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Prognostic factors in relation to the racial disparity in advanced colorectal cancer survival

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Introduction

Since the early 1980s, colorectal cancer (CRC) incidence and mortality rates have decreased significantly for all races[1]. Despite these favorable trends, there is a growing disparity in CRC survival between African Americans (AA) and European Americans (EA) with both incidence and mortality rates significantly higher in AA than EA[2]. The disparity is present for each tumor stage, but is especially pronounced among advanced stage patients[1, 3].

The treatment of metastatic CRC (mCRC) has advanced considerably during the past 15 years thanks to the approval of several new therapies[1, 3–5]. New combination chemotherapy regimens (e.g. FOLFOX and FOLFIRI) were approved in the early 2000s and monoclonal antibodies (e.g. bevacizumab and cetuximab) were approved in 2004 to augment these regimens[1, 3–5]. The combination chemotherapy regimens in patients with limited metastatic disease have shown tumor response rates in the range of 55–65% and many patients are successfully down-staged to candidates for surgical resection[6]. These therapeutic advances have lengthened the median survival among all mCRC patients from 8–12 months in the mid-1990s to 18–24 months by 2008[6]. However, despite these overall improvements, the racial disparity in mortality has increased during the past 15 years from a 21% difference between AA and EA in the mid-1980s to a 72% difference by the mid-2000s[3, 7]. The reasons for the racial disparity and widening gap in mCRC survival are not known.

One possible contributing factor is racial differences in access to and/or utilization of the newer CRC treatments. AA have been observed to be less likely than EA to receive the standard of care for CRC and to decline therapy at a higher rate than EA[8–12]. Another

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Conflict of Interest Page

All other authors state that they have no conflicts of interest.

Colorectal cancer mortality rates are higher in African-Americans (AA) than European-Americans (EA). We studied the role of race and survival in a small set of advanced stage patients. The risk of death was 145% higher among younger AA compared to EA but only 16% higher in older patients. Future studies should examine why the disparity was larger among younger patients.

possibility is that AA compared to EA have a higher prevalence of poor prognostic indicators at diagnosis, leaving them predisposed to poorer outcomes. For example, factors such as obesity, diabetes, hyperlipidemia, and higher WBC levels are associated with poorer CRC outcomes in most studies[13–17] and the prevalence of obesity and diabetes in the general population are consistently higher in AA compared to EA[18, 19]. These four factors are also positively correlated with inflammation, growth factors and oxidative stress -- features linked to enhanced tumorigenicity and chemotherapeutic resistance[20–22]. Anemia (i.e. low hemoglobin levels) is associated with chronic inflammation, cancer, sickle cell disease, or iron deficiency, and is typically higher among AA and predisposes to cardiovascular (CVD) events and all-cause mortality[23–27].

Another possible reason for the racial difference in survival is that a subset of younger AA patients may have a biologically more aggressive disease. AA are consistently diagnosed with CRC at earlier ages and have a proclivity for proximally based tumors[28–31], which are associated with poorer survival[32, 33]. Earlier age at diagnosis, in general, is associated with more aggressive CRC biology, including higher genome copy number and increased genomic complexity[34–36].

Previously, using statewide South Carolina cancer registry data[37], we documented the presence of a disparity between AA and EA in survival from mCRC that was largely concentrated among those who were diagnosed at younger age. A recent study performed within an equal access health care system also reported poorer survival among younger AA compared to EA patients but not among older.[38]. The present study was conducted to follow-up on our earlier finding by studying a cohort of patients with more in-depth clinical information to better assess the underlying reasons for the racial difference in advanced stage CRC. In this retrospective study, we investigate the impact of demographic and clinical factors on the racial disparity in survival in younger and older patients while taking into account the impact of treatment, and prognostic factors.

Methods

To study the potential role of clinical- and treatment-related factors on the racial disparity in survival from mCRC, we carried out a retrospective cohort study of 82 patients (26 AA, 56 EA), collecting data from the electronic medical records of mCRC patients treated at a single institution from 6/1/2004 through 5/31/2008 with follow-up through 6/30/2010. The study focused on the period after 2003 since mCRC has standard recommendations and a documented change in chemotherapy usage in 2004. All research activities took place at the Hollings Cancer Center (HCC) of the Medical University of South Carolina, and were approved by the Institutional Review Board of the Medical University of South Carolina.

