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# An overview of cancer health disparities: new approaches and insights and why they matter

Tsion Zewdu Minas, Maeve Kiely, Anuoluwapo Ajao, and Stefan Ambss<sup>\*,</sup>

Laboratory of Human Carcinogenesis, Center of Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892–4258, USA

\*To whom correspondence should be addressed. Laboratory of Human Carcinogenesis, National Cancer Institute, Bldg. 37/Room 3050B, Bethesda, MD 20892–4258, USA. Tel: +1 240 760 6836; Email: [ambss@mail.nih.gov](mailto:ambss@mail.nih.gov)

## Abstract

Cancer health disparities remain stubbornly entrenched in the US health care system. The Affordable Care Act was legislation to target these disparities in health outcomes. Expanded access to health care, reduction in tobacco use, uptake of other preventive measures and cancer screening, and improved cancer therapies greatly reduced cancer mortality among women and men and underserved communities in this country. Yet, disparities in cancer outcomes remain. Underserved populations continue to experience an excessive cancer burden. This burden is largely explained by health care disparities, lifestyle factors, cultural barriers, and disparate exposures to carcinogens and pathogens, as exemplified by the COVID-19 epidemic. However, research also shows that comorbidities, social stress, ancestral and immunobiological factors, and the microbiome, may contribute to health disparities in cancer risk and survival. Recent studies revealed that comorbid conditions can induce an adverse tumor biology, leading to a more aggressive disease and decreased patient survival. In this review, we will discuss unanswered questions and new opportunities in cancer health disparity research related to comorbid chronic diseases, stress signaling, the immune response, and the microbiome, and what contribution these factors may have as causes of cancer health disparities.

## Introduction

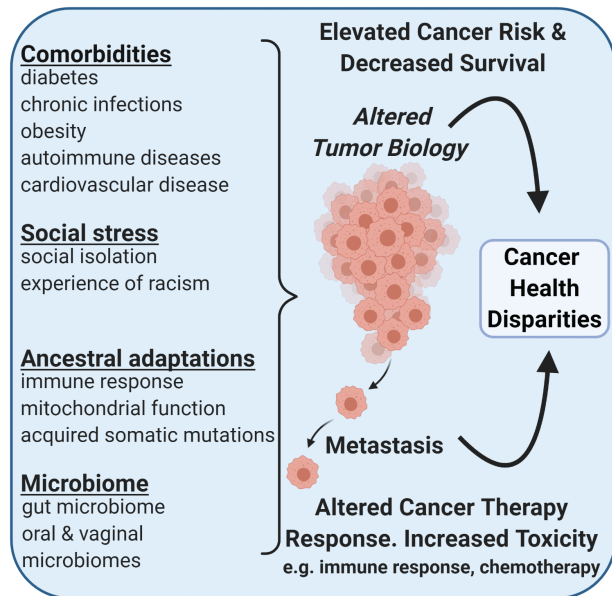
Cancer death rates in the United States (U.S.) reached their high point in the 1990s (1). They have been declining from that time on because of reduced tobacco use among adults, more widespread cancer screening and early detection, and improved cancer therapies (1). Declines in deaths from lung cancer, melanoma, and other leading cancers, like breast, colorectal, and prostate cancer, account for much of the advances in reducing the U.S. cancer mortality. These improvements are more pronounced among younger than older Americans (2). Nevertheless, cancer health disparities persevere. In this review, we will first summarize our understanding of cancer health disparities in the U.S. and abroad and then evaluate the contribution that comorbid chronic diseases, chronic stress exposure, population differences in immune response, and a dysbiosis may have as causes of these disparities (Figure 1). The advent of COVID-19 infections reinforced the notion that diseases other than cancer

influence cancer survival and may contribute to an excessive mortality in underserved communities.

## Cancer health disparities in the United States and globally

Cancer disparities continue to persist across geographic areas, socioeconomic strata, and different racial and ethnic groups. Rural communities experience higher death rates from lung, cervical, and colorectal cancers than urban communities because of poverty, health risk behavior, and lower vaccination and screening rates (3), consistent with the widening disparity in life expectancy between rural and urban areas (4).

Low educational attainment is an indicator of socioeconomic deprivation and strongly correlates with elevated all-cause death rates in the general population. 40–50% of all pre-mature



**Figure 1.** Comorbid chronic diseases, stress exposure, population differences in immune response, and dysbiosis are factors that contribute to cancer health disparities.

deaths might not occur if all segments of the U.S. population would experience the death rates of college graduates (5). Socioeconomic status is a key determinant of cancer mortality as well. About a quarter of all cancer deaths may not occur if all Americans were college-educated (6). Cancer survival increases with higher socioeconomic status for all U.S. racial and ethnic groups (7). Yet, socioeconomic patterns in cancer mortality have changed markedly over time (8). Into the 1980s, socioeconomic status positively correlated with U.S. cancer mortality rates, showing a higher risk of cancer deaths among the affluent. This correlation has now turned into the opposite direction, with affluent Americans being less likely of dying from cancer because of advances in disease prevention, early cancer detection, and cancer therapy that benefit patients with private health insurance more so than others. Presently, socioeconomic inequalities contribute most strongly to the excess mortality from lung, colorectal, cervical, stomach, and liver cancer among Americans who live in deprived areas (8). While the prostate cancer mortality did not vary much by socioeconomic status in the past, an inverse socioeconomic gradient appears now to exist (8,9). Neighborhood socioeconomic deprivation can further be linked to shortened telomere length, an indicator of pre-mature aging, and lethal cancer (10–12).

