Published in final edited form as:

Gastroenterology. 2020 January ; 158(2): 354–367. doi:10.1053/j.gastro.2019.10.029.

Causes of Socioeconomic Disparities in Colorectal Cancer and Intervention Framework and Strategies

John M. Carethers¹, Chyke A. Doubeni^{2,3}

¹Division of Gastroenterology, Department of Internal Medicine, Department of Human Genetics and Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan

²Center for Health Equity and Community Engagement Research, Mayo Clinic, Rochester, MN

³Department of Family Medicine, Mayo Clinic, Rochester, MN

Abstract

Colorectal cancer (CRC) disproportionately affects people from low socioeconomic backgrounds and some racial minorities. Disparities in CRC incidence and outcomes might result from differences in exposure to risk factors such as unhealthy diet and sedentary lifestyle; limited access to risk-reducing behaviors such as chemoprevention, screening, and follow up of abnormal test results; or lack of access to high-quality treatment resources. These factors operate at the individual, provider, health system, community, and policy levels to perpetuate CRC disparities. However, CRC disparities can be eliminated. Addressing the complex factors that contribute to development and progression of CRC with multicomponent, adaptive interventions, at multiple levels of the care continuum, can reduce gaps in mortality. These might be addressed with a combination of healthcare and community-based interventions and policy changes that promote healthy behaviors and ensure access to high-quality and effective measures for CRC prevention, diagnosis, and treatment. Improving resources and coordinating efforts in communities where people of low-socioeconomic status live and work would increase access to evidence-based interventions. Research is also needed to understand the role and potential mechanisms by which factors in diet, intestinal microbiome, and/or inflammation contribute to differences in colorectal carcinogenesis. Studies of large cohorts with diverse populations are needed to identify epidemiologic and molecular factors that contribute to CRC development in different populations.

Keywords

cancer disparity; cancer disparity interventions; racial disparity; cancer epidemiology

Correspondence: John M. Carethers, M.D., Division of Gastroenterology, Department of Internal Medicine, University of Michigan, 3100 Taubman Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5368, TEL: 734-615-1717, FAX: 734-615-2645, address: jcarethe@umich.edu.

Author Contributions: JMC and CAD contributed equally to the concept, writing, and editing of this manuscript.

Disclosure of Potential Conflicts of Interest: No potential conflicts of interest are disclosed.

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Colorectal cancer (CRC) is the second leading cause of cancer death in the United States (US), but its distribution within the population varies among racial and ethnic groups. Among both men and women, African Americans (AAs) have the highest incidence of CRC. Similarly, for both sexes combined, the CRC mortality rate is highest in AAs, followed by American Indians/Alaskan Natives (AI/AN), Non-Hispanic whites (NHWs), Hispanics, and Asians/Pacific Islanders (APIs).^{1,2} Data indicate that the incidence disparity begins earlier than the typical age for CRC screening, with AAs having higher CRC incidence rates (7.9/100,000) than NHWs (6.7/100,000) and APIs (6.3/100,000) between the ages of 20 years and 44 years.^{3,4} Overall trends for CRC death have decreased among AAs and NHWs during the past 25 years with relatively unchanged mortality disparity in AAs.⁵ AAs present with a higher percentage of CRCs at distant stage than NHWs, and overall AA survival rates are 7% less than NHWs (58% vs 65% 5-year survival).¹ AAs also have lower 5-year survival compared with NHWs for localized disease (86% vs 90%), regional disease (65% vs 72%) and distant disease (10% vs 14%).¹

Many factors have been identified that affect risk of CRC development, including age and genetic risk factors.^{6–8} CRC is an age-related disease, so risk increases with patient age—guidelines recommend that average-risk individuals initiate screening at age 50 years.⁶ The relationships between socioeconomic status (SES) and race/ethnicity with CRC are, however, complex.^{8,9} Modifiable factors associated with CRC risk are also associated with SES, including unhealthy diets and sedentary lifestyle. Lifestyle factors may affect the local colonic environment including the microbiome and colonic stem cell biological behavior. Healthy dietary patterns, such as those conforming to the Mediterranean diet, use of hormone therapy, and use of aspirin or non-steroidal anti-inflammatory drugs, might reduce CRC risk;⁸ exposure to such factors may also be related to SES and healthcare access. SES-related factors such as income, education level, and healthcare insurance affect access to health services and resources.⁸ We explore the inter-relatedness of risk factors for CRC and strategies for intervention.

Socioeconomic Features of CRC Disparities

SES is one of the strongest and most consistent predictors of health, overall disease burden, and premature death. One study found larger socioeconomic disparities in risk for overall mortality among healthy people than in people with poor self-rated health.¹⁰ CRC outcomes are also socioeconomically patterned. People with low SES have poorer outcomes throughout the entire CRC care continuum, with reasons ranging from differences in risk factors (such as dietary and other behavioral factors)^{11,12} to screening participation and treatment.^{13–16} Disparities tend to be more apparent in situations in which there is a high potential for improving outcomes, such as for patients with early-stage,¹⁷ rather than late-stage, CRC.

