CEBP FOCUS

Air Pollution across the Cancer Continuum: Extending Our Understanding of the Relationship between Environmental Exposures and Cancer

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ABSTRACT

Previous studies of the environment and cancer have focused on etiology, showing that extrinsic factors in the environment contribute to 70% to 90% of cancers. Cancer patients and survivors often continue to live in the same neighborhoods they resided in before their cancer diagnosis. Thus, patients and survivors are exposed to the same environmental contexts that likely contributed to their original cancer, but little is known about the health effects of continued exposure to carcinogens after a cancer diagnosis. This commentary provides a summary of studies of the association between $PM_{2.5}$ and cancer mortality among patients and $PM_{2.5}$ and posttreatment morbidity among cancer survivors, and proposes new directions and opportunities for future research on such topics.

See all articles in this *CEBP Focus* section, "Environmental Carcinogenesis: Pathways to Prevention."

Introduction

In this special section of *Cancer Epidemiology, Biomarkers & Prevention*, there are several reports detailing the importance of environmental exposures on cancer etiology. The majority of research has focused on pollutants as a risk factor for new cancer development. However, cancer patients and survivors are exposed to environmental pollutants across their course of care and throughout survivorship. Environmental pollutants and other extrinsic factors contribute to an estimated 70% to 90% of cancers in humans (1), including ambient air pollution, which has been declared carcinogenic to humans (2). Since 2016, emissions of ambient air pollution across the United States have increased, and with it an additional estimated 10,000 deaths in geographic regions where air pollution has worsened (3, 4). The majority of cancer patients and survivors continue to live in the same place they resided in before their diagnosis (5). Their unchanged environmental context contains pollutants and other extrinsic factors that likely contributed to their initial cancer. We propose broadening the scope of understanding of air pollution's effect on cancer from cancer etiology to include examinations of the effects of air pollution on the health of cancer patients during treatment and through survivorship. We suggest three key research priorities that are important for understanding the relationship between air pollution, cancer morbidity, and cancer mortality.

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Priority #1—Disentangling the Relationship between Ambient Air Pollution, Cancer Survival, Tumor Aggressiveness, and Recurrence

$PM_{2.5}$ is the most often studied environmental carcinogen in the context of cancer patient mortality thus far (6–11). Exposure to $PM_{2.5}$ after diagnosis is associated with a significant increase in the risk for mortality among adult patients with lung, breast, kidney, bladder, and liver cancer even after controlling for socioeconomic status, race, and stage at diagnosis (6–13). In this issue, we report significant associations between $PM_{2.5}$ and mortality among adolescent and young adult patients with central nervous system, breast, melanoma, and colorectal cancers, and mortality in patients with pediatric lymphoma, lymphoid leukemia, and central nervous system tumors. However, little is known about the timing of $PM_{2.5}$ exposure that may be most critical to patient outcomes or the biological mechanisms at play. Proposed mechanisms by which $PM_{2.5}$ may lead to cancer mortality are similar to those that induce or promote the original cancer, including genotoxic and epigenetic alterations, inflammation, xenogeneic effects or hormone dysregulation, or by reducing the immune system's ability to fight the cancer (6–10). These mechanisms may also reduce the tumor's sensitivity to cancer treatment, which is a novel mechanism unique to patients with cancer.

Studies of $PM_{2.5}$ and cancer mortality that incorporate molecular markers and measures of cancer aggressiveness can enrich our understanding of the underlying mechanisms leading to mortality. For example, comparing the association of $PM_{2.5}$ and mortality in patients with ER^+, PR^+, or $HER2^+$ breast cancer to mortality among patients with triple-negative breast cancers would provide more information about whether $PM_{2.5}$ is operating through hormonal pathways. Our article in this issue and other studies of adult cancers report that the association of $PM_{2.5}$ and mortality is higher among patients diagnosed with early-stage tumors (10, 11). Longitudinal measures of tumor aggressiveness would provide needed information about the effects of $PM_{2.5}$ on cancer progression in these early-stage tumors (14, 15). Studies of $PM_{2.5}$ and recurrent cancers are rare (11), but $PM_{2.5}$ may be associated with overall recurrence, more aggressive recurrent cancers, and mortality from these recurrent cancers. Studies should also expand the types of pollutants studied to include the other five criteria air pollutants and air toxics.

