

CLINICAL AND SYSTEMATIC REVIEWS

Colorectal Cancer in African Americans: An Update

Prepared by the Committee on Minority Affairs and Cultural Diversity, American College of Gastroenterology

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This review is an update to the American College of Gastroenterology (ACG) Committee on Minority Affairs and Cultural Diversity's paper on colorectal cancer (CRC) in African Americans published in 2005. Over the past 10 years, the incidence and mortality rates of CRC in the United States has steadily declined. However, reductions have been strikingly much slower among African Americans who continue to have the highest rate of mortality and lowest survival when compared with all other racial groups. The reasons for the health disparities are multifactorial and encompass physician and patient barriers. Patient factors that contribute to disparities include poor knowledge of benefits of CRC screening, limited access to health care, insurance status along with fear and anxiety. Physician factors include lack of knowledge of screening guidelines along with disparate recommendations for screening. Earlier screening has been recommended as an effective strategy to decrease observed disparities; currently the ACG and American Society of Gastrointestinal Endoscopists recommend CRC screening in African Americans to begin at age 45. Despite the decline in CRC deaths in all racial and ethnic groups, there still exists a significant burden of CRC in African Americans, thus other strategies including educational outreach for health care providers and patients and the utilization of patient navigation systems emphasizing the importance of screening are necessary. These strategies have been piloted in both local communities and Statewide resulting in notable significant decreases in observed disparities.

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Subject Category: Clinical Review

INTRODUCTION

Colorectal cancer (CRC) remains the third most common cause of malignancy-related death in men and women in the United States.¹ It is estimated that 134,490 new cases and 49,190 deaths will occur in 2016.¹ Among all racial and ethnic groups, African-American men and women continue to have the highest rate of death and shortest survival for CRC.² Currently, multiple medical societies recommend CRC screening in average risk asymptomatic individuals to begin at age 50.^{3,4} In 2005, the American College of Gastroenterology (ACG) published new guidelines for the screening of African Americans for CRC to begin at age 45.⁵ This was based on a systematic literature review on the issues relating specifically to this racial group and the health disparities that continue to exist.

The goals of this update are to further explore the important epidemiology of CRC in African Americans, discuss age-related differences, and to highlight patient as well as physician-related barriers to screening in addition to proposing strategies to diminish those barriers.

Search methods. A medical librarian conducted a comprehensive literature search in the following databases:

Biological Abstracts (1946–present), Biosis Citation Index (BCI) (1926–present), the Cumulative Index to Nursing and Allied Health (CINAHL) (1937–present), the Cochrane Library, Embase Classic (Ovid) (1947–present), PubMed/Medline (1946–present), and Web of Science (1900–present). The Grey literature was also searched using the NY Academy of Medicine Grey Literature database, OIAster and Open Grey.

The search strategy was constructed using a combination of Medical Subject Headings (MeSH) as well as additional relevant subject headings from the other databases. Relevant keywords/text words were also included. The primary strategy is provided below and was adapted appropriately when searching the unique databases.

(Blacks or Black Americans OR African Americans OR West Indian American OR Caribbean Americans) AND (Mass screening OR Screening OR prevention) AND (Colon cancer OR colon neoplasms OR Colonic Cancer OR Colonic Neoplasms OR CRC OR colorectal carcinoma OR colon carcinogenesis OR sigmoid carcinoma OR colon adenocarcinoma OR colon carcinogenesis).

The following limits were applied: English Language and publication years 2005 to the present.

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Current screening guidelines. The United States Preventative Services Task Force, American Cancer Society, American Gastroenterological Association, and the American Society of Colon and Rectal Surgeons currently recommend CRC screening in asymptomatic and average risk individuals to begin at age 50.^{3,4,6} A few societies have adopted an earlier screening protocol, namely the ACG and American Society of Gastrointestinal Endoscopists (ASGE), both of whom recommend CRC screening in African Americans to begin at age 45. As a part of their best practice advice, the American College of Physicians has recommended the screening age of 40 years for African Americans.⁷ Different screening modalities include annual fecal occult blood tests, fecal DNA testing every 3 years, annual fecal immunochemical testing (FIT), colonoscopy every 10 years, CT colonography every 5 years, and flexible sigmoidoscopy every 5 years.⁸

OUTCOMES AND PRESENTATION

Incidence, mortality, and survival. Incidence and mortality differ significantly among African Americans compared with other races (Figures 1 and 2). With an estimated 17,240 new cases and 7,030 deaths in 2016, CRC still remains the third leading cause of cancer death among African-American men and women.² CRC incidence rates were 25% higher and mortality rates were 50% higher in African Americans versus Caucasians between the years 2006–2010.⁹ Data from the Surveillance, Epidemiology, and End Results (SEER) Program reported that between 1975 and 2010 the incidence rates in white men and women had declined significantly by an overall average of 40–45% (Figure 3). During the same time period, the incidence for African-American men had increased until 2004, after which a steady decline was noted. For African-American men in particular, the incidence rate of CRC cancer was 20–25% higher than white men. The trend for African-American women for this same time period showed that their incidence rate was 30% higher than white women.^{10,11} As per a recent annual report by the American Cancer Society, incidence rates for CRC has declined to 47.1 and 59.1 per 100,000 in whites and blacks, respectively.¹²

African Americans continue to have the worst survival of any racial group for colon cancer.¹³ According to the SEER database, the 5-year relative survival for CRC between 2003 and 2009 was 57.3% for African Americans and 67% for their white counterparts. African-American men had the lowest survival rate for all stages of CRC. As for stage distribution, it was shown between 2003 and 2009 that 24% of African Americans presented with distant metastasis compared with 20% in whites.¹¹ The likelihood of the diagnosis of an advanced tumor is higher in African Americans, which has been attributed to lower screening rates in minorities,^{14,15} later stage of disease at presentation,^{16–19} and diminished access to health care.^{20–22}

Proximal colonic lesions in African Americans. Although there has been an overall decrease in the incidence of CRC, there has been a noted increase in the diagnosis of right-sided tumors across racial groups.²³ Within this trend it is

