EXPERT REVIEW

Neighborhood deprivation, racial segregation and associations with cancer risk and outcomes across the cancer-control continuum

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The racial/ethnic disparities in cancer incidence and outcome are partially due to the inequities in neighborhood advantage. Mounting evidences supported a link between neighborhood deprivation and cancer outcomes including higher mortality. In this review, we discuss some of the findings related to work on area-level neighborhood variables and cancer outcomes, and the potential biological and built/natural environmental mechanisms that might explain this link. Studies have also shown that residents of deprived neighborhoods or of racially or economically segregated neighborhoods have worse health outcomes than residents of more affluent neighborhoods and/or less racially or economically segregated neighborhoods, even after adjusting for the individual-level socioeconomic status. To date, little research has been conducted investigating the biological mediators that may play roles in the associations of neighborhood deprivation and segregation with cancer outcomes. The psychophysiological stress induced by neighborhood disadvantage among people living in these neighborhoods could be a potential underlying biological mechanism. We examined a number of chronic stress-related pathways that may potentially mediate the relationship between area-level neighborhood factors and cancer outcomes, including higher allostatic load, stress hormones, altered epigenome and telomere maintenance and biological aging. In conclusion, the extant evidence supports the notion that neighborhood deprivation and racial segregation have unfavorable impacts on cancer. Understanding how neighborhood factors influence the biological stress response has the potential to inform *where* and *what* types of resources are needed within the community to improve cancer outcomes and reduce disparities. More studies are warranted to directly assess the role of biological and social mechanisms in mediating the relationship between neighborhood factors and cancer outcomes.

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INTRODUCTION

In the United States, historic and present-day residential segregation has shifted access to neighborhood and community resources such that a greater percentage of minoritized individuals are living in more disadvantaged neighborhoods. The racial/ethnic disparities in cancer incidence and outcome are believed to be, in part, due to the inequities in neighborhood advantage and the community stress this induces among people in these neighborhoods. Thus, where one grows up and resides matters to one's cancer risk and one's ability to recover from the disease. This interest in neighborhood factors and how they relate to health has been a cornerstone in the field of social epidemiology for several years. Fueled by the availability of geospatial data and advanced analytics, increased interest in this area has emerged rapidly over the past 20 years. While neighborhood determinants can refer to and include the natural environment (e.g., pollution and exposures to toxins), green space (e.g., access to parks), and retail environments (e.g., food deserts) herein we focus on the social, systemic, and structural characteristics of the neighborhood and the ways in which these area-level characteristics have been examined in relation to cancer.

A consistent finding across several studies is that residents of deprived neighborhoods or of racially or economically segregated neighborhoods have worse health outcomes than residents of more affluent neighborhoods and/or less racially or economically segregated neighborhoods, even after adjusting for the individual-level socioeconomic status (SES) [1–3]. Characteristics of neighborhood deprivation have included either area-level components (e.g., low SES of residents, high concentration of rental homes, low home property value, poverty, neighborhood crime/violence) or indices of these components (e.g., Neighborhood Deprivation Index) [1, 4, 5]. Measures of segregation have included measures such as the percent of residents in a geographic area who belong to a racial or ethnic minority group, and other measures, such dissimilarity (uneven distribution of individuals from African American (AA) and Caucasian backgrounds), isolation (probability of AA individual encountering another AA individual), concentration (density of AA individuals), centralization (degree to which AA individuals are located in urban centers) or combinations of these characteristics, such as hyper segregation (simultaneous occurrence of these) and the Index of Concentration at the Extremes, which combines area-level residential household income and racial segregation data [6].

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Unfavorable neighborhood conditions related to deprivation and segregation are associated with an increased risk of morbidity and mortality of chronic diseases, including diabetes, hypertension, cardiovascular diseases, depression, and, as highlighted in this review, cancer [7–9].

In this review, we discuss some of the previous literature and more recent findings related to work on area-level neighborhood variables and cancer outcomes along the cancer-control continuum. By cancer-control continuum we mean papers that have examined outcomes related to early detection (screening), incidence and stage of diagnosis, mortality and survivorship. We organize our discussion around papers that have examined (i) characteristics of neighborhood deprivation and (ii) racial and economic segregation and cancer outcomes and then (iii) evaluate several potential (iii) biological and (iv) social mechanisms linking neighborhood variables to cancer outcomes. We conclude with a discussion of next steps for future research.

