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Racial Disparities in Recurrence and Overall Survival in Patients With Locoregional Colorectal Cancer

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Abstract

Background: The purpose of this study was to determine the association between race and long-term cancer outcomes (recurrence and overall survival) within a population of US patients with locoregional colorectal cancer (CRC). **Methods:** A cohort study of primary patient data merged with the National Cancer Database as part of a Commission on Cancer Special Study was performed. The study population was a random sample of patients undergoing surgery for stage I to III CRC between years 2006 and 2007 with 5 years of follow-up. Propensity-weighted multivariable Cox regression was performed with pooled results to yield statistical inferences. Prespecified sensitivity analysis was performed only for patients who received guideline concordant care (GCC) of primary CRC. All statistical tests were 2-sided. **Results:** The study population included 8176 patients, 9.9% (n = 811) Black and 90.1% (n = 7365) White. Black patients were more likely to be uninsured or underinsured, have lower household income, and lower educational status (all P < .001). Rates of GCC were higher among Black vs White patients with colon cancer (76.9% vs 72.6%, P = .02), and Black and White patients with rectal cancer were treated with radiation at similar rates (69.1% vs 66.6%, P = .64). Black race was independently associated with increased risk of recurrence (hazard ratio [HR] = 1.48, 95% confidence interval [CI] = 1.26 to 1.73) and mortality (HR = 1.37, 95% CI = 1.18 to 1.59). In sensitivity analysis of only patients who received GCC, observed effects for recurrence (HR = 1.51, 95% CI = 1.27 to 1.79) and overall survival (HR = 1.40, 95% CI = 1.18 to 1.66) persisted. **Conclusions:** Despite higher rates of GCC for CRC, Black patients experience a higher risk of recurrence and mortality compared with White patients.

Although incidence and mortality rates of colorectal cancer (CRC) are declining in the United States, racial disparities persist. From 2012 to 2016, the incidence of CRC in Black patients was approximately 20% higher than in non-Hispanic White patients (45.7 vs 38.6 per 100 000 population), and the mortality rate was 40% higher (19.0 vs 13.8 per 100 000 population) (1). Black patients present more often with advanced disease but have worse cancer-specific survival for every stage category compared with White patients (1). However, very little is known about racial differences in CRC recurrence rates following definitive treatment.

Recurrence data are not currently available for analysis within national cancer registries; therefore, recurrence rates among CRC patients have been reported predominately in either single-institution studies or within the context of clinical trials. In 1 compilation of 18 randomized trials of stage III

patients treated with adjuvant chemotherapy, the majority (80%) of recurrences occurred within the first 3 years (2). To date, only 1 study has reported recurrence data using national cancer registry data, which was collected as part of a Commission on Cancer (CoC) special study. In that study, the median time to detection of recurrence was approximately 15 months, and 5-year cumulative recurrence rates were 20% in colon cancer patients and 24% in rectal cancer patients (3). In the absence of population-based data or multi-institutional studies, however, contemporary data on CRC recurrence outside the context of a clinical trial are sparse, and even less is known about racial differences in recurrence rates within routine clinical practice.

The purpose of this study was to determine the association between race and long-term cancer outcomes (recurrence and

overall survival [OS]) within a large population of US patients presenting with locoregional CRC. The hypothesis was that Black patients would experience higher rates of recurrence and worse survival compared with White patients.

Methods

Study Population

Patients older than 18 years with American Joint Committee on Cancer (AJCC) stage I, II, or III adenocarcinoma of the colon or rectum treated with definitive surgical resection in 2006-2007 were identified from the National Cancer Database (NCDB). A random sample of up to 10 patients with CRC from each Commission on Cancer (CoC) facility was selected for detailed primary data collection regarding surveillance testing and recurrence as part of the commission's special study as previously described (3). For facilities with fewer than 10 eligible patients, data for all eligible patients were abstracted. These data were then merged with corresponding NCDB records. The study period (2006-2007) was selected to allow for a minimum of 5 years of follow-up.

Patient race was determined from predefined NCDB data based on assignment by a CoC registrar according to fixed categories (4). Only patients of White or Black race were included for the primary study analysis. Patients with unknown tumor location, income, education, distance traveled, or race were excluded. Patients who did not undergo any surveillance testing following treatment of the primary cancer were also excluded because they could not be assessed for the primary outcome of recurrence.

