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Colorectal cancer disparities beyond biology: Screening, treatment, access

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1. ABSTRACT

African Americans in the United States are more likely than their white counterparts to experience greater incidence and mortality due to colorectal cancer (CRC). Present for decades, these disparities have prompted researchers to investigate underlying causes and potential explanations. While some biological variations have been observed between races, evidence shows that approximately 50% of these disparities can be attributed to differences and disparities in CRC screening, resulting in reduced polyp removal for CRC prevention and/or early detection of CRC among African Americans. Other major contributors to CRC disparities are differences in treatment and access to care. Significant efforts are needed to increase CRC screening among African Americans through targeted interventions to reduce barriers such as increasing education, promoting physician recommendations, and providing affordable and quality care. Intervention is also needed to educate the medical community about these issues and to change health policy to provide a multilevel approach with the best chance of success in reducing racial disparities in CRC.

2. INTRODUCTION

2.1. Colorectal cancer incidence and mortality in the U.S.

Excluding skin cancers, colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women in the United States (1). The American Cancer Society estimates that, in 2016, 134,490 new cases of CRC will be diagnosed (1). The lifetime risk of developing CRC is approximately 1 in 21 for men and 1 in 23 for women (1). CRC is the second leading cause of cancer-related deaths in the United States among cancers that affect both men and women (2). In 2016, 49,190 deaths are estimated to occur as a result of CRC (1). Both CRC incidence and mortality rates increase with age. The overwhelming majority of new cases and deaths (90% and 93%, respectively) occur in individuals aged 50 and above (3). CRC diagnosis is most frequent among individuals aged 65-74 with a median age at diagnosis of 68 years old, while CRC mortality is highest among those aged 75-84 with a mean age of 73 years old (4).

Rates of CRC vary at the population level with respect to different individual-level characteristics. One of the most distinctive biological differences noted is that CRC incidence and mortality rates among men are estimated to be 30%-40% higher than those of women (5). Some researchers posit that this significant difference may be attributable to complex interactions between gender-related differences when exposed to hormones and various risk factors (6). Another significant variation in CRC incidence and mortality is that observed between races.

2.2. Variations by race

CRC incidence in the United States increased steadily from 1975 through the 1980s, but has since been

on the decline, particularly in the last decade (5). These encouraging declining rates have been primarily attributed to increases in CRC screening (7). The disease's slow progression from a precancerous polyp to an invasive cancer (typically over a 10-20 year period) provides a singular chance for prevention and early detection (8, 9). This is available in the form of CRC screening which provides opportunity for (a) detection of precancerous growths and offering potential for their removal before CRC develops (10-12); and (b) detection of CRC in an early, localized stage when it is most treatable with highest likelihood of survival (5, 13, 14). Observed decreases in CRC mortality in recent years are also largely attributed to the uptake of CRC screening (7, 15). For patients diagnosed with localized stage disease, CRC survival rates are nearly 90%; however, only an estimated 40% of CRC patients are diagnosed in this stage, demonstrating that the need for intervention to increase screening is still present (5).

While overall rates of CRC incidence and mortality have decreased significantly in recent years, racial disparities within these rate changes have remained evident. Before the early 1980s, CRC incidence was generally greater among whites versus African Americans (60.2. versus 56.9. in 1975) (16). However, as overall CRC incidence rates began declining in the late 1980s, CRC incidence has become consistently higher among African Americans (47.0. versus 37.6. in 2012) (17). Although incidence among African Americans has also since decreased, this decline began later and has occurred at a substantially slower rate than that observed among white individuals (5). When considered together, this disparity is thought to reflect greater access to and uptake of CRC screening among whites (18). Trends in decreasing CRC mortality have mirrored those of incidence over time, including delayed declines and remaining racial disparities between African American and white individuals (5). Whites experienced a sharp decline in CRC mortality even as far back as in the early 1980s; however, a similar decrease was not observed among African Americans until the late 1990s. Although the gap in mortality rates between the two groups has narrowed, particularly in the last decade, CRC mortality rates continue to be significantly greater among African Americans than those of white individuals (5).

