

Patterns of Early-Onset Colorectal Cancer Among Nigerians and African Americans

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PURPOSE Colorectal cancer (CRC) incidence rates are increasing among individuals < 50 years of age (early-onset CRC) globally with causes unknown. Racial/ethnic disparities in early-onset CRC have also grown more pronounced, because Black individuals have higher early-onset CRC incidence and poorer survival compared with White individuals. We describe the prevalence and burden of early-onset CRC among Africans in Nigeria and African Americans (AAs) in the United States.

PATIENTS AND METHODS We identified Black individuals diagnosed with a first primary CRC ages 18 to 49 years between 1989 and 2017 at Ahmadu Bello University Teaching Hospital in Zaria, Nigeria (Nigerians), and in the United States (AAs) using the National Institutes of Health/National Cancer Institute's SEER program of cancer registries. Multivariable logistic regression models were used to investigate clinical and demographic differences between Nigerians and AAs with early-onset CRC, adjusted for age, sex, tumor site, and histology.

RESULTS A total of 5,019 Black individuals were diagnosed with early-onset CRC over the study period (379 Nigerians; 4,640 AAs). Overall, approximately one third of young Black patients were diagnosed with rectal tumors (35.8%). Nigerian individuals with early-onset CRC were eight-fold more likely to be diagnosed with rectal tumors (odds ratio [OR], 8.14; 95% CI, 6.23 to 10.62; $P < .0001$) and more likely to be diagnosed at younger ages (OR, 0.87; 95% CI, 0.86 to 0.89; $P < .0001$) compared with young African Americans in adjusted models.

CONCLUSION Compared with AA individuals diagnosed with early-onset CRC, Nigerian individuals harbor distinct features of early-onset CRC. Additional investigation of the histopathologic and biologic heterogeneity of early-onset CRCs among Black individuals is critical for understanding racial disparities in susceptibility and outcomes, which may have implications for tailored early-onset CRC prevention, detection, and treatment strategies.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant neoplasm among both men and women worldwide. It is estimated that 1,800,977 individuals will be diagnosed with CRC and 861,663 will die of this disease annually.¹ Although the CRC burden has been described among individuals in developed countries such as the United States, the burden of disease in countries such as Nigeria remains poorly understood.² In the United States, implementation of routine CRC screening among individuals ≥ 50 years of age has led to reductions in the absolute number of patients with CRC. Yet, among individuals diagnosed before 50 years of age (early-onset CRC), CRC incidence rates have continued to increase annually by 1.5% since 1992.^{3,4} In Nigeria, organized CRC screening has only recently been identified as a strategic

priority.^{2,5} Consequently, CRC has continued to emerge over the last four decades in West Africa, particularly among young patients.^{6,7} This alarming epidemic of early-onset CRC worldwide has emerged as an urgent public health problem⁸ because underlying causes remain unexplained.

Aligned with the increasing burden of early-onset CRC, racial/ethnic disparities among young patients with CRC have also grown more pronounced.⁹ The proportion of patients with early-onset CRC is nearly two-fold higher among Blacks compared with Whites.¹⁰ Moreover, we previously discovered that survival after CRC diagnosis is significantly worse among young Black patients compared with Whites, even among patients with early-stage disease.¹¹ Given this disproportionate burden of CRC among young Black patients, the American College of Gastroenterology

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CONTEXT

Key Objective

Despite the disproportionate burden of early-onset (age < 50 years) colorectal cancer (CRC) among Black individuals, comparative data on the clinical/demographic patterns of early-onset CRC among Nigerian and African American populations are lacking. What are the characteristics of Black individuals diagnosed with early-onset CRC in Nigeria and the United States?

Knowledge Generated

Early-onset CRC harbors distinct clinical and demographic phenotypes between Nigerian and African American individuals.

Relevance

Heterogeneity in early-onset CRC among Black individuals can inform the discovery of risk factors and tumor biomarkers and may also lead to a better understanding of racial disparities in early-onset CRC.

issued recommendations in 2008 that CRC screening commence at 45 years of age rather than 50 years of age for Black men and women at average disease risk.^{9,12} Together, these patterns are consistent with a unique burden of early-onset CRC among Black patients, including Nigerians and African Americans (AAs). The purpose of our international cohort study was to characterize clinical and demographic features of CRCs among young Nigerians and AAs to describe the prevalence and burden of early-onset CRC among Black patients.