Neighborhood deprivation

The relationship that neighborhood deprivation has with cancer outcomes has been highlighted by Gomez et al. the authors reviewed published papers between 2010 and 2014 ($n = 34$) and concluded that a majority of these papers support a link between a harmful social or built environment attributes and a cancer outcome, including a higher incidence, later stage of diagnosis, poorer treatment outcomes, poorer quality of life and higher mortality [10].

More recent articles have emerged showing similar findings as those in this previous review. For instance, recommended screenings for cancers (e.g., breast, cervical, and colorectal) have been shown to be lower for individuals living in the most deprived neighborhoods compared with the least deprived [11]. Neighborhood deprivation has also been linked to a higher incidence of lung cancer, especially among black men who are current or former smokers [12] and a higher incidence of liver cancer among individuals identifying as Hispanic [13]. Examining triple-negative breast cancer (TNBC) data, Hossain et al. found that neighborhood deprivation was related to disparities between AA and Caucasian women in stage at diagnosis and survival (later stage and poor survival among AA women). Notably, disparities in incidence were not observed with respect to neighborhood deprivation [14]. Poorer patient reported outcomes and health related quality of life among cancer survivors has also been associated with greater neighborhood deprivation [15, 16].

Of note, area-level socioeconomic status and neighborhood deprivation in relation to cancer outcomes has been examined across several different countries. Registry data from England for women diagnosed with breast cancer found wide disparities in survival by neighborhood deprivation, regardless of whether they were up-to-date on screening or not, suggesting that the neighborhood effects were independent of access [17]. In a Swedish population study, increased incidence of lung cancer incidence and mortality have been observed in the most deprived neighborhood [18]. Increased incidence of head and neck cancers have also been found in relation to the European Deprivation Index in a French study [19]. Using British Columbia cancer registry data on oral cancers collected between 1981 and 2009, greater proportions of oral cavity cancer cases were diagnosed at later-stage disease for both sexes residing in deprived neighborhoods [20].

Related to neighborhood deprivation are emerging studies of persistent poverty in relation to cancer outcomes. Persistent poverty has been defined as areas where at least 20% of residents have lived below the federal poverty line for several decades. These areas often designated rural and/or have higher percent of individuals from minoritized backgrounds. In two recent papers, Moss and colleagues demonstrated a 12% higher county-level cancer mortality rate in counties designated as persistently poor and 7% higher cancer mortality rate in counties designated as currently poor [21]. In a follow-on study, the team investigated how the intersection between race and poverty relates to these mortality rates by showing that rural black residents had some of the highest cancer mortality rates for several of the more common types of cancers (colorectal, oropharyngeal, breast, cervical and prostate) [22]. Recent executive orders [23], as well as the National Cancer Institute's recent strategic budget, have highlighted a need for more research on the "systemic traits of persistent poverty that lead to cancer disparities." [24] Continued research examining the different aspects and intersection of neighborhood socioeconomic conditions are needed to improve our understanding of how best to tackle the iniquities on cancer outcomes we observe here in the US and elsewhere.

Discrimination, racial segregation, and redlining and cancer outcomes

Studies of racial segregation in relation to cancer outcomes have been highlighted in two reviews, one by Landrine et al. [25] and another by Fang and Tseng [26]. Landrine et al. reviewing papers primarily focused on breast cancer ($n = 17$), noted several papers in their review supported a link between residential segregation and Black-white cancer disparities (higher likelihood of later-stage diagnosis, higher mortality rates, and lower survival rates) [25]. Fang and Tseng reviewed papers examining racial and ethnic minority density—the percentage of residents in a geographic area who belong to a racial or ethnic minority group [26]. Minority density has been examined as a cancer risk factor, as it can be a proxy for neighborhood segregation. In some instances, however, these "ethnic enclaves" may be protective, as they preserve social-cultural cohesion and support. From their review, these authors concluded that racial and ethnic density was related to a higher incidence for cancers of an infectious origin (e.g., liver, cervical) but a lower risk for breast and colorectal cancers among Hispanic/Latinx and Asian Americans [26]. Also, Hispanic density was related to later-stage diagnosis and Black density was related to a higher cancer mortality.