The study analysis was considered exempt by The University of Texas MD Anderson Cancer Center Institutional Review Board.

Covariates

CRC clinical and pathologic stage was defined based on the AJCC 6th edition staging manual (5). High-risk stage II colon cancer was defined by the presence of 1 or more of the following features: T4 tumor (based on AJCC T-stage), fewer than 12 lymph nodes (LN) examined, positive margin, high tumor grade (grades 3-4), perineural invasion, or lymphovascular invasion.

Assessment of receipt of treatment of primary colon cancer was based on LN retrieval and chemotherapy. Guideline concordant care (GCC) was defined as 1) removal of at least 12 LN and all nodes negative (AJCC stage I or low-risk stage II), 2) removal of fewer than 12 LN but receipt of chemotherapy (high-risk stage II), or 3) removal of at least 12 LN and 1 or more nodes positive and receipt of chemotherapy (stage III). Failure to receive GCC was defined as 1) removal of fewer than 12 LN and no receipt of chemotherapy (high-risk stage II), or 2) removal of any number of LN with at least 1 or more nodes positive and no receipt of chemotherapy (stage III). Assessment of GCC among patients with rectal cancer was defined as receipt of neoadjuvant or adjuvant radiation in patients with either clinical stage II or III or pathologic stage II or III disease.

Surveillance testing included computed tomography, magnetic resonance imaging, positron emission tomography, or carcinoembryonic antigen tests as previously described (3).

Outcome Measures

The primary outcomes of interest were disease recurrence (locoregional or distant) and OS. Local recurrence was defined as recurrence at the site of primary tumor, anastomosis, or adjacent structure. Regional recurrence was considered recurrence at the regional LN associated with the primary tumor site, and distant recurrence was defined as recurrence outside the local or regional sites. Recurrence could be confirmed either clinically or pathologically. If synchronous locoregional and distant recurrence were diagnosed, both were recorded.

A prespecified sensitivity analysis was performed to assess recurrence rates and OS only among patients who received GCC, defined above.

Statistical Analysis

Baseline clinical and demographic characteristics were compared across racial groups using the χ^2 test for categorical variables, t test for means, and Kruskal-Wallis test for medians of continuous variables. Patients were censored at the time of death, loss to follow-up, or end of the surveillance study period (5 years). Cumulative recurrence rates were determined using the Kaplan-Meier method and tested using log-rank test. Multivariable Cox proportional hazards regression model was performed to yield statistical inferences. The proportional hazards assumption was verified graphically using the log-log plot, where the -ln{−ln(survival)} curves of the covariate vs ln(analysis time) were checked. Inverse probability of treatment weighting using propensity score was performed to confirm the findings. Covariates adjusted in Cox and logistic regression for propensity score estimation were based on the previously published recurrence risk model and included age at diagnosis, sex, histology, pathologic tumor stage, index of metastasis (number of positive LN divided by total number of LN examined), lymphovascular invasion, perineural invasion, surgical margin status, chemotherapy, and tumor site, as well as Charlson-Deyo comorbidity index (6). Two variables had greater than 5% missing values: lymphovascular invasion and perineural invasion. Multiple imputation by chained equations was used to substitute predicted values for missing values with 20 imputed values.

All tests were 2-sided, with an alpha of .05. All analyses were performed using SAS software (version 9.1.3; SAS Institute Inc) for data processing and Stata MP (version 13.1; StataCorp) for statistical analyses. Study findings are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines (7).

