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ORIGINAL ARTICLE

Outcome disparities in colorectal cancer: a SEER-based comparative analysis of racial subgroups

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Abstract

Purpose Previous studies of ethnic disparities in colorectal cancer (CRC) have focused mainly on patients of Caucasian and African-American descent. We aimed to evaluate outcomes for a range of races, representing a broader demographic of the US population.

Methods The Surveillance, Epidemiology, and End Results database was queried to identify patients with CRC diagnosed between 1994 and 2014. We performed unadjusted Kaplan-Meier test and multivariable covariate-adjusted Cox models to calculate the overall and CRC-specific survival of patients according to their race.

Results We identified 401,723 patients diagnosed with CRC between 1994 and 2014. Overall survival (OS) and CRC-specific survival were compared across different races stratified by age, sex, marital status, disease stage and grade, and undergoing surgery as a treatment. Overall, Asian/Pacific Islanders and Hispanics had improved CRC-specific survival compared to Whites (HR = 0.873, 95%CI 0.853–0.893, $P < .001$, and HR = 0.958, 95%CI 0.937–0.979, $P < .001$, respectively). Blacks had the worst CRC-specific survival outcomes when compared to Whites (HR = 1.215, 95%CI 1.192–1.238, $P < .001$). Racial disparity persisted when looking at two different time periods (1994–2003 and 2004–2014).

Conclusions Asians/Pacific Islanders have improved outcomes from CRC compared to other races. Multifactorial, including genetic, environmental, and socioeconomic factors appear to influence outcomes and need to be addressed separately in order to reduce racial disparities among patients with CRC.

Keywords Colorectal cancer · Racial disparities · Cancer outcomes · SEER

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Introduction

In the USA, colorectal cancer (CRC) has an estimated number of 140,250 new cases in 2018, making it the third most common cancer, and an expected mortality of > 50,000 deaths in 2018 [1]. With a lifetime risk of developing CRC of approximately 4–5%, the incidence rates have been slowly declining in the USA over the last 2 decades [2]. The introduction of novel therapeutic agents in the treatment of CRC over the last decade has improved survival, but the influence of these factors on disease course and outcomes across patient demographics, especially minority races, has not been explored.

Previous studies of CRC have shown the presence of racial disparities in the management and outcomes of patients with the disease. However, these studies focused on Black and White populations only [3, 4]. Current knowledge suggests a higher incidence of CRC and worse survival among Blacks compared to Whites. Socioeconomic status (SES) has been

alluded to as a factor in CRC incidence and mortality differences between groups with low socioeconomic groups having around 30% increase in the risk of developing CRC [5]. Furthermore, there is no data addressing variations among other subgroups, including Asians/Pacific Islanders and/or American Indians/Alaska Natives. Thus, a comprehensive evaluation of racial disparities in CRC beyond Whites and Blacks may help elucidate the impact on the US population in the future.

Methods

Study design

The study is a retrospective cohort that follows the guidelines of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology Statements) checklist [6].

Data source

We received approval from the National Cancer Institute (NCI) and used the Surveillance Epidemiology and End Results (SEER) public database (SEER 18) based on the November 2016 submission. The database contained data on up to 27.8% of the US general population [7]. SEER*stat software (version 8.3.4) was used to obtain the data [8].

Study population

Patients diagnosed with colorectal adenocarcinomas between 1994 and 2014 were included. We used "Site Recode ICD-O-3/WHO codes: C180-C189, C199, C209, C260" and "Histology recode - broad groupings codes: 8140-8389" for this selection. Patients were divided according to their race into five categories: non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic Asian/Pacific Islander, non-Hispanic American Indian/Alaska Native, or Hispanics (all races). We excluded patients with no pathological confirmation, cases with multiple malignancies, and cases with unknown race.

From included patients, we collected the following information: race, age at diagnosis, sex, marital status at diagnosis of CRC, state of residence, stage of CRC (using SEER historic stage A), grade of CRC, exposure to radiation/ chemotherapy for treatment, undergoing surgery for treatment, survival months, and the cause of death.