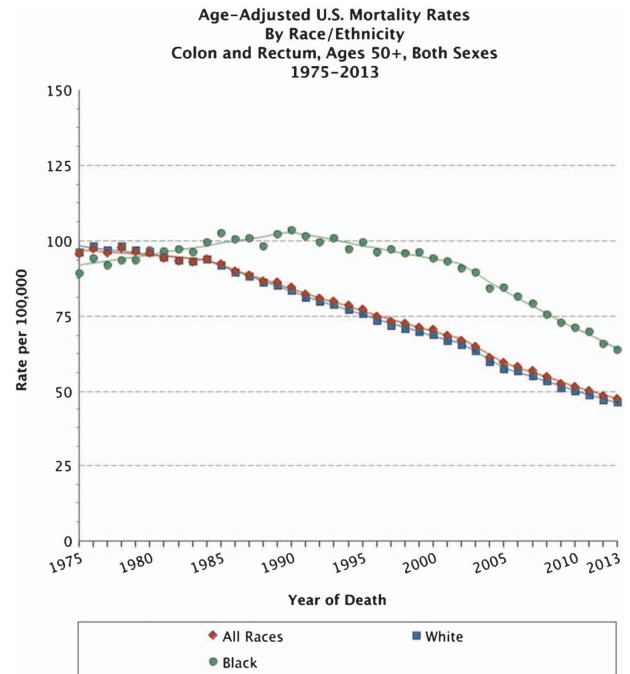


Figure 1 Age-adjusted US mortality rates by race/ethnicity colon and rectum, ages 50+, both sexes 1975–2013. Graph obtained from seer.cancer.gov.

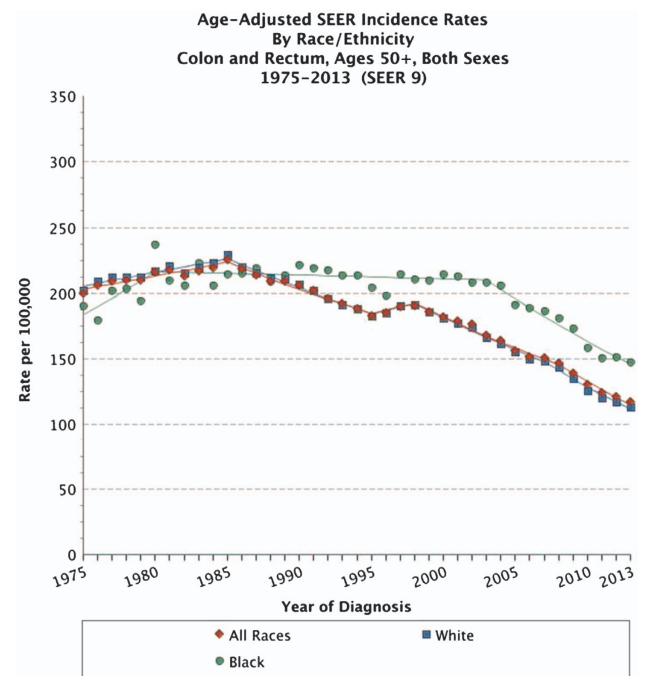


Figure 2 Age-adjusted SEER incidence rates by race/ethnicity colon and rectum, age 50+, both sexes 1975–2013 (SEER 9). Graph obtained from seer.cancer.gov.

important to highlight the impact within the African-American community. A 2007 study analyzed 254,469 patients from the SEER database to examine the anatomic subsite distribution of tumors across racial groups. Multivariate regression analysis found that the adjusted odds of a diagnosis of

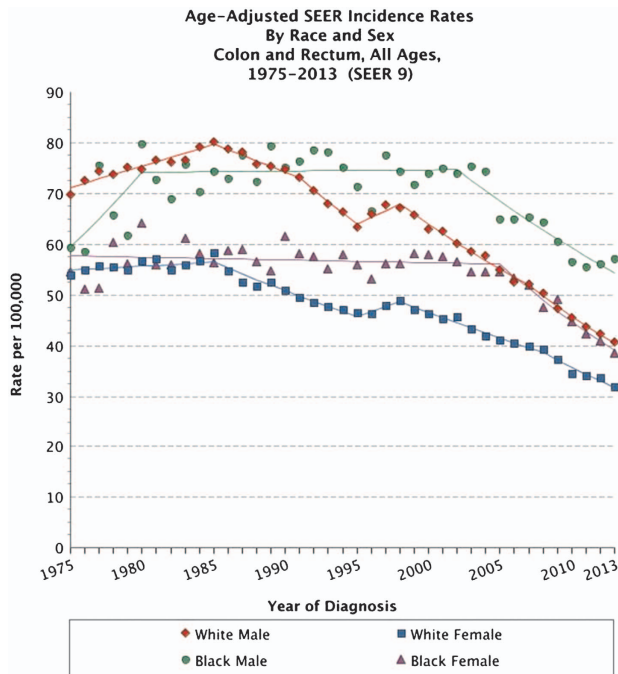


Figure 3 Age-adjusted SEER incidence rates by race and sex all sites, all ages, 1975–2013 (SEER 9). Graph obtained from seer.cancer.gov.

cancer proximal to the sigmoid colon (odds ratio (OR) 1.37, 95% confidence interval (CI): 1.33–1.42) or splenic flexure (OR 1.09, 95% CI: 1.06–1.13) were significantly higher in African Americans compared with non-Hispanic whites.²⁴ Furthermore, looking specifically at polyp prevalence, a 2013 study evaluating the prevalence of adenomas detected by age, sex, race/ethnicity and location in over 20,000 patients found that proximal adenoma prevalence was higher among blacks than whites (OR = 1.26; CI: 1.04–1.54).²⁵ Whereas both analyses provide evidence for a proximal shift in African Americans, the absolute difference of less than one is notably small. Within the Clinical Outcomes Research Initiative (CORI) database, African Americans older than 60 years of age were found to have more proximal polyps >9 mm in size compared with their white counterparts with an absolute difference of 1.5%.²⁶ It should be noted, however, that unlike the study previously reported by Corley *et al.*,²⁵ these data does not include polyp histology.

Alternatively, a cross-sectional analysis of asymptomatic average risk, African-American and Latino patients found a combined 20% prevalence of right-sided adenomas with a higher percentage of proximal advanced adenomas observed in their Latino participants. The observed difference, however, was not statistically significant (5.9% black vs. 8.9% Latino, $P=0.17$).²⁷ On the basis of this analysis, it was concluded that there was a high prevalence of adenomas, advanced adenomas, and proximal adenomas in their African-American and Latino participants with a higher percentage of proximal advanced adenomas observed in their Latino participants. Contrastingly, another study found the prevalence of advanced adenomas to be higher in whites in comparison with blacks (6.8% vs. 5.0%, $P=0.039$); however, there was a higher percentage of proximal adenomas in blacks

(52% vs. 39%).²⁸ It is worthwhile to note that serrated adenomas have been found to be less frequent in African Americans compared with Caucasians (relative risk 0.65, 95% CI: 0.50–0.85).²⁹ The clinical significance of this finding is important as serrated adenomas are shown to have a role in the diagnosis of interval CRC and the its current pathway of colorectal tumorigenesis results in tumors with high microsatellite instability that have been associated with a longer survival.^{30,31}

Overall, the importance of colon cancer location in African Americans is emphasized as proximal colon cancers have been associated with a worse prognosis compared with distal cancers.³² Given the limited data on adenoma prevalence more research is needed to investigate the location of colonic lesions as it may have a significant role in the disparate survival outcomes of this racial group.

