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Racial Disparity in Gastrointestinal Cancer Risk

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Abstract

Cancer from the gastrointestinal tract and its associated excretory organs will occur in over 300,000 Americans in 2017, with colorectal cancer responsible for over forty percent of that burden; there will be over 150,000 deaths from this group of cancers in the same time period. Disparities among subgroups related to these cancers' incidence and mortality exist. The epidemiology and risk factors associated with each cancer bear out differences for racial groups in the United States. Esophageal adenocarcinoma is more frequent in Non-Hispanic Whites, whereas esophageal squamous cell carcinoma with risk factors of tobacco and alcohol is more frequent among Blacks. Liver cancer has been most frequent among Asian/Pacific Islanders chiefly due to hepatitis B vertical transmission, but other racial groups show increasing rates due to hepatitis C and emergence of cirrhosis from non-alcoholic fatty liver disease. Gastric cancer incidence remains highest among Asian/Pacific Islanders likely due to gene-environment interaction. In addition to esophageal squamous cell carcinoma, cancers of the small bowel, pancreas and colorectum show the highest rates among Blacks, where the explanations for the disparity are not as obvious and are likely multifactorial, including socio-economic and health care access, treatment and prevention (vaccination and screening) differences, dietary and composition of the gut microbiome, as well as biological and genetic influences. Cognizance of these disparities in gastrointestinal cancer risk, as well as approaches that apply precision medicine methods to populations with the increased risk, may reduce the observed disparities for digestive cancers.

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INTRODUCTION

The incidence and mortality from gastrointestinal (GI) cancers highlight health disparities for specific populations. For instance, it is well known that native Asians from specific countries have a high incidence of gastric cancer. However, their immigrant counterparts in the U.S. show a different incidence, likely due to changes in environmental influences from a new geographical location [1]. Another example is colorectal cancer (CRC); whereas native Africans have a very low incidence of this disease, African Americans portray a much higher one, and are at the highest incidence among U.S. racial/ethnic groups [2]. Immigrant populations to the U.S. have shown changes in GI cancer risk from their country of origin generally within 1–2 generations, suggesting that gene-environment interations are at play. Many GI cancers present with higher risk within Westernized countries, and the observed risk is suggested to originate from the more abundant availability of calories, red meat and fat, and subsequent interaction with the gut microbiome [3,4]. Genetically-susceptible populations might not demonstrate risk for GI cancers until a switch from legume and grain diets to the Westernized high caloric diets [5]. Other GI cancers, such as gastric cancer, are at high incidence in specific countries but low risk in the U.S., in part due to an evironment with low *H. pylori* prevalence [6]. Within the U.S., fundamental causes of health inequalities including socio-economic factors, insurance status, access to healthcare, screening and treatment biases are additional issues that contribute to GI cancer disparities [7]. Understanding the differential effects of cancer epidemiology among U.S. populations as they pertain to GI cancers is the focus of the present review. Because cancer data is more complete for Non-Hispanic Whites and Blacks in the U.S. than other racial/ethnic groups, this article emphasizes these two populations (Figure 1), although key data for Hispanic, Asian/Pacific Islander, and American Indian/Alaskan natives are also presented.

For 2017, GI cancers occurred in 310,440 people in the U.S., of which over 40 percent is CRC with 135,430 new cases. Similarly, death from CRC (50,260 people) is one-third of all GI cancer mortality (157,700 people) (Table 1) [8]. The overall number of GI cancers by each race is not entirely known, as some GI cancers are not broken down in datasets in this fashion. Among specific GI cancers, CRC is being closely monitored by the Centers for Disease Control (CDC) Health Disparity and Inequality Report (CHDIR), given that it is the GI cancer with the highest incidence and mortality, and it is potentially preventable [9]. In this manuscript, we pay particular attention to CRC disparities, even though other GI cancers also have important disparities that we highlight in each of the sections. Along with age and family history, common GI cancer risk factors include: smoking, excessive alcohol consumption, diet high in animal fat, obesity and genetic predisposition. Viruses also play key etiological factors for some GI cancers such as hepatocellular and anal cancers. How these risk factors lead to different outcomes in different populations remains to be further

elucidated and is the subject of current research. Here, we highlight the epidemiology, risk factors, and approaches that might reduce cancer disparities for seven GI cancers. A comprehensive review of GI cancer disparities has not been published and is critical to identify knowledge gaps that should be addressed in order to optimize efforts to reduce disparities in the US.

Esophageal Cancer

In 2017, there were 16,940 new cases and 15,690 deaths from esophageal cancer in the U.S. (Table 1). There are 2 primary histological sub-types of esophageal cancer: adenocarcinoma and squamous cell carcinoma (SCC). While SCC is the most common sub-type worldwide especially in East Asia, Africa and Southern Europe, esophageal adenocarcinoma is the most common sub-type in the U.S. and Northern Europe [10,11]. Of all esophageal cancers in the U.S., adenocarcinoma accounts for nearly 60%, while SCC accounts for about 34%, the remaining 6% are of other histological sub-types [12]. Overall, 5-year survival for all esophageal cancer sub-types is only 18% due to advanced disease often at presentation (Table 2). Males are about 3 times more likely to develop espophageal cancer than females (Table 3).

Among racial and ethnic groups in the US, there are differences in the distribution of histological sub-types of esophageal cancer. In non-Hispanic Whites (NHWs), adenocarcinoma accounts for nearly 68% of esophageal cancers, whereas this sub-type accounts for only 15% of cases in Blacks. Conversely, while SCC accounts for 26% of esophageal cancer cases in NHWs, it accounts for 80% of cases in Blacks. Among Hispanics, the rates of SCC and adenocarcinoma are 41% and 53%, respectively [12]. Considering all esophageal cancer sub-types, Blacks are more likely to present with later stage disease [13] and have poor outcomes [14].

