

RESEARCH ARTICLE

Cancer Epidemiology

Association between ambient exposure to PM_{2.5} and upper aerodigestive tract cancer in Los Angeles

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Abstract

Fine particulate matter (PM_{2.5}) contains carcinogens similar to those generated by tobacco smoking, which may increase the risks of developing smoking-related cancers, such as upper aerodigestive tract (UADT) cancers, for both smokers and never-smokers. Therefore, it is imperative to understand the relation between ambient PM_{2.5} exposure and risk of UADT cancers. A population-based case-control study involving 565 incident UADT cancer cases and 983 controls was conducted in Los Angeles County from 1999 to 2004. The average residential PM_{2.5} concentration 1 year before the diagnosis date for cases and the reference date for controls was assessed using a chemical transport model. The association between ambient PM_{2.5} and the UADT cancers was estimated by unconditional logistic regression, adjusting for confounders at the individual and block-group level. Stratified analyses were conducted by sex, tobacco smoking status and UADT subsites. We also assessed the interaction between PM_{2.5} and tobacco smoking on UADT cancers. PM_{2.5} concentrations were associated with an elevated odds of UADT cancers (adjusted odds ratio = 1.21 per interquartile range [4.5 µg/m³] increase; 95% confidence interval: 1.02, 1.44). The association between PM_{2.5} and UADT cancers was similar across UADT subsites, sex and tobacco smoking status. The interaction between PM_{2.5} and tobacco smoking on UADT cancers was approximately additive on the odds scale. The effect estimate for PM_{2.5} and UADT cancers was similar among never smokers. Our findings support the hypothesis that exposure to PM_{2.5} increases the risk of UADT cancers. Improvements in air quality may reduce the risk of UADT cancers.

KEYWORDS

air pollution, esophageal cancer, head and neck cancer, particulate matter, upper aerodigestive tract cancers

What's new?

Fine particulate matter (PM_{2.5}) contains carcinogens similar to those generated by tobacco smoking and is associated with adverse health outcomes, including cancer. This population-based case-control study assessed the association between residential ambient exposure to

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PM_{2.5} and upper aerodigestive track cancers in Los Angeles County from 1999 to 2004. Ambient PM_{2.5} concentrations were associated with elevated odds of upper aerodigestive track cancers, and tobacco smoking status did not appear to modify this association. Improvement in air quality may reduce the risk of upper aerodigestive track cancers.

1 | INTRODUCTION

Upper aerodigestive tract (UADT) cancers include cancers of the oral cavity, larynx and pharynx (head and neck cancer [HNC]) and cancer of the esophagus. Although each HNC site accounts for a small number of cases, combining all these subsites makes HNC the 6th most common cancer and the 7th most common cause of death from cancer in the world.¹ Most HNCs occur in the oral and nasal cavities and squamous cell carcinoma accounts for 90% of HNC cases.² Males have a higher risk of developing HNCs, accounting for 75% of incident cases and HNC mortality.¹ The majority of HNC cases can be attributed to tobacco and alcohol use and their interaction.^{2–5} Sustained infection from certain strains of human papillomavirus virus is also an established risk factor for HNCs.² Due to the heterogeneity of cancer sites, each HNC site might have its distinct risk profile.^{2,6} Esophageal cancer, including squamous cell carcinoma and adenocarcinoma, was ranked the 8th most common cancer and the 6th most common cancer deaths globally.¹ Although globally the major subtype is squamous cell carcinoma, in some countries, including the United States, the incidence of adenocarcinoma exceeds that of squamous cell carcinoma and becomes the predominant subtype.^{7,8} The two histological types of esophageal cancer have distinctive risk profiles aside from the risk due to tobacco use.⁹ Alcohol consumption elevates risk of both cancers, but the association is weaker for adenocarcinoma. While obesity and gastro-esophageal reflux are established risk factors for esophageal adenocarcinoma, these risk factors are not clearly associated with squamous cell carcinoma of the esophagus.⁸

