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Disparities in Surgical Oncology: Management of Advanced Cancer

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Abstract

Significant variations in the patterns of care, incidence, and mortality rates of several common cancers have been noted. These disparities have been attributed to a complex interplay of factors, including genetic, environmental, and healthcare-related components. Within this review, primarily focusing on commonly occurring cancers (breast, lung, colorectal), we initially summarize the burden of these disparities with regard to incidence and screening patterns. We then explore the interaction between several proven genetic, epigenetic, and environmental influences that are known to contribute to these disparities.

Racial and ethnic disparities in healthcare are common and are a complex result of biologic, environmental, behavioral, and socioeconomic factors (Fig. 1). A large body of research has consistently demonstrated worse outcomes in minority patients. One of the most concerning components is that of increased incidence and mortality in Black Americans.[1] Encouragingly, a growing awareness of this issue, combined with strong advocacy, has led to the implementation of targeted interventions resulting in noticeable progress, thereby narrowing the gap between Black and White Americans over the last 2 decades.[2,3]

While there are improvements in health outcomes for Black patients, there remains a concomitant lack of awareness, understanding, and common learned knowledge regarding those factors, which drive these disparities. This article serves as a foundational primer to provide a framework for understanding these disparities. The structure is formatted to highlight the layers and multilevel facilitators of disparities and identify areas in which clinicians may focus efforts to ameliorate worse outcomes. We will focus primarily on the disparities between Black and White Americans as the data on these populations are most robust, although there are differences that exist between other racial and ethnic groups.

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DIFFERENCES IN BURDEN OF DISEASE (INCIDENCE, SURVIVAL, STAGE DISTRIBUTION, TUMOR HISTOLOGY/PHENOTYPE)

While the overall incidence of new cancers is similar between Black and White patients, variations based on cancer type exist. Notably, Black patients have a disproportionately high all-cancer mortality (Fig. 2).[4] Multiple studies have repeatedly demonstrated that underrepresented minorities have an increased incidence of advanced-stage cancers at diagnosis, which is further compounded by the fact that they are less likely to receive treatment and have worse survival per stage. Such findings are confounded by discrepancies in access to care and socioeconomic status (SES). In addition, more recent data have demonstrated differences in tumor biology of certain cancer types between individuals of different races.[5] This suggests that the observed discrepancy in outcomes is likely multifactorial, involving biology, cultural, social, and economic factors, and, additionally, requires consideration of individual factors and intersectionality when discussing such outcomes.[6]

Incidence

Historically, Black Americans have endured an increased overall cancer incidence compared with White Americans; however, recent trends demonstrate a similar overall incidence between these groups (Fig. 2).[1,3] Surveillance, Epidemiology, and End Results (SEER) data demonstrate that the rate of new cancers for White Americans is 425.8 (per 100,000 persons), and 429.6 in Black Americans, and even lower in Hispanics, Asians, and American Indians;[7] however, there is significant variability in cancer incidence depending on sex and cancer type (Fig. 3).[7,8] When broken down by sex, Black men have the highest incidence of new cancers (501.9 per 100,000) and Black women (379.0 per 100,000) have the lowest, with White men and women falling in between (453.4 and 409.8 per 100,000, respectively). The lifetime probability of being diagnosed with cancer is higher for both White men and women compared with Black men and women.[3,4]

When focusing on the incidence of new cases of female breast cancer, the incidence rate is greater in White patients compared with Black patients. In contrast, a greater incidence of prostate, colorectal, and lung cancer was observed in Black male patients (Fig. 4).[7] Notably, prostate cancer accounts for the largest discrepancy in incidence between races, with a significantly increased incidence in Black men.[2,7] Lung cancer is unique in its incidence, as approximately 80% of cancers are related to tobacco use. Nevertheless, studies have shown that Black Americans have an increased incidence of lung cancer, even when controlling for pack-year smoking history while consuming a lower number of cigarettes per day,[9] indicating that there are other factors associated with this discrepancy in incidence. Undoubtedly, disparities in incidence of any cancer type can be attributed to underlying differences in various areas, such as risk factors, routine cancer screening, or access to care. In the following sections, we will explore these issues in detail.

Survival

Black Americans have the highest death rate from all cancer sites combined; specifically, lung, colorectal, breast, and prostate cancers carry the highest mortality rates across all races

(Fig. 5). Cancer mortality has been greater for Black patients compared with White patients since the 1960s, and although mortality rates have decreased over the last 2 decades in both groups, there remains a significant disparity in cancer-related mortality between Black and White Americans (Fig. 2). The age-adjusted all-cancer mortality rate is approximately 1.3 times higher in Black males compared with White males, and 1.2 times higher in Black females compared with White females.[1,10] This trend is seen in all cancer types, with an increased relative risk of mortality ranging between 1.1 and 2.37 for colorectal, lung, gastric, liver/biliary, esophageal, breast, cervical, and prostate cancers.[1]

Many factors that have been shown to be associated with overall survival, including SES, stage at diagnosis, tumor biology, treatment, and access to healthcare. Some of these topics will be covered later in this review, in additional sections. In particular, patients belonging to a lower SES group have worse outcomes overall, regardless of race. However, Singh and Jemal demonstrated that across each of their five classified socioeconomic groups, Black American patients repeatedly demonstrated lower cancer-associated survival compared with non-Hispanic White (NHW) American patients.[1] Furthermore, data have demonstrated that stage at diagnosis has the greatest impact on mortality in breast, prostate, and colorectal cancer (CRC), accounting for approximately 25% of differences.[11]

Breast cancer has been shown to have one of the greatest disparities in cancer-associated mortality rates. Mortality secondary to breast cancer ranges from 1.1- to 2-fold higher in Black women compared with White women.[1,11] Even when statistical models adjust for confounding variables, breast cancer-associated mortality remains significantly greater in Black women.[12-14] Individual studies have demonstrated that stage at diagnosis and individual tumor characteristics amplify such differences as the risk of mortality varies based on stage, hormone receptor status, and molecular subtype.[11,12,15-18]

Racial/ethnic disparities exist in colon cancer in both men and women. Multiple studies have demonstrated that Black race is associated with lower survival as well as an increased risk of recurrent colon cancer.[19,20] A study by Lai et al. showed that in a cohort of Black and White patients with CRC, 5-year overall survival difference was 8.3% when matching for SES, 5% when further matching for stage at presentation, and 4.9% when matching for treatment.[21] A second study confirmed such results, with a 5-year overall survival difference of 9.9% when matching for demographics, 4.9% when further matching for stage, and 4.3% when including treatment.[22] Even in populations that are matched for basic patient and tumor characteristics, overall survival in Black Americans remains 4–5% lower than that of their White counterparts.

Stage at Diagnosis

Black American patients tend to be diagnosed at later stages than White American patients, in many solid organ tumor types. Consequently, a greater percentage of Black patients compared with White patients are diagnosed with metastatic versus localized disease in breast, prostate, colorectal, and lung cancers.[2,11] Such findings are also true in other cancer types that are less common in the US, including gastric and liver/biliary cancers.[2] This is thought to reflect tumor biology and differences in screening and access to health care,

and has been shown to contribute to the increased cancer mortality rates seen in Black Americans.

