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Fine Particulate Matter Air Pollution and Mortality among Pediatric, Adolescent, and Young Adult Cancer Patients

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ABSTRACT

Background: Air pollution is a carcinogen and causes pulmonary and cardiac complications. We examined the association of fine particulate matter pollution ($PM_{2.5}$) and mortality from cancer and all causes among pediatric, adolescent, and young adult (AYA) patients with cancer in Utah, a state with considerable variation in $PM_{2.5}$.

Methods: We followed 2,444 pediatric (diagnosed ages 0–14) and 13,459 AYA (diagnosed ages 15–39) patients diagnosed in 1986–2015 from diagnosis to 5 and 10 years postdiagnosis, death, or emigration. We measured average monthly $PM_{2.5}$ by ZIP code during follow-up. Separate pediatric and AYA multivariable Cox models estimated the association of $PM_{2.5}$ and mortality. Among AYAs, we examined effect modification of $PM_{2.5}$ and mortality by stage while controlling for cancer type.

Results: Increases in $PM_{2.5}$ per 5 $\mu g/m^3$ were associated with cancer mortality in pediatric lymphomas and central nervous system (CNS) tumors at both time points, and all cause mortality in lymphoid leukemias [$HR_{5\text{-year}} = 1.32$ (1.02–1.71)]. Among AYAs, $PM_{2.5}$ per 5 $\mu g/m^3$ was associated with cancer mortality in CNS tumors and carcinomas at both time points, and all cause mortality for all AYA cancer types [$HR_{5\text{-year}} = 1.06$ (1.01–1.13)]. $PM_{2.5}$ ≥12 $\mu g/m^3$ was associated with cancer mortality among breast [$HR_{5\text{-year}} = 1.50$ (1.29–1.74); $HR_{10\text{-year}} = 1.30$ (1.13–1.50)] and colorectal cancers [$HR_{5\text{-year}} = 1.74$ (1.29–2.35); $HR_{10\text{-year}} = 1.67$ (1.20–2.31)] at both time points. Effect modification by stage was significant, with local tumors at highest risk.

Conclusions: $PM_{2.5}$ was associated with mortality in pediatric and AYA patients with specific cancers.

Impact: Limiting $PM_{2.5}$ exposure may be important for young cancer patients with certain cancers.

Introduction

Air pollution is classified as a carcinogen and is associated with mortality from cancer, pulmonary, and cardiac causes (1–4). Fine particulate matter air pollution ($PM_{2.5}$) is a risk factor for cancer incidence and mortality among the general adult population (3, 5–7), but its effect among patients with cancer after diagnosis and during treatment is largely understudied. Continued exposure to $PM_{2.5}$ after diagnosis may accelerate cancer progression and increase risk for cancer mortality. Increased $PM_{2.5}$ exposure is associated with cancer mortality among adult patients with breast, liver, and lung cancer (8–12). $PM_{2.5}$ may have a similar association with mortality from cancer or additional causes in young patients with cancer. A study of childhood cancer survivors provides evidence that $PM_{2.5}$ may be a significant contributor to pulmonary morbidity (13), which is a leading cause of death in childhood cancer survivors (14).

To our best knowledge, no studies have investigated how $PM_{2.5}$ exposure affects mortality in pediatric, adolescent, and young adult (AYA) patients with cancer (13). Studies examining disparities in pediatric cancer mortality primarily focus on genetics, cancer biology, treatment-related factors, or race and health behaviors (15, 16). Similarly, studies of AYA cancer mortality include investigations of disparities in survival by race and ethnicity, delays in diagnosis, lack of access to specialists, and histologic differences between cancers in AYAs and older adults (17–19). Since low-income and minority populations who have worse cancer outcomes are more likely to live in communities with higher levels of air pollution (20, 21), pollution may be unaccounted for in these studies. As cancers in young patients are unique in the types of cancers that occur and their underlying biology (17, 19, 22), studies of the association of $PM_{2.5}$ and mortality in older adult patient populations cannot be easily extrapolated to younger patients with cancer.

$PM_{2.5}$ is a major public health problem in the state of Utah (23–26). Population density in Utah is growing rapidly with a minimum of 80% of Utah's population living on 20% of its landmass (27, 28). Heavy reliance on cars for transportation and close residential proximity to major roadways exposes the population to traffic-based air pollution (29, 30). This same majority population lives in county-sized valley basins surrounded by mountains. During the winter, cold temperatures create a layer of air that traps pollutants over the most populated counties, resulting in periods of hazardous $PM_{2.5}$ concentrations (31). The effects of chronic and acute $PM_{2.5}$ exposure on the morbidity and mortality of the Utah population has been studied extensively (23–25, 32, 33), but the effect of $PM_{2.5}$ on mortality among Utah's cancer patient population is unknown.

We examined the association between $PM_{2.5}$ and mortality from cancer and all causes among pediatric and AYA patients with

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cancer in Utah. Previous studies of $PM_{2.5}$ and cancer mortality quantified $PM_{2.5}$ exposure by residence at diagnosis but could not account for residential history postdiagnosis (8–10). Our cohort was derived from a statewide database that allowed us to document patients' residential ZIP codes and the dates associated with those locations after diagnosis. Because $PM_{2.5}$ is postulated to accelerate cancer progression (8–11), we examined effect modification of the association of $PM_{2.5}$ and mortality by stage at diagnosis among AYA patients.

Materials and Methods

Data sources and cohort

We identified pediatric patients (0–14 years) and AYA patients with cancer (15–39 years) diagnosed while residing in Utah from 1986 to 2015 using the Utah Cancer Registry (UCR). UCR provided month and year of diagnosis, race/ethnicity, age at diagnosis, cancer diagnosis, histology, and stage for AYA cancers using the Surveillance, Epidemiology, and End Results (SEER) summary stage (local, regional, distant, and unstaged). Patients were classified by year of diagnosis (1986–1995, 1996–2005, and 2006–2015). Exact day of diagnosis was not released from UCR, so the first was used as a substitute.

UCR records are linked to statewide inpatient hospitalization records from the Utah Department of Health and administrative records (marriage and divorce, driver license, vital records) from the Utah Population Database (UPDB). The UPDB is also linked to electronic emergency department data from two health care systems serving approximately >85% of Utah's population and to outpatient records from one of the same health care systems. All health care records started from a patient's first appearance in the system prior to cancer diagnosis and ended at death or last known record. Health care records contained race and the ICD-9/10 codes associated with the visits. Residential history for our cohort was constructed using a person's first appearance in the database to their last known date of residence in Utah or death. UPDB provided sex, race, and date and cause of death.