METHODS

This study population included Black patients ages 18–49 years diagnosed with pathologically confirmed CRC between 1989 and 2017 from Ahmadu Bello University Teaching Hospital (ABUTH) in Zaria, Nigeria, using the hospital-based Zaria Cancer Registry (n = 379) and from population-based cancer registries across the United States using the National Institutes of Health–National Cancer Institute's SEER program (n = 4,640¹³; Fig 1). For Nigerian patients at ABUTH, records derived from the hospital-based Zaria Cancer Registry,¹⁴ which serves the northwest region of Nigeria. Patients recorded in the Zaria Cancer Registry were identified if they were diagnosed in the Department of Pathology at ABUTH or were referred to hospital clinics. Secondary cases included tissue blocks/histology slides for review and a relevant diagnosis before treatment. Pathologic/histologic reports in the Zaria Cancer Registry were reviewed to abstract age, diagnosis year, sex, histology (adenocarcinoma, signet ring cell carcinoma, squamous cell carcinoma, and other histologic subtypes) and tumor site. For AA/non-Hispanic Black patients diagnosed at a hospital inpatient/outpatient center or clinic, a patient listing session in SEER*Stat was run on the SEER9 incidence dataset¹⁵ to collect clinicodemographic variables, including age, diagnosis year, sex, histology, and primary tumor site (C18.0–C18.9 was categorized as colon cancer, C19.9/C20.9 as rectosigmoid junction/rectal cancer, and C26.0 as unspecified CRC).

Differences in clinicodemographic features between Nigerians and AAs with early-onset CRC were examined by χ^2 and *t* tests for categorical and continuous variables, respectively. To quantify associations among clinicodemographic features between Nigerians and AAs, multivariable logistic regression was used to estimate odds ratios (ORs) and 95% CIs where the reference outcome category was AAs. Associations between clinicodemographic characteristics and Black individuals (Nigerians and AAs) were assessed in models adjusted for age, sex, tumor site, and histology on the basis of patients' records having complete information for these covariates. Data were analyzed using SAS version 9.4 statistical software (SAS Institute, Cary, NC). All tests were two-sided, and *P* < .05 was considered to be statistically significant. This study was approved by the institutional health research board (IRB) at the Ministry of Health and Human Services of Kaduna State in Nigeria for ABUTH and the IRB of Vanderbilt University for Nigerian patients and was exempt from IRB approval for AA patients because SEER datasets are publicly available.

RESULTS

A total of 605 and 35,125 patients with CRC were diagnosed among Nigerians (Zaria, Nigeria) and AAs (United States) patients, respectively, in hospitals and clinics over the 28-year study period (Fig 1). More than 60% of Nigerian patients (n = 379) were diagnosed with early-onset CRC. In contrast, approximately one of every eight AAs (13.2%) were diagnosed with CRC before 50 years of age (n = 4,640; *P* < .0001). Subsequent analyses focused on the subset of this population diagnosed with early-onset CRC, which included 5,019 Black individuals (379 Nigerian and 4,640 AA patients).

The demographic and clinical characteristics of 5,019 Black patients with early-onset CRC are listed in Table 1. Mean age at diagnosis in this cohort was 41.7 years (standard deviation [SD], ± 6.6 years) and differed between Nigerians (34.8 years; SD, ± 8.4 years) and AAs (42.3 years; SD, ± 6.1 years; *P* < .0001; Table 1; Fig 2).

