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ORIGINAL ARTICLE

Distribution of colorectal cancer in young African Americans: implications for the choice of screening test

Tarek H. Hassab[1,2] · Lior Segev[3] · Matthew F. Kalady[1,4] · James M. Church[1,4]

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Abstract

Background We recently reported on a left-sided predominance of colorectal cancers in the young (under age 50). Given the predilection of young African Americans for the disease, we wondered if there may be a difference in the biology of colorectal carcinogenesis between this group and Caucasians.

Objective Compare the distribution of colorectal cancer in African American patients and Caucasians under age 50, and describe implications for screening in these groups.

Patients Colorectal cancer patients diagnosed under the age of 50 between the years 2000 and 2016. All races other than African American and Caucasian and all patients with hereditary colon cancer or inflammatory bowel disease were excluded. Outcome measures: race, age at diagnosis (5 subgroups: < 20, 20–29, 30–39, 40–44, and 45–49 years) and cancer location; right (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure), left (descending colon and sigmoid colon), or rectal.

Results 759 patients were included; 695 (91.6%) were Caucasian and 64 (8.4%) were African American. Most cases were diagnosed between ages 40 and 49 (African American = 75%, Caucasian = 69.5%). Rectal cancer was most common in both races, although significantly more common in Caucasian than in African American patients (64.2% vs 39.1%). Right colon cancer was more commonly found in African Americans (37.5%) compared with Caucasians (18%) ($p = 0.0002$). The ratio of rectal to right-sided colon cancer in African Americans was 1:1 compared with 3.6:1 in Caucasians.

Limitations Relatively low number of African American patients

Conclusion The high rate of right-sided cancer in young African American patients means that they should be screened with colonoscopy. The increased incidence of right-sided cancers may represent a different biology of carcinogenesis in African Americans and deserves further study.

Keywords Colorectal cancer · Cancer location · Race

Introduction

Screening for colorectal cancer (CRC) has led to a reduction of the incidence of the disease in the general population. However, screening is not offered to people less than 50 years old, and the incidence of colorectal cancer is rising in this age group [1]. CRC is the second most common cancer and the third leading cause of cancer-related death in people less than 50 years old in the USA [2]. Until recently, only African Americans were recommended to start CRC screening before age 50 (at age 45) [3] but new guidelines from the American Cancer Society recommend CRC screening to start for all average-risk individuals at age 45 [4]. Screening options for CRC include colonoscopy, flexible sigmoidoscopy, computed

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✉ James M. Church
churchj@ccf.org

[1] Department of Colorectal Surgery, Digestive Diseases and Surgery Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, USA

[2] Medical Research Institute, University Of Alexandria, Alexandria, Egypt

[3] Sackler Faculty Of Medicine, Tel Aviv University, Tel Aviv, Israel

[4] Sanford R. Weiss, MD, Center for Hereditary Colorectal Neoplasia, Cleveland Clinic, Cleveland, OH, USA

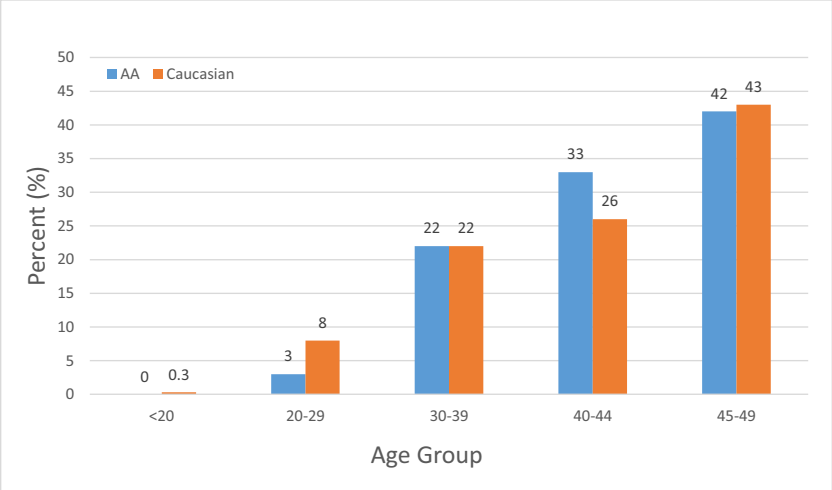

Fig. 1 Age distribution of colorectal cancer according to race

tomography colonography, fecal immunohistochemical test, and stool DNA tests, with only the endoscopic options offering prevention by polyp removal. The choice of endoscopic test depends on many factors, including resource availability, cost, the type of program being offered, and at a patient level, the location of the cancer within the colorectum [5]. The anatomic distribution of CRC in the younger population is relevant [6]. We have recently shown that CRCs diagnosed under age 50 are predominately left-sided, suggesting a role for screening with flexible sigmoidoscopy [7]. Advantages of flexible sigmoidoscopy include increased convenience (a sedation-free exam, bowel preparation with enemas), with lower risks and lower costs compared with a full colonoscopy. Failure to examine the entire colon is the main disadvantage [6], but if most cancers are left-sided, this makes the compromise of flexible sigmoidoscopy more acceptable as a screening test.