In breast cancer, multiple studies have shown that Black women are more likely to be diagnosed with later stage disease compared with White, Hispanic, and Asian women.[12-14] It is thought that 10–30% of survival differences in breast cancer between Black and White Americans can be attributed to stage at presentation.[11,12,17] This is largely thought to be secondary to tumor biology, as prior data have demonstrated that Black women with tumors < 2 cm in size were more likely to have positive nodal disease and distant metastases than White women, as well as triple-negative breast cancers in addition to access to screening and care.[13]

Similarly, compared with White patients, Black patients are also diagnosed with CRC at a later stage. This finding is more pronounced in women compared with men, and in elderly patients.[23,24] Studies have demonstrated that stage at presentation in patients with colon cancer accounted for 40–50% of the disparity in 5-year survival between Black and White Americans.[21,22] Some of this is thought to be due to environmental and dietary factors, genetics, and also secondary to screening and access to care.

Phenotype/Histology

In many cases, differences regarding tumor phenotype closely mirror racial/ethnic disparities among stage at diagnosis. Tumor biology has been shown to be different among different races, which is secondary to multiple factors, including genetics, gene and protein expression, epigenetics, histology and the microbiome, and the complex interactions between them. Herein, we focus on the differences in phenotype between common cancers that contribute to disparities in outcomes.

For instance, hormone receptor status has been shown to account for 9–23% of excess mortality in Black women compared with White women.[11,12] Compared with other ethnicities, Black women had the highest proportion of aggressive variants, such as triple-negative breast cancer,[13,15] but there was some variation with age.[25] The risk of overall mortality varies based on hormone receptor status and molecular subtype.[12,15,16,18] The results of several studies have demonstrated that there were significant disparities in survival between patients with estrogen receptor-negative (ER−) or progesterone receptor-positive (PR?) tumors,[12,15,18] but the results are mixed with regard to human epidermal growth factor receptor 2-positive (HER2?) tumors.[12,15] Most studies did not demonstrate differences in survival between racial/ethnic groups in patients with triple-negative breast cancer.[12,15,16] Other studies have shown that receptor status impacts outcome differently for Black versus White Americans, but this is dependent on the stage of disease at diagnosis.[26]

In colon cancer, multiple differences have been described in tumor biology between Black and White patients. Distinct differences in genetic, epigenetic, microRNA and gene expression have been identified.[27,28] Such topics will be covered in greater detail in further sections. Additionally, differences in immunophenotype and the role of inflammation have been noted between Black and White Americans. Recent data also suggest that there are

differences between inflammation-related genes and tumor immune cell infiltrates in Black and White Americans, yet further validation of these findings is warranted.[29-31]

The importance of identifying differences in tumor biology between race/ethnicity is critical in decreasing the disparities in outcomes. As we gain a deeper understanding of the processes underlying tumor development and progression, we will be better able to address how such differences impact disparities in outcomes. For example, in breast cancer, Black Americans experience worse survival outcomes than White Americans with the luminal A subtype (hormone receptor-positive [HR+]/HER2−), but less so in triple-negative cancers. This subtype has an overall good prognosis, suggesting that differences in treatment, access to healthcare, or other behavioral factors account for worse outcomes. Similarly, as we learn more about tumor initiation and progression in colon cancer, we can develop a better understanding of why Black Americans are diagnosed at a younger age. Ultimately, these new insights can hopefully aid in the identification of novel risk factors, facilitate improved screening regimens, and allow for the development of uniquely tailored treatment modalities that can be utilized to improve patient outcomes.

RACIAL DISPARITIES IN SCREENING AND TREATMENT AMONG BREAST, COLORECTAL, AND LUNG CANCER PATIENTS

Black patients with breast, colorectal, and lung cancer face significant barriers and challenges in accessing healthcare across the cancer continuum. Racial disparities in screening and treatment continue to portend higher mortality rates for Black patients.[32,33] Specifically, Black patients are more likely to present with advanced disease stages at younger ages than their White counterparts.[34] Explanations for racial disparities in screening and treatment include underlying tumor characteristics in conjunction with a myriad of social determinants of health, such as insurance, geography, finances, and healthcare access.[1,35,36] This section provides an overview of disparities in screening and treatment among Black and White patients, with a focus on breast, colorectal, and lung cancers.

Breast

Screening—Recent screening mammography utilization estimates suggest non-Hispanic Black (NHB) women undergo screening at equivalent rates to NHW women.[37] Unfortunately, increased screening has not improved mortality from breast cancer for Black women.[38] Compared with their White counterparts, Black women are more likely to present with advanced stages of disease and more aggressive subtypes (i.e. triple-negative breast cancer).[3,38] Notably, the majority of age-based screening guidelines do not consider the aforementioned racial disparities, nor do they include race or ancestry in their recommendations. The lack of race or ancestry-based screening recommendations is problematic as studies indicate racial differences in age distribution patterns at diagnosis.[39] Specifically, White breast cancer patients peak in their 60s compared with non-White patients, who peak in their 40s.[39] To date, the American College of Radiology screening guidelines, released in 2018, are one of the first to provide screening guidelines that mention race explicitly.[40] In order to narrow the stage and mortality disparity between Black and White women, future screening guidelines may need to consider the implications of race and

ancestry on presentation and clinical outcomes (i.e. recurrence and mortality) among Black patients with breast cancer.

Treatment—Advancements in multimodal treatments for breast cancer have translated into increased survival among White patients but not their Black counterparts.[38] Black women face barriers in accessing high-quality and guideline-concordant surgical care, systemic treatment, and radiation therapy.[41] Compared with White women, Black women are more likely to have surgery omitted, face delays in time to surgery, and have lower post-mastectomy reconstruction rates.[42-44] Moreover, a recent study showed Black women were less likely to undergo sentinel lymph node biopsy after axillary downstaging post neoadjuvant chemotherapy than White women.[45] Disparities in locoregional management extend beyond surgery to include radiation therapy. For example, Black breast cancer patients undergoing breast conservation therapy (breast conservation surgery and radiation) are less likely to receive radiation therapy.[46] Possible contributors to disparities in radiation therapy and surgical management include geography, SES, and specialists' availability.[47-49]

Racial differences in chemotherapy initiation and modification (i.e. dosing, frequency) continue to adversely contribute to poor outcomes for Black women.[50] Delays in chemotherapeutic treatment initiation, lower rates of adherence to guideline-concordant regimens by clinicians, and reductions in dosing and frequency are primary drivers of racial disparities in the receipt and administration of chemotherapeutic agents.[51,52] Of note, developing data suggest African ancestry may play a role in increased susceptibility to adverse effects, e.g. peripheral neuropathy from taxanes.[53] Regrettably, racial disparities in chemotherapy are mirrored in the utilization of targeted therapies such as trastuzumab.[54]

Hormone-positive breast cancers are the most common breast cancer subtype and have the highest survival rates.[38] Substantial improvements in survival and reductions in recurrence are attributed to the utilization of selective estrogen receptor modulators and aromatase inhibitors;[55,56] however, lower initiation and adherence to endocrine therapies may be preventing Black women from fully benefitting from these treatment modalities.[57] The reasons for racial differences in endocrine therapy and its implications on clinical outcomes are significant areas of research interest.[58-60] Emerging data suggest that higher mortality rates from hormone-positive cancers in Black women could be mostly driven by tumor biology rather than hormone therapy adherence.[61] Furthermore, it appears recurrence scores based on the genomic test Oncotype DX may be less prognostic in Black women.[61] Continued research is needed in this area to understand the intersection of adherence, ancestry, and mortality.