Age-related differences. With better-designed healthcare databases over the years, there has been a notable overall shift in the age-related incidence of CRC with an increasing incidence in patients in all racial and ethnic groups under 50 years of age.^{33,34} Ongoing health disparities within the African-American community have played a pivotal role in earlier cancer screening recommendations for this population. For example, when prostate-specific antigen was used for prostate cancer screening, the United States Preventative Services Task Force had recommended prostate-specific antigen testing in African Americans beginning at the age of 45 vs. 50 years for average risk patients.³⁵ A 2007 analysis comparing the age at diagnosis in African Americans and whites for the 12 most common cancers found that the relative risk of cancer diagnosis before the age of 45 was higher in African Americans (relative risk = 1.26, 95% CI: 1.15–1.37, $P<0.0001$).³⁶ A population-based retrospective cohort analysis of the SEER registry found that patients under 50 with CRC were more likely to be African American (14.8% vs. 12%) or American Indian/Alaska Native (10.6% vs. 8.5%), which was statistically significant with a $P<0.001$.³³ With respect to CRC specifically, there is a paucity of investigative studies involving African Americans under the age of 50 years.

The CORI was developed to investigate gastrointestinal endoscopic outcomes. With an endoscopic database of over one million patients, the group analyzed how race, ethnicity, and sex affected the risk for large polyps, defined as >9 mm in size. Results showed that black men had a higher prevalence compared with white men at 50–54 years (OR = 1.17, 95% CI: 1.02–1.35), 55–59 years (OR = 1.16, 95% CI: 0.996–1.36), and 60–64 years (OR = 1.38, 95% CI: 1.18–1.61). There were similar findings for black women, where they had a higher prevalence of large polyps at age 50–54 years (OR = 1.23, 95% CI: 1.06–1.47), 55–59 years (OR = 1.51, 95% CI: 1.25–1.82), and 60–64 years (OR = 1.35, 95% CI: 1.09–1.67).³⁷ For participants <50 years old, no difference was found between African Americans and whites. This may have been secondary to the small sample size within this age range. A recent joinpoint regression analysis evaluated the upward trend of age-adjusted incidence rates by race, this analysis sought to identify at which point (join point) the incidence rates increased significantly by race.³⁸ They identified a joinpoint in the age

range of 40–55 years and found a joinpoint for CRC as a whole at age 43 years for African Americans (95% CI: 42–45) and 47 years for whites (95% CI: 45–49). A 2009 study by Lansdorp-Vogelaar *et al.*³⁹ used a MISCAN-Colon micro-simulation model investigating three different strategies of screening. The individualization strategy was the one that showed an increase in life-years gained in blacks, namely 14% of total life-years were saved with screening. This strategy showed a decrease in the disparities in incidence and survival when blacks were screened 6 years earlier than whites.³⁹ Moreover, these findings strongly confirmed and validated the recommendation for earlier CRC screening for African Americans at the age of 45 years.

BARRIERS TO SCREENING

Routine screening. There are various modalities available for CRC screening. It is the responsibility of the physician to present all options to their patient. On the basis of the current body of evidence, colonoscopy is still the preferred CRC prevention test recommended by the ACG.⁸ The advantages of colonoscopy include visualization of the entire colon, the ability to obtain a biopsy sample of abnormal mucosa, and the opportunity to remove adenomatous polyps. It should be performed every 10 years in a patient without polyps or significant personal or family history and it is considered the gold standard for the detection and removal of colorectal polyps. The National Polyp study followed over 1,400 patients and demonstrated that colonoscopic polypectomy of adenomatous polyps prevented colon cancer.⁴⁰ Analysis of over 88,000 patients for over one million person-years found a lower incidence of CRC in patients who underwent lower endoscopy. For colonoscopy specifically, they found a lower mortality for right and left sided CRC in comparison with those who have never had a lower endoscopy.⁴¹

There are data to suggest that African Americans have a preference for colonoscopy as a screening choice. A 2008 study evaluated preferences for CRC screening among a racially diverse population and found that African Americans were significantly associated with a preference for colonoscopy. These findings were consistent with a prior study that found race and education were associated with patient preferences on univariate analysis, specifically 70.1% of their African-American patients who had a preference for colonoscopy over stool DNA or occult blood.^{42,43} Although some studies have shown a preference for colonoscopy over fecal testing, a group from San Francisco Community Health Network found that whites were more likely to complete a colonoscopy in comparison with non-whites (OR 3.2; 95% CI: 1.7–6.1). In this study, when offered a choice, African Americans were more likely to choose a stool-based test.⁴⁴ This preference for a non-invasive test was also observed in a randomized trial evaluating the effectiveness of FIT versus colonoscopy outreach in an underserved community. Of 5,994 patients that were randomized, 24% were black. When stratified by race, screening participation rates were higher in the FIT group vs. colonoscopy (48.1% vs. 28.7%, $P < 0.001$).⁴⁵ Whereas colonoscopy should be used as the primary screening tool for African Americans, given the proximal shift

Table 1 Patient barriers to colorectal cancer screening

Lack of knowledge
Lack of time
Cost of the exam(s)
Fear of a cancer diagnosis
General lack of interest in screening
Low perceived personal risk of colorectal cancer

in CRC distribution observed in this population,^{46–50} non-invasive testing should be aggressively utilized to increase rates of screening in this population.

Patient barriers. The barriers noted within the African-American community to CRC screening have undoubtedly contributed to the growing health disparities in this population. These barriers are multifactorial and not mutually exclusive (Table 1). Studies have shown that adherence to CRC screening guidelines among African Americans are lower than their white counterparts. Multiple contributing factors such as lack of knowledge, lack of time, cost, fear of a CRC diagnosis, and lack of interest have been indicated.^{14,16,51–54} Other factors included lower socioeconomic status, which can result in delayed access to health care along with lack of proper follow up after the diagnosis.^{14,55,56} In order to understand the behavioral aspects of CRC screening in African Americans a qualitative study in 2011 evaluated knowledge and attitudes regarding colon cancer screening among African Americans of age 45 years and older. Data from seven focus groups were collected along with additional interviews. The study concluded that lack of knowledge, low perceived risk, and general attitudes about CRC screening may be important targets for interventions.