However, reasons behind these disparate rates of incidence and mortality have not been conclusively determined, begging questions about whether these disparities are biologically-driven or the result of other influencing factors. Some non-biological factors thought to increase these disparities include: low socioeconomic status, poor access to health care (19), lacking health insurance (20, 21), lesser quality of health care (22, 23), and decreased screening engagement (17, 18, 23). These issues are explored in the current review to add more definitive, comprehensive evidence to the drivers of these disparities and assist in identifying strategies with which they can be addressed (Figure 1).

3. IS BIOLOGY TO BLAME?

Several studies have attempted to explain the disproportionate burden of CRC experienced by African Americans by examining biological differences. In a study by Slattery and colleagues, African Americans were determined to be more likely to have the BLFA haplotype of the vitamin D receptor than whites in the study (41.2.% versus 6.5.% respectively). This haplotype was found to be significantly associated with greater risk of CRC (OR=2.4.; 95% CI 1.3.8-4.3.8) (24). Other investigators have examined arachidonate lipoxygenase (ALOX) and cyclooxygenase (COX), genes cited as influential in the development of colon cancer. These studies have found that ALOX5-1752 and ALOX5-1699 polymorphisms significantly lower the risk of colon cancer in whites and that A alleles at these gene positions are associated with decreased risk of colon cancer in whites but not in African Americans (25). In another study, Koshiji *et al.* found that N-myc downstream-regulated gene 1 (NDRG1) expression is associated with HIF-1 alpha expression and histopathological type in whites but not African Americans. Additionally, investigators found that NDRG1 expression was significantly associated with worse survival only among African Americans (26). Other studies have attempted to explain biological differences by looking at potential interactions between specific polymorphisms and lifestyle behaviors such as cigarette smoking (27) and folate intake (28). However, trends over time in CRC incidence and mortality among African Americans and whites lead the vast majority of researchers to theorize that biological factors are likely only minimally responsible for observed disparities (5, 23, 29). Cultural and lifestyle factors exclusive of biological interactions are hypothesized to also play a role in the incidence and mortality disparities observed in African Americans. There are numerous behaviors associated with increased CRC risk such as obesity (30-32), alcohol consumption (33, 34), smoking (35, 36), and low physical activity (37, 38). Lifestyle factors such as these may contribute to the observed disparities in CRC risk (39, 40). Rates of alcohol consumption, smoking, and obesity have been consistently higher among African Americans in recent decades, as have lower rates of physical activity (41). A summary of these factors and their observed effects are given in Table 1.

4. THE ROLE OF SCREENING

4.1. Colorectal cancer screening recommendations and methods

The U.S. Preventive Services Task Force (USPSTF) recommends that adults 50-75 years old, at average risk of developing CRC, undergo screening using one or more of the following methods: (a) fecal occult

Table 1. Genetic and lifestyle influences on colorectal cancer risk

Risk factor	Type	Observed effects in African Americans	Observed effects in whites	Setting and sample size	References
BLFA Haplotype (Vitamin D receptor)	Genetic	Minimal lowering of cancer risk, gene only expressed in 6.5.% of the population	Substantially greater effect of lowering cancer risk due to increased expression in 42.2.% of the population	Comparison of two large case-control studies: (a) colon cancer (1,574 cases and 1,970 controls) (b) rectal cancer (791 cases and 999 controls)	(24)
ALOX5-1752 and ALOX5-1699	Genetic	No effect on risk of colon cancer	Lowers risk of colon cancer	Analysis of 293 colon cancer cases, 229 hospital controls, and 304 hospital-based controls	(25)
NDRG1	Genetic	Associated with worse survival	No correlation between the gene and survival rates	Comparative study of 157 colorectal cancer specimens (80 Japanese and 77 US patients)	(26)
Cigarette Smoking	Lifestyle	No association between smoking and colon cancer	Increased risk of colon cancer associated with cigarette smoking	Association supported by the analysis of 554 cases and 874 controls	(27)
Folate Intake	Lifestyle	Folate intake <400mg per day held a weakly associated increased risk of colon cancer		Analysis of 55 cases (244 African American and 311 white) and 875 controls (331 African Americans and 544 whites)	(28)
Obesity	Lifestyle	Obesity was found to be a risk factor for colorectal cancer.		Three meta-analyses focused on the correlation between obesity and colon cancer risk	(30-32)
Alcohol	Lifestyle	Drinking more than one drink per day associated with increased risk of colorectal cancer		Two meta-analyses studies focused on the correlation between the alcohol consumption and colon cancer risk	(33, 34)
Physical Activity	Lifestyle	Lower rates of physical activity leading to an increased risk of colon cancer	Higher rates of physical activity and a reduced risk of colon cancer	Literature review to determine inverse association between physical activity and colon cancer	(38)

