

# Looking at cancer health disparities without the colored lenses

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## ABSTRACT

Cancer health disparities (CHDs), defined as the adverse differences in cancer incidence and mortality, are prevalent in certain racial and ethnic groups. Underlying causes of CHDs are multi-factorial and debatable. While low socioeconomic status, geographical location, lifestyle and behavioral factors are mostly believed to contribute to CHDs, regardless of ethnic and racial background, significant data now also exist to support a genetic basis of such disparities as well. Clearly, CHDs could best be understood by studying the interplay of multiple (genetic and non-genetic) factors and then translating the resulting knowledge into effective approaches for reducing the existing disparity gaps. This review article highlights these aspects in brief and calls the people of different expertise to work together to make an impact and tackle the challenges associated with CHDs.

**KEYWORDS:** Cancer, health disparities, socioeconomic status, genetics, epigenetics, ancestry

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## INTRODUCTION

Cancer is the second most leading cause of deaths in the United States (US). American Cancer Society estimates that 1,735,350 new cancer cases will be reported and 609,640 lives will be taken by this devastating disease in 2018 (Siegel et al., 2018). As a result, besides being cause of pain and despair to the affected individuals and their families, cancer also remains a huge economic burden to the society. National Cancer Institute (NCI) reported that the total expenditures for the cancer care in the US was about \$125 billion in 2010, and it could reach up to \$156 billion by 2020 (<https://www.cancer.gov/about-cancer/understanding/statistics>). Moreover, federal agencies spend significant amount of money on cancer research to develop a better understanding of tumor biology at the molecular level and to find novel ways for its prevention and therapy. Several private foundations also provide funding support at the local and national levels for ground-breaking cancer research. Consequently, we have witnessed some decline in cancer-associated mortality since early 1990s for several tumor types; however, not every section of the society has benefitted equally (DeSantis et al., 2016; Deshmukh et al., 2017).

Cancer health disparities (CHDs) are the most evident among certain racial and ethnic minorities living in America. National Cancer Act of 1971 founded Surveillance, Epidemiology, and End Results (SEER) database within the National Cancer Institute (NCI) to track the progress in cancer care outcomes and to better analyze CHDs. NCI-SEER collects and maintains race and ethnicity information for all cancer types, which is helpful in analyzing the incidence, mortality and survival in different racial and ethnic groups such as African-American/Black, European-American/White, Asian/Pacific Islander, American Indian/Alaska Natives, and Hispanic/Latino

(Polite et al., 2017)). The SEER data suggest that the people of some racial minorities are disproportionately affected by cancer in terms of incidence, mortality and co-morbidities associated with cancer. Considering these evidence, NCI and other funding agencies are investing in CHDs research to tackle them at various levels.

## UNDERLYING CAUSES OF CANCER HEALTH DISPARITIES

CHDs are multi-factorial. It is believed that various complex and interrelated factors are involved in disparate cancer incidence and clinical outcomes. These include differences in socioeconomic status (SES), geographical location, genetic predisposition, race, ethnicity, gender/sex identity, language barrier, food habits, cultural acuties, and access to health-care system (Polite et al., 2017; Raghavan, 2007; Winkleby et al., 1992).

**Socioeconomic factors:** There is no doubt that SES determinants influence cancer risk globally and there is evidence to suggest that cancer mortality rates are declining at relatively slow rates in low SES individual/families as compared to those with higher SES (Ward et al., 2004). Residential segregation is an important SES factor associated with health disparities, and it is more prevalent among African Americans in the US as compared to other minorities (O'Keefe et al., 2015). For example, lung cancer mortality rate is very high in African American patients living in segregated neighborhoods (Hayanga et al., 2013). The residential segregation limits the access to better healthcare, recreational facilities and clean environment, which may all serve as risk factors for cancer development and/or enhanced mortality (Moore et al., 2008; O'Keefe et al., 2015; Williams, 1999). Several racial and ethnic minorities in the US live close to the industrial areas

or work in the agriculture fields wherein they expose themselves to pollutants, insecticides and pesticides, which potentially put them at a greater risk for developing cancer. Study suggests that Hispanics have high cumulative cancer risks (CCRs) due to their high exposure to hazardous air pollutants (HAPs) such as chloroform and benzene as compared to white people (Hun et al., 2009). The linkage of SES with CHDs is not limited to the people living in the United States. In fact, Australian women living in the remote or rural areas were also reported to have high rates of breast cancer death as compared to the residents of metropolitan cities (Yu et al., 2015). Similarly there is evidence for the high rates of advanced stage breast cancer in Australian and Pakistani women living in deprived regions (Aziz et al., 2008; Baade et al., 2011). Low SES groups, Maori and Pacific Island of New Zealand, are also reported to have greater cancer incidence and mortality as compared to European populations (Jeffreys et al., 2005).