People with low SES have higher rates of incidence for CRC.^{13,17} In a study of the NIH-AARP cohort, comprising more than 500,000 participants, individual-level and area-based socioeconomic measures were independently associated with risk of diagnosis with CRC. Residents of the most deprived neighborhoods (defined by census tract) had a 31% higher risk of CRC diagnosis than residents of the most affluent quartile, after adjustments for age,

sex, race and ethnicity, family history of CRC in a first-degree relative, and state of residence.¹³ There was a 16% increase in risk after further adjustments for behavior risk factors (such as diet, physical activity, or obesity) and individual-level education. Analysis on individual levels found a 42% higher risk of CRC diagnosis in people with fewer than 12 years of education compared to people with post-graduate education. The risk was 19% higher after further adjustment for neighborhood deprivation.¹³ Among patients with a diagnosis of CRC, rates of survival vary among geographic area and SES.¹⁵

One manifestation of the effects of SES is clustering of CRC risk in areas with concentrated social disadvantage.^{18,19} States and counties in the US with high social disadvantage, such as high poverty rates and low education levels, generally have higher CRC incidence and mortality, including well-documented geographic hotspots (Figure 1A).^{18,19} One example is the CRC mortality hotspot in the Mississippi River Delta area, which encompasses 94 counties in Arkansas, Illinois, Kentucky, Louisiana, Mississippi, Missouri, and Tennessee.¹⁹ Based on 2009–2011 rates, persons in the lower Mississippi delta hotspot have a 40% higher risk of CRC death than in non-hotspot areas of the US, and the incidence rate in AAs did not decrease over time period as it did for whites.¹⁹

Another manifestation of socioeconomic disadvantage is in racial/ethnic disparities. For decades, AAs have remained the group with the highest incidence and mortality rate from CRC than any other racial or ethnic group. In studies at integrated delivery systems, where there may be fewer barriers to healthcare service, AAs were more likely to be diagnosed at late-stage and also have lower CRC survival, with a statistically significant difference that remained even after accounting for differences in tumor stage.²⁰

The age-adjusted overall incidence of CRC in AAs was 55.2 per 100,000 in males and 40.7 per 100,000 in females, and mortality rate was 24.4 per 100,000 in men and 16.0 per 100,000, in women. For other racial/ethnic groups, mortality from CRC for both sexes combined range from 15.9 per 100,000 in AI/NA, 14.0 per 100,000 in NHWs, 11.2 per 100,000 in Hispanics, and 9.9 per 100,000 in APIs.¹

Data from the Surveillance, Epidemiology, and End Results (SEER) Program for 2015 show that the age-adjusted incidence of CRC in men 50 years and older was 171.6/100,000 in AAs, 143.3/100,000 in AI/NA, 134.2/100,000 in NHWs, 125.5/100,000 in Hispanics, and 113.3/100,000 in API (Figure 1B).²¹ For women, the age-adjusted incidence rate was 119.6/100,000 in AAs, 127.3/100,000 in American Indians/Alaskan Natives, 101.0/100,000 NHWs, 86.2/100,000 in Hispanics, and 82.6/100,000 in APIs (Figure 1B). Among US men 65–74 years old, the age-adjusted CRC mortality rate was 87.0/100,000 persons per year for AAs compared with 38.8/100,000 in APIs. Similarly, among women 65–74 years old, the mortality for AAs and API were 52.3/100,000 and 23.7/100,000, respectively (Figure 1C).²¹ AA men or women therefore have a more than 2-fold higher CRC mortality than APIs, with similar differences observed for people 50–64 years old (men: AA=37.1/100,000 vs 15.5/100,000 in APIs and women: AA=23.5/100,000 vs 11.7/100,000 in APIs).²¹

Explanations for Socioeconomic Disparities in CRC

Evidence from observational and experimental studies offer plausible explanations for SES disparities and could provide guidance for interventions. Socioeconomic measures are related to social determinants of health—conditions people are exposed to during their life course that are shaped by the distribution of money, power, and resources.^{22,23} Within that context, the relation of SES to health outcomes can be conceptualized as the social or economic position of individuals or populations that affect exposure to health risks and access to healthful behaviors and healthcare resources, or affect self-management ability. Socioeconomic measures used in research typically assess individual or community ranking based on social, education, and economic measures and therefore include race and ethnicity because of its social construction. Because of the challenges of collecting individual-level data, many measures in common use are based on geography, at varying levels of aggregation from countries or states to neighborhoods. Frequently, especially in the context of area-based socioeconomic variables, multiple measures (such as education and home value) are summarized as indices.^{10,24}

Well-documented socioeconomic gradients are consistent with their conceptualization as markers of increased exposure to risk factors, reduced access to evidence-based preventive and treatment interventions, and decreased ability of individuals to adhere to effective therapy. Although not empirically tested in research studies, documentation of disparities throughout the continuum of CRC care from risk factors to screening and survival lend support to the premise that disparities in CRC health outcomes are the result of cumulated inequalities along the continuum of CRC care and along the life course, not just a single event at a single time point. The continuum of CRC care ranges from unhealthy health behaviors,¹¹ to preventive and early detection interventions such as screening,^{14,25} to treatment and surveillance.²⁶