blood testing (FOBT) every year; (b) sigmoidoscopy every 5 years with high-sensitivity FOBT every 3 years, or (c) colonoscopy every 10 years (42). Two of the most prevalent methods for CRC screening are colonoscopy and FOBT. Colonoscopy is widely considered the gold standard for CRC screening, providing direct visual examination of the entire colon and the opportunity to remove polyps during the procedure (43). Sensitivity and specificity for this test are estimated to be 93% and 99%, respectively (44); however, many experts emphasize that colonoscopy accuracy depends largely on the operating physician (45). A quality colonoscopy is defined by adequate exam time during the procedure; a physician should spend more than six minutes to examine the colon. This minimum examination time ensures that the physician has sufficient opportunity to thoroughly examine the colon and identify any precancerous polyps, allowing for removal and/or recommendation to appropriate follow-up (45). Although colonoscopy is currently the most sensitive CRC detection method (46), an estimated 20% of adenomas go undetected. Typically these lesions have a flat shape and are located in areas that make them more difficult to identify (47). Physicians who do not follow examination guidelines run a higher risk of missing these obscure lesions. Of FOBT methods available, recent studies have demonstrated the fecal immunochemical test (FIT) to be the most efficacious (46, 47), detecting human globin in stool using a sensitive immunochemical assay (48). A recent review of studies using FIT found an overall 95% accuracy rate for CRC detection, test sensitivity of 79%, and specificity of 94% (49). Patients perform FIT screening at home, using assistance only if needed, and do not have to perform bowel cleansing or adhere to dietary restrictions prior to use. FIT screening offers greater convenience, more privacy, less expense, and is less invasive than colonoscopy, making it preferable for many patients when choosing a CRC screening method (50).

4.2. Uptake of and engagement in screening

Although the value of CRC screening has been thoroughly demonstrated, in 2010 only 59% of

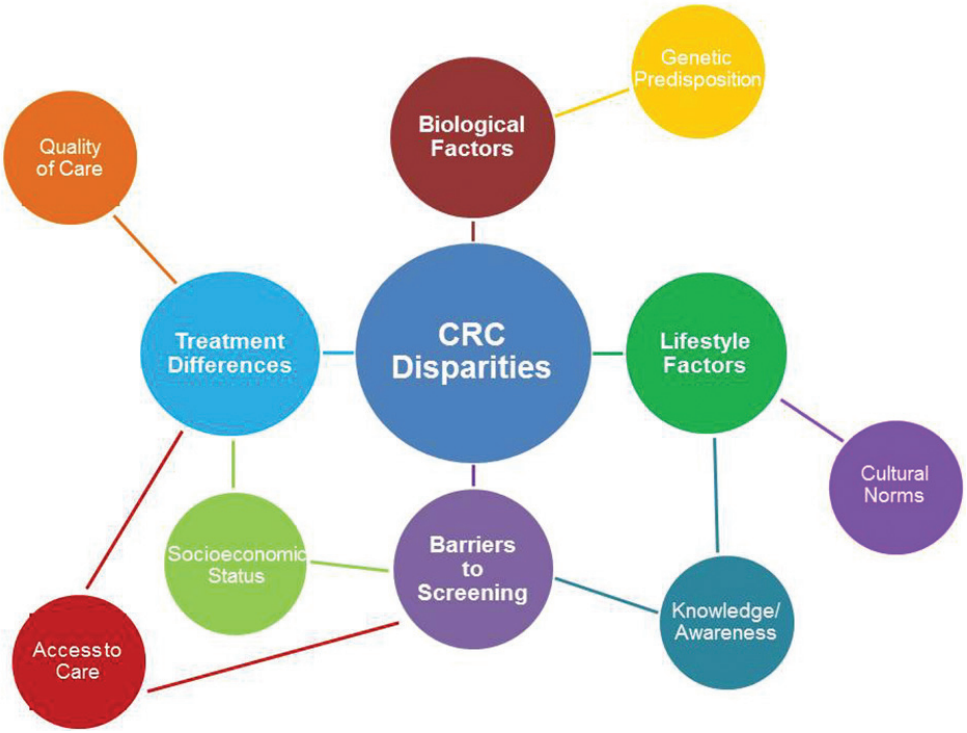

Figure 1. Factors contributing to colorectal cancer disparities.