African Americans have an earlier age of onset for CRC compared with all other races. According to the SEER database, the incidence of CRC in the African American population is 20% higher than that in the white population (49.2/100,000 to 40.2/100,000 respectively) [8]. Also, the SEER database age-specific incidence rates from 2010 to 2014 show almost a doubling in risk between age 40–44 and age 45–49 (African American 19.8/100,000 to 39.8/100,000; Caucasian 17.4/100,000 to 30.3/100,000) [8]. Furthermore, the SEER database age-specific mortality rates show that Caucasians 40–44 years old have a 4.2/100,000 mortality rate compared with 5.7/100,000 mortality rate in African Americans. In patients 45 to 49 years old, mortality rates are 7.7/100,000 (Caucasian) and 11.7/100,000 (African Americans) [8]. Although African Americans have lower utilization of available screening compared with Caucasians, this does not completely explain the difference in disease incidence or outcome since other races (such as Hispanics) do not properly utilize screening but have similar outcomes to Caucasians [9].

The goal of this study was to compare the distribution of CRCs in young African American patients with that in Caucasians, to help determine the role of screening sigmoidoscopy in the African American population.

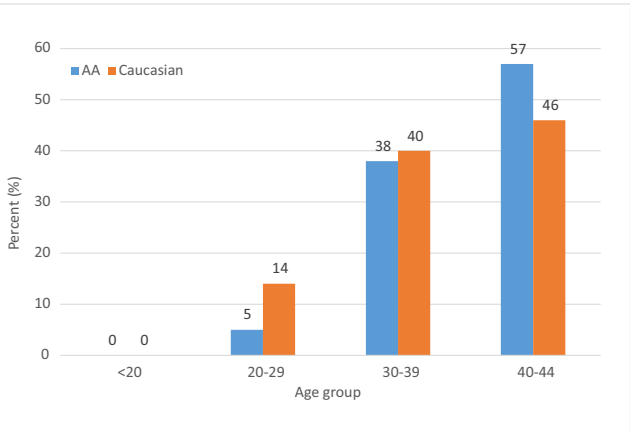

Fig. 2 Age distribution of colorectal cancer patients less than 45 years old according to race

Methods

Patients with colon or rectal cancer diagnosed under the age of 50 between the years 2000 and 2016 were accessed from a departmental CRC database. Exclusion criteria included all races other than African American and Caucasian, and patients with high risk for CRC including positive family history, hereditary colon cancer, or inflammatory bowel disease. Patients were categorized by race and each group was subdivided by age into 5 subgroups: < 20, 20–29, 30–39, 40–44, and 45–49 years old. We subdivided the decade of the 40's because age 45 has been used as a recommended starting point for average risk surveillance [3]. The CRC site was documented as right (cecum, ascending colon, hepatic flexure, transverse

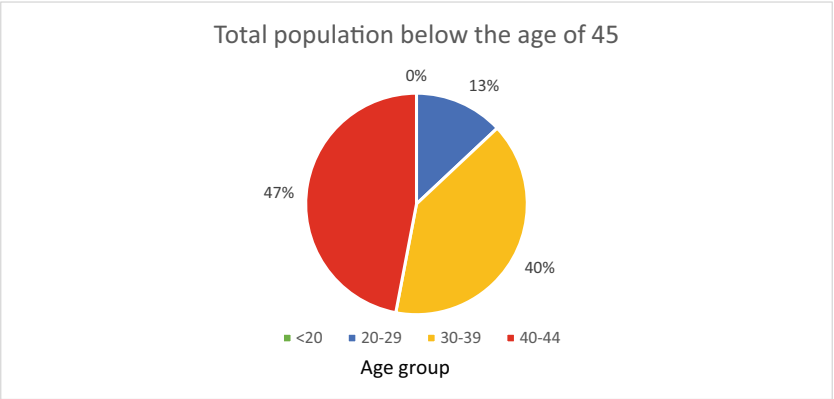

Fig. 3 Distribution of colorectal cancers according to age for patients younger than 45 years

colon, splenic flexure), left (descending colon and sigmoid colon), or rectum.