Colorectal

Screening—Due to higher rates of advanced disease at diagnosis and a younger age of onset, American College of Gastroenterology guidelines recommend CRC screening for Black patients, starting at age 45 years.[62] Nevertheless, despite improvements in CRC screening rates among both Black and White patients, Black men and women continue to lag behind their White counterparts.[37] Estimates from the National Health Interview survey from 2000 to 2015 show increasing CRC screening rates of 32–62% for Black patients

aged 50 years and older, compared with 40–65% among NHW patients.[63,64] These racial disparities in screening rates persist among patients 45 years and older.[63] Explanations for the differences in screening rates are a multifactorial interplay between social determinations of health, including SES, insurance, low health literacy, and medical knowledge.[65,66] Moreover, other factors such as poor doctor–patient relationships mired by mistrust and inadequate communication further contribute to disparities in screening.[67] Avenues to reduce racial inequalities in CRC screening include increased telehealth utilization, a clear description of the screening process, and training providers to effectively communicate with patients centering health literacy and cultural competency needs.[68,69]

Treatment—Black patients with CRC cancer are less likely to undergo surgery, chemotherapy, or radiation therapy than White patients.[70,71] Additionally, when Black patients do undergo treatment, they incur higher cost compared with White patients, even after controlling for potentially confounding variables such as stage, SES, geographic region, comorbidities, and treatment type.[70] Racial disparities in CRC treatment are most likely secondary to issues with access to care, quality of care, and patient-related characteristics.[72] Studies suggest institutional drivers of racial disparities in treatment include Black patients receiving care at facilities with lower volumes of CRCs, fewer oncologic specialists, and lower rates of providing guideline-concordant care.[72,73] Breslin et al.'s examination of the implications of hospital-level factors on CRC mortality indicate they account for almost half the excess late mortality risk.[73]

The impact of equitable access to care on clinical outcomes such as survival and recurrence among CRC patients is unclear. An evaluation of care in the Military Health Systems by Eaglehouse et al. indicated that Black and White patients experienced similar delays in time to treatment in this equal-access setting;[74] however, Eaglehouse and colleagues did not explore the implications of delays in time to treatment on survival. Examinations of integrated health systems in California suggest Black patients receiving treatment at these facilities were more likely to receive guideline-concordant care and had similar survival rates to White patients.[75] Furthermore, Laryea et al. noted that prior disparities in treatment and survival at their institution were eliminated after administering equal treatment to both White and Black patients.[76] Conversely, a recent study by Snyder et al. suggests Black patients with locoregional disease receiving guideline-concordant care similar to White patients still had higher rates of recurrence and mortality.[19] These inconsistent results across studies warrant further exploration and clarification; however, they do not negate the need or impetus for improving access and quality of care for Black CRC patients.

Lung

Screening—Lung cancer is the leading cause of cancer-related mortality among Black men and women.[37] Initial 2011 screening recommendations by the US Preventative Service Task Force (USPSTF) were based on the seminal National Lung Cancer Screening Trial (NLST). The NLST reported a 20% relative reduction in lung cancer mortality among heavy smokers randomized to undergo annual chest low-dose computed tomography compared with a chest X-ray.[77] Based on this trial, the USPSTF screening recommendations focused on individuals aged 55–80 years with a 30 pack-year smoking history who quit within

15 years, or current smokers. This recommendation was problematic as it reduced the number of eligible high-risk Black smokers.[78] Black smokers have fewer pack-years and are intermittent or light smokers compared with White smokers.[9] Furthermore, Black patients with lung cancer have earlier ages of diagnosis, with age-adjusted incidence rates higher at ages 50–54 years than White patients.[79] Nevertheless, uptake of screening recommendations is low across all racial and ethnic groups, with only 2% of the 7.6 million eligible smokers undergoing screening in 2016. Recent screening guidelines by the USPSTF address prior criteria, excluding high-risk Black smokers. Current USPSTF guidelines recommend annual low-dose computed tomography screening for individuals aged 50–80 years, with a reasonable life expectancy, and with a 20 pack-year smoking history who quit smoking within 15 years or who are current smokers.[80] Nonetheless, additional efforts to educate patients and providers are needed to increase awareness and participation across all racial and ethnic groups.

Treatment—An evaluation of the SEER–Medicare program showed Black patients with lung cancer aged ≥ 65 years were more likely to have treatment omitted than White patients.[81] In the review of SEER patients aged ≤ 64 years by Taioli and Flores, early-stage (stage I) Black patients with lung cancer received radiation therapy more often than surgery.[82] Moreover, patients treated surgically were less likely to undergo guideline-recommended mediastinal lymph node evaluation.[83] In the study by Fang et al., among stage I non-small cell lung cancer (NSCLC) patients, 60% of Black patients versus 75% of White patients underwent treatments with curative intent, and for stage III patients, 36% of Black patients versus 41% of White patients also underwent treatments with curative intent.[84] Curative intent for stage I patients was defined as stereotactic body radiation or surgery, and, for stage III patients, curative intent was defined as radiation therapy or surgery plus chemotherapy.[84] These studies highlight the difficulties Black patients with lung cancer face in accessing and receiving guideline-concordant care across all ages and stages. The review by Lin et al. of cultural factors associated with racial disparities in lung cancer care indicate Black patients with lung cancer have higher rates of *mistrust, fatalism*, and *negative treatment beliefs*.[85] To address these issues, it is important to examine how patient–institution and patient–physician relationships influence these cultural beliefs and practices.

RACIAL DISPARITIES IN CANCER INCIDENCE: AFRICAN GENETIC ANCESTRY, EPIGENETICS, ALLOSTATIC LOAD, AND THE MICROBIOME

The disparities in cancer incidence that are outlined in earlier sections of this review illustrate the immense challenges experienced by disadvantaged communities. In order to address these disparities appropriately, there is a critical need to understand the myriad of factors and the complex nature with which they interplay. Undoubtedly, genetics and baseline characteristics may contribute to a certain degree; however, it is increasingly clear that environmental and societal cultural influences, social determinants of health, can in turn adversely affect the inherited traits of individuals, especially epigenetics, and this may ultimately lead to cancer. In these following sections, we will explore data examining the role of genetics in explaining disparities, with a focus on germline African American ancestry and epigenetics. We will discuss the concept of allostatic load and its known

associations with race-related disparities, with a focus on disparities relevant to cancer incidence. Lastly, we will consider the role of the microbiome and associated changes that pertain to these common cancers.