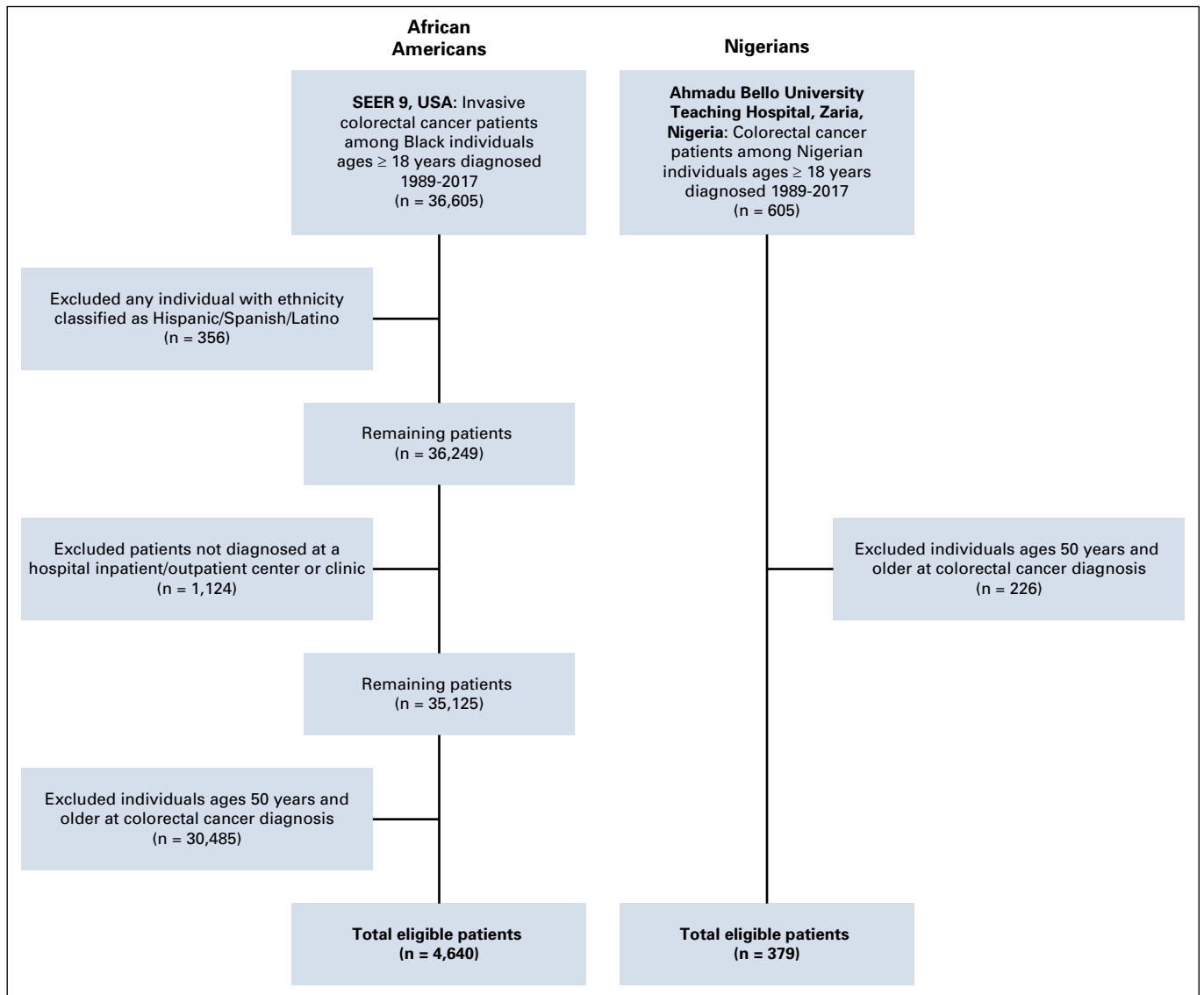


FIG 1. Composition of the study population with exclusion criteria. CRC, colorectal cancer.

Males comprised a higher proportion of Nigerian patients with early-onset CRC compared with AA patients (58.3% v 48.7%, respectively; $P = .0003$; Table 1). Overall, more than one third of young Black patients were diagnosed with rectal cancers (35.8%). Among AA patients, one third of patients were diagnosed with cancers of the rectum (32.5%), whereas 76.5% of young Nigerian patients were diagnosed with rectal tumors ($P < .0001$). Among all young Black patients with early-onset CRC, 84.7% were diagnosed with colorectal adenocarcinomas. Colorectal adenocarcinomas were more frequent among young Nigerian patients compared with AAs (93.4% v 84.0%, respectively; $P < .0001$).

To investigate associations between clinical and demographic features of patients with early-onset CRC between Nigerians and AAs, we modeled adjusted multivariable logistic regressions (Table 2). In models

adjusted for patient age, sex, tumor site, and histology, Nigerian individuals with early-onset CRC were more likely to be diagnosed at younger ages (OR, 0.87; 95% CI, 0.86 to 0.89; $P < .0001$) and were eight-fold more likely to be diagnosed with rectal cancers compared with young AAs (OR, 8.16; 95% CI, 7.12 to 12.47; $P < .0001$). In contrast, no significant associations were observed between young Nigerian and AA individuals diagnosed with CRC by sex (OR, 1.16; 95% CI, 0.91 to 1.48; $P = .23$) or by signet ring cell carcinoma (OR, 0.51; 95% CI, 0.21 to 1.25; $P = .14$) as well as squamous cell carcinoma (OR, 0.59; 95% CI, 0.25 to 1.40; $P = .23$) histologic subtypes (Table 2).