Screening is a well-established intervention for reducing risk of death from CRC, so being up to date on screening substantially reduces risk of death from CRC.^{27–30} People from low-income or lower-education backgrounds are less likely to undergo screening than people from high-income or high-education backgrounds.^{14,31} Modeling studies that used data from the 2008 National Health Interview Survey showed that differences in uptake of screening account for 42% of the disparity between AAs and whites in CRC incidence and 19% of the difference in mortality.³² People of low SES are more likely to have economic and structural barriers to health care including having a usual source of care. Uptake of screening varies among people of different SESs. A study of data from the Medicare Beneficiary Survey found large gaps in uptake of screening by race/ethnicity and educational status—there were large gaps according to annual income (less than \$10,000 vs more than \$40,000) in 2000 and 2005.¹⁴ In a separate analysis of data from the Medicare Beneficiary Survey, patients without supplemental insurance had lower rates of screening in 2005 than in 2000 in people with supplemental insurance (5 years earlier).²⁵ People of low SES are less likely to have supplemental insurance;³³ a lack of supplemental insurance is a barrier to CRC screening in Medicare beneficiaries.^{34,35}

Therefore, access to health care services or resources might contribute to CRC disparities.²⁶ Having a usual source of care and receiving a provider recommendation to screen are 2 of

the strongest correlates to screening uptake, in part because most healthcare systems in the US rely on face to face office visits for screening delivery. People who reported that their provider had discussed CRC screening with them were more likely to be up to date on screening than those who did not report such as discussion.³⁶

The quality of screening varies among people of different SESs. In a study of the SEER-Medicare database, Fedewa et al found that AAs had a higher overall risk of interval CRCs. The disparity was most apparent in the highest quartiles for colonoscopy quality, measured by polyp detection rate—AAs were more likely to receive their colonoscopy from providers in the lower polyp-detection quartiles.¹⁷ Therefore, access and quality of CRC care each contribute to disparities.²⁶ These findings indicate the potential to reduce socioeconomic disparities in CRC outcomes via improvements in healthcare settings.

Features of CRC That Associate With Disparities

There are few data on racial/ethnic differences in molecular features of colorectal tumors because most published studies come from cohorts of almost exclusively NHW patients.³⁷ Only recently have publications addressed potentially differentiating factors.³⁸

Adenomas are the direct precursors to most CRCs, with advanced adenomas the most proximate to CRC onset.^{39,40} Studies of adenomas might therefore provide insight to the mechanisms of CRC disparities and potential interventions. As for CRC, some studies have reported a higher prevalence of advanced adenomas among AAs compared with NHWs, overall (7.7% vs 6.2%), and higher ratios of advanced adenomas at every 5-year age interval older than 50 years.^{41,42} Additionally, AAs have higher prevalence (7%–15%) of proximal (right-sided) colorectal tumors than NHWs.⁴³ The distribution of advanced adenomas parallel observations for proximal CRCs in AAs. In 2 studies, AAs had 1.26-fold and 1.15-fold higher incidence of proximal advanced adenomas than NHWs.^{41,43} With observations that screening may be less effective in reducing mortality from proximal than for distal CRC,^{44–46} a higher prevalence of proximal lesions, which are harder to detect, could amplify the magnitude of the disparity for AAs.^{8,9} There is no strong evidence that sessile serrated adenomas, one of the highest-risk precursor lesions, are more prevalent in AAs than in NHWs. One study found that 0.3% of all colon lesions in AAs were sessile serrated polyps or adenomas, vs 0.2% in NHWs,⁴⁷ but no large comparative study has been conducted. Analyses of serrated adenomas from a large AA cohort with more than 10,000 colonoscopies reported a prevalence rate of 2.5% and more often distal location.⁴⁸ In these serrated adenomas, 56% had the BRAF^{V600E} mutation and 25% had the CpG island methylator phenotype. The serrated adenomas also expressed higher levels of *MUC6* (12.9-fold), *SEMG1* (10.7-fold), and *TRNP1* (5.8-fold) than non-involved colon.⁴⁸

It is not clear whether genetic differences in colorectal tumors that vary among races or ethnicities can be used to select treatment or predict disease progression. Aside from founder mutations such as APC I1307K associated with the Ashkenazis, there is no evidence that germline genetic variants associated with AAs or other specific racial/ethnic groups affect risk of adenomatous polyposis syndromes (such as familial adenomatous polyposis, MYH-associated polyposis, polymerase proofreading polyposis, Lynch syndrome, or familial CRC

type X).^{7,49} Within a cohort of AAs with Lynch syndrome, two-thirds of families had a mutation in *MLH1* that affected risk for CRC similar to that of NHWs with Lynch syndrome.⁵⁰ There were multiple variants in *MLH1* in the AA Lynch syndrome families that were not in Lynch syndrome mutation databases, so there could be racial or ethnic differences in *MLH1* polymorphisms.⁵⁰

