ORIGINAL ARTICLE

Outdoor Ultrafine Particulate Matter and Risk of Lung Cancer in Southern California

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Abstract

Rationale: Particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) is an established cause of lung cancer, but the association with ultrafine particulate matter (UFP; aerodynamic diameter < 0.1 μm) is unclear.

Objectives: To investigate the association between UFP and lung cancer overall and by histologic subtype.

Methods: The Los Angeles Ultrafines Study includes 45,012 participants aged ⩾50 years in southern California at enrollment (1995–1996) followed through 2017 for incident lung cancer ($n = 1{,}770$). We estimated historical residential ambient UFP number concentrations via land use regression and back extrapolation using $PM_{2.5}$. In Cox proportional hazards models adjusted for smoking and other confounders, we estimated associations between 10-year lagged UFP (per 10,000 particles/cm^3 and quartiles) and lung cancer overall and by major histologic subtype (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma). We also evaluated relationships by smoking status, birth cohort, and historical duration at the residence.

Measurements and Main Results: UFP was modestly associated with lung cancer risk overall (hazard ratio [HR], 1.03 [95% confidence interval (CI), 0.99–1.08]). For adenocarcinoma, we observed a positive trend among men; risk was increased in the highest exposure quartile versus the lowest (HR, 1.39 [95% CI, 1.05–1.85]; P for trend = 0.01) and was also increased in continuous models (HR per 10,000 particles/cm^3, 1.09 [95% CI, 1.00–1.18]), but no increased risk was apparent among women (P for interaction = 0.03). Adenocarcinoma risk was elevated among men born between 1925 and 1930 (HR, 1.13 [95% CI, 1.02–1.26] per 10,000) but not for other birth cohorts, and was suggestive for men with ⩾10 years of residential duration (HR, 1.11 [95% CI, 0.98–1.26]). We found no consistent associations for women or other histologic subtypes.

Conclusions: UFP exposure was modestly associated with lung cancer overall, with stronger associations observed for adenocarcinoma of the lung.

Keywords: air pollution; particulate matter; lung neoplasms

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Data availability: The research data, code book, and analytic code will be made available per relevant NIH data-sharing policies. Requests should be submitted to the NIH–AARP Diet and Health Study Steering Committee at https://www.nihaarpstars.com.

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This article has a related editorial.

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At a Glance Commentary

Scientific Knowledge on the Subject: Much of the epidemiologic evidence for air pollution associations with lung cancer risk comes from studies of fine particulate matter (diameter < 2.5 μm), but whether ultrafine particulate matter (UFP; aerodynamic diameter < 0.1 μm) is associated with lung cancer risk is unclear. This relationship is understudied in part because of the sparseness of measurements of UFP, a highly spatially varying and unregulated pollutant.

What This Study Adds to the Field: Conducted among older adults residing in one of the most heavily polluted areas of the United States historically, this study represents the first evaluation of estimated long-term outdoor UFP exposure and lung cancer risk by histologic subtype. The findings of this novel investigation shed new light on the association between UFP and lung cancer that may have important public health implications.

Outdoor air pollution is classified by the International Agency for Research on Cancer as carcinogenic to humans on the basis of consistent evidence of a relationship with the development of lung cancer (1). Much of that evidence includes observed associations with particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) and nitrogen dioxide (NO_2); however, whether ultrafine particulate matter (UFP; aerodynamic diameter < 0.1μm) is associated with lung cancer risk is unclear. UFP exhibits high spatial variability, with contributions to outdoor particle number concentrations varying considerably by distance to roadways and other sources, such as airports (2). Biologic plausibility exists for UFP-related physiologic effects because of its high reactivity, high particle numbers, and increased uptake in the body (3). The greater internal dose of UFP, driven by its unique morphological characteristics and behavior, may translate to increased health risks (4), especially for individuals residing in proximity to sources (5).

Epidemiologic studies of UFP associations with cancer are limited primarily by the difficulty in estimating long-term exposure in the absence of routine monitoring for this pollutant. Measurements of UFP and $PM_{2.5}$ are typically poorly correlated (3), motivating efforts to characterize UFP independently. Studies of health effects have often used modeling approaches, such as land use regression (LUR), to estimate UFP at fine spatial scales (2). A large cohort study in Toronto, Canada, used LUR to estimate long-term UFP exposure and demonstrated no relationship with incident lung cancer (6). In contrast, a recent study in the Netherlands revealed a positive association between UFP and lung cancer mortality (7). Both studies investigated possible heterogeneity in effects across strata of age and sex, but not by lung cancer histology, and did not directly adjust for individual-level smoking.

Leveraging a state-of-the-art LUR model (2), our aim was to investigate the relationship between long-term outdoor UFP exposure at the residential address and lung cancer risk in a cohort in southern California, with adjustment for smoking and other confounders. We evaluated the association between UFP and lung cancer by histologic type and assessed effect modification by sex and smoking status. We also explored the influence of residential mobility and exposure before years for which UFP concentrations were estimable.