Using the HCC Cancer Registry for ascertainment, the study population was comprised of all newly diagnosed patients of AA or EA descent with stage IV colorectal cancer. Patients with a histologically confirmed CRC adenocarcinoma were included. Following a defined protocol and pretested data abstraction form, study data were abstracted from the electronic medical records and entered it into a secured study database by a trained research assistant. For quality control, a clinical fellow independently reviewed 10% of the records, and discrepancies were resolved by the lead study investigator (KW). Of the 92 patients with a diagnosis of advanced stage CRC from 2004 to 2008 at the HCC, 82 had histologically confirmed stage IV adenocarcinoma of the colon or rectum and were included in the study.

The main study outcome was survival. Independent variables included demographic characteristics, clinical variables related to the mCRC diagnosis, and mCRC treatment received. Sociodemographic characteristics included age, sex, distance (in miles) from home

to medical center and marital status. Clinical data (see Table 1 for complete list of variables) included the diagnostic factors of date of diagnosis, histology (adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma), grade, and colonic location. The location of the primary tumor within the colorectum was classified as proximal (cecum, ascending colon, hepatic flexure transverse colon), distal (splenic flexure, descending colon, sigmoid colon) or rectal (recto-sigmoid, or rectum). Tumor grade was classified as low grade (well differentiated, moderately differentiated) or high grade (poorly differentiated, undifferentiated). Tumor histology was coded as adenocarcinoma not otherwise specified (NOS) or mucin-containing (mucinous or signet ring cell adenocarcinoma). Treatment-related clinical variables included receipt of all first-line therapies, including chemotherapy (and type when possible).

Statistical analysis

Survival time was calculated as the time from diagnosis with distant stage CRC to death from any cause through December 31, 2010; subjects alive as of this date were censored at the end of follow-up. Kaplan-Meier methods were used to generate median survival time and corresponding 95% confidence intervals by race and age. The decision to stratify our results by age was guided by an a priori hypothesis that the racial disparity in survival would be more pronounced among younger patients compared to older. To investigate this hypothesis we did the following. First, we observed that survival curves appeared to be visually different by race among the younger and older age groups. Second, we observed that survival time was different in younger and older patients by race. Third, to characterize the observed difference in race and age more formally, we performed a Stratified Wilcoxon (Breslow) test for equality of survivor functions where the stratified variable was median age and the p-value for the difference was 0.04. Prognostic factors associated with survival were evaluated by fitting Cox proportional hazards regression models for younger patients (< 61 years) and older patients (≥ 61 years). For each age group, we then fit multivariable models for race plus each one of the following prognostic variables by itself (e.g., model 1: race plus age, model 2: race plus sex, etc): age, sex, obesity (BMI), prediagnostic CEA (median), diabetes (yes), hemoglobin level (median), white blood cell count (median), hyperlipidemia (yes), tumor histology, colonic location. We selected this modeling approach out of concern for over-fitting data with sparse stratum sizes especially considering that several of our key prognostic variables had missing data points (e.g. CEA, hemoglobin). All statistical tests were considered significant at level 0.05.

Results

The median age was 56.7 years for AA and 61.6 years for EA (Table 1). As anticipated based on our previous findings using statewide registry data[37], we observed a difference in survival between younger and older patients by race (Stratified Wilcoxon, $p = 0.04$). These findings justified our plan to make the racial comparisons separately for those above and below the median age (i.e. 61 years) by race (Table 1).

Younger Patients

Descriptive Findings—While not statistically significant, AA compared to EA were younger, more likely male, had a higher prevalence of hypertension, diabetes, hyperlipidemia and higher CEA levels. Compared to EA, AA had similar rates of any chemotherapy initiation (76% to 80%) and FOLFOX or FOLFIRI specifically (73% vs. 80%) but lower rates of bevacizumab usage (36% vs. 50%). The tumors among younger AA compared to EA were more likely to be located in the colon (69% vs. 50%) and mucinous (27% vs. 4%) and were less likely to be poorly differentiated (7% vs. 19%).