Variable definitions

Our outcomes were overall survival (OS) and CRC-specific survival according to race (in overall CRC population, and stage IV CRC). The definition of OS was considered as the interval (in months) between the date of CRC diagnosis and the date of death. Patients were followed until death or censored at the end of 2014. When calculating CRC-specific survival, patients were also censored when the cause of death was anything other than cancer itself.

Furthermore, patients were stratified based on the year of diagnosis into two cohorts (1994–2003 and 2004–2014) to study the impact of advances in treatments of CRC on outcomes. The period between 1994 and 2003 was when 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX) were standard for adjuvant therapy, and the period after 2004 had marked improvements in biologic and molecularly targeted therapies (e.g., bevacizumab, cetuximab).

Statistical analysis

We used SPSS software (version 23, IBM, NY) to perform survival analysis; we conducted an unadjusted Kaplan-Meier test, log-rank test, and multivariable covariate-adjusted Cox models. In Cox models, we adjusted for the following factors: age, sex, marital status, stage of CRC, grade of CRC, and undergoing surgery as a treatment option for CRC. Kaplan-Meier curves were constructed according to the race of patients. All statistical tests were two-sided. A P value of less than .05 was considered significant.

Results

Patient and tumor characteristics

A total of 401,723 patients with CRC were included. About half were males (50.9%), aged between 65 and 84 years (46.8%), and married (53.8%) at the time of CRC diagnosis. Most were non-Hispanic Whites (70%) (Table 1).

Survival trends

Overall and colorectal cancer-specific survival in overall population

The median OS for the entire population was 75 months (95% CI [74.324–75.676]), with the highest median OS observed in non-Hispanic Asian/Pacific Islanders (115 months; 95% CI [111.055–118.945]), followed by Hispanics (89 months; 95% CI [85.971–92.029]), non-Hispanic American Indians/Alaska Natives (73 months; 95% CI [65.290–80.710]), non-Hispanic Whites (73 months; 95% CI [72.246–73.754]), and non-Hispanic Blacks (56 months; 95% CI [54.419–57.581]) (all $P < .001$) (Fig. 1) (Supplementary Table 1).

When adjusted for age, sex, marital status, stage of CRC, grade of CRC, and undergoing surgery as a treatment option for CRC, multivariable covariate-adjusted Cox models

Table 1 Baseline characteristics of included colorectal cancer patients ($n = 401,723$)

Baseline characteristic	Cases, no (%)
Overall	401,723 (100)
Race	
White	281,094 (70)
Black	46,498 (11.6)
Asian or Pacific Islander	33,353 (8.3)
American Indian/Alaska Native	2523 (0.6)
Hispanic	38,255 (9.5)
Year of diagnosis	
1994–2003	148,151 (36.9)
2004–2014	253,572 (63.1)
Sex	
Male	204,602 (50.9)
Female	197,121 (49.1)
Age	
18–64	174,080 (43.3)
65–84	188,076 (46.8)
> 84	39,567 (9.8)
Marital status[a]	
Married	216,082 (53.8)
Single	54,536 (13.6)
Widowed	72,696 (18.1)
Divorced	33,923 (8.4)
Separated	3633 (0.9)
State	
California	152,634 (38)
Connecticut	24,129 (6)
Michigan	24,964 (6.2)
Hawaii	9348 (2.3)
Iowa	22,257 (5.5)
Alaska	847 (0.2)
New Mexico	9969 (2.5)
Washington	22,222 (5.5)
Utah	8688 (2.2)
Georgia	40,756 (10.1)
Kentucky	22,275 (5.5)
Louisiana	21,830 (5.4)
New Jersey	41,804 (10.4)
Stage[b]	
Localized	164,443 (40.9)
Regional	140,129 (34.9)
Distant	82,384 (20.5)
Grade	
Well differentiated; Grade I	36,166 (9)
Moderately differentiated; Grade II	247,358 (61.6)
Poorly differentiated; Grade III	60,837 (15.1)
Undifferentiated; anaplastic; Grade IV	4900 (1.2)
Radiation	
No/unknown	347,671 (86.5)
Yes	54,052 (13.5)
Surgery	
No	54,382 (13.5)
Yes	346,210 (86.2)
Chemotherapy	
No/unknown	261,491 (65.1)
Yes	140,232 (34.9)