Methods

Study Population and Cancer Ascertainment

The Los Angeles (LA) Ultrafines Study ($n = 53,833$ participants) is a subcohort of the prospective NIH–AARP Diet and Health Study residing in LA and parts of California's Riverside and Orange counties at enrollment in 1995 and 1996; it has been described previously (2, 8), and additional details are available in the online supplement. Participants were queried on demographics, lifestyle and reproductive factors, dietary intake, and family history of cancer. Lung cancer cases were identified through probabilistic linkage to cancer registries in California and three additional states where participants tended to move (Arizona, Nevada, and Texas), and vital status was confirmed annually through linkage with the Social Security Administration Death Master File and supplemented with the National Death Index (9). This approach detects about 90% of incident cancer cases (10). Over a median of 22 years of follow-up, 1,770 primary lung cancers were newly diagnosed. Major histologic subtypes defined according to the International Classification of Diseases for Oncology, Third Edition (codes C340–C349), including adenocarcinoma (47%), small-cell carcinoma (9%), and squamous-cell carcinoma (16%). The remaining 28% of mixed or unknown subtype were excluded from histology-specific analyses. We followed subjects from enrollment until the first date of lung cancer diagnosis, relocation from the registry areas, death, or December 31, 2017. The NIH Institutional Review Board approved the study protocol.

Exposure Assessment

The UFP exposure assessment has been described (2) and is further detailed in the online supplement. Briefly, in 2016, we measured outdoor UFP in the study area and developed a LUR model to predict average concentrations at participants' residential addresses (97%; $n = 52,164$). That effort yielded robust model-explained variance ($R^2 = 0.66$); important predictors included distance to airports, density of major roads, and traffic intensity. For the present analysis, we back extrapolated UFP exposures annually to 1980 using yearly $PM_{2.5}$ (1980–2016) and NO_2 (1990–2016) residential-level estimates from validated spatiotemporal models (11–13). To evaluate how well our LUR model reflected historical UFP, we extracted measurements from exposure studies in the study area from 2000 to 2009, predicted UFP at the same locations, and compared the measurements with our estimates. These studies are referenced in the online supplement.

Statistical Analyses

We excluded participants with preenrollment cancer diagnoses except nonmelanoma skin cancer ($n = 5,034$), cancer deaths not found in registries ($n = 1,029$), proxy respondents ($n = 1,067$), missing and/or poorly geocoded addresses ($n = 1,669$), and cases with inestimable person–time ($n = 22$). We used time-varying Cox proportional-hazards models with age as the time variable to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of

the association between UFP (5-yr moving average, lagged 10 yr) and lung cancer, overall and by histologic type and sex. We defined risk sets on the basis of 2-year intervals throughout the follow-up period. In each interval, we estimated a new 5-year average, 10-year lagged exposure for all participants remaining in the risk set (including cases diagnosed in this interval and all other noncensored participants). We evaluated relationships by smoking status (never, former, or current). We explored the potential influence of exposures before periods when they could be estimated by evaluating relationships separately by birth cohort (1925–1930, 1931–1936, and 1937–1945). To evaluate an assumption of stability in the historical exposure contrast, we also stratified by residential duration before enrollment, which was available for approximately 66% of participants (8). In sensitivity analyses, we excluded cases diagnosed in the first 10 years of follow-up.

We considered literature-based potential confounders to create a directed acyclic graph (*see* Figure E1 in the online supplement), with final models including age at enrollment, sex, race and/or ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other, and unknown), and smoking status and frequency. Given their moderate correlation (*see* Table E1), we separately conducted analyses of $PM_{2.5}$ and UFP with a common referent group of low exposure to both pollutants (less than median $PM_{2.5}$ and the first tertile of UFP). We evaluated statistical interactions and linear trends using Wald statistics and used restricted cubic splines to evaluate possible nonlinear associations. Analyses were conducted using SAS (SAS Institute, Cary, NC) version 9.4.

Results

Correlations between the 2016 LUR-estimated UFP exposures and preenrollment NO_2 concentrations were weak (rho = 0.27) and with preenrollment $PM_{2.5}$ were moderate (rho = 0.57) (*see* Table E1). $PM_{2.5}$-anchored back-extrapolated UFP estimates were more strongly correlated with the UFP LUR estimates (rho = 0.94–0.95) than NO_2-anchored UFP (rho = 0.68). The 2016 LUR model yielded an approximate residential exposure contrast of a factor of 2.3 from the 5th percentile (8,341 particles/cm^3) to the 95th percentile (19,008 particles/cm^3; 1.3 from quartile 1 [Q1] vs. Q4) (*see* Table E2). Contrasts were similar for the $PM_{2.5}$-anchored back-extrapolated averages. Correlations between average UFP from historical measurements collected from 2001 to 2009 (*see* Figure E2) and the 2016 LUR-estimated UFP exposures were moderate overall (rho = 0.58) and stronger in South Central LA (rho = 0.78; *see* Table E3). Back-extrapolated predictions at the historical monitoring sites were on average lower than the measurements collected from 2000 to 2009 but still reflected nearly twofold higher average exposures compared with our 2016 LUR model (*see* Table E4).