DISCUSSION

In this international cohort study of Black individuals diagnosed with CRC younger than 50 years of age, approximately one third of patients were diagnosed with rectal tumors. Three of every four Nigerians with early-onset CRC

TABLE 1. Clinical and Demographic Characteristics by Ethnicity for African American (United States) and Nigerian (Zaria, Nigeria) Individuals Diagnosed With Early-Onset Colorectal Cancer: 1989-2017

Characteristic	Total		African American		Nigerian		P ^a
	No.	%	No.	%	No.	%	
Total	5,019		4,640		379		
Age at diagnosis (years)							< .0001
< 30	325	6.5	222	4.8	103	27.2	
30-39	1,124	22.4	1,000	21.6	124	32.7	
40-49	3,570	71.1	3,418	73.7	152	40.1	
Mean (SD)	41.7 (± 6.6)		42.3 (± 6.1)		34.8 (± 8.4)		< .0001
Sex							.0003
Female	2,538	50.6	2,380	51.3	158	41.7	
Male	2,481	49.4	2,260	48.7	221	58.3	
Tumor site							< .0001
Colon	3,215	64.1	3,129	67.4	86	22.7	
Rectosigmoid junction/rectum	1,798	35.8	1,508	32.5	290	76.5	
Unspecified	6	0.1	3	0.1	3	0.8	
Histology							< .0001
Adenocarcinoma	4,250	84.7	3,898	84.0	352	92.9	
Signet ring cell carcinoma	86	1.7	79	1.7	7	1.8	
Squamous cell carcinoma	63	1.3	56	1.2	7	1.8	
Other ^b	620	12.4	607	13.1	13	3.4	

Abbreviation: SD, standard deviation.

^aP value calculations do not include unknown values.

^bOther histologic subtypes include, but are not limited to, carcinoid tumor, small-cell carcinoma, neuroendocrine tumor, GI stromal tumor, medullary carcinoma, and carcinoma, not otherwise specified.

had tumors located in the rectum, and young Nigerian patients with CRC were eight-fold more likely to be diagnosed with rectal tumors compared with young AA individuals in the United States. Nigerian individuals were also more likely to be diagnosed with early-onset CRC at younger ages compared with AA individuals with early-onset CRC. However, no associations between young AA and Nigerian patients with CRC were observed by sex or signet ring cell and squamous cell carcinoma histologic subtypes in this cohort.

Patterns of cancer among patients diagnosed before 50 years of age provide unique insight into recent changes in exposure to carcinogenic factors and to the future overall cancer burden.¹⁶ The incidence of CRC in Nigeria has nearly tripled over the last 40 years,¹⁷ and reports to date reveal the average age of Nigerians at CRC diagnosis is between 43 to 46 years,¹⁸⁻²¹ suggesting that more than half of all patients with CRC in Nigeria are patients with early-onset CRC. This disproportionate burden of early-onset CRC among Nigerian individuals is aligned with the population age distribution in the country, because more than 92% of the Nigerian population is younger than age 55 years.²² In contrast, approximately 70% of the overall US population is younger than age 55 years,²² although

population age distribution differs by race/ethnicity in the United States. Nevertheless, differences in population age distributions between AAs in the United States and Nigerians may partly explain our findings that nearly two thirds of the Nigerian population diagnosed with CRC were diagnosed with early-onset disease compared with one in every eight AAs in the United States and that Nigerians with early-onset CRC were more likely to be diagnosed at younger ages compared with AAs. Given these pronounced differences in age distribution across countries, population-based studies calculating age-standardized CRC rates among young Nigerians and AAs are also needed to better compare age patterns of early-onset CRC across geographic regions.

