Cancer Epidemiology 63 (2019) 101618

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Analysis of racial disparities in the treatment and outcomes of colorectal cancer in young adults

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ARTICLE INFO

Keywords:
Young adults
Colorectal cancer
Health disparities
Racial disparities

ABSTRACT

Background: The incidence of colorectal cancer (CRC) in young adults is increasing. Minority populations with CRC are known to have worse survival outcomes. The aim of this study is to evaluate adults under age 50 years with CRC by race and ethnicity.

Methods: Data were obtained from all US hospitals that contributed to the National Cancer Database (NCDB) between 2004 and 2013. Univariate and multivariable testing was done to identify factors associated with patient outcome. Kaplan-Meier analysis and Cox proportional hazards models were used for association between patient characteristics and survival.

Results: A total of 83,449 patients between 18 and 50 years of age were identified. Median age was 45 years (SD ± 6), with male preponderance (53.9%). 72% were non-Hispanic Whites (NHW), Blacks (AA) were 15.1% and Hispanics (who did not identify as Blacks) were 8.3% of the study population. Distribution across stages I–IV was 15.6%, 22.4%, 33.9% and 27% consecutively. 41.8% of NHW and 28.4% of AA had rectal cancers ($p < 0.001$). Despite equally receiving standard of care (SOC) as per national guidelines, AA had significantly lower 5-year survival rates (58.8%) compared to Hispanics (64.8%) and NHW (66.9%; HR 1.42; 1.38-1.46; $p < 0.001$). Furthermore, NHW (HR 0.85; 0.81-0.88; $p < 0.001$) and Hispanics (HR 0.75; 0.70-0.79; $p < 0.001$) were more likely to benefit from chemotherapy compared to AA. SOC utilization was associated with improved survival across all racial groups, especially in AA (HR 0.64; 0.60-0.69; $p < 0.001$).

Conclusion: Despite comparable rates of SOC utilization, AA young adults had worse survival outcomes compared to other races. More colon (compared to rectal) cancers in AA may have contributed to their worse outcomes.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related death in males and females in the United States [1]. Despite decreasing CRC incidence in the general population, early onset CRC shows rising incidence [2]. Rates increased among adults below 55 years by 1.4% for colon cancer, and by 2.4% for rectal cancer between 2005 and 2014 [2]. The corresponding death rate increased by 1% [2]. Traditionally, recommendations for screening average-risk subjects starts at age 50 years, although 11% of colon cancers and 18% of rectal cancers are diagnosed in adults below this age cut-off [3]. This led to the recent recommendations by the American Cancer Society (ACS) that adults aged 45 years and older with an average risk of CRC undergo regular screening [4]. Racial disparity in CRC is not well understood [5]. Compared to other races, African Americans (AA) have higher overall incidence, diagnosis with stage IV, attributable mortality, and lower survival rates [6–11]. CRC is the second most common cause of cancer and cancer-related death in Hispanics in the United States [12]. Despite increased screening and more effective treatments for CRC, racial differences persist in CRC survival outcomes [13]. Previously reported reasons include treatment inequality [14], lower socioeconomic status [7,15,16], comorbidities [17], lifestyle differences [18], genetic mutations [19], and tumor biology [13].

With the increasing incidence and mortality rates among younger adults with CRC, it is important to evaluate racial disparities in the

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https://doi.org/10.1016/j.canep.2019.101618
Received 8 July 2019; Received in revised form 24 September 2019; Accepted 29 September 2019

pattern of presentation and treatment, survival indices, and factors affecting outcomes in this group of patients. Compared to older patients, adults with CRC younger than 50 years of age are more likely to present with more advanced stages of their disease [20]. The inferior survival outcomes in these patients are thought to be due to unfavorable tumor characteristics such as poorly differentiated histology, signet ring cell morphology, epigenetic changes and higher frequency of lymph node and distant metastases [3]. It is therefore imperative to understand the role of age, race and ethnicity in disparities seen in the care of these patients. Our hypothesis was that racial disparities are amplified in younger CRC patients due to unfavorable tumor biology associated with earlier age at diagnosis. The National Cancer Database (NCDB) is a hospital-based cancer registry capturing 70% of all incident cancers in the United States. We used the NCDB to evaluate the pattern of disease presentation, treatment received, survival outcomes and and prognostic factors in adults younger than 50 years who were diagnosed with CRC from 2004-2013.

2. Materials and methods

We obtained data from the NCDB for the interval between 2004 and 2013 as previously described [21]. With more than 1500 Commission-on-Cancer-accredited cancer programs participating, the database contains clinical and demographic information on majority of US cancer patients. Selection criteria for the study included age 18 to 50 years at diagnosis of CRC, using the International Classification of Diseases for Oncology (ICD-O, 3rd edition) codes 814, 821, 822, 848, 849 and 856. Exclusion criteria were histology other than adenocarcinoma, in-situ or non-invasive disease, carcinoma of unknown primary, and patients with missing demographics, treatment and outcome data. We also excluded patients with multiple cancers, either in the colon/rectum, or other primaries. The primary outcome was overall survival between the different racial groups. Patient-specific covariates included age at diagnosis, gender, race, insurance status, year of diagnosis, primary site, AJCC stage (using the 5th or 6th editions of the American Joint Committee on Cancer staging manual, depending on the year of diagnosis), tumor grade, diagnostic confirmation, treatment received (including surgical resection, chemotherapy and radiation). Survival rates are computed in the database by the actuarial method, compounding survival in one-month intervals from the date of diagnosis, with death from any cause as the endpoint. Comparison between two time periods (2009 2013 vs. 2004 2008) was done to reflect introduction of newer systemic agents in clinical practice. National guidelines such as the Ethical approval was not required for the study since patient information in the database is completely de-identified and the database is legally accessible to the public. We suppressed data for facility location and type as appropriate to ensure privacy and HIPPA compliance as per NCDB guidelines. We explored the role of facility location and type due to limited data suggesting that patients treated in rural areas have more challenges accessing adequate care, due to shortage of healthcare providers, proximity to treatment centers, etc [22,23]. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in Oncology were used to define the Standard of Care (SOC).