We observed few differences in the back-extrapolated UFP exposure distribution across lung cancer risk factors and demographic characteristics (Table 1). Mean $PM_{2.5}$ and NO_2 concentrations increased slightly with

Table 1. Selected Demographic and Other Baseline Characteristics of the Los Angeles Ultrafines Study Population across Quartiles of Residential UFP Number Concentrations (Back-Extrapolated 5-yr Average, 1980–1984)

	UFP Quartile			
Characteristic	**Q1 (8,032–26,246 particles/cm^3)**	**Q2 (26,247–31,314 particles/cm^3)**	**Q3 (31,315–37,066 particles/cm^3)**	**Q4 (37,067–261,166 particles/cm^3)**
Age, yr, mean (SD)	61.8 (5.3)	62.0 (5.2)	62.0 (5.3)	61.9 (5.3)
Sex, %				
Male	60.0	58.4	55.9	54.3
Female	40.0	41.6	44.1	45.7
Race and ethnicity, %				
Non-Hispanic White	90.0	89.4	85.8	72.8
Non-Hispanic Black	2.2	1.5	3.0	11.7
Hispanic	3.1	4.1	4.5	6.0
Other	3.4	3.6	4.9	7.4
Unknown	1.4	1.5	1.8	2.1
Smoking status, %				
Never	37.9	37.3	37.7	37.5
Former	47.2	47.2	45.9	45.2
Current	11.7	12.0	12.3	13.4
Unknown	3.2	3.6	4.1	3.8
Highest schooling achieved, %				
Less than high school	3.0	2.9	3.8	4.3
Completed high school	11.5	11.4	12.0	14.1
Post–high school or some college	35.8	34.6	34.7	35.9
College and postgraduate	47.1	48.4	46.7	42.2
Unknown	2.6	2.7	2.8	3.5
NO_2, ppb, mean (SD)*	27.0 (10.2)	34.0 (11.1)	34.1 (10.3)	31.6 (9.7)
$PM_{2.5}$, μg/m^3, mean (SD)*	18.3 (3.4)	20.2 (2.1)	21.0 (1.8)	21.8 (1.6)

Definition of abbreviations: $PM_{2.5}$ = particulate matter ≤2.5 μm in aerodynamic diameter; Q = quartile; UFP = ultrafine particulate matter.
*Average from 1990 to 1994.

Table 2. Association between 10-yr Lagged Residential UFP Number Concentrations and Risk of Lung Cancer, Overall and by Histologic Type

Group/UFP Exposure	All Lung Cancers		Adenocarcinoma		Small Cell Carcinoma		Squamous Cell Carcinoma	
	n Cases	HR (95% CI)	*n* Cases	HR (95% CI)	*n* Cases	HR (95% CI)	*n* Cases	HR (95% CI)
Overall*								
Q1	468	1.0 (Ref)	205	1.0 (Ref)	36	1.0 (Ref)	86	1.0 (Ref)
Q2	439	0.97 (0.85–1.10)	216	1.09 (0.90–1.32)	40	1.11 (0.71–1.74)	60	0.72 (0.52–1.00)
Q3	482	1.15 (1.01–1.31)	235	1.29 (1.07–1.56)	47	1.33 (0.86–2.07)	73	0.98 (0.72–1.34)
Q4	381	1.04 (0.90–1.19)	173	1.09 (0.88–1.34)	37	1.13 (0.71–1.81)	70	1.11 (0.80–1.53)
P for trend		0.24		0.22		0.51		0.32
Continuous†	1,770	1.03 (0.99–1.08)	829	1.02 (0.96–1.10)	160	1.00 (0.86–1.18)	289	1.03 (0.92–1.15)
Men‡								
Q1	268	1.0 (Ref)	102	1.0 (Ref)	24	1.0 (Ref)	54	1.0 (Ref)
Q2	243	0.97 (0.82–1.16)	112	1.19 (0.91–1.55)	24	1.03 (0.59–1.82)	34	0.68 (0.44–1.04)
Q3	267	1.18 (0.99–1.40)	116	1.38 (1.05–1.80)	29	1.24 (0.72–2.14)	46	1.04 (0.70–1.55)
Q4	221	1.14 (0.95–1.36)	99	1.39 (1.05–1.85)	24	1.08 (0.60–1.94)	43	1.18 (0.78–1.78)
P for trend		0.06		0.01		0.69		0.25
Continuous	999	1.04 (0.98–1.11)	429	1.09 (1.00–1.18)	101	1.01 (0.83–1.23)	177	1.06 (0.92–1.22)
Women‡								
Q1	200	1.0 (Ref)	103	1.0 (Ref)	12	1.0 (Ref)	32	1.0 (Ref)
Q2	196	0.96 (0.79–1.17)	104	0.99 (0.75–1.30)	16	1.24 (0.59–2.63)	26	0.79 (0.47–1.32)
Q3	215	1.12 (0.92–1.36)	119	1.20 (0.92–1.56)	18	1.47 (0.71–3.07)	27	0.88 (0.53–1.48)
Q4	160	0.93 (0.75–1.15)	74	0.82 (0.60–1.11)	13	1.20 (0.54–2.68)	27	1.01 (0.60–1.70)
P for trend		0.76		0.40		0.61		0.89
Continuous	771	1.02 (0.95–1.09)	400	0.93 (0.82–1.05)	59	0.98 (0.75–1.28)	112	0.98 (0.80–1.20)
P for interaction§		0.37		0.03		0.50		0.47