Among all individuals diagnosed with CRC in Nigeria, cancers of the rectum are more common than colon cancers.¹⁷ Approximately six of every 10 patients with early-onset CRC annually diagnosed in Nigeria are cancers of the rectum.^{1,23-25} Similarly, we reported that more than three quarters of patients with CRC diagnosed among young Nigerians were cancers of the rectum and that young Nigerians with CRC were eight-fold more likely to be diagnosed with rectal cancers compared with young AAs. Rectal cancers harbor a distinct molecular landscape

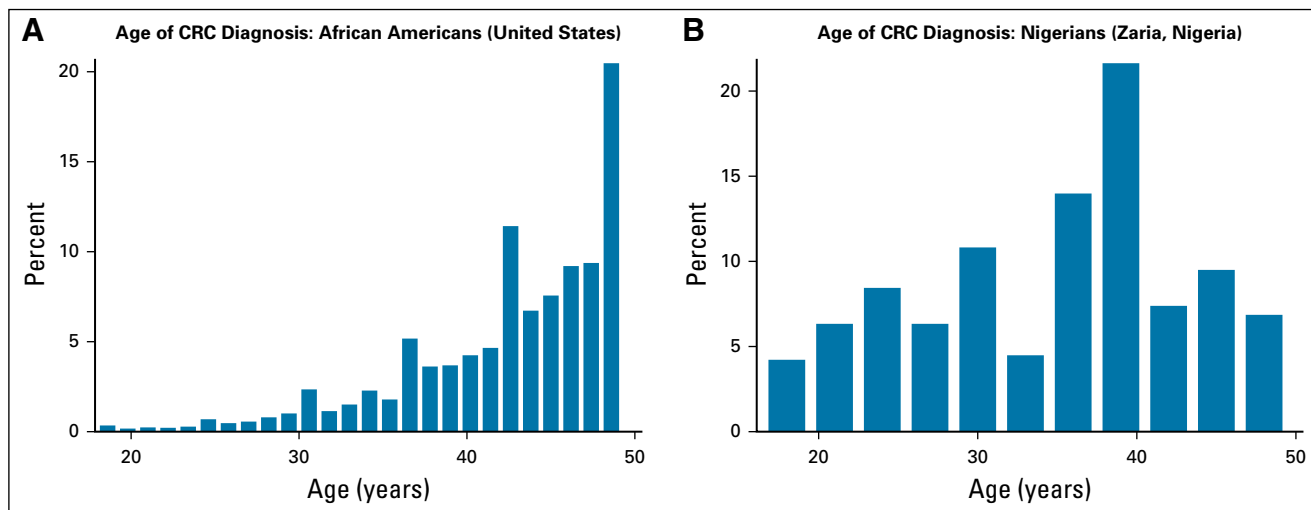


FIG 2. Age patterns for (A) African American and (B) Nigerian individuals diagnosed with early-onset colorectal cancer (CRC): 1989-2017.

compared with tumors of the colon,^{26,27} and patients with rectal tumors more often present with signs and symptoms compared with patients with colon cancer.²⁸ A single US institution study of patients diagnosed with early-onset CRC in the United States revealed that young patients diagnosed with rectal tumors were significantly more likely to present with signs and symptoms—including rectal bleeding, changes in bowel habits, and rectal pain—at diagnosis

compared with patients with early-onset colon cancer.²⁸ Because early detection of CRC is based on awareness of early signs and symptoms as well as screening programs, studies have suggested that fecal immunochemical testing for CRC screening may be a practical approach to introduce organized CRC screening in Nigeria^{2,5}; yet, additional infrastructure is also vital to ensure screening modalities are effective in this limited-resource environment.^{2,29}

TABLE 2. Multivariable Logistic Regression for Clinical and Demographic Factors Between Nigerian and African American Individuals Diagnosed With Early-Onset Colorectal Cancer: 1989-2017

Observational Study Estimate	Nigerian v African American Patients ^a		
	OR	95% CI	P
Age at diagnosis	0.87	0.86 to 0.89	< .0001
Sex			
Female	Ref		
Male	1.16	0.91 to 1.48	.23
Tumor site			
Colon	Ref		
Rectosigmoid junction/rectum	8.14	6.23 to 10.62	< .0001
Histology			
Adenocarcinoma	Ref		
Signet ring cell carcinoma	0.51	0.21 to 1.26	.14
Squamous cell carcinoma	0.59	0.25 to 1.40	.23
Other ^b	0.11	0.06 to 0.19	< .0001

Abbreviations: OR, odds ratio; ref, reference.