Germline African Genetic Ancestry, Epigenetics, and Allostatic Load

When we begin to unravel racial/ethnic disparities, a natural starting point is the consideration of baseline differences in their respective inherited genomes, and the possibility of germline mutations. Germline mutations refer to inheritance of specific alleles across generations that may predispose individuals to certain types of genetic variants, clinical phenotypes, and the subsequent development of cancer.[86] Germline mutations, such as those observed with *PALB2*,[87] as well as *MTCL1*[88] and *GNB5*,[88] may partially explain the occurrence of racial disparities in breast cancer between Black and White women. Similarly, a number of inherited germline mutations have been implicated in the development of lung[89-92] and CRCs.[93,94] Conversely, African heritage may be protective against certain cancers. For instance, a genome-wide analysis of 54 Black Americans with esophageal cancer or Barretts esophagus found no associations of genetic regions with excess African ancestry and disease. In fact, patients with malignancy included those with a rich European ancestry.[95] As noted by Palmer et al., there is also a considerable overlap of susceptibility genes between White and Black American women who develop breast cancer.[86] This is not surprising, as the ‘melting pot’ nature of American society where many people possess a rich and diverse ancestral background has led to a considerable level of shared genetic information. A recent large-scale genetic study supports this stance. In this study, individuals who claimed African American heritage, on average, possessed up to one-quarter of their genes from traditionally European DNA.[96] This would suggest that while inherited genetics may partially contribute to the observed racial disparities in cancer incidence, as a singular cause, it cannot fully explain the wide gap observed between White and Black patients.

A more careful investigation of the cause of racial disparities therefore requires a closer examination of the complex interplay between environmental exposures and genetics. A possible link between these two elements may involve epigenetic changes and the role of allostatic load.[97-102] A growing consensus has emerged suggesting that an individual with repetitive or low-level chronic exposure to both chemical and non-chemical stressors over a life course may gradually incorporate traces of those stressors within their genetic material in the form of epigenetic changes.[103,104] Epigenetic changes involve alterations of gene expression that are mediated by the raveling and unravelling of DNA at the histone level, without any alteration within the actual DNA sequence.[105] These changes may even be passed on across generations, in a heritable fashion.[106] Thus, the health outcomes observed today may be a direct consequence of repetitive, chronic stress experienced by prior generations. Several recent studies have demonstrated that Black patients develop distinct epigenetic profiles in a variety of cancers.[107-112] For instance, within a cohort of breast cancer patients derived from The Cancer Genome Atlas, as many as 142 genes were found to be differentially expressed in Black patients compared with White patients.[113] Similar differences were also noted in a genome-wide methylation analysis, thus suggesting that there are separate race-specific mutations producing cancers, dependent on

specific oncogenic pathways.[109] A number of comprehensive reviews examining epigenetic alterations and its associations with race have explored this topic in detail.[5,97,98,114,115]

A multitude of environmental and societal factors may precede the development of epigenetic changes. These include, for instance, diet,[116] pollutants,[117] maternal stress,[118] and residence in low-income households.[119] Recognizing the genomic impact of these factors is critical for many reasons. First, they provide a potential avenue for widespread, impactful risk-modifying interventions at a community level. Second, they can be addressed in a targeted fashion as potential therapeutic modalities.[120] The latter approach may become increasingly relevant as the drive towards adopting 'precision medicine' continues to gain momentum with a narrow, focused, and effective targeted approach towards disease. Recognizing and acknowledging the fundamental differences in tumor biology is therefore increasingly paramount. This highlights the importance of critically assessing therapeutic outcomes of clinical trials in the US, particularly given the woefully low recruitment and participation of Black populations within clinical trials.[121]

Similar to these environmentally mediated epigenetic alterations, chronic psychosocial stress has also been postulated as a mediator of health-related racial and ethnic disparities. This notion was first introduced by McEwen and Stellar, who, in their landmark paper, introduced the term 'allostatic load'.[122] This concept highlighted the underrecognized contribution of repetitive, chronic stress towards disease processes. Central to this framework is the dysregulation of the hypothalamic-pituitary-adrenal axis, thereby impairing the body's ability to achieve homeostasis appropriately.[123] This can then be further quantified into a numerical estimate by measuring biomarkers such as cortisol, epinephrine, DHEA-S, etc.[124] Several studies have examined the relationship between allostatic load and cancer and were recently consolidated into a meta-analysis.[125] Notably, the authors found that a one-unit increase in allostatic load dramatically elevated the risk of cancer-specific mortality by 9%. A race-specific examination found that elevated allostatic load was associated with a history of breast cancer in Black women, a relationship not seen in White women, suggesting that Black women experienced a greater biological toll.[126] However, a larger, more recent prospective study suggested that the association of allostatic load with cancer-specific mortality was similar across both races.[127] These confounding results indicate the need for further investigations.

Microbiome

The microbiome refers to the collective community of microscopic organisms that reside within our bodies.[128] This collection of various bacteria, fungi, and viruses are known residents of our skin and various hollow viscus organs, most notably the gastrointestinal tract.[129] Here, they largely function in a symbiotic fashion, aiding the immune and digestive systems.[130] The microbiome can be influenced by a number of external factors,[131] and recently, changes in the microbiome have been noted to influence the development and progression of cancer.[132] Given the unique heritage and rich nature of Black American culture, this raises the possibility of ethnicity-specific microbiome signatures that may influence the development of certain cancers.

This relationship is perhaps easiest to explore within the gastrointestinal tract, a system that is known to be heavily populated with a rich and diverse microbial community. This microbiome is known to be influenced by environmental influences such as diet. An initial pilot study that examined the relationship of microbiome constituents across various ethnicities found that distinct differences with regard to the proportion of various species are present.[133] Furthermore, these authors also noted a decrease in various substrates known to be influenced by bacterial degradation, such as butyrate. Previous work has illustrated butyrate as a potential factor for the prevention of colon cancer.[134,135] Similar findings demonstrating the presence of proinflammatory bacteria such as Fusobacterium and Enterobacter were also seen in a larger, more recent study.[136] Fusobacterium, in particular, has emerged as a key point of interest, with recent investigations pointing to an associated poorer prognosis, potentially mediated via enhanced chemoresistance.[137-139]

Similarly, there may be an underrecognized contribution of the microbiome in breast cancer where Black women are known to be disproportionately affected by aggressive variants such as triple-negative breast cancer. An observational analysis of the microbiome of these tumors in comparison with adjacent normal tissue demonstrated that Black women had markedly less microbial diversity in tumor samples,[140] which was in contrast to the findings observed in White patients. A similar investigation also demonstrated that the microbiome profile of Black American individuals significantly differed from their NHW peers.[141] These findings provide a strong foundation for future work to investigate microbial dysbiosis as a potential contributor towards cancer disparities. Unravelling this link could permit the development of novel biomarkers and potential therapeutic targets in an effort to reduce race-related disparities.