Factors Associated with Survival—In the univariate analyses among patients < 61 years, factors significantly associated with poorer survival were younger age, diabetes, median CEA level ng/mL, hyperplipidemia, and mucinous tumor type (Table 2). Sex, marital status, distance to cancer center, receipt of therapy, median WBC, and obesity were not statistically associated with survival.

Among patients < 61 years, AA had significantly poorer survival compared to EA (log-rank test p= 0.02) (Table 3). In the univariate Cox Proportional Regression analysis of race and survival among younger participants, AA race was associated with a 2.45 (1.15–5.23; p= 0.02) higher risk of death (Table 2 & 3). Adjusting for one covariate at a time, AA race remained significantly associated with survival after adjusting for sex, therapy, distance to treating cancer center, marital status, diabetes, obesity, hyperlipidemia, median CEA level, and colonic location (Table 3). Adjustment for age (HR 1.8) and WBC (HR 2.05) attenuated the association so that it was no longer statistically significant, but the estimates were still in the same direction. Median hematocrit level appreciably attenuated the relationship between race and survival (HR 1.17 (0.44–3.15)).

With regard to the impact of clinicopathologic features on the association between race and survival, mucinous histology and colonic location attenuated the effect of race on survival. The small number of cases with mucin-containing tumors was a limiting factor; nevertheless, all patients in the study with mucinous tumors died compared with only 69% of those with nonmucinous tumors. In the younger group AA presented with 80% (i.e., 4 out of 5) of the mucinous tumors. Among younger patients mortality also differed by colonic location: 80% of the patients with of colonic tumors died compared to 59% of the patients with rectal tumors. All of the AA patients with rectal cancer died compared to 46% of the EA patients. Median survival for AA and EA patients with rectal cancer was 8.9 months and 35 months, respectively. For colon cancer, 77% of AA died with colon cancer and 85% of EA. Median survival for AA and EA was 13 months and 27 months, respectively.

Older Patients

Descriptive Findings—While not statistically significant, among older patients, AA were more likely to be male and have hypertension and diabetes (Table 1). AA also had lower WBC and hemoglobin levels and higher CEA levels compared to EA. AA had higher rates of initiation of chemotherapy (72% vs. 47%) but similar rates of FOLFOX/FOLFIRI and Bevacizumab regimens (75% vs. 69%). Compared to EA, AA had a slightly higher prevalence of colonic tumors and adenocarcinomas not otherwise specified (100% vs. 83%).

Factors Associated with Survival—Among patients > 61 years, older age diabetes, median CEA level ng/mL, and mucinous tumor type were all significantly associated with poorer survival (Table 2). Higher median WBC levels were marginally associated with increased risk of death among older patients, HR 1.94 (0.94–4.01; p=0.07). Sex, receipt of therapy, distance to medical center, obesity, hyperlipidemia, and colonic location were not statistically significant related to mortality.

Median survival was similar between AA and EA in the older group (log-rank test p= 0.72) (Table 3). In the univariate analysis Cox Proportional Regression, race was not an important determinant of death: HR 1.16 (0.49–2.73; p=0.74) (Table 2 &3). In multivariable analysis, race was not associated with an increased risk of death with the addition of any of the prognostic variables.

Discussion

The purpose of this study was to investigate with more in-depth clinical data than previous studies why younger AA have worse survival from advanced CRC than younger EA. The findings of this smaller, more in-depth study corroborated our previous observation that in mCRC patients younger AA compared to younger EA had worse overall survival[37]. The racial difference was most pronounced among CRC patients under 61 years of age, the median age. In our study, rates of chemotherapy usage did not differ by race, so the difference in survival is not likely due to differential receipt of treatment. However, clinical conditions and serum measures such as diabetes, CEA level, hyperlipidemia, and hemoglobin and were strongly associated with increased mortality.