Reasons for differences in incidence by race/ethnicity are likely explained by different risk factors for each sub-type. Primary risk factors for SCC are alcohol and tobacco use [11,15]. Among Asians, variants in genes involved in alcohol metabolism confer increased risk of SCC [10]. A case-control study found that tobacco and alcohol use accounted for 94% of the difference in esophageal cancer annual incidence rates [16]. An epidemiological study suggested that population-specific screening and prevention programs are warranted for esophageal SCC in Black men exposed to alcohol and tobacco given that rates of SCC approached those for esophageal adenocarcinoma in NHW men with reflux disease, a group in whom screening is advocated [17]. A number of genome-wide association studies (GWAS) of esophageal SCC have been performed in Asian populations and identified functional variants in alcohol metabolizing genes, *ALDH2* and *ADH1B*, that, when combined with lifestyle factors, significantly increase risk of SCC [18]. These genetic risk variants are only found in East Asian populations [19]. Moreover, variants in *PLCE1* [20,21] were associated with SCC in 2 GWAS evaluations, and the allele frequencies of these variants are similar across populations [19], but have not been studied as risk factors in non-Asian populations.

Risk factors for esophageal adenocarcinoma include age, male gender, gastroesophageal reflux disease (GERD) especially erosive esophagitis, Barrett's esophagus, obesity and

tobacco use [11]. Non-steroidal anti-inflammatory drugs' usage and *H. pylori* infection are protective against adenocarcinoma [11]. Regarding race/ethnicity, NHW men have the highest risk of esophageal adenocarcinoma and represent a group in which the American Gastroenterological Association (AGA) recommends consideration for endoscopic screening for Barrett's esophagus on an individual basis, if multiple risk factors are present [22]. Reasons for increased risk in NHWs compared with Blacks could be due to higher rates of erosive esophagitis [23] and Barrett's esophagus [24] in NHWs and/or decreased rates of *H. pylori* infection in Blacks [25]. GWAS for Barrett's esophagus and esophageal adenocarcinoma in individuals of European descent have identified a number of genetic variants in *CRTC1, BARX1, FOXP1, GDF7, TBX5* and *HLA* [26–28]. The risk variant in *CRTC1* [26] has 30% higher allele frequency in European Americans compared with Blacks [29]; however, the other GWAS variants do not have large allele frequency differences or have higher frequency of the risk allele in Blacks and would not explain differences in risk between populations. Additional work is needed to understand the contribution of genetic variants in addition to known environmental risk factors for adenocarcinoma in Whites compared with other US populations.

Gastric cancer

Gastric cancer is the fourth most common malignancy in the world, after lung, breast and colorectal cancers, with about 75% of cases in Asia, predominantly in China [30,31]. Globally, gastric cancer rates in females are nearly half those encountered in males. It is worth noting, however, that while the incidence in females is lower than in males, the prognosis in females is generally poor (presenting with 8% and 13% more poorly-differentiated gastric cancer and signet ring carcinoma over males, respectively) and the age of onset is lower (55.0 years of age in females vs 57.9 years of age in males) [32].

Within the U.S., 28,000 new gastric cancer cases will be diagnosed in 2017 with 17,750 cases in males and 10,250 in females (Table 1). Incidence and death rates by race/ethnicity differ. During 2010–2014, Asian/Pacific Islander males displayed the highest incidence and mortality when compared to all other groups and genders, with 14.0 new cases/100,000 and 7.1 deaths per 100,000 (Table 3). Blacks developed gastric cancer at nearly the same rate as Asian/Pacific Islanders (Table 3). Hispanic females topped Asian/Pacific Islander females for the highest incidence, while in the same time period, NHW females have the lowest incidence (3.7/100,000) and mortality (1.7/100,000) rates. A direct comparison of such values for Black vs. NHW males revealed an absolute difference of +5.4 and +5.2 for incidence and mortality that translate into ratios of 1.66 and 2.53, respectively (Table 3). A similar pattern was observed when comparing these values for Black vs. NHW females where the absolute differences and ratios for incidence were +4.1 and 2.11, respectively, for mortality these values were +2.4 and 2.41, respectively (Table 3). U.S. population studies confirm that racial/ethnic minorities have a 40%–50% increase in risk of gastric cancer over NHWs, with race as an independent risk factor [25]. These differences highlight health disparities for which the contributing risk factors need to be investigated.

Risk factors differ between non-cardia and cardia gastric cancers. *H. pylori* infection is the primary risk factor for non-cardia cancer. *H. pylori* infection rates remain high in both

Blacks and Hispanics [6]. This persistent high prevalence likely contributes to the Black and Hispanic high incidence and mortality from gastric cancer (Table 3). Non-cardia gastric cancer is associated with patient low socioeconomic status (SES) where general living conditions might be conducive to higher *H. pylori* infection and dissemination. While many studies have advocated eradication of *H. pylori* to reduce non-cardia gastric cancer incidence, strong evidence for this approach is still lacking [33]. Cardia gastric cancer tends to be encountered in patients with higher SES and associates strongly with smoking and obesity. Smoking is also a factor in non-cardia cancers, but its effect is relatively minor when compared to *H. pylori* infection. Diets rich in fruit and vegetables are suggested to have protective effects against gastric cancer while higher BMI is suggested to be a risk factor for cardia gastric cancer. Among Asians, low penetrance genetic variants in *PSCA*, *PLCE1*, *PRKAA1* and *MUC1* increase risk for gastric cancer and among Europeans, loss of function of *ATM* increases gastric cancer risk [34–36]. Inactivating mutations in the *E-Cadherin* gene (*CDH1*) leads to hereditary diffuse gastric cancer syndrome in a small fraction of individuals. This same gene is the target of inactivation through methylation in the presence of *H. pylori* infection [37]. Lynch syndrome and other patients with specific polyposis syndromes are also at high risk for gastric cancer.