Somatic analyses of colorectal tumors have identified mutations that are specific to tumors from AAs that might contribute to carcinogenesis (Table 1). Whole exome sequencing of 103 AA and 129 NHW CRCs found three mutated genes that were exclusive to AA CRCs: *EPHA6* (mutational frequency 5.83%), *FLCN* (mutational frequency 2.91%), and *HTRIF* (mutational frequency of 2.91%).³⁸ More extensive examination of mutated *EPHA6* found missense and splice site mutations, and mutated *FLCN* showed frameshifts and non-sense mutations, indicating that these AA CRC somatic mutations were deleterious.³⁸ At present, it is not clear if these potential driver genes in AA CRCs contribute to CRC disparity. Additional somatic findings that are found among AA CRCs include: (a) higher frequency of *KRAS* mutations that make CRCs have a more aggressive behavior, and (b) lower frequency of *APC* mutations that are substituted with higher frequency of methylation of genes that regulate the Wnt signaling pathways.^{51,52}

Colorectal tumors have a high frequency of microsatellite instability (MSI-H), a marker of defective DNA mismatch repair typically. This is usually caused by hypermethylation of the *MLH1* promoter. Patients whose tumors are MSI-H have longer survival times than patients whose tumors are not.^{39,40} In a population-based study of 503 patients with CRC, of which 45% were AA, 14% of tumors from NHWs were MSI-H compared with 7% of tumors from AA.⁵³ A meta-analysis found that the odds ratio for frequency of MSI-H in colorectal tumors from AAs was 0.78 compared with tumors from NHWs. However, this difference was not statistically significant, due in part to the small number studies and small sample sizes.⁵⁴ Because of the longer survival times of patients with MSI-H tumors, groups with lower frequencies of MSI-H tumors would have shorter overall survival times. Furthermore, checkpoint inhibitor therapies are effective against only MSI-H colorectal tumors, so patients without MSI-H tumors are not candidates for this treatment.⁵⁵

Inflammation-associated microsatellite alterations, also called elevated microsatellite alterations at selected tetranucleotide repeats (EMAST), differ in frequency between tumors of AAs vs NHWs.^{56–58} EMAST is induced by inflammation and interleukin 6 (IL6) signaling, which could be a consequence of alterations to the intestinal microbiome, including the presence of *F nucleatum*.⁵⁹ Patients with tumors with EMAST have shorter survival times than patients whose tumors do not have EMAST.^{56–60} In a population-based cohort study of more than 160 patients, 49% of rectal tumors in AAs had EMAST compared with 26% of tumors in NHWs.⁵⁸ Increased inflammation-associated microsatellite alterations in rectal tumors of AAs might therefore contribute to disparities in outcomes. Strategies to reduce levels of inflammation, through diet or other interventions, might improve outcomes of AAs with CRC.

Immune surveillance of colorectal tumors also affects patient outcomes. The presence of CD8⁺ and granzyme B⁺ cytotoxic T cells, as well as CD45RO⁺ memory T cells in tumors,

associate with outcome.^{61,62} MSI-H colorectal tumors, in particular, activate a CD8⁺ T-cell mediated immune response and CD45RO⁺ memory T cells—the increased number of genetic alterations in tumor cells leads to production of neoantigens, which are immunogenic.^{40,55,62} Because AAs have a lower frequency of tumors with MSI-H, they are less likely to activate an anti-tumor immune response or respond to immune checkpoint therapy.⁵⁵ Comparative analysis of intraepithelial CD8⁺ T cells in colorectal tumors from AAs vs NHWs found that AA MSI-H colorectal tumors did not contain a high number of CD8⁺ T cells, indicating a subtle defect in immune surveillance.⁵³ In an analysis of 250 microsatellite-stable colorectal tumors from a population-based cohort, tumors from AAs had reduced intraepithelial and intra-tumor granzyme B⁺ cytotoxic T cells compared to tumors from NHWs.⁶³ The fewer cytotoxic T cells in colorectal tumors in AAs might contribute to observed disparities in outcome.

Another factor that might contribute to disparities in CRC incidence is the association between antibodies against *Helicobacter pylori* in serum and CRC (in addition to gastric cancer). In a comparison of 4063 incident cases of CRC (41% with a positive result from a serologic test for *H pylori* VacA) and 4063 matched individuals without CRC (40% with a positive result), detection of *H pylori* VacA in serum increased odds of CRC by 11%.⁶⁴ However, in AAs, a positive result from the serologic test was associated with a 45% increase in risk of CRC.⁶⁴ Further studies are needed to determine how *H pylori* infection might increase risk of CRC in AAs to a greater extent than in NHWs.