Discrimination. Discrimination can come in the form of implicit and explicit biases and discrimination in health care access and delivery of quality care may lead to disparities in cancer treatments and, consequently, outcomes [27]. Using data from the California Cancer Registry collected during 2004 to 2016, Black patients and those on Medicaid were less likely to receive guideline-concordant medications, compared with white patients and those who had managed care insurance plans [28]. Patients of lower socioeconomic status were also less likely to receive NCCN-adherent care across all cancer types except cervical cancer ($P < 0.0001$). Studies have also shown that discrimination may influence certain behavioral risk factors for cancer, through heightened levels of stress and depressive symptoms [29, 30]. For example, Shariff-Marco et al. reported that community residents who reported experiencing more racism (being treated unfairly or receiving poorer medical care because of race) were more likely to smoke, binge drink, and be overweight [30]. In another study, men who reported experiencing more racism in the health care system were less likely to be up-to-date on antigen screening for prostate cancer [31].

Racial segregation and redlining. Residential segregation in the U.S. is one indicator of structural racism [32–34]. Structural racism like this operates such that institutions and governmental systems on the federal, state, and local level develop, implement, and enforce laws and policies that explicitly or implicitly advantage whites and disadvantage Blacks and other racial or ethnic minority groups [35, 36]. For decades, starting at least in the 1930s, low-income and minority communities were intentionally cut off from lending and investment through a system known as redlining [37].

The practice of redlining was explicit in its targeting of African Americans. While Latino or Hispanic residents, low-income white residents, noncitizens, communists, and other populations the federal government deemed "risky" were often included in redlining, they were not targeted in the same manner as Black residents. Today, neighborhoods that fall within once-redlined areas are more likely to have a higher concentration of Black residents as well as lower incomes, lower home values, and greater social vulnerability. Those same neighborhoods also suffer from lower life expectancy and higher incidence of chronic diseases [38–41].

Racial segregation has been made operational in geospatial and area-level studies in a number of different ways. As mentioned above, one method has been to examine racial and ethnic density of an area-level variable. Yet other methods have proposed examining racial isolation, or the probability of contact between Black and white residents across neighborhoods [42]. The relationship between racial isolation or ethnic density and cancer has been discussed in a previous review by Fang and Tseng [26]. Since that review, additional studies have been published further assessing the relationship between segregation and cancer [43, 44]. In the Mississippi Delta region, a U-shaped relationship was found between racial segregation and colorectal cancer mortality rates among Black residents in urban counties indicating that for Black residents living in highest and least segregated areas were most at risk [43] In Florida, in a large sample of racially diverse women diagnosed with malignant epithelial ovarian cancer (EOC), Westrick et al. reported that the influence of economic and racialized economic residential segregations on EOC survival was more significant than racial segregation in both non-Hispanic Black and Hispanic women [44]. In further race specified model, Hispanic women had a statistically significant increased hazard of death after controlling for covariates in neighborhood segregations. Examining racial and economic segregation using the Index of Concentration at the Extremes (ICE), an estimate of racial and economic segregation, have also been found to be associated with higher cancer mortality at the county level [45] and a higher hazard of breast cancer mortality at the individual level [46].

Though still very limited, a few studies have explored the relationship between historical redlining and cancer outcomes. In a recent study of residence at Greater Atlanta area, living in redlined census tracts was found associated with a nearly 1.6-fold increase in breast cancer mortality [47]. In another study using data from the Massachusetts Cancer Registry between 2001 and 2015, residing in a previously redlined area imposed an elevated risk for late-stage cervical, breast, lung, or colorectal cancer diagnosis, even for residents of census tracts with present-day economic and racial privilege. The best historical grade was not protective for residents of census tracts without current privilege [48].

Psychophysiological and biological stress pathways

To date, most of the studies about the influence of neighborhood deprivation and segregation on cancer have ignored potential pathways and little research has been conducted investigating the biological and psychophysiological mediators that may play a role in these association. In the broader epidemiologic literature, the biological imbedding of neighborhood disadvantage and the ways it impacts physiological stress pathways has been highlighted by Krieger and Smith and others [49]. Below, we discuss several potential biological mechanisms that could be the focus of further study within the cancer literature, including higher allostatic load (AL), stress hormones, altered epigenome and telomere maintenance and cellular aging.