We included patients diagnosed with malignant tumors (n = 17,636) who did not have deaths from injury, accidents, and poisonings. From that cohort, we excluded patients who survived <1 month from diagnosis (n = 334) and patients who were missing month of diagnosis, race, SES status at diagnosis, or stage at diagnosis (n = 245).

We followed patients from 1 month after diagnosis to the clinically relevant time points of 5 years and 10 years after diagnosis (34, 35). If a patient's last known date in Utah occurred before the end of either follow-up period, the date of their last record in Utah was used as their end of follow-up. All cause and cancer-specific mortality were defined by ICD-9 and ICD-10 codes from death certificate records linked to the UPDB. In models examining effect modification by stage, we also examined 1-year mortality estimates to determine whether mortality shortly following a diagnosis was also associated with $PM_{2.5}$.

Residential histories and $PM_{2.5}$ exposure

We constructed residential histories using ZIP codes and counties found in all records from first cancer diagnosis to the end of follow-up. Each month during follow-up was assigned a ZIP code. For subjects ages <18 years, parental administrative records and other UPDB records tracked their residential ZIP codes.

Stationary monitors in four Utah counties that contain 80% of Utah's population and major cities, including Salt Lake City (28), measured PM_{10} from 1986 to 1998. For those years we imputed daily county-level $PM_{2.5}$ using no intercept regression models correlating PM_{10} and $PM_{2.5}$ while accounting for stagnation, an approach used in other studies in Utah (36). Data from stationary $PM_{2.5}$ monitors across the state were used to generate ZIP code estimates from 1999 to 2015. We first estimated daily $PM_{2.5}$ from 1999 to 2015 for the 2010 population-weighted centroid of each residential ZIP code using data from the U.S. Environmental Protection Agency (EPA) Datamart (37). Using topographical features, we delineated 20 air basins across the state. Air basins were defined as areas where lateral air movement was reduced due to mountain ranges. Six air basins were in the four counties containing 80% of Utah's population. We assigned each monitor and ZIP code centroid to the air basin where it was located and estimated daily $PM_{2.5}$ using inverse distance weighting, with estimates limited to each air basin because we assumed each basin had a distinct pollution profile.

We calculated each patient's cumulative average $PM_{2.5}$ exposure for the entirety of follow-up, starting at diagnosis. If a patient was followed up between 1986 and 1998, we calculated each patient's cumulative average county-level $PM_{2.5}$ exposure using the imputed $PM_{2.5}$ values. If a patient was followed up from 1999 onward, we calculated their cumulative average $PM_{2.5}$ at every patient's ZIP code. If $PM_{2.5}$ was missing, we substituted the county-level $PM_{2.5}$.

We excluded patients who were missing $PM_{2.5}$ exposure information at the time of diagnosis (n = 1,154). For patients who had $PM_{2.5}$ exposure available from diagnosis onward, we stopped follow-up if $PM_{2.5}$ exposure information became missing before the end of the observational periods.

Cancer variables

Pediatric patient diagnoses were classified using the International Classification for Childhood Cancer (ICCC) Chapters, which each have a unique staging system rarely captured by cancer registries (38, 39). The schema may include patient's age, stage, lymph node involvement, tumor location, tissue histology, or a combination of these criteria. Guided by the Children's Oncology Group criteria for pediatric cancer staging and input from a pediatric oncologist, we determined which cancers had staging criteria that could be approximated using the adult staging criteria [lymphomas, central nervous system (CNS) tumors, malignant bone tumors, germ cell, other malignant, and other/unspecified neoplasms], cancers requiring both stage and histology (soft-tissue sarcomas, neuroblastoma, hepatic tumors), cancers requiring histology alone (renal tumors), and cancers for which staging or risk group criteria were not available (leukemias, retinoblastomas; refs. 40–49).

AYA patients were classified using AYA SEER groupings (50). AYA carcinomas were combined with SEER site codes to identify breast, cervical, colorectal, kidney and renal pelvis, lung, testicular, thyroid, and other carcinomas. AYA cancer stage was defined by the adult cancer stage. Staging does not apply to leukemias which are all categorized as distant. The final AYA stage variable consisted of the categories local, regional, distant, unstaged, and NA (leukemias only).

Other variables

Race/ethnicity (White, non-Hispanic, or non-White) was ascertained from UPDB. If any record mentioned that a participant was not white, they were indicated as such. If race/ethnicity was missing, race/ethnicity was obtained from UPDB birth records containing the self-reported race of the participant's parents.

Census-tract socioeconomic status (SES) at diagnosis was computed by UCR using the Yost index (51). If census tract at diagnosis was unavailable, the Yost index was calculated by county. Patients

were categorized into one of four quartiles (highest, high, low, and lowest SES).

Smoking among AYAs prior to diagnosis was ascertained using ICD-9 (305.1, 649.0-649.04, 989.84, V15.82) and ICD-10 codes (F17.21, 099.330-O99.335, P04.2, P96.81, T65.22, Z57.31, Z71.6, Z72.0, Z77.22, Z87.891) in the health care records that were linked to our cohort. Health care records with smoking ICD codes were only available from 1996 onward.

Statistical models

Multilevel discrete-time survival analysis was used to measure the association between cumulative $PM_{2.5}$ exposure and mortality from cancer and all causes. Follow-up, measured in months, started one month after diagnosis and ended at the month of death, emigration from Utah, missing $PM_{2.5}$, or end of follow-up. In the cause-specific cancer models, individuals were censored if the cause of death was not cancer. Cumulative average $PM_{2.5}$ was measured using a time-varying lag covariate that averaged exposure from the month of diagnosis (t_0) to the month prior to observation (t_{-1}). We modeled $PM_{2.5}$ using both continuous (per 5 $\mu g/m^3$) and categorical measures (EPA 3-year standard of <12 $\mu g/m^3$ or ≥12 $\mu g/m^3$).

Pediatric models were stratified by ICCC Chapters (leukemias, lymphoid leukemias, lymphomas, CNS tumors, neuroblastomas, bone tumors, soft-tissue sarcomas, and hepatic tumors; all other Chapters were excluded due to small sample sizes) and for all pediatric cancers together. Pediatric models for specific ICCC Chapters controlled for sex, diagnosis age, race/ethnicity, census-tract SES clustered by county, and stage and/or histology when applicable. The leukemia-specific model did not include risk groups. The model containing all pediatric cancers included a separate baseline hazard for each ICCC Chapter. Due to the diverse methods of categorizing pediatric cancer stage, this model did not control for stage or histology.