THE ROLE OF LIFESTYLE IN EXPLAINING DISPARITIES

In this final section, we discuss in further detail the associations between various lifestyle traits and cancer disparities. It is well-recognized that behavioral choices regarding diet, tobacco use, physical exercise, etc., as well as an individual's external environment, contribute to the risk of cancer development. These factors may be responsible for up to 90% of all cancers.[142] Importantly, many of these influences are modifiable, therefore an improved understanding of these factors would permit the potential implementation of targeted, cost-effective interventions that could reduce the burden of disparities by primary prevention.[143-145]

Diet

Differences in nutritional intake are increasingly recognized as important contributors to cancer risk.[146,147] A more thorough understanding of nutritional elements has identified certain dietary components that are carcinogenic and inflammatory in nature, and others that aid in immunity and may potentially thereby decrease the risk of cancer.[148] By virtue of cultural and socioeconomic influences, dietary differences across ethnicities are well known.[149-151] Various authors[152-154] have examined the historical context of this variability. Similarly, the social duress and economic hardship currently faced by Black communities undoubtedly limits their purchasing power, thereby artificially restricting their ability to

access healthier options.[154] Consequently, as noted by Hargreaves et al., despite indicated preferences towards healthy eating, grocery shopping patterns in Black households are simply overwhelmed by the powerful forces of 'access, traditions, social influences, habits and price'.[155] It is therefore possible, to a certain degree, that these dietary differences may play a role in contributing towards cancer disparities.

With regard to colon and prostate cancer, for instance, the consumption of processed meat has recently been implicated as a potential carcinogen.[156] Black men have been noted to have higher rates of red meat intake.[157] This intake, and in particular the presence of cooked, processed meat such as sausages and bacon, was noted to disproportionately increase the risk of prostate cancer in Black men compared with their White counterparts.[157] Similarly, for colon cancer, Yazici et al. noted that in addition to greater daily servings of meat, their Black participants consumed diets with higher fat and protein ratios. They also linked these dietary changes to an increased proportion of sulfidogenic bacteria in biopsy samples. These organisms have been implicated in the downstream development of colon cancer.[158] Conversely, Black adults have been noted to have a lower consumption of dietary fiber.[150,159] The protective effects of fiber are becoming increasingly highlighted. A recent prospective screening trial demonstrated that elevated dietary fiber intake was associated with a lower risk of distal polyp and colon cancer development.[160] Moreover, diets in Black households have been noted to be lacking in folate and calcium intake, two other elements that also have a protective effect against colon cancer.[148,161,162] A similar dietary association was noted by Boggs et al. in their study of breast cancer risk in Black women. These authors noted an inverse association of breast cancer risk with increased intake of both carrots and cruciferous vegetables.[163]

Obesity and Exercise

Obesity and obesity-associated conditions account for approximately 20% of all cancers.[164] The resultant chronic proinflammatory state and metabolic alterations caused by obesity can significantly alter host immune responses, thereby promoting the development of different cancers.[165,166] Likewise, obesity may attenuate the effect of chemotherapy and radiation, thereby further worsening outcomes for patients.[164] Recent estimates from the population-based National Health and Nutrition Examination Survey have placed the prevalence of obesity in the general population at approximately 44%.[167] Among these participants, Blacks subjects were noted to have higher rates compared with White participants (49.6% vs. 42.2%), with a markedly larger difference in women (56.9% vs. 39.8%).[167] These universally high rates of obesity appear to predispose individuals to cancer, regardless of race.[168] However, the higher rates of obesity may predispose Black patients to the development of certain malignancies. A comparison of male US veterans found that Black veterans were at a significantly elevated risk for cancers of the colon, prostate, thyroid, extrahepatic bile duct, and various hematologic malignancies.[168] Similarly, in women, obesity has been linked to the development of triple-negative breast cancer, a subtype well-documented to disproportionately affect Black women.[169] An analysis of the National Surgical Adjuvant Breast and Bowel Project data demonstrated that compared with their White peers, Black women with ER− breast cancer had a less favorable prognosis with poorer disease-free survival and a higher risk of non-breast cancer death.[170] Surprisingly, a

protective relationship between BMI and survival in Black patients with NSCLC has been observed in contrast to their White peers. The authors of this study hypothesized that this may relate to the higher lean mass observed in their cohort of Black patients, in contrast to the higher rates of sarcopenic obesity seen in White patients.[171]

Closely tied to the issue of obesity is the role of physical exercise. Several studies have conclusively demonstrated the protective benefits of physical activity against cancer development.[172-174] Unfortunately, Black individuals have been noted to inconsistently engage in leisurely physical activity.[175] There are several barriers that lead to these low rates of activity, including intrapersonal barriers such as lack of time, access to healthy outdoor spaces, access and cost of gym memberships, as well as interpersonal barriers such as caregiver responsibilities and lack of social support.[176] Additionally, several environmental barriers, including safety concerns and lack of facilities, prevent the appropriate engagement of disenfranchised communities in such activities.[176] For instance, neighborhoods with higher percentages of Black subjects have less green space coverage and larger distance to parks, thereby hindering community engagement.[177]

Alcohol and Smoking

While alcohol is an established risk factor for several malignancies, it has generally not been considered a significant contributor to healthcare disparities. However, recently, a statement from the American Society of Clinical Oncology stated that ‘alcohol drinking may be a contributing factor to cancer disparities’ and supported the conduct of further research into this area.[178] Future studies will be required to further delineate this relationship. Conversely, smoking is a well-known lifestyle determinant of many cancers. Approximately 21% of all cancer deaths globally can be linked to smoking.[179] Several well-described mechanisms link smoking to various carcinogenic pathways.[180] Although smoking prevalence appears to be similar across ethnicities,[181] variations in smoking patterns may still influence cancer disparities.[182] For instance, Black patients are less likely to receive counseling for smoking cessation,[183] and are also more often excluded from community interventions targeted towards smoking cessation.[184] Additionally, Black individuals have been noted to have a higher intake of nicotine per cigarette (and potentially tobacco carcinogens), suggesting that they may be more susceptible to the harmful effects of smoking despite consuming a lower number of cigarettes per day.[9,185] As a result, smoking significantly contributes to the Black–White gap in life expectancy above the age of 50 years.[186] Additionally, Black workers are far more likely to experience environmental or workplace exposure to secondhand smoke.[187] Approximately 7/10 children between the ages of 3 and 11 years in Black households also face exposure to secondhand smoke.[188] This early exposure can precipitate a cascade of health-related issues; therefore, tobacco control and reforms aimed at reducing exposure represent a critical avenue for combatting cancer disparities.