We examined several known clinical prognostic factors to evaluate their associations with survival by age and race. Of the five variables we hypothesized to be associated with poorer outcomes (i.e. diabetes, obesity, anemia, high WBC count, hyperlipidemia), most were associated with poorer/worse survival except obesity. Presence of diabetes was a strong negative prognostic factor in both age groups (younger RR 4.47 (95% CI 1.21–16.40); older RR 4.81 (95% CI 1.87–12.36)); the prevalence was higher among AA compared to EA in younger (13% AA, 8% EA) and older (36% AA, 17% EA) groups. Despite this high prevalence, the HR for race in the younger age group was essentially unchanged in the multivariable models, indicating that diabetes does not explain the racial difference in survival among younger patients. This finding was surprising given prior studies have consistently shown higher rates of diabetes in AA as well as an association among diabetes, insulin resistance and risk of CRC and, recently, with poorer CRC specific mortality[39–41]. AA had lower hemoglobin levels than EA. Lower levels of hemoglobin have been found to be an important predictor of death and reportedly also interfere with the efficacy of chemotherapy[42, 43]. Additionally, the association between race and survival among the younger patients was diminished when controlling for hemoglobin perhaps because EA with higher hemoglobin levels survive longer but AA with higher levels do not.

On a population level, the racial disparity in CRC survival is growing, especially among those with advanced disease[1, 3]. Similar to our earlier report[37], we again observed poorer CRC survival in younger AA compared to EA but no strong difference among older patients. Two recent studies that examined the impact of the new platinum and biologically based regimens among advanced stage CRC patients have not observed differences in overall survival by race[44, 45]. These reports differ in some key ways from the present study results. In both studies, despite similar survival rates by race, AA had lower response rates to treatment, which may translate to poorer survival over time; moreover, a racial difference was observed in one study among patients receiving fluorouracil-based regimens[45]. Also, in both studies, approximately one-third of patients had previous adjuvant therapy (meaning that patients were diagnosed at earlier stage which then progressed) whereas all of our patients were incident stage IV cases (i.e. metastatic at diagnosis), preventing direct comparisons between the results of the two studies to ours. Although we had limited information on treatment utilization, we did not observe a strong protective association between therapy and survival among younger AA. Our findings raise the possibility that the poorer survival in AA is due to something unique about the clinical or tumor profiles of CRC in younger AA.

Racial differences in tumor phenotype at diagnosis are a potential source of the difference in survival. AA are known to be diagnosed with CRC at an earlier age[28], and earlier age of onset is associated more advanced, aggressive and hereditary CRC[34–36, 46, 47]. Although our sample size is limited, we identified a higher proportion of mucinous-type tumors in the younger AA vs. EA (27% vs. 4%) and a different pattern among older AA vs. EA (0% vs.

14%). Colonic versus rectal location also exhibited a different pattern by race and age respectively: <61 yrs (AA 70%, EA 50% colon); >= 61 (AA 70%, EA 80% colon). Mucinous histology and proximal location in the context of advanced stage cancer have been consistently associated with poorer CRC outcomes[48–50]. In our investigation, we observed that mucinous histology (HR 1.44) and--to a lesser extent --colonic location (HR 1.97) attenuated the association between race and survival among the younger persons. In future investigations, it will be important to have more detailed pathologic, molecular genetic, and epigenetic marker data to more precisely characterize the racial differences in tumor characteristics.

The advantages of our study include an evaluation of a reasonably thorough set of prognostic factors that allowed us to include in our analyses patients who would have likely been too sick to participate in a prospective study. Important limitations of our study include: the small sample size, lack of data on the personal characteristics, poor or missing data with respect to key prognostic factors (e.g. obesity), limited data on treatment, and no data on treatment response or adverse events. The small sample size combined with our focus on analyses stratified by age resulted in small strata sizes not only limited the statistical precision but also limited our ability to carry out the multivariable analyses that would be optimal for addressing the complex topic of racial differences in colorectal cancer survival. The results of the present study should thus be considered hypothesis generating.

Conclusion

The present study has generated new clues about factors that may contribute to the racial disparity among the younger AA compared to EA. One possibility is that measuring a constellation of poor prognostic factors – rather than a single marker— will better capture the tumor promoting `milieu'. For example, disease states such as diabetes combined with obesity (or other prognostic markers) act synergistically to together create an inflammatory, growth factor rich environment favorable to tumor growth, chemotherapeutic resistance, and decreased immune capacity [51–53]. Other potentially important prognostic variables, which were not considered in this study, such as alcohol consumption, smoking, physical activity, diet and a thorough consideration of comorbidities, would be important to include in future investigations.