Sensitivity analyses included models stratified by specific AYA Group (leukemias, lymphomas, CNS tumors, bone tumors, melanomas, carcinomas, sarcomas) and a model that included all AYA cancers together. We also ran models that stratified the AYA carcinomas by SEER site. All AYA models controlled for sex, diagnosis age, race/ethnicity, census-tract SES at diagnosis clustered by county, and included a separate baseline hazard for stage except for the leukemia-specific AYA model. Models for AYA cancer of all types included a separate baseline hazard for each cancer and stage.

We display model results for cancers with stable effect estimates defined by event count ≥10 and stability of the confidence interval (CI). We indicate imprecise CIs defined by an upper-to-lower 95% CI ratio (CIR) ≥ 3 when rounded to the nearest whole number (52, 53). Results are considered significant if the CI does not include the null value. Effect modification is significant if the $P < 0.05$ for the test of trend.

Effect modification by stage, smoking, and SES

We examined effect modification of $PM_{2.5}$ by stage using an interaction term among all AYA cancers for which stage applies (lymphomas, CNS tumors, bone tumors, melanomas, carcinomas, soft-tissue sarcomas, miscellaneous specified, unspecified malignant). AYA leukemias were excluded from this analysis. Models for the effect modification by stage controlled for sex, diagnosis age, race/ethnicity, census-tract SES at diagnosis clustered by county, and included a separate baseline hazard for each AYA cancer group. We did not examine effect modification by stage for all pediatric cancers due to the unique classification of stage for each ICCC Chapter.

We examined effect modification by smoking among AYAs diagnosed from 1996 onward using an interaction term between smoking (yes/no) and $PM_{2.5}$ per 5 $\mu g/m^3$. We conducted a sensitivity analysis to assess the impact of smoking in models of $PM_{2.5}$ and mortality among AYA cancers. We also examined effect modification of the association of $PM_{2.5}$ and cancer mortality by census-tract SES among pediatric and AYA cancers of all types at 5 and 10 years after diagnosis. In *post hoc* analyses, we stratified models for cervical cancer by stage due to observed differences in the estimates for this group by stage.

Results

We included 2,444 pediatric patients and 13,459 AYA patients with cancer diagnosed from 1986 to 2015 who were largely White-Caucasian (**Table 1**). Roughly 14% of AYA patients diagnosed from 1996 to 2015 had a record of smoking. The most common pediatric cancers were leukemias, CNS tumors, and lymphomas. The most common AYA cancers were carcinomas, lymphomas, and melanomas. Breast, testicular, and thyroid cancers were the most predominant carcinomas.

After 10 years, approximately 17.5% of pediatric and 16.0% of AYA patients were deceased with 88.8% of pediatric and 81.3% of AYA deaths attributed to cancer. Most deaths occurred within 5 years of diagnosis (pediatric: 89.7%, AYA: 83.1%). On average, pediatric patients had 1.8 residential ZIP codes (range: 1–9) and AYA patients had 1.8 ZIP codes (range: 1–16). After 10 years, the mean cumulative average $PM_{2.5}$ exposure was 10.5 $\mu g/m^3$ (4.96–15.41) among pediatric patients and 10.4 $\mu g/m^3$ (4.6–15.5) among AYA patients. AYA and pediatric patients with cumulative average $PM_{2.5}$ ≥12 $\mu g/m^3$ were in the upper 90% of $PM_{2.5}$ exposure.

We found significant positive associations between $PM_{2.5}$ per 5 $\mu g/m^3$ and cancer mortality among pediatric lymphomas and CNS tumors at 5 and 10 years postdiagnosis (**Table 2**). We found significant associations between $PM_{2.5}$ and all cause mortality among patients diagnosed with lymphomas and CNS tumors at both time points, lymphoid leukemias at 5 years postdiagnosis, and hepatic tumors at 10 years postdiagnosis. Among pediatric cancers of all types, the associations between $PM_{2.5}$ and mortality from cancer or all causes at both time points are marginally nonsignificant, but positive and precise with a CIR of 1. In the categorical analysis representing pediatric patients in the upper 90% of those exposed, $PM_{2.5}$ ≥12 $\mu g/m^3$ and all cause mortality was significant among lymphoid leukemias at 5 years postdiagnosis.

Among AYA patients (**Table 3**), we found significant associations between $PM_{2.5}$ per 5 $\mu g/m^3$ and cancer mortality among CNS tumors and carcinomas at 5 and 10 years postdiagnosis. The association of $PM_{2.5}$ and cancer mortality among all AYA cancers is marginally nonsignificant, but positive and precise. The association for $PM_{2.5}$ and cancer mortality among sarcomas at 10 years postdiagnosis is inverse and marginally nonsignificant, likely driven by sarcomas of other sites. $PM_{2.5}$ had a significant positive association per 5 $\mu g/m^3$ with all cause mortality among all AYA patients with cancer at 5 years postdiagnosis and AYA CNS tumor and carcinoma patients at both time points.

We report significant associations between $PM_{2.5}$ ≥12 $\mu g/m^3$ and cancer mortality among patients of all AYA cancer types, CNS tumors, and carcinomas both time points, and patients with melanoma at 5 years postdiagnosis. The association between $PM_{2.5}$ ≥12 $\mu g/m^3$ and all cause mortality was positive and significant among AYA patients of all cancer types, CNS tumors, melanomas, and carcinomas at 5 and 10 years postdiagnosis, and among AYAs diagnosed with lymphomas at 5 years postdiagnosis.

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Table 1. Characteristics of pediatric and AYA patients with cancer.