Diet, the Intestinal Microbiome, and CRC Disparities

Interactions between diet and the intestinal microbiome might contribute to CRC disparities. There is increasing evidence that diet and composition of the intestinal microbiome affect risk of adenoma and CRC.^{8,65–67} Adenomas develop from aberrant crypt foci, which are the earliest detectable neoplastic growths in the colon.^{39,40} They are presumed to result from local environmental effects on stem cells within colonic crypts, which induce mutations and neoplasia via alterations in the Wnt signaling pathway.^{39,40} Bacteria that produce hydrogen sulfide induce inflammation and hyperproliferation of cells that are more abundant in non-tumor colon tissues of AA patients with CRC compared with NHW patients.⁶⁶ Other inflammatory bacteria, such as *Fusobacterium nucleatum* and *Enterobacter* species, are found in significantly higher proportions of colon tissues from AAs compared with NHW, based on samples collected during screening colonoscopy.⁶⁷ *F nucleatum* has been associated with biofilms on advanced adenomas and proximal colorectal tumors; individuals have a 5-fold higher risk of CRC when a biofilm is present.⁶⁵ These biofilms can induce IL6 signaling via STAT3 and proliferation in human colonic crypts.⁶⁵

A dietary swap experiment showed that dietary factors affect the colon environment. A 2-week diet swap between AAs who were on a typical high-fat, low-fiber Western diet and rural Africans (who typically have a high-fiber, low-fat African-style diet) produced marked changes in colon mucosa biopsies.⁶⁸ Compared to pre-diet biopsies, post-swap biopsies had reciprocal changes in biomarkers; AAs who switched to the African-style diet had 50% lower crypt proliferation and reduced intraepithelial lymphocyte infiltration, whereas rural Africans who switched to the Western diet had signs of crypt proliferation with increased

epithelial inflammation.⁶⁸ Butyrate, generated by intestinal microbes, is a short-chain fatty acid that is a normal fuel molecule for colonocytes. Levels of butyrate increased in the colons of AAs when they switched to the African-style diet, whereas levels of deoxycholic acid, a secondary bile acid associated with carcinogenesis, decreased.⁶⁸ The reverse was observed in colons of Africans who switched to the Western diet.⁶⁸ Such effects of the Western diet, over a lifetime, could increase mutations in colon stem cells along with cell proliferation and inflammation, providing a mechanism for the observed epidemiologic association between unhealthy diet and CRC risk.⁸ Populations at increased risk for CRC, such as AAs, might be able to reduce their risk via long-term changes in diet.

Interventions

Strategies to reduce disparities in CRC incidence and mortality should aim to reduce risk of CRC and improve detection and treatment. Interventions have generally focused on increasing access to existing health services. However, less attention has been paid to improving community resources as an essential component of enabling access to evidence-based interventions (EBI) for CRC health promotion, screening, diagnosis, and treatment.

EBIs to improve screening participation can reduce or eliminate CRC disparities, but the effectiveness of other strategies, such as dietary interventions and chemoprevention, have to be extrapolated from epidemiology or experimental studies. However, evidence is limited on whether genetic factors associated with CRC risk or mortality in low-SES groups are also involved. Applying health equity principles therefore offers a tangible and practical approach for eliminating CRC disparities. Health equity principles involve facilitating access and removing barriers to effective interventions throughout the CRC care continuum, from prevention, to early detection, to high-quality treatment and survivorship care. We discuss behavioral, chemoprevention, and screening interventions.

Guiding integrated framework to eliminate disparities

We propose a framework for eliminating CRC disparities that combines population health with community-based (such as increasing demand, capacity, or resources) and policy-based interventions. This integrated cross-sector approach applies principles of health equity and social determinants of health as well as relevant behavioral, systems and ecological theories. The approach advances multilevel, multi-component interventions for patients, healthcare teams, and delivery systems and addresses the needs of people who do not make regular healthcare visits or use a usual place for routine care. The approach also addresses the need for capacity in communities where low-income people live or receive their care (Figure 2). Healthcare-based interventions involve multicomponent population-based approaches to enhance delivery of preventive interventions. We propose a dual approach, combining population-based outreach with office visit-based strategies. These require delivery of interventions to all reasonable contacts of healthcare systems or facilities (visit-based), in addition to using population-based outreach to people who do not have upcoming visits or missed opportunities during prior encounters (Figure 2). To increase the reach of interventions, community outreach and community-based programs may aim to improve

resources. Finally, policies are set in place to remove barriers and promote uptake of preventive EBIs.

The application of this framework to CRC draws on experiences at longstanding screening programs that pair system-wide population-based outreach with screening delivery at every feasible patient contact (including pharmacies and dental settings) through practice transformation and health information technology tools.^{69–71} Electronic health record (EHR) systems with automated monitoring of screening status and completion of follow up are used to optimize workflows and improve communication and teamwork. It therefore involves interconnected strategies, each serving as a safety net for others, to mitigate multiple barriers and is broadly applicable to many preventive interventions. However, barriers to information sharing in communities provide substantial hurdles that may be mitigated with health information exchanges, to share key preventive or screening information in real-time or through registries with linkage to individual patient records in individual EHR systems. Policies or programs to eliminate EHR system fragmentation or silos will increase risk assessment and enable applicability of the approach in broad community settings (Figure 2).