**Geographical factors:** Cancer incidence and mortality rates vary among geographical locations. For example, the incidence of leukemia is greater in Australia and New Zealand, but reported least in Western Africa (Miranda-Filho et al., 2018). Similarly, mortality related to cervical cancer is three times higher in the Caribbean and Latin America as compared to North America (Melan et al., 2017). However, incidence and mortality related to this malignancy is less in many developed countries. Even within the United States, we see disparate incidence in cancer types and their clinical outcomes depending upon the geographical locations, which could be related to their exposure to certain pollutants and environmental conditions (Mahal et al., 2014; Miller et al., 2014; Zonderman et al., 2014). Ground water near superfund sites is highly contaminated in Florida and people living near those

geographical locations have higher chances of developing cancer (Kirpich and Leary, 2017). Similarly, the incidence of lung, brain and bladder cancer is higher in areas with increased content of copper, arsenic and cadmium present in soil, respectively (Lopez-Abente et al., 2018). People living in Louisiana and Mississippi have high cadmium exposure and study have shown the correlation between high cadmium exposure and increased risk of pancreatic cancer (Luckett et al., 2012). Drinking water is significantly contaminated with arsenic in New Hampshire and Wisconsin regions and retrospective studies suggested the link between arsenic exposure and skin cancer (Mayer and Goldman, 2016).

**Life style and other behavioral factors:** It is observed that the highest incidence of gastric cancer is in the Eastern Asian and South American countries. *Helicobacter pylori* infection is shown to put people at six fold higher risk of developing gastric cancer (Giesecke, 1993). An earlier study suggested a close association of diet and *H. pylori* infection in gastric cancer. Consumption of high salt and fermented foods is also associated with *H. pylori* infection (Rocco and Nardone, 2007). This suggests that life style factors and food habits could be responsible for existing disparities in gastric cancer (Luo et al., 2017). High rates of hepatitis B and C infection and aflatoxin exposure through diet lead to higher incidence of hepatocellular cancer in the region of sub-Sahara Africa and China. Hepatitis B and C virus infection are associated with chronic liver disease, and these viral infections are more prevalent in many low income countries due to lack of knowledge about the route of transmission, awareness and some tribal rituals (Coppola et al., 2015). In the US, hepatitis, which is more common in Latino and Asian immigrants, is an established risk factor for hepatocellular cancer development (Jemal et al., 2010). Prostate, breast and pancreatic malignancies are linked with obesity and

are more common in North America, Australia/New Zealand, and Europe as compared to the developing countries. In fact, looking at the yearly trends, we notice that the incidence rates of breast and prostate cancer have started to increase in people of Asia and Africa continents, which could be due to changes in their life style, diet and reproductive behavior-associated factors in addition to increases in the reporting and awareness (Wallace et al., 2011).

**Gender and sexual orientation:** High numbers of non-sex specific cancer cases and cancer-associated deaths have been reported in males as compared to females (Dorak and Karpuzoglu, 2012; Najari et al., 2013). Certain types of malignancies like brain cancer (meningioma), thyroid cancer and bladder cancer are more common in women as compared to men and this could be due to the differences in sex hormones and prevalence of autoimmune disorders and gallbladder stone-induced chronic inflammation among them (Dorak and Karpuzoglu, 2012). In the US, sexual and gender minorities (SGM) have greater chance of developing cancer as compared to heterosexual people. A recent study suggests that people from sexual minorities avoid social gatherings, living in isolated places and more likely to be poor than heterosexual (McCabe et al., 2018). Approximately 30% of SGM do not take advantage of preventative healthcare services due to the lack of insurance or undercoverage for related mental health, gender affirmation surgery, hormone therapy, and coverage to partners (Quinn et al., 2015). In fact, a majority of SGM members do not disclose their sexual orientation due to the fear of discrimination and social stigma (Brown and McElroy, 2018). Collectively, all these factors contribute to the increasing cancer incidence in SGM relative to heterosexuals. Moreover in the US, many health-related surveillance registries do not have sexual orientation and gender identity (SOGI) questions,

which may lead to ignorance of many health comorbidities including cancer in SGM people (Brown and McElroy, 2018; Obedin-Maliver, 2017).