Overall, a decrease or cessation of tobacco use, a balanced diet with more fruits and vegetables, reduction in obesity, and better monitoring of *H. pylori* infection could lower gastric cancer disparities within the U.S. population and lead to a lower burden of the disease especially in minority populations, such as Blacks and Hispanics. While screening programs for gastric cancer exist in high prevalence regions and have been shown to reduce gastric cancer mortality, screening in a low prevalence country like the US is debated. Based on higher incidence of gastric cancer among racial and ethnic minorities in the US, targeted screening programs should be considered.

Pancreatic cancer

In the U.S., Black men and women have the highest incidences of pancreatic cancer at 17.0 and 15.0/100,000 persons, respectively (Table 3). NHW and Hispanic women have incidences of 12.8 and 10.0/100,000, respectively, while it is higher in NHW men compared with Hispanic men: 14.6 vs. 12.3/100,000, respectively. In addition to their highest incidence, Blacks also have the worst pancreatic cancer prognosis of all U.S. populations (Table 2) [38] with more advanced stage and more non-resectable disease at presentation as well as less surgical treatment [39]. Pancreatic adenocarcinoma remains one of the most deadly cancers. The 5-year survival is a dismal 8% (Table 2). In 2017, it is estimated that there will be 53,670 cases and 43,090 deaths (Table 1). Most pancreatic adenocarcinomas present at an advanced stage likely accounting for poor survival rates.

Risk factors for pancreatic adenocarcinoma include genetic and non-genetic factors. Clustering of pancreatic cancer in families increases an individual's risk up to 32-fold [40]. Hereditary syndromes (such as those due to germline mutations in *STK11, BRCA1/2, PALB2, CDKN2A*, and DNA repair genes) significantly increase pancreatic cancer risk, especially with family history of pancreatic cancer in a first-degree relative [41]. There is no data on differences in pancreatic cancer risk by race/ethnicity in these high-risk syndromes.

GWAS studies have identified 16 chromosomal loci with significant associations with pancreatic cancer [42,43]. These studies have included only a modest number of Blacks [44,45]) limiting evaluation of associations in this high-risk population.

Non-genetic risk factors for pancreatic adenocarcinoma include tobacco use, diabetes, obesity and chronic pancreatitis [46,47]. A case-control study [48] found that tobacco use, diabetes and family history accounted for 46% of pancreatic cancer risk in Black men compared with 37% risk in White men. Among women, heavy alcohol use and elevated BMI accounted for most of the excess risk among Black women compared with White women. In contrast, a study using data from the prospective American Cancer Society Cancer Prevention Study [49] did not replicate these findings and concluded that known risk factors do not account for racial disparities in pancreatic cancer. Thus, the contribution of non-genetic risk factors to racial disparities is still unclear and additional studies are warranted. Addressing pancreatic cancer disparities is a challenge given that clinical presentation occurs late in the disease course and there are no established screening recommendations. Clearly, additional work in biomarker development and screening modalities is needed to address the overall cancer burden as well as disparities.

Small bowel cancer

Cancers of the small intestine are rare, accounting for only 0.5% of cancers and 1–2% of gastrointestinal neoplasms [8]. There are several types of small bowel cancers including neuroendocrine tumors (e.g., carcinoid), adenocarcinoma, lymphoma and sarcoma (e.g., gastrointestinal stromal tumor or GIST). In 2017, it is estimated that there will be 10,190 cases and 1,390 deaths from small bowel cancer in the US, with increasing incidence over time (Table 1). Five-year survival is 66.9% for all small bowel cancers. Overall, adenocarcinoma is the most common followed by carcinoid tumors [50].

In the US, Blacks have the highest incidence of small bowel cancers with an incidence of 3.4 and 4.3/100,000 for Black women and men, respectively [12]. The most common sub-types in Blacks are carcinoids and adenocarcinoma. The rates of small bowel cancer for NHW women and men are 2.1 and 2.8/100,000, while Hispanics and Asian/Pacific Islanders have even lower incidences for both genders (Table 3). Notably, small bowel GIST tumors show highest incidence among Asian/Pacific Islanders [51]. However, when considering GIST tumors in any part of the gastrointestinal tract, Blacks have highest incidence of all populations [52,53].

There are several known risk factors for small bowel adenocarcinoma including familial adenomatous polyposis (especially in the duodenum), Lynch syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Crohn’s disease and celiac disease [54]. Given the rarity of small bowel adenocarcinoma in general, it is not known the extent to which these risk factors impact differences among races. It is unlikely, however, that celiac disease is a significant risk factor in Blacks given its low incidence in this population [55,56]. For small bowel neuroendocrine tumors, GWAS evaluations have identified risk variants upstream of *ELK3*, though the impact of these variants by race is not known [57]. Additional risks for neuroendocrine tumors include family history, BMI, diabetes and tobacco [58]. The extent to which these factors account for racial differences has not been established. As is the case in

pancreatic cancer, there are no screening strategies for small bowel cancer given its low incidence. Evaluation of symptoms especially in at-risk populations is the only strategy currently employed.

Colorectal cancer

CRC is the third most common cancer worldwide, one of the leading causes of cancer-related deaths, and among the best studied GI cancers due to access to precursor lesions [4,59,60]. It is more common among Westernized nations than in other parts of the world. It is a multifactorial disease where genetics, epigenetics, diet, lifestyle and environment have been cited as risk factors. Heritable forms of CRC such as familial adenomatous polyposis and Lynch syndrome account for <5%, with another ~25% clustering in families suggestive of weaker Mendelian genetic inheritance [61,62]; however, the vast majority of CRCs are sporadic. Screening and surveillance guidelines for CRC include age and heritable components based on family history or an identified or suspected high risk syndrome that change the age and frequency for screening according to published guidelines. Guidelines previously did not include race as a factor even though there is evidence that this engenders increase risk for CRC [4,63]; however the 2017 U.S. Multisociety Task Force on Colorectal Cancer has concluded that race is a determinant that may lower the initial screening age [64]. In the CHDIR report [9], the CDC has concluded that CRC should be closely monitored in the population as it is common and exhibits large disparities, but is potentially preventable. Successful screening programs can greatly reduce current racial disparities for CRC incidence [65–69]. In 2017, there were 135,430 new cases that were relatively equally distributed between males (71,420) and females (64,010) in the U.S. population, as well as between males and females among Blacks (8,690 and 8,550, respectively) (Table 1). Overall CRC incidence has fallen since the mid-1980s for unclear reasons initially; further decrease has been accelerated with the implementation of national screening efforts in the U.S. [8]. However, the rate is on the rise for younger Americans and more so in young Blacks [70–72].