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Clinical Practice Points

- Although based on a small sample, our results reinforce our previous findings that the racial disparity in mCRC survival is concentrated in younger patients.
- Our finding of a higher burden of comorbid conditions among younger AA highlights the importance of focusing on careful clinical management to treat any underlying comorbid condition which may help to improve adherence and/or response to therapy
- Increased awareness of the poor prognosis among younger AA patients may help to highlight the need for rapid referral to clinical trials among patients not responding to front-line therapy.

Table 1

Characteristic of younger and older patients[a] at diagnoses by race

Characteristics	Younger (< 61 years)		Older (≥ 61 years)	
	AA (n=15)	EA (n=26)	AA (n=11)	EA (n=29)
Male, n (%)	10 (66.7)	14 (53.9)	4 (36.7)	14 (46.7)
Age, mean (SD) Age, median	47.9 (8.7) 49.9	51.9 (8.0) 54.6	67.6 (6.9) 65.5	68.9 (8.0) 65.3
BMI, mean (SD)	25.8 (11.0)	29.3 (6.2)	24.8 (4.3)	27.9 (6.5)
Family History of CRC, n (%)				
No	5 (33.3)	16 (61.5)		
Yes	1 (6.7)	3 (11.5)	2 (18.2)	5 (16.7)
Unknown	9 (60.0)	7 (26.9)	4 (45.6)	10 (50.0)
Personal medical history				
Hypertension, yes, n (%)	10 (38.5)	4 (26.7)	6 (54.6)	13 (43.3)
Diabetes, yes, n (%)	2 (13.3)	2 (7.7)	4 (36.4)	5 (16.7)
Hypercholesterolemia, yes, n (%)	3 (11.5)	0 (0.0)	2 (18.2)	5 (16.7)
Hyperlipidemia, yes, n (%)	2 (13.3)	2 (7.8)	2 (18.2)	3 (10.0)
Serum Biomarkers, mean (SD)				
White Blood Count -- k/ul	9.2 (3.7)	8.9 (4.9)	6.9 (2.5)	8.7 (2.8)
CEA Level-- ng/ml	637.6 (1897.3)	289.6 (641.4)	346.3 (506.6)	296.5 (632.8)
Hemoglobin g/dL	11.0 (1.7)	12.2 (2.2)	11.0 (2.3)	12.5 (4.8)
1st line chemotherapy, n (%)				
No	2 (7.7)	0 (0.0)	2 (18.2)	2 (6.7)
Yes	20 (76.2)	12 (80.0)	8 (72.3)	14 (46.7)
Unknown	4 (15.4)	3 (20.0)	1 (9.1)	14 (46.7)
Type of Treatment[b], n (%)				
FOLFOX or FOLFIRI	8 (72.7)	16 (80.0)	6 (75.0)	9 (69.2)
Bevacizumab	4 (36.4)	10 (50.0)	6 (75.0)	9 (69.2)
[2]Pathology, n (%)				
Colon				
Proximal	4 (30.8)	7 (26.9)	2 (20.0)	14 (46.7)
Distal	5 (38.5)	6 (23.1)	5 (50.0)	10 (33.3)
Rectal	4 (30.8)	13 (50)	3 (30.0)	6 (20.0)
[3]Histologic Type, n (%)				
Adenocarcinoma (NOS)	11 (73.3)	25 (96.2)	11 (100)	24 (82.8)
Mucinous	3 (20.0)	1 (3.9)	0	4 (13.8)
Signet cell	1 (6.7)	0	0	0
Grade, n (%)				
Well differentiated	3 (20.0)	5 (19.2)	1 (9.1)	1 (3.5)
Moderately differentiated	4 (26.7)	10 (38.5)	6 (54.6)	21 (72.4)

Characteristics	Younger (< 61 years)		Older (≥ 61 years)	
	AA (n=15)	EA (n=26)	AA (n=11)	EA (n=29)
Poorly differentiated	1 (6.7)	5 (19.2)	1 (9.1)	1 (3.5)
Unknown	7 (46.7)	6 (23.1)	3 (27.3)	6 (20.7)

[a] age was dichotomized at the median (<61 years, ≥ 61 years)

[b] based on n=60; FOLFOX (i.e., Folinic acid (leucovorin), Fluorouracil (5-FU), and Oxaliplatin (Eloxatin) or FOLFIRI (i.e., leucovorin, 5-FU, and irinotecan (Camptosar))

Table 2

Association of demographic and clinical variables and survival in younger and older patients.