[a] At the time of CRC diagnosis

[b] Using SEER historic stage A

showed that non-Hispanic Whites had better survival outcomes when compared to non-Hispanic Blacks (HR = 1.1173, 95% CI [1.155–1.191], $P < .001$), and non-Hispanic

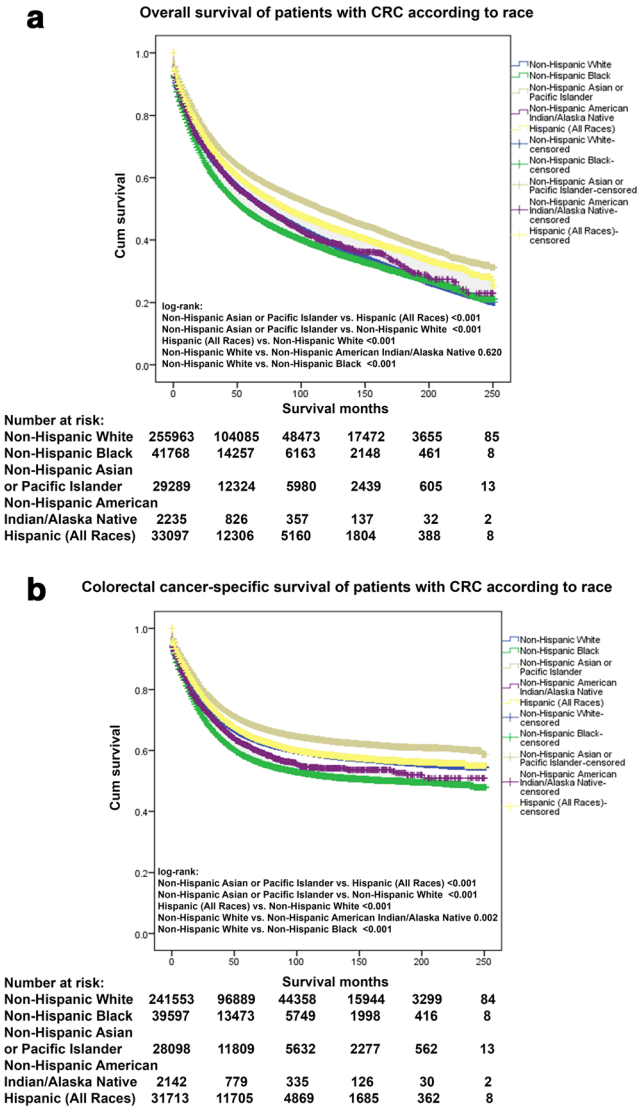

Fig. 1 Overall survival (**a**) and colorectal cancer-specific survival (**b**) of patients with CRC according to race

American Indians/Alaska Natives (HR = 1.109, 95% CI [1.038–1.185], $P = .002$). However, non-Hispanic Whites had shorter survival outcomes compared with non-Hispanic Asians/Pacific Islanders (HR = 0.831, 95% CI [0.816–0.847], $P < .001$), and Hispanics (HR = 0.934, 95% CI [0.917–0.951], $P < .001$) (see Table 2). Interestingly, cox models also showed that female sex was associated with improved overall and colorectal cancer-specific survival outcomes (HR = 0.816, 95%CI [0.807–0.824], $P < .001$). Being married was also associated with favorable outcomes when compared to other marital statuses (Table 2).