Global disparities in cancer incidence and mortality rates are evident for most cancer sites and indicate socioeconomic inequalities and significant differences in risk factor exposure (13). Rates of cancers including breast, colorectal, and prostate vary greatly between high-income and low-income countries, geographic areas, and race/ethnic groups. Differences in health care and modifiable risk factor exposure are major drivers of these global disparities, as shown by migration studies for breast and other cancers (14–16). Lung cancer is the leading cause of cancer death worldwide but is prominently under-represented in sub-Saharan Africa because of a low smoking prevalence. Prostate cancer is the most common cancer among men worldwide but shows large geographical differences in occurrence, with low incidence rates in East Asia and high rates in Western countries. With the westernization of lifestyles in East Asia, the

incidence difference has narrowed (17). Notably, prostate cancer is the leading cause of cancer death among men in sub-Saharan Africa and the Caribbean (18), which led to the hypothesis that genetic ancestral factors may predispose men of sub-Saharan African ancestry to prostate cancer and a more aggressive disease. Recent findings are consistent with this hypothesis (19–22). Cervical cancer is a major cause of cancer deaths among women in sub-Saharan Africa and South-East Asia because of human papillomavirus infections and delayed disease detection. Stomach and esophageal cancer are two other cancers with high incidence and mortality rates in Eastern Asia. *Helicobacter pylori* and salted foods are major risk factors for stomach cancer. This cancer is particularly common on the Korean peninsula due to a combination of regional dietary risk factors and chronic *H. pylori* infections whereas Malawi in Eastern African is especially impacted by esophageal cancers, having the highest global disease rates due to factors that have yet to be identified. Lastly, the burden of liver cancer is greatest in Northern and Western Africa and South East Asia and is a primary cause of cancer death in Mongolia. Chronic hepatitis B & C virus infections and exposure to aflatoxin are key causes of the disease in these areas while heavy alcohol use and non-alcoholic fatty liver disease are drivers of the increasing liver cancer incidence in many high-income countries.

### Cancer health disparities between population groups in the United States

Large differences in cancer incidence and mortality do also exist between U.S. population groups (1,2). These disparities are largely explained by differences in access to health care, diet, lifestyle, cultural barriers, and disparate exposures to pathogens and carcinogens (23,24). Disparities in liver cancer occur across U.S. states and race/ethnic groups (25,26). This cancer affects American Indians/Alaska Natives, American Asians, and Hispanic Americans more so than African Americans and European Americans. American Indians/Alaska Natives have the lowest 5-year cancer survival across all cancer types and experience elevated rates for many malignancies and major risk factors, like comorbid conditions, when compared to European Americans (1,27,28). In contrast, Hispanics/Latinos and Asian Americans tend to have lower cancer incidence rates than other U.S. population groups. Asian Americans, by themselves a rather heterogeneous population group, have the lowest cancer-specific mortality by reasons that are yet unclear but may relate to better treatment responses (29). Among Hispanics/Latinos, infection-related cancers are over-represented and women and men are more likely to be diagnosed with late stage cancer when compared to U.S. European Americans (25). While prostate cancer is generally less common among Hispanic/Latino men, it is the leading cause of cancer death among men in Puerto Rico, indicating heterogeneity in cancer risk within the Hispanic population. African Americans disproportionately bear the cancer burden and have the highest death rates from malignancies of the breast, gastrointestinal tract, lung, and prostate, and develop multiple myeloma more commonly than other population groups (23,30). Reasons of why these specific cancer disparities exist have been extensively reviewed (31–37). Therefore, they will not be the focus of this review. Nonetheless, cancer risk profiles among African Americans are not uniform and vary whether they are Sub-Saharan African-, Caribbean-, or U.S.-born (38,39). African Americans have an excess risk of developing early-onset cancer, which is reminiscent of disease presentation in Africa (40); however, African populations and African Americans in the U.S. are generally younger than the U.S.

European American population which may bias cancer-onset comparisons (41). In recent years, cancer incidence and death rates declined faster among African Americans than European Americans, a very positive development that is mainly due to reductions in lung, colorectal, and prostate incidence and mortality (2,30). Barriers still exist and current lung cancer screening guidelines may often exclude African American smokers at increased risk of lung cancer (42). Moreover, men of African ancestry continue to have 2–3-times higher absolute rates of fatal prostate cancer in both the U.S. and England (43).