Fine particulate matter (particles with aerodynamic diameter ≤ 2.5 μm in diameter, PM_{2.5}) is regarded the most widespread environmental source of carcinogens.¹⁰ In the United States, air pollution is the 9th leading risk factor for death and 3.8% of the total mortality in 2016 has been attributed to this factor.¹¹ PM_{2.5} may affect diseases via a variety of mechanisms such as altering immune response, increasing oxidative stress, causing inflammatory injury, inducing mutagenicity and resulting in respiratory tract cell damage.^{12–14} Increases in ambient PM_{2.5} concentrations have been associated with elevated cancer risk, especially the risk of lung cancer.^{15–17} In addition, indoor air pollution has been shown to affect specific sites among UADT cancers.^{18–23} However, few studies have investigated associations between ambient air pollution and all UADT cancers combined. When examining the associations between PM_{2.5} and specific UADT subsites, inconsistent results have been reported in studies from Asia,^{24–30} the United States^{31,32} and Europe.^{33,34} These inconsistency in the literature might be due to the different PM_{2.5} exposure levels and toxic PM_{2.5} components at the different study locations, indicating the potential limitations of comparing findings

from geographical locations with different exposure levels and composition. Levels of air pollution in Los Angeles (LA) are higher in proximity to traffic and emitting industries, including local and regional emissions from sources such as airports and container ports, and these sources contribute to the distinct air pollution profile of LA. Here, we examine whether PM_{2.5} is associated with UADT cancer outcomes in LA County in a population-based case-control study with availability of individual-level confounders.

2 | MATERIALS AND METHODS

The UCLA Cancer Study (LA study) is a population-based case-control study of newly diagnosed lung and UADT cancers, which was conducted in LA County from 1999 to 2004. To meet the eligibility criteria for the study, all subjects were (a) residents of LA County at the time of case diagnosis or at the time of recruitment (reference date) for controls; (b) between 18 and 65 years of age during the study period, 1999 to 2004; and (c) English or Spanish speakers, or with translators at home. Study details have been described previously.³⁵ Briefly, lung and UADT cancer patients without a history of previously diagnosed cancers of the lung and UADT sites were identified by the Cancer Surveillance Program for LA County. Controls were individually matched to cases on age decade, sex and residential neighborhood, which was done based on a sequence of 30–40 households in the neighborhood of each enrolled case based on a predefined algorithm. The household selection sequence was expanded if no eligible or willing controls were identified. We are using data of UADT cancer cases and all controls, matched to both lung and UADT cancer cases, for the analysis evaluating associations between ambient PM_{2.5} exposures and UADT cancer risks.

Annual average ambient PM_{2.5} concentrations from 1998 to 2003 across North America at a resolution of 1 km by 1 km were estimated using a chemical transport model (GEOS-Chem) and satellite observation of aerosol optical depth by the Atmospheric Composition Analysis Group.³⁶ The estimation was further calibrated with ground-level monitor observations using a Geographically Weighted Regression. The estimations were reported to be highly consistent with ground-based measurements with R^2 of .70 for the entire North America.³⁷ The layers of annual average PM_{2.5} concentrations were overlaid with the residential addresses on the diagnosis date for cases or on the reference date for controls. These addresses were geocoded to latitude and longitude coordinates using address locators in ESRI ArcGIS (Redlands, CA). The annual average PM_{2.5} concentration 1 year before the diagnosis date for cases or before the reference date for controls were used as the exposure of interest and the

correlation between annual average $PM_{2.5}$ concentrations from 1998 to 2003 at each residential address was estimated.