	Pediatric patients[a] (*N* = 2,444) *n* (%)	AYA patients[a] (*N* = 13,459) *n* (%)
Female	1,150 (47.1)	7,938 (59.0)
White, non-Hispanic	1,950 (79.8)	11,113 (82.6)
Smoking prior to diagnosis (diagnosed 1996–2015)[b]	—	1,434 (10.7)
Diagnosis year		
1986–1995	603 (24.7)	2,955 (22.0)
1996–2005	795 (32.5)	4,296 (31.9)
2006–2015	1,046 (42.8)	6,208 (46.1)
Census-tract SES quartiles[c]		
Highest SES	762 (31.2)	3,867 (28.7)
High SES	660 (27.0)	3,897 (29.0)
Low SES	591 (24.2)	3,113 (23.1)
Lowest SES	431 (17.6)	2,582 (19.2)
Cancer diagnosis		
Leukemias[d]	722 (29.5)	586 (4.4)
Lymphoid leukemia	*581 (23.8)*	—
Lymphomas[d]	256 (10.5)	1,420 (10.6)
Hodgkin lymphomas	*84 (3.4)*	*729 (5.9)*
Non-Hodgkin lymphomas	*96 (3.9)*	*628 (4.7)*
CNS, cranial, and spinal neoplasms[d]	569 (23.3)	714 (5.3)
Malignant bone cancers[d]	120 (4.9)	286 (2.1)
Sarcomas, all sites[d]	160 (6.6)	356 (2.7)
Soft tissue and heart	*94 (3.8)*	*283 (2.1)*
Germ cell, trophoblastic, and gonad tumors[d]	93 (3.8)	184 (1.4)
Neuroblastoma and peripheral nervous cell tumors[e]	177 (7.2)	—
Retinoblastoma[e]	55 (2.3)	—
Renal tumors[e]	124 (5.1)	—
Hepatic tumors[e]	48 (2.0)	—
Other malignant epithelial neoplasm and melanomas[e]	108 (4.4)	—
Other and unspecified malignant neoplasms[e]	12 (0.5)	—
Melanoma and skin carcinomas[f]	—	2,140 (15.9)
Carcinomas[f]	—	7,361 (54.7)
Breast	—	*1,365 (10.1)*
Cervical	—	*714 (5.3)*
Colorectal	—	*555 (4.1)*
Kidney and renal pelvis	—	*182 (1.4)*
Lung	—	*123 (0.9)*
Testicular	—	*1,323 (9.8)*
Thyroid	—	*2,292 (17.0)*
Other	—	*807 (6.0)*
Miscellaneous specified neoplasms, NOS[f]	—	396 (2.9)
Unspecified malignant neoplasms[f]	12 (0.5)	16 (0.1)
Stage at diagnosis		
Distant	373 (15.3)	1,369 (10.2)
Localized	917 (37.5)	7,922 (58.9)
Regional	381 (15.6)	3,241 (23.9)
Unstaged	51 (2.1)	319 (2.4)
Deaths within 10 years		
All cause deaths	428 (17.5)	2,156 (16.0)
Cancer-related deaths	380 (15.6)	1,753 (13.0)

Note: Italics indicate values for a subset.
Abbreviation: NOS, not otherwise specified.
[a]Pediatric patients diagnosed with their first primary cancer 0–14 years; AYA patients diagnosed with their first primary cancer 15–39 years.
[b]Denominator is AYA 10,501 patients diagnosed from 1996–2015.
[c]Computed using the Yost index.
[d]Common cancers between the ICCC and AYA ICD-O-3/WHO 200 classification (AYA/WHO) systems.
[e]Cancers specific to the ICCC.
[f]Cancers specific to the AYA/WHO.

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Table 2. Fine particulate matter ($PM_{2.5}$) and mortality among pediatric patients with cancer.

	$PM_{2.5}$ per 5 μg/m³		$PM_{2.5}$ ≥12 μg/m³	
	5 years postdiagnosis HR (95% CI)	10 years postdiagnosis HR (95% CI)	5 years postdiagnosis HR (95% CI)	10 years postdiagnosis HR (95% CI)
Cancer mortality				
All cancer types[a]	1.12 (0.98–1.28)	1.09 (0.98–1.22)	1.09 (0.75–1.58)	1.07 (0.79–1.45)
Leukemias, all types[a]	1.10 (0.87–1.39)	1.04 (0.86–1.27)	0.96 (0.61–1.50)	0.88 (0.59–1.31)
Lymphoid leukemia[a]	1.22 (0.87–1.71)	1.06 (0.72–1.58)	1.33 (0.78–2.26[b])	1.05 (0.64–1.71[b])
Lymphomas[c]	1.34[d] (1.06–1.68)	1.34[d,e] (1.06–1.68)	—	—
Central nervous system and intracranial/spinal neoplasms[c]	1.30[d] (1.08–1.56)	1.27[d] (1.05–1.52)	1.41 (0.83–2.38[b])	1.41 (0.91–2.16)
Malignant bone tumors[c]	1.04 (0.37–2.90[b])	0.99 (0.42–2.30[b])	0.42 (0.07–2.66[b])	0.39 (0.06–2.60[b])
Neuroblastoma and other peripheral nervous tumors[f]	1.12 (0.85–1.48)	1.20 (0.95–1.51)	1.30 (0.64–2.62[b])	1.41 (0.68–2.95[b])
Soft-tissue sarcomas[f]	0.81 (0.44–1.47[b])	0.75 (0.42–1.36[b])	0.73 (0.31–1.72[b])	0.67 (0.29–1.54[b])
Hepatic tumors[f]	—	2.10 (0.73–6.06[b])	—	2.14 (0.84–5.44[b])
All cause mortality				
All cancer types[a]	1.09 (0.98–1.20)	1.05 (0.96–1.15)	1.15 (0.87–1.51)	1.10 (0.87–1.39)
Leukemias, all types[a]	1.15 (0.94–1.39)	1.08 (0.91–1.28)	1.23 (0.91–1.66)	1.11 (0.84–1.48)
Lymphoid leukemia[a]	1.32[d] (1.02–1.71)	1.15 (0.82–1.61)	1.69[d] (1.13–2.52)	1.33 (0.90–1.97)
Lymphomas[c]	1.29[d] (1.03–1.62)	1.33[d] (1.11–1.60)	—	—
CNS and intracranial/spinal neoplasms[c]	1.25[d] (1.09–1.44)	1.22[d] (1.04–1.42)	1.41 (0.91–2.19)	1.38 (0.96–1.99)
Malignant bone tumors[c]	0.90 (0.37–2.19[b])	0.89 (0.43–1.85[b])	0.34 (0.06–1.98[b])	0.31 (0.05–1.89[b])
Neuroblastoma and other peripheral nervous tumors[f]	1.00 (0.70–1.41)	1.10 (0.81–1.50)	1.30 (0.63–2.68[b])	1.40 (0.67–2.92[b])
Soft-tissue sarcomas[f]	0.79 (0.43–1.47[b])	0.67 (0.41–1.09[b])	0.70 (0.29–1.70[b])	0.56 (0.27–1.17[b])
Hepatic tumors[f]	2.40 (0.71–8.11[b])	1.20[a] (1.07–1.35)	—	—

Note: Cumulative average monthly $PM_{2.5}$ over all residential ZIP codes over 5 and 10 years postdiagnosis; models for all cancer types are adjusted for cancer diagnosis, and all models are adjusted for sex, race/ethnicity, age at diagnosis, and census-tract SES clustered by county; estimates rounded to the nearest hundredth; and — denotes event count <10.