With the introduction of the patient navigation system into the healthcare environment over several years, there is a growing body of evidence that this process not only can facilitate healthcare access but also improves outcomes. Patient navigation has been advocated and evaluated as a means to increase colonoscopy screening rates among minorities and decrease patient barriers. A patient navigator provides a patient with individualized education and assistance with completing CRC screening. This often includes, but is not limited to, scheduling, explaining, and outlining details for the test, and identifying potential barriers to screening as well as possible ways to overcome them. The use of a patient navigator for CRC screening has been shown to increase screening adherence among African Americans. A randomized controlled trial in 2011 comparing a patient navigation-based intervention to usual care in ethnically diverse low-income patients found that intervention patients were more likely to undergo CRC screening compared with controls (33.6% vs. 20%; $P < 0.001$). In a subgroup analysis the navigator intervention was beneficial to black patients (39.7 vs. 16.7%; $P = 0.004$) and patients with a primary language other than English (39.8% vs. 18.6%; $P < 0.001$).⁵⁷ Similar results were found in another randomized control trial conducted in 2009, which used a culturally tailored, language-concordant navigator program. This intervention significantly improved CRC screening compared to those who received usual care (any CRC screening modality completed: 27%

vs. 12% ($P < 0.001$); colonoscopy completion: 21% vs. 10%, $P < 0.001$).⁵⁸ In a randomized controlled trial in 2014, 764 African-American patients were randomized into a standard intervention group that received a mailed stool blood test kit and colonoscopy instructions or in a tailored navigation group that received telephone navigation in addition to either a mailed stool blood test kit or colonoscopy instruction based on their stated preference. Results showed that patients in the tailored navigation group had a statistically significant higher adherence rate compared with the standard intervention group (OR 2.1, 95% CI: 1.5–2.9).⁵⁹ Thus, this study provided evidence that patient navigation tailored to a patient's stated preference for screening modality could enhance adherence to CRC screening among blacks.

Engaging patients in a discussion about their barriers is a critical step towards increasing adherence to CRC screening among African Americans. Providing support in the form of patient navigation not only helps facilitate this discussion but also can aid in the process of identifying the means through which these barriers can be overcome.

Physician barriers. There has been a growing interest in the role of physicians and their barriers to recommending colorectal cancer screening for their patients. Physician recommendation for screening has been shown to be a major factor in patients completing their screening exams.⁶⁰ Prior studies have shown that a recommendation from a healthcare provider is a strong predictor of CRC screening.^{52,61} Even with this knowledge, some studies have shown that physician recommendation for CRC screening is suboptimal. Klabunde *et al.*⁶² in 2005 sought to compare barriers with CRC screening as reported by the primary care physician vs. average risk adults. It was reported that both primary care physician and adults cited a lack of patient awareness and physician recommendation as key barriers. In looking at adults of screening age who were not current with testing and who had a doctor visit in the past year, only 10% received a screening recommendation.⁶²

With respect to whom physicians are recommending for screening, disparities between blacks and whites have been reported when it came to obtaining a physician's recommendation. After adjusting for age, blacks were approximately one-third less likely than whites to get a recommendation for CRC screening (OR 0.61, 95% CI: 0.53–0.71). The disparity persisted even after controlling for gender, family income, education level, and number of physician visits per year with an odds ratio of 0.82 (95% CI: 0.68–0.99). The lower the reported income, the less likely a patient would get a recommendation for CRC screening. The higher the education reported, the more likely the patient would get a recommendation for CRC screening by the physician. Of note, insurance status was not a significant predictor of a recommendation in this study.⁶³

The physician barriers to CRC screening are multifactorial. Lack of time, patient refusal, confusion about which tests to recommend, as well as lack of knowledge of screening guidelines have been reported in the literature.^{60,64} One group surveyed 801 patients in a rural setting and found that 61% of patients indicated that they did not discuss CRC screening or did not have sufficient to discuss CRC screening with their

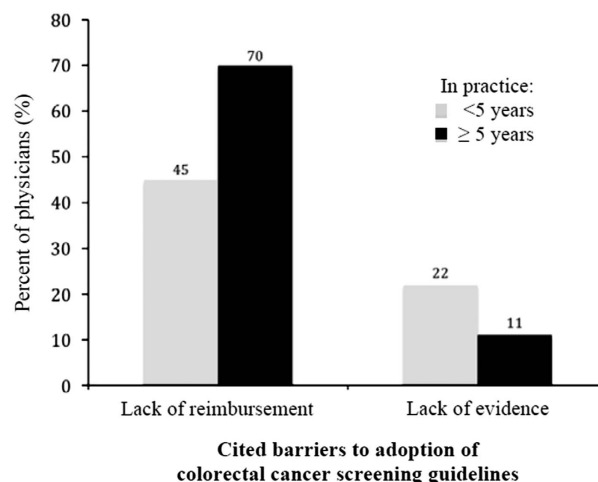


Figure 4 Physician barriers to recommending screening of high-risk populations based on years in practice. (Physicians who were in practice more than five years cited lack of reimbursement as barrier more often than physicians who were in practice less than five years. Lack of evidence for screening was cited as a barrier more often among physicians practicing less than five years versus physicians practicing more than 5 years).

doctors. Having time to discuss CRC screening with patients was the most powerful predictor of screening adherence.⁶⁵ One study reported a lack of knowledge of insurance coverage for screening as a barrier to recommending it while another study cited inadequate physician explanation about CRC.^{53,60} A survey given to Internists, Family Medicine physicians, and Gastroenterologists revealed that across specialties there was a lack of knowledge of screening guidelines for high-risk populations.⁶⁴ The study also reported a difference in barriers to screening recommendation based on years in practice. Lack of reimbursement was reported more by physicians practicing more than 5 years whereas lack of evidence to support the screening was reported more by physicians practicing less than 5 years (Figure 4). Having reminder systems in place for physicians as well as a means to keep up-to-date with recent guidelines may help diminish this barrier.⁶⁶

