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Risk of Colorectal Cancer Among Caucasian and African American Veterans with Ulcerative Colitis

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Abstract

Background—African Americans are at an increased risk of developing sporadic colorectal cancer (CRC) compared to Caucasians. Ulcerative colitis (UC) is a risk factor for developing CRC; however, risk differences for CRC between African Americans and Caucasians with UC are unknown.

Methods—We performed a cohort study of patients with a diagnosis of UC during fiscal years 1998 to 2009 using the national Veterans Affairs administrative datasets. Cumulative CRC incidence rates and incidence rate ratios were calculated and Cox proportional hazards models were used to examine the association between race and the CRC risk.

Results—The cohort comprised of 20,949 patients with UC. A total of 168 incident cases of CRC were identified during 112,243 patient-years (PY) of follow-up; overall CRC incidence rate was 163/100,000 PY (95% confidence interval [CI] 139–187/100,000 PY). The CRC incidence rates were 158/100,000 PY (95% CI 134–181/100,000 PY) and 180/100,000 PY (95% CI 155–205/100,000 PY) in Caucasians and African Americans, respectively, with an incidence rate ratio of 1.17 (95% CI 0.69–1.97). The 3, 5, and 10-year cumulative incidence rates for CRC were 0.36%, 0.76%, 1.79% for African Americans and 0.41%, 0.76%, 1.43% for Caucasians. African Americans were not at an increased risk for CRC (adjusted hazard ratio: 1.10, 95% CI 0.65–1.87) compared to Caucasians.

Conclusions—In a national cohort of UC patients the risk of developing CRC in African Americans was no higher than in Caucasians. The reasons for lack of racial differences compared to sporadic CRC are not clear; access to care, genetic factors, and molecular pathways require further study.

Keywords

inflammatory bowel disease; race; disparity; colorectal cancer

Ulcerative colitis (UC) is associated with a marked increased risk of colonic dysplasia and colorectal cancer (CRC), estimated to be 1.5–5 times higher than that of non-UC controls.^{1–3}

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Inflammation has been associated with an increased risk of dysplasia in UC⁴ and progression to dysplasia in UC may differ from the adenoma-carcinoma pathway associated with sporadic CRC. As the etiology of dysplasia in UC-associated and sporadic CRC may differ, risk factors for UC associated CRC and sporadic CRC may differ.⁵

Racial differences have been consistently observed in sporadic CRC in the United States. African Americans are more likely to develop CRC overall, cancer in the proximal colon, CRC at a younger age, advanced CRC at diagnosis, and have higher CRC-related mortality.^{6–11} There are several proposed mechanisms of racial disparities in CRC risk between African Americans and Caucasians including differences in access to medical care, perceptions of surveillance, frequency and method of surveillance, and genetics.^{12–15}

There are no data evaluating racial disparity in the risk of UC-associated CRC. Early studies suggested African Americans may have more severe or extensive disease compared to Caucasians, but a recent systematic analysis reported similar severity and extent.¹⁶ Recognition of disparities in UC-associated CRC may alter surveillance practices, whereas an absence of racial disparity will suggest a separate mechanism of CRC risk in UC compared to sporadic CRC. Our aims were to evaluate if a racial difference exists between African American and Caucasian patients with UC and identify associated risk factors.

PATIENTS AND METHODS

Data Source

We performed a retrospective cohort study of patients identified with UC during fiscal years 1998 to 2009 (October 1997 to September 2009) in the national Veterans Affairs (VA) administrative datasets, specifically, the Patient Treatment Files (PTF) and the Outpatient Care (OPC) Files. The PTF and OPC contain individual level data from inpatient and outpatient encounters, respectively, from all VA facilities with information on demographics (age, gender, ethnicity), encounters (date, frequency, inpatient, outpatient), International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes, and procedure codes (Current Procedural Terminology). Death information was obtained from the vital statistics file.

Study Population

Inclusion criteria required the presence of two ICD-9 diagnosis codes for UC (556.x) on at least two occasions with at least one code from an outpatient encounter. The first VA encounter with a UC code was considered the index date (not necessarily the diagnosis date) for follow-up. We excluded patients who had colectomy (ICD-9 45.8, 45.73) within 1 year after or 2 years prior to UC index date, patients older than 90 years at UC index, or patients whose index CRC was within 1 year of UC index date. A subset of UC patients were diagnosed postoperatively after colectomy. As CRC risk after colectomy is dramatically reduced, patients with colectomy prior to UC index were excluded ($n = 114$). Similarly, patients with colectomy within 1 year of UC index were excluded. Incident CRC cases after the first year of follow-up were identified based on the presence of ICD-9 codes (153.x or 154.x) with at least one inpatient or two outpatient diagnosis codes as previously described.^{17,18} Last date of follow-up was the earliest of date of CRC, death, or last VA encounter or September 30th, 2009. Race information was obtained from the PTF and OPC with an algorithm assigning race in cases of conflicting classification in the patient's encounter history. A sensitivity analysis using different algorithms of race classification was used to identify the robustness of our findings. As surrogate indicators of VA use and socioeconomic status, information was collected on history of endoscopy in the VA and VA priority level. All VA users are assigned a VA priority level 1–8 based on income level and