[a]Stage or risk group not included in model.

[b]Ratio of upper-to-lower 95% CI is ≥3.

[c]Stage included in model.

[d]HRs significant if null value not included in the 95% CI.

[e]No additional deaths.

[f]Stage and histology in model.

Among AYA patients with carcinomas (**Table 4**), we found positive significant associations between $PM_{2.5}$ per 5 μg/m³ and cancer mortality among AYA colorectal cancers and kidney cancers at 5 and 10 years postdiagnosis. The point estimate for kidney cancer is large, but the CIR suggests that these estimates are not precise or stable. The association of $PM_{2.5}$ and mortality from cancer or all causes among breast cancers is marginally nonsignificant but positive with a precise CIR. Among cervical cancers, $PM_{2.5}$ had a significant inverse association with all cause mortality at 10 years postdiagnosis. This inverse association is driven by late-stage cervical cancers (Supplementary Table S1). Local-stage cervical cancers have a positive but nonsignificant association between $PM_{2.5}$ and any type of mortality. Results for $PM_{2.5}$ ≥12 μg/m³ are similar with the addition of a significant association between $PM_{2.5}$ and mortality from all causes and cancer among AYA patients with breast cancer (**Table 4**).

We examined effect modification by stage of the association of $PM_{2.5}$ ≥12 μg/m³ and mortality among all AYA cancers. There was significant effect modification of the association of $PM_{2.5}$ and mortality at 1, 5, and 10 years postdiagnosis (**Table 5**). Compared to tumors diagnosed at more advanced stages, local tumors generally had the highest effect estimates. When examined by year of follow-up, these effect estimates declined in a dose–response fashion in the order of local, regional, distant, and unstaged tumors. We also found evidence of significant effect modification by smoking for the association of $PM_{2.5}$ and all cause mortality among all AYA patients with cancer at 5 years after diagnosis (no smoke HR = 1.06, CI = 0.94–1.19; smoke HR = 0.82, CI = 0.68–0.99; $P_{interaction} = 0.02$; data not in tables). We also found significant effect modification of the association of $PM_{2.5}$ and mortality from cancer and all causes by census-tract SES among AYA patients with cancer (**Fig. 1**) but not among pediatric patients.

We did not see significant differences in the association of $PM_{2.5}$ and mortality between the smoking-adjusted or smoking-unadjusted models (Supplementary Table S2). The sensitivity analysis only included patients with cancer diagnosed from 1996 onward which excluded 22% of our sample. Thus results for the sensitivity analysis are different than the main tables.

Discussion

$PM_{2.5}$ is associated with short- and longer-term mortality for young patients diagnosed with specific cancers in this statewide cohort. Pediatric patients with lymphoma and CNS tumors had a minimum HR of 1.25 for the association of cancer mortality and per 5 μg/m³ increase in $PM_{2.5}$ after 5 and 10 years from diagnosis. We found significant positive associations between $PM_{2.5}$ and mortality for AYA patients with CNS tumors, carcinomas, melanomas, breast, and colorectal cancers, which also align with studies of the effects of air pollutants among older adult patients with cancer (3, 9, 10).

A longitudinal study of the Medicare population found a significant association between $PM_{2.5}$ and an increase in all cause mortality of 7.3% (CL: 7.1–7.5) per 10 μg/m³ of $PM_{2.5}$ (54). Although our study is not directly comparable with the Medicare study, our results suggest

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Table 3. Fine particulate matter ($PM_{2.5}$) and mortality among AYA patients with cancer.

	$PM_{2.5}$ per 5 μg/m³		$PM_{2.5}$ ≥12 μg/m³	
	5 years postdiagnosis HR (95% CI)	10 years postdiagnosis HR (95% CI)	5 years postdiagnosis HR (95% CI)	10 years postdiagnosis HR (95% CI)
Cancer mortality				
All cancer types	1.06 (0.99–1.12)	1.04 (0.96–1.12)	1.21[a] (1.16–1.26)	1.21[a] (1.14–1.28)
Leukemias	0.98 (0.78–1.22)	0.93 (0.77–1.13)	1.26 (0.91–1.74)	1.27 (0.96–1.67)
Lymphomas	0.89 (0.73–1.08)	0.91 (0.76–1.09)	1.19 (0.85–1.66)	1.33 (0.94–1.87)
CNS and intracranial/spinal neoplasms	1.20[a] (1.06–1.36)	1.20[a] (1.04–1.38)	1.49[a] (1.24–1.79)	1.63[a] (1.45–1.83)
Bone tumors	1.00 (0.81–1.23)	0.96 (0.75–1.24)	0.94 (0.55–1.59[b])	0.97 (0.63–1.49)
Melanoma and skin carcinomas	1.17 (0.90–1.52)	1.13 (0.83–1.52)	1.53[a] (1.17–2.01)	1.33 (0.97–1.82)
Carcinomas	1.14[a] (1.06–1.22)	1.10[a] (1.02–1.18)	1.24[a] (1.18–1.31)	1.18[a] (1.11–1.25)
Sarcomas, all sites	0.89 (0.79–1.01)	0.87 (0.76–1.00)	0.85 (0.61–1.17)	0.82 (0.59–1.14)
Soft-tissue and heart sarcomas	0.93 (0.74–1.17)	0.93 (0.74–1.17)	0.96 (0.67–1.37)	0.88 (0.62–1.24)
Sarcomas, other sites	0.77 (0.30–1.94[b])	0.77 (0.30–1.94[b])	0.53 (0.11–2.67[b])	0.66 (0.21–2.04[b])
All cause mortality				
All cancer types	1.06[a] (1.01–1.13)	1.04 (0.96–1.12)	1.25[a] (1.22–1.29)	1.23[a] (1.17–1.28)
Leukemias	0.98 (0.77–1.25)	0.94 (0.76–1.16)	1.18 (0.89–1.56)	1.18 (0.92–1.50)
Lymphomas	0.96 (0.75–1.23)	0.95 (0.75–1.18)	1.27[a] (1.02–1.58)	1.26 (0.98–1.61)
CNS and intracranial/spinal neoplasms	1.22[a] (1.12–1.33)	1.19[a] (1.05–1.36)	1.47[a] (1.26–1.71)	1.56[a] (1.33–1.83)
Bone tumors	1.00 (0.79–1.26)	0.97 (0.73–1.28)	1.13 (0.91–1.39)	1.18 (0.93–1.49)
Melanoma and skin carcinomas	1.13 (0.91–1.41)	1.08 (0.86–1.37)	1.76[a] (1.43–2.16)	1.56[a] (1.30–1.88)
Carcinomas	1.14[a] (1.08–1.20)	1.09[a] (1.03–1.16)	1.27[a] (1.18–1.37)	1.19[a] (1.13–1.26)
Sarcomas, all sites	0.85 (0.71–1.01)	0.84 (0.69–1.01)	0.81 (0.56–1.18)	0.79 (0.55–1.13)
Soft-tissue and heart sarcomas	0.87 (0.66–1.16)	0.84 (0.61–1.15)	0.91 (0.66–1.26)	0.84 (0.60–1.17)
Sarcomas, other sites	0.77 (0.30–1.94[b])	0.88 (0.48–1.59[b])	0.53 (0.11–2.67[b])	0.66 (0.21–2.04[b])