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; Q = quartile; Ref = reference; UFP = ultrafine particulate matter.
Quartile cut points were as follows: Q1, <22,735 particles/cm^3; Q2, <22,736–27,126 particles/cm^3; Q3, 27,127–32,310 particles/cm^3; and Q4, >32,310 particles/cm^3.
*Models were adjusted for age, sex, race/ethnicity, and smoking status and frequency.
†Association per 10,000 particles/cm^3.
‡Models were adjusted for age, race/ethnicity, and smoking status and frequency.
§*P* value for interaction between continuous UFP exposure and sex.

Table 3. Association between 10-yr Lagged Residential UFP Number Concentrations and Risk of Lung Cancer, by Smoking Status at Study Enrollment

Group	All Lung Cancers		Adenocarcinoma		Small Cell Carcinoma		Squamous Cell Carcinoma	
	n Cases	HR (95% CI)*	*n* Cases	HR (95% CI)	*n* Cases	HR (95% CI)	*n* Cases	HR (95% CI)
Never-smokers								
Overall†	157	1.05 (0.89–1.23)	102	1.02 (0.82–1.27)	2	—	9	—
Men‡	71	1.15 (0.98–1.34)	41	1.17 (0.97–1.40)	2	—	7	—
Women‡	86	0.89 (0.67–1.18)	61	0.81 (0.57–1.15)	0	—	2	—
P for interaction§		0.11		0.07		—		—
Former smokers								
Overall	837	1.01 (0.94–1.09)	429	1.03 (0.94–1.14)	61	1.01 (0.77–1.31)	130	1.06 (0.91–1.24)
Men	527	1.04 (0.95–1.12)	255	1.10 (1.00–1.21)	42	0.99 (0.72–1.36)	88	1.05 (0.87–1.27)
Women	310	0.96 (0.84–1.09)	174	0.88 (0.73–1.07)	19	1.04 (0.64–1.67)	42	1.08 (0.82–1.43)
P for interaction§		0.21		0.03		0.86		0.82
Current smokers								
Overall	714	1.07 (1.01–1.13)	270	1.02 (0.91–1.14)	89	1.03 (0.85–1.24)	138	1.04 (0.89–1.21)
Men	362	1.05 (0.95–1.16)	115	1.05 (0.88–1.25)	50	1.07 (0.84–1.35)	76	1.07 (0.86–1.33)
Women	352	1.07 (1.00–1.15)	155	0.99 (0.85–1.16)	39	0.96 (0.69–1.34)	62	1.01 (0.80–1.28)
P for interaction§		0.95		0.74		0.41		0.53

Definition of abbreviations: — = inestimable; CI = confidence interval; HR = hazard ratio; UFP = ultrafine particulate matter.
*Association per 10,000 particles/cm^3.
†Models were adjusted for age, sex, race/ethnicity, and smoking status and frequency.
‡Models were adjusted for age, race/ethnicity and smoking status and frequency. Associations for categories with <10 cases are not shown.
§*P* value for interaction between continuous ultrafine particulate matter exposure and sex.