The overall number of deaths expected from CRC in 2017 is 50,260, demonstrating an overall mortality:incidence ratio of 37.1%. The Black mortality:incidence ratio was 40.7%, the higest among races in the U.S. (Table 1). Overall, as with incidence, CRC death rates have declined since the 1980s. Despite a rate of decline being observed for both Blacks and NHWs for CRC deaths, the timing and rate of decline are markedly different between the two groups. NHW males and females experienced a decline in CRC death rates beginning in the early 1980s, with continued steady decline since. Black males and females, who showed nearly identical rates to Whites around 1980, did not begin a decline in CRC deaths until the mid-1990s about 15 years later than NHWs, with a slow rate of decline that allowed generation of a growing disparity over time [8]. Interestingly, CRC death rates were slightly lower for Blacks than NHWs in the 1970s, markedly different than current data [8,73]. Thus, genetics is not the full story; however, gene-environment interaction could play a role as well as SES and health insurance access, given that since 1980, metabolic syndrome and obesity have risen disproportionately in minority populations, along with a growing income gap between the wealthiest and poorest quartiles of income.

As mentioned above, Blacks have the highest incidence and death rates for CRC, whereas Hispanics and Asian/Pacific Islanders have the lowest rates (Table 3). Furthermore, Blacks have a distribution of CRC that favors metastatic disease compared to NHWs (Table 2). For each of localized, regional, or distant CRC disease, Blacks show lower 5-year survival as compared to NHWs (Table 2). What is generating this disparity for CRC incidence and mortality in Blacks? The answer is likely multifactorial (Table 4). Environmental contributions amount to 65–70% of CRC risk. These include factors that directly or indirectly influence the colonic epithelium and colonic stem cells that become primed to commence the neoplastic process, and include high fat, red meat, high caloric diet, excess BMI, the use of tobacco products, alcohol intake, low serum levels of vitamin D and calcium, low intake of fish oils, and uniqueness of the gut microbiome makeup [4]. Additionally, the use of hormone replacement therapy and aspirin or NSAIDs that may reduce CRC risk are not as well utilized in minority populations. Many of these environmental factors are disproportionately and adversely represented in the U.S. Black population and are in theory, correctable. For instance, dietary swaps between U.S. Blacks (high fat, low fiber) and South Africans (low fat, high fiber) demonstrated marked reciprocal changes in mucosal biomarkers of cancer risk, changes in microbiota and metabolites known to affect cancer risk including increased butyurogenesis and suppressed secondary bile acid generation in U.S. Blacks on the South African diet [5]. Heritable factors contribute 25–30% of CRC risk. For known Mendelian disorders such as familial adenomatous polyposis or Lynch syndrome, there does not appear to be an excess of founder mutations or prevalence of these conditions among Blacks [62,74]. With Lynch syndrome, the cumulative risk for CRC in Blacks and NHWs with a germline mismatch repair mutation was nearly identical; however, the mutational spectrum of the mismatch repair genes was different, likely reflecting the genetic diversity of the Black population [62]. A family history of CRC or adenomatous polyps, even without evidence for a Mendelian disorder, lowers the age for screening to 40 years [63,64]. Many minority populations do not know or convey their paternal history of cancer or have fear of transmitting it to health care providers, and thus are less likely to be screened at 40 years of age [4].

Societal factors also play a role in racial CRC disparity incidence and mortality. Blacks tend to have: (a) lower SES, lower level of health insurance coverage, and lower level of education, and (b) less access to medical care, particularly prevention approaches [4]. Specific to CRC is the utilization of screening and surveillance, which has not been equally and uniformly applied or accessed by all populations. There is strong evidence that screening reduces morbidity and mortality from CRC, and with successful implementation and utilization, will likely reduce or eliminate the observed CRC disparity between Black and NHW populations [65,66,75,76]. While overall screening rates in the U.S. continue to rise, a disparity still exists for utilization among races. Screening in Blacks still lags behind NHWs, but is improving [8,73]. Diagnostic colonoscopy for follow-up of a CRC screening test lags behind among Black patients compared to NHW patients [77], and was even observed for the follow-up of frank rectal bleeding [78]. Diligent follow-up, as well as the use of patient navigators might improve the utilization of necessary CRC screening and diagnostic procedures [79,80].

Biological factors may contribute to some of the observed CRC disparity. Blacks tend to present 5–8 years younger on average with CRC (e.g. mean age of 62 vs. mean of age of NHWs at 69 years of age), and have a higher proportion of CRCs under the age of 50 years (10.6%) compared to NHWs (5.5%) [4,81]. As with over 50 years of age, Blacks showed the highest incidence for CRC in the 40–49 year age group, suggesting early triggers for neoplasia are present than any other racial group [71,72]. High risk adenomas (>9 mm), the precursor to most CRCs, appear to be more prevalent among Blacks beginning at age 50 years [82,83]. Additionally, Blacks show a higher proportion of both high risk adenomas and CRC in the proximal colon [4,75,82,83], a 7–15% more right colon distribution than NHWs. Proximal colon polyps, in particular, may be harder to spot at colonoscopy, and the reduction from CRC mortality with colonosocpy is lower than the left side of the colon [84–86], potentially amplifying the disparity.