**Genetics and epigenetic factors:** Gene mutations, deletion, amplification, and polymorphism in key growth homeostasis genes are considered the underlying causes of cancer etiology, progression and poor clinical outcomes. Although socio-economic, life style and other factors were long believed to be the major determinants of CHDs, emerging data now also clearly suggest that there could be a genetic and/or epigenetic basis as well (Deshmukh et al., 2017). High frequencies of triple negative breast cancer and intra-tumor genetic heterogeneity are tied with aggressive variant of disease in African American women (Keenan et al., 2015). Deregulation of immune system due to polymorphisms in IL-6 and IFN- $\gamma$  gene has also been reported in African American women (Park and Kang, 2013). Increased serum levels of pro-inflammatory cytokines, IL-6 and resistin, have also been associated with breast cancer disparity (Deshmukh et al., 2015). In another study, difference in the haplotype, PTEN/10q, is associated with disparate incidence and outcome of endometrial cancer in African American and Caucasian American women (Sutton et al., 2015). Prostate cancer burden is quite high in African American people and several mutations and polymorphism in genes associated with androgen biosynthesis, metabolism and androgen receptor signaling has been reported in this group (Bhardwaj et al., 2017). Another study identified locus 8q24 as a risk factor for prostate cancer in African American men (Freedman et al., 2006; Wallace et al., 2011). Mutations and amplification of phosphatidylinositol 3-kinase catalytic subunit alpha (*PI3KCA*) gene has been reported in cervical cancer. *PI3KCA* mutations and amplification rate found to be higher in American

Indian population (Femi, 2018). Higher rate of alterations in mitochondrial genes of African lineage is also linked with cancer predisposition and disparities (Choudhury and Singh, 2017). Apart from genetic factors, epigenetic determinants are also suggested to be involved in CHDs. High hypermethylated CpG islands are associated with cell signaling, survival, cellular communication and cell death, in normal breast tissues of African American women as compared to their Caucasian counterparts. Promoters of many genes tied with epithelial-to-mesenchymal transition (EMT) and cell cycle are found to be hypermethylated in African American breast cancer patients (Ahmad et al., 2017). Differential methylation pattern of CD44 gene may also be involved in the prostate cancer pathogenesis in African American cancer patients (Woodson et al., 2003).

Considering these data, it has become imperative that we pay attention how we categorize patients into different racial groups. Currently, people living in the United States are categorized into different racial and ethnic groups primarily based on their self-reporting. This could be problematic considering the fact that inter-racial marriages are common and more so in modern times leading to the genetic admixtures rather than defined racial/ethnic identities. Indeed, genetic analyses have suggested that some of the self-reported African Americans have up to 99% of European ancestry (Merisha and Abebe, 2015). In the US, Hispanics are highly diverse population and study suggest that self-reported Hispanic individual could be more close to being of African, European, or Native American lineage due to population admixtures (Lee et al., 2010). To overcome these artifacts, we should rely on genetic ancestry profiling by using advanced molecular techniques such as single nucleotide polymorphisms (SNPs) and short tandem repeat (STR) typing. In