Statistical analysis

Categorical variables were summarized as percentages. Quantitative variables were summarized as mean ± standard deviation (SD) for normal distribution and summarized as median (interquartile range [IQR]) for nonparametric distribution. A two-sample Student's *t* test was used to compare age between the African American and Caucasian groups. Pearson's chi-square test or Fisher's exact test was used to compare the male to female ratio; right, left, and rectal cancer frequencies; and the rectal to right cancer ratio between the two groups. $p < 0.05$ was considered statistically significant.

Results

Seven hundred fifty-nine patients met the inclusion criteria: 695 (91.6%) were Caucasian while 64 (8.4%) were African American. The African American group had a similar male to female ratio as the Caucasian group (1.5:1 vs 1.2:1, $p = 0.34$).

Age distribution is presented in Fig. 1. Most cases were diagnosed in patients aged 45–49 (African American = 42%, Caucasian = 43%) while the age group 40–44 included 33% and 26% of African Americans and Caucasians respectively. The mean age of each cohort was slightly higher in African Americans (42.4 ± 5.9 years) compared with Caucasians (41.6 ± 6.8 years; $p = 0.33$).

In a subset analysis of the population younger than 45 years old ($n = 430$) (not covered by new screening guidelines), our data show that 57% of African Americans and 46% of Caucasians are 40–44 years old (Fig. 2). If we exclude race, 47% (202/430) of those less than 45 years of age are 40–44 years old (Fig. 3).

Cancer location is shown in Table 1. The rectum was the most common site in both races, but rectal cancer was significantly more common in Caucasian patients (64.2% vs 39.1%). Right-sided colon cancer was more commonly found in African Americans (37.5%) compared with Caucasians (18%) ($p < 0.0002$) (Fig. 4). This pattern was seen in every age group (Table 2). There was a significantly different ratio of right-sided to rectal cancer in African Americans compared with Caucasians (3.57 vs 1.04).

Discussion

This manuscript demonstrates a significant difference in the distribution of CRC in young patients between Caucasians and African Americans. The increased number of right-sided colon cancers in the latter group suggests that screening by flexible sigmoidoscopy would not be adequate and thus African Americans should be screened by colonoscopy. Also, as 47% of the population currently uncovered by

Table 1 Demographics and distribution of colorectal cancers in African American and Caucasian patients under age 50

	African American ($n = 64$)	Caucasian ($n = 695$)	*p* value
Age (mean ± SD, years)	42.4 ± 5.9	41.6 ± 6.8	0.33
Male/female (ratio)	38/26 (1.5:1)	396/333 (1.2:1)	0.34
Right colon cancer (%)	24 (37.5%)	125 (18%)	0.0002*
Left colon cancer (%)	15 (23.4%)	124 (17.8%)	0.27
Rectal cancer (%)	25 (39.1%)	446 (64.2%)	< 0.0001*
Ratio of rectal to right colon cancer	1:1	3.6:1	< 0.0001*

*Statistically significant difference between both groups

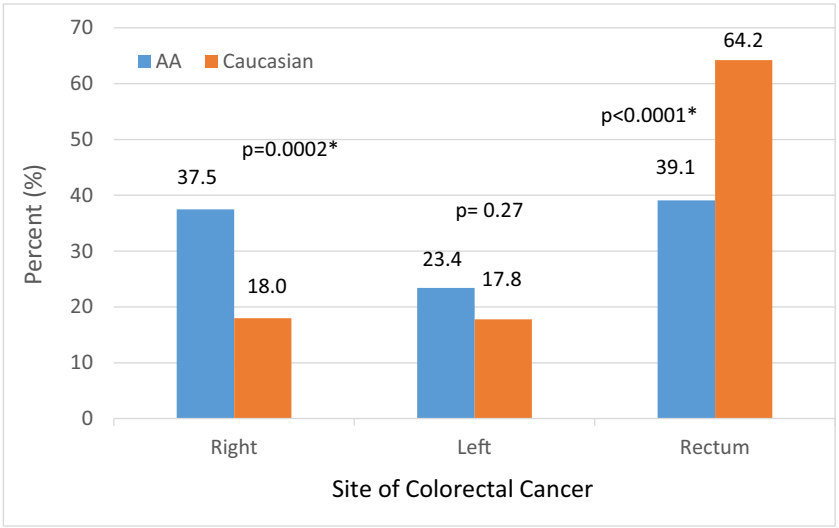

Fig. 4 Anatomic distribution of colorectal cancers according to race

screening recommendations are 40–44 years old, beginning screening at 40 years is a reasonable compromise between finding or preventing all cancers and the practicalities of a screening program.