Figure 1 shows CRC-specific survival curves for different racial groups. Multivariable covariate-adjusted Cox models for CRC-specific survival showed that non-Hispanic Whites were associated with significantly better survival outcomes when compared to non-Hispanic Blacks (HR = 1.215, 95% CI [1.192–1.1238], $P < .001$), and non-Hispanic American Indians/Alaska Natives (HR = 1.135, 95% CI [1.050–1.227], $P = .001$). However, non-Hispanic Whites had shorter survival outcomes compared with non-Hispanic Asians/Pacific Islanders (HR = 0.873, 95% CI [0.853–0.893], $P < .001$), and Hispanics (HR = 0.958, 95% CI [0.937–0.979], $P < .001$) (see Table 2).

Overall and CRC-specific survival stratified by time period

We divided the sample according to the year of diagnosis into two groups: 1994–2003 and 2004–2014, and then studied racial disparities in each group (Fig. 2). In both groups, patients of non-Hispanic Asian/Pacific Islander origins were found to have the best overall and CRC-specific survival, followed by non-Hispanic Whites, Hispanics, and American Indians/Alaska Natives. Blacks had the worst CRC-specific survival.

Table 2 Multivariable covariate-adjusted Cox models for overall and colorectal cancer-specific survival with adjustment for the following factors: race, age at diagnosis of CRC, sex, marital status, stage of CRC, grade of CRC, and undergoing surgery as a treatment option for CRC

Patient characteristics	All-cause HR* (95% CI)†	All-cause P‡	Colorectal cancer-specific HR* (95% CI)†	Colorectal cancer-specific P‡
Race (vs. white)				
Black	1.173 (1.155–1.191)	< .001	1.215 (1.192–1.238)	< .001
Asian or Pacific Islander	0.831 (0.816–0.847)	< .001	0.873 (0.853–0.893)	< .001
American Indian/Alaska Native	1.109 (1.038–1.185)	.002	1.135 (1.050–1.227)	.001
Hispanic	0.934 (0.917–0.951)	< .001	0.958 (0.937–0.979)	< .001
Age (vs. 18–64)				
65–84	2.090 (2.067–2.115)	< .001	1.532 (1.512–1.553)	< .001
> 84	4.420 (4.345–4.497)	< .001	2.666 (2.607–2.727)	< .001
Sex (vs. male)				
Female	0.816 (0.807–0.824)	< .001	0.891 (0.880–0.903)	< .001
Stage (vs. localized)				
Regional	1.569 (1.550–1.588)	< .001	2.707 (2.657–2.757)	< .001
Distant	5.968 (5.886–6.051)	< .001	12.797 (12.554–13.044)	< .001
Grade (vs. well differentiated; grade I)				
Moderately differentiated; grade II	1.133 (1.112–1.154)	< .001	1.260 (1.227–1.293)	< .001
Poorly differentiated; grade III	1.521 (1.491–1.553)	< .001	1.882 (1.830–1.936)	< .001
Undifferentiated; anaplastic; grade IV	1.637 (1.568–1.709)	< .001	2 (1.901–2.105)	< .001
Marital status# (vs married)				
Single	1.275 (1.256–1.295)	< .001	1.195 (1.174–1.217)	< .001
Widowed	1.377 (1.359–1.396)	< .001	1.251 (1.229–1.273)	< .001
Divorced	1.227 (1.205–1.249)	< .001	1.157 (1.132–1.182)	< .001
Separated	1.222 (1.160–1.287)	< .001	1.089 (1.023–1.158)	< .001
Surgery (vs no)				
Yes	0.423 (0.417–0.430)	< .001	0.404 (0.397–0.411)	< .001

*The hazard ratio for all-cause and colorectal cancer-specific death for the above co-variables. All statistical tests were two-sided

† 95% confidence interval

‡ Two-sided P value was calculated from multivariable covariate-adjusted Cox models