Results

Study Population

A total of 8176 patients were identified for study inclusion, of whom 9.9% (n = 811) were Black and 90.1% (n = 7365) were White (Figure 1). A larger proportion of Black patients were female (56.6% vs 50.5%) and younger (median 62 years vs 68 years old) compared with White patients (P < .05) (Table 1). Additionally, Black patients were more likely to have Medicaid insurance (8.4% vs 2.9%) or to be uninsured (7.5% vs 2.3%, P < .001). Median household income and zip code–based educational status were also markedly lower among Black patients (P < .001). Within the study cohort, a larger proportion of Black
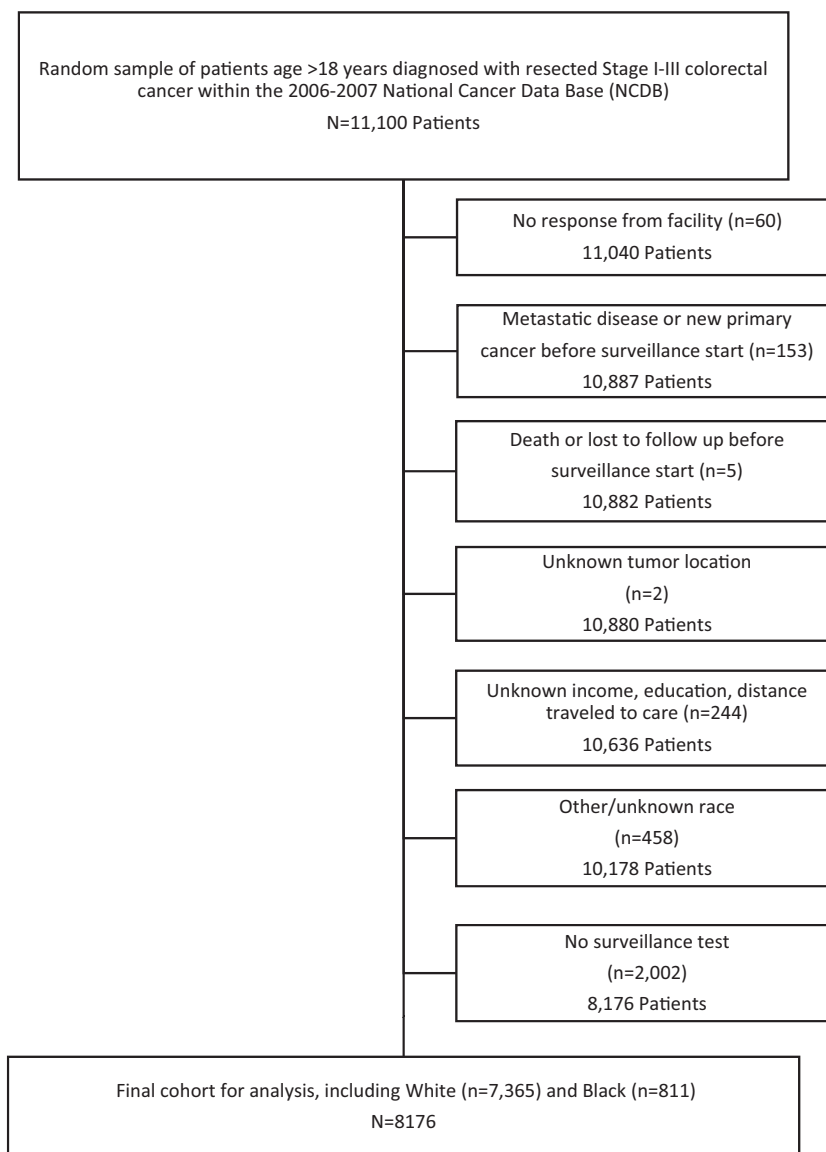
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Random sample of patients age >18 years diagnosed with resected Stage I-III colorectal cancer within the 2006-2007 National Cancer Data Base (NCDB)
N=11,100 Patients

No response from facility (n=60)
11,040 Patients

Metastatic disease or new primary cancer before surveillance start (n=153)
10,887 Patients

Death or lost to follow up before surveillance start (n=5)
10,882 Patients

Unknown tumor location
(n=2)
10,880 Patients

Unknown income, education, distance traveled to care (n=244)
10,636 Patients

Other/unknown race
(n=458)
10,178 Patients

No surveillance test
(n=2,002)
8,176 Patients

Final cohort for analysis, including White (n=7,365) and Black (n=811)
N=8176

Figure 1. Cohort selection for surveillance cohort. CRC = colorectal cancer; NCDB = National Cancer Data Base.

patients was diagnosed with pathologic stage III CRC (44.4% vs 38.1%, $P = .005$). No difference in tumor sidedness between White and Black patients was observed ($P = .11$). Black patients were more likely to be treated at an academic facility (31.2% vs 16.0%) and to travel a shorter distance for care (median 47 vs 63 miles, $P < .001$). Clinical and tumor characteristics were similar among Black and White patients (Supplementary Table 1, available online).

