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Race in Cancer Health Disparities Theme Issue

REVIEW

Colorectal Cancer Disparity in African Americans

Risk Factors and Carcinogenic Mechanisms

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African Americans have the highest incidence and mortality rates of colorectal cancer (CRC) of any ethnic group in the United States. Although some of these disparities can be explained by differences in access to care, cancer screening, and other socioeconomic factors, disparities remain after adjustment for these factors. Consequently, an examination of recent advances in the understanding of ethnicity-specific factors, including genetic and environmental factors relating to risk of CRC, the biology of CRC progression, and the changes in screening and mortality, is important for evaluating our progress toward eliminating the disparities. An overarching limitation in this field is the number and sample size of studies performed to characterize the etiological bases of CRC incidence and mortality in African Americans. Despite this limitation, significant differences in etiology are manifest in many studies. These differences need validation, and their impacts on disparities need more detailed investigation. Perhaps most heartening, improvements in CRC screening can be attributed to the smallest difference in CRC incidence between African Americans and whites since the late 1980s. Cancer mortality, however, remains a persistent difference. *(Am J Pathol 2017, ■: 1–13; https://doi.org/10.1016/j.ajpath.2017.07.023)*

Colorectal cancer (CRC) is the third most common cancer in both men and women in the United States and the second most common cause of cancer-related death.[1] African Americans bear a disproportionate burden, with an incidence of CRC that is >20% higher than in whites and an even larger difference in mortality.[2] In particular, African Americans are more often diagnosed with CRC at an earlier age and with more advanced disease; and African Americans have a greater proportion of CRCs in the proximal colon.[3] Although some of these differences can be explained by access to care, screening, and other socioeconomic factors, a significant portion of the disparity remains after adjustment for these factors.[4] In this review, we examine the recent literature on genetic and environmental risk factors, molecular characteristics of CRC tumors, screening, and cancer-related mortality, and how these factors contribute to our understanding of the cancer health disparity in African Americans.

Impact of Risk Factors on CRC Incidence

Endoscopic Screening Reduces Cancer Incidence

Data from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute [Incidence—Surveillance, Epidemiology, and End Results 9 Regs Research Data, November 2016 Sub (1973 to 2014) <Katrina/Rita Population Adjustment>; *https://seer.cancer.gov/data/seerstat/nov2016*] show that CRC incidence has been decreasing in recent years (Figure 1A). The change in CRC

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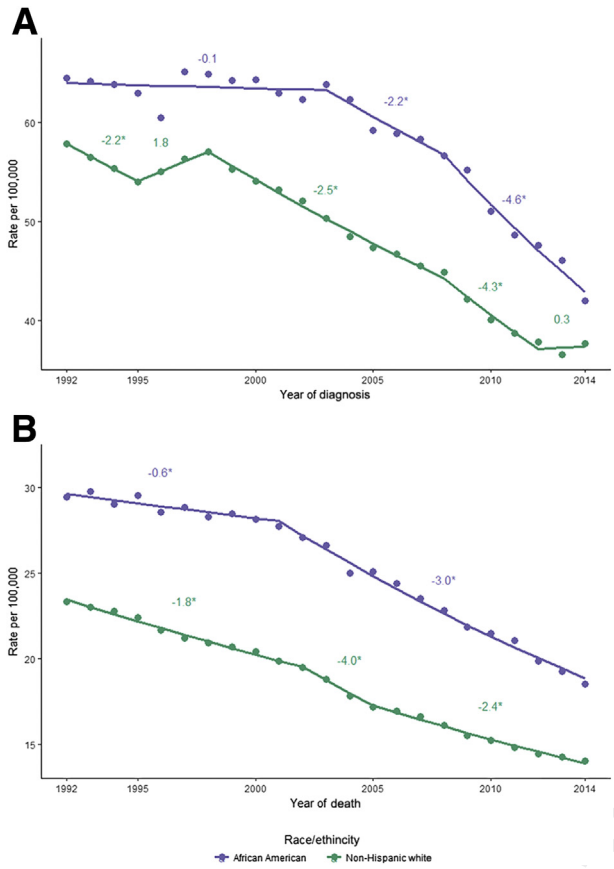