Priority #2—Quantifying the Additive and Synergistic Effects of Ambient Air Pollution and Cancer Treatment on the Cardiovascular and Pulmonary Outcomes of Cancer Survivors

Air pollution and cancer treatments are associated with morbidity and mortality from the same underlying pulmonary and cardiovascular diseases (**Table 1**), yet little is known about the effects of dual exposure to these two risk factors among cancer patients and survivors. Pulmonary and cardiovascular diseases are among the leading noncancer causes of death among cancer patients and survivors (16–27). These diseases are a product of the pulmonary-toxic and cardiotoxic effects of chest radiation, surgeries, and certain chemotherapies used to treat cancer (18, 28). Because of these treatment-induced physiologic vulnerabilities, cancer survivors and patients may be more susceptible to pollution-related pulmonary or cardiovascular morbidity and mortality than the general public (29).

The idea that cancer treatments can produce significant physiologic vulnerability to environmental pollutants is novel. Our earlier case-crossover study was the first to examine effect modification of the association of $PM_{2.5}$ by cancer treatment in relation to childhood cancer survivor morbidity (29). We found that childhood cancer survivors treated with chemotherapy have significantly higher odds for a respiratory hospitalization after exposure to $PM_{2.5}$ than the general public. Young adult and older adult cancer patients also suffer from treatment-related pulmonary and cardiovascular diseases and

Table 1. Pulmonary and cardiovascular diseases associated with cancer therapies and air pollution.

Diseases reported among cancer survivors	Cancer therapies[a]	Air pollutants[a]
Pulmonary diseases		
Asthma	C (28)	$PM_{2.5}$ (51–53)
Cough	C (18)	$PM_{2.5}$ (52)
Restrictive lung disease	R (54)	$PM_{2.5}$ (55)
Bronchitis	C (18)	$PM_{2.5}$, NO_2 (56)
Pulmonary fibrosis	R, C (18, 28)	NO_2, O_3 (57)
Pneumonia	R (18)	$PM_{2.5}$ (58)
Cardiovascular diseases		
Ischemic heart disease	R (30)	$PM_{2.5}$ (59)
Heart failure	R, C (28) (60)	$PM_{2.5}$, NO_2 (61)
Hypertension	C (16, 20, 28)	$PM_{2.5}$, SO_2, NO_2 (62)
Arteriosclerosis		$PM_{2.5}$ (63)
Atherosclerosis	R, C (64, 65)	$PM_{2.5}$ (66)
Coronary heart or artery disease	C (67)	$PM_{2.5}$ (68, 69)
Heart failure	R, C (30)	$PM_{2.5}$ (63)
Stroke	R, C, S (70, 71)	$PM_{2.5}$, O_3, NO_2 (63)
Cardiac arrhythmia	R, C (20)	NO_2 (72–74)
Ischemic heart disease	R, C(30)	$PM_{2.5}$ (59)
Myocardial infarction	R, C (28) (67)	$PM_{2.5}$, NO_2 (63)
Cardiovascular mortality	R, C (19, 20)	$PM_{2.5}$ (63)

Abbreviations: C, chemotherapy; NO_2, nitrogen dioxide; O_3, ozone; R, radiation; S, surgery; SO_2, sulfur dioxide.
[a]References for evidence of the association are in parentheses.

are at high risk for pulmonary and cardiovascular death (20, 30). For example, patients with breast cancer with triple-negative tumors are at extremely high risk for cardiovascular illness and death due to the chemotherapy and chest radiation used in their treatment (20, 30). Yet, no studies have examined effect modification or interaction of $PM_{2.5}$ or other pollutants by cancer treatments in relation to morbidity or mortality in adults.