Note: Cumulative average monthly $PM_{2.5}$ over all residential ZIP codes over 5 and 10 years; models for all cancer types are adjusted for cancer diagnosis, and all models are adjusted for sex, race/ethnicity, age at diagnosis, and census-tract SES at diagnosis clustered by county; separate baseline hazard included for stage of diagnosis; and estimates rounded to the nearest hundredth.

[a]HRs significant if null value not included in the 95% CI.

[b]Ratio of upper-to-lower 95% CI is ≥3.

Table 4. Fine particulate matter ($PM_{2.5}$) and mortality among AYA patients with carcinoma cancers.

	$PM_{2.5}$ per 5 μg/m³		$PM_{2.5}$ ≥12 μg/m³	
	5 years postdiagnosis HR (95% CI)	10 years postdiagnosis HR (95% CI)	5 years postdiagnosis HR (95% CI)	10 years postdiagnosis HR (95% CI)
Cancer mortality				
Breast	1.18 (0.91–1.54)	1.16 (0.97–1.39)	1.50[a] (1.29–1.74)	1.30[a] (1.13–1.50)
Cervical	0.84 (0.62–1.13)	0.83 (0.67–1.02)	0.83 (0.61–1.13)	0.78 (0.57–1.06)
Colorectal	1.36[a] (1.06–1.75)	1.23[a] (1.00–1.52)	1.74[a] (1.29–2.35)	1.67[a] (1.20–2.31)
Kidney and renal pelvis	4.06[a] (2.06–7.99[b])	6.95[a] (3.10–15.59[b])	—	—
Lung	0.94 (0.68–1.29)	0.86 (0.59–1.26)	—	—
Testicular	0.92 (0.54–1.58[b])	0.88 (0.54–1.42[b])	—	—
Thyroid	—	1.16 (0.61–2.19[b])	—	—
Other	1.09 (0.98–1.22)	1.05 (0.94–1.19)	1.03 (0.88–1.20)	1.00 (0.84–1.18)
All cause mortality				
Breast	1.26 (0.98–1.62)	1.20 (0.99–1.45)	1.62[a] (1.42–1.84)	1.36[a] (1.19–1.55)
Cervical	0.86 (0.74–1.01)	0.83[a] (0.76–0.90)	0.85 (0.62–1.18)	0.73[a] (0.54–0.99)
Colorectal	1.31[a] (1.04–1.66)	1.21 (0.99–1.49)	1.65[a] (1.35–2.03)	1.64[a] (1.31–2.04)
Kidney and renal pelvis	2.86[a] (2.09–3.91)	2.09[a] (1.16–3.79[b])	—	—
Lung	1.02 (0.77–1.34)	0.93 (0.67–1.29)	—	—
Testicular	0.99 (0.58–1.70[b])	0.95 (0.62–1.46)	—	—
Thyroid	—	1.28 (0.74–2.23[b])	—	—
Other	1.07 (0.98–1.18)	1.04 (0.94–1.15)	1.01 (0.84–1.21)	0.99 (0.82–1.19)

Note: Cumulative average monthly $PM_{2.5}$ over all residential ZIP codes over 5 and 10 years; models adjusted for sex, race/ethnicity, age at diagnosis, and census-tract SES at diagnosis clustered by county; separate baseline hazard included for stage of diagnosis; estimates rounded to the nearest hundredth; and — denotes event count <10.

[a]HRs significant if null value not included in the 95% CI.

[b]Ratio of upper-to-lower 95% CI is ≥3.

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Table 5. Effect modification of the association of cumulative average fine particulate matter ($PM_{2.5}$) ≥12 μg/m^3 and mortality among AYA patients with cancer by stage at diagnosis.

	1 year postdiagnosis		5 years postdiagnosis		10 years postdiagnosis	
	HR (95% CI)	Joint test *P*	HR (95% CI)	Joint test *P*	HR (95% CI)	Joint test *P*
Cancer mortality						
Local	1.15 (0.82–1.60)	<0.001[a]	1.44[b] (1.29–1.61)	<0.001[a]	1.44[b] (1.24–1.66)	<0.0001[a]
Regional	1.46 (0.95–2.25)		1.25[b] (1.04–1.49)		1.07 (0.96–1.19)	
Distant	0.95 (0.78–1.16)		1.09 (0.93–1.26)		1.16[b] (1.03–1.30)	
Unstaged	0.62[b] (0.45–0.87)		0.82 (0.57–1.18)		0.88 (0.67–1.17)	
All cause mortality						
Local	1.30 (0.92–1.83)	<0.001[a]	1.54[b] (1.37–1.73)	<0.001[a]	1.43[b] (1.22–1.67)	<0.0001[a]
Regional	1.63[b] (1.05–2.53)		1.32[b] (1.09–1.60)		1.17[b] (1.03–1.32)	
Distant	0.89 (0.75–1.05)		1.05 (0.85–1.29)		1.11 (0.94–1.32)	
Unstaged	0.78 (0.55–1.10)		1.05 (0.75–1.48)		1.06 (0.80–1.41)	

Note: Models used 5- and 10-year average $PM_{2.5}$ for all residential ZIP codes categorized by EPA yearly standard of 12 μg/m^3 $PM_{2.5}$; 95% CI ratio is ≤2 for all analyses; models adjusted for sex, age at diagnosis, race/ethnicity, and census-tract SES at diagnosis clustered by county; separate baseline hazard for cancer type included (leukemias excluded from this analysis); and estimates rounded to the nearest hundredth.