Genetic factors may contribute to biological reasons for CRC disparity. Black patients display a higher frequency of *KRAS* mutations in tumors, increasing the aggressiveness of the CRC [87]. Mutations in the driver genes *EPHA6* and *FLCN* were found exclusively in Black CRCs, suggesting a unique behavior modifying role for these CRCs [88]. Another study identified novel somatic alterations in well-known CRC genes (*APC, BRAF, KRAS*, and *PIK3CA*) among Blacks [89]. Microsatellite instability (MSI), a good prognostic biomarker caused by the hypermethylation of the DNA mismatch repair gene *MLH1*, shows a lower frequency among Blacks [81], although a meta-analysis did not reach statistical significance to show a difference [90]. Elevated microsatellite alterations at selected tetranucleotide repeats, a poor prognostic biomarker generated by inflammation-initiated nuclear-to-cytosolic transfer of the DNA mismatch repair protein MSH3, shows a higher frequency among Blacks [91,92]. *MSH3* was also frequently somatically-mutated among a cohort of Blacks using whole exome sequencing [89]. Somatic epigenetic differences have not been adequately studied between races; insulin and TGFβ pathway genes (*GAS7, BMP3, GPR75*) were observed epigenetically inactivated among Blacks, but without comparison with their NHW counterparts [93,94]. GWAS evaluations for CRC have largely included patients of European descent; there is a lack of studies that show specific risk loci among U.S. Black patients. Of the more than 50 CRC risk loci identified to date [60], none show risk loci specific for Blacks, since only few patients of African descent have been included in such studies [95,96]. One study demonstrated that among 10 CRC risk alleles examined between Blacks and NHW CRC patients, there was significant heterogeneity with variation of risk between the populations at different chromosome loci [97,98].

Immunological factors could also play a role in biological causes of CRC disparities. Histological evaluation of Black CRCs as compared to NHW CRCs demonstrate: (a) an absence of high levels of $CD8^+$ T cell counts in MSI tumors [81] and (b) lower infiltration of immune cells expressing granzyme B, a cytotoxic marker, particularly at the invasive borders of the tumor [99]. These observations of reduced immune function against cancer cells contribute to the aggressiveness of the tumor. Additionally, if the frequency of MSI is less among Black CRC patients, a process that generates novel immunogenic truncated proteins from frameshifted transcribed genes [100], the benefit from PD-1 immune checkpoint blockade that appears to be effective for MSI tumors [101,102] is relatively curtailed in this population.

Quality of care factors, particularly an endoscopist's adenoma detection rate (ADR), contributes to patient outcome that contributes towards CRC mortality disparity. Increased ADR through proposective performance feedback has been shown to reduce interval CRCs (adjusted hazard ratio 0.63 [CI 0.45–0.68]) and cancer death (adjusted hazard ratio 0.50 [CI 0.27–0.95]) in patients undergoing screening colonscopy [103]. In a population-based cohort study examining Medicare patients age 66 to 75 years who received screening colonoscopy, 52.8% of Blacks as compared to 46.2% of NHWs received colonoscopy from physicians with lower polyp detection rates, despite no difference in the proportions of persons in either race receiving screening colonosocpy (Blacks 79.5% vs NHWs 80.7%) or polypectomy (Blacks 23.4% vs NHWs 24.7%) [104]. Furthermore, the probability of interval cancer was 7.1% in Blacks (adjusted hazard ratio 1.32 [CI 1015–1.51]), as compared to 5.8% in NHWs, 4.4% in Hispanics, and 3.8% in Asians [104]. Analysis suggested that variations in polyp detection rate cold not explain the differences between Blacks and NHWs, but that the disparity in risk for interval cancer was more pronounced for distal colorectal cancer than for proximal colon cancer [104].

The disparity for CRC in the U.S., particularly between Blacks and NHWs, is likely multifactorial (Table 4). It is not clear whether overcoming SES differences and providing equal access to health care can fully override some of the observed biological factors that make CRC more aggressive among Blacks. Reducing the high rate of metabolic syndrome disorders in this population should help. Several strategies have recently been outlined [105] to decrease the CRC disparity among Blacks, including: (a) improve patient education to reduce patient-level barriers to screening, (b) improve provider education for increasing recommendations for screening in Blacks, (c) implement patient navigation, which is cost-effective in increasing colonoscopic screening among Blacks, (d) increase the overall CRC screening rates among Blacks to be on par with screening rates for NHWs, and (e) modify the age of screening in Blacks due to the differences in observed biology, and which have been recommended by several organizations [4,75,105] and most recently by the 2017 U.S. Multi-Society Task Force on Colorectal Cancer recommendations [64]. The US Preventive Services Task Force recommends screening average risk persons at age 50 years of age, but recognizes CRC disparities and endorses efforts to ensure that specific populations at risk receive recommended screening and follow up [106]. Based on the higher incidence of proximal CRCs among Blacks, colonoscopy is preferred per ACG recommendations [75]. There is growing evidence that fully-implemented CRC screening would greatly reduce or abolish the observed CRC disparity [68,69,76]. Additionally, CRC screening should be from providers with high quality based on ADRs [103,104]. Inclusion of minority populations in clinical and comparative effectiveness trials for CRC should help identify subpopulation differences that can be addressed in personalized medicine approaches. Many past trials, including GWAS studies, CRC screening trials, and treatment trials have not utilized diverse populations in their cohorts. Overcoming patient, provider, and perceived barriers will be key for inclusion.