Despite the potential for adverse effects, cancer treatments are necessary to save lives. In contrast, patient exposure to environmental pollutants is completely unneeded and preventable through the enforcement of air quality standards that protect the public. We advocate for more studies of the consequences of exposure to environmental pollutants on the noncancer morbidity and mortality among cancer patients and survivors, with a focus on effect modification of this association by different cancer treatments.

Priority #3—Identifying Populations of Cancer Patients and Survivors with the Highest Risk for the Adverse Effects of Ambient Air Pollution

Racial and ethnic minorities often live in more polluted neighborhoods and have reduced cancer survival compared with non-Hispanic White populations (31–38). Clinical studies of racial and ethnic disparities in cancer survival and posttreatment morbidity acknowledge that individual differences, such as tumor biology and healthcare access, are important contributors to excess disease and death (31–38). Studies of the effects of the environment on cancer survivor health have primarily been focused on the built environment (e.g., street connectivity, healthy food availability; refs. 39–41) or the social environment as measured by ethnic enclaves, ethnic density, or racial residential segregation (42–44). These studies acknowledge that neighborhoods with a higher percent of racial and ethnic minorities have more exposure to traffic-based air pollution and air toxics, which is a pattern also found in nationwide studies reporting disproportionately higher exposure to environmental pollutants among minority populations (45–47). To our best knowledge, the direct association of pollution exposure with morbidity and mortality among cancer patients and survivors who are racial and ethnic minorities has not been addressed in any studies.

Building Research Infrastructure to Meet These Priorities

To our best knowledge, no federal funding mechanisms from the NIH have been awarded to investigators studying the effect of environmental carcinogens on cancer patients or survivors. We conducted a search of research studies funded by the NIH with the words "air pollution" and "cancer" in the project terms, title, and abstract between fiscal years 2010 and 2020, including active and inactive projects. All but one of the 68 funded studies were limited to pollution and cancer etiology or studies of exposure assessment. The one study of the environment and cancer survival focused on racial segregation and racism as measures of the environment. At the same time, greater investments in surveillance of recurrent cancers, chemotherapy and radiation doses as reported electronic treatment records, and recording of cancer patient residential histories are needed to accomplish such research. Claims data merged with cancer incidence data, such as SEER-Medicare, may be a good resource for such research, but do not provide coverage of cancer patients under the age of 65. Because young adult patients with cancer and survivors of childhood cancers may be at risk for $PM_{2.5}$-related health problems, new data sources to study these younger populations are needed. Although research along this topic may prove challenging, improved funding opportunities and data resources can facilitate the growth of studies that examine how environmental carcinogens and other pollutants are associated with the health outcomes of cancer patients and survivors.

As our understanding of the adverse effects of air pollution has grown, so has our knowledge of its particularly adverse effect in special populations. Those populations are currently defined by age (children and older adults), preexisting lung or heart disease, specific genetic polymorphisms, and low socioeconomic status (48). More studies are needed to determine whether cancer survivors should be considered a susceptible population. Cancer patients and survivors may be candidates for this consideration on the basis that cancer may increase their susceptibility to pollution-related mortality, and prior exposure to treatment with pulmonary and cardiotoxic therapies may also increase their risk for pollution-related morbidity.

The passing of health-based regulatory standards for the six criteria air pollutants and the recognition of air pollution as a carcinogen were significant victories for public health. Yet, new scientific studies are continually needed to support evidence-based public health policies while pushing the boundaries of what we know. Identifying new vulnerable populations is one way to strengthen the case for better policies surrounding air pollution and other environmental pollutants linked to cancer mortality, aggressiveness, and recurrence (15, 49). Nearly 17 million people in the United States have ever been diagnosed with cancer and the number of people who survive cancer is growing with advances in detection and treatment (50). Although etiology is still vital to study, it is time forge onward and examine environmental carcinogenesis across the full cancer continuum.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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