The differences in cancer survival between U.S. race/ethnic groups and their underlying causes have been investigated. This research showed that disparities in stage at diagnosis may have the largest contribution to these survival disparities, followed by socioeconomic factors and marital status as other key contributing factors (44,45). The importance of marital status suggests that social isolation and stress may contribute to these racial/ethnic disparities. Still, private insurance provides the single most protective effect against being diagnosed with advanced stage disease, emphasizing the importance of access to health care in reducing the cancer survival health disparity among U.S. population groups (46).

### **Influence of sex and gender on cancer risk and outcomes**

Sex and gender are modifiers of health and contribute to disparities in disease development and outcome (47). Men are at an increased risk of dying from cancer (1,2). Many non-reproductive cancers show a 2:1 male predominance worldwide. Sex hormone signaling and Y chromosome-encoded oncogenes are drivers of sex- and gender-related cancer disparities. Sex differences in cancer genetics have been recognized (48). The androgen receptor has key roles in the progression of liver diseases like fatty liver, cirrhosis, and liver cancer, consistent with a 2:1 to 7:1 male predominance in the liver cancer incidence globally (49). The response to cancer therapy may differ between women and men. For example, the therapy benefit from immune checkpoint inhibitors is sex-dependent and these therapies provide more benefit to men (50). Although sex is a well-established modifier of cancer risk, the biology of sex-related cancer disparities remains incompletely understood. Nonetheless, it has been recommended that clinicians should consider sex and gender in their approach to diagnosis, prevention, and treatment of diseases (47). To end with, there are also cancer health disparities related to sexual behavior. For example, anal cancer incidence rates are increasing in both men and women across the globe and will require population-based preventive measures including advocacy for safe sexual behaviors and human papillomavirus vaccination (51).

### **Impact of health care access and the Affordable Care Act on cancer health disparities**

Access to health care and health insurance coverage are key determinants of receipt of cancer care and cancer survival (52). A survival disparity for African American men with prostate cancer exists in the U.S. population, but is not observed in clinical trials or for men served by the Veteran Affairs equal-access health care system (53), highlighting the importance of equal access to health care in reducing cancer health disparities. Furthermore, insurance status provides the single most protective effect against the diagnosis of metastatic cancer (46). In 2010, the Patient Protection and Affordable Care Act, also termed “the Affordable Care Act”, was signed into law. Its primary goal

was to improve health insurance coverage (54). The preliminary impact of this legislation has now been assessed. Disparities in the percentage of uninsured patients have been diminished in Medicaid expansion states under the Affordable Care Act (55–57). Americans living in areas of greater deprivation and rurality still have lower rates of recommended cancer screening than others (58). With the Affordable Care Act, however, colorectal cancer screening uptake seems to have increased, albeit modestly (59), yet race/ethnic disparities persist (60). On the other hand, Medicaid expansion shows consistent relationships with lower odds of having either advanced stage or metastatic cancer at diagnosis among low-income Americans (55,56,61). It also increased care affordability among cancer survivors in Medicare expansion states, but not in nonexpansion states, and increased utilization of cancer surgery by low-income Americans (57,62). Still, race/ethnic disparities remain (62), and Medicaid expansion may not have lowered the disparity in breast cancer mortality between African American and European American women (63). With the continuation of an impact by the Affordable Care Act on both secondary prevention of cancer and cancer care, future analyses of Surveillance, Epidemiology, and End Results program data should provide more clarity to what extent the Affordable Care Act has reduced cancer survival health disparities in low-income communities and across race/ethnic groups.

### **Chronic diseases modify cancer risk and survival and contribute to health disparities**

Comorbidities in cancer patients are chronic diseases that commonly co-occur with cancer because of shared risk factors (64). Common comorbid diseases include obesity, diabetes, and metabolic syndrome, cardiovascular, liver, and autoimmune diseases, chronic infections, but also dysbiosis and neurological and stress-related disorders. They influence cancer diagnosis, tumor biology and metastasis, and the utilization of cancer therapy. Comorbidities do not affect all segments of the US populations equally. American Indians and African Americans have significantly higher rates of comorbidities, when compared to other U.S. population groups (27). Four of these comorbidities, obesity, diabetes, chronic kidney disease, and hypertension, contribute disproportionately to the mortality disparity between African Americans and European Americans. Although not a chronic condition, COVID-19 infections have recently been associated with an excessive mortality among African Americans (65) and cancer patients (66).

Diabetes, hyperinsulinemia, and obesity are closely related comorbid conditions. They are all cancer risk factors (67,68). Because these conditions are more prevalent in underserved and minority populations, one would predict that they contribute to a disproportionate cancer burden in these communities. However, the evidence that link comorbidities to cancer health disparities remains rather sparse, partly because these investigations were either not done or focused on only a few comorbid conditions. Diabetes approximately doubles the risk for liver and pancreas cancer and is additionally associated with the risk of breast, colorectal, endometrial, esophageal, and gallbladder cancer (67,69). Diabetes-related advanced glycation end products have been linked to a cancer health disparity (70). Diabetes is thought to promote cancer development and progression through insulin and insulin-like growth factor signaling, oxidative stress, and excessive inflammation (71). This comorbidity is excessively high among African Americans and in the Hispanic/Latino community (27,72). Insulin resistance and the metabolic syndrome have been found to contribute to disparities in breast cancer

outcomes between African American and European American women (73,74). Diabetes also increases the risk of pancreatic cancer in African American and Hispanic/Latino (75), however, the data do not indicate that the conferred risk is higher in these two population groups than in European-Americans.