Behavioral and chemoprevention interventions to reduce risk for CRC

Evidence on the effectiveness of lifestyle and chemopreventive interventions for elimination of CRC health disparities is limited. There is however considerable empirical evidence on the benefits of such interventions for indirect support in the context of addressing health disparities in populations of low SES.^{72,73} One study estimated the population attributable risk percent for CRC from lifestyle factors in men to be as high as 70%.⁷⁴ Evidence shows that dietary patterns affect gut microbiome, level of intestinal inflammation, and the ability to mount adequate immune responses (and thus affect CRC outcomes) (Figure 3). However, interventions focused on dietary change remain challenging to implement broadly and evidence on long-term impact is limited.⁸ Further, many of the effective interventions, such as for weight loss, require intensive multicomponent strategies that may be challenging to implement in primary care and less accessible to people of low SES.⁷³

Studies consistently show that dietary patterns, such as those conforming to Mediterranean diets, may reduce risk for CRC and other chronic diseases.¹² Dietary patterns vary according to SES, physical environment, and the types of food available (Figure 3). Given the broad range of potential health benefits, successful interventions for populations of low SES to achieve and maintain healthy dietary patterns and recommended levels of physical activity is crucial and may have a multitude of benefits, including affecting the biology of the colon. Lifestyle interventions would ideally be provided through fully integrated behavioral health services and options exist for referral to a variety of programs in many communities⁷⁴, in addition to policy options.⁷⁵ Another potential area for intervention is chemoprevention, including USPSTF recommended aspirin use to prevent to CRC,⁷⁶ but evidence is limited on whether there are differences in uptake of chemopreventive therapies that contribute to SES or racial/ethnic disparities in CRC outcomes. However, broad increase in participation in screening for CRC might mitigate socioeconomic and racial/ethnic disparities in CRC mortality regardless of underlying behavioral risk factors.^{72,77}

Healthcare-based interventions in the screening continuum

Interventions to improve screening participation to address CRC disparities are developing rapidly. There are many national programs to increase screening, such as those from the National Colorectal Cancer Roundtable and US Department of Health and Human Services, including the National Institutes of Health, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, and Health Resources and Services Administration. These efforts are supported by screening recommendations by the USPSTF (Grade A)⁷⁸ and Community Preventive Services Task Force,^{79–81} as well as performance measures endorsed by the National Committee for Quality Assurance. Their benchmarks for improving CRC screening uptake are tracked by providers, health systems, and health insurers. Rates of CRC screening are required to be reported in the Uniform Data System, by federally qualified health centers, to the Health Resources and Services Administration. These reporting requirements provide incentives to increase delivery of screening.^{82,83} However, there is substantial variation nationwide in screening rates, with particularly low rates in low-income communities.^{84,85} A health equity-based framework might enable access to EBIs to reduce variations in screening uptake across populations and communities.

Many effective interventions increase community demand and provider delivery of CRC screening (as recommended by the Community Preventive Services Task Force). Many interventions apply or can be mapped to behavioral theories. Interventions such as reminders, incentives, use of small media and mass media, and education increase patient awareness and knowledge.⁸⁶ Recent studies have addressed challenges of delivering preventive services relating to the immediate costs. Because of benefits cannot be determined until the future, there is no certainty that CRC-related fatalities are averted for any individual. In contrast to the intangible benefits, failures of screening are tangible. Those countervailing factors may lead to inertia and a potential for screening to be deprioritized in favor of more immediate competing needs. Such influences on CRC screening are being addressed in recent studies by applying behavioral economic principles. However, studies testing the effect of financial incentives to overcome present-time or status quo bias have shown inconsistent results,^{87,88} and the implementation of such incentives is unclear. In adequately resourced settings, providing choice in screening may promote uptake,⁸⁹ but studies of choice architecture have also shown inconsistent results.⁹⁰ However, having clinical workflows that promote delivery of CRC screening as the default using an opt-out approach has been shown to increase uptake (Figure 4).⁹⁰

A key intervention strategy for advancing CRC health equity is to eliminate barriers to screening, which was an goal of Affordable Care Act provisions.⁹¹ Persons of low SES might benefit the most from removing economic barriers such as out of pocket costs or co-payments, as well as structural barriers to all steps in the screening process. Although the evidence on cost-sharing is less consistent, there is strong evidence that navigation to overcome structural barriers is effective and should be considered essential to the delivery of CRC screening.^{92,93} Navigation models are, however, heterogeneous, and the cost and feasibility of implementation (such as budget impact) are unclear, which hinders widespread adoption to support CRC screening. It may be impractical to support stand-alone navigators that are dedicated to CRC screening alone, and 1 size does not fit all. Patients' needs can

range from written instructions, to telephone support, to direct 1 on 1 support. Navigation services can also be provided by a variety of healthcare workers, including community health workers, with various levels of training and experience. Thus, an alternative strategy is to design navigation services to address multiple services – healthcare delivery systems generally integrate elements of navigation services to help people get to an appointment, find directions, and provide testing instructions.