2.1. Statistical analysis

Appropriate descriptive statistics for variable type and distribution were used to summarize clinical and demographic characteristics of the patients. Univariate and multivariate analyses were conducted to identify factors associated with patient outcome. All clinically meaningful variables were included and subsequently eliminated based on the level of significance. To assess the association between patient characteristics and survival, Cox proportional hazards models were fitted with a backward elimination method (removal criteria $p = 0.05$). Likelihood ratio test (LRT) was used to compare the model with the covariate being assessed; both added with the model and with the assessed covariate dropped. An alpha level of 0.05 was used, and any covariate with LRT p-value < 0.05 was removed from the final multivariate model. We used backward elimination to automate the LRTs, and determine the final model with the covariates presented. Kaplan-Meier curves were generated for overall survival. All analyses were done using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) with a significant level of 0.05.

Table 1
Selection/Exclusion Criteria.

Selection and Exclusion Criteria	Sample Size	Excluded
NCDB CRC PUF (participant user files) Cancer Cases	1100035	–
Include histology of: 814, 821, 822, 848, 849, 856	905197	194838
Include patients who were between 18 to 50 years old	111943	793254
Exclude primary tumor BEHAVIOR of uncertain invasiveness, in situ or non-invasive characteristics	109562	2381
Exclude CLASS OF CASE = 0 (cases diagnosed at the reporting facility but did not receive any treatment at that facility)	105842	3720
Include SEQUENCE_NUMBER in (0 1) – excludes non-malignant and borderline cases	99275	6567
Remove observation with missing outcome	88355	10920
Analytic stage group in 0-4	84347	4008
Unknown Race	83,449	898

3. Results

3.1. Patient demographics and tumor characteristics

We identified 83,449 patients between ages 18 and 50 years for the study (Table 1). The median age at diagnosis was 45 years (SD ± 6), and the patients were predominantly male (53.9%) (Table 2). Distribution across stages I–IV was 15.6%, 22.4%, 33.9% and 27% respectively. Most of the tumors were moderately differentiated (62.8%) followed by poorly differentiated/undifferentiated (18.8%) and well differentiated (8%). A higher number of patients were diagnosed between 2009 and 2013 for all racial groups, compared to 2004–2008 ($p < 0.001$). Primary sites were divided into colon (60.5%) and rectum (39.5%). About 42.3% of the patients were treated at community practices, while 28.6% were treated at academic or research cancer centers. The median number of regional lymph nodes resected at surgery was 18 (range 1–90).

Non-Hispanic Whites (NHW) constituted 72% of the study population. In addition, AA made up 15% and Hispanics 8.31% of the study population. Races and ethnicities other than NHW, AA, and Hispanic were combined into "Other" due to small numbers. Distribution across stages I–IV and grade were similar in the different racial groups ($p < 0.001$). The proportion of patients in each racial group with primary cancers located in the colon were NHW (58.2%), AA (71.6%), and Hispanics (61.47%; $p < 0.001$). The mean age at diagnosis was similar between NHW (43.85 years), AA (43.84 years), and Hispanics (42.36 years) ($p < 0.001$). There was a male preponderance among NHW (54.99%) and Hispanics (54.6%), but a slight female preponderance in AA (51%) ($p < 0.001$). Insurance coverage among the study population was mostly private (71.9%), compared to Medicaid (11.3%) and Medicare (5.6%). A lower proportion of NHW were uninsured (9%), compared to AA (16.6%) and Hispanics (22.4%; $p < 0.001$).

3.2. Treatment

Most of the patients (77.8%) received standard of care (SOC) as per national guidelines (Table 3). Standard of care was similar between NHW (78.3%), AA (77.1%), and Hispanics (75.5%) ($p < 0.001$) (Table 4). Among the study population who had indication for surgical

Table 2
Descriptive Statistics for all variables of interest.

Variable	Level	N (%) = 83,449
Sex	Male	44974 (53.9)
	Female	38475 (46.1)
Year of Diagnosis	2004-2008	40089 (48.0)
	2009-2013	43360 (52.0)
Primary Site	Rectum Cancer	32935 (39.5)
	Colon Cancer	50514 (60.5)
Facility Type	Community Cancer Program	35320 (42.3)
	Academic/Research Program	23847 (28.6)
	Integrated Network Cancer Program	7283 (8.7)
	Suppressed for patients aged 0-39 at DX	16999 (20.4)
Facility Location	Northeast	12962 (15.5)
	South	26875 (32.2)
	Midwest	16172 (19.4)
	West	10441 (12.5)
	Suppressed for patients aged 0-39 at DX	16999 (20.4)
Primary Payer	Not Insured/Unknown	9285 (11.1)
	Private	60009 (71.9)
	Medicaid	9449 (11.3)
	Medicare/Other Government	4706 (5.6)
Median Income Quartiles	Not Available	3193
	< $30,000	11206 (14.0)
	$30,000 - $35,999	13715 (17.1)
	$36,000 - $45,999	21667 (27.0)
	$46,000 +	33,668 (42.0)
Urban/Rural	Metro	68799 (82.4)
	Urban	10430 (12.5)
	Rural	1309 (1.6)
	Unknown	2911 (3.5)
AJCC Analytic Stage Group	Stage I	13901 (16.7)
	Stage II	18717 (22.4)
	Stage III	28284 (33.9)
	Stage IV	22547 (27.0)
Grade	Well Differentiated	6672 (8.0)
	Moderately Differentiated	52412 (62.8)
	Poorly Differentiated/ Undifferentiated	15704 (18.8)
	Cell Type Not Determined	8661 (10.4)
Age at Diagnosis	Mean	43.69
	Median	45.00
	Minimum	18.00
	Maximum	50.00
	Std Dev	6.08
	Missing	0.00
Last Contact or Death, Months from Dx	Mean	49.64
	Median	42.64
	Minimum	0.00
	Maximum	143.05
	Std Dev	34.00
	Missing	0.00

procedures, 89% had surgical resection (Table 2). About 8.8% of the patients who underwent resection had positive margins, with worse overall survival outcome (HR 3.66; 3.54–3.78; $p < 0.001$) (Table 5). Surgery rates were clinically similar between NHW (89.9%), AA (86.2%), and Hispanics (86%) ($p < 0.001$). The rates of positive surgical margins were also clinically similar between NHW (8.6%), AA (9.4%), and Hispanics (9.5%) ($p < 0.001$).