Among 601 UADT cancer cases, we excluded those whose residence could not be geocoded ($n = 3$), with missing $PM_{2.5}$ concentration ($n = 26$) and missing covariates ($n = 7$). Among 1040 controls, we excluded those who could not be geocoded ($n = 1$), with missing $PM_{2.5}$ concentration ($n = 50$) and missing covariates ($n = 6$). As a result, the final analytical data set included 565 UADT cancer cases and 983 controls. Unconditional logistic regression models were employed in the analysis of the associations between $PM_{2.5}$ and UADT cancers, adjusting for potential confounders, including age, sex, education (less than high school, high school, some college, college or graduate school), race/ethnicity (non-Hispanic White, African American, Hispanic or other), tobacco smoking (never smokers, defined as those smoked less than 100 cigarettes and ever smokers), pack-years, alcohol drink-years, indoor air pollution variables (exposure to solid fuel use for cooking or heating or environmental tobacco exposure since adulthood) and block-group median household income in 1999. Median household income at the block-group level was obtained from the census data and all other covariates at the individual level were assessed by in-person interview using a standardized questionnaire as described in an earlier publication.³⁵ Stratified analyses by histologic type, sex and tobacco smoking status were performed. Adjusted odds ratio (OR) and 95% confidence intervals (CI) are reported. A product term between $PM_{2.5}$ (dichotomized into $>19.1 \mu g/m^3$ vs $\leq 19.1 \mu g/m^3$, which was the median concentration among all controls 1 year before the reference date) and tobacco smoking (ever vs never) was introduced into the regression model together with both $PM_{2.5}$ and tobacco smoking; we also calculated the ORs for never smoker with high level of $PM_{2.5}$ exposure (OR_{10}), ever smokers with low level of $PM_{2.5}$ exposure (OR_{01}) and ever smokers with high level of $PM_{2.5}$ exposure (OR_{11}). Potential interactions on an additive and multiplicative scale between $PM_{2.5}$ and tobacco smoking were assessed, by comparing the observed OR_{11} to the expected values. The expected values on the additive scale and on the multiplicative scale were calculated as $OR_{10} + OR_{01} - 1$ and $OR_{10} \times OR_{01}$, respectively.

Recognizing the limitations in study design that controls were matched to cases based on residential neighborhoods, we applied a conditional logistic regression model to account for the matching design. However, owing to the nature of matching on neighborhood and the resolution of the exposure layers, the informative sample size diminished, resulting in a grossly imprecise estimate of the OR in the matched analysis. In addition, we conducted sensitivity analyses by exclusively using controls originally matched to lung cancer cases (swapped controls), rather than including all controls, in an unconditional logistic regression model. Sensitivity analyses additionally adjusted for household income, body mass index (BMI), nation of origin, duration of LA County residency and exposure to environmental tobacco smoking (ETS). Subgroup analyses were conducted among those residing in LA County for more than 5 years and those for more than 10 years. All analyses were performed in SAS 9.4 (Cary, NC).

TABLE 1 Mean and standard deviation (SD) of UADT cases and all controls, by category of selected baseline characteristics ($n = 1548$).

	UADT cases	Controls
Total no. of subjects	565	983
	Mean (SD)	Mean (SD)
Age, year	50.4 (7.6)	49.9 (7.3)
Block group median household income in 1999, \$1000	51.0 (24.4)	54.1 (25.6)
	N (%)	N (%)
Sex		
Male	426 (75.4)	585 (59.5)
Female	139 (24.6)	398 (40.5)
Education		
Less than high school	125 (22.1)	115 (11.7)
High school	138 (24.4)	178 (18.1)
Some college	147 (26.0)	266 (27.1)
College	93 (16.5)	191 (19.4)
Graduate school	62 (11.0)	233 (23.7)
Race/Ethnicity		
Non-Hispanic White	314 (55.6)	587 (59.7)
African American	68 (12.0)	98 (10.0)
Hispanic	108 (19.1)	201 (20.5)
Other	75 (13.3)	97 (9.9)
Tobacco smoking		
Never users	164 (29.0)	445 (45.3)
Former users	319 (56.5)	347 (35.3)
Current users	82 (14.5)	191 (19.4)
Alcohol drinking		
Never users	113 (20.0)	255 (25.9)
Ever users	452 (80.0)	728 (74.1)

3 | RESULTS

A total of 565 UADT cancers cases and 983 controls were eligible and included in our study and the distributions of their demographic characteristics and UADT cancers risk factors are presented in Tables 1 and 2. Briefly, UADT cancer cases had a higher number of tobacco smoking pack-years, drank more alcohol, were less likely to have received a college or higher degree, and more likely to be males. The mean average $PM_{2.5}$ concentrations 1-year before the reference date was $18.8 \mu g/m^3$ among controls.