individuals in the U.S. who met recommendation criteria were screened for CRC, falling far short of the Healthy People 2020 national goal of a 70.5.% CRC screening rate by 2020 and the Centers for Disease Control and Prevention and the American Cancer Society's national priority of achieving an 80% CRC screening rate by 2018 (51, 52). Many researchers and clinicians emphasize that many CRC deaths are avoidable because screening is underutilized. Using a Microsimulation Screening Analysis model to assess the proportion of CRC deaths in the U.S. among those aged 50 and older, Meester *et al.* estimate that 63% (approximately 32,200) CRC deaths in the U.S. in 2010 could be attributed to non-screening (53). Previous studies have helped modern intervention design by identifying some individual-level factors associated with decreased likelihood of engaging in CRC screening. When compared to the general population of adults 50 years and older, screening among adults under 65 years old was lower among minorities (including African Americans), those with less than 13 years of education, and those who lacked health insurance (54).

CRC screening rates in the U.S. have been consistently lower among African American individuals compared with whites since the introduction and uptake of these tests in the 1980s (Figure 2) (18, 55-57). Low rates of CRC screening engagement are thought by many to be one of the primary explanations for racial disparities in CRC incidence and mortality (Figure 3) (58-60). In addition, delayed screening among African Americans is considered to be a significant driver of late-stage CRC diagnosis and corresponding poor outcomes and higher mortality (Figure 4; Figure 5) (61, 62). Investigators of one recent study claim that as much as 35% of the racial disparities in CRC mortality can be explained by differences in stage-specific relative CRC survival (23).

Studies have identified many patient barriers to CRC screening including: patient perceived low risk; displaying no symptoms; fear; inconvenience; embarrassment; lack of a physician recommendation; and cost (63-66). Screening rates have been particularly low among patients without a usual source of care or insurance (17.8.% and 23.5.% respectively) and such individuals have experienced large, persisting disparities in screening (19, 67-70). Even among those with health insurance, publicly insured individuals are less likely to report engaging in screening than those privately insured (67). African Americans are more likely to lack insurance and face other socioeconomic challenges to obtaining screening (58, 71, 72). Researchers have noted that differences in CRC rates are likely associated with differences in socioeconomic status and resulting limited access to screening (73). Barriers specific to minorities, particularly African Americans include religious beliefs, past negative experiences with screening, and mistrust of medical providers (64).

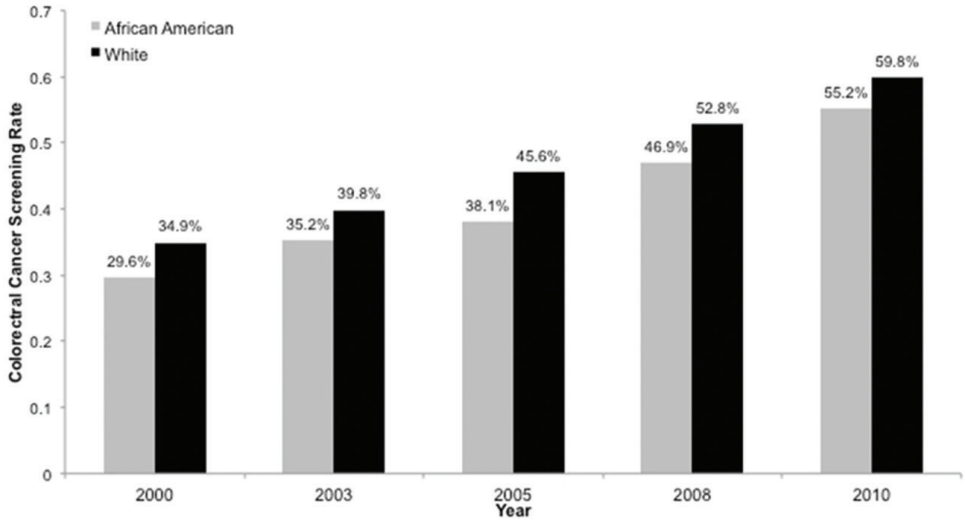

Figure 2. Average colorectal cancer screening rates by race, 2000-2010.