Chemotherapy was administered in 71.5% of the patients and radiotherapy was administered in 26.7% of the patients in the study population. Chemotherapy utilization was similar between NHW (71.9%), AA (69%), and Hispanics (71.9%) ($p < 0.001$) (Table 4). AA had the least frequency of radiation therapy (20%) compared to NHW (28.2%), and Hispanics (25.6%). The median interval from diagnosis to treatment was clinically similar amongst racial groups with 13 days for NHW, 11 days for AA, and 13 days for Hispanics ($p < 0.001$).

Table 3
Treatment Received by Study Participants.

Variable	Level	N (%) = 83,449
Surgery at Primary Site based on SOC guidelines	No	9149 (11.0)
	Yes	74242 (89.0)
	Unknown	58 (0.1)
Surgical Margin	Negative	64450 (77.2)
	Positive	7339 (8.8)
	Unknown	2511 (3.0)
	No Surgery	9149 (11.0)
Radiation	No	59940 (71.8)
	Yes	22292 (26.7)
	Unknown	1217 (1.5)
Chemotherapy	No	21371 (25.6)
	Yes	59632 (71.5)
	Unknown	2446 (2.9)
Standard of Care	No	16206 (19.4)
	Yes	64884 (77.8)
	Unknown	2359 (2.8)
Treatment Started, Days from Diagnosis	Mean	493.99
	Median	13.00
Definitive Surgical Procedure, Days from Dx	Mean	42.32
	Median	14.00
Radiation started, Days from Dx	Mean	60.36
	Median	36.00
Number of Regional Lymph Nodes Positive	Mean	5.08
	Median	3.00
Number of Regional Lymph Nodes Examined	Mean	20.21
	Median	18.00

3.3. Disparities in overall survival

The median follow-up period for the patients included in the analysis was 42 months. AA had inferior median overall survival compared to NHWs (HR 1.42; 1.38–1.46; $p < 0.001$) (Table 5). The same was true for Hispanics compared to NHWs (HR 1.07; 1.02–1.12; $p = 0.004$). The median overall survival (OS) differed by race (Fig. 1). AA had similar median OS of 84.6 months in the period 2004–2008, and 77 months between 2009 and 2013. The median OS for the other racial groups for both 2004–2008 and 2009–2013 ha d not been reached at the time of data analysis. AA had also significantly lower 5-year survival rates compared to NHW in both treatment group periods. Similarly, for stages I—IV, AA had the lowest 5-year survival rates compared to NHW (Fig. 2). Patients with metastatic disease had worse survival indices. The median OS for AA with Stage IV disease was 20.1 months, with a 5 year survival rate of 14.8%. The median OS for NHW, Hispanics and other races were 26.4months, 26.2months and 25.5 months respectively. Their corresponding 5-year survival rates were 21.8%, 21.5% and 23.6%.

Despite equally receiving SOC as per NCCN guidelines, AA had significantly lower median OS (103.3 months) compared to NHW (139.2 months). AA also had worse 5-year survival rates (58.8%; HR 1.42; 1.38–1.46; $p < 0.001$), as well as Hispanics (64.8%; HR 1.07, 1.02–1.12, $p < 0.001$) compared to NHW (66.9%) (Fig. 3A). Among patients who did not receive SOC, AA had significantly lower median OS (44.6months) and 5-year survival rates (44.6%; HR 1.42; 1.38–1.46; $p < 0.001$), compared to Hispanics (60%; HR 1.07, 1.02–1.12, $p < 0.001$) and NHW (63.9%) (Fig. 3B). In terms of survival, NHW (HR 0.84; 0.81-0.88; $p < 0.001$) and Hispanics (HR 0.75; 0.70-0.79; $p < 0.001$) were more likely to benefit from chemotherapy compared to AA (Table 5). As expected, SOC utilization was associated with improved survival across all racial groups, especially in AA (HR 0.64; 0.60-0.69; $p < 0.001$).

Female patients had better outcomes than their male counterparts (HR 0.87; 0.85-0.89; $p < 0.001$) and income levels were directly associated with better survival outcomes across the quartiles of distribution. Well differentiated (HR 0.37; 0.35-0.4; $p < 0.001$) and moderately differentiated (HR 0.51; 0.5-0.53; $p < 0.001$) histology

Table 4
Univariate Association with Race.