Comorbidities are associated with an elevated cancer mortality. They impede the participation of cancer patients in clinical trials and adversely affect trial participation (76). Accordingly, clinical trial participation of U.S. minorities remains low (77,78), which may partly relate to barriers in enrollment due to comorbidities. The presence of a comorbidity will influence treatment selection and the use of surgery and chemotherapy (79,80). Cancer patients with a comorbidity are generally less likely to receive curative treatment than those without the comorbidity (81). These deaths are preventable with lifestyle changes and other intervention strategies that target these chronic diseases. Moreover, the negative impact of comorbidities on cancer outcomes tends to increase with the number and severity of the comorbidities. Their impact is generally larger for cancers that have otherwise better survival. Thus, future cancer health disparity research should develop an increased focus on comorbidities and how they contribute to existing U.S. cancer outcome disparities.

### Mechanisms linking stress exposure to cancer metastasis and survival and disparate outcomes

The concept of a public health exposome was developed for targeted community health intervention and includes exposure to

stressors, their signaling, and the causes of the stress exposure (82). Posttraumatic stress because of a cancer diagnosis may disproportionately affect minority populations (83). Social adversity in early life can lead to decreased glucocorticoid and increased pro-inflammatory signaling in humans (84). Intrauterine stress exposures associate with a shortened telomere length in young adulthood (85), which may predispose these individuals to premature aging and cancer. Perceived experiences of racism show relationships with breast cancer and cancer-promoting health behaviors, such as increased tobacco and alcohol consumption (86,87). In breast tumors, social isolation may lead to reprogramming of tumor biology (88,89). Thus, stress exposures may alter cancer susceptibility and disproportionately affect socially deprived and minority populations (Figure 2).

Behavioral comorbidities (e.g. depression, fatigue, anxiety, cognitive impairment) are prevalent in cancer patients and a target for therapy (90). Cancer patients have higher rates of depression than most Americans (91). Major depression affects about 5–8% of the U.S. population but approximately 15% of cancer patients. Race- and gender-based discrimination and social isolation of the elderly are common events and create chronic stress exposures in affected individuals. Chronic stress and depressive disorders are associated with an increased cancer mortality (92–94). They are cancer risk factors and have been linked to elevated concentrations of circulating pro-inflammatory cytokines and chemokines (90–92).

Stress exposures and depression transduce their biological effects through the hypothalamic-pituitary-adrenal axis. This signaling pathway is characterized by hypersecretion of the

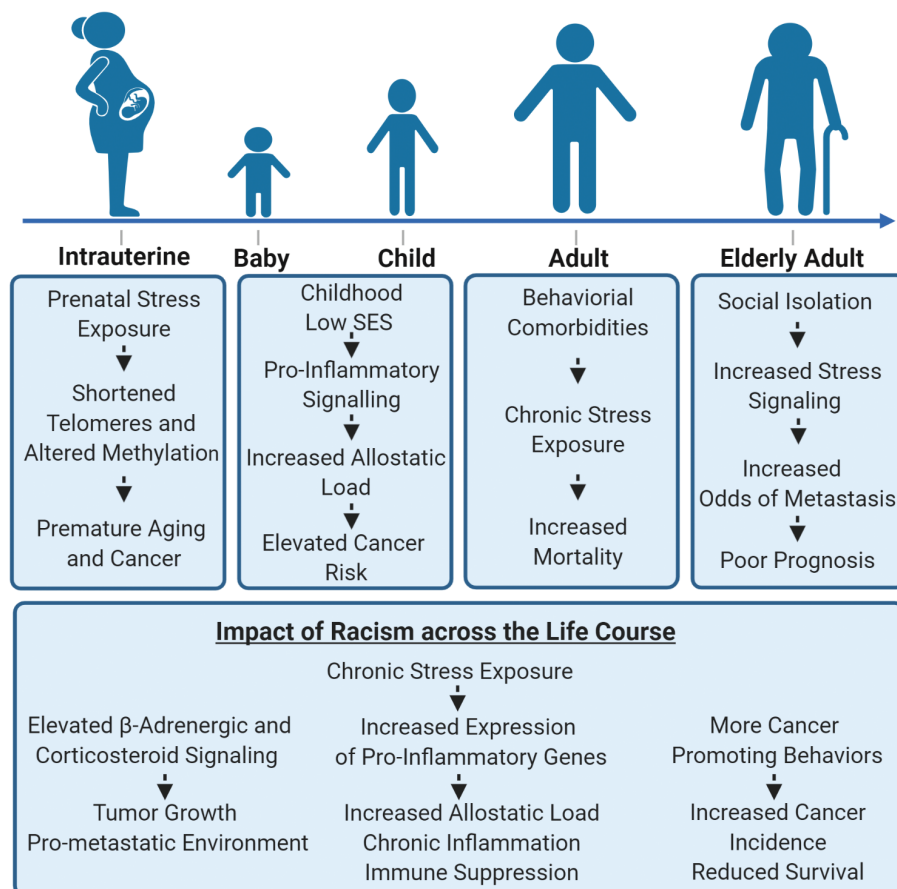


Figure 2. Stress exposure over the life course and its potential impact on socially deprived and minority populations.