Other healthcare team-based interventions aim to promote discussion, recommendations, and delivery of screening. Examples include the use of incentives, reminders, and EHR prompts to set up offer of screening as a default (Figure 4).^{94,95} Social theories are leveraged in audit and feedback of provider performance compared to quality of care targets and/or to peers. Although typically conceptualized as provider-based interventions, they should however aim to involve the healthcare team. Combining such interventions with direct outreach to patients might overcome the limitation that healthcare-based interventions are less effective for people who do not have regular office visits or have competing medical needs that detract from screening.⁹⁶ For example, the use of mailed outreach for fecal immunochemical tests uses the endowment effect from behavioral economics.

Interventions such as mailed outreach, reminders, audit and feedback, and navigation produce only modest increases in screening participation when used individually (15% or lower in minority populations). Multi-component interventions are more effective at improving the delivery of screening than single component interventions, in part, because they address multiple barriers.^{80, 97–99} One such strategy is use of mailed outreach for fecal immunochemical testing, coupled with navigation or support, reminders, tracking systems to identify completion and screening status, and systems for communicating with patients and providers. Integrated approaches, such as adaptations made by highly successful programs in Kaiser Permanente in Northern and Southern California, are therefore necessary to mitigate barriers.^{100,101}

Community resources and community-based interventions

Creating linkages between healthcare-based intervention and community resources is important for reducing CRC disparities.^{102,103} One reason for the difference between persons of high vs low SES could be the paucity of resources in communities that serve people of disadvantaged backgrounds to deliver CRC screening or timely follow up. A facilitation program supported by the Centers for Disease Control and Prevention reported a 5.4% higher CRC screening participation rate 1 year after the intervention, compared with baseline, but increases were smaller in clinics with small numbers of eligible patients or high numbers of uninsured patients.¹⁰³ This indicates that clinic capacity and patient factors can each influence success, and highlights the need to increase our understanding of resources needs in areas where patients of low SES patients receive care.

People from low-socioeconomic backgrounds are more likely to receive care in under-resourced healthcare settings such as community health centers or have limited or no access to colonoscopy.^{104–106} Colonoscopy detects adenomas with high levels of sensitivity (50%–95%), as well as CRC (75%–95% specificity),¹⁰⁷ and allows for evaluation of detected lesions at the time of screening, without the need for an additional test. The infrequent

screening interval might be advantageous to patients from underserved backgrounds who have frequent changes in contact information and/or insurance. Despite the essential role for primary screening or follow-up testing for patients who receive an abnormal result from a non-colonoscopy test, access to colonoscopy is frequently a challenge to implementation of screening.^{104–106} It is therefore important to evaluate local resources in developing screening programs.

Addressing policy barriers

It is important to continue to push for legislative action to remove barriers posed by coinsurance requirements for people with Medicare insurance, to enable receipt of colonoscopy for screening and follow-up testing.³⁴ Despite the USPSTF Grade A recommendation that enables coverage without cost-sharing under Affordable Care Act, 91,107 provisions of the Balance Budget Act of 1997 prevent Medicare from waiving the coinsurance for confirmatory colonoscopies or screening colonoscopies with abnormal findings.^{35,108} Medicare therefore requires beneficiaries to contribute to the cost of screening colonoscopy when it is performed to confirm a positive result from a non-colonoscopy screening test, or if a biopsy is performed during the course of a screening examination. The benefits of screening cannot be realized if confirmational analyses of tissues are not performed or positive results cannot be followed up. Therefore, legislative action is long overdue to remove poverty cost-sharing by Medicare for people who are unable to afford supplemental insurance to cover the coinsurance.

Progress in removing poverty cost-sharing could be facilitated by greater recognition that colonoscopy examination of patients with positive results from fecal immunochemical or other non-colonoscopy tests is a follow-up screening test. Coding these examinations as screening or creating a separate CPT (current procedural terminology) code for them might be part of the solution. Additionally, guideline groups should adopt a definition of CRC screening that encompasses confirmation of findings and removal of lesions during colonoscopy—the American Cancer Society has moved in this direction and endorsement of that concept by other societies will advance health equity.¹⁰⁹

Future Directions

Disparities persist in CRC incidence and mortality despite national efforts—AAs have the highest rates among all racial and ethnic groups in the US. Low SES is associated with higher rates of CRC, and might contribute to changes in the colon, via lifestyle factors such as diet. Diets high in fat and red meat and low in fiber can alter the intestinal microbiome, promote inflammation, and disrupt immune surveillance to contribute to initiation and progression of CRC (Figure 3). Widespread screening for CRC is a preventive intervention that could reduce these disparities and even overcome the negative effects of lifestyle factors.^{72,77}