^aAdjusted for patient age, sex, tumor site, and histology, as appropriate.

^bOther histologic subtypes include, but are not limited to, carcinoid tumor, small-cell carcinoma, neuroendocrine tumor, GI stromal tumor, medullary carcinoma, and carcinoma, not otherwise specified.

In addition to barriers to CRC screening, the growing burden of untreated CRC and late presentation of disease in Nigeria may also be attributable to low health care literacy, personal beliefs, and limited access to recommended treatments. A recent report by Sharma et al³⁰ in Nigeria revealed that limiting factors for receipt of cancer treatment in Nigeria include the financial burden/cost of treatment, loss to follow-up, and personal reasons. Late presentation of CRC in West Africa is also speculated to be due to limited access to hospital services/diagnostic modalities, unique tumor biologic features, and patient beliefs, because traditional healers in the region often provide treatments for common benign colorectal complaints.³¹ In the United States, AAs and individuals with low socioeconomic status are also reported to have lower rates of CRC screening, because these populations may face additional barriers, including inadequate insurance coverage, limited financial resources, and inequalities with regard to access to high-quality care.³² Additionally, given differences in (1) CRC prevention and detection modalities by geographic region and race/ethnicity (eg, access to colonoscopy/sigmoidoscopy), (2) the biology and presentation of rectal tumors compared with tumors of the colon,^{26,27} and (3) our observation that there are distinct patterns of early-onset CRC between Nigerians and AAs, these findings support additional investigation into CRC heterogeneity among young Black patients. A particular focus on patterns of disease presentation as well as signs and symptoms, particularly

among patients with rectal cancer, is needed to improve comprehensive cancer control, including health care literacy, and eliminate disparities in early-onset CRC worldwide.

Shifts in diets and lifestyles may also be contributing to distinct features of CRC in young patients compared with individuals 50 years of age and older diagnosed with CRC.^{11,33-36} In particular, lower dietary fiber consumption and a higher intake of animal protein and fat in developed countries contributes to higher CRC rates among AAs compared with rural Africans, including among young patients.³⁷ Recent findings from a case-control study examining dietary patterns in Zaria, Nigeria, revealed that compared with matched controls, patients with CRC (of whom greater than 85% of patients were diagnosed with early-onset disease) had significant differences in intake of foods rich in dietary fiber, including yams, cassavas, oranges, and carrots.³⁸ In our study, we were unable to ascertain information about individual-level characteristics, such as dietary patterns, family history, history of colorectal polyps, environmental exposures, and health behaviors (eg, body mass index, smoking history) that are associated with CRC risk. Consequently, the change in CRC-related risk factors over time may be associated with the evolving burden of early-onset CRC, because a recent multiomics study of early-onset CRC among European Americans implicated metabolic imbalance via *NRF2*-mediated oxidative stress response and glutathione metabolism as a unique hallmark of early-onset sporadic CRCs.³⁴ However, additional study of molecular phenotypes distinct to early-onset CRC is needed by race/ethnicity and geographic region,^{39,39a} because environmental or genetic differences more common in the Black population may partly explain distinct patterns of early-onset CRC among Black patients. Together, these findings support the development of large international cohort studies to examine early-onset CRC disparities worldwide.

Colorectal polyps among patients of all ages are less prevalent in Nigeria compared with the Western world.^{40,41} A prospective study of colonoscopy examinations at a single institution in Nigeria revealed that nearly one in every six Nigerians of all ages presented with a colorectal polyp.⁴² However, studies to date have reported conflicting evidence on the most common polyps diagnosed among Nigerians of all ages. Although previous reports in Ile-Ife, Nigeria, have suggested that the most common polyps detected are adenomas,⁴² a study of rectal polyps in Zaria, Nigeria, reported that among 34 patients with rectal polyps (94.1% of whom were younger than 50 years of age), 53% had juvenile polyps of the rectum.⁴³ It is important to note that the distribution of polyps may reflect diagnostic capacities of an individual institution or regional differences in Nigeria, because rectal polyps are easily diagnosed on rectal examination and do not require use of flexible endoscopy compared with colorectal polyps. Juvenile polyps are typically diagnosed at young ages and are characterized