At the time of CRC diagnosis

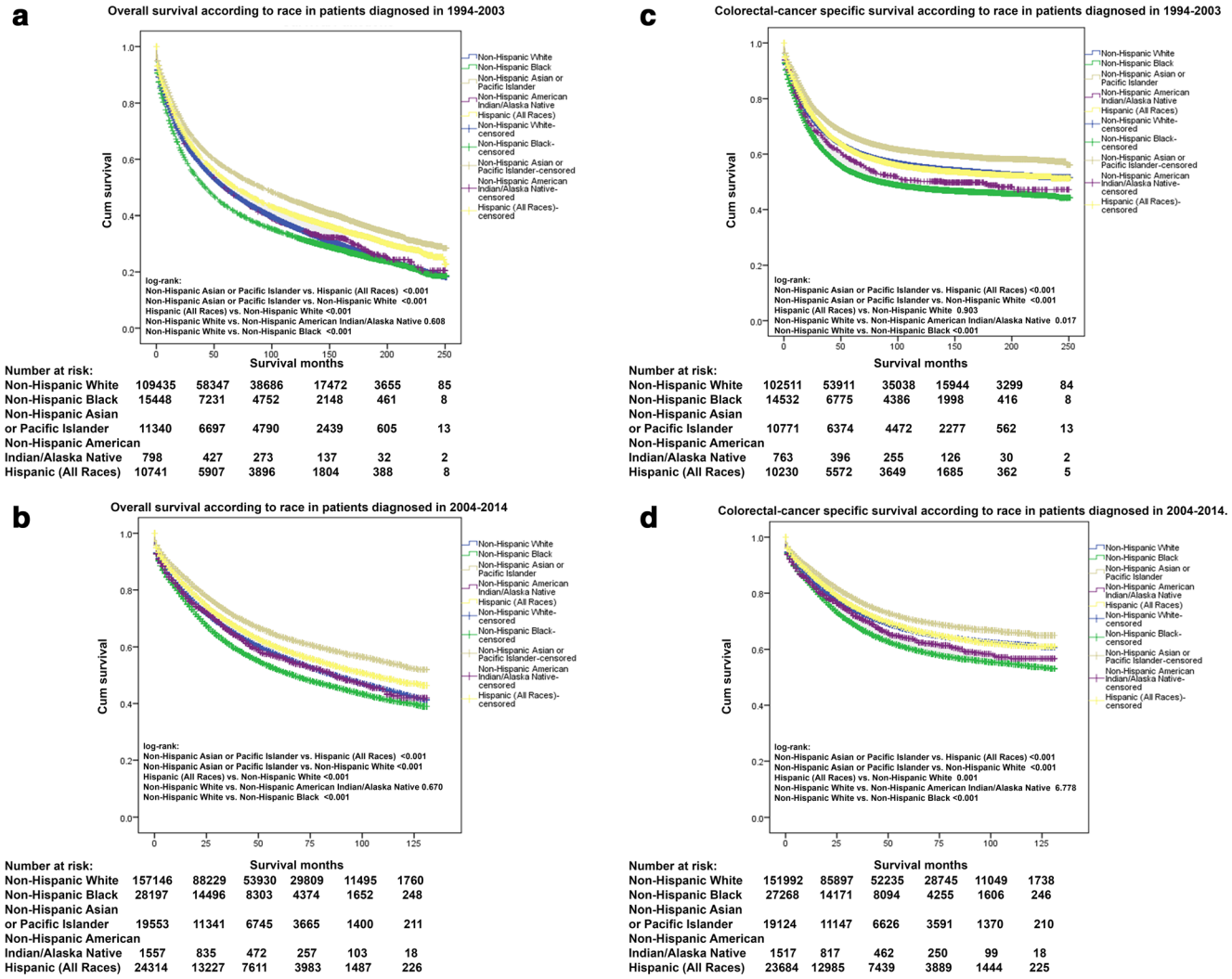

Fig. 2 Overall survival according to race in patients diagnosed in **a** 1994–2003 and **b** 2004–2014, and colorectal cancer-specific survival according to race in patients diagnosed in **c** 1994–2003 and **d** 2004–2014

Overall survival and CRC-specific survival for stage IV CRC

The median OS of the entire population with stage IV CRC was 12 months, 95% CI [11.840–12.160]. Log-rank test on Kaplan-Meier curves showed patients of non-Hispanic Asian/Pacific Islander origin (median OS = 15 months, 95% CI [14.404–15.596]), and Hispanics (median OS = 15 months, 95% CI [14.422–15.578]) to have statistically significant better survival when compared to non-Hispanic Whites, Blacks, and American Indians/Alaska Natives (Fig. 3).