Environment and Neighborhood

Lastly, we considered the influence of local environments and residential neighborhoods on cancer disparities. The connections between where we live and the significant influences these portend on our health are becoming increasingly recognized. Several of the causative agents that were outlined earlier are directly affected by an individual’s residence. For

instance, dietary factors can be traced to the quality and availability of local groceries. Similarly, the ability to engage in physical exercise ties directly with the presence or absence of recreational facilities. A review of the California Cancer Registry showed that neighborhood SES was a crucial determinant for all types of cancer and in particular for minorities such as Black subjects.[11] A similar review performed in Ohio found that estimates of neighborhood conditions derived from census data strongly influenced the development of lung cancer, despite controlling for individual variables.[189]

De la Roca et al. noted that despite the decline in ethnic segregation, many neighborhoods continue to experience high levels of separation, with Black subjects continuing to reside in more disadvantaged neighborhoods.[190] This results in a clear barrier to healthcare access, leading to a variety of healthcare-related disparities. For instance, lower rates of CRC screening are evident in segregated communities.[191]. Similarly, individuals in Florida, residing in more segregated communities, were less likely to receive surgery for treatment of lung cancer.[192] A systematic review by Landrine et al. examining this association in breast cancer found that of the 17 articles that met their inclusion criteria, 70% indicated in their analyses that neighborhood segregation contributed to cancer and racial cancer disparities.[193] This new understanding has led to the development of a “place-based approach towards health, where community needs are prioritized thereby focusing on ‘upstream drivers of health outcomes’”.[194] Such strategies will be vital in addressing cancer disparities.

CONCLUSION

Despite significant advancements in the screening and treatment of breast, colorectal, and lung cancers, Black patients continue to present with advanced stages of cancer and face challenges in accessing treatment. Much research has been conducted in the last decade to increase the understanding of the multifactorial nature of disparities in cancer care, and we have learned that discrepancies in incidence, diagnosis, and outcomes result from a complex interplay of individual behavior, SES, access to healthcare, and tumor biology. As health equity moves to the forefront of national discourse, future studies should utilize multidimensional frameworks that integrate genetic ancestry, social determinants of health, behavior, healthcare access, structural inequalities and systemic racism to better define and address these persistent disparities.

DISCLOSURES

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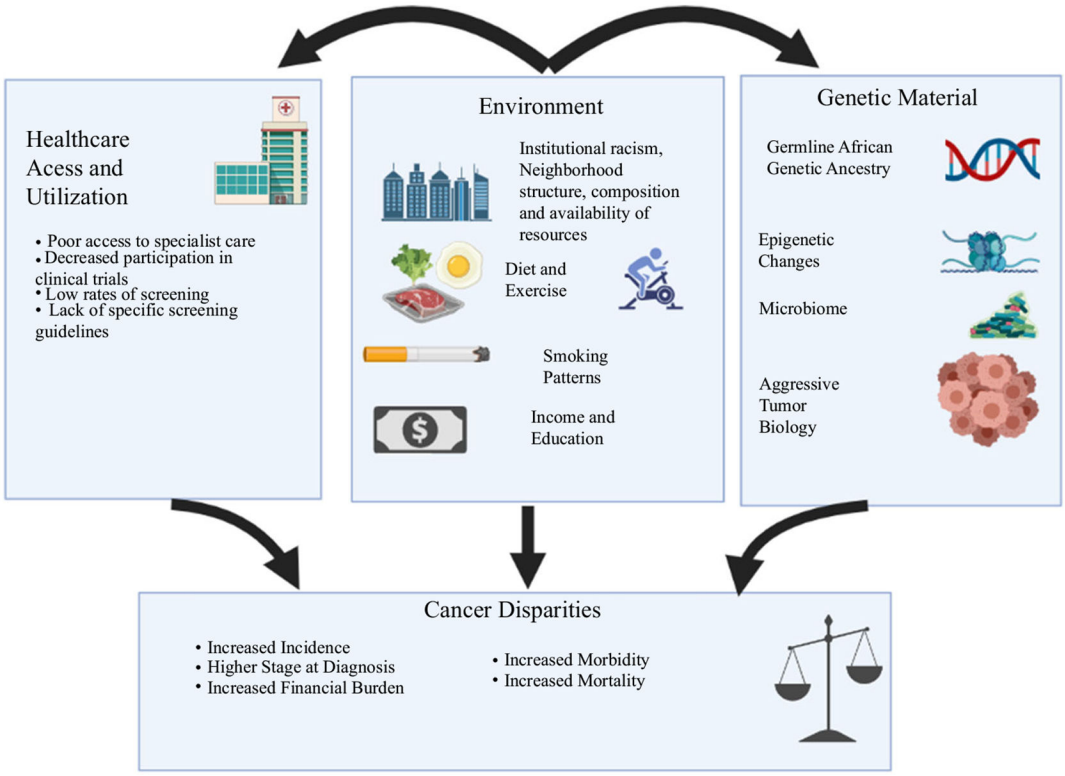

FIG. 1.

Outline of factors contributing to cancer health disparities, as well as the interconnected nature of these influences (created with BioRender.com)