level of service connectivity. We defined patients of priority levels 1–6 as a surrogate indicator of low income status and priority level 7–8 as a surrogate indicator of high income status.

Validation of UC Codes

Validity of ICD-9 codes of UC in the VA OPC and PTF has been previously reported with a sensitivity of 84%, specificity of 99%, and positive predictive value (PPV) of 82%.¹⁹ We further validated the accuracy of our UC definition of least two ICD-9 codes with at least one outpatient code in 50 randomly chosen subjects from the study cohort who received care at the Houston VA. Chart review was performed by a gastroenterologist (J.H.) using the Computerized Patient Record System (CPRS) to confirm diagnosis of UC based on clinical history, endoscopy, radiology, and pathology to determine the positive predictive value (PPV) of our UC definition.

Statistical Analysis

The cumulative CRC incidence rates and incidence rate ratios were calculated for the entire UC cohort and for African American and Caucasian patients with UC separately using the Kaplan–Meier method. Univariate and multivariate analyses were performed with Cox proportional hazards models with time to incident CRC as the dependent variable and race, gender, history of VA endoscopy, frequency of VA encounters, UC index year, age at UC index, comorbidities (Deyo score), and VA priority level (surrogate for income) as independent variables. Variables with *P*-values less than or equal to 0.2 were included in multivariate analyses. Hazard ratios (HR) were calculated with 95% confidence intervals (CI). To avoid creating an overestimation bias in these incidence analyses, death was treated as a preempting event (competing risk) rather than as a censoring event for CRC. Statistical analysis was performed using SAS (v. 9.1, Cary, NC).

Ethical Considerations

This study was approved by the Institutional Review Boards of Baylor College of Medicine and the Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas.

RESULTS

Validation of UC Cohort

We performed chart review of 50 randomly chosen patients who satisfied inclusion criteria for our UC cohort. Of the 50 charts reviewed, seven cases were incorrectly designated as UC for a PPV of 86% (95% CI 62.4%–100%). Actual diagnoses of these seven cases included *Clostridium difficile* infection, ischemic colitis, and radiation proctitis.

Characteristics of VA UC Cohort

The cohort comprised 20,949 patients with UC; 95% were males and the racial distribution was 7% African American, 71% Caucasian, 3% Hispanic, 2% other, and 17% unknown (Table 1). Mean age at index VA encounter with UC was 61.6 years (standard deviation [SD] 14.6). Mean length of follow-up (from UC index to CRC index, death, last VA encounter, or September 2009) was 5.03 years (SD 2.8).

Characteristics of African Americans and Caucasians with UC

A total of 1541 African Americans and 14,949 Caucasian patients with UC were identified in this cohort (Table 2). African American patients were significantly younger than Caucasians at UC index (53.2 vs. 62.3 years, *P* < 0.01). Although statistically significant, the difference in mean follow-up between African Americans and Caucasians was small (5.7 vs.

5.4 years, $P < 0.01$). A greater proportion of African Americans with UC were female compared to Caucasians (13.4% vs. 4.7%, $P < 0.01$).

CRC Incidence in African Americans and Caucasians with UC

A total of 168 incident cases of CRC were identified (97% male, 10% African American, and 79% Caucasian) during 112,243 patient-years (PY) of follow-up; CRC incidence rate was 163/100,000 PY (95% CI 139–187 per 100,000 PY) (Fig. 1). Patients with CRC were older at UC index compared to non-CRC patients (65 vs. 61.6 years, $P = 0.01$). Cumulative CRC incidence rates were 158/100,000 PY (95% CI 134–181 per 100,000 PY) and 180/100,000 PY (95% CI 155–205 per 100,000 PY) for Caucasians and African Americans, respectively, with an incidence rate ratio (IRR) of 1.17 (95% CI 0.69–1.97). The 3, 5, and 10-year cumulative incidence rates for CRC were 0.36%, 0.76%, 1.79% for African Americans and 0.41%, 0.76%, 1.43% for Caucasians; the incidence rate ratios were 0.88 (95% CI 0.35–2.20), 0.97 (95% CI 0.49–1.93), and 1.12 (95% CI 0.66–1.92), respectively. In a Cox proportional hazard model, African American race was not associated with a significant increased risk for CRC (adjusted HR: 1.10, 95% CI 0.65–1.87, $P = 0.73$) compared to Caucasian race (Table 3). In a sensitivity analysis using alternate race classification algorithms to favor African American or Caucasian race in cases with conflicting race identification, there was no statistical difference in CRC risk in either algorithm.