Several older studies have shown that, overall, CRC in African American patients is more often found in the right colon [10–15]. This is also true for polyps [10] and advanced adenomas [16]. However, in this study, we provide more current data and extend the observations specifically to young African Americans. In particular, calculating the ratio of rectal cancer to right colon cancer demonstrates that young Caucasians are 3.5 times more likely to get a rectal cancer than a right-sided cancer, while young African Americans are equally as likely to get a right-sided cancer as a rectal cancer. This speaks to the need for colonoscopy screening in young African Americans. In contrast, the predominance of rectal and left-sided cancers in Caucasian patients suggests that screening with flexible sigmoidoscopy would be a reasonable approach here. Addition of a fecal blood or DNA test would allow early diagnosis of the rare right-sided cancers in Caucasians, while the flexible sigmoidoscopy would detect and can remove the more common left-sided premalignant lesions.

The reason for the difference in colon cancer locations according to race in young patients with CRC is unknown, but potentially relates to differences in cancer biology, perhaps driven by differences in the microbiome [17], diet, lifestyle, and hereditary factors [10]. In broad terms, there are two main genetic pathways leading from normal mucosa through a precursor lesion to CRC. These are the serrated pathway, driven by a *BRAF* mutation and promoter hypermethylation, and the chromosomal instability pathway, driven by mutations in *APC* and *KRAS* [18]. *BRAF* mutations are limited almost exclusively to the right colon, as is promoter hypermethylation. It is tempting to suggest that the prominence of right-sided cancers in the AA population is due to excess numbers of this type of CpG island methylator (CIMP) cancer. However, a recent meta-analysis showed no evidence of any enhancement of microsatellite unstable tumors in the African American population [19]. Other studies have shown patterns of methylation of potential cancer suppressor genes that are unique to African American patients [20–22]. In young patients overall, rectal, sigmoid, and descending colon cancers account for > 80% of all cancers [7]. Our findings suggest that this is due to the Caucasian part of the sample. It implies that the

Table 2 Location of colorectal cancer in different age groups in both races

	African American ($n = 64$)						Caucasians ($n = 695$)					
	Age group						Age group					
	< 20	20–29	30–39	40–44	45–49	Total	< 20	20–29	30–39	40–44	45–49	Total
Right	0	1 (50%)	4 (28.6%)	8 (38.1%)	11 (40.7%)	24 (37.5%)	2 (100%)	11 (20.4%)	27 (17.3%)	30 (16.6%)	55 (18.2%)	125 (18%)
Left	0	0	5 (35.7%)	3 (14.2%)	7 (25.9%)	15 (23.4%)	0	14 (25.9%)	29 (18.6%)	33 (18.2%)	48 (15.9%)	124 (17.8%)
Rectum	0	1 (50%)	5 (35.7%)	10 (47.6%)	9 (33.3%)	25 (39.1%)	0	29 (53.7%)	100 (64.1%)	118 (65.2%)	199 (65.9%)	446 (64.2%)
Total	0	2	14	21	27	64	2	54	156	181	302	695

methylator pathway plays a minimal role in colorectal carcinogenesis in the young. This may not be the case in young African Americans. However, the precursor lesion for this pathway is the sessile serrated adenoma, and there is no evidence that this sort of polyp is more common in African Americans [23].

Another possible biological explanation for our finding is elevated microsatellite alterations at selected tetranucleotide repeats (EMAST). EMAST is a biomarker that appears to be due to loss of function of the DNA mismatch repair protein hMSH3 [24]. Unlike MSI, EMAST is a poor prognostic factor. A study by Devaraj et al. showed that EMAST is associated more commonly with metastatic disease compared with non-EMAST (62% vs 37%, $p = 0.02$). Also, almost half (49%) of CRCs in AAs showed EMAST compared with only a quarter (26%) of CRCs in Caucasians [25]. Further genetic evaluation of young African American CRC is needed to test these hypotheses.

We recognize limitations of our study. First, the power may be limited by the low number of African American patients. However, the data are strong enough to demonstrate significant statistical differences in cancer location between Caucasians and African Americans. Second, although this is a striking observation, we have not uncovered the underlying reason for this phenomenon, and future studies are warranted to determine different biological influences.

In summary, the distribution of CRC in young African Americans favors the right colon, which is in direct contrast to CRC in young Caucasians which favors the rectum and sigmoid. This information has significant implications for screening and future research. Given this pattern, nearly 40% of CRC in young African Americans would be missed using flexible sigmoidoscopy as a screening tool. We thus recommend screening of the average-risk population at the age of 40 using a flexible sigmoidoscope for non-African Americans and a colonoscopy for African Americans. Further prospective studies on the efficacy of screening in the young population are required.

Authors' contribution • Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

• Drafting the work or revising it critically for important intellectual content; AND

• Final approval of the version to be published; AND

• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

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

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