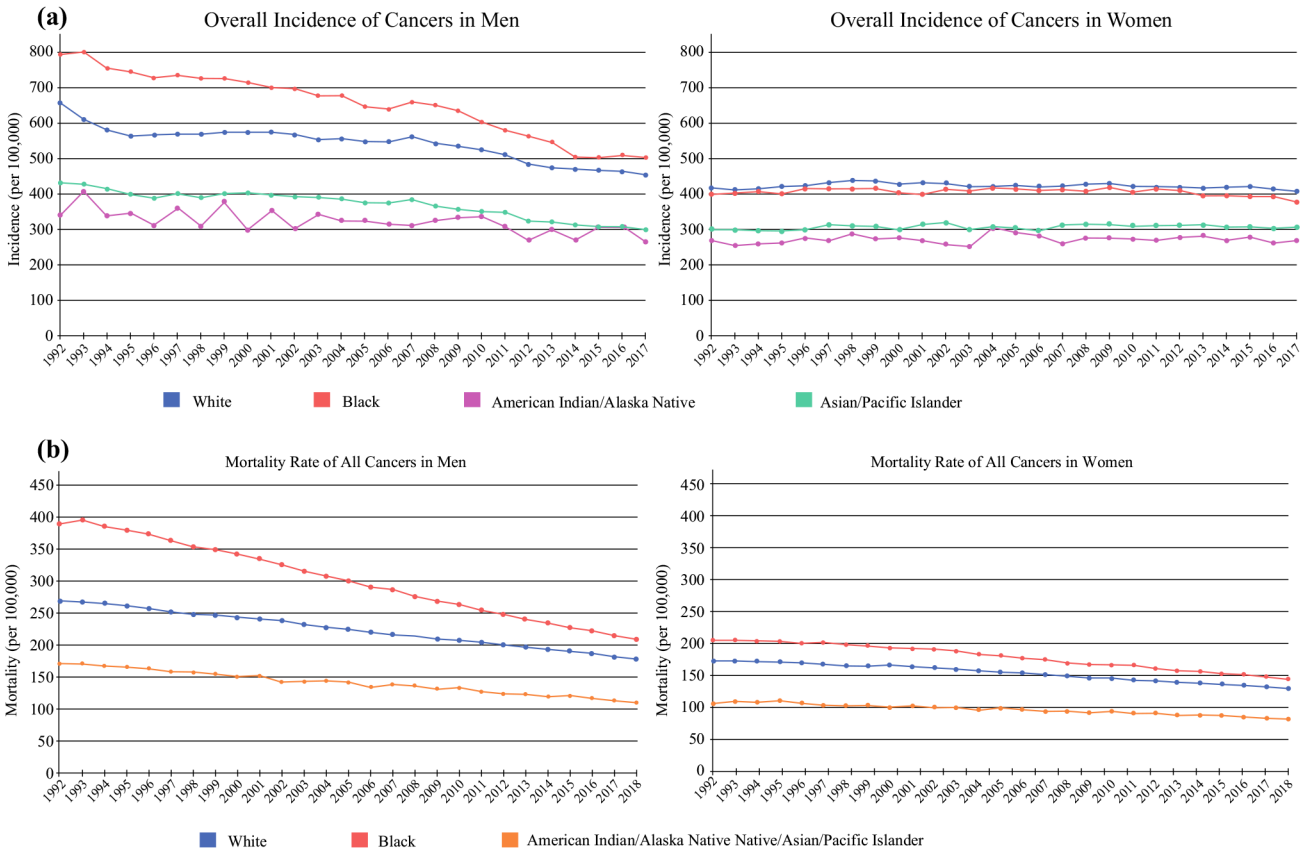

FIG. 2.

Trend in the incidence of **a** all cancers in men and women, and **b** mortality from all cancers in men and women. Incidence data from SEER Research Data, 13 Registries, Nov 2019 Sub (1992–2017), and mortality data from Mortality-All COD, Aggregated with State, Total US (1969–2018). Rates are age-adjusted per 100,000. *SEER* Surveillance, Epidemiology, and End Results

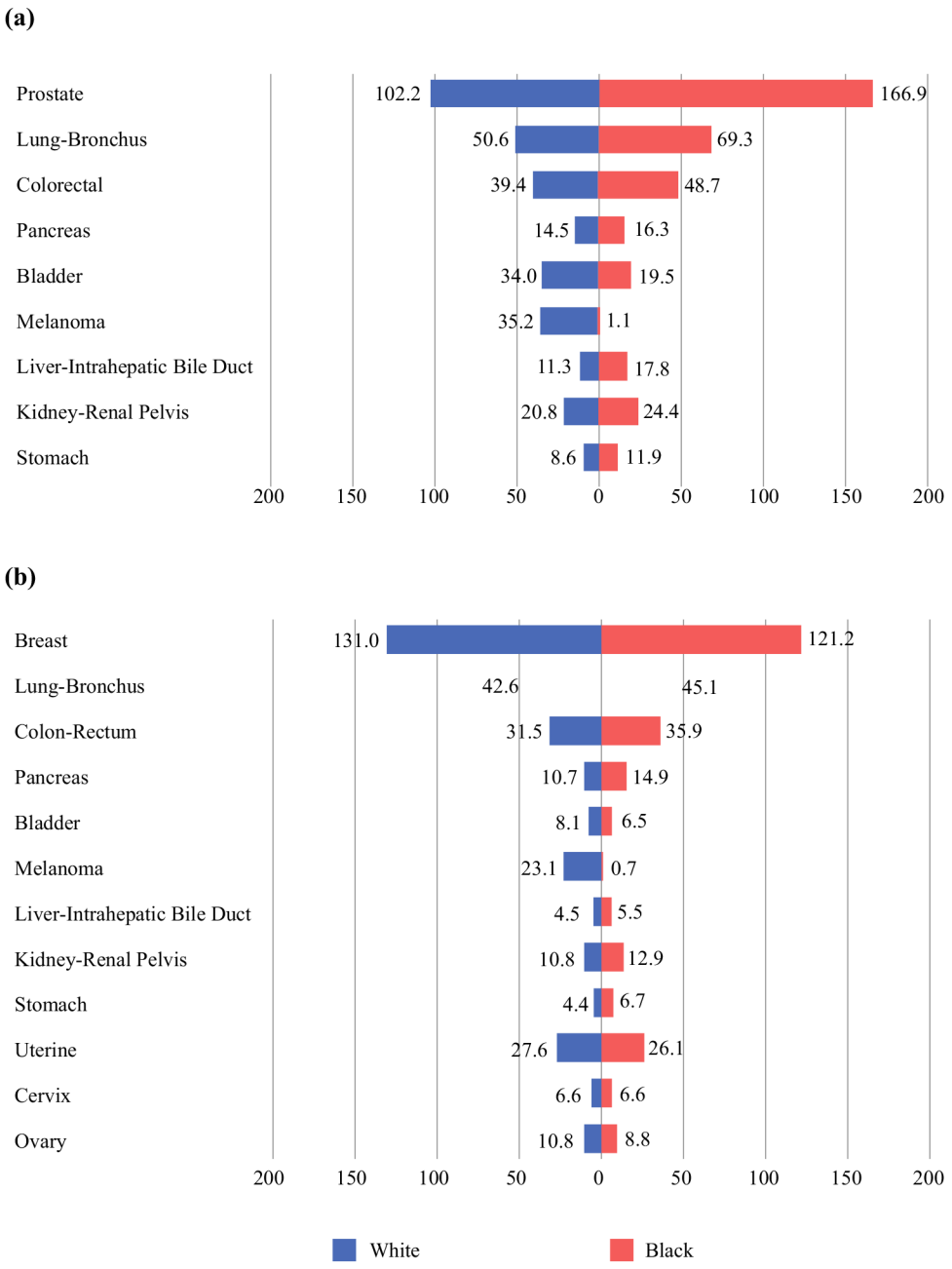

FIG. 3.

Incidence of the most common cancers of White and Black American **a** men and **b** women between 1992 and 2017. Data from SEER Research Data, 13 Registries, Nov 2019 Sub (1992–2017). Rates are age-adjusted per 100,000. *SEER* Surveillance, Epidemiology, and End Results