Table 2 shows the overall association between ambient $PM_{2.5}$ 1-year before diagnosis and UADT cancer odds. After adjusting for matching variables (age and sex) and potential confounders, an increase of 21% in UADT cancer odds was observed with each inter-quartile range (IQR of $4.5 \mu g/m^3$, range 16.7 – $21.2 \mu g/m^3$, Table S2) increase in ambient $PM_{2.5}$ concentration 1-year before diagnosis (OR of 1.21; 95% CI: 1.02–1.44). Table 3 shows the ORs between $PM_{2.5}$ and UADT cancers incidence stratified by cancer subtype, sex

TABLE 2 Main effects between upper aerodigestive track cancers odds and major risk factors.

	UADT cases		Controls
Total no. of subjects	565		983
	Mean (SD)	Mean (SD)	Adjusted OR per 4.5 $\mu\text{g}/\text{m}^3$ increase (95% CI)
PM _{2.5} concentration ^a 1-year before diagnosis ^b , $\mu\text{g}/\text{m}^3$	19.3 (3.2)	18.8 (3.3)	1.21 (1.02–1.44)
	N (%)	N (%)	
Household indoor air pollution since adulthood ^c			Adjusted OR (95% CI)
No	221 (39.1)	459 (46.7)	Reference
Any	344 (60.9)	524 (53.3)	1.09 (0.85–1.39)
Tobacco smoking, pack-years ^d			
0	164 (29.0)	445 (45.3)	Reference
1–19	137 (24.3)	341 (34.7)	0.93 (0.70–1.24)
20 or more	264 (46.7)	197 (20.0)	2.20 (1.60–3.02)
Alcohol drinking, drink-years ^e			
0	113 (20.0)	255 (25.9)	Reference
1–19	144 (25.5)	422 (42.9)	0.86 (0.63–1.19)
20 or more	308 (54.5)	306 (31.1)	1.53 (1.10–2.13)

^aThe interquartile range (IQR) for PM_{2.5} concentration 1-year before reference date was 4.5 $\mu\text{g}/\text{m}^3$ (from 16.7 to 21.2 $\mu\text{g}/\text{m}^3$) among all controls.

^bModels adjust for age, sex, education, race/ethnicity, tobacco smoking (ever/never), tobacco smoking pack-years, alcohol drinking drink-years, block group median household income in 1999 and household indoor air pollution since adulthood.

^cHousehold indoor air pollution includes exposure to environmental tobacco use and solid fuel use for heating or cooking includes fireplace, wood, coal, oil, kerosene, charcoal, wood and coal stove; Models adjust for age, sex, education, race/ethnicity, tobacco smoking (ever/never), tobacco smoking pack-years, alcohol drinking drink-years, block group median household income in 1999 and PM_{2.5} concentration 1-year before reference date.

^dThe IQR for tobacco smoking was 27.14 pack-years (from 2.86 to 30.00 pack-years) among all smoking controls; Models adjust for age, sex, education, race/ethnicity, alcohol drinking drink-years, block group median household income in 1999, household air pollution since adulthood and PM_{2.5} concentration 1-year before reference date.

^eThe IQR for alcohol drinking was 35.80 drink-years (from 4.47 to 40.27 pack-years) among all drinking controls; Models adjust for age, sex, education, race/ethnicity, tobacco smoking (ever/never), tobacco smoking pack-years, block group median household income in 1999, household air pollution since adulthood and PM_{2.5} concentration 1-year before reference date.

and tobacco smoking status. The association remained similar (OR = 1.22, 95% CI: 1.01–1.47) among those with UADT squamous cell carcinoma, which accounts for the majority of UADT subtypes. Although the point estimate of ORs associated with each IQR increase in ambient PM_{2.5} range from 1.16 (95% CI: 0.94–1.42) for squamous cell carcinoma that occurred in the oropharynx to 1.54 (95% CI: 0.78–3.02) for esophageal squamous cell carcinoma, their 95% CIs overlapped mostly due to the limited sample sizes after stratifying by UADT subtypes. The associations between ambient PM_{2.5} and UADT cancers were similar in males (OR = 1.20, 95% CI: 0.97–1.48) and in females (OR = 1.25, 95% CI: 0.91–1.72).