Table 4. Association between 10-yr Lagged Residential UFP Number Concentrations and Risk of Lung Cancer, by Birth Cohort and Residential Duration

	All Lung Cancers		Adenocarcinoma		Small Cell Carcinoma		Squamous Cell Carcinoma	
Group	***n* Cases**	**HR (95% CI)***	***n* Cases**	**HR (95% CI)**	***n* Cases**	**HR (95% CI)**	***n* Cases**	**HR (95% CI)**
Birth cohort								
1925–1930								
Overall†	673	1.05 (0.98–1.13)	307	1.08 (0.97–1.19)	49	0.91 (0.65–1.28)	104	1.03 (0.85–1.25)
Men‡	405	1.06 (0.97–1.16)	174	1.13 (1.02–1.26)	34	0.90 (0.61–1.33)	68	1.08 (0.89–1.32)
Women‡	268	1.04 (0.91–1.18)	133	0.92 (0.75–1.14)	15	0.93 (0.50–1.73)	36	0.88 (0.58–1.35)
1931–1936								
Overall	660	1.01 (0.93–1.10)	313	1.00 (0.88–1.13)	64	1.09 (0.87–1.37)	115	0.97 (0.78–1.21)
Men	374	1.00 (0.89–1.12)	167	1.03 (0.88–1.21)	41	1.12 (0.86–1.46)	66	0.98 (0.73–1.30)
Women	286	1.03 (0.91–1.16)	146	0.95 (0.78–1.15)	23	1.02 (0.65–1.58)	49	0.97 (0.69–1.35)
1937–1945								
Overall	437	1.00 (0.91–1.10)	209	0.96 (0.83–1.12)	47	0.96 (0.70–1.31)	70	1.08 (0.91–1.28)
Men	220	1.03 (0.90–1.18)	88	1.04 (0.84–1.28)	26	0.87 (0.53–1.42)	43	1.13 (0.88–1.46)
Women	217	0.97 (0.85–1.11)	121	0.90 (0.72–1.13)	21	1.01 (0.73–1.41)	27	1.05 (0.82–1.34)
P for interaction§								
Overall		0.62		0.38		0.59		0.86
Men		0.72		0.49		0.42		0.71
Women		0.58		0.79		0.91		0.91
Years at baseline address preenrollment								
⩾5 yr‖								
Overall	846	1.07 (1.00–1.13)	416	1.03 (0.94–1.14)	74	0.88 (0.66–1.18)	122	1.07 (0.92–1.25)
Men	482	1.03 (0.94–1.13)	215	1.10 (0.98–1.22)	50	0.78 (0.53–1.13)	78	1.10 (0.92–1.31)
Women	364	1.07 (0.99–1.16)	201	0.92 (0.77–1.09)	24	1.02 (0.74–1.39)	44	0.98 (0.70–1.37)
⩾10 yr¶								
Overall	591	1.04 (0.97–1.13)	302	1.02 (0.91–1.15)	45	0.89 (0.62–1.30)	83	1.05 (0.85–1.29)
Men	334	1.02 (0.91–1.14)	160	1.11 (0.98–1.26)	26	0.79 (0.46–1.34)	52	1.05 (0.82–1.34)
Women	257	1.03 (0.93–1.14)	142	0.87 (0.70–1.07)	19	0.99 (0.66–1.48)	31	0.97 (0.66–1.42)
⩾15 yr**								
Overall	331	1.00 (0.89–1.13)	173	1.05 (0.91–1.21)	22	0.84 (0.47–1.48)	41	1.03 (0.76–1.39)
Men	207	0.99 (0.85–1.15)	101	1.09 (0.91–1.29)	16	0.91 (0.48–1.74)	29	0.97 (0.68–1.38)
Women	124	0.99 (0.81–1.22)	72	0.95 (0.72–1.27)	6	—	12	1.09 (0.57–2.09)
P for interaction††								
Overall		0.14		0.48		0.58		0.91
Men		0.39		0.77		0.84		0.97
Women		0.19		0.35		—		0.94

Definition of abbreviations: — = inestimable; CI = confidence interval; HR = hazard ratio; UFP = ultrafine particulate matter.
*Association per 10,000 particles/cm^3.
†Models were adjusted for age, sex, race/ethnicity, and smoking status and frequency.
‡Models were adjusted for race/ethnicity and smoking status and frequency. Associations for categories with <10 cases are not shown.
§*P* value for interaction between continuous UFP exposure and birth cohort.
‖Includes 22,726 participants with this duration (among 29,838 with histories estimated).
¶Includes 16,425 participants.
**Includes 10,612 participants.
††*P* value for interaction between continuous UFP exposure and continuous years of residential duration.

increasing UFP quartiles. Although Black and Hispanic participants constituted just 4.6% and 4.4% of the analytic sample, respectively, their proportions increased with increasing UFP exposure quartiles.