corticotrophin-releasing hormone and activation of the peripheral autonomic and sympathetic nervous system, which has direct effects on tumor biology and immune response, promoting inflammation, angiogenesis, mesenchymal differentiation, and metastasis (95). Chronic stress influences tumor biology through two major pathways involving catecholamines (adrenaline, noradrenaline) and glucocorticoids (96). Socially isolated ovarian cancer patients were found to have elevated tumor noradrenaline levels (97). In mouse models of ovarian and breast cancer, chronic stress promotes invasive tumor growth and metastasis in a  $\beta$ -adrenergic signaling-dependent manner (98–100). Here, catecholamines activate  $\beta$ -adrenergic signaling in cancer cells and tumor-associated macrophages (95,99), leading to a pro-metastatic tumor microenvironment. Consistent with these observations, a pro-metastatic niche has been described for breast tumors from socially isolated women (101) and a decrease in chronic depression may slow metastasis in breast cancer patients (102). In other studies, social stress was found to up-regulate inflammatory gene expression in monocytes through  $\beta$ -adrenergic signaling (103). Likewise, African Americans with exposure to racial discrimination showed up-regulation of these genes (104).

Social isolation may contribute to racial and ethnic differences in cancer survival. Ellis *et al.* reported that marital status is a contributing factor to these survival disparities (45). Being married provides a survival benefit while being unmarried, a surrogate for social isolation, is a risk factor. There are other studies that link stress exposure and  $\beta$ -adrenergic signaling to cancer survival.  $\beta$ -adrenergic receptor expression may predict a poor prognosis for breast cancer patients (105).  $\beta$ -blocker use after a disease diagnosis reduces disease recurrence and improves survival of breast cancer patients (106), while regular users of the  $\beta$ -blocker, propranolol, are less likely to develop advanced breast cancer and have a reduced breast cancer-specific mortality (107). Beta-blocker use has been associated with improved recurrence-free survival in triple-negative breast cancer as well (108). Together, these data indicate that stress may alter breast cancer biology through activation of the pro-metastatic catecholamine pathway, leading to an aggressive disease in a subpopulation of patients who would benefit from stress management. Lastly, a high prevalence of major depression has been reported for African American men with prostate cancer (109). This condition and other social stress exposures may predispose these men to aggressive disease as it has recently been shown that stress-related signaling pathways are up-regulated in prostate tumors that progressed into lethal disease (110). In summary, it is well documented that stress exposures, which impact underserved and minority communities more so than affluent communities, can adversely affect tumor biology, cancer survival, and quality of life of cancer patients (Figure 2). Yet, a knowledge gap persists. Still few studies have examined the impact of various stress exposures in minority and socially deprived communities using large and well-designed studies. These studies should be conducted as the detrimental impact of chronic stress and depression in cancer patients is preventable using community engagement, psychosocial support, and therapies like  $\beta$ -adrenergic blocking agents.

### Ancestry and population differences in immune response as underlying factors of cancer health disparities

Differences in pan-cancer mitochondrial function were found to distinguish African American from European American

cancer patients, suggesting an ancestral link (111). Recent observations have shown that population differences in genetic ancestry can contribute to population differences in cancer susceptibility (19,20,112–114). Genetic ancestry and natural selection are underlying causes of population differences in immune response to pathogens (115,116). Those differences may relate to cancer (37,117). Relationships of ancestry with expression levels of inflammatory cytokines are evident in human populations (118,119). These differences may contribute to lung cancer disparities (120,121). Two studies investigated gene expression variations between subjects of European and West African ancestry using lymphoblastoid cell lines (122,123) and observed that these variations can cluster in cancer-related pathways and influence pathway signaling. Thus, genetic differences among population groups may lead to population-specific susceptibilities for common diseases, like certain cancers, because of their effect on the transcriptome (114,124).