Guideline Concordance

Among patients with colon cancer, rates of adequate lymphadenectomy (removal of at least 12 LN) did not differ by race (Black, 72.2% vs White, 69.6%, $P = .06$). Among patients with high-risk stage II colon cancer, no difference was observed in rates of adjuvant chemotherapy use (Black, 37.5% vs White, 30.5%, $P = .45$). However, a greater proportion of Black patients with stage III colon cancer were treated with adjuvant chemotherapy compared

with their White counterparts (83.1% vs 76.3%, $P = .005$). Overall rates of guideline concordant colon cancer care were higher among Black patients compared with White patients (76.9% vs 72.6%, $P = .02$). Black and White patients with clinical stage II or III or pathologic stage II or III rectal cancer were treated with radiation at similar rates (69.1% vs 66.6%, $P = .64$) (Figure 2).

Primary Outcome: Recurrence and OS

Black race was independently associated with increased risk of CRC recurrence and worse OS by adjusted analysis (Figure 3, A and B). By regression analysis adjusting for clinical factors previously demonstrated to be predictive of recurrence, risk of recurrence was also higher in Black patients (hazard ratio [HR] = 1.53, 95% confidence interval [CI] = 1.32 to 1.78). When socioeconomic factors, specifically insurance status, income, and population density of residence, were added to the model, Black race remained associated with risk of recurrence (HR = 1.48, 95% CI

Table 1. Baseline demographics and clinical characteristics of study cohort (N = 8176)

| Characteristics	White (n = 7365) No. (%)	Black (n = 811) No. (%)	P
Median age (interquartile range)	68 (58-77)	62 (52-71)	<.001
Sex[a]			.004
Male	3646 (49.5)	352 (43.4)	
Female	3717 (50.5)	459 (56.6)	
Comorbidity score			.78
0	5195 (70.5)	564 (69.5)	
1	1598 (21.7)	179 (22.1)	
2	572 (7.8)	68 (8.4)	
Insurance status			<.001
Private	2839 (38.5)	310 (38.2)	
Uninsured	172 (2.3)	61 (7.5)	
Medicaid	214 (2.9)	69 (8.5)	
Medicare	3977 (54)	348 (42.9)	
Managed care	54 (0.7)	8 (1)	
Unknown	109 (1.5)	15 (1.8)	
Median income			<.001
<$30 000	1269 (17.2)	385 (47.5)	
$30 000-$35 000	1971 (26.8)	180 (22.2)	
$35 000-$45 999	2026 (27.5)	143 (17.6)	
$46 000+	2099 (28.5)	103 (12.7)	
Proportion without high school degree by zip code			<.001
29% +	1289 (17.5)	357 (44.0)	
20%-28.9%	2043 (27.7)	268 (33.0)	
14%-19.9%	2466 (33.5)	128 (15.8)	
<14%	1567 (21.3)	58 (7.2)	
Population density			<.001
Metro area	5533 (75.1)	710 (87.5)	
Urban area	1451 (19.7)	82 (10.1)	
Rural area	186 (2.5)	7 (0.9)	
Unknown	195 (2.6)	12 (1.5)	
Pathologic stage			.005
0/1	1955 (26.5)	192 (23.7)	
2	2577 (35)	258 (31.8)	
3	2808 (38.1)	360 (44.4)	
Unknown	25 (0.3)	1 (0.1)	
Facility type			<.001
Community	2098 (28.5)	189 (23.3)	
Comprehensive	4055 (55.1)	369 (45.5)	
Other or unknown	1179 (16)	253 (31.2)	
Others or unknown	33 (0.4)	0 (0)	
Distance traveled for care, miles	63 (24-146)	47 (19-95)	<.001
Tumor site			.11
Right colon, including transverse	3597 (48.8)	420 (51.8)	
Left colon, rectosigmoid and rectum	3768 (51.2)	391 (48.2)	

[a]Unknown sex (n = 2).