FACTORS INFLUENCING OBSERVED DISPARITIES

Incidence and mortality. There are many factors that influence the disparities shown in incidence and mortality. Disparities were persistent across different socioeconomic strata in a recent retrospective review of the 2000–2011 SEER database evaluating age specific incidences of colorectal cancer in African Americans compared with whites.³⁸ Lack of access to medical services and poor utilization of health care services were also shown to have an impact.⁶⁷ Alternatively, when equal access to healthcare services was available, there were no differences in survival among racial groups as reported in a review of 214 patients treated in the Veterans Affairs Hospital.⁶⁸ Lower screening rates, higher rates of obesity, and poorer nutrition were also cited as additional contributing factors.^{14,15,69–73} A MISCAN-microsimulation model used in a study by Lansdorp-Vogelaar *et al.*⁷⁴ concluded that 42% of the disparity in incidence and

19% of the disparity in mortality were due to differences in rates of screening. Moreover, a study by Lieberman⁷⁵ found that active cigarette smoking was linked to an increased risk of advanced neoplasia (OR, 2.12; 95%CI, 1.49-3.01) while increased physical activity had a trend toward a reduction in CRC risk, although this did not reach statistical significance. These additional factors that impact disparities in African Americans should be considered as lower levels of physical activity and increased rates of smoking have been noted more in blacks as compared with whites.⁷⁶ How these lifestyle characteristics exactly contribute to the higher incidence in blacks is unknown.

Survival and therapy for colorectal cancer. Different factors may influence the lower survival rates observed in this population. One analysis found that black patients with metastatic colon cancer had lower rates of consultation with medical oncology, surgery and radiation oncology.⁷⁷ This disparity in consultative care may be a factor that adversely influences survival. There have been various studies investigating the health disparities that exist in the therapeutic interventions for African Americans with colorectal cancer.^{22,76,78,79} In comparison with whites, African Americans were shown to have 50–60% decreased odds of receiving surgery for CRC⁸⁰ and a 67% decreased odds of receiving surgery for rectal cancer alone.⁸¹ Black patients are also less likely to receive adjuvant chemotherapy for resectable colorectal cancer or radiation for rectal cancer.⁸⁰ Similar findings were shown in other studies where African-American patients had a lower likelihood of receiving surgery for stage IV disease, less likely to receive adjuvant chemotherapy, and were treated less frequently with chemotherapy and radiation in comparison with whites.^{78,82–84}

Racial disparities in treatment were shown to persist even after consultation with medical oncologists. In 2005, a group investigated the receipt of chemotherapy in black and white Medicare-insured patients after stage III colon cancer resection. Although both groups were equally likely to consult with a medical oncologist, black patients who had seen an oncologist were less likely than white patients to receive chemotherapy (59.3% vs. 70.4%, $P < 0.001$).⁸⁵ Similar results were seen in a study done in 2008 among black and white patients who were diagnosed with resectable stage II or III rectal cancer. The study revealed that after consultation with a medical oncologist, black patients compared with white patients were less likely to receive chemotherapy (54.1% vs. 70.2%, $P = 0.006$), less likely to consult with both a medical oncologist and a radiation oncologist (49.2% vs. 58.8%, $P = 0.03$), less likely to receive radiation therapy (73.7% vs. 83.4%, $P = 0.06$), and less likely to receive both chemotherapy and radiation treatments (60.6% vs. 76.9%, $P = 0.008$).⁷⁹ Even though an equal opportunity exists to learn about therapeutic options from a medical oncologist, black patients have been shown not to receive these therapies at equal rates compared with white patients.

In a survey of over 1000 racially and ethnically diverse colon cancer patients, African Americans reported more problems with coordination of care ($P < 0.001$), psychosocial care ($P = 0.03$), access to cancer care ($P = 0.03$), and health information ($P < 0.001$) compared with their white

counterparts.⁸⁰ More studies are needed to investigate other possible barriers for black patients in receiving medical therapies for colorectal cancer, which ultimately influences survival.

DISCUSSION

CRC screening rates among African Americans has improved since the original ACG publication in 2005. In the National Health Interview Survey from 2000 to 2008 on racial patterns and uptake of CRC screening they reported the rates of utilization of specific screening modalities and adherence to CRC screening guidelines among blacks, Hispanics and non-whites. Black respondents that had received a guideline consistent colorectal screening exam via colonoscopy increased from 6.5% in 2000 to 30.6% in 2008.⁸⁶ An analysis of 2010 data from the Behavioral Risk Factors Surveillance System found up-to-date CRC screening rates of 66.3% (95% CI: 65.9–66.7) among whites and 65.0% (95% CI: 63.8–66.3) among blacks, respectively.⁸⁷ However, given these facts health disparities continue to prevail in this population. This issue has been addressed and corrected on the state level in New York City and Delaware. The Delaware Cancer Advisory Council was established in 2001 with the goal of developing a Statewide cancer control program. This program provided reimbursement and covered 2 years of the cost of care for newly diagnosed CRC for the uninsured. Special programs to reach the African American community were put in place partnering with community organizations. Between 2001 and 2009 they equalized the screening rates between blacks and whites and significantly diminished the gaps in mortality. In 2001, the CRC mortality was 31.2 per 100,000 in blacks and 19.5 per 100,000 in whites in 2001. In 2009 these numbers decreased to 18.0 per 100,000 and 16.9 per 100,000, respectively.⁸⁸ In New York the 2003 formation of the New York Colon Cancer Control Coalition (C5) initiative in had a major role in eliminating disparities across racial groups. Members of the C5 coalition included physicians, hospitals, medical societies, health plans, and patients with the goal to reduce the incidence and mortality of CRC in New York City. With funding sources from national and state levels this initiative instituted programs aimed at increasing screening rates and utilized a patient navigator system Citywide. In 2012, screening rates in New York City increased to 65% with equalization of early stage diagnosis; and in 2010 among black and white men and women based on the data from the New York City Department of Health Cancer Registry.⁸⁹ Both of these programs are examples of successful initiatives that utilized multiple resources resulting in a significant decrease in disparities. These initiatives created equal access to screening that is similar to the equal access system within the Veterans Affairs Hospitals. In the Veterans Affairs system, all patients have access to screening and treatment options and there has been no difference in outcomes of CRC between African Americans and whites. A reduction in ethnic disparities and no difference in treatment have been observed in Veterans Affairs colon cancer patients.⁶⁸ A study in 2013 evaluated the association of race and preventative health practices in an integrated community where the patients had equal access to health care. African-American men were

found to have nearly twice the odds of being screened for colon cancer.⁹⁰ Equalizing access to health care for African Americans is a key factor in decreasing the disparity gap.

Equalizing access to health care is only one of portion of the solution; educational outreach programs may also have a vital role in decreasing disparities. May *et al.*⁵⁴ queried a focus group of participants on sources of their health information and elicited suggestions for interventions. Among their recommendations were television and internet resources, celebrity endorsements, health fairs, and culturally sensitive educational materials that highlight the increased risk of CRC in the African-American community.⁵⁴ The Delaware Cancer Consortium and the C5 Coalition both utilized culturally sensitive educational outreach and patient navigation on a community level to achieve their respective goals.