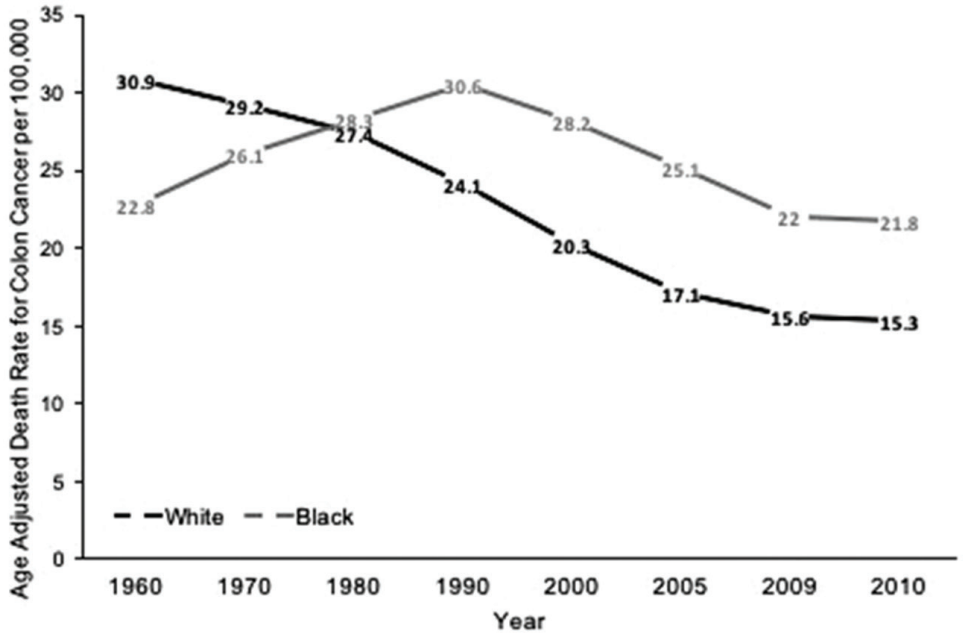

Figure 3. Age-adjusted death rates from colon cancer by race, 1960-2010.

4.3. Interventions designed to decrease barriers and promote screening

Various interventions have been designed and implemented to address the aforementioned barriers. Physician recommendation is one of the strongest motivators for patients to engage in CRC screening; however, the literature indicates that it is not uncommon for physicians to fail to recommend screening to their patients. This has led many studies to utilize audit and feedback systems to prompt physicians which has demonstrated effectiveness in significantly increasing screening rates (74-76). An early study by Fleming *et al.* found that implementing a physician feedback system for clinic FOBT screening increased rates from 12% to 23% (77). Other interventions have focused on lessening the barriers often associated with colonoscopy such as fear, bowel preparation, and inconvenience (64, 78, 79). One such study addressed all of these barriers by utilizing FOBT testing and overcoming issues of inconvenience by offering the screening with