The median CRC-specific survival of the entire population with stage IV CRC was 13 months, 95% CI [12.825–13.175]. CRC-specific survival of non-Hispanic Asians/Pacific Islanders and Hispanics was significantly higher than all other races (Fig. 3). Adjustment for age, sex, marital status, grade of CRC, and undergoing surgery as a treatment option for CRC, showed the same effects of race on OS and CRC-specific survival of stage IV CRC that was shown in the general CRC population (data not shown).

Discussion

Our analysis of more than 400,000 patients with CRC diagnosed between the 1994 and 2014 showed significant differences in survival between races, with Asians/Pacific Islanders as well Hispanics having relatively better survival outcomes, Whites and American Indians/Alaska Natives having similar CRC-specific survival, and Blacks having the shortest survival outcomes. Furthermore, when our sample was divided by time period: 1994–2003 (when 5-FU and FOLFOX were standard for adjuvant therapy) versus 2004–2014 (when new biologic and molecularly targeted therapies like bevacizumab and cetuximab were being used), these racial differences in outcomes persisted.

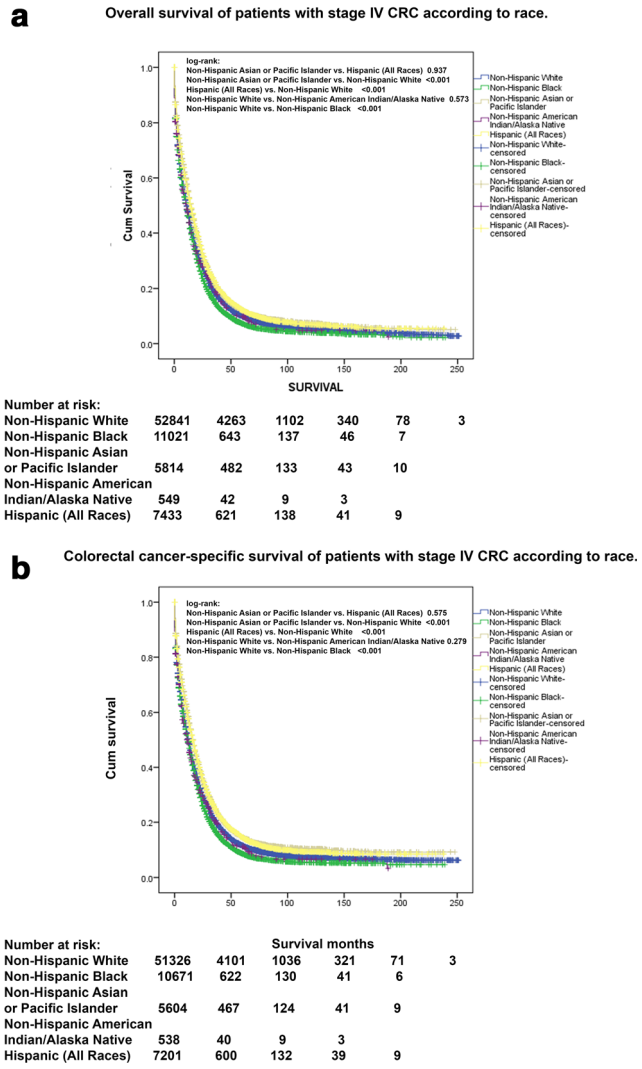

Fig. 3 Overall survival (**a**) and colorectal cancer-specific survival (**b**) of patients with stage IV CRC according to race

Several factors have been explored as contributors to racial disparity. They include differences in socioeconomic levels, access to health care and behavioral factors affecting implementation of effective screening, as well as genetic factors [9–11]. White et al. assessed a cohort of more than 37,000 patients with stages I–III cancer and observed that Blacks had shorter CRC-specific survival than Whites, and Asians/Pacific Islanders had longer survival than Whites [12]. SES and comorbidities were implicated as important factors contributing to the shorter survival of Blacks, with significant differences in survival, even after controlling for numerous variables [12, 13]. In another study by Tawk et al. that evaluated differences in CRC outcomes by race and insurance status, Blacks had higher odds of late-stage CRC as compared to Whites, the risk of CRC-related death was higher among Blacks than Whites and was higher among uninsured and Medicare patients than insured patients [14].