We are in agreement with the recommendation that professional gastroenterological societies should participate in programs aimed at highlighting the issues that exist with regard to CRC in African Americans.⁸ Interventions that seek to increase screening among African Americans have been found to be successful when they target individuals or communities, address known barriers to screening, use multiple methods of message delivery, and are delivered over multiple time points.^{74,76} Implementing earlier screening does have its challenges, while some insurance companies such as AETNA may cover earlier screening,⁹¹ most insurance companies currently pay for screening colonoscopies starting at age 50 years in the average risk patient. There has been data to suggest that insurance companies have not adopted ACG guidelines, even in states with a large African-American population.⁹² There needs to be more advocacy to influence current health policy as equalizing access to health care and patient education is challenging given the history of disparate screening within this group.

Colorectal cancer remains one of the leading causes of malignancy related deaths in the United States. Current data present a compelling rationale as to why African Americans are a high-risk population in need of earlier screening. African Americans continue to have the highest incidence, highest mortality, and lowest survival among any other racial group. Various studies have shown that African Americans are diagnosed with CRC at an earlier age and present with more advanced stages of cancer. Currently, the ACG and ASGE recommend CRC screening in average risk African Americans at 45 years of age. The MISCAN-Colon microsimulation model discussed found an increase in life-years in blacks and a decrease in the disparities in incidence and survival when an individualization strategy was implemented that screened blacks 6 years earlier than whites, which supports the ACG's recommendation to begin earlier screening.³⁹ Guidelines already exist for early screening of patients with a personal history, genetic predisposition, or family history of CRC, all of whom are considered high risk for the disease. The ACG guidelines serve as a means to recognize and categorize African Americans as a high-risk population. Since the original publication in 2005, we now have multiple studies supporting the ACG's current recommendation for CRC screening for African Americans at 45 years of age, a recommendation with which we are in agreement.

CONFLICT OF INTEREST

Guarantor of the article: Renee Williams, MD.

Specific author contributions: Drafting of the manuscript; critical revision of the manuscript for important intellectual content: Renee Williams; drafting of the manuscript; critical revision of the manuscript for important intellectual content: Pascale White; critical review and revision of the manuscript for important intellectual content: Jose Nieto; systematic literature search, critical review and revision of the manuscript for important intellectual content: Dorice Vieira; critical review and revision of the manuscript for important intellectual content: Fritz Francois; critical review and revision of the manuscript for important intellectual content: Frank Hamilton.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ African Americans have the highest mortality among the racial groups in regards to colorectal cancer.
- ✓ African Americans have the lowest survival for colorectal cancer.
- ✓ African Americans have a higher propensity for proximal (right sided) lesions.

WHAT IS NEW HERE

- ✓ A review of age-related differences.
- ✓ Highlight on two Statewide programs that successfully decreased screening disparities.
- ✓ Physician-related barriers that contribute to the disparities in this population.

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**: 7–30.
2. American Cancer Society. Cancer Facts & Figures for African Americans 2016-2018. 2016. Available at: <http://www.cancer.org/research/cancerfactsstatistics/cancer-facts-figures-for-african-americans>, 2016.
3. United States Preventative Services Task Force. Colorectal Cancer: Screening 2008. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf/uspstfcolo.htm>. Accessed 25 February 2014.
4. Levin B, Lieberman DA, McFarland B *et al.* Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; **134**: 1570–1595.
5. Agrawal S, Bhupinderjit A, Bhutani MS *et al.* Colorectal cancer in African Americans. *Am J Gastroenterol* 2005; **100**: 515–523; discussion 514.
6. Simmang CL, Senatore P, Lowry A *et al.* Practice parameters for detection of colorectal neoplasms. The Standards Committee, The American Society of Colon and Rectal Surgeons. *Dis Colon Rectum* 1999; **42**: 1123–1129.
7. Qaseem A, Denberg TD, Hopkins RH Jr. *et al.* Screening for colorectal cancer: a guidance statement from the American College of Physicians. *Ann Intern Med* 2012; **156**: 378–386.
8. Rex DK, Johnson DA, Anderson JC *et al.* American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 2009; **104**: 739–750.
9. American Cancer Society. Colorectal Cancer Facts and Figures 2014-2016. Colorectal Cancer Facts and Figures 2014. Available at: <http://www.cancer.org/research/cancerfacts-statistics/colorectal-cancer-facts-figures>. Accessed 15 August 2015.
10. American Cancer Society. Colon Cancer Facts and Figures 2011-2013. Available at: <http://www.cancer.org/research/cancerfactsfigures/colorectal-cancer-facts-figures/colorectal-cancer-facts-figures-2011-2013-page>. Accessed 26 November 2014.