= 1.26 to 1.73) (Table 2). Similar findings were observed for OS. Black race was associated with increased risk of death (HR = 1.44, 95% CI = 1.26 to 1.66) compared with White race. This finding also persisted after adjusting for measured socioeconomic factors (HR = 1.37, 95% CI = 1.18 to 1.59) (Table 2). These findings were also confirmed by propensity weighted analysis (data not shown).

Secondary Outcomes and Sensitivity Analysis

Among those with locoregional or distant recurrent disease, White patients were treated with surgical therapy either alone or in combination with chemotherapy or radiation more often than Black patients (24.0% [n = 288] vs 16.8% [n = 32], P = .04). Accordingly, White patients were treated less often with chemotherapy or chemoradiation alone compared with Black patients (40.9% [n = 490] vs 49.0% [n = 93], P = .04).

Sensitivity analysis was performed to include only the cohort of patients who received GCC for their primary CRC (Supplementary Table 2, available online). This demonstrated a similar increased hazard for recurrence and mortality among Black compared with White patients (HR = 1.51, 95% CI = 1.27 to 1.79; and HR = 1.40, 95% CI = 1.18 to 1.66) (Supplementary Table 3, available online).

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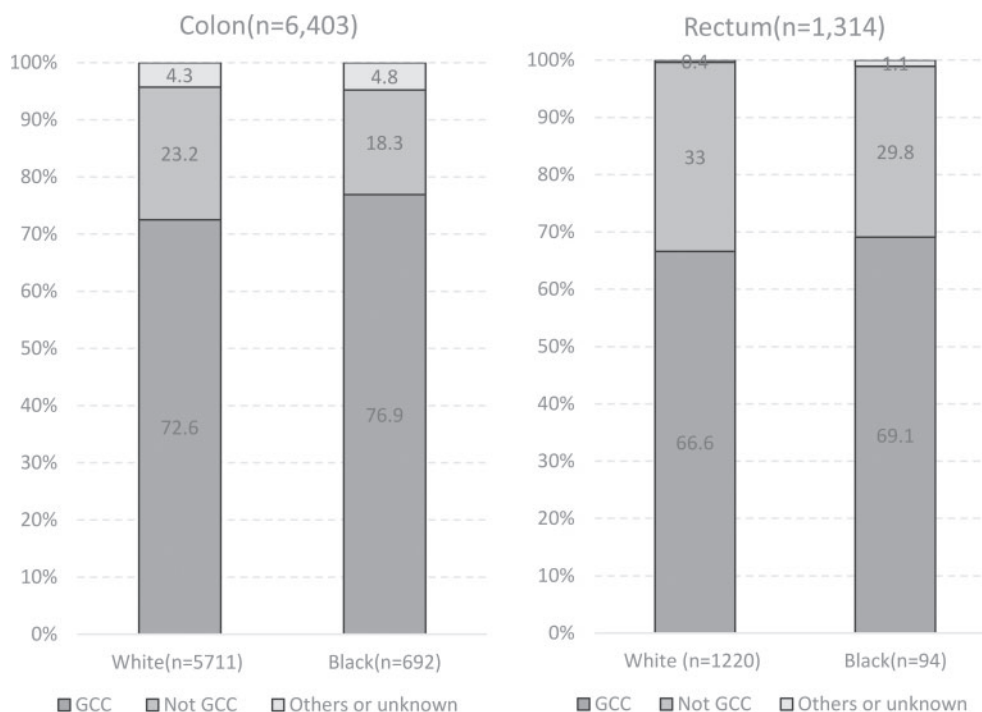
Figure 2. Treatment of primary colon and rectal cancer by race. Colon cancer guideline concordant care (GCC) was defined as removal of at least 12 lymph nodes (LN) and all LN negative (American Joint Committee on Cancer stage I or low-risk stage II); or removal of fewer than 12 LN but the patient received adjuvant chemotherapy (high-risk stage II); or removal of at least 12 LN and 1 or more LN positive and the patient received adjuvant chemotherapy (stage III). Rectal cancer GCC was defined as receipt of neoadjuvant or adjuvant radiation in patients with either clinical stage II or III or pathologic stage II or III disease.