One mechanism by which ancestry-related factors affect cancer outcomes is by inducing an adverse tumor biology (125). Research has now documented that tumors from patients of either African, Asian, or European descent show notable differences in acquired somatic mutations (126). Two large studies investigated the relationship of African and European ancestry with mutational signatures and gene expression across 33 cancer sites in the Cancer Genome Atlas (TCGA) database and reported associations of African ancestry with somatic mutations that tended to be cancer type-specific (127,128). At a pan-cancer level, the mutational burden of tumors and associated signatures were not significantly different between patients from these two ancestries, nor were there significant differences in chromosome arm-level copy number alterations. TP53 mutations were enriched in African American patients in a subset of cancers, most notable in breast cancer, whereas genomic alterations in genes of the phosphatidylinositol 3-kinase pathway were less frequent in this patient group. After adjusting for tumor subtype differences between African American and European American patients, few significant associations between ancestry and either tumor somatic mutations or chromosomal aberrations remained (128). Notably, mutations in the gene, FBXW7, showed a pan-cancer association with African ancestry. FBXW7 is a tumor suppressor gene that is involved in the proteasome-mediated degradation of many oncoproteins such as cyclin E, c-Myc, Mcl-1, mTOR, Jun, Notch, and AURKA (129). Mutations in other genes, such as VHL, PBRM1, HRAS, and NFE2L2, showed only cancer-specific associations with ancestry.

Other investigators focused on specific cancer types, such as breast, colorectal, lung, and prostate cancer. The breast cancer studies reported an overall increased mutation frequency, and specifically for TP53, and fewer PIK3CA mutations in African American and Nigerian women, together with an over-representation of triple negative breast tumors among these women (130,131). The latter is consistent with many previous reports (40,132). Breast tumors from Nigerian women were also characterized by the occurrence of GATA3 mutations and a homologous recombination deficiency signature. A smaller study of triple-negative breast tumors that applied whole genome sequencing identified the over-representation of CTNNA1 deletions in African American patients (133). Among patients with colorectal cancer, African Americans seem to acquire KRAS, EPHA6, and FLCN mutations more frequently than other patients whereas APC loss-of-function and oncogenic BRAF mutations may manifest less frequently in their tumors (33,134–136). Lung cancer is the most fatal cancer and is highly heterogeneous as a disease and presents with geographic differences

in acquired mutations and the therapeutic response of lung cancer patients (31). Mutations in the gene encoding the epidermal growth factor (EGFR) are generally more prevalent in non-small cell lung tumors from smokers and nonsmokers of East Asian ancestry (137,138) whereas mutations in KEAP1 and CDC27 are over-represented in lung adenocarcinomas from patients of European ancestry when compared to East Asian patients, independent of smoking history (138). Furthermore, lung adenocarcinomas from European ancestry patients featured a comparatively high genomic instability score, perhaps explaining some of the reported ethnicity-related differences in survival outcome among non-small cell lung cancer patients (139). Research into racial/ethnic differences in lung cancer mutational profiles has been extended to African Americans. While one study did not find significant differences between African American and European American lung cancer patients (140), another study discovered the distinct occurrence of PTPRT and JAK2 mutations in lung adenocarcinomas among African Americans and their association with increased STAT3 signaling (141).

### A role of tumor biology and the immune response in cancer health disparity: the example of prostate cancer

The most prominent population differences in tumor biology have been reported for prostate cancer. This disease can be classified into subtypes, such as those with ETS-fusion gene arrangements and other subtypes that are negative for ETS-fusion gene arrangements and either overexpress the SPINK1 oncogene or carry a SPOP mutation (142,143). Localized prostate cancer contains few recurrent mutations in oncogenes or tumor suppressor genes (144,145). Instead, prostate tumors are characterized by gene fusions (e.g. ETS gene fusions), allelic gains of the MYC gene, and deletions of the PTEN, TP53, and NKX3-1 tumor suppressors, with additional common changes in DNA methylation that increase aggressiveness (146,147). Multiple reports have now shown that prostate tumors from patients of either European, African, or Asian descent exhibit notable differences in acquired chromosomal aberrations (e.g. ERG fusion events and PTEN loss) and subtype distribution (143,148–150), indicating disparities in disease etiology and mutational events among these population groups. Chinese prostate cancer patients were found to acquire mutations in FOXA1 at a high frequency (41%) (150). By contrast, this gene is mutated at <10% in European-ancestry populations. Comparing African American with European American patients in TCGA, significant differences were observed in the frequency of TMPRSS2-ERG fusions (29.3% African American versus 39.6% European American), SPOP mutations (20.3% African American versus 10% European American), and PTEN deletions (11.5% African American versus 30.2% European American), consistent with other studies in the United States and Africa (143,151–153). The application of whole genome sequencing to the disease in African men, currently performed on only few tumors (154), should provide further insight into the etiology of prostate cancer in Africa. Currently, we do not know how the disease in Sub-Saharan Africa relates to the disease in men of African ancestry in the United States, the Caribbean, or in European and South American countries. However, whole genome sequencing already revealed an elevated tumor mutational burden in prostate cancer patients from South Africa and the frequent loss of the LSAMP locus in African American patients (154,155).