Continuous UFP exposure was associated with a small increased risk of lung cancer overall (HR, 1.03 [95% CI, 0.99–1.08] per 10,000 particles/cm^3); in categorical analyses, elevated risk was observed in the third exposure quartile (HR_{Q3vsQ1}, 1.15 [95% CI, 1.01–1.31]), especially among men (HR_{Q3vsQ1}, 1.18 [95% CI, 0.99–1.40]) (Table 2). Risk of adenocarcinoma was similarly elevated in Q3 (HR_{Q3vsQ1}, 1.29 [95% CI, 1.07–1.56]), with no monotonic trend across quartiles. Among men, a marginally increased risk was apparent for adenocarcinoma (HR, 1.09 [95% CI, 1.00–1.18] per 10,000 particles/cm^3) but was not observed among women (HR, 0.93 [95% CI, 0.82–1.05]) (*P* for interaction = 0.03). For men, adenocarcinoma risk also increased across UFP exposure quartiles (*P* for trend = 0.01). Categorical analyses among women were null. These associations were all robust to mutual adjustment for $PM_{2.5}$ (*see* Table E5) and in models excluding smoking status and frequency (*see* Table E6). When we used the 2016 LUR-estimated UFP values (without back extrapolation), the association with adenocarcinoma among men was also apparent ($HR_{continuous}$, 1.14 [95% CI, 0.94–1.38]; *see* Table E7). Patterns of association with small cell and squamous cell carcinomas in models of both continuous

and categorical exposures were inconsistent, exhibiting no trend or clear differences by sex, either in models of back-extrapolated exposures (Table 2) or the 2016 LUR-estimated values (*see* Table E7). In spline analyses, we found no evidence of nonlinearity in the main associations (P values >0.05; data not shown). In sensitivity analyses excluding cases diagnosed in the first 10 years of follow-up, we observed the same general pattern of elevated risk of adenocarcinoma among men (*see* Table E8).

When evaluated as independent exposures in models coadjusted for UFP, we observed an association between continuous $PM_{2.5}$ and lung cancer overall among men (HR, 1.35 [95% CI, 1.06–1.73] per 10 $\mu g/m^3$) but not women (HR, 0.88 [95% CI, 0.68–1.15]) (P for interaction = 0.01) and elevated risks for small cell carcinoma subtype among men (HR, 2.51 [95% CI, 1.12–5.61]) but not women (HR, 0.99 [95% CI, 0.37–2.62]; P for interaction = 0.04) (*see* Table E9). For NO_2, a positive association with lung cancer overall was apparent only among men (P for interaction = 0.04; *see* Table E10). In analyses using a common referent group, adenocarcinoma risk among men was stronger across tertiles of UFP for those with $PM_{2.5}$ values less than the median versus values greater than or equal to the median, although CIs overlapped and none of the associations was statistically significant (*see* Table E11).

By smoking status, the strongest relationships with UFP were observed among male never smokers, both for lung cancer overall (HR, 1.15 [95% CI, 0.98–1.34] per 10,000 particles/cm^3 for men vs. 0.89 [95% CI, 0.67–1.18] for women; P for interaction = 0.11) and for adenocarcinoma subtype (HR, 1.17 [95% CI, 0.97–1.40] vs. 0.81 [95% CI, 0.57–1.15]; P for interaction = 0.07) (Table 3). Among former smokers, risk of adenocarcinoma was elevated among men (HR, 1.10 [95% CI, 1.00–1.21]) but not women (HR, 0.88 [95% CI, 0.73–1.07]; P for interaction = 0.03), and the association was weakest among current smokers (HR, 1.05 [95% CI, 0.88–1.25] in men vs. 0.99 [95% CI, 0.85–1.16] in women; P for interaction = 0.74). There were too few cases of small cell and squamous cell carcinoma to compare sex-specific associations among never-smokers, but the patterns of association for these subtypes among former and current smokers varied overall and by sex.

An increased risk for lung cancer associated with UFP was suggested among men in the oldest birth cohort, who were aged ⩾65 years at study enrollment (HR, 1.06 [95% CI, 0.97–1.16] per 10,000 particles/cm^3; Table 4) but not in the other birth cohorts (P for interaction = 0.72); risk was likewise increased for adenocarcinoma only in this group of older men (HR, 1.13 [95% CI, 1.02–1.26]; P for interaction = 0.38). For women, we found no lung cancer associations, overall or by subtype, across birth cohorts (P for interaction > 0.6). We saw a suggestive increased risk of lung cancer overall among women residing at their baseline addresses for at least 5 years before enrollment (HR, 1.07 [95% CI, 0.99–1.16]) that was not evident across subtypes. Although a statistical interaction was not evident, risk of adenocarcinoma was increased for men with ⩾5 years' historical duration (HR, 1.10 [95% CI, 0.98–1.22]) and for those with ⩾10 years (HR, 1.11 [95% CI, 0.98–1.26]; P for interaction = 0.77). No clear patterns by residential duration were observed for small cell or squamous cell carcinomas, associations for which were null overall and for both sexes.

Discussion

In this first evaluation of estimated long-term outdoor UFP exposure and lung cancer risk by histologic type, we found a modest association for lung cancer overall. In analyses by histologic subtype, we observed an increased risk of adenocarcinoma among men but not women. This association was evident in never smokers and former smokers but not current smokers. We also found that risk was increased in male participants who were oldest at the time of study enrollment, suggesting that higher historical exposures are relevant to this observed relationship.