Allostatic load. Several conceptual frameworks have been proposed to delineate how neighborhood deprivation may be biologically imbedded and, consequently, influence cancer risk, mortality, and disparities. The major theme of those frameworks is that disadvantaged neighborhoods elicit chronic stress, resulting in weathering of endocrine and inflammatory response systems in the body. Living in residential areas that have been systematically devalued may increase stress by long-term direct exposure to environmental, physiological, and psychological stressors associated with the neighborhood environment, and by triggering unhealthy behavioral responses (e.g., increased smoking, alcohol consumption, lack of sleep and exercise, and poor diet). Normally, stress will activate the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis—the classic stress systems—which release chemicals to combat the perceived threat [50]. However, when challenged with prolonged or exaggerated stress stimuli, the normal physiological regulatory systems will be disrupted and consequently cause greater "wear and tear" on the body. Studies have attempted to capture levels of the body's responses to chronic stress using an AL score, which is a multi-system, multi-dimensional composite index, usually involving neuroendocrine, immunological, cardiovascular, and metabolic components.

Though AL has been used in other chronic diseases, its application in cancer research is still limited. Using National Health and Nutrition Examination Survey (NHANES) data, a history of breast cancer was found to be associated with elevated AL in Black women, but not in white women [51]. In our own study, AL was found to be higher in Black and Hispanic than white breast cancer patients ($P = 0.001$ and 0.032, respectively) [52]. AL was also found associated with poorer tumor grade and estrogen receptor negative (ER-) tumors. These findings were similar to those reported recently by Xing et al. [53]. In another recent study within the REGARDS cohort, Blacks were found to have a higher AL compared with whites ($P < 0.001$) at baseline [54]. Then, during the follow-up, a higher baseline AL score was associated with increased risk of all-cause and cancer-specific mortality among both Black and white participants. Similarly, in the NHANES III study, individuals in the highest quartile of multi-systemic biological risk (MSBR), a proxy for AL, had a 64% increased risk of cancer mortality, compared to those in the lowest quartile of MSBR [55].

Stress hormones. Studies in the past decade have shown that living in disadvantage neighborhood is not only associated with lower serum or saliva cortisol but also altered cortisol response to stressors [56–59]. For example, Dublin-Keita et al. reported that higher neighborhood disorder exposure resulted in lower serum cortisol over time compared to individuals in socially ordered neighborhoods among children [56]. Interestingly, the association is seemingly modified by race and gender [56, 57]. Also, disadvantaged neighborhood was found associated with a flatter rate of cortisol decline throughout the day [58]. In terms of stress response, Hackman et al. found that neighborhood disadvantage was associated with cortisol reactivity and this relationship was moderated by gender, such that higher disadvantage predicted higher cortisol reactivity and steeper recovery in boys but not in girls [59].

Chronic stress and excessive levels of stress hormones promote carcinogenesis through several different molecular pathways. First, they can directly affect tumor suppressor genes (e.g., p53) or oncogenes (et al., MDM2, c-myc), damage DNA, and compromise DNA repair capacity [60]. Second, excessive stress hormones lead to inflammation and suppress immunity, thereby disrupting immune surveillance [50, 61]. Third, excessive stress hormones can act on tumor and stromal cells in the tumor microenvironment to promote tumor growth, invasion, and metastasis [62]. Fourth, emerging evidence suggests that chronic stress may affect the microbiota-gut-brain axis [63, 64], and disrupt the metabolic homeostasis. However, we need to be cautious to interpret the

findings since to date most of them were from cell line or animal-based studies. There are few human studies, but not in the context of neighborhood deprivation.

Excessive stress hormones (e.g., catecholamines and glucocorticoids) have been shown to promote tumorigenesis through distinct signaling pathways. For example, catecholamines can trigger the cAMP-protein kinase A (PKA) signaling pathway [65, 66], which further leads to inducing DNA damage, degrading p53, and up-regulating vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP-2 and MMP-9). Chronic stress has also been involved in angiogenesis. In stressed animals, significantly increased tumor blood vessel formation was observed [67].