by mucus-filled glands, dense infiltration with inflammatory cells, and a distinct cystic architecture.⁴⁴ Adenomatous polyps were less common in Zaria—only one in every eight patients had adenomatous polyps of the rectum. Because adenomas can be further characterized into conventional adenomas or sessile serrated polyps and surveillance guidelines after the removal of adenomas differed by polyp number and size,⁴⁵ additional studies are needed to understand the histologic features of colorectal polyps among Nigerians, including regional differences, particularly among patients younger than 50 years of age. Moreover, because juvenile polyps are not common in the general population and a clinical diagnosis is made for patients with five or more juvenile polyps, these findings could suggest there is a founder germline mutation in one of the juvenile polyposis genes (eg, *BMPRIA*, *SMAD4*) in Nigeria and warrant additional study.

Although the prevalence of colorectal polyps is more common in the United States, AAs are not more likely to develop colon polyps compared with White patients.⁴⁶ Indeed, a single-institution study reported that among AAs of all ages who had a colonoscopy, approximately one in every three patients had colorectal polyps.⁴⁷ To date, the prevalence of colorectal polyps in young patients with CRC—particularly among minorities—remains unknown. Initial work by Perea Garcia et al⁴⁸ has shown that approximately half of young Spanish patients diagnosed with CRC had colorectal polyps. Because fecal microbiota profiling of 12 patients has initially identified differences in microbial composition between healthy patients and those with colon polyps,⁴⁹ understanding comprehensive patterns and histologic features of colorectal polyps among young patients with CRC, particularly among Blacks, may shed light on etiologies underlying the alarming early-onset CRC epidemic and the disproportionate disease burden among young Black patients.

Our international cohort study is novel in that we focused on comparing clinical and demographic features between AAs and Nigerians diagnosed with CRC younger than 50 years of age. Although our findings may shed light on heterogeneity among young Black patients that contributes to racial disparities in early-onset CRC, we acknowledge that our study has limitations. Although previous findings have suggested that a majority of patients diagnosed in Nigeria have late-stage CRC,⁵⁰ we were unable to assess tumor stage as well as specific colon tumor location among Nigerians diagnosed with early-onset CRC. In addition, the potential for nondifferential misclassification of tumor grade among young Nigerians limited our capacity to assess the association of tumor grade between Nigerians and AAs in our current study. Although the use of the Zaria Cancer Registry—a hospital-based cancer registry—allowed for the inclusion of pathologically confirmed cases of cancer with early-onset CRC in Nigeria, we acknowledge the inability to capture all patients with CRC in this geographic

region. Although previous studies have confirmed that the Zaria Cancer Registry is reflective of the cancer burden in the larger population of this region,¹⁴ early-onset CRC patterns may vary across Nigeria, as well as across the African continent, and warrant additional investigation. Moreover, because race/ethnicity classification in SEER is based on self-identification, it is also subject to misclassification for young AA patients with CRC. Finally, SEER does not routinely collect data regarding molecular phenotypes of CRC that may differ between young Nigerians and AAs. Additional studies are underway to unravel comprehensive histopathologic and molecular differences between Nigerians and AAs with early-onset CRC to explore distinct disease patterns among Black patients.

Despite these limitations, our findings yield important clinical implications. We observed distinct patterns of early-onset CRC between Nigerians and AAs, because young Nigerians were more likely to be diagnosed with rectal tumors compared with AAs with early-onset CRC. We also observed that Nigerians with early-onset CRC were more likely to be diagnosed at younger ages versus AA

counterparts, whereas no significant differences in early-onset CRC were observed by patient sex or by signet ring cell and squamous cell carcinoma histologies. Consequently, our study strongly supports the continued development and implementation of organized CRC screening in Nigeria for all individuals—and could suggest routine use of sigmoidoscopy for CRC screening given the propensity for rectal tumors within this population. With the disproportionate burden of early-onset CRC incidence and mortality among Black patients,^{9,11} and the under-representation of Black patients in genetic studies of CRC,⁵¹ additional studies of early-onset CRC are also urgently needed to explore clinical and molecular features of early-onset CRC among young Black patients and the association of these unique patterns with prognostic outcomes. Heterogeneity in early-onset CRC among Black patients can inform the discovery of tumor biomarkers and risk factors, which may have implications for CRC prevention, early detection, and treatment tailored to young Black patients and may also lead to a better understanding and elimination of racial disparities in early-onset CRC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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