Unreported race was associated with a decreased risk of CRC in univariate analysis. Apart from race in univariate analysis, history of endoscopy in the VA, higher number of inpatient VA encounters, Deyo score greater than 2, and older age at UC index were associated with increased risk of CRC.

In multivariate analysis, history of endoscopy in the VA, frequency of VA encounters, and age at UC index remained significantly associated with increased risk of CRC. African American race was also not associated with increased risk of CRC compared to Caucasians in a sensitivity analysis for patients with VA priority level 1–6 (surrogate for low income status). In multivariate analysis of this subset of only patients of priority levels 1–6 ($n = 14,088$), history of VA endoscopy and frequency of VA encounters were no longer statistically significant. Only associations of older age at UC index and unreported race remained significantly associated with CRC risk.

DISCUSSION

We examined racial differences in CRC risk in one of the largest UC cohorts in the United States. A total 168 incident cases of CRC were identified in 20,949 veterans with UC from 1998 to 2009. The UC cohort consisted of 14,949 Caucasian (71%) and 1541 African American (7%) patients and the cumulative CRC incidence rates were 158 and 180 per 100,000 PY in African Americans and Caucasians, respectively. African American race was not associated with an increased (or decreased) risk of CRC in veterans with UC. These findings persisted in multivariate analyses that adjusted for several factors including, gender, frequency of VA encounters, history of endoscopy in the VA, age at UC index, year of UC index, comorbidities, and VA priority level as a surrogate of income status.

Racial disparities of CRC risk in patients with UC have not been previously examined. African Americans have been observed to have an increased risk of sporadic CRC, a younger age at diagnosis, higher stage at diagnosis, and decreased survival when compared to Caucasians.^{6–8,10} The etiology of the racial disparities in sporadic CRC is unknown, but possibilities include socioeconomic class, obesity, comorbidity, and genetic causes. A recent VA study of sporadic CRC reported no differences in CRC outcomes based on race,

suggesting access to healthcare may play an important role in CRC outcomes based on race.²⁰ Equal access to healthcare in the VA may also contribute to the lack of racial disparity in CRC incidence in UC patients observed in our study.

The findings of prior studies of CRC in UC confer a measure of external validity to our study. The overall incidence rate of CRC in UC (163 per 100,000) in this study is comparable to previous reports of CRC risk in IBD. Söderlund et al²¹ recently reported an incidence of 110 per 100,000 person years in an IBD cohort (CD and UC) in Sweden. The population studied in our cohort differed from the Söderlund et al study, which may explain a higher incidence in our study. Our cohort had a mean age of 62.6 years at UC index compared to a much younger population in the Söderlund study, where more than 75% were less than 44 years of age at IBD diagnosis. In addition, our study included only patients with UC, whereas both CD and UC patients were included in the Söderlund et al study. Looking at only UC patients, the 10-year risk of CRC in patients with pancolitis was 1.4% in men and 1.3% in women in that study, which is similar to our finding of 10-year CRC risk of 1.43% in Caucasians.

In our study we observed an increase in CRC risk with increasing age at UC index. This may reflect either an age-related risk of CRC or highlight a population of UC patients with long disease duration such as subclinical or undiagnosed UC. A meta-analysis reported a trend of increased risk of CRC with a younger age at UC diagnosis, but was not statistically significant.²² The age at UC index in our study may not be the same as age of UC onset, so this finding will require further validation. In addition, mean age at UC index was nearly 10 years younger in African Americans compared to Caucasians. This has not been observed in other studies of UC in African Americans in the non-VA population. In our analysis, increased age at UC index was associated with an increased risk for CRC. However, African American race was not associated with an increased risk of CRC with inclusion of age at UC index in the multivariate analysis.