Discussion

In this study of a real-world population of US patients with locoregional CRC, statistically significant racial disparities in recurrence and survival were identified. Black patients with colon cancer appeared to receive equivalent or superior quality of care compared with their White counterparts, measured by increased adjuvant chemotherapy use among stage III patients and higher rates of overall GCC. However, despite receiving equivalent or superior quality of care, rates of recurrence were higher among Black compared with White patients, and OS was worse. There were measurable differences in socioeconomic status between Black and White patients, including insurance status and household income; however, even after controlling for these differences, Black patients were still at higher risk for recurrence and mortality. To our knowledge, this is the first report of racial differences in CRC recurrence rates within the routine, clinical practice setting.

These findings are consistent with secondary analyses of patients enrolled in clinical trials in the United States, which have also found shorter time to recurrence, worse disease-free survival, and worse OS in Black patients (8-10). In a secondary analysis of patients with stage III colon cancer enrolled on the Alliance N0147 clinical trial and treated with 5-FU, leucovorin, and oxaliplatin (FOLFOX) chemotherapy, Black patients younger than 50 years had a shorter disease-free survival compared with White patients (HR = 2.84, 95% CI = 1.73 to 4.66), as did those with N1 disease (HR = 1.54, 95% CI = 1.04 to 2.29) (9). A pooled analysis of over 14 000 patients with stage II and III colon cancer enrolled in 12 randomized adjuvant chemotherapy trials also demonstrated worse recurrence-free survival in Black compared with White patients (3-year recurrence-free survival = 64.4% vs 72.1%, HR = 1.14, 95% CI = 1.04 to 1.24) (10).

In this study, the finding that Black patients with colon cancer were more likely to receive GCC than White patients was unexpected. Most prior studies have demonstrated persistent racial disparities in CRC treatment, including lower rates of surgery for stage I and stage IV CRC, adjuvant chemotherapy for stage III colon cancer, radiation for stage II or III rectal cancer, and targeted therapy for stage IV CRC (11-15). The cohort of Black patients treated at CoC sites and included in this study was more often from a metro area (87.5% vs 75.1) and more likely to receive care at an academic or research facility than White patients (31.2% vs 16.0%), which could explain higher rates of GCC. It is certainly possible that this finding is not generalizable to patients treated at non-CoC sites.