As a key discovery of the study of prostate tumors in African American men, Wallace et al. was the first to describe a prevalent immune-inflammation signature in prostate tumors of African American patients (156), followed by others (157). This finding has been validated in TCGA (127). The signature contains elements of a viral mimicry signature and could be functionally related to the previously described interferon-related DNA damage resistance signature, also termed IRDS (158,159). Thus, tumors with this signature may not respond as well to radiation and chemotherapy as tumors without the signature, as was shown for breast cancer (159). Yet, these tumors may have an improved response to immunotherapies, and specifically to cancer vaccines, and perhaps ADAR1 inhibitors (160). In agreement with our hypothesis, Sartor et al. recently reported that African American men with metastatic castration-resistant prostate cancer who were treated with the cancer vaccine, Sipuleucel-T, in the PROCEED trial had significantly better survival than the European American patients (161). Our group explored the link between regular use of aspirin and prostate cancer in African American men and found that regular aspirin use significantly reduces the risk of both advanced prostate cancer and disease recurrence in these men (162). The finding is consistent with a similar observation in a previous study (163) and the hypothesis that inflammation is a driver of tumor biology in African American men. There is only a weak association of the immune-inflammation signature with previously described germline genetic risk loci for prostate cancer (127); however, we described a significant relationship with the presence of the interferon- $\gamma$   $\Delta$ G genotype that is common in West African ancestry populations and influences the host viral response (124,158). The precise origin of the signature remains poorly understood and may include an infection history in the context of the interferon- $\gamma$   $\Delta$ G genotype (164), dietary factors (165), or changes to the epigenome, manifesting in the re-activation of endogenous retroviral sequences (166,167). We described up-regulation of HERV-K retroviral sequences in African American prostate cancer patients (166). In addition, a pro-inflammatory diet that associates with high-grade prostate cancer is more commonly consumed by African American than European American men (165). Others described the up-regulation of the transcription factor, Kaiso, in prostate tumors of African-American men (168). Kaiso regulates pathways related to epithelial-to-mesenchymal transition, apoptosis, and inflammation and may have a significant role in the cancer biology of prostate and breast cancer patients of African descent.

The presence of a distinct immune-inflammation signature has been reported for breast tumors in African American patients as well. Such a signature describes a subset of triple-negative breast tumors (169). Recruitment of tumor-associated macrophages is elevated in breast tumors of African and African-American women, as described by us and others (170–173). Moreover, Martin et al. observed an increased microvessel density in these tumors (170). An elevated tumor vascularization in African-American breast cancer patients was confirmed by Lindner et al. (174). Tumor angiogenesis correlates with breast cancer metastasis and poor survival (175). In Nigerian breast cancer patients, a prominent interferon signature was detected in luminal-type tumors whereas macrophage infiltration was more commonly observed in the basal subtype tumors (131). Hence, current data suggest that inflammation-induced breast cancer progression could be more prevalent in patients of African descent and may relate to increased inflammatory cytokine levels in these women (119,125).

### Microbiome and cancer health disparities: impact of geography, ethnicity, and genetics on the human microbiome composition

The gut microbiome affects human health (176,177). A dysbiosis can increase cancer risk and modify the cancer therapy response (178–181). Diet and genetics shape the gut microbiome (182–184) and may contribute to cancer health disparities through their effects on the gut microbiome (Figure 3). Likewise, comorbidities may confer their cancer risk through effects on the gut microbiome (185,186). Hence, there is evidence that a dysbiosis can be a cause of cancer (179). An altered microbiome and the accumulation of microbiome-derived metabolites have been reported for various human cancers (187–189). Alterations to the human microbiome can induce an aggressive tumor biology (190), linking the microbiome to cancer survival outcomes.

Geographic location and ethnicity strongly associate with the diversity of the gut microbiome (191,192) although geography (e.g. rural versus urban) usually confers a larger effect than ethnicity (193,194). Dissimilarities in the gut microbiota among ethnic groups with a shared environment have been reported, as shown for Amsterdam, a city in the Netherlands (192). Here, the gut microbiome diversity was significantly associated with ethnicity. Other factors, besides ethnicity, influenced the microbiome diversity. Nevertheless, ethnicity was the strongest determinant of gut microbiome diversity in models that included other non-dietary and dietary factors. Similarly, a U.S. study reported that ethnicity captures the gut microbiome with a stronger effect size than body mass, age, and sex, albeit the effect of all these factors was not as impactful as geographic location (194). Microbial community richness was greatest in Hispanics and decreased further from European Americans to Asian-Pacific Islanders to African Americans. However, the authors pointed out that there is more similarity than dissimilarity in the gut microbiome between the four studied U.S. population groups, thus the differences were comparably small. In addition, ethnicity may influence only a subset of the gut microbiome

while other microbiome components remained unrelated to the ancestral background. Lastly, immigrants into the United States acquire a “westernized” gut microbiome (195), which is reminiscent of findings from migration studies that immigrants tend to acquire cancer rates of their new home country within two generations (15,196).