Liver cancer

The incidence of hepatocellular carcinoma (HCC) is increasing in the U.S. and has doubled over the last 2 decades. In the U.S., there was an estimated 40,710 new cases and 28,920

deaths in 2017 (Table 1). HCC is the third leading cause of cancer-related deaths worldwide. Gender distribution is nearly 3:1 with males making up 29,200 and females 11,510 cases in 2017 (Table 1). In addition to gender differences, the incidence of HCC differs among racial groups (Table 3). Chronic hepatitis B virus (HBV) correlates with HCC in most areas around the globe and in specific ethnic groups in the U.S., particularly Asian Americans, due to vertical transmission of HBV at birth [107]. Most patients in the U.S. who develop HCC have hepatitis C virus with cirrhosis, although other conditions that lead to cirrhosis (such as chronic alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), exposure to aflatoxin B1 or vinyl chloride or androgenic steroids, and untreated metabolic and inflammatory diseases (e.g. alpha-1 antitrypsin, Wilson's, hemachromatosis, glycogen storage diseases, autoimmune chronic active hepatitis, primary biliary cirrhosis) in addition to HBV) can cause HCC [107]. New nucleotide/nucleoside and protease inhibitors that clear HCV viral loads theoretically should reduce HCC over time for those who can obtain the expensive treatment [108,109], but other conditions such as NAFLD will likely become the dominant etiology among populations in the U.S. Rates of NAFLD are highest among Hispanic patients compared to NHWs and Blacks [110,111], and without a clear definitive treatment path for NAFLD to date, a relative increased disparity could develop for HCC in Hispanics in the future. Variants for NAFLD risk exist in single nucleotide polymorphisms in or near *PNPLA3* and *PPP1R3B* genes in Hispanic Americans and *PNPLA3*, *NCAN*, *GCKR*, and *PPP1R3B* genes in Blacks [112].

At present, the highest incidence and death rates for HCC in the U.S. are among Asian Americans, likely due to the prevalence of HBV vertical transmission, and Hispanics, likely due to NAFLD and HCV. Rates are next highest for American Indian/Alsakan natives and Blacks. With the growing risk factors from metabolic syndrome, obesity/diabetes and NAFLD, non-Asian populations may overtake the incidence and mortality of Asian Americans (Table 3). Influences such as HBV vaccination and treatment, HCV treatment, HCC surveillance in high risk populations, and societal efforts to curb obesity and treat metabolic syndrome with statins and metformin [113] may alter these populations' risk projections.

Anal cancer

The incidence of anal cancer in 2017 in the U.S. was 8,200 new cases of which 5,250 were in females and 2,950 in males (Table 1). Anal cancer rates have been on the rise for the past three decades [114–116]. This increase has been attributed to the HIV epidemic, HPV infection, and changes in sexual behavior and attitudes [117]. The highest increase was noted in Black men [118], who show the highest incidence for anal cancer, followed by NHW women (Table 3). Black men also had a poor prognosis with lower survival rate. Their five-year survival rate with early stage anal cancer was 62% versus 79% for Caucasian men [119]. The overall expected deaths from anal cancer are 1,100 for 2017 (Table 1).

Histological sub-types of anal cancer include SCC and adenocarcinoma, each with different incidence, clinical features and risk factors. Women show higher rates of SCC and lower rates of adenocarcinoma than men [120]. Blacks appear to have lower rates of SCC than NHWs, but higher rates of adenocarcinoma. Anal cancer incidence was higher in men and

Blacks aged <40 years [120]. Most anal cancers are of the SCC type, with adenocarcinoma only accounting for 9–14% of total diagnosed cases in the U.S. and are possibly extensions of rectal lesions [118]. Ninety percent of anal SCCs are caused by HPV infection, while only a small portion of adenocarcinoma is associated with HPV [120,121]. As such, little is known about the etiology of the adenocarcinoma type. Smoking is reported as a risk factor that correlates with anal cancer, especially in those with HPV infections [122,123].

HPV vaccination of both females and males will likely play a role in greatly reducing anal squamous cell carcinoma. However, not all patients have anal cancer as a result of HPV serotypes 16 and 18, which accounts for 70% of all cervical cancers, as other high risk serotypes have been detected among anal cancers [124]. One available vaccine also is effective against serotypes 6 and 11, and together with serotypes 16 and 18 account for 90% of all cases of genital warts. Black populations, particularly women, may have a higher HPV incidence than other U.S. populations [125,126], despite similar incident HPV infection rates. The prevalence disparity may be generated by slower clearance of HPV among African American women, taking 601 days on average to clear the virus compared to European American women requiring only 316 days [126]. Additional disparities might be generated with provider recommendation for HPV vaccination, age for commencement of the vaccine, and compliance with all doses of the HPV vaccination [127,128]. Educational programs for both providers and patients and their communities may mitigate these issues with vaccination.

CONCLUSIONS

Digestive tract cancers are among the most frequent and deadly cancers in Americans. Several GI tract cancers show disparate incidence and mortality rates within racial/ethnic populations of the U.S., with Blacks demonstrating the highest rates for five of seven cancers highligted in this article (esophageal squamous cell carcinoma, gastric, small bowel, pancreas, colorectal and anal cancer) (Figure 1 and Table 3). Some differences between races can be explained (e.g. vertical HBV transmission for HCC risk in Asians), while other causes for cancer disparity are likely multifactorial – from biological and genetic influences, dietary and microbiome make-up, to socio-economic, healthcare access, and biases toward treatment or screening. Strategies that involve knowledge and education of patients and physicians, reduction of obesity and ingestion of low fat and high fiber diets, moderation of alcohol and tobacco usage, and vaccination programs all will help curb incidence in all populations [129]. CRC, in particular, might have the current disparity between Blacks and NHWs greatly reduced with a fully-implemented screening and surveillance program in these populations. These strategies as well as the inclusion of diverse populations in clinical trials for digestive cancer prevention and care may highlight alternative and personalized medicine approaches to mitigate some of the observed disparities.

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Abbreviations

NHB	Non-Hispanic Black
NHW	Non-Hispanic White
CRC	colorectal cancer
SCC	squamous cell carcinoma
HCC	hepatocellualr carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
HPV	human papilloma virus
GI	gastrointestinal
CDC	Center for Diseases Control
CHDIR	CDC Health Disparity and Inequality Report
SES	socio-economic status

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Author names in **bold** designate shared co-first authorship.