	< 61 years HR (95% CI)	≥61 years HR (95% CI)
Race[a]	2.45 (1.15 – 5.23)	1.16 (0.49–2.73)
Age	0.89 (0.84–0.93)	1.04 (1.0–1.09)
Sex	1.73 (0.81–3.71)	1.76 (0.84–3.68)
Married	0.57 (0.27–1.20)	1.73 (0.81–3.68)
First line Therapy	0.84 (0.53–1.31)	0.89 (0.61–1.31)
No	1.31 (0.17–9.18)	0.19 (0.06–0.62)
Yes (reference)	1.0	1.0
Unknown	1.18 (0.14–10.24)	0.37 (0.11–1.16)
Distance to HCC --median	0.93 (0.45–1.96)	1.15 (0.57–1.32)
Diabetes-- yes	4.47 (1.21– 16.40)	4.81 (1.87–12.36)
Obesity—yes	0.57 (0.19– 1.77)	0.59 (0.23–1.50)
CEA median	2.59 (1.09–6.16)	3.50 (1.40–8.73)
White Blood Count (WBC)-- median	0.77 (0.35–1.70)	1.94 (0.94–4.01)
Hyperlipidemia-- yes	3.61 (1.21–10.75)	1.69 (0.42–4.61)
Hemoglobin (Hgb)-- median	0.43 (0.19–0.93)	0.76 (0.36–1.58)
Mucinous tumor	5.07 (1.72–14.9)	4.57 (1.45–14.4)
Colonic location		
Proximal	0.93 (0.37–2.37)	1.26 (0.56–2.83)
Distal	1.0	1.0
Rectal	0.48 (0.19–1.20)	0.64 (0.23–1.73)

[a] the p-value from the Cox Regression Model for the difference by race for those < 61 years is p=0.02 and those ≥ 61 years p=0.74

Table 3

Association of race and risk of death among younger and older patients

	< 61		>=61	
	EA	**AA**	**EA**	**AA**
N	26	15	30	11
Median survival (95% CI)	31.0 (17.1–35.6)	12.7 (6.7–23.6)	16.4 (8.3–32.5)	11.7 (7.2– α)

	RR (95% CI)	**RR (95% CI)**
Race alone	2.45 (1.15 – 5.23)	1.16 (0.49–2.73)
Race and		
Age	1.80 (0.79–4.08)	1.09 (0.46–2.57)
Sex	2.64 (1.22–5.71)	1.17 (0.49–2.73)
Therapy	2.76 (1.25–6.10)	1.35 (0.53–3.39)
Distance HCC	2.72 (1.18–6.24)	1.23 (0.51–2.98)
Married	2.25 (1.03–4.91)	1.61 (0.62–4.16)
Diabetes	2.41 (1.12– 5.17)	1.03 (0.43–2.46)
Obesity[a]	3.77 (1.36– 10.42)	0.97 (0.36–2.57)
Hyperlipidemia	2.54 (1.18–5.48)	1.09 (0.44–2.65)
CEA median[b]	3.14 (1.26–7.83)	0.95 (0.36–2.46)
WBC median[c]	2.03 (0.92–4.47)	1.48 (0.58–3.77)
Hgb median[c]	1.17 (0.44–3.15)	1.04 (0.44–2.45)
Mucin Histology	1.44 (0.82–4.50)	1.45 (0.59–3.57)
Colonic Location	1.97 (0.86–4.55)	1.07 (0.43–2.67)

[a] Obesity (younger, n=28; older, n=34)—defined as BMI >=30;

[b] CEA5 (younger n=32, older n= 30)

[c] WBC and HGB (younger n=36, older n=37)