Covariate	Statistics	Level	Race Group				P-value*
			White N = 59641	Black N = 12,642	Hispanic N = 6935	Others# N = 4231	
Facility Type	N (Col %)	Community Cancer Program	26720 (44.81)	4704 (37.21)	2308 (33.28)	1588 (37.53)	< **.001**
	N (Col %)	Academic/Research Program	16320 (27.36)	4183 (33.09)	1985 (28.62)	1359 (32.12)	
	N (Col %)	Integrated Network Cancer Program	4999 (8.38)	1324 (10.47)	672 (9.69)	288 (6.81)	
	N (Col %)	Suppressed for patients aged 0-39 at DX	11602 (19.45)	2431 (19.23)	1970 (28.41)	996 (23.54)	
Facility Location	N (Col %)	Northeast	9863 (16.54)	1556 (12.31)	904 (13.04)	639 (15.1)	< **.001**
	N (Col %)	South	17950 (30.1)	6133 (48.51)	2020 (29.13)	772 (18.25)	
	N (Col %)	Midwest	13302 (22.3)	1982 (15.68)	424 (6.11)	464 (10.97)	
	N (Col %)	West	6924 (11.61)	540 (4.27)	1617 (23.32)	1360 (32.14)	
	N (Col %)	Suppressed for patients aged 0-39 at DX	11602 (19.45)	2431 (19.23)	1970 (28.41)	996 (23.54)	
Sex	N (Col %)	Male	32796 (54.99)	6201 (49.05)	3784 (54.56)	2193 (51.83)	< **.001**
	N (Col %)	Female	26845 (45.01)	6441 (50.95)	3151 (45.44)	2038 (48.17)	
Primary Payor	N (Col %)	Not Insured/Unknown	5162 (8.66)	2101 (16.62)	1556 (22.44)	466 (11.01)	< **.001**
	N (Col %)	Private	46265 (77.57)	7286 (57.63)	3553 (51.23)	2905 (68.66)	
	N (Col %)	Medicaid	5063 (8.49)	2282 (18.05)	1510 (21.77)	594 (14.04)	
	N (Col %)	Medicare/Other Government	3151 (5.28)	973 (7.7)	316 (4.56)	266 (6.29)	
Median Income Quartiles	N (Col %)	< $30,000	5762 (10.04)	3593 (29.58)	1432 (21.5)	419 (10.32)	< **.001**
	N (Col %)	$30,000 - $35,999	9584 (16.7)	2397 (19.73)	1323 (19.86)	411 (10.12)	
	N (Col %)	$36,000 - $45,999	15816 (27.56)	3041 (25.03)	1893 (28.41)	917 (22.58)	
	N (Col %)	$46,000 +	26,223 (45.7)	3116 (25.65)	2014 (30.23)	2315 (56.99)	
Urban/Rural 2013	N (Col %)	Metro	47485 (79.62)	11,147 (88.17)	6381 (92.01)	3786 (89.48)	< **.001**
	N (Col %)	Urban	8876 (14.88)	957 (7.57)	346 (4.99)	251 (5.93)	
	N (Col %)	Rural	1111 (1.86)	138 (1.09)	17 (0.25)	43 (1.02)	
	N (Col %)	Unknown	2169 (3.64)	400 (3.16)	191 (2.75)	151 (3.57)	
Year of Diagnosis	N (Col %)	2004-2008	29012 (48.64)	6164 (48.76)	3043 (43.88)	1870 (44.2)	< **.001**
	N (Col %)	2009-2013	30629 (51.36)	6478 (51.24)	3892 (56.12)	2361 (55.8)	
Primary Site	N (Col %)	Rectum Cancer	24907 (41.76)	3588 (28.38)	2672 (38.53)	1768 (41.79)	< **.001**
	N (Col %)	Colon Cancer	34734 (58.24)	9054 (71.62)	4263 (61.47)	2463 (58.21)	
AJCC Analytic Stage Group	N (Col %)	Stage 0	702 (1.18)	99 (0.78)	70 (1.01)	42 (0.99)	< **.001**
	N (Col %)	Stage I	10013 (16.79)	1578 (12.48)	843 (12.16)	554 (13.09)	
	N (Col %)	Stage II	13251 (22.22)	2799 (22.14)	1651 (23.81)	1016 (24.01)	
	N (Col %)	Stage III	19988 (33.51)	4276 (33.82)	2470 (35.62)	1550 (36.63)	
	N (Col %)	Stage IV	15687 (26.3)	3890 (30.77)	1901 (27.41)	1069 (25.27)	
Grade	N (Col %)	Well Differentiated	4782 (8.02)	995 (7.87)	586 (8.45)	309 (7.3)	< **.001**
	N (Col %)	Moderately Differentiated	37516 (62.9)	8016 (63.41)	4252 (61.31)	2628 (62.11)	
	N (Col %)	Poorly Differentiated/ Undifferentiated	11235 (18.84)	2225 (17.6)	1378 (19.87)	866 (20.47)	
	N (Col %)	Cell Type Not Determined	6108 (10.24)	1406 (11.12)	719 (10.37)	428 (10.12)	
Surgery at Primary Site	N (Col %)	No	5977 (10.02)	1732 (13.7)	965 (13.91)	475 (11.23)	< **.001**
	N (Col %)	Yes	53620 (89.9)	10,903 (86.24)	5965 (86.01)	3754 (88.73)	
	N (Col %)	Unknown	44 (0.07)	7 (0.06)	5 (0.07)	2 (0.05)	
Surgical Margin	N (Col %)	Negative	46801 (78.47)	9382 (74.21)	5039 (72.66)	3228 (76.29)	< **.001**
	N (Col %)	Positive	5110 (8.57)	1188 (9.4)	660 (9.52)	381 (9)	
	N (Col %)	Unknown	1753 (2.94)	340 (2.69)	271 (3.91)	147 (3.47)	
	N (Col %)	No Surgery	5977 (10.02)	1732 (13.7)	965 (13.91)	475 (11.23)	
Radiation	N (Col %)	No	42052 (70.51)	9906 (78.36)	5031 (72.55)	2951 (69.75)	< **.001**
	N (Col %)	Yes	16798 (28.17)	2527 (19.99)	1774 (25.58)	1193 (28.2)	
	N (Col %)	Unknown	791 (1.33)	209 (1.65)	130 (1.87)	87 (2.06)	
Chemotherapy	N (Col %)	No	15155 (25.41)	3496 (27.65)	1680 (24.22)	1040 (24.58)	< **.001**
	N (Col %)	Yes	42889 (71.91)	8727 (69.03)	4989 (71.94)	3027 (71.54)	
	N (Col %)	Unknown	1597 (2.68)	419 (3.31)	266 (3.84)	164 (3.88)	
Standard of Care	N (Col %)	No	11415 (19.14)	2492 (19.71)	1460 (21.05)	839 (19.83)	< **.001**
	N (Col %)	Yes	46668 (78.25)	9749 (77.12)	5233 (75.46)	3234 (76.44)	
	N (Col %)	Unknown	1558 (2.61)	401 (3.17)	242 (3.49)	158 (3.73)	
Age at Diagnosis	N		59641	12,642	6935	4231	< **.001**
	Mean		43.85	43.84	42.36	43.14	
	Median		46	46	44	45	
	Min		18	18	18	18	
	Max		50	50	50	50	
	Std Dev		5.96	6.03	6.83	6.32	
Treatment Started, Days from Diagnosis	N		59641	12,642	6935	4231	< **.001**
	Mean		430.41	501.82	811.43	846.48	
	Median		13	11	13	14	
Definitive Surgical Procedure, Days from Dx	N		52518	10719	5731	3563	< **.001**
	Mean		43.34	36.22	42.93	44.61	
	Median		15	9	12	15	
Radiation, Days from Dx	N		16235	2460	1648	1109	< **.001**
	Mean		58.51	67.22	67.24	61.87	
	Median		35	43	42	38	

(*continued on next page*)

Table 4 (*continued*)