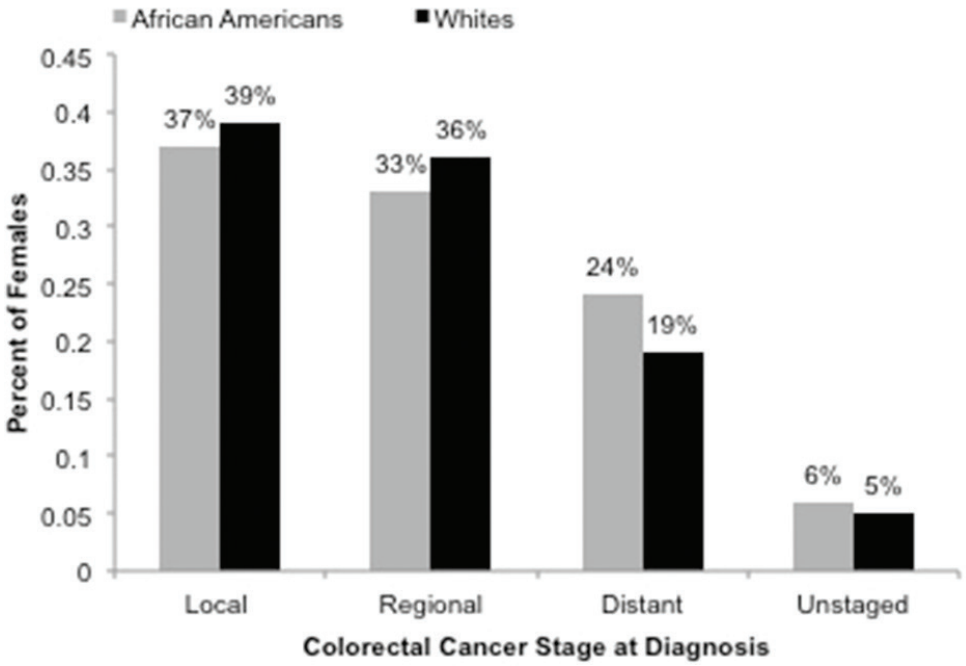

Figure 4. Rates of colorectal cancer by stage and race among females, 2003-2009.

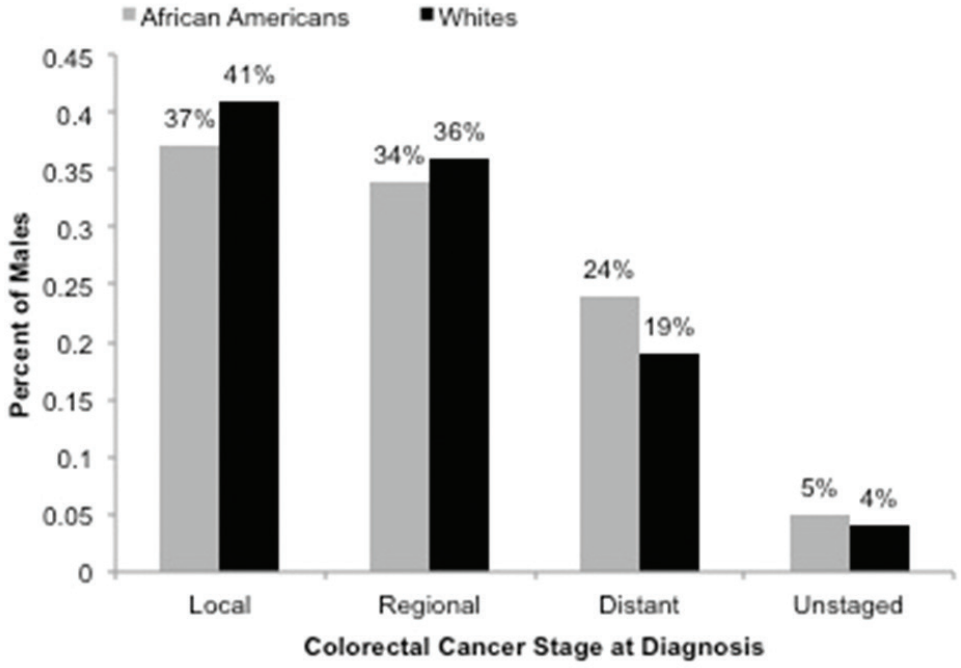

Figure 5. Rates of colorectal cancer by stage and race among males, 2003-2009.

patients' annual flu vaccination either in office or with an option to perform it at home. Patients in the control group (who received regular care) had a screening rate of 52.9.% versus the intervention group who improved from a baseline screening rate of 54.5.% to 84.3.% at the completion of the intervention (80, 81). These findings indicate that the barriers addressed may be key obstacles for patients that can be overcome with

fairly simple, time- and cost-effective solutions with the potential for great increases in screening. The barrier of low CRC knowledge has also been found to be especially significant, particularly among minority populations, and a significant driver of low screening rates (65, 82, 83). However, in intervention studies addressing knowledge as a barrier among ethnic minority subsets, patient navigation has been demonstrated as an effective tool to increase screening by providing patient education and assisting in gaining access to care (84, 85). Providing patients with other modes of education such as pamphlets, videos, visual images, and other materials have also been utilized with some success in raising the low awareness of minority populations, including African Americans (65, 86-88). Specifically among African American populations, interventions with a community focus and those emphasizing cultural sensitivity have demonstrated effectiveness in increasing CRC screening rates (89, 90).