Chronic stress and stress hormones can induce the expression of stress-related pro-inflammatory genes, thus increasing the release of pro-inflammatory cells and the production of pro-inflammatory cytokines, which results in the activation of inflammatory responses and leads to tumor initiation, promotion, and metastasis [68]. Norepinephrine (a catecholamine-family hormone) is known to increase levels of C-reactive protein (CRP) and the cytokine interleukin 6 (IL-6), both of which function as pro-inflammatory molecules and tumorigenesis. Elevated levels of corticosteroids during stress induce immune suppression via the pro-inflammatory nuclear factor (NF-κB) signaling [69], which helps tumor initiation and progression [70]. Moreover, research shows that stress management in patients with early-stage breast cancer can reverse the up-regulation of the stress-related pro-inflammatory genes in white blood cells [71].

Chronic stress may also activate pro-tumorigenic immune cells (e.g., tumor-associated macrophages (TAMs), dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), and tumor-infiltrating lymphocytes (TILs)). These cells can further promote tumorigenesis [72]. Moreover, activated inflammatory cells produce excess reactive oxygen species (ROS) to drive inflammation and mutagenesis through different pathways [73]. The released cytokines can activate key transcription factors such as NF-κB [74–76] and STAT3 [77], and further promote tumor progression.

Epigenome. Interest in the epigenome has grown rapidly in recent years because it is exquisitely plastic—particularly in early life—and can be programmed or reprogrammed by environmental experience [78]. The epigenome also represents a potential mechanism by which social exposures early in life are embodied at the molecular level, affecting phenotypic expression. Disadvantaged neighborhoods have the potential to disproportionally expose members to community stress and multiple other environmental assaults, which will consequently become imprinted in different epigenomic signatures and affect biological factors underlying multiple disease pathways [79]. In the Multi-Ethnic Study of Atherosclerosis, multiple neighborhood indexes were found to influence DNA methylation and subsequent gene expression of stress- and inflammation-related genes, even after accounting for individual socioeconomic factors [80]. In another study, children raised in more socioeconomically disadvantaged neighborhoods appeared exhibited greater differential DNA methylation in genes involved in inflammation relative to their peers living in more advantaged settings as they entered young adulthood [81].

Recently developed "epigenetic clocks" are a class of biological age estimators that use DNA methylation at predetermined CpG sites to estimate biological variation among those with the same chronologic age [82]. These clocks may be a more sensitive measure of biological aging and are better at estimating biological age than other markers. Interestingly, in a recent study of 2630 women who had a sister with breast cancer but had not had breast cancer themselves, those with the greatest (>75th percentile) neighborhood deprivation had higher epigenetic age acceleration [83].

Telomere length and cellular aging. Telomeres naturally shorten with age [84, 85], but also shorten prematurely in response to stress [86, 87]. Paradoxically, both shorter and longer telomere length has been associated with various types of chronic diseases, including cancer, diabetes, depression, and cardiovascular disease [86–91]. Several studies have shown that telomere length is shorter among African Americans relative to their Caucasian counterparts, suggesting a putative biological stress response to discrimination and inequities [92–95]. Telomere length has also been shown to differ by level of poverty and interact with race and ethnicity to predict TL differently across racial and ethnic groups [96]. Studies also show associations between shorter telomere length and other individual-level exposures that correlate with poor neighborhood circumstances and psychosocial stressors [86, 87, 96].

An inverse relationship between shorter telomere length and a number of area-level neighborhood deprivation factors has been observed, including neighborhood socioeconomic status [97–99], neighborhood disadvantage [100–102], unfavorable social environment [97, 103] and perceived neighborhood quality [103, 104]. In a recent study using the data from the 1999–2002 NHANES, neighborhood deprivation was inversely associated with leukocyte telomere length among individuals living in neighborhoods with medium neighborhood deprivation index (NDI) ($\beta = -0.043$, $P = 0.0005$) and high NDI ($\beta = -0.039$, $P = 0.003$) [105]. Telomere shortening in high deprivation neighborhoods represented 7.5 years of accelerated aging. And the association was more evident among men than women. In another study among breast cancer survivors, higher levels of everyday discrimination were associated with longer telomere length, adjusting for age, race, ethnicity, breast cancer stage, and breast cancer subtype [106]. The opposing direction of associations is interesting, though it may simply reflect differences across the study populations. Clearly, more research is needed.