Covariate	Statistics	Level	Race Group White N = 59641	Black N = 12,642	Hispanic N = 6935	Others[#] N = 4231	P-value[*]
Radiation Ended, Days from Start of Radiation	N		15539	2350	1555	1071	0.520
	Mean		40.54	40.94	40.52	39.89	
	Median		40	40	40	39	
Number of Regional Lymph Nodes Positive	N		26234	5765	3027	1938	< **.001**
	Mean		5.13	4.68	5.3	5.24	
	Median		3	3	3	3	
Number of Regional Lymph Nodes Examined	N		50061	10217	5569	3527	**0.001**
	Mean		20.23	19.86	20.67	20.3	
	Median		17	18	18	17	
Last Contact or Death, Months from Dx	N		59641	12,642	6935	4231	< **.001**
	Mean		51.25	45.02	45.19	48.09	
	Median		44.68	36.86	37.78	41.3	

* The parametric p-value is calculated by ANOVA for numerical covariates and chi-square test for categorical covariates.
[#] All races and ethnicities other than NHW, AA, and Hispanic were combined into "Others" due to small numbers.

were significantly associated with better survival outcomes compared to poorly differentiated subtypes. Other worse prognostic factors included ages 18–34 vs. 35–50 (HR 1.15; 1.11–1.2; $p < 0.001$), regional lymph nodes harvested below the median number of 18 (HR 1.19; 1.16–1.23; $p < 0.001$) and rectal vs. colon cancer (HR 1.21; 1.18–1.24; $p < 0.001$).

Multivariable analyses showed that compared to AA, other racial groups benefited more from chemotherapy: Hispanics (HR 0.75; 0.7-0.79; $p < 0.001$), NHW (HR 0.84; 0.81-0.88; $p < 0.001$) and other racial groups (HR 0.81; 0.76-0.87; $p < 0.001$) (Table 6). Even in the absence of chemotherapy, the outcomes for AA were still inferior to other races: Hispanics (HR 0.62; 0.55-0.70; $p < 0.001$), NHW (HR 0.83; 0.78-0.9; $p < 0.001$) and other racial groups (HR 0.67; 0.57-0.78; $p < 0.001$).

4. Discussion

The current study is the largest to evaluate racial disparities among younger CRC patients [24,25]. We showed a significantly worse 5-year survival for young AA, compared to Hispanics and NHW patients at every stage of the disease, despite equal access to standard of care (SOC). AA had significantly lower 5-year survival rates compared to NHW in both treatment group periods, and across stages of the disease. These findings are important for several reasons. In this age group (< 50 years), most of the patients would not have had routine CRC screening. Previous studies attributed racial disparities in the outcomes of CRC to the low rates of CRC screening among AA, related to lower SES, and less access to high-quality oncology care [24,26]. This study shows that even in a population which is not routinely screened, AA have poor outcome, suggesting other contributing factors for the observed racial disparities.

About 19% of the patients included in this analysis did not receive standard of care as per national guidelines. This frequency is relatively high given the population is young in age and most probably has lower comorbidities than the general CRC population. While cancer care is individualized with modifications of conventional norms, the large proportion in our study necessitates widespread adoption of the guidelines with respect to age appropriate treatment strategies. In addition, these results raise the concern that the social, financial, and psychological challenges young adults with CRC face are different than older patients. Having a support system designed to address these unique challenges may enhance the ability of young adults to receive SOC treatment leading to an improvement in their outcomes.

Although differences in SOC could contribute to racial disparities in CRC outcomes, randomized clinical trials of adjuvant chemotherapy in patients with stage III CRC demonstrated worse overall and recurrence-free survival for AA compared with NHW [27,28]. Outcome inequalities exist for different racial groups despite receiving comparable rates of SOC as shown in our study, possibly due to other factors such as differences in the biology of the disease [29]. A higher frequency of DNA mismatch repair genes involving novel variants have been reported in AAs [30]. Another multiplatform study found distinct subtype of CRC that is very common in AA; affecting a younger population, and associated with lack of APC mutation, lower mutation burden, and distinctive methylation changes when compared with non-Hispanic Whites [31]. Colon cancer was most common in AA (71.6%) compared to NHW (58.2%) and Hispanics (61.5%) which may have contributed to their worse outcomes [32,33]. In our study, patients with colon cancer had a worse outcome compared to rectal cancer (HR 1.21; 1.18–1.24; $p < 0.001$). Primary site (colonic versus rectal) location has been shown to vary by race in previous studies [34,35]. Young AA were less likely to have radiation possibly because they had a lower prevalence of rectal cancer. Disparities in treatment and inferior overall outcome in AA could also have been due to insurance coverage [36,37]. In our study population, uninsured patients were more likely to be AA [36], and thus less likely to receive treatment. In our study, around 9% of NHW were uninsured compared to AA (16.6%) and Hispanics (22.4%) ($p < 0.001$).

CRC incidence has been on the rise in patients younger than 50 years [24]. The increase in the number of our reported cases between 2009–2013 (52%) and 2004–2008 (48%) is consistent with reported trends. The current recommendation of colorectal cancer screening at 50 years has been challenged due to these epidemiologic trend [38]. The American College of Gastroenterology (ACG) listed the AA race as a high-risk population, proposing screening moderate-risk AA patients with colonoscopy starting at 45 years of age [39]. More appropriately, the American Cancer Society recommends age 45 for initiation of colorectal screening in all adults with average risk for developing the cancer [4]. Findings of the CONCORD-2 study revealed that the five-year survival among AA who were diagnosed with colon cancer between 2004–2009 still had not reached the level of survival among NHW who were diagnosed around 15–20 years earlier between 1990–1994 [40]. In addition, the study revealed little improvement in overall survival for patients with rectal cancer, with persistent disparities noted between AA and NHW for all stages of the disease at the time of presentation [41]. Strategies are needed to diminish outcome disparities among racial minorities.

The limitations of this study are related to the retrospective database analysis design. Even though fairly complete and recognized to capture the largest number of cancer patients in the US, disease-specific mortality, recurrence indices, details about length of treatment and completion of planned course, response to treatment and prior history

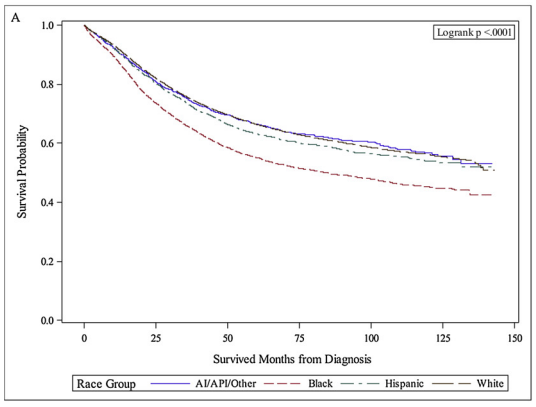
Table 5
Univariate association with overall survival.