Our findings can be contrasted with results from the two previous studies that investigated this relationship. A large cohort analysis in Toronto including 12,908 incident lung cancer cases revealed no evidence of association overall (HR, 1.00 [95% CI, 0.97–1.03] per interquartile range increase) or across strata of age and sex (6). The exposure assessment in this study was like that in ours; an LUR model developed from a mobile monitoring campaign (measurements collected in 2014 vs. ours in 2016), with a comparable model R^2 and similar key predictors (e.g., roadways, airport proximity). The UFP exposure distribution was similar, with average exposures slightly lower in Toronto compared with our back-extrapolated estimates (mean, 28,473 particles/cm^3 in Toronto vs. 32,364 particles/cm^3 in our study; median, 26,000 vs. 31,314 particles/cm^3). UFP was collected on roads in Toronto using a different instrument (Model 3007; TSI) than we used (DiSCmini; Testo), and our mobile monitoring involved 30-minute stationary periods at the sites (2), although previous studies have indicated that these approaches would yield similar predictions in a LUR for the same geographic area (14). Analyses of more than 70,000 lung cancer deaths in a Dutch cohort used a UFP-monitoring campaign and a LUR model with similar performance to ours for exposure assessment and also demonstrated a positive, albeit somewhat stronger, association with lung cancer mortality (HR, 1.04 [95% CI, 1.03–1.05] per interquartile range increase; 2,723 particles/cm^3) (7). The inconsistent findings between the Toronto study and those of our investigation may be due to differing chemical composition of UFP between Toronto and LA or possibly the Toronto study's lack of direct control for cigarette smoking, the predominant risk factor for lung cancer, raising concerns about residual confounding. That study also used a 5-year exposure lag, which may have been insufficient in view of the long latency for lung cancer. Neither of the prior studies evaluated the relationship by histologic subtype.

Several other studies have indirectly signaled that lung cancer risks from outdoor air pollution are associated with exposures closest to emission sources, suggesting that UFP may be relevant (15, 16). For example, in the Nurses' Health Study, the association between roadway proximity and lung cancer risk was higher among those residing within 50 versus ⩾200 m of a major highway (HR, 2.48 [95% CI, 1.04–5.90]) (16). Similarly, studies have also linked NO_2 to lung cancer (15), although it is not an established carcinogen; this suggests that other, correlated pollutants in highest concentrations near roadways, such as UFP, or the unique mixture of traffic-related pollutants may be driving lung cancer associations.

The association between UFP exposure and lung cancer risk is biologically plausible. Key toxicological mechanisms associated with UFP exposure include oxidative stress and inflammatory responses generated from reactive oxygen species, with pulmonary,

cardiovascular, and neurodegenerative outcomes among the most commonly identified (4). Genotoxicity and mutagenic activity have been demonstrated, including in association with the constituents commonly bound to UFP, such as polycyclic aromatic hydrocarbons (4, 17). At least one toxicity study has suggested that biologic responses to inhaled diesel exhaust are dominated by the UFP fraction (18).

Our observation of an association between UFP and adenocarcinoma is plausible given known etiologic heterogeneity across lung cancer histologic subtypes and their changing incidence patterns (19). Several studies of $PM_{2.5}$ have shown the strongest associations with adenocarcinoma versus other subtypes (16, 20), although a recent investigation among MEC (Multiethnic Cohort Study) participants in California revealed no elevated adenocarcinoma risk (21). Since the 1980s, the proportion of lung cancers that are adenocarcinoma has increased among both men and women in the United States, accompanied by declines in squamous and small cell carcinomas (22, 23). One possible explanation for this shift in histopathology is changes in smoking habits and cigarette characteristics (23), although population-level characterization of temporal trends in lung cancer incidence rates among never smokers is lacking (24). Secular trends in adenocarcinoma incidence are consistent with trends in air pollution from urbanization and industrialization (25, 26). The increase in adenocarcinoma incidence (22) despite widespread smoking cessation and its peak more than 30 years after the peak in cigarette consumption (25) also point to environmental drivers. Our findings are controlled for cigarette smoking. Furthermore, the association with adenocarcinoma was elevated among the never-smoking men, and a weaker relationship was observed among their former smoker counterparts. These findings suggest that our UFP effect is not likely due to residual confounding by smoking.

Several explanations for the disparity in the adenocarcinoma association by sex are possible. First, the degree to which ambient UFP concentrations at the residence reflect personal exposures may vary, as we could not characterize important determinants, such as time spent outdoors, potentially leading to different degrees of exposure misclassification between men and women. Occupational information was not available for the cohort, and occupational exposures could also result in differing degrees of UFP exposure misclassification by sex. In addition, occupational exposures that cause lung cancer could have also been more correlated with ambient residential UFP exposure in men, such as if men more frequently worked at the airport or other UFP sources near their homes, thus confounding associations between UFP and lung cancer more for men. Therefore, sex differences in exposure misclassification or uncontrolled confounding may explain our findings. Furthermore, the literature on smoking does not currently show evidence of sex differences in associated lung cancer risk (27). Lastly, it is also possible that the associations we found in men are due to chance.