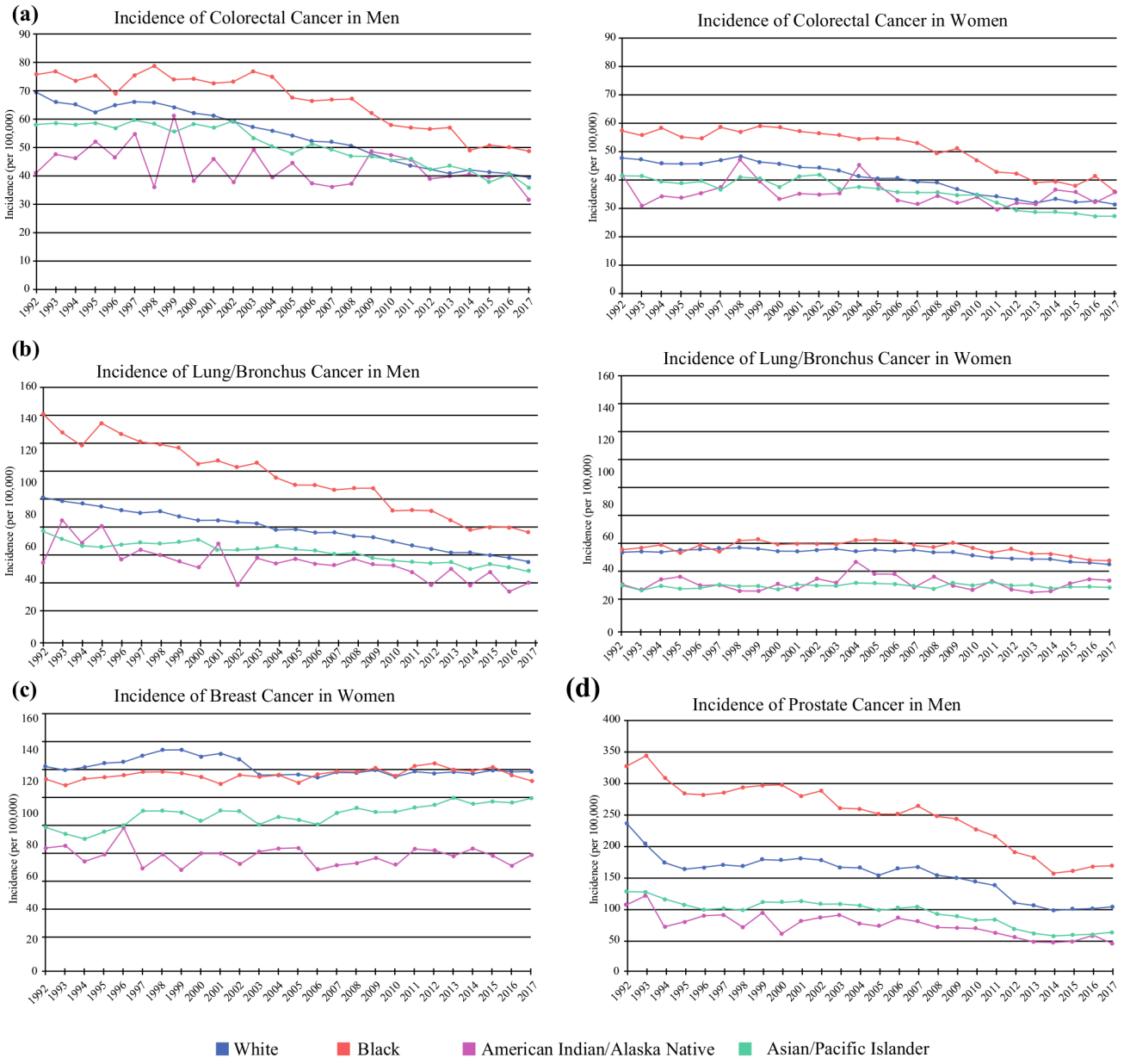

FIG. 4.

Trend in the incidence of **a** colorectal cancer, **b** lung/bronchus cancer, **c** breast cancer in women, and **d** prostate cancer in men. Data from SEER Research Data, 13 Registries, Nov 2019 Sub (1992–2017). Rates are age-adjusted per 100,000. *SEER* Surveillance, Epidemiology, and End Results

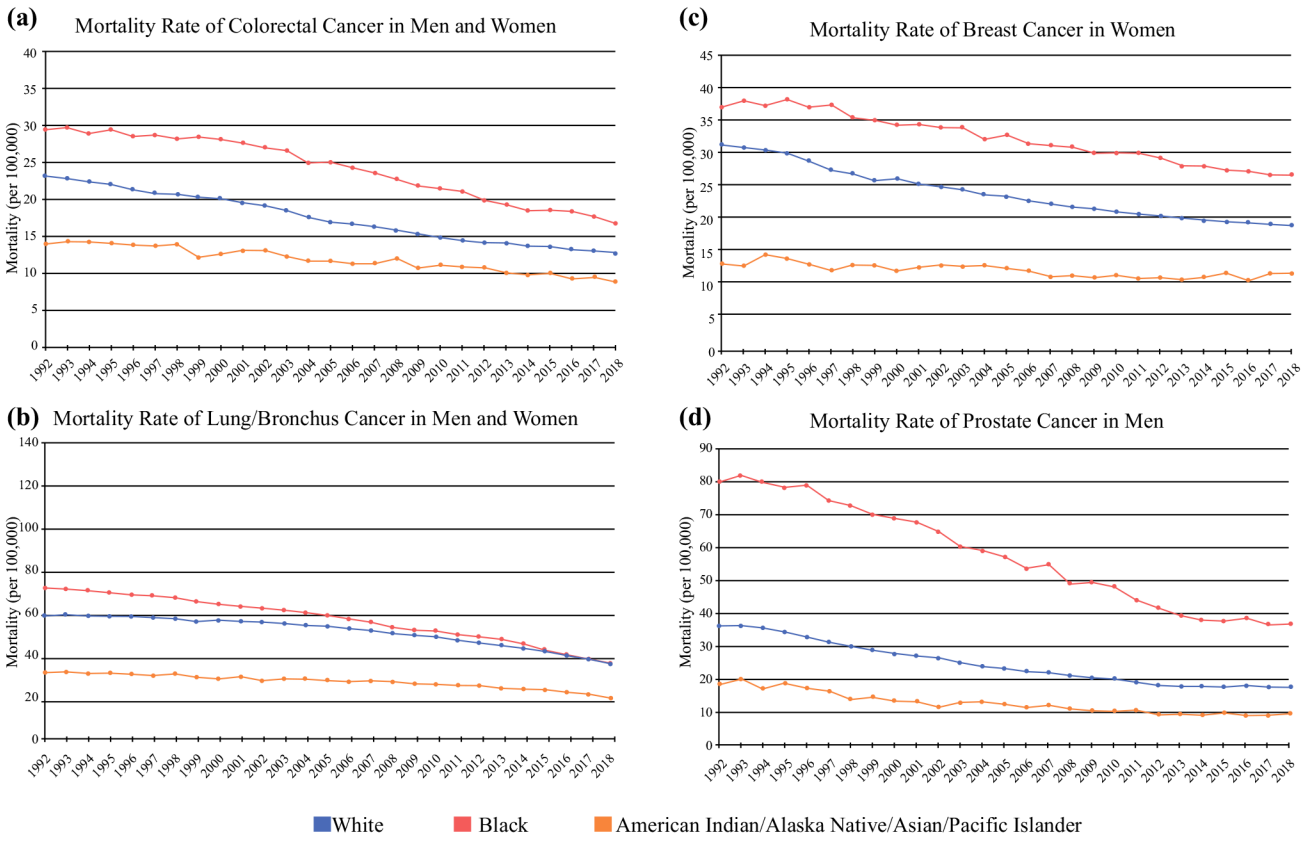

FIG. 5.

Trend in the mortality of **a** colorectal cancer, **b** lung/bronchus cancer, **c** breast cancer in women, and **d** prostate cancer in men. Mortality data from Mortality-All COD, Aggregated with State, Total US (1969–2018). Rates are age-adjusted per 100,000.