			Survived Months from Diagnosis		
Covariate	Level	N	Hazard Ratio (95% CI)	HR P-value	Log-rank P-value
Race Group	Others[#]	4231	0.96 (0.91-1.02)	0.207	< **.001**
	Hispanic	6935	1.07 (1.02-1.12)	**0.004**	
	Black	12,642	1.42 (1.38-1.46)	< **.001**	
	White	59641	–	–	
Facility Type	Academic/Research Program	23847	1.06 (1.02-1.09)	< **.001**	< **.001**
	Integrated Network Cancer Program	7283	0.98 (0.93-1.02)	0.347	
	Suppressed for patients aged 0-39 at DX	16999	1.08 (1.04-1.12)	< **.001**	
	Community Cancer Program	35320	–	–	
Facility Location	Suppressed for patients aged 0-39 at DX	16999	1.15 (1.10-1.20)	< **.001**	< **.001**
	West	10441	1.06 (1.01-1.11)	**0.016**	
	Midwest	16172	1.08 (1.03-1.12)	< **.001**	
	South	26875	1.16 (1.11-1.20)	< **.001**	
	Northeast	12962	–	–	
Sex	Female	38475	0.87 (0.85-0.89)	< **.001**	< **.001**
	Male	44974	–	–	
Primary Payor	Not Insured/Unknown	9285	1.66 (1.60-1.72)	< **.001**	< **.001**
	Medicaid	9449	2.00 (1.93-2.07)	< **.001**	
	Medicare/Other Government	4706	1.73 (1.66-1.82)	< **.001**	
	Private	60009	–	–	
Median Income Quartiles	$46,000 +	33,668	0.67 (0.65-0.70)	< **.001**	< **.001**
	$36,000 - $45,999	21667	0.83 (0.80-0.86)	< **.001**	
	$30,000 - $35,999	13715	0.92 (0.88-0.96)	< **.001**	
	< $30,000	11206	–	–	
Urban/Rural 2013	Unknown	2911	1.43 (1.35-1.52)	< **.001**	< **.001**
	Rural	1309	1.11 (1.01-1.21)	**0.029**	
	Urban	10430	1.16 (1.12-1.20)	< **.001**	
	Metro	68799	–	–	
Year of Diagnosis	2009-2013	43360	0.98 (0.95-1.00)	0.093	0.092
	2004-2008	40089	–	–	
Primary Site	Colon Cancer	50514	1.21 (1.18-1.24)	< **.001**	< **.001**
	Rectum Cancer	32935	–	–	
AJCC Analytic Stage Group	Stage 0	913	0.05 (0.04-0.07)	< **.001**	< **.001**
	Stage I	12988	0.05 (0.05-0.05)	< **.001**	
	Stage II	18717	0.10 (0.10-0.11)	< **.001**	
	Stage III	28284	0.19 (0.19-0.20)	< **.001**	
	Stage IV	22547	–	–	
Grade	Well Differentiated	6672	0.37 (0.35-0.40)	< **.001**	< **.001**
	Moderately Differentiated	52412	0.51 (0.50-0.53)	< **.001**	
	Cell Type Not Determined	8661	1.05 (1.01-1.09)	**0.021**	
	Poorly Differentiated/Undifferentiated	15704	–	–	
Surgery at Primary Site	No	9149	5.59 (5.43-5.74)	< **.001**	< **.001**
	Unknown	58	2.06 (1.40-3.03)	< **.001**	
	Yes	74242	–	–	
Surgical Margin	No Surgery	9149	6.86 (6.67-7.07)	< **.001**	< **.001**
	Unknown	2511	1.84 (1.73-1.97)	< **.001**	
	Positive	7339	3.66 (3.54-3.78)	< **.001**	
	Negative	64450	–	–	
Standard of Care	Unknown	2359	0.64 (0.59-0.69)	< **.001**	< **.001**
	Yes	64884	0.79 (0.76-0.81)	< **.001**	
	No	16206	–	–	
Age at Diagnosis	18-34	7721	1.15 (1.11-1.20)	< **.001**	< **.001**
	35-50	75728	–	–	
Number of Regional Lymph Nodes Examined	Below Median(18)	37653	1.19 (1.16-1.23)	< **.001**	< **.001**
	Above Median	31721	–	–	
Number of Regional Lymph Nodes Positive	Below Median(3)	19212	0.45 (0.43-0.46)	< **.001**	< **.001**
	Above Median	17752	–	–	

[#] All races and ethnicities other than NHW, AA, and Hispanic were combined into "Others" due to small numbers.

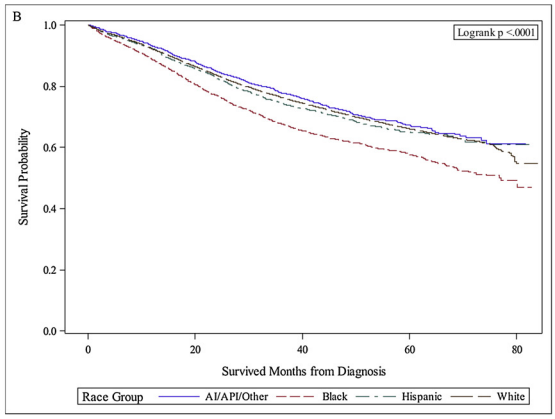
of malignancies are not captured by the NCDB [14]. Race/ethnicity was reported in the database based on self-identification, and a lower capture rate of Hispanic cancer patient cases may also lead to under-representation in the analysis [14]. Lack of data on potential confounding factors such as physical activity, dietary habits, and co-morbid medical conditions such as metabolic syndrome may contribute to poorer outcome in CRC patients [17,18,42–44]. Despite these limitations, our findings have important implications. This is the largest population-based study evaluating racial disparities among young CRC patients, obtained from a large number of institutions nationwide. The data is therefore representative and generalizable. The rising incidence of CRC in patients younger than the current generally accepted age of 50years at commencement of CRC screening reinforces the argument for the revision of this cut-off age. The number of patients included in our analysis was more than 80,000, a strong argument for prospective studies to determine an age cut-off that would incorporate these patients and still be cost-effective with minimal unintended consequences of false positive cancer screening.