5. THE HEALTH CARE SYSTEM AND COLORECTAL CANCER RACIAL DISPARITIES

5.1. Treatment differences between African American and white patients

While screening disparities are thought to account for approximately 50% of racial disparities in CRC outcomes and mortality (23), the majority of remaining CRC racial disparities are thought by many to be the result of differences in treatment and access to care. African Americans diagnosed with CRC frequently present with a more advanced stage of disease when compared to whites, often attributed to a lack of regular health care and/or not receiving the same physician prompts for screening as whites (62, 91). Treatment disparities have been observed contributing to poorer CRC survival in African Americans than whites (92, 93). When controlling for socioeconomic status and comorbidities, this disparity was reduced, but still significant (94). Also with respect to treatment, studies have also shown that whites are more likely to be treated with both chemotherapy and radiation than African Americans with the same disease burden (17, 95, 96). In a study of a large cohort of white and African American CRC patients, Baldwin *et al.* found that individuals of both races were equally likely to consult with a medical oncologist, but African American patients were less likely than their white counterparts to receive chemotherapy (97). Two large clinical trials have been conducted to examine treatment disparities between white and African American patients. Albain and colleagues' findings did not reflect disparities between the two racial groups for colon cancer; however, the authors note that the cases examined were early stage and that the sample size (n=1,244; 5.6.% African American) might not have been large enough to draw conclusive evidence (98). Conversely, Dignam *et al*. found that overall survival was significantly lower among African American patients receiving adjuvant therapy for rectal cancer compared with whites (99). Recurrence-free survival among African Americans in this study was also lower than that of whites although these rates for the two groups were less disparate than that of overall survival. These studies present conflicting perspectives regarding survival outcomes between the two races even with similar treatment. Further, larger trials are needed to determine the effects of standardized treatment on survival by race more conclusively in order to support to arguments that biological differences in prognosis may be negligible compared with the impact of equitable treatment (98-100).

5.2. Variations in quality of and access to care by race

Disparities between races can be explained not only by access to care but, more specifically, access to quality care. Physicians treating African American patients have been found to have less training and expertise in performing screening procedures. They also have less access to clinical resources than those treating white patients (22, 101). Physicians whose patients are predominantly minorities are less likely to be board certified, and are nearly twice as likely to be International Medical Graduates who may be less familiar with traditional screening methods and practices in the U.S. These physicians often have fewer resources and receive less insurance reimbursements than physicians whose practices are not primarily composed of minorities. Physicians in high minority practices receive nearly one-third of their income from Medicaid patients (101). Limitations such as less funding, older technology, understaffing, and higher patient volume affect the quality of care that these physicians are able to provide. Low-income racial and ethnic minorities, including African Americans, tend to be geographically clustered, thus having a smaller pool of healthcare providers from whom to choose. This frequently results in overburdening of already limited medical resources in these areas. (101). Additionally, many African Americans, appear to choose lower quality healthcare facilities. A study that included all California hospitals showed that African Americans were more likely to use lower quality, low volume hospitals, and this trend continued even for patients living closer to a higher quality hospital (102).

6. AFRICAN AMERICANS AND COLORECTAL CANCER: WHERE DO WE GO FROM HERE?

There are demonstrated and significant racial disparities with respect to CRC incidence and mortality between African American and White individuals. A small percentage of these disparities may be accredited to biological variations, but the overwhelming majority are attributable to differences in factors related to screening, treatment, and access to care. Substantial work is needed to reduce racial disparities in the area of CRC. Although

numerous studies have been conducted and national surveys are in place, comprehensive data regarding CRC incidence and mortality for African Americans is lacking (23). Greater efforts should be made to obtain representative data on these and related matters such as screening rates, barriers, treatment, and access to care. More detailed information on these issues will assist in informing and guiding efforts to decrease discrepancies in African American CRC incidence and mortality. As the importance of regular screening has been well-established, future endeavors should include public health emphasis on increasing CRC screening among African Americans through increasing awareness and education, promoting physician recommendations, addressing barriers to screening, and working to make screening more affordable and available to low-resource populations. Similarly, significant efforts must be made to reduce and ultimately remove racial disparities in treatment and access to care. This work should include educating the medical community about such disparities to raise awareness and promote equal treatment in the health care setting as well as lobbying for improved health policies to provide necessary and equitable access to care for minorities.

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