Since tobacco smoking is a major risk factor for UADT cancers, we also stratified by tobacco smoking status to examine effect modification by tobacco smoking and to assess the association between PM_{2.5} and UADT cancers among never smokers, as results are not confounded by active tobacco smoking. Though limited by sample sizes (164 UADT cancer cases and 445 controls who never smoked), the odds ratio for UADT cancer in never-smokers associated with each IQR increase in PM_{2.5} concentration was 1.16 (95% CI: 0.89–1.52), slightly lower than the estimate among all participants (OR = 1.21, 95% CI: 1.02–1.44) and among ever smokers

(OR = 1.26, 95% CI: 1.01–1.58), as shown in Table 3. Compared to never smokers exposed to lower levels of PM_{2.5} ($\leq 19.1 \mu\text{g}/\text{m}^3$), both never smokers exposed to higher levels of PM_{2.5} ($> 19.1 \mu\text{g}/\text{m}^3$) and ever smokers exposed to lower levels of PM_{2.5} experienced increases in odds of UADT cancer, with OR₁₀ of 1.36 (95% CI: 0.93–2.00) and OR₀₁ of 1.34 (95% CI: 0.93–1.92), respectively. Those with exposure to both tobacco smoking and higher levels of PM_{2.5} concentration had the greatest elevation in UADT cancer odds (OR₁₁ = 1.70, 95% CI: 1.18–2.46). The estimated interaction between binary measures of PM_{2.5} and tobacco smoking was additive on the odds scale, as the expected OR for the joint effect of the two exposures under additivity was equivalent to the observed joint effect (1.70, Table 4).

Sensitivity analyses show similar results when additionally adjusting for household income, BMI, nation of origin, duration of LA County residency and ETS and when comparing UADT cancer cases only to controls who were originally matched to lung cancer patients. Similar results were also observed among those living in LA County for at least 5 or 10 years (Table S1). The result from the conditional logistic regression was too imprecise to be informative, with a remarkably wide CI from 0.10 to 17.85 (results not shown) due to the

TABLE 3 Associations between each interquartile range increase^a in PM_{2.5} concentration 1-year before diagnosis and upper aerodigestive track cancers risks stratified by cancer type, sex and smoking status.

Stratified variables	UADT cancers, N	Controls, N	Adjusted OR per 4.5 µg/m ³ increase in PM _{2.5} (95% CI)
Cancer type^b			
UADT squamous cell carcinoma	413	983	1.22 (1.01–1.47)
Oropharyngeal squamous cell carcinoma	320	983	1.16 (0.94–1.42)
Nasopharyngeal squamous cell carcinoma	46	983	1.41 (0.84–2.35)
Esophageal squamous cell carcinoma	32	983	1.54 (0.78–3.02)
Esophageal adenocarcinoma	68	983	1.22 (0.82–1.82)
Sex^c			
Male	426	585	1.20 (0.97–1.48)
Female	139	398	1.25 (0.91–1.72)
Tobacco smoking status^d			
Never smokers	164	445	1.16 (0.89–1.52)
Ever smokers	401	538	1.26 (1.01–1.58)

^aThe interquartile range (IQR) for PM_{2.5} concentration 1-year before reference date was 4.5 µg/m³ (from 16.7 to 21.2 µg/m³) among all controls.

^bModels adjust for age, sex, education, race/ethnicity, tobacco smoking (ever/never), tobacco smoking pack-years, alcohol drinking drink-years, block group median household income in 1999 and household indoor air pollution since adulthood.