Figure 1 **A:** Age-adjusted incidence rates of colorectal cancer (CRC) in African Americans (purple) and whites (green; explicitly non-Hispanic whites) from 1992 to 2014, all ages, both sexes [data from Surveillance, Epidemiology, and End Results (SEER) 13, Incidence—SEER 13 Regs Research Data, November 2016 Sub (1992 to 2014) <Katrina/Rita Population Adjustment>; *https://seer.cancer.gov/data/seerstat/nov2016*]. Annual percentage change is depicted as text above data, where negative values indicate a decreasing trend and positive values indicate an increasing trend. Values between -2 and 2 are considered stable trends. **B:** Age-adjusted US mortality rates of CRC in African Americans (purple) and whites (green; explicitly non-Hispanic whites) from 1992 to 2014, all ages, both sexes (data from SEER 13). Annual percentage change is depicted as text above data, where negative values indicate a decreasing trend.

incidence is mostly attributed to increased endoscopic examination of the colorectum and the resulting removal of adenomatous and other polyps that are precancerous lesions.[1] The Surveillance, Epidemiology, and End Results program also reports trends that reflect annual percentage change of rates across certain time segments, which we have included above each corresponding segment. Whites have seen a decrease in CRC incidence since the 1990s. The incidence of CRC in African Americans began to decrease in the early 2000s. The incidence in the United States of CRC in African Americans was 26% higher than whites in 2013. The newest data from the Surveillance, Epidemiology, and End Results program show that African Americans have an 11% higher incidence than whites, the lowest difference since the late 1980s. Although screening has clearly achieved substantial reductions in incidence, less than full compliance, early-onset CRCs, and missed lesions will resist further reductions; therefore, efforts to understand genetic and environmental risk factors continue to be important.

The increased risk of disease and cancer-related death in African Americans has led to changes in the screening recommendations in this population, specifically in lowering the age to begin colonoscopic screening to 45 years.[5–7] Historically, African Americans have had lower compliance to CRC screening guidelines. Efforts to increase screening have resulted in an increase in compliance, which has been reviewed elsewhere.[8] Increased colonoscopic screening in African Americans has been cited as a major reason for the recent decrease in incidence in this population[2] (Figure 1A).

Continued efforts to increase knowledge of new screening guidelines in African American communities are necessary. In addition, because patient follow-up is lower in African Americans after an abnormality is found, community-based support programs should be developed to improve follow-up rates.[9] More important, access to screening options and affordable care are essential to decrease the burden of CRC faced by African Americans, and these barriers must be addressed by communities across the country.[5]

Genetic Risk Factors and CRC Incidence

It is estimated that genetic factors contribute as much as 35% to the overall risk of CRC.[10] Our understanding of genetic risk factors is anchored in mendelian genetics (ie, in single-gene defects that are associated with a high risk of CRC development).[11] Mutations in the adenomatous polyposis coli (*APC*) gene are linked to familial adenomatous polyposis. *APC* mutations ablate a key factor in the regulation of the WNT signaling pathway (Figure 2). WNTs are a large family of secreted glycoproteins that regulate cell proliferation, differentiation, polarity, and migration.[12] In the adult intestine, WNTs control homeostasis by maintaining stem cell populations in the base of the crypts. In the canonical WNT signaling cascade, WNT stimulation prevents degradation of the transcription factor β-catenin by inhibition of the destruction complex. The destruction complex consists of the APC protein, axis inhibition protein, glycogen synthase kinase 3, and casein kinase 1 isoforms. In the absence of WNT, the complex mediates the phosphorylation of β-catenin, which targets β-catenin to the proteasome. In the presence of WNT, β-catenin degradation is inhibited; and it migrates into the nucleus, where it mediates the transcriptional activation of genes, such as *MYC* and cyclin D1. Biallelic mutation of *APC* is associated with failure to down-regulate β-catenin, causing overexpansion of the stem cell compartment and the development of an adenomatous polyp. Over time, adenomatous polyps can progress to carcinoma as other cancer driver mutations in genes, such as *KRAS*, *SMADs*, and *TP53*, arise in the polyp. Familial adenomatous polyposis is a classic autosomal dominant condition in which individuals inherit a mutation