11. Howlader NNA, Krapcho M, Garshell J et al. (eds). SEER Cancer Statistics Review, 1975-2010. 2012. Available at: http://seer.cancer.gov/csr/1975_2010/. Accessed 25 February 2014.
12. Ryerson AB, Ehemann CR, Altekruse SF et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer* 2016; **122**: 1312-1337.
13. Surveillance Epidemiology and End Results Program. SEER Stat Facts Sheet: colon and rectum. Available at: <http://seer.cancer.gov/staffacts/html/colorect.html>. Accessed June 2016.
14. Jepson C, Kessler LG, Portnoy B et al. Black-white differences in cancer prevention knowledge and behavior. *Am J Public Health* 1991; **81**: 501-504.
15. Ioannou GN, Chapko MK, Dominitz JA. Predictors of colorectal cancer screening participation in the United States. *Am J Gastroenterol* 2003; **98**: 2082-2091.
16. Chen VW, Fenoglio-Preiser CM, Wu XC et al. Aggressiveness of colon carcinoma in blacks and whites. National Cancer Institute Black/White Cancer Survival Study Group. *Cancer Epidemiol Biomarkers Prev* 1997; **6**: 1087-1093.
17. Mayberry RM, Coates RJ, Hill HA et al. Determinants of black/white differences in colon cancer survival. *J Natl Cancer Inst* 1995; **87**: 1686-1693.
18. Ward E, Jemal A, Cokkinides V et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA Cancer J Clin* 2004; **54**: 78-93.
19. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71-96.
20. Marcella S, Miller JE. Racial differences in colorectal cancer mortality. The importance of stage and socioeconomic status. *J Clin Epidemiol* 2001; **54**: 359-366.
21. Roetzheim RG, Pal N, Gonzalez EC et al. Effects of health insurance and race on colorectal cancer treatments and outcomes. *Am J Public Health* 2000; **90**: 1746-1754.
22. Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. *J Natl Cancer Inst* 2002; **94**: 334-357.
23. Cheng L, Eng C, Nieman LZ et al. Trends in colorectal cancer incidence by anatomic site and disease stage in the United States from 1976 to 2005. *Am J Clin Oncol* 2011; **34**: 573-580.
24. Shavers VL. Racial/ethnic variation in the anatomic subsite location of in situ and invasive cancers of the colon. *J Natl Med Assoc* 2007; **99**: 733-748.
25. Corley DA, Jensen CD, Marks AR et al. Variation of adenoma prevalence by age, sex, race, and colon location in a large population: implications for screening and quality programs. *Clin Gastroenterol Hepatol* 2013; **11**: 172-180.
26. Lieberman DA, Holub JL, Moravec MD et al. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. *JAMA* 2008; **300**: 1417-1422.
27. Lee KK, Jandorf L, Thelemaque L et al. Colorectal neoplasia detection among black and Latino individuals undergoing screening colonoscopy: a prospective cohort study. *Gastrointest Endosc* 2014; **79**: 466-472.
28. Schroy PC 3rd, Coe A, Chen CA et al. Prevalence of advanced colorectal neoplasia in white and black patients undergoing screening colonoscopy in a safety-net hospital. *Ann Intern Med* 2013; **159**: 13-20.
29. Wallace K, Grau MV, Ahnen D et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2310-2317.
30. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 2005; **23**: 609-618.
31. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010; **138**: 2088-2100.
32. Wong R. Proximal tumors are associated with greater mortality in colon cancer. *J Gen Intern Med* 2010; **25**: 1157-1163.
33. Abdelsattar ZM, Wong SL, Regenbogen SE et al. Colorectal cancer outcomes and treatment patterns in patients too young for average-risk screening. *Cancer* 2016; **122**: 929-934.
34. Bailey CE, Hu CY, You YN et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. *JAMA Surg* 2015; **150**: 17-22.
35. United States Preventive Services Task Force. Prostate Cancer: Screening. 2012. Available at: <http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/prostate-cancer-screening>, 2014.
36. Karami S, Young HA, Henson DE. Earlier age at diagnosis: another dimension in cancer disparity? *Cancer Detect Prev* 2007; **31**: 29-34.
37. Lieberman DA, Williams JL, Holub JL et al. Race, ethnicity, and sex affect risk for polyps > 9 mm in average-risk individuals. *Gastroenterology* 2014; **147**: 351-358; quiz e314-e355.
38. Paquette IM, Ying J, Shah SA et al. African Americans should be screened at an earlier age for colorectal cancer. *Gastrointest Endosc* 2015; **82**: 878-883.
39. Lansdorp-Vogelaar I, van Ballegoijen M, Zauber AG et al. Individualizing colonoscopy screening by sex and race. *Gastrointest Endosc* 2009; **70**: 96-108, 108, e101-e124.
40. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977-1981.
41. Nishihara R, Wu K, Lochhead P et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013; **369**: 1095-1105.
42. Hawley ST, Volk RJ, Krishnamurthy P et al. Preferences for colorectal cancer screening among racially/ethnically diverse primary care patients. *Med Care* 2008; **46**: S10-S16.
43. Schroy PC 3rd, Lal S, Glick JT et al. Patient preferences for colorectal cancer screening: how does stool DNA testing fare? *Am J Manage Care* 2007; **13**: 393-400.
44. Inadomi JM, Vijan S, Janz NK et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. *Arch Intern Med* 2012; **172**: 575-582.
45. Gupta S, Halm EA, Rockey DC et al. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. *JAMA Intern Med* 2013; **173**: 1725-1732.
46. Theuer CP, Taylor TH, Brewster WR et al. The topography of colorectal cancer varies by race/ethnicity and affects the utility of flexible sigmoidoscopy. *Am Surg* 2001; **67**: 1157-1161.
47. Gonzalez EC, Roetzheim RG, Ferrante JM et al. Predictors of proximal vs. distal colorectal cancers. *Dis Colon Rectum* 2001; **44**: 251-258.
48. Nelson RL, Persky V, Turyk M. Carcinoma in situ of the colorectum: SEER trends by race, gender, and total colorectal cancer. *J Surg Oncol* 1999; **71**: 123-129.
49. Sharma VK, Vasudeva R, Howden CW. Changes in colorectal cancer over a 15-year period in a single United States city. *Am J Gastroenterol* 2000; **95**: 3615-3619.
50. Johnson H Jr., Carstens R. Anatomical distribution of colonic carcinomas. Interracial differences in a community hospital population. *Cancer* 1986; **58**: 997-1000.
51. Greiner KA, Born W, Nollen N et al. Knowledge and perceptions of colorectal cancer screening among urban African Americans. *J Gen Intern Med* 2005; **20**: 977-983.
52. Wong CR, Bloomfield ER, Crookes DM et al. Barriers and facilitators to adherence to screening colonoscopy among African-Americans: a mixed-methods analysis. *J Cancer Educ* 2013; **28**: 722-728.
53. Sly JR, Edwards T, Shelton RC et al. Identifying barriers to colonoscopy screening for nonadherent African American participants in a patient navigation intervention. *Health Educ Behav* 2013; **40**: 449-457.
54. May FP, Whitman CB, Varlyguina K et al. Addressing Low Colorectal Cancer Screening in African Americans: Using Focus Groups to Inform the Development of Effective Interventions. *J Cancer Educ* 2015; **1-8**; doi: 10.1007/s13187-015-0842-z; e-pub ahead of print.
55. Pfister DG, Benson AB 3rd, Somerfield MR. Clinical practice. Surveillance strategies after curative treatment of colorectal cancer. *N Engl J Med* 2004; **350**: 2375-2382.
56. James AS, Daley CM, Greiner KA. Knowledge and attitudes about colon cancer screening among African Americans. *Am J Health Behav* 2011; **35**: 393-401.
57. Lasser KE, Murillo J, Lisboa S et al. Colorectal cancer screening among ethnically diverse, low-income patients: a randomized controlled trial. *Arch Intern Med* 2011; **171**: 906-912.
58. Percac-Lima S, Grant RW, Green AR et al. A culturally tailored navigator program for colorectal cancer screening in a community health center: a randomized, controlled trial. *J Gen Intern Med* 2009; **24**: 211-217.
59. Myers RE, Sifri R, Daskalakis C et al. Increasing colon cancer screening in primary care among African Americans. *J Natl Cancer Inst* 2014; **106**: dju344; doi: 10.1093/jnci/dju344.
60. Nichols C, Holt CL, Shipp M et al. Physician knowledge, perceptions of barriers, and patient colorectal cancer screening practices. *Am J Med Qual* 2009; **24**: 116-122.
61. Myers RE, Trock BJ, Lerman C et al. Adherence to colorectal cancer screening in an HMO population. *Prev Med* 1990; **19**: 502-514.
62. Klabunde CN, Vernon SW, Nadel MR et al. Barriers to colorectal cancer screening: a comparison of reports from primary care physicians and average-risk adults. *Med Care* 2005; **43**: 939-944.
63. Coleman Wallace DA, Baltrus PT, Wallace TC et al. Black white disparities in receiving a physician recommendation for colorectal cancer screening and reasons for not undergoing screening. *J Health Care Poor Underserved* 2013; **24**: 1115-1124.
64. White PM, Sahu M, Poles MA et al. Colorectal cancer screening of high-risk populations: a national survey of physicians. *BMC Res Notes* 2012; **5**: 64.
65. Greiner KA, Engelman KK, Hall MA et al. Barriers to colorectal cancer screening in rural primary care. *Prev Med* 2004; **38**: 269-275.
66. O'Malley AS, Beaton E, Yabroff KR et al. Patient and provider barriers to colorectal cancer screening in the primary care safety-net. *Prev Med* 2004; **39**: 56-63.
67. Lee W, Nelson R, Mailey B et al. Socioeconomic factors impact colon cancer outcomes in diverse patient populations. *J Gastrointest Surg* 2012; **16**: 692-704.
68. Robinson CN, Balentine CJ, Marshall CL et al. Ethnic disparities are reduced in VA colon cancer patients. *Am J Surg* 2010; **200**: 636-639.
69. Kauh J, Brawley OW, Berger M. Racial disparities in colorectal cancer. *Curr Probl Cancer* 2007; **31**: 123-133.
70. Coughlin SS, Thompson TD, Seeff L et al. Breast, cervical, and colorectal carcinoma screening in a demographically defined region of the southern U.S. *Cancer* 2002; **95**: 2211-2222.
71. Hoffman-Goetz L, Breen NL, Meissner H. The impact of social class on the use of cancer screening within three racial/ethnic groups in the United States. *Ethn Dis* 1998; **8**: 43-51.
72. O'Malley AS, Forrest CB, Mandelblatt J. Adherence of low-income women to cancer screening recommendations. *J Gen Intern Med* 2002; **17**: 144-154.
73. Richards RJ, Reker DM. Racial differences in use of colonoscopy, sigmoidoscopy, and barium enema in Medicare beneficiaries. *Dig Dis Sci* 2002; **47**: 2715-2719.
74. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB et al. Contribution of screening and survival differences to racial disparities in colorectal cancer rates. *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 728-736.
75. Lieberman DA, Prindiville S, Weiss DG et al. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA* 2003; **290**: 2959-2967.
76. Tammana VS, Laiyemo AO. Colorectal cancer disparities: issues, controversies and solutions. *World J Gastroenterol* 2014; **20**: 869-876.
77. Simpson DR, Martinez ME, Gupta S et al. Racial disparity in consultation, treatment, and the impact on survival in metastatic colorectal cancer. *J Natl Cancer Inst* 2013; **105**: 1814-1820.