We observed that unreported race and lack of endoscopy in the VA are protective against CRC and this is likely an artifact of the dataset. Patients with unreported race in the VA have fewer encounters and likely represent patients who are receiving care outside of the VA, hence less likely to have a diagnosis code for CRC. Likewise, the association of VA endoscopy with increased risk of CRC likely represents a detection bias toward patients who are receiving care in the VA. It is possible that patients in the UC cohort would seek healthcare elsewhere and that CRC is underdetected in patients seeking care in non-VA facilities. To account for this we limited the analysis cohort to patients with at least two diagnosis codes and adjusted for healthcare use (VA endoscopy and VA encounters). Prior studies have shown VA users with low priority level (surrogate for low income) receive most of their care in the VA, whereas patients of high priority level are more likely to receive care outside of the VA. To test this hypothesis we performed a sensitivity analysis evaluating only patients of low priority level and observed history of VA endoscopy and VA encounter frequency were no longer significantly associated with CRC risk.

This study has several strengths. This is one of the largest cohorts of UC and CRC reported and is the largest single cohort of African Americans with UC. There are no prior studies investigating the effect of race on CRC incidence in UC. Prior studies have reported conflicting results regarding racial disparities in disease characteristics of UC, many of which have been limited by a small sample size of African Americans with UC. We utilized the VA administrative files, which have been previously used to examine surgical outcomes and survival in patients with CRC.^{17,18} All patients in the cohort received some or most of their care through the VA system and findings were adjusted for priority level, a surrogate

for income, therefore reducing bias in access to healthcare between African Americans and Caucasians.

This study also has limitations inherent to an administrative dataset. Our definitions are based on the accuracy and completeness of ICD-9 coding. The ICD-9 codes for UC have been previously validated in a VA dataset and showed a sensitivity of 84%, specificity of 99%, and a PPV of 82%.¹⁹ We used the additional criteria of having at least two UC codes with at least one code from an outpatient encounter and observed an increase in PPV to 86% in our own chart validation study. The extent of UC was not included in our analyses, as these data were not available in the VA administrative datasets; the effect of missing this information on the observed associations is not clear. One systematic review of IBD in African Americans reported African Americans with UC may have more distal disease compared to Caucasians¹⁶; however a systematic review we performed²³ and our local data²⁴ did not observe significant differences in disease distribution in UC between African Americans and Caucasians. We used the VA UC index date to estimate duration of disease. However, VA UC index date may not correlate with UC diagnosis date. The effect of race on VA UC index date and its relation to duration of disease could not be determined using this administrative dataset. The African American cohort had a higher proportion of women and was significantly younger than the Caucasian cohort. These differences could have biased our results toward showing a lower risk of CRC in the African American cohort. However, both of these variables were included in the multivariate analysis, and the nonsignificant difference in the risk of CRC by race persisted. Data on medications, such as aspirin or mesalamine, were not available in the datasets utilized. Although our previous study in non-VA patients with IBD did not show any significant difference in medication utilization between African Americans and Caucasians with UC,²⁴ this question will require further study utilizing the VA administrative pharmacy files. Lastly, our results reflect the VA IBD population and may not be representative of the non-VA IBD populations in age, race distribution, or healthcare delivery. However, the VA databases allow comparison of CRC risk between racial groups with similar access to healthcare.

In conclusion, we found a CRC incidence of 163 per 100,000 PY in a cohort study of 20,949 veterans with UC identified and followed during 1998–2009. African American race was not associated with a significant increased risk of CRC compared to Caucasian race among veterans with UC. The reason for lack of racial differences in CRC risk in veterans with UC compared to sporadic CRC is unclear.

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FIGURE 1.

Cumulative colorectal cancer incidence by Kaplan–Meier method in African American and Caucasian veterans with colorectal cancer between 1998 and 2009.

TABLE 1

Demographic Characteristics of VA Users with Incident Ulcerative Colitis from 1998–2009

	Ulcerative Colitis (<i>n</i> = 20,949)	CRC (<i>n</i> = 168)	Non-CRC (<i>n</i> = 20,781)	<i>P</i> -value*
Age at UC index, years median (IQR)	63 (53–73)	67 (56–74)	63 (53–73)	0.01
Follow-up, years median (IQR)	4.9 (3.0–7.4)	3.6 (2.3–5.3)	4.9 (3.0–7.4)	<0.01
Gender <i>n</i> (%)				
Males	19,827 (94.6)	163 (97.0)	19,664 (94.6)	0.17
Females	1122 (5.4)	5 (3.0)	1117 (5.4)	
Ethnicity <i>n</i> (%)				
Caucasian	14,949 (71.4)	132 (78.5)	14,817 (71.3)	Ref
African American	1541 (7.4)	16 (9.5)	1525 (7.3)	0.54
Hispanic	624 (3.0)	7 (4.2)	617 (3.0)	0.53
Other	325 (1.5)	3 (1.8)	322 (1.6)	0.94
Unknown	3510 (16.7)	10 (6.0)	3500 (16.8)	<0.01
History of endoscopy <i>n</i> (%)				
Yes	9710 (46.4)	104 (61.9)	9606 (46.2)	<0.01
No	11,239 (53.6)	64 (38.1)	11,175 (53.8)	
VA encounters (1 yr pre UC index)	0.15 (0.5)	0.30 (0.8)	0.15 (0.5)	<0.01
VA encounters (1 yr post UC index)	0.15 (0.6)	0.33 (0.9)	0.15 (0.6)	<0.01
UC index year <i>n</i> (%)				<0.01
1998–2002	8511 (40.6)	107 (63.7)	8404 (40.4)	
2003–2008	12,438 (59.4)	61 (36.3)	12,377 (59.6)	
Priority level				0.09
7–8 (%)	6723 (32.6)	44 (26.2)	6679 (32.1)	
1–6 (%)	14,088 (67.3)	124 (73.8)	13,964 (67.2)	
Not available (%)	138 (0.1)	0 (0)	138 (0.7)	