Built and natural environmental pathways

Neighborhood deprivation and segregation have restructured aspects of the built and natural environment which may represent mechanisms through which deprivation and segregation impact cancer outcomes. Indeed, research has documented a link between food deserts and colorectal cancer incidence [107] and breast and colorectal cancer mortality [108] and food insecurity has been associated with being up-to-date for cancer screening practices [109]. Pollution (e.g., area-level PM2.5) has also been associated with a higher incidence of all types of cancer [110] and specific types such as breast cancer [111–114] and breast density [111], a putative risk factor for breast cancer. Green space, on the other hand, has been associated with reduced cancer incidence of prostate and lung cancer [110]. Also, as highlighted across a number of studies, the tobacco retail environment has been associated with tobacco use, a behavioral risk factor for cancer.

Although often overlooked, there is likely a great deal of correlation between neighborhood deprivation and segregation and other built and natural environmental drivers of health. Research in this area has tended to examine many of these factors in isolation without taking into consideration how structural characteristics of neighborhoods related to segregation, access to educational opportunities, and poverty may drive other aspects of the built and natural environment. Additional work is need to model and understand what aspects of the community environment relate most strongly to cancer outcomes. Given the potential multicollinearity of area-level variables, modeling procedures such as Bayesian index regression models, can be useful in estimating area-level components of neighborhood deprivation along with aspects of the built environment may be most relevant in predicting particular outcomes [115]. For instance, in some of our work, we have found that when considering the importance of both the built environment (tobacco retail environment) and

neighborhood deprivation in relation to prenatal smoke exposure, it is aspects of neighborhood deprivation that have the strongest association [116]. Bringing together multiple area-level variables to examine independent, moderating and mediating roles of neighborhood deprivation along with built and natural environmental variables has the potential to improve our efforts at addressing the inequities that arise in relation to these drivers.

Discussion and future directions

In this review we highlighted the role of neighborhood factors on cancer outcomes, with an eye toward describing the potential biological and built/natural environmental mechanisms that might explain this link. Convincing evidence has supported the notion that neighborhood deprivation has an unfavorable impact on cancer, including lower screening rates, heightened cancer lifestyle risk factors, higher cancer incidence of some types of cancer, more challenging tumor characteristics, higher mortality, and worse survival rates. Though, there are some exceptions where studies find that "ethnic enclave" may serve a protective factor, economic and racial segregation have deleterious associations with cancer outcomes. We further reviewed the literature examining the roles of discrimination, racial segregation, and redlining with cancer outcomes. Though the number of existing studies is still limited, the extant evidence shows that racial segregation and redlining are associated with increased mortality among cancer patients.

Departing from previous reviews, this paper examined a number of mechanisms worth exploring that may mediate the relationship between area-level neighborhood factors and cancer outcomes. The broader scientific literature has highlighted the embodiment hypothesis to explain how neighborhood conditions get "under the skin" and alter psychophysiological stress, immune, and epigenetic pathways. In this review, we highlight how some of these mechanisms are also clearly linked with cancer biology underlying tumorigeneses and progression. In particular, AL, stress hormones, and epigenetics (including telomere biology) are all linked with cancer biomarkers and could be examined further as mediating mechanisms linking neighborhood factor to cancer outcomes, such as stage, tumor progression, and survival. Indeed, as we have highlighted, emerging literature is beginning to show how some of these biomarkers are linked with cancer outcomes. Thus, the logical next step is to examine within existing or new cancer cohorts the link between neighborhood stressors, biomarkers and cancer outcomes. Such findings would highlight more clearly which aspects of neighborhoods relate most to perturbations in which biomarker to impact which outcomes. Honing down on these processes has the potential to then begin to think about how to alter these pathways in favor of preventing and controlling cancer effectively within the population.

While we have highlighted biomarkers that have been linked in independent analyses to upstream structural factors and downstream to cancer progression and outcomes, there may be others to consider. For instance, in ongoing studies, members of our group are exploring protein arginine methyl transferases 6 (PRMT6). PRMT6 expression is increased in AA men compared to Caucasian Men, is stimulated by smoking, and is overexpressed in in vivo models driving lung cancer development. In one of the largest cohorts of black men being screened for lung cancer to date, the team is examining to what degree neighborhood stressors relate to PRMT6 expression and interact with smoking to increase the risk of lung cancer. The findings hold promise at identifying the combination of biomarkers, behavior and neighborhood conditions that could be evaluated to improve early detection of lung cancer among this group of men who have higher rates of lung cancer mortality.