78. Morris AM, Wei Y, Birkmeyer NJ et al. Racial disparities in late survival after rectal cancer surgery. *J Am Coll Surg* 2006; **203**: 787–794.
79. Morris AM, Billingsley KG, Hayanga AJ et al. Residual treatment disparities after oncology referral for rectal cancer. *J Natl Cancer Inst* 2008; **100**: 738–744.
80. Dimou A, Syrigos KN, Saif MW. Disparities in colorectal cancer in African-Americans vs Whites: before and after diagnosis. *World J Gastroenterol* 2009; **15**: 3734–3743.
81. Hines RB, Markossian TW. Differences in late-stage diagnosis, treatment, and colorectal cancer-related death between rural and urban African Americans and whites in Georgia. *J Rural Health* 2012; **28**: 296–305.
82. Demissie K, Oluwole OO, Balasubramanian BA et al. Racial differences in the treatment of colorectal cancer: a comparison of surgical and radiation therapy between Whites and Blacks. *Ann Epidemiol* 2004; **14**: 215–221.
83. Rogers SO, Ray WA, Smalley WE. A population-based study of survival among elderly persons diagnosed with colorectal cancer: does race matter if all are insured? (United States). *Cancer Causes Control* 2004; **15**: 193–199.
84. Govindarajan R, Shah RV, Erkmann LG et al. Racial differences in the outcome of patients with colorectal carcinoma. *Cancer* 2003; **97**: 493–498.
85. Baldwin LM, Dobie SA, Billingsley K et al. Explaining black-white differences in receipt of recommended colon cancer treatment. *J Natl Cancer Inst* 2005; **97**: 1211–1220.
86. Shavers VL, Jackson MC, Sheppard VB. Racial/ethnic patterns of uptake of colorectal screening, National Health Interview Survey 2000–2008. *J Natl Med Assoc* 2010; **102**: 621–635.
87. Joseph DA, King JB, Miller JW et al. Prevalence of colorectal cancer screening among adults—Behavioral Risk Factor Surveillance System, United States, 2010. *MMWR Suppl* 2012; **61**: 51–56.
88. Grubbs SS, Polite BN, Carney J Jr. et al. Eliminating racial disparities in colorectal cancer in the real world: it took a village. *J Clin Oncol* 2013; **31**: 1928–1930.
89. Itzkowitz SH, Winawer SJ, Krauskopf M et al. New York Citywide Colon Cancer Control Coalition: A public health effort to increase colon cancer screening and address health disparities. *Cancer* 2016; **122**: 269–277.
90. Thorpe RJ Jr., Bowie JV, Wilson-Frederick SM et al. Association between race, place, and preventive health screenings among men: findings from the exploring health disparities in integrated communities study. *Am J Men's Health* 2013; **7**: 220–227.
91. AETNA. Colorectal Cancer Screening. Available at: http://www.aetna.com/cpb/medical/data/500_599/0516.html. Accessed 2 December 2015.
92. Uradamo L, A M, Borum M. Insurance Coverage for Screening Colonoscopy at age 45 for African Americans: Low Adherence to Guidelines in States With Large African American Populations. Paper presented at: Digestive Diseases Week, 2011.



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