Cancer health disparity research has just begun to investigate the contribution of the microbiome to disparities in cancer risk and survival. Observations are sparse and validation of findings is non-existent. Differences in both the oral and vaginal microbiome have been reported comparing subjects of African and European descent (197,198). These studies did not include cancer patients. An exploratory investigation reported a rich bacterial content in high-risk prostate tumors from 6 men of South African ancestry when compared to 16 Australian men (199). In a study of breast cancer, differences in the breast tumor microbiome were observed comparing African American with European American women. Only 12 of the 64 tumors in the study came from African American women. Previously, the microbiome of breast tumors has been described from TCGA data but a separate analysis of African American tumors was not performed (200). Lastly, a large study of the non-cancerous colonic mucosa from 197 African Americans and 132 European Americans with or without colorectal cancer described a robust association of sulfidogenic bacteria with being African American, regardless of disease status (201). Abundance of these bacteria has previously been linked to diet (202) and the up-regulation of these bacteria in the African American study participants might have been related to their high intake of dietary fat and protein, as the authors concluded.

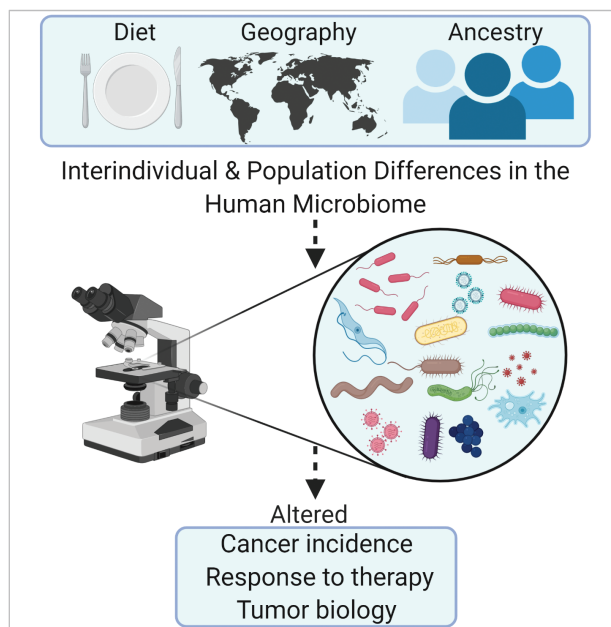
As shown by these few studies, cancer disparity-related differences in the gut, oral, and vaginal microbiome may exist. Future investigations are needed to assess the microbiome as an underlying factor or potential driver of cancer health disparities.

### Conclusions and outlook

Minority, immigrant, and other underserved populations continue to experience an excessive cancer burden not only due to barriers in access to health care, but also because of disparate exposure to carcinogens, pathogens, co-morbidities, environmentally induced stress, and ancestry-related risk factors (Figure 1). These factors, singularly or in combination, are the likely causes of cancer health disparities in the U.S. and globally. There is convincing evidence from migration and epidemiological studies that the environment defines cancer risk but there is also indication that population differences in genetic ancestry can lead to population differences in cancer susceptibility.

Genetic ancestry and natural selection are underlying causes of population differences in immune response. Those differences may relate to cancer risk and therapy response. Current data suggest that inflammation-induced cancer progression could be more prevalent in patients of African descent, manifesting in a distinct tumor immune environment. Inflammation-induced cancer progression can be targeted by therapy. Tumors with an immune-inflammation signature may respond favorably to immune therapy.

Comorbidities influence cancer diagnosis, tumor biology and metastasis, and the utilization of cancer therapy. Many comorbidities are cancer risk factors. They do not affect all segments of the US populations equally. Because these conditions are more prevalent in underserved and minority populations, one would predict that they contribute to a disproportionate cancer burden in these communities. Yet, the evidence that link



**Figure 3.** Diet, geographic location, and ethnicity strongly associate with the diversity of the gut microbiome and may increase the risk of dysbiosis, a cancer risk factor.



comorbidities to cancer health disparities remains sparse. Thus, future cancer health disparity research should develop an increased focus on cancer comorbidities.

Chronic stress and depressive disorders are associated with an increased cancer mortality and directly influence tumor biology (Figure 2). Chronic stress after a cancer diagnosis may disproportionately affect minority populations. Likewise, social isolation and perceived experiences of racism show relationships with cancer-promoting health behaviors and cancer development. Thus, stress exposures may alter cancer susceptibility and disproportionately affect socially deprived and minority populations. Still, few studies have examined the impact of these exposures in minority and socially deprived communities using large and well-designed studies. These studies should be conducted as the detrimental impact of chronic stress and depression in cancer patients is preventable using community engagement, psychosocial support, and therapeutic approaches. RESPOND is such study that focuses on prostate cancer among African American men and investigates the impact of social stress (<https://respondstudy.org/>).

Geographic location and ethnicity strongly associate with the diversity of the gut microbiome (Figure 3). Recent advances have shown that the microbiome is causatively linked to cancer. A dysbiosis can increase cancer risk and modify cancer therapy response. Diet and genetics shape the gut microbiome and may contribute to cancer health disparities through their effects on the gut, oral, and vaginal microbiome may exist. Future investigations are needed to assess the microbiome as an underlying factor or potential driver of cancer health disparities.

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