* Colorectal cancer vs. noncolorectal cancer.

CRC, colorectal cancer; UC, ulcerative colitis; SD, standard deviation.

TABLE 2

Demographic Characteristics of African Americans and Caucasians with Incident Ulcerative Colitis from 1998–2009

	African American (<i>n</i> = 1541)	Caucasian (<i>n</i> = 14,949)	<i>P</i> -value
Age at UC index, years median (IQR)	53 (43–64)	64 (55–73)	<0.01
Follow-up, years median (IQR)	5.2 (3.1–8.4)	4.9 (3.0–7.5)	<0.01
Gender <i>n</i> (%)			
Males	1335 (86.6)	14,253 (95.3)	<0.01
Females	206 (13.4)	696 (4.7)	
History of endoscopy in VA, <i>n</i> (%)			
Yes	1133 (73.5)	7052 (47.2)	<0.01
No	408 (26.5)	7897 (52.8)	
VA encounters (1 yr pre UC index)	0.31 (0.8)	0.16 (0.6)	<0.01
VA encounters (1 yr post UC index)	0.32 (0.9)	0.16 (0.6)	<0.01
UC index year <i>n</i> (%)			0.01
1998–2002	680 (44.1)	6081 (40.7)	
2003–2008	861 (55.9)	8868 (59.3)	
Priority level			<0.01
7–8 (%)	221 (14.4)	4638 (31.0)	
1–6 (%)	1315 (85.3)	10,227 (68.4)	
Not available (%)	5 (0.3)	84 (0.6)	

CRC, colorectal cancer; UC, ulcerative colitis; SD, standard deviation.

TABLE 3

Cox Proportional Hazards Model of Risk for Ulcerative Colitis Associated CRC in VA Users

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	Wald <i>P</i> -value	HR (95% CI)	Wald <i>P</i> -value
Race				
Caucasian	ref		ref	
African American	1.09 (0.65–1.83)	0.74	1.10 (0.65–1.87)	0.73
Hispanic	1.16 (0.54–2.48)	0.71	1.17 (0.55–2.51)	0.69
Other	0.97 (0.31–3.05)	0.96	1.04 (0.33–3.27)	0.95
Unreported	0.36 (0.19–0.69)	<0.01	0.43 (0.22–0.82)	0.01
Gender				
Male	ref		ref	
Female	0.55 (0.23–1.34)	0.19	0.73 (0.30–1.81)	0.5
History of endoscopy in VA	1.63 (1.20–2.23)	<0.01	1.71 (1.21–2.42)	<0.01
VA encounters (1 yr pre UC index)	1.30 (1.12–1.51)	<0.01	1.07 (0.87–1.32)	0.53
VA encounters (1 yr post UC index)	1.38 (1.20–1.59)	<0.01	1.23 (1.02–1.49)	0.03
UC index year				
1998–2002	ref		ref	
2003–2008	0.92 (0.65–1.29)	0.61	1.00 (0.71–1.41)	0.99
Age at UC index				
< 49	ref		ref	
50–69	1.90 (1.12–3.21)	0.02	1.99 (1.16–3.43)	0.01
>70	2.71 (1.59–4.61)	<0.01	3.40 (1.92–6.01)	<0.01
Deyo score				
0	ref		ref	
1	1.22 (0.83–1.78)	0.31	1.03 (0.70–1.51)	0.90
>2	1.80 (1.24–2.62)	<0.01	1.19 (0.80–1.77)	0.40
Priority level				
7–8	ref		ref	
1–6	1.25 (0.89–1.77)	0.20	1.07 (0.74–1.54)	0.73

HR, hazard ratio; UC, ulcerative colitis; Ref, reference.