^cModels adjust for age, education, race/ethnicity, tobacco smoking (ever/never), tobacco smoking pack-years, alcohol drinking drink-years, block group median household income in 1999 and household indoor air pollution since adulthood.

^dModels adjust for age, sex, education, race/ethnicity, alcohol drinking drink-years, block group median household income in 1999, household indoor air pollution since adulthood and tobacco smoking pack-years if applicable.

TABLE 4 Joint effect between PM_{2.5} concentration^a 1-year before diagnosis and smoking on upper aerodigestive track cancers risks.

	Never smokers	Ever smokers
	Adjusted OR ^b (95% CI)	
PM _{2.5} ≤ 19.1 µg/m ³	Reference	1.34 (0.93–1.92)
PM _{2.5} > 19.1 µg/m ³	1.36 (0.93–2.00)	1.70 (1.18–2.46)

^aThe median of ambient PM_{2.5} concentration 1-year before the reference date among controls was 19.1 µg/m³.

^bModels adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999 and the household indoor air pollution.

reduced sample size, despite the point estimate of 1.30 being in the range of other estimates as shown in Tables 2 and S1. In addition, the annual average PM_{2.5} concentrations were highly correlated over the study period (Table S3).

4 | DISCUSSION

In this LA cancer study, we examined the association between ambient PM_{2.5} and the odds of UADT cancers. Our results suggest that each IQR (4.5 µg/m³, range 16.7–21.2 µg/m³) increase in ambient PM_{2.5} concentration is associated with an increased UADT cancer risk with an estimated OR of 1.21 (95% CI: 1.02–1.44). We did not observe the association to be different across different UADT cancer

subsites. Sex and tobacco smoking status did not appear to modify the association between ambient PM_{2.5} levels and UADT cancers risk. The estimated effect of PM_{2.5} and tobacco smoking on UADT cancer risk was approximately additive on the odds scale.

Previous studies reported inconsistent associations between UADT cancer or subtypes of UADT cancer and PM_{2.5} across different locations. The positive association between ambient PM_{2.5} and UADT cancer risk found in this study is consistent with findings from some Asian studies that showed positive associations between ambient PM_{2.5} and different subsites of UADT cancers, but the PM_{2.5} concentrations were reported to be much higher than the ones reported in the United States with means or medians above 30 µg/m³ (Table S4).^{24–30} For Taiwanese residents, increased incidence rates of nasopharyngeal cancer (hazard ratio [HR] = 1.97, 95% CI: 1.13–3.43) and oral cancer (OR = 1.43, 95% CI: 1.17–1.74) were reported among those living in areas within the highest compared to the lowest quartile of PM_{2.5} exposure.^{24,27} An elevated mortality rate of upper digestive tract cancer due to PM_{2.5} was observed in Hong Kong (HR = 1.42 per 10 µg/m³ increase, 95% CI: 1.06–1.89),²⁹ and the incidence rate of esophageal cancer was increased in China by at least 1.03% for each 1-µg/m³ increase in PM_{2.5}.³⁰ However, when examining specific sites of UADT cancer, our results did not suggest such differences by subsite possibly due to limited statistical power. The investigators of the Cancer Prevention Study II (CPS-II) in the United States did not observe associations between PM_{2.5} and site-specific UADT cancer mortality but they did not investigate cancer incidence.³² Mortality as the outcome might not be comparable to incidence as some UADT cancers have relatively higher survival rates. The European Study of Cohorts for Air Pollution

Effects (ESCAPE) reported a hazard ratio (HR) of 1.05 (95% CI: 0.62–1.77) for each $5\text{-}\mu\text{g}/\text{m}^3$ increase between $\text{PM}_{2.5}$ and UADT cancer incidence. However, when stratifying by different study locations, results were inconsistent ($I^2 = 35.3\%$) but some locations had very few cases.³³ Similarly, the Surveillance, Epidemiology and End Results program (SEER) study observed little or no associations between $\text{PM}_{2.5}$ and different subsites of UADT cancer incidence, other than oral cancer, but lacked information on important risk factors such as smoking history at the individual level.³¹ With the availability of tobacco smoking status at the individual level, we observed an association between $\text{PM}_{2.5}$ and UADT cancers among never smokers (OR = 1.16; 95% CI: 0.89–1.52). Excluding ever smokers, the potential for confounding due to active tobacco smoking, which is an important risk factor of UADT cancers, was minimized, although there might still be residual confounding due to other unmeasured risk factors.