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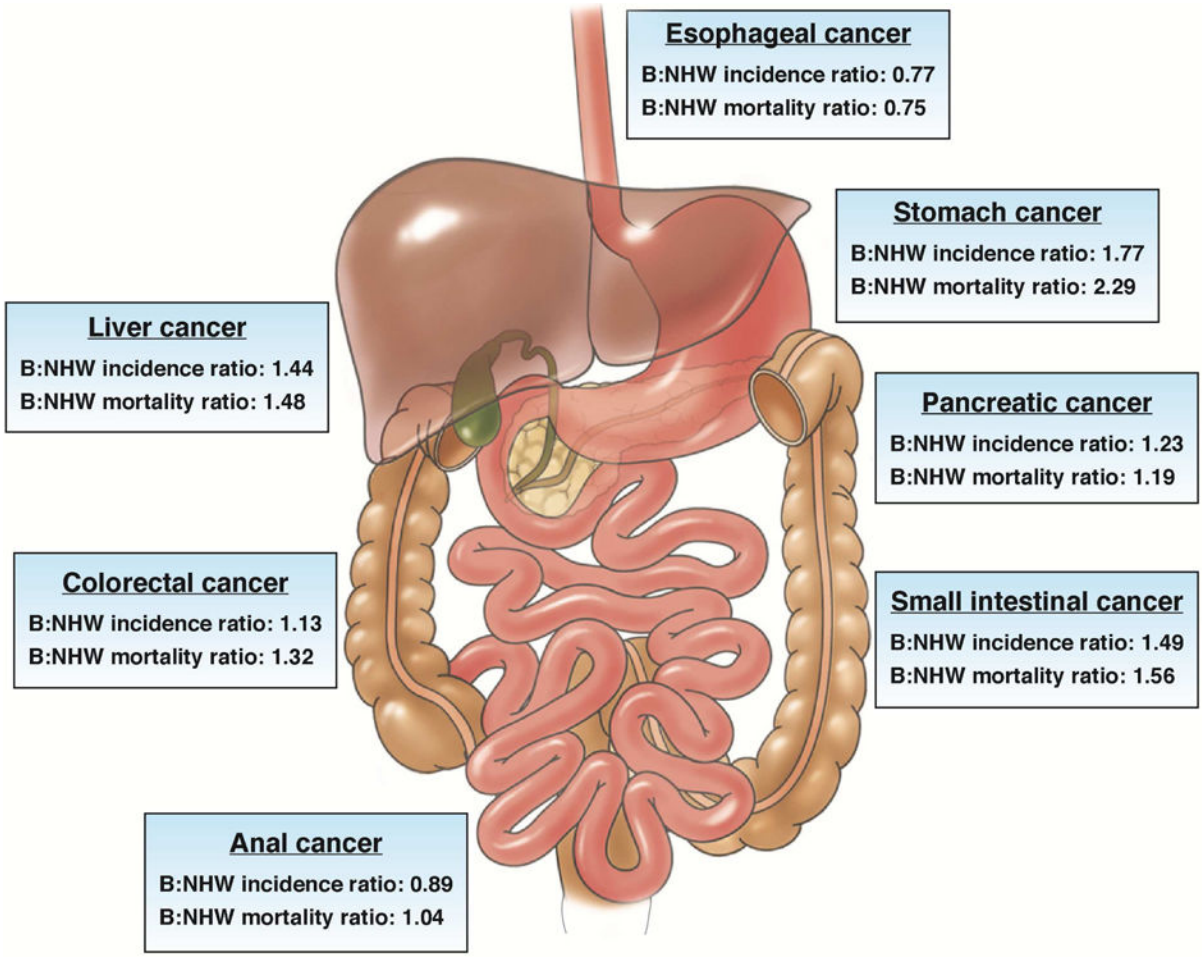

Figure 1.

Black:Non-Hispanic White (NHW) ratios for seven gastrointestinal track cancers, both genders, for 2014. Data derived from seer.cancer.gov. Note the higher incidence and mortality ratio for NHWs for esophageal cancer, and same incidence and mortality ratio for both Blacks and NHWs for anal cancer. All other cancers show higher incidence and mortality ratios for Blacks as compared to NHWs. In some cases, the mortality ratio is more excessive than the incidence ratio for Blacks, including that for stomach, colorectal, and small intestinal cancer.

Table 1

Estimated new gastrointestinal cancer cases and deaths by gender, for all races and Blacks in the United States for 2017.

Cancer	Overall Incidence	Male Incidence	Female Incidence	Black Male Incidence	Black Female Incidence	Overall Deaths	Black Male Deaths	Black Female Deaths
Esophageal*	16,940	13,360	3,550			15,690	920	
Stomach	28,000	17,750	10,250			10,960	1,160	
Small Intestine	10,190	5,380	4,810			1,390		
Pancreas	53,670	27,970	25,700	3,230	3,490	43,090	2,390	2,550
Liver and Intrahepatic Duct	40,710	29,200	11,510	4,250		28,920	2,880	1,020
Gallbladder and Other Biliary	11,740	5,320	6,420			3,830		
Colorectal	135,430	71,420	64,010	8,690	8,550	50,260	3,800	3,230
Anus	8,200	2,950	5,250			1,100		
Other Digestive Organs	5,560	2,300	3,260			2,460		
Total Digestive System	310,440	175,650	134,790			157,700		

Data derived from Siegel RL, Miller KD, Jemal A. CA Cancer J Clin. 2017;67:7–30 and DeSantis CE, Siegel RL. Sauer AG, Miller KD, Fedewa SA, Alcaraz KI, Jemal A. CA Cancer J Clin 2016;66:290–308. Blank cells are due to unobtainable data.

*Includes adenocarcinoma and squamous cell carcinoma.

Table 2

Stage distribution and 5-year survival of selected gastrointestinal cancers by race for 2006–2012.