In conclusion, the apparent racial disparities require urgent interventions that can address the factors leading to poorer outcomes. This would lead to improvements in overall survival for some of the affected patients [14]. Finally, further studies regarding the clinical and



Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	1870	NA (131.2, NA)	90.6% (89.2%, 91.9%)	66.5% (64.3%, 68.7%)
Black	6164	84.6 (76.2, 94)	87.6% (86.7%, 88.4%)	55.1% (53.8%, 56.4%)
Hispanic	3043	NA (131.3, NA)	90.8% (89.7%, 91.8%)	63.2% (61.3%, 64.9%)
White	29012	NA (138.3, NA)	91.9% (91.6%, 92.2%)	66.4% (65.8%, 66.9%)

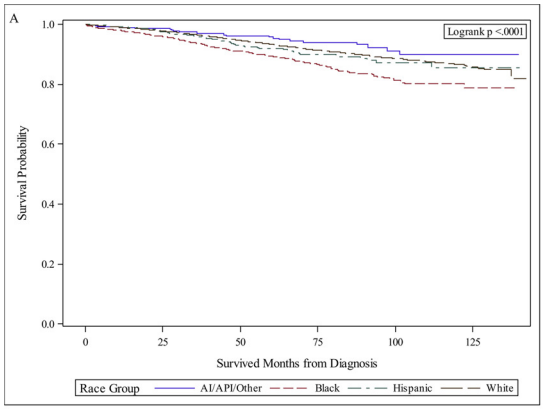
*NA – Not yet attained/reached



Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	2361	NA* (NA, NA)	93.1% (92.0%, 94.1%)	67.3% (64.6%, 69.8%)
Black	6478	77 (71, NA)	88.7% (87.9%, 89.4%)	57.6% (56.0%, 59.2%)
Hispanic	3892	NA (NA, NA)	92.3% (91.4%, 93.1%)	65.0% (63.0%, 67.0%)
White	30629	NA (NA, NA)	92.2% (91.9%, 92.5%)	66.1% (65.4%, 66.8%)

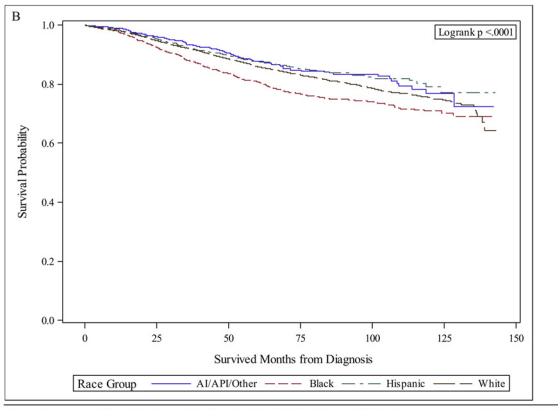
*NA – Not yet attained/reached

Fig. 1. (A) Survival Curves by Race, diagnosed in year 2004–2008. (B) Survival Curves by Race, diagnosed in year 2009–2013.



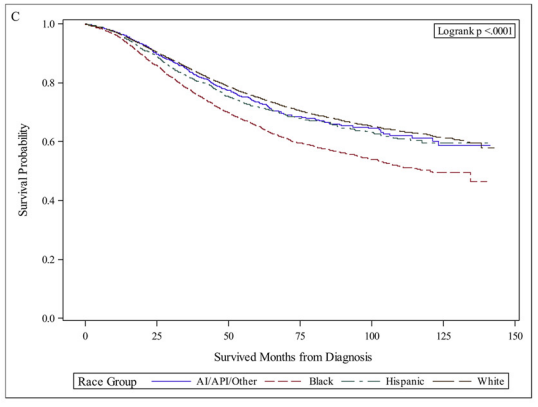
Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	554	NA (NA, NA)	98.9% (97.5%, 99.5%)	95.8% (93.3%, 97.3%)
Black	1578	NA (NA, NA)	97.7% (96.9%, 98.4%)	89.4% (87.5%, 91.0%)
Hispanic	843	NA (NA, NA)	99.1% (98.2%, 99.6%)	91.8% (89.2%, 93.7%)
White	10013	NA (NA, NA)	98.9% (98.6%, 99.1%)	93.3% (92.7%, 93.9%)

*NA – Not yet attained/reached



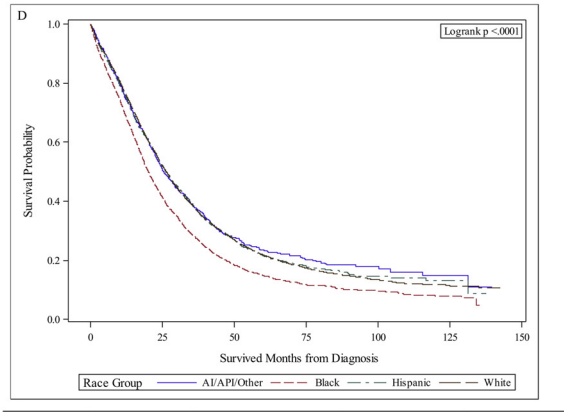
Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	1016	NA (NA, NA)	98.9% (98.0%, 99.4%)	87.8% (85.2%, 90.0%)
Black	2799	NA (NA, NA)	97.5% (96.8%, 98.0%)	80.8% (79.1%, 82.4%)
Hispanic	1651	NA (NA, NA)	98.4% (97.7%, 98.9%)	87.6% (85.5%, 89.4%)
White	13251	NA (NA, NA)	98.0% (97.8%, 98.2%)	85.9% (85.2%, 86.6%)