We found the most pronounced association between UFP and adenocarcinoma among men who were born between 1925 and 1930, possibly because of high historical exposures. LA was once one of the most polluted U.S. cities; traffic-related pollution controls began nationally under the 1976 Clean Air Act, and the LA region was one of the first to establish even stricter mitigation policies (28). As such, air pollution from traffic has been tightly controlled in the area since the 1980s and 1990s; however, our cohort participants, who were on average 62 years old at enrollment in 1995 and 1996, likely experienced high traffic-related air pollution exposures during much of their adult lives. Moreover, the oldest participants (born between 1925 and 1930, 65–70 years old at enrollment) would have experienced the peak air pollution exposures of the late 1940s as young adults, around the time when smog became a major concern in the region (28). The oldest birth cohort likely also had longer duration of exposure and longer latency for the development of lung cancer. Because lifetime residence histories or air pollution estimates before 1980 are unavailable, we cannot support these assumptions empirically. However, our finding of the strongest adenocarcinoma association among the oldest participants provides some support for this interpretation.

Strengths and Limitations

Our study leveraged individual residence-based exposure assessment and included a large number of incident cases with which to estimate these association overall and by histologic type. We adjusted for smoking and other potential confounders. Although the latency of lung cancer development after UFP exposure is not known, studies have approximated a minimum latency of about 10 years for cigarette smoking (19, 29). With a retrospective exposure assessment going back 15 years before enrollment and many years of prospective follow-up we expect that our study had an adequate latent period for the development of lung cancer.

Other major strengths include the long-term UFP exposures characterized for all participants on the basis of LUR models and validated historical $PM_{2.5}$ and NO_2 estimates. We also had some historical UFP measurements across the LA Basin, enabling comparison with the UFP concentrations from our 2016 LUR model, which was based on measurements collected 20 years after enrollment. The historical measurements suggest that our model underestimated historical UFP exposures, consistent with the expected decline in ambient UFP concentrations over time because of vehicle and air pollution controls. In addition, the modest correlations between annual average UFP estimates and these historical measurements collected at subannual time frames may be due to the fact that measurement techniques were different from our more recent study or because of the strong seasonal variation of UFP in the LA Basin. However, our mean back-extrapolated exposures were similar to the means of these measurements, providing a historical picture of UFP exposure in LA that is lacking in other epidemiologic studies of long-term UFP exposure. Oil refineries are a known UFP source (30, 31) but were not considered in our LUR development; in *post hoc* evaluation, we found that including the distance between refineries and a UFP monitoring site marginally improved UFP predictions (∼1–2% change in variance), and adjustment for residential proximity to refineries also had little impact on associations with lung cancer (data not shown).

Exposure misclassification is the major limitation of this work. As back-extrapolated UFP estimates were anchored on historical trends in $PM_{2.5}$, the associations we observed may be partially explained by this pollutant. However, we found that $PM_{2.5}$ did not exhibit a strong independent association with adenocarcinoma, and our results for back-extrapolated UFP were essentially the same on the basis of 2016 LUR-estimated UFP concentrations, for which we expect the

historical spatial contrasts would largely be stable. Our analyses also suggested that associations between UFP and adenocarcinoma among men were stronger when $PM_{2.5}$ concentrations were relatively low, and among men residing at least 10 years at their address before enrollment, for whom we expect exposures to be less misclassified. We alternatively used NO_2 for back extrapolation and observed similar patterns of association. This consistency in effects regardless of the pollutant anchoring historical UFP estimates may be because the airport, not traffic, was a dominant UFP source in our catchment area, as has been observed in other studies (2, 3, 32). LA International Airport began commercial service in 1946 (33) and has consistently ranked in the top 10 airports globally on the basis of aircraft movement (34); nearby monitoring has shown elevated UFP concentrations since measurement first began in the early 2000s (35, 36). These observations, together with the positive associations observed largely among never- and former-smoking men, support an UFP effect. However, inference is limited by the paucity of historical UFP monitoring data, and understanding this potential health hazard will require more consistent monitoring in the future. Other limitations include a lack of information on potential confounders such as occupation or environmental tobacco smoke, suboptimal power in some stratified analyses, and that residence history information was not available for all participants.

Conclusions

We found that ambient UFP exposure was modestly associated with lung cancer overall and that it may increase the risk of adenocarcinoma of the lung. The reason for the observed sex-specific effect is unclear. Replication in populations with a diversity of UFP exposure sources or where early air pollution mitigation may not have obscured effects will be informative. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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