Because Black patients experience higher recurrence rates and worse survival even in the context of randomized controlled trials in which patients receive standard therapy, it has been suggested that underlying differences in tumor biology may be responsible for disparate outcomes. Recent evidence suggests that KRAS mutation rates differ by race, with a higher proportion of KRAS codon 13 mutations among Black patients (16,17). Additionally, in a secondary analysis of the CALGB/SWOG 80405 randomized trial in metastatic CRC patients, a higher rate of extended RAS mutations (noncodon 12 or 13) was identified in Black compared with White patients, and these extended mutations were associated with worse OS (17). Correlative studies of patients with metastatic CRC treated in the CALGB/SWOG 80405 randomized trial recently investigated the association of consensus molecular subtypes and tumor mutational burden with OS and progression-free survival (PFS) (18,19). Although consensus molecular subtypes and tumor mutational burden are prognostic for survival, the specific profiles of each did not differ by race ; however, this was not the primary focus of either analysis.
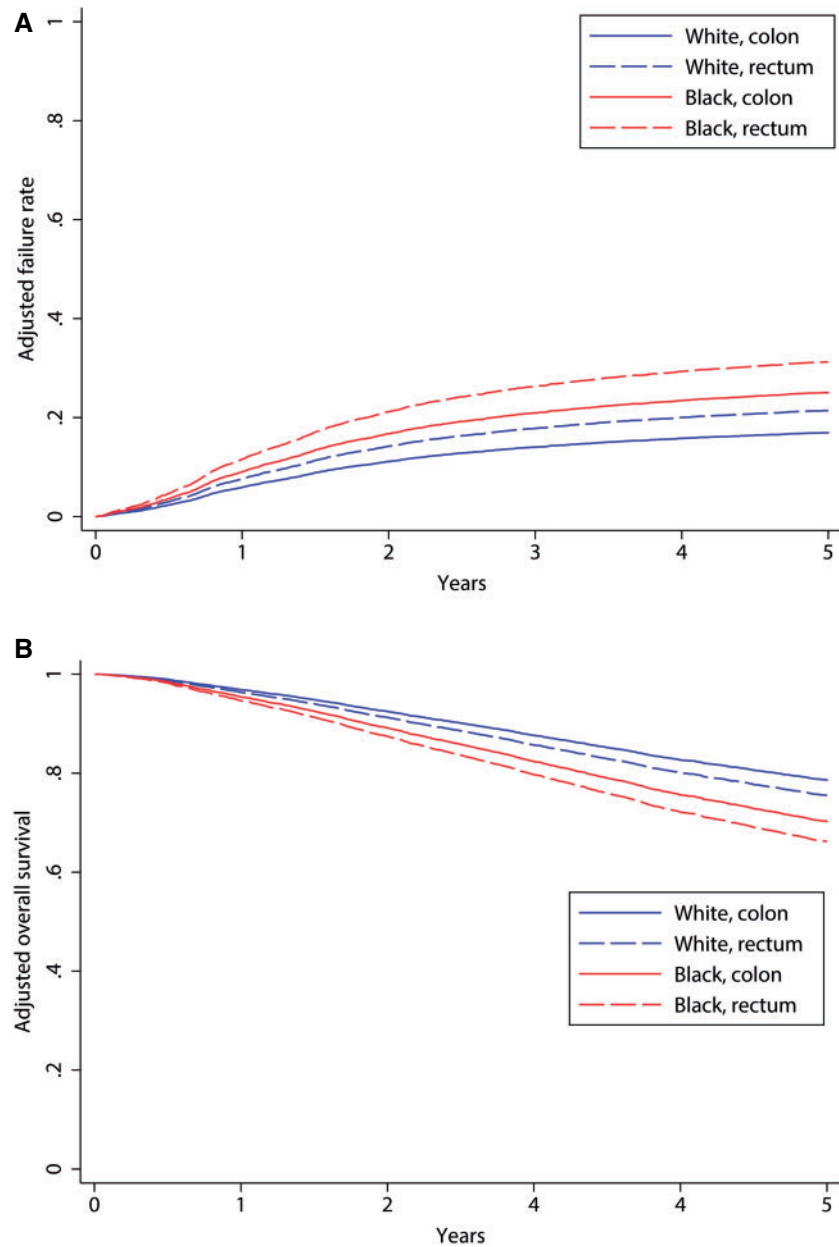
Figure 3. Regression-adjusted recurrence rates and overall survival rates by tumor site and race (N = 8176).

Table 2. Regression-adjusted risk of recurrence and OS among Black compared with White patients (N = 8176)

Model[a]	Total cohort		Colon cancer		Rectal cancer	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Recurrence	1.53 (1.32 to 1.78)	<.001	1.55 (1.31 to 1.82)	<.001	1.44 (1.00 to 2.07)	.047
OS	1.44 (1.26 to 1.66)	<.001	1.40 (1.22 to 1.63)	<.001	1.74 (1.23 to 2.46)	.002
Model + SES[b]						
Recurrence	1.48 (1.26 to 1.73)	<.001	1.53 (1.28 to 1.82)	<.001	1.31 (0.89 to 1.93)	.16
OS	1.37 (1.18 to 1.59)	<.001	1.35 (1.15 to 1.59)	<.001	1.61 (1.11 to 2.32)	.01

[a]Adjusted for age at diagnosis, sex, histology, pathologic tumor stage, index of metastasis, lymphovascular invasion, perineural invasion, surgical margin status, receipt of chemotherapy, tumor site, and Charlson-Deyo comorbidity index. CI = confidence interval; HR = hazard ratio; OS = overall survival; SES = socioeconomic status.
[b]Added adjustment for SES also performed, including median income quartile, education, and population density.

Several studies have recently demonstrated an association between patient race and tumor sidedness. A Surveillance, Epidemiology, and End Results Program analysis of stage IV CRC patients found that right-sided cancers were more common in Black compared with White patients (odds ratio = 1.45, 95% CI = 1.33 to 1.58) and that right-sided cancers were associated with a greater risk of death (HR = 1.27, 95% CI = 1.22 to 1.32) (20). Several smaller state or hospital-based cohort studies also found higher rates of proximal cancers in Black compared with White patients (21-23). In this study, a statistically significant difference in the frequency of proximal tumors between White and Black patients was not seen (48.8% vs 51.8%, respectively, P = .11). However, based on recent data as well as the findings presented in this study, further study of potential differences in tumor biology appears warranted.