*NA – Not yet attained/reached



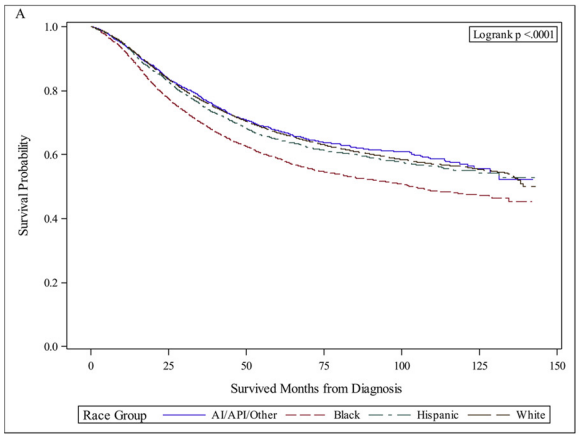
Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	1550	NA (NA, NA)	96.8% (95.8%, 97.6%)	73.4% (70.7%, 75.9%)
Black	4276	120.4 (106.7, NA)	95.4% (94.7%, 96.0%)	65.2% (63.5%, 66.8%)
Hispanic	2470	NA (NA, NA)	96.6% (95.8%, 97.3%)	71.8% (69.6%, 73.9%)
White	19988	NA (NA, NA)	96.6% (96.3%, 96.8%)	75.1% (74.4%, 75.8%)

*NA – Not yet attained/reached



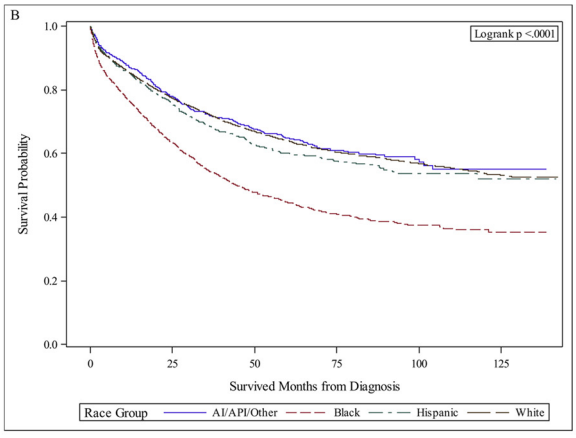
Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	1069	25.5 (23.9, 28.2)	74.8% (72.0%, 77.3%)	23.6% (20.6%, 26.7%)
Black	3890	20.1 (19.4, 20.9)	69.4% (68.0%, 70.9%)	14.8% (13.5%, 16.1%)
Hispanic	1901	26.2 (24.5, 27.7)	75.9% (73.9%, 77.8%)	21.5% (19.2%, 23.8%)
White	15687	26.4 (25.8, 27)	76.7% (76.0%, 77.4%)	21.8% (21.0%, 22.5%)

Fig. 2. (A) Survival Curves by Race, Stage 1. (B) Survival Curves by Race, Stage 2. (C) Survival Curves by Race, Stage 3. (D) Survival Curves by Race, Stage 4.



Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	3234	NA (128.3, NA)	93.1% (92.2%, 93.9%)	67.6% (65.7%, 69.5%)
Black	9749	103.3 (96.2, 111.8)	91.1% (90.5%, 91.7%)	58.8% (57.7%, 59.9%)
Hispanic	5233	NA (131.3, NA)	93.3% (92.6%, 94.0%)	64.8% (63.2%, 66.3%)
White	46668	139.2 (138.3, NA)	93.7% (93.4%, 93.9%)	66.9% (66.4%, 67.4%)

*NA – Not yet attained/reached



Race Group	No. of Subject	Median Survival (95% CI)	12 Mo Survival	60 Mo Survival
AI/API/Other	839	NA (104.3, NA)	87.0% (84.5%, 89.1%)	64.9% (61.1%, 68.4%)
Black	2492	44.6 (40.8, 49.4)	76.3% (74.6%, 77.9%)	44.6% (42.4%, 46.8%)
Hispanic	1460	NA (117.6, NA)	85.1% (83.1%, 86.9%)	60.0% (57.0%, 62.8%)
White	11415	NA (NA, NA)	85.3% (84.7%, 86.0%)	63.9% (63.0%, 64.9%)

*NA – Not yet attained/reached

Fig. 3. (A) Survival Curves by Race among patients who received Standard of Care. (B) Survival Curves by Race among patients who did not receive Standard of Care.

molecular features of young-onset CRCs are needed to explore the potential interactions between tumor and treatment associated with racial disparities in survival [24].

Sources of support for the work

There was no specific funding for this study.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email messages.

Authorship contribution

Conception and design: OBA, RJ, KMZ, CW, MA, WS, MB, BEF.
Acquisition of data: OBA, RJ, MB, BEF.
Analysis and interpretation of data: OBA, RJ, MB, BEF.
Writing - original draft: OBA, RJ, KMZ, CW, MA, WS, MB, BEF.
Writing - review and editing: OBA, RJ, KMZ, CW, MA, WS, MB, BEF.

Table 6
Multivariable Survival Analysis of OS – interaction with Chemotherapy.

		Survived Months from Diagnosis		
Covariate Comparisons Stratified by Chemotx:	Level* Race Group :	Hazard Ratio (95% CI) –	HR P-value** –	P-value*** 0.017
No	Hispanic vs. Black	0.62 (0.55-0.70)	< **.001**	–
	Others# vs. Black	0.67 (0.57-0.78)	< **.001**	
	White vs. Black	0.83 (0.78-0.90)	< **.001**	
Unknown	Hispanic vs. Black	0.58 (0.42-0.79)	< **.001**	–
	Others vs. Black	0.67 (0.45-0.99)	**0.045**	
	White vs. Black	0.79 (0.64-0.97)	**0.023**	
Yes	Hispanic vs. Black	0.75 (0.70-0.79)	< **.001**	–
	Others vs. Black	0.81 (0.76-0.87)	< **.001**	
	White vs. Black	0.84 (0.81-0.88)	< **.001**	

* Number of observations in the original data set = 83,449. Number of observations used = 80,256.

** Backward selection with an alpha level of removal of 0.05 was used. No variables were removed from the model.

*** The estimated stratified treatment effect was controlled by: AJCC Analytic Stage Group, Facility Type, Grade, Median Income Quartiles 2000, Primary Payor, Primary Site, Radiation, Sex, Standard of Care, Surgery at Primary Site, Systemic/Surgery Sequence, Year of Diagnosis.

All races and ethnicities other than NHW, AA, and Hispanic were combined into "Others" due to small numbers.

Declaration of Competing Interest

None. There are no competing financial and personal disclosures by all authors.

Acknowledgements

Data is derived from a de-identified NCDB file. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

Research reported in this publication was supported in part by the Winship Research Informatics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292.

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