In addition, the discrepancy between our findings and previous studies finding no clear associations might be due to differences in $\text{PM}_{2.5}$ exposure levels. The concentration of $\text{PM}_{2.5}$ observed in LA county (mean = $18.8 \pm 3.3\text{ }\mu\text{g}/\text{m}^3$ among controls) was much higher than in the CPS-II study (mean = $12.6 \pm 2.8\text{ }\mu\text{g}/\text{m}^3$, 95th percentile concentration = $17.0\text{ }\mu\text{g}/\text{m}^3$),³² the SEER study (mean = $11.50 \pm 2.60\text{ }\mu\text{g}/\text{m}^3$),³¹ and the ESCAPE study (mean ranging from 7.1 ± 1.3 to $19.4 \pm 1.8\text{ }\mu\text{g}/\text{m}^3$ depending on the study location).³³ In Asia, where concentrations of $\text{PM}_{2.5}$ are generally higher than in LA county with means or medians above $30\text{ }\mu\text{g}/\text{m}^3$, elevated risks for different UADT subsites were reported.^{24–30} The current study could not detect such differences in associations for $\text{PM}_{2.5}$ and subtypes of UADT cancer due to its limited sample size. Moreover, since some Asian studies categorized $\text{PM}_{2.5}$ into quartiles,^{24,27} the magnitude of effect sizes might not be comparable to those reported in the current study, where $\text{PM}_{2.5}$ were measured on a continuous scale. As a result, future studies need to assess the linearity assumption we made between UADT odds and $\text{PM}_{2.5}$ concentrations on the log scale. Our study suggests that the $\text{PM}_{2.5}$ concentrations in LA county were in a range that allowed us to estimate increased UADT cancer risks during our study period with sufficient statistical power when assuming linearity. Other air pollutant measures were not available for co-adjustment, and we did not have information on specific sources of particulate pollution. Also, distinguishing the composition of $\text{PM}_{2.5}$ is beyond the scope of the current study. Thus, future studies are warranted. In addition, though $\text{PM}_{2.5}$ mass concentrations in LA county have been greatly reduced since the study period (1999–2004), this population-based case-control study still provides valuable information for those who are currently at risk and have been exposed to high level of $\text{PM}_{2.5}$, due to the long latency period of cancer development. Furthermore, LA county still experiences higher level of $\text{PM}_{2.5}$ pollution compared to the rest of the country and 9 out of the 15 most polluted cities in the United States are located within LA county.³⁸

There are several additional limitations in our study. The main methodologic limitations are due to overmatching bias in the study design as controls were matched to cancer cases on neighborhood, especially when assessing exposures that are strongly correlated with neighborhood, such as residential ambient $\text{PM}_{2.5}$. We conducted a

matched analysis, but unfortunately the effect estimation of $\text{PM}_{2.5}$ from the conditional logistic model were excessively imprecise as indicated by the exceedingly wide CI (aOR = 1.30, 95% CI: 0.10–17.85, results not shown) due to the limited number of discordant pairs available. An alternative approach involved breaking the matching by including all controls in the study, comprising those matched to lung cancer cases and those matched to UADT cancer cases, as demonstrated in our analyses. Although we adjusted for the block-group level median household income as a surrogate for neighborhood, our results remained susceptible to potential selection bias. Sensitivity analyses using UADT cases and swapped controls, matched to cancer cases other than UADT cancers, suggested a similar magnitude point estimate, with only slightly wider confidence intervals (OR = 1.21; 95% CI: 0.99–1.47, Table S1). However, these controls may not necessarily represent the source population of UADT cancer cases as well. We acknowledge the limitation of the study design, especially the matching on residential neighborhoods, and recognize that the current analyses have not adequately addressed this concern. Nevertheless, due to the greater similarity in exposure for cases and controls resulting from the matched design, the observed estimate (OR = 1.21 per $4.5\text{ }\mu\text{g}/\text{m}^3$ increase; 95% CI: 1.02–1.44) for ambient residential $\text{PM}_{2.5}$ and UADT cancers tends to be conservative (likely biased towards the null) and needs to be interpreted with caution. In addition to considering an alternative study design, future studies may consider employing a finer spatial resolution for $\text{PM}_{2.5}$ to enhance the ability to discern differences in exposure between cases and controls.