In addition to tumor biology, differences in socioeconomic status likely contribute to much of the racial disparity in CRC outcomes. A recent pooled analysis of randomized controlled trials in a variety of cancer types found that patients with Medicaid or without insurance did not receive the same benefit of experimental therapy as did patients with private insurance (24). This would suggest that other unmeasured social determinants of health, such as financial strain or transportation access, for example, influence outcomes, even in the setting of equal access to high-quality treatment (25). Many of the same social determinants of health that correlate with insurance status may also correlate with race and could affect multiple aspects of care delivery, such as treatment adherence or access to survivorship care, for example. Therefore, it is likely that the racial differences in recurrence rates and survival identified here also reflect unmeasured differences in socioeconomic conditions and health-care access. Prioritization of collecting better data specific to social determinants of health will be critical to make meaningful progress in cancer health disparities research.

Several studies have identified racial differences in response to therapy and treatment toxicity in both the locoregional and metastatic setting. In a large randomized controlled trial of patients with high-risk stage II or stage III colon cancer treated with 5-FU chemotherapy, African American patients had lower rates of treatment-related toxicity than Caucasian patients, including lower rates of diarrhea, nausea, vomiting, stomatitis, and overall toxicity (P < .05) (8). Similarly, a secondary analysis of the National Cancer Institute-sponsored (N9741) randomized trial of patients with metastatic CRC treated with standard chemotherapy found lower response rates in Blacks compared with Whites (28% vs 41%, P = .008) and lower rates of grade 3 or higher adverse events among Black patients (34% vs 48%, P = .004) (26). Finally, a prospective observational study of patients with metastatic CRC treated with bevacizumab also found lower response rates in Black compared with White patients (37.5% vs 46.3%; adjusted odds ratio = 0.67, 95% CI = 0.50 to 0.90) (27). Taken together, these findings seem to suggest racial differences in sensitivity to systemic therapy that deserve further investigation.

There are several limitations to this study. First, the purpose of the study was to measure differences in outcomes between Black and White patients; therefore, patients of other racial and ethnic groups were excluded (other race, n = 362; unknown race, n = 96). Because patients were not prospectively enrolled to include equal numbers of patients in each race category, the cohort size of Black patients (n = 811) was much smaller than the cohort of White patients (n = 7365). This resulted in a small number of Black patients with rectal cancer (n = 94), thereby limiting subgroup analysis. Differences were observed in measured socioeconomic factors between Black and White patients. Although these were included in the multivariable regression model, it is possible that other confounders related to social determinants of health, such as marital status, exist that were not available within the dataset. Because the study cohort is comprised of patients diagnosed in 2006-2007, these findings may not be representative of contemporary clinical outcomes. These dates were selected to allow at least 5 years of follow-up data for detection of recurrence. Because this is a retrospective study, it is possible that recurrence could be underestimated. To account for this, if patients sought treatment or follow-up at another institution, registrars were asked to collect these data for data completeness. Additionally, it would be expected that any variation in recurrence detection would be similar between racial groups and would be unlikely to alter the findings. Selection criteria for the study cohort could introduce potential bias, specifically the exclusion of patients who did not receive surveillance testing. However, the proportions of Black and White patients without any surveillance testing did not differ (21.9% vs 19.4%, P = .05). Additionally, the patient population within the NCDB consists of patients treated at CoC sites. It is possible that the observed racial differences in receipt of GCC are unique to the population of patients treated at CoC sites and may not be generalizable to patients treated in other clinical settings. Despite this limitation, because the NCDB represents 70% of newly diagnosed cancer cases nationwide, it is considered an acceptable representation of the national cancer patient population. Finally, NCDB does not capture data on performance status or response to therapy, which could result in unmeasured confounding. Despite receiving equivalent or superior quality of care, Black patients experience a higher risk of recurrence and worse OS compared with White patients.

Notes

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Data Availability

Data cannot be shared for ethical/privacy reasons.

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