[a]*P* value for effect modification significant at $P < 0.05$.

[b]HRs significant if null value not included in the 95% CI.

that $PM_{2.5}$ may have a greater association with mortality among certain groups of pediatric patients and patients with AYA cancer than subjects in the Medicare study. Pediatric cancer survivors diagnosed before the age of 21 have rates of frailty similar to older adults, suggestive of early aging attributed to cancer, its therapies, and morbidities common to the aging process (55). Although not directly comparable, early aging could explain in part why our pediatric and AYA cohort has risk estimates similar to or greater than the elderly.

AYAs with cancer may face different risks from $PM_{2.5}$ than older patients with cancer. We found a significant positive association between $PM_{2.5}$ and mortality among AYA patients with colorectal cancer that was present for nitrogen dioxide but not for $PM_{2.5}$ in a study of older adults with cancer (3). Although our AYA kidney cancer sample is small with an imprecise CIR, the HR for the association of $PM_{2.5}$ and cancer mortality 10 years after diagnosis among AYA patients with kidney cancer is greater than an earlier study reporting an adult kidney cancer HR of 1.14 (CI = 1.03–1.27) for $PM_{2.5}$ per 4.4 μg/m^3 (3). Although nonsignificant, the estimate for $PM_{2.5}$ and all cause mortality among AYA patients with kidney cancer is more precise and shows a HR greater than seen in adult patients with kidney cancer (3). The association of $PM_{2.5}$ and all cause mortality in our AYA patients with breast cancer is similar to adult studies reporting a HR of 1.12 (95% CI = 0.96–1.30) per 10 μg/m^3 (3). Patients with breast cancer in the upper 90% of those exposed ($PM_{2.5}$≥12 mg/m^3) may have the greatest risk for $PM_{2.5}$-related mortality from all causes or cancer (10, 56). Further investigation is required to confirm these results.

Stage of diagnosis may play a role in $PM_{2.5}$ and cancer mortality. We report significant effect modification by stage at diagnosis among AYA cancers while controlling for cancer type. Similar to studies of adult patients with lung cancer (8), the association between $PM_{2.5}$ and mortality was highest among patients with localized tumors, suggesting that $PM_{2.5}$ may be driving cancer progression in tissues susceptible to further tumor development. Regional and distant stage tumors may be so developed that $PM_{2.5}$ does not affect further progression of the cancer, or patients diagnosed at later stages may not survive long enough for the adverse effects of chronic $PM_{2.5}$ exposure to be observed. At the same time, patients with local stage disease may remain active or spend more time outdoors, potentially increasing their exposure to $PM_{2.5}$ more than patients with more advanced disease.

Low SES and residence in low-income neighborhoods are associated with elevated residential exposure to air pollutants,

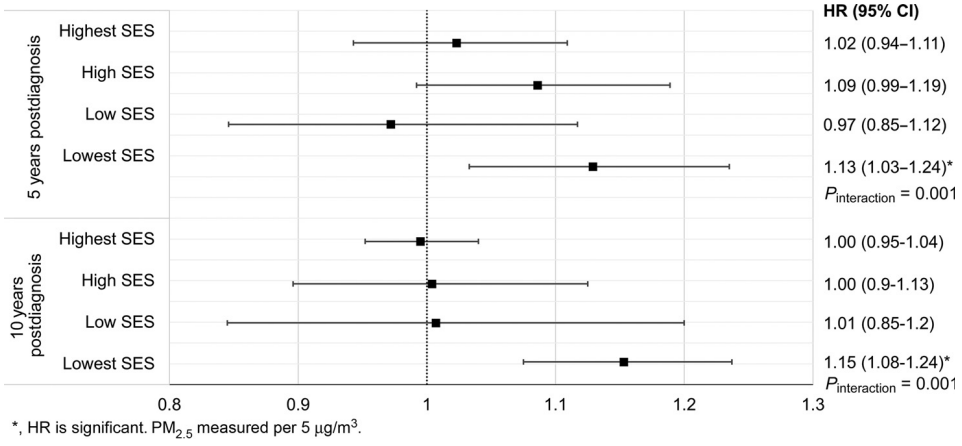

Figure 1.
Effect modification by census-tract SES of the association of fine particulate matter ($PM_{2.5}$) and cancer mortality among AYA patients with cancer. A forest plot for the effect modification by SES of the association of $PM_{2.5}$ and cancer mortality among AYA patients is shown. Cancer mortality was measured at 5 and 10 years after diagnosis. The black squares denote the SES quartile-specific HRs, and the capped horizontal bars indicate the bounds of the 95% CIs. $P_{interaction}$ of SES and $PM_{2.5}$ in the main model is written underneath the HR for the lowest SES quartile. $P_{interaction}$ in the 5- and 10-year models is shown.

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advanced cancer diagnosis, and mortality from cancer among individuals ages <65 years (21, 57, 58). We found significant effect modification of the association of $PM_{2.5}$ and mortality by census-tract SES for AYA cancers of all types, with the greatest effects among the lowest SES patients. Because $PM_{2.5}$ is correlated with residence in a low-income neighborhood (21), $PM_{2.5}$ could operate along separate or interactive etiologic pathways to increase risk for mortality among cancer patients living in low-income neighborhoods and is an important area for future research.

$PM_{2.5}$ levels in the United States have increased over the past 2 years with changes in regulatory policy (59). Our results suggest that chronic $PM_{2.5}$ exposure higher than the current EPA standard of $PM_{2.5}$ ≥12 μg/m^3 may be particularly deleterious for young patients diagnosed with certain cancers. For example, the risk for cancer mortality among AYA patients with colorectal cancer chronically exposed to $PM_{2.5}$ ≥12 μg/m^3 is approximately 20%–30% higher than patients with less exposure. Also, the pediatric and AYA cancers with positive associations between $PM_{2.5}$ and mortality in this study had prior evidence, to varying degrees, of an association with $PM_{2.5}$ and incidence of those same cancers. $PM_{2.5}$ is associated with incident pediatric leukemia, lymphomas, brain astrocytomas, and adult breast and colorectal cancers (60–65). Further research is needed to confirm our findings and elucidate the underlying mechanisms of these associations.

