†] M 95% CI	[‡] P(S)	P(S) 95% CI
Age <50 years										
Male	Distal	EA	EA	416	241	35	26	(23,31)	0.20	(0.15, 0.27)
			AA	91	65	35	25	(20,31)	0.02	(0.00, 0.14)
	Proximal	EA	EA	281	191	23	19	(16,23)	0.16	(0.11, 0.22)
			AA	85	60	32	18	(15,25)	0.09	(0.03, 0.22)
	Rectal	EA	EA	507	312	42	26	(23,29)	0.18	(0.14, 0.24)
			AA	87	60	33	21	(14,23)	0.14	(0.06, 0.31)
		OVERALL	EA	1204	744		24	(23,26)	0.18	(0.15, 0.22)
			AA	263	185		22	(19,24)	0.07	(0.04, 0.14)
Female	Distal	EA	EA	432	257	42	27	(25,32)	0.17	(0.13, 0.23)
			AA	83	58	35	21	(18,27)	0.14	(0.07, 0.28)
	Proximal	EA	EA	272	196	26	17	(14,20)	0.17	(0.12, 0.23)
			AA	100	69	43	15	(12,20)	0.09	(0.04, 0.23)
	Rectal	EA	EA	329	188	32	29	(27,33)	0.21	(0.16, 0.29)
			AA	52	41	22	17	(15,22)	0.12	(0.05, 0.27)
		OVERALL	EA	1033	641		25	(24,27)	0.18	(0.15, 0.22)
			AA	235	168		18	(16,20)	0.12	(0.08, 0.19)

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Age	Gender	Colonic Location	Race	n	*n _e	Prevalence (%)	$\hat{t}_M$ (mos)	$\hat{t}_M$ 95% CI	$\hat{P}(S)$	$\hat{P}(S)$ 95% CI
Age 50 years										
Male	Distal	EA	2029	1450	31	19	(17,20)	0.12	(0.10, 0.14)	
			AA	333	250	32	14	(12,18)	0.10	(0.06, 0.15)
	Proximal	EA	2499	1957	38	12	(11,12)	0.08	(0.07, 0.10)	
			AA	447	358	43	11	(9,13)	0.05	(0.03, 0.09)
	Rectal	EA	2006	1407	31	18	(17,20)	0.11	(0.09, 0.13)	
			AA	251	186	24	15	(11,17)	0.08	(0.04, 0.13)
OVERALL		EA	6534	4814		16	(15,16)	0.10	(0.09, 0.11)	
		AA	1031	794		13	(11,14)	0.07	(0.05, 0.10)	
Female	Distal	EA	1535	1107	28	17	(16,19)	0.13	(0.11, 0.15)	
			AA	321	237	30	16	(12,20)	0.07	(0.04, 0.13)
	Proximal	EA	2607	2079	48	10	(9,11)	0.09	(0.08, 0.11)	
			AA	572	450	53	13	(11,14)	0.07	(0.05, 0.11)
	Rectal	EA	1269	942	23	14	(13,16)	0.10	(0.08, 0.13)	
			AA	178	134	17	15	(11,21)	0.07	(0.03, 0.16)
OVERALL		EA	5411	4128		13	(12,13)	0.10	(0.09, 0.11)	
		AA	1071	821		14	(12,15)	0.07	(0.05, 0.10)	

* n_e= number of events;
 $\hat{t}_M$ =median;

$\hat{P}(S) = \text{five-year survival probability}$

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Table 3

Summary of results from Cox proportional hazards regression models

Variable	Level	Cases < 50 years				Cases 50 years			
		Male n=1467		Female n=1268		Male n=7565		Female n=6482	
		Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Age ^a		0.89 (0.80, 1.00)	0.94 (0.84, 1.05)	0.96 (0.86, 1.07)	0.97 (0.87, 1.08)	1.33 (1.30, 1.37)	1.34 (1.30, 1.37)	1.39 (1.35, 1.42)	1.37 (1.34, 1.42)
Race	EA	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	AA	1.25 (1.06, 1.47)	1.29 (1.10, 1.52)	1.48 (1.25, 1.75)	1.39 (1.17, 1.65)	1.18 (1.09, 1.27)	1.24 (1.15, 1.34)	1.03 (0.95, 1.11)	1.09 (1.01, 1.18)
Colonic Location	Distal	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Proximal	1.30 (1.10, 1.54)	1.17 (0.99, 1.40)	1.46 (1.24, 1.72)	1.34 (1.13, 1.58)	1.36 (1.28, 1.45)	1.27 (1.19, 1.35)	1.35 (1.26, 1.44)	1.17 (1.09, 1.25)
	Rectal	1.05 (0.90, 1.22)	1.07 (0.92, 1.24)	0.96 (0.81, 1.14)	1.01 (0.85, 1.19)	0.98 (0.92, 1.05)	1.04 (0.97, 1.11)	1.06 (0.98, 1.15)	1.03 (0.95, 1.12)
Grade	Low	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	High	1.63 (1.42, 1.86)	1.56 (1.35, 1.79)	1.49 (1.29, 1.72)	1.36 (1.17, 1.59)	1.46 (1.38, 1.55)	1.40 (1.32, 1.49)	1.48 (1.40, 1.58)	1.48 (1.39, 1.57)
Histology	Adeno NOS	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Mucinous	1.32 (1.04, 1.67)	1.30 (1.02, 1.66)	1.11 (0.86, 1.43)	1.06 (0.82, 1.37)	0.98 (0.89, 1.09)	0.93 (0.84, 1.03)	0.98 (0.88, 1.08)	0.93 (0.84, 1.03)
	Signet Cell	2.48 (1.84, 3.35)	2.05 (1.49, 2.82)	2.16 (1.55, 2.99)	1.90 (1.35, 2.68)	1.80 (1.52, 2.14)	1.51 (1.27, 1.80)	1.41 (1.16, 1.72)	1.22 (1.00, 1.50)
CEA	Normal	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Elevated	1.37 (1.15, 1.62)	1.55 (1.30, 1.85)	1.67 (1.38, 2.01)	1.70 (1.41, 2.05)	1.43 (1.34, 1.54)	1.55 (1.45, 1.67)	1.57 (1.45, 1.70)	1.71 (1.58, 1.85)

Model 1: Univariate

Model 2: Covariates included age, race, colonic location, tumor grade, histologic type, and CEA

^aHR and 95% CI for age correspond to a 10 yr increment