While differences in SES can impact CRC-specific survival within ethnic groups [15, 16], it is also apparent that other factors contribute to the racial differences of CRC survival, including genetic and tumor biology-related factors. For example, CRC in Blacks is more likely to have microsatellite instability (MSI-high) compared to other ethnic groups [17]. Farhana et al. showed that the elevated incidence of CRC in Blacks may be explained by an increased number of cancer stem cells in colonic mucosa and certain microRNA profiles [18]. Furthermore, Blacks and Hispanics tend more to develop proximal (right-sided) CRC [19, 20], and Blacks are also more likely to present with CRC at an earlier age and with more advanced disease [3, 14].

Behavioral differences driven by cultural or financial influences may also factor in ethnic and social disparities. Multiple studies that investigated this point have found that patients of higher SES, mostly White patients, undergo screening colonoscopies more frequently [21, 22]. Furthermore, Black patients, particularly in rural areas, undergo surgery for CRC less frequently and are also less likely to be treated with adjuvant chemo or radiotherapy [4, 13]. Blacks also suffered from more problems with care coordination, access to cancer care, and health information compared to Whites [4]. May et al. suggested several interventions to increase rates of CRC screening in Black communities, with more screening allowing early detection of lesions and thus enhancing the survival of black patients, including using commercials, influential public figures, health fairs, addressing race-specific barriers in a culturally sensitive way among other social interventions [23]. However, one of the main limiting factors to regular screening programs in Black communities is higher rates of uninsured patients without affordable access to regular screening [24].

Chan et al. reported that Blacks appear to present with more advanced stages of CRC, an observation that is supported by our results, with approximately three in every four patients presenting with stages III and IV [24]. Such results may be attributed to biologic factors in addition to the previously studied social factors, and further solidify the need to implement better screening regimens in minorities in order to address the higher numbers of advanced disease in those populations [25].

Interestingly, these disparities have persisted over years as our data shows that Blacks still have had the worst survival while Asians have had the best survival outcomes. However, we noted that the survival for all groups have been improving consistently over time with the best survival being in patients diagnosed after 2004. Other studies have showed results consistent with our current observation with continuously improving survival of CRC over time [26, 27].

This study is not without limitations. Sources of bias could not be controlled for due to the retrospective nature of the study. The SEER database is missing key comorbidities and information regarding patient baseline functional status and specific therapies that were utilized. Another limitation is that

the SEER database does not capture the environmental exposure or individual lifestyle habits which limited our ability to further study such controversial factors. Moreover, SEER lacks sufficient information on radiation and systemic chemotherapy, and the present information is not sensitive enough to make comparisons between patients who did/did not receive radiation and/or chemotherapy [28]. However, by using the SEER database that covers approximately 28% of the US population, our sample size is, to our knowledge, the largest assessing racial disparities in CRC outcomes. Furthermore, while most studies only assess the outcomes of Whites versus Blacks, we also included other racial populations like Asians/Pacific Islanders, as well as American Indians/Alaska Natives.

Conclusions

In conclusion, despite the health burden of CRC, racial disparities in outcomes exist, with Asians/Pacific Islanders, Hispanics, and Whites having more favorable outcomes than Blacks. While variations in tumor biology may play a role, other factors such as varying SES, cancer screening, and management strategies all seem to influence outcomes as well and need to be addressed separately in order to reduce racial disparities. Additionally, most studies focus on differences in outcomes between Blacks and Whites; more emphasis to include other racial and ethnic groups when studying disparities is needed, which may ultimately illustrate underlying biologic and social factors contributing to the observed disparities.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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