Cancer	Distribution for Localized Disease	Distribution for Regional Disease	Distribution for Distant Disease	5-Year Survival Localized Disease	5-Year Survival Regional Disease	5-Year Survival Distant Disease	All Stage 5-Year Survival
Esophageal *	White:20%	31%	38%	44%	24%	5%	19%
	Black:18%	31%	40%	22%	17%	4%	12%
	All:20%	31%	38%	41%	23%	5%	18%
Liver and Intrahepatic Duct	White:43%	27%	18%	30%	11%	3%	17%
	Black:42%	28%	20%	24%	7%	2%	13%
	All:43%	27%	18%	31%	11%	3%	18%
Pancreas	White:9%	29%	52%	29%	11%	3%	8%
	Black:10%	26%	57%	26%	11%	2%	7%
	All:9%	29%	52%	29%	11%	3%	8%
Colorectal	White:39%	36%	20%	91%	72%	14%	66%
	Black:38%	32%	25%	87%	65%	10%	58%
	All:39%	35%	21%	90%	71%	14%	65%

Data derived from Siegel RL, Miller KD, Jemal A. CA Cancer J Clin. 2017;67:7–30. ‘All’ refers to all races assessed, including White, Black, Asian/Pacific Islander, American Indian/Alaskan Native, and Hispanic.

* Includes adenocarcinoma and squamous cell carcinoma.

Table 3

Gender-based incidence and mortality rate ratios per 100,000 (adjusted to the 2000 U.S. standard population) for selected gastrointestinal cancers for 2010–2014, with comparing Blacks to Non-Hispanic Whites (NHWs).

Cancer	All Races	Asian/Paci fic Islander	American Indian/Ala skan	Hispanic	Black	NH White	Absolute Difference (Black-NHW)	Black:NHW Rate ratio
Esophageal *								
Incidence	M:7.3	3.5	5.1	5.1	6.9	8.2	−1.3	0.84
	F:1.7	0.8	1.4	1.1	2.3	1.8	+0.5	1.28
Mortality	M:7.3	2.9	4.2	4.2	6.3	8.0	−1.7	0.79
	F:1.5	0.7	1.1	0.8	1.9	1.6	+0.3	1.19
Stomach								
Incidence	M:9.9	14.0	13.7	13.5	13.6	8.2	+5.4	1.66
	F:5.2	8.0	8.1	8.8	7.8	3.7	+4.1	2.11
Mortality	M:4.4	7.1	4.9	3.4	8.6	3.4	+5.2	2.53
	F:2.3	4.3	2.5	1.7	4.1	1.7	+2.4	2.41
Small Intestine								
Incidence	M:2.6	1.3	1.5	1.9	4.3	2.8	+1.5	1.54
	F:2.0	0.9	–	1.5	3.4	2.1	+1.3	1.62
Mortality	M:0.5	0.3	–	0.3	0.7	0.5	+0.2	1.40
	F:0.3	0.2	–	0.2	0.5	0.3	+0.2	1.67
Liver and Intrahepatic Duct								
Incidence	M:13.3	20.2	18.7	20.6	16.7	10.4	+4.3	1.61
	F:4.6	7.6	8.6	7.9	5.0	3.5	+1.5	1.43
Mortality	M:9.2	14.	10.1	13.8	13.0	8.0	+5.0	1.63
	F:3.7	6.1	4.7	6.1	4.5	3.3	+1.2	1.36
Pancreas								
Incidence	M:14.2	11.0	11.1	12.3	17.0	14.6	+2.4	1.16
	F:11.1	9.2	8.3	10.8	14.3	11.0	+3.3	1.30
Mortality	M:12.6	8.2	7.1	10.0	15.0	12.8	+2.2	1.17

Cancer	All Races	Asian/Paci fic Islander	American Indian/Ala skan	Hispanic	Black	NH White	Absolute Difference (Black-NHW)	Black:NHW Rate ratio
	F:9.5	7.3	6.0	8.1	12.1	9.5	+2.6	1.27
Colorectal								
Incidence	M:46.0	40.2	45.5	41.5	56.4	45.9	+10.5	1.23
	F:35.1	28.8	37.5	29.9	43.2	35.3	+7.9	1.22
Mortality	M:17.7	12.4	14.0	15.8	25.3	17.3	+8.0	1.46
	F:12.4	8.8	10.0	9.7	16.5	12.3	+4.2	1.34
Anal Cancer								
Incidence	M:1.5	0.5	–	0.9	2.2	1.6	+0.6	1.38
	F:2.1	0.5	1.2	1.5	1.8	2.2	−0.4	0.82
Mortality	M:0.2	0.1	–	0.1	0.3	0.2	+0.1	1.50
	F:0.3	0.1	–	0.2	0.2	0.3	−0.1	0.67

Data derived seer.cancer.gov. ‘M’ = male; ‘F’ = female; NH = Non-Hispanic; ‘–‘ = number of cases too small to estimate ratios.

* Includes adenocarcinoma and squamous cell carcinoma. For Black:NHW rate ratios, a ratio of “1” means that the Black rate and NHW rates are equal, and rates >1.0 means that Blacks have higher rates than NHWs, and rates <1.0 means NHWs have higher rates than Blacks.

Table 4

Factors likely contributing to colorectal cancer disparities between Blacks and Whites

Environmental factors	*Diet*	High fat & calories
		Low fiber
		High red & processed meats
		Low vitamin D & calcium
		Low fish oils
	Co-morbid conditions	Obesity
		Metabolic syndrome
		Type 2 diabetes
	Habits	Lack of physical activity
		Tobacco use
		Alcohol use
	Medications	Non-steroidal anti-inflammatory drugs
		Aspirin
		Hormone replacement therapy
	Microbiome & metabolites	Microbial composition
		Bile acid, butyrate & other metabolite composition
Genetic factors	*Mutations*	Somatic mutations
		Germline susceptibility variants
	Microsatellite instability	Microsatellite instability including at tetranucleotide repeats
	Immunological factors	Immune cell infiltration especially intratumoral T cells
Societal factors	*Socioeconomics*	Low socioeconomic status
		Less education
	Insurance and access to care	Health insurance coverage
		Access to medical care especially screening
	Screening behaviors	Screening uptake & adherence
		Physician recommendation to screen