Selection bias could also be a result from differential selective participation by exposure levels, such as refusal of UADT cancer cases due to impending death or poor health conditions in less affluent neighborhoods with higher air pollution.³⁵ Moreover, we could not identify or recruit matched controls for every case and we have also included controls for another cancer site, both could results in selection bias leading to a differential bias to either direction. In addition, we could not rule out the possibility of error in measuring the participants' exposure to $\text{PM}_{2.5}$. Without a history of residential addresses, we could only ascertain participants' residential exposure to ambient $\text{PM}_{2.5}$ 1 year before the date of diagnosis or before the reference date, which might have changed differentially between cases and controls. Long-term residential exposure to ambient $\text{PM}_{2.5}$ concentrations could not be estimated because modeled $\text{PM}_{2.5}$ data were available only starting 1 year before the start of cancer case ascertainment (1999). Thus, our exposure assessment covering the annual average $\text{PM}_{2.5}$ concentration 1 year before cancer diagnosis possibly did not capture long-term $\text{PM}_{2.5}$ exposure during the long latency period of cancer development. However, it may still serve as a proxy for long-term ambient exposure to $\text{PM}_{2.5}$ under the assumption that the spatial distribution of $\text{PM}_{2.5}$ did not change much over time in LA County, as suggested by the high correlations between $\text{PM}_{2.5}$ concentrations in our study from 1998 to 2002 (Table S3).

We cannot rule out residual confounding due to unknown or unmeasured UADT risk factors. To minimize the bias due to uncontrolled confounding, we additionally include block-group level median household income to adjust for neighborhood characteristics, which is

correlated with air pollution level and possibly UADT cancer susceptibility. Though block group from the census is different from neighborhood as it has been defined in our study for control selection, it remains the most feasible and easily available measure allowing us to adjust for confounding due to neighborhood. Moreover, our results remained consistent in the sensitivity analyses when additional covariates were included in the model. Although the sample size was adequate for detecting the effect of PM_{2.5} in the total sample (565 cases and 983 controls), precision and power were much less when examining effects for subtypes of UADT cancers (Table 3). Moreover, there is much less power for detecting interactions between PM_{2.5} and smoking than for detecting associations between PM_{2.5} and UADT cancers (Table 4).

Our study is the first to report a positive association between residential PM_{2.5} and UADT cancer risk in LA County, despite limitations due to possible overmatching, residual confounding and measurement error. Our findings are consistent with the hypothesis that carcinogens contained in fine particulate matter increase the risk of UADT cancers. Improvement of air quality may potentially reduce the risk of UADT cancers.

AUTHOR CONTRIBUTIONS

Fang Fang: Formal analysis; methodology; writing – original draft preparation. **Beate Ritz:** writing – review & editing. **Jianyu Rao:** Writing – review & editing. **Yifang Zhu:** Writing – review & editing. **Donald P. Tashkin:** Writing – review & editing. **Hal Morgenstern:** funding acquisition; Writing – review & editing. **Zuo-Feng Zhang:** Conceptualization; funding acquisition; methodology; supervision; writing – review & editing. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The air pollution data is public available from the Atmospheric Composition Analysis Group and is accessible from <https://sites.wustl.edu/acag/>. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Our study was approved by the Institutional Review Boards of the University of California at Los Angeles and the University of Southern California. Informed consent was obtained from each participant.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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