In addition to understanding the biological pathways, aspects such as the retail environment and environmental toxics have been linked to cancer outcomes. It is important to note, however, that these types of environmental factors do not randomly emerge. The structural conditions related to neighborhood deprivation and racial segregation precondition other area-level factors that increase unhealthy lifestyles and exposure to environmental toxins. While continued research is clearly needed, these structural characteristics of our society may be more clearly important to the psychophysiological and biological response than other conditions, like clustering of tobacco outlets or exposure to pollution, that result because of them. While there has been increasing attention in the public health and cancer prevention literature to developing policies that correct for certain types of built and natural environmental conditions (e.g., reducing tobacco retail outlet density, reducing food deserts, minimizing city pollution, etc.), less work has been dedicated to thinking through how to begin to modify the historical and structural conditions that underly neighborhood disadvantage. Given the growing evidence highlighted in this review that neighborhood deprivation and segregation are clearly linked to cancer outcomes, it is imperative to now consider how, we as a field, can begin to correct these systemic injustices. Policies that were once thought to be outside the field of cancer prevention, such as reducing food insecurity, improving stable housing, advancing education equity, addressing systemic racism where it occurs, implementing universal basic income strategies, and other structural interventions could be considered [117]. Addressing these structural factors is not without challenges and will require successful community engagement and partnership. Such efforts are also disease agnostic and do not fit neatly into the National Cancer Institute's funding models which prioritize clear focus on cancer biology and outcomes. Thus, bottom up and top down efforts will be needed to increase our field's focus on addressing these more systemic conditions that clearly matter to multiple health outcomes, including cancer.

It is important to be cautious in interpreting the results from these studies, because few studies have directly assessed the role of molecular mechanisms in mediating the relationship between neighborhood factors and cancer outcomes. Thus, the results from those studies need to be further confirmed. In the future, large cancer cohort studies with detailed information at neighborhood (e.g., neighborhood deprivation), individual (e.g., healthy behaviors and demographics), and molecular levels (e.g., biomarkers) are needed to better understand how unfavorable neighborhood factors may become embedded biologically to influence cancer outcomes [118, 119]. We will also need to consider how exposure to neighborhoods change over time, by incorporating residential histories.

Reducing cancer disparities remains at the top of the national agenda for the National Cancer Institute as well as many other organizations (American Cancer Society, American Society of Clinical Oncology, etc.), and there is an increasing recognition that a radical approach is needed to get to the root of problem. While there is a need to understand ancestry and how it may influence cancer risk or response to treatment, modern cancer disparities are likely largely rooted in the historical and present-day racist practices and structural factors, such as neighborhood deprivation [120]. Moving forward to solve iniquities in cancer outcomes requires looking back to better understand how discriminatory practices have contributed to social determinates of health, fair access to health care and the quality of care delivery. Thus, to advance work in this area, we need to study how neighborhood deprivation and segregation have contributed to cancer outcomes and explore the potential biological and social/behavioral mechanisms that may be driving these effects [121].

The driving force of the modern cancer center is to learn from and partner with members of the community to improve cancer outcomes. Thus, understanding how neighborhood factors influence stress and the biological stress response has the potential to inform the cancer center's "place-based" outreach strategies, and such efforts have the potential to reduce cancer disparities [122].

The findings from such studies can also help inform *where* and *what* types of resources are needed within the community to improve cancer outcomes and reduce disparities. In addition, the data from such studies have the potential to inform local policy strategies by identifying structural factors that create disparities. Shining a light, with data, on the ecosystems that are detrimental to cancer outcomes can inform local community and health system efforts that can be leveraged to correct disparities—a laudable mission of any cancer center.

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AUTHOR CONTRIBUTIONS

Statement: BFF provided an initial conceptualization and outline for the review. JS conducted initial and ongoing literature reviews. BFF, JS, and HZ contributed equally to drafts of the paper. RW and BFF jointly supervised the work and provided final editorial review.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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