Air pollution's relationship to mortality among patients with cancer could be induced through the mechanisms that initially caused the cancer. Air pollution is a mixture of compounds with genotoxic, cytotoxic, and inflammatory properties (8, 66). In addition to $PM_{2.5}$, air pollution also includes benzene, heavy metals, and polycyclic aromatic hydrocarbons that may promote cancer progression through the aforementioned mechanisms (67–70). $PM_{2.5}$ particles can also promote the proliferation of estrogen receptor (ER)–positive breast cancer cells and inhibit E2-induced cell proliferation (71). Thus, $PM_{2.5}$ exerts both estrogenic and antiestrogenic abilities *in vitro*, qualifying $PM_{2.5}$ as a xenoestrogen (9).

Furthermore, we found that at $PM_{2.5}$ exposure ≥12 μg/m^3, AYA patients with colorectal cancer and breast cancer had the largest risk estimates for the association between $PM_{2.5}$ and mortality. These cancers have estrogenic components to their etiology (72–78). Although estrogen is thought to protect against colorectal cancer (78, 79), the effects of endogenous and exogenous estrogen on the risk of colorectal cancer is still unclear (75). Xenoestrogens may also have different effects on colorectal cancers than endogenous hormones (80). Our results support the theory that $PM_{2.5}$ could induce cancer mortality by acting as a xenoestrogen on hormone-sensitive tissue.

$PM_{2.5}$ may act as an immunosuppressant in patients with cancer by reducing function of T cells and macrophages to fight off the infection (27, 32, 81–83). This pathway may be particularly relevant for skin melanomas. Immunosuppression is strongly proposed as the underlying mechanism for the association of smoking and mortality among melanoma patients (84–87). Similar to cigarette smoke, $PM_{2.5}$ and other pollutants that are inhaled with it are also linked to respiratory and systemic immunosuppression. Although the effect of $PM_{2.5}$ is much smaller than the overall effect of smoking, our significant results for $PM_{2.5}$ ≥12 mg/m^3 and mortality among AYA patients with melanoma implies that $PM_{2.5}$ may have an immunosuppressant effect in patients with melanoma cancer.

A nationwide study found a significant positive association between $PM_{2.5}$ and mortality among patients with cervical cancer (88). We report an inverse association for $PM_{2.5}$ and mortality in patients with cervical cancer but our sample size is limited. This inverse association appears to be driven by cancers diagnosed at late stage, but warrants additional research.

Certain limitations exist with our study. Although our AYA cohort was robust in size, our pediatric cohort was smaller with less precise CIs to provide adequate conclusions for certain sites. Loss to follow-up may also have occurred as 14% of pediatric and 18% of AYA patients with cancer had dates of last residence in Utah that occurred before the end of follow-up.

Modeling $PM_{2.5}$ values for the years 1986 to 1999 could be a source of measurement error. This potential measurement error could have also produced an over or underestimate of effect, particularly in lower-populated counties where air pollution monitoring data were not available. This measurement error may be responsible for the inverse associations seen in the patients with cervical cancer in counties with smaller populations.

Although we used the adult staging and/or pediatric histology to approximate the pediatric staging, these approximations are not direct substitutes for the actual pediatric risk classifications. We were not able to control for risk group in the analyses of leukemias. An additional limitation was a lack of molecular subtype data. For example, as $PM_{2.5}$ may exert xenogeneic effects, future studies should examine the association between $PM_{2.5}$ and mortality in patients with breast cancer by ER^+, PR^+, $HER2^+$, and triple-negative tumor status. We did not control for smoking in the main models. However, Utah has the nation's lowest percent of historic and current smokers, so smoking in patients diagnosed from 1986 to 1995 is likely to be similarly low (89).

While Utah's low smoking limits generalizability, this low smoking rate and low potential exposure to secondhand smoke may increase our ability to the detect effects of $PM_{2.5}$ in this population. Our majority White-Caucasian patient population limits our ability to apply our results to states with a different demographic profile or on a national level. In addition, our cohort is relatively small compared with cancer patient populations in larger states. Further investigation in a larger patient population is needed to confirm our findings.

Strengths of this study include the inclusion of residential histories which reduces exposure misclassification from using ZIP code at diagnosis as the only measure of patient residence. We also implemented a novel model that reduces bias from the high correlation between short survival and high $PM_{2.5}$ exposure. Despite our small sample size, the majority of our reported estimates are precise with upper-to-lower CIRs ≤2.

This study is the first to identify $PM_{2.5}$ air pollution as a significant risk factor for cancer mortality in young patients diagnosed with specific cancers. We also provide support for studies that theorize how air pollution can influence the progression of cancer after diagnosis, thereby building upon the theoretical foundation that supports this work.

Cancer is a leading cause of death in the United States and worldwide (90). While improvements in detection and treatment are of great importance to reducing cancer mortality, understanding how continued exposure to pollutants with known carcinogenic effects such as $PM_{2.5}$ is also important but largely unknown. The majority of cancer patients and survivors live in the same places in which they resided before their diagnosis (91). Their unchanged environmental context contains pollutants and other extrinsic factors that likely contributed to their cancer and may further their risk for mortality after diagnosis. Studies such as this can lead to patient recommendations to reduce their personal exposure to air pollution through home-based or behavioral interventions. One

means is through expanding air pollution alerts to target patients with cancer. More importantly, current changes in policies and protocols have reduced the ability of regulatory bodies to enforce standards for $PM_{2.5}$ and other pollutants (92, 93). Studies are needed to support existing policies and to advocate for further protections of vulnerable populations who may be at great risk for illness and death due to this preventable exposure.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.Y. Ou, H.A. Hanson, J. VanDerslice, A.C. Kirchhoff
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.L. Leiser, J. VanDerslice, A.C. Kirchhoff
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.Y. Ou, H.A. Hanson, J.M. Ramsay, C.A. Pope III, C.L. Leiser, J. VanDerslice, A.C. Kirchhoff
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Study supervision: J.Y. Ou, A.C. Kirchhoff
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