Addressing modifiable risk factors for CRC might reduce CRC disparities. Behavioral risk factors might be difficult to change because of limited resources, factors in the physical environment such as access to healthy food, and cultural influences. Further studies are needed to understand whether improving access to lifestyle interventions in underserved

populations will reduce disparities in CRC due to SES. Prospective studies of the effects of diet, alterations to the microbiome, and/or inflammation¹¹⁰ and the immune response on CRC development and progression are needed and should include adequate numbers of persons of different races and ethnicities. Integrating community involvement through participatory research must be a key effort of consortiums, to collect diverse data and specimens.¹¹¹

A broad effort, using multiple strategies,¹¹² to increase participation in CRC screening for people of all SES and racial and ethnic populations should be a national priority. This effort will save lives that are needlessly lost to CRC and may reduce cost from CRC. Efforts should continue at local and national levels to remove barriers to colonoscopy screening and follow-up testing in populations of low SES. These would include increasing screening capacity in all communities, and for the scientific community to adopt a definition of CRC screening that aligns with the current state of science. Studies are needed to determine the economic impact of implementing screening programs at individual clinics.

It is essential to formally test the effectiveness of combining practice facilitation and direct outreach in increasing CRC screening participation in underserved and hard to reach populations. Instead of a standalone service, patient navigation might be more feasible as an integrated function of existing healthcare teams, which are trained to assess needs and provide services of different types and intensities of support. Studies should assess whether these models enable widespread adoption of navigation services for populations of low SES. To implement CRC screening, community efforts should assess and track not just the extent of disparities, but assets such as coloscopy capacity, resources for population health management, and local public-private partnerships (Figure 2). Studies are needed of contextually informed, multi-level, multi-component strategies that target patients, providers, health systems, and communities. These should assess whether collaborative strategies to enable sharing of resources (potentially through existing associations of community health centers) can overcome the challenges of implementing EBIs in clinics in low-resource communities. A crucial but understudied strategy is the use of community-wide approaches, such as honest brokers, to facilitate population-based screening and gain economies of scale, rather than be limited by individual resource constraints. Additionally, using health information technology to promote sharing of screening data, much like immunization records are shared, through registries could reduce duplication of efforts and identify more people who are eligible for screening.

Few strategies to increase rescreening have been tested, and few interventions have been found to be effective at improving follow-up testing of patients with abnormal results.^{97,98,113} Those steps are crucial for stool-based screening tests, which require frequent rescreening intervals and follow-up testing of persons with positive results¹¹⁴

Acknowledgements

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This work was supported by the United States Public Health Service (R01 CA206010 to JMC and R01CA213645 and R38HL143613 to CAD) and the A. Alfred Taubman Medical Research Institute of the University of Michigan (to JMC).

Abbreviations

CRC	colorectal cancer
EHR	electronic health record
IT	information technology
EBI	evidence-based interventions
API	Asian Pacific Islander
AA	African American
NHW	Non-Hispanic White
MSI-H	microsatellite instability (-high)
EMAST	elevated microsatellite alterations at selected tetranucleotide repeats
SES	socioeconomic status
USPSTF	US Preventive Services Task Force
NCQU	National Committee for Quality Assurance

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Figure 1.

Age-adjusted data on (A) CRC death in different US regions, (B) CRC incidence among races and ethnicities, ages 50 years and older, and (C) death from CRC among races and ethnicities, ages 50–64 years (left panel) and 65–74 years (right panel).

Figure 2. Intervention framework for CRC disparities with healthcare community-linked strategies and policy interventions.

Figure 3.
Connections and consequences of socioeconomic disparities in development and progression of CRC.

Interventions to increase screening uptake

Increase community demand

- **Patient reminders**
 - Follow-up printed
 - Telephone reminders
- **Patient incentives**
- **Small media**
 - Letters, brochures, and newsletters on screening options
- **Mass media**
- **Group education**
- **One-on-one education**
 - Interactive sessions

Increase community access

- **Reducing structural barriers**
 - Flexible office hours and **outreach**
 - Help with:
 - Appointment scheduling
 - Transportation
- **Reduce out-of-pocket costs**
 - Vouchers
 - Reimbursements and co-pays
 - Bowel prep

Increase provider delivery of screening services

• Assessment and feedback • Incentives	• Reminders • Workflows and processes

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Figure 4.
Interventions to increase uptake of CRC screening.

Table 1.

Genetic and Cellular Alterations Associated With Colorectal Tumors from AAs

Genetic Alteration	Patient Outcome
Lower frequency of MSI-H in colorectal tumors	Reduced survival time; decreased response to immune checkpoint inhibitors
Higher frequency of EMAS in rectal tumors	Reduced survival time
Mutations of <i>EPHA6</i> , <i>FLCN</i> , and <i>HTRIF</i>	Unknown
Lower frequency of mutations in <i>APC</i> mutations; higher methylation of genes that regulate Wnt signaling	Unknown
Higher frequency of activating mutations in <i>KRAS</i>	More aggressive tumors
Reduced numbers of CD8 ⁺ T cells	Reduced survival time
Reduced numbers of granzyme B ⁺ T cells	Reduced survival time