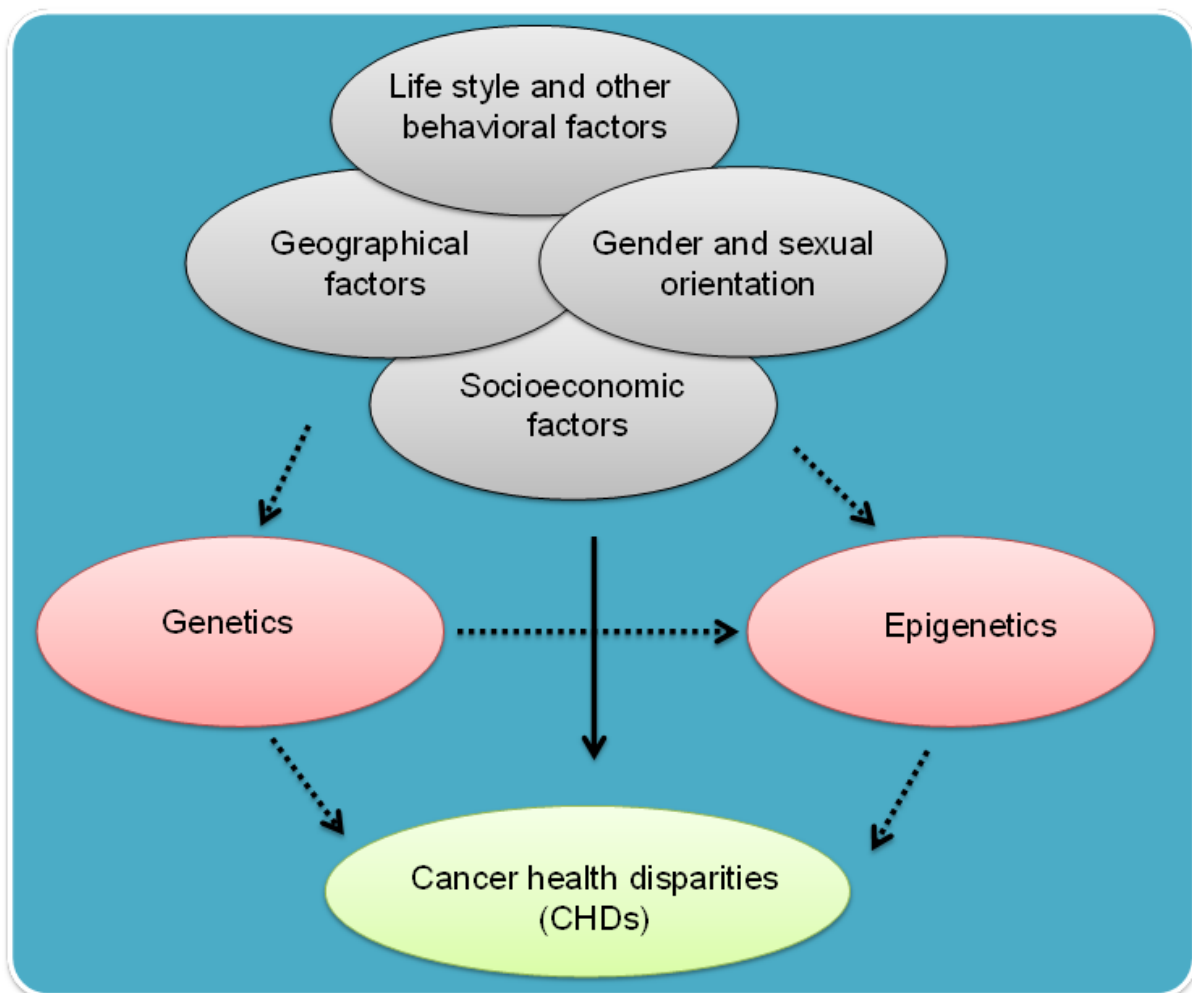
addition, haploid markers like Y-SNPs and mitochondrial DNA can also be used for determination of paternal and maternal lineage (Egeland et al., 2004; Phillips et al., 2007). Some of our recent studies took advantage of modern genomic technologies to classify patients based on their racial genetic admixtures and noticed that categorization of patients based on their racial genetic admixtures provided more accurate determination of clinical outcomes (Rocconi et al., 2016; Ross et al., 2017).

## EMERGING OUTLOOK

Years of money and manpower investment in cancer research has resulted in effective screening approaches and therapies for several cancers leading to considerable improvements in patient's survival. Although not all sections of the society have benefitted equally, we have succeeded in recognizing such health inequalities and have developed an improved understanding of underlying causes. We have learnt that differences in SES, life style, and geographical location impact cancer incidence and mortality rates regardless of race and ethnic identities. Moreover, gender-based inequalities are also common that could in part be associated with life style factors, but may also have a biological basis as well. In addition, many new findings have also suggested certain races and ethnic groups experience greater incidence and mortality of cancer even when SES and other factors are accounted for. In support of such observations, several genetic and epigenetic differences in people belonging to these minority groups have also been reported. Therefore, while the skin color and ethnicity may not be the primary determinant of CHDs, there is strong evidence to suggest a genetic basis as well. In fact, the emerging notion now is that it is the interplay of multiple (genetic and non-

genetic) factors that underlies the prevalent CHDs (Figure 1). Therefore, finding these connections at the molecular levels and translating the resulting knowledge into effective approaches for prevention and clinical management are of utmost importance to reduce existing disparity gaps. In addition, currently, the race and ethnicity classification is based on self-reporting, which could be socio-political or cultural rather than being based on genetics and biology of the individual (Rebbeck and Sankar, 2005; Wallace et al., 2011). Therefore, it is important to include genetic screening in categorizing race and

ethnicity of the participant groups to avoid any artifacts. It is also the need of the hour that people of different expertise (public health professional, physical scientists, biologists, social scientist, epidemiologists, and community members) work together to make an impact. More research funding opportunities emphasizing minority health disparities, commitment of research centers and hospitals and improvisation of research policies will also be helpful in addressing the challenges associated with CHDs.



**Figure 1:** Schematic diagram showing cross-talk between biological and non-biological factors involved in cancer health disparities (CHDs).

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### Conflict of interest

APS and SS are co-founders and serve on executive management team of Tatva Biosciences, LLC, which is involved in the development of tools and models for cancer health disparity research. SKS is the Director of Cell Biology and Genetics at Tatva Biosciences LLC.

### Authors' contributions

Conception and design: MAK, GKP, SKS, SS and APS. Writing, review, and revision of the manuscript: MAK, GKP, SKS, JEC, JYP, RPR SS and APS.

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