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Particulate Matter Air Pollution Exposure, Distance to Road, and Incident Lung Cancer in the Nurses' Health Study Cohort

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Abstract

Background: A body of literature has developed suggesting an elevated risk of lung cancer associated with particulate matter and traffic-related pollutants.

Objective: We examined the relation of lung cancer incidence with long-term residential exposures to ambient particulate matter and residential distance to roadway, as a proxy for traffic-related exposures.

Methods: For participants in the Nurses' Health Study, a nationwide prospective cohort of women, we estimated 72 month average exposures to PM_{2.5}, PM_{2.5-10}, and PM₁₀ and residential distance to road. Follow-up for incident cases of lung cancer occurred from 1994 to 2010. Cox proportional hazards models were adjusted for potential confounders. Effect modification by smoking status was examined.

Results: During 1,510,027 person years, 2,155 incident cases of lung cancer were observed among 103,650 participants. In fully adjusted models, a 10 µg/m³ increase in 72 month average PM₁₀ (HR = 1.04; 95% CI: 0.95, 1.14), PM_{2.5} (HR = 1.06; 95% CI: 0.91, 1.25), or PM_{2.5-10} (HR = 1.05; 95% CI: 0.92, 1.20) was positively associated with lung cancer. When the cohort was restricted to never smokers and former smokers who had quit at least 10 years ago, the associations appeared to increase and were strongest for PM_{2.5} [(PM₁₀: HR = 1.15; 95% CI: 1.00,1.32) (PM_{2.5}: HR = 1.37; 95% CI: 1.06,1.77) (PM_{2.5-10}: HR = 1.11; 95% CI: 0.90,1.37)]. Results were most elevated when restricted to the most prevalent subtype, adenocarcinomas. Risks with roadway proximity were less consistent.

Conclusions: Our findings support those from other studies indicating increased risk of incident lung cancer associated with ambient PM exposures, especially among never and long-term former smokers.

Introduction

A number of general population studies around the world have demonstrated adverse associations between chronic exposures to ambient particulate matter (PM) and/or traffic related pollutants with lung cancer (Beelen et al. 2008a; Beelen et al. 2008b; Beeson et al. 1998; Cao and Gao 2012; Carey et al. 2013; Cesaroni et al. 2013; Hales et al. 2013; Hart et al. 2011; Heinrich et al. 2013; Hystad et al. 2013; Jerrett et al. 2013; Katanoda et al. 2011; Krewski et al. 2009; Lepeule et al. 2012; Lipsett et al. 2011; McDonnell et al. 2000; Naess et al. 2007; Nafstad et al. 2003; Nyberg et al. 2000; Pope et al. 2002; Raaschou-Nielsen et al. 2010; Raaschou-Nielsen et al. 2011; Raaschou-Nielsen et al. 2013; Turner et al. 2011). Many of these studies have observed effect modification by smoking status, providing evidence for the link between PM exposure and lung cancer in the absence of the strong influence of smoking behavior. Based primarily on the findings of these studies and evidence from occupationally exposed populations, the International Agency for Research on Cancer (IARC) has recently declared outdoor air pollution, generally, and PM specifically, as Group 1 human carcinogens (Loomis et al. 2013).

To date, the pollutants/exposures examined and the time periods and spatial scale of those exposures have been somewhat inconsistent across the literature. The majority of studies in the literature have focused primarily on PM less than 10 microns in aerodynamic diameter (PM_{10}) or less than 2.5 microns ($PM_{2.5}$); however, a number have also considered black carbon/black smoke, NO_2 , NO_x , SO_2 , O_3 , and VOCs (Beelen et al. 2008a; Beelen et al. 2008b; Dockery et al. 1993; Filleul et al. 2005; Heinrich et al. 2013; Jerrett et al. 2013; Krewski et al. 2009; Nafstad et al. 2003; Nyberg et al. 2000; Raaschou-Nielsen et al. 2010; Raaschou-Nielsen et al. 2011; Villeneuve et al. 2013; Vineis et al. 2006). A few studies have focused on traffic exposures: modeling NO_2 from traffic sources alone (Nafstad et al. 2003; Nyberg et al. 2000; Raaschou-

Nielsen et al. 2010; Raaschou-Nielsen et al. 2011)) or using distance to major roadways or traffic volume surrounding a location (Beelen et al. 2008a; Beelen et al. 2008b; Cesaroni et al. 2013; Hystad et al. 2013; Raaschou-Nielsen et al. 2011; Raaschou-Nielsen et al. 2013; Vineis et al. 2006). Many studies have relied on area level assessment of exposure; however, a number have also modeled air pollution at the residential level with the intent to decrease measurement error. Studies have also used a variety of periods of exposure relative to disease diagnosis, given that the relevant time period of exposure is unknown. Furthermore, with a few exceptions (Cao and Gao 2012; Lipsett et al. 2011) potential confounders have only been assessed once, even in prospective cohort studies. Despite these inconsistencies in the current body of literature, a link between lung cancer and ambient air pollution has been demonstrated.

The current study is based in the United States within the all-female Nurses' Health Study (NHS) cohort. Our objective is to examine the association of lung cancer incidence with residential-level chronic exposure to $PM_{2.5}$, particulate matter between 2.5 and 10 microns in diameter ($PM_{2.5-10}$), PM_{10} , and residential distance to road. With a wealth of time-varying information on exposures and potential confounders, this cohort provides a unique opportunity to examine these associations.

Methods

Study population

The Nurses' Health Study (NHS) is an ongoing prospective cohort of 121,700 female nurses who were enrolled in 1976 when they were between 30 and 55 years of age. Participants initially were recruited from 11 states, but as of the mid 1990s nurses now reside in each of the 50 states. A map of all residential addresses is presented in Supplemental Material, Figure S1. Participants complete mailed biennial questionnaires to provide information on potential risk factors and to

self-report new diagnoses of health outcomes. The response rates are over 90% for each follow-up cycle. Vital status is ascertained through next-of-kin and the National Death Index; both methods have identified an estimated 98% of deaths in the cohort. The analytical population for this study excluded all women who were dead or had a previous diagnosis of cancer (with the exception of non-melanoma skin cancer) prior to follow-up or did not have information for the exposures of interest. The study was approved by the Internal Review Board of Brigham and Women's Hospital, Boston, MA; and informed consent was implied through return of the questionnaires. In addition, this study was approved by the Connecticut Department of Public Health (DPH) Human Investigations Committee. Certain data used in this publication were obtained from the DPH.

Case ascertainment

Lung cancers were self-reported by the participants, next of kin, or identified from death certificates; and first reports were subsequently confirmed with medical records by physicians blinded to exposure status. Medical records were obtained for 83% of reported cases, and of those 87% had primary lung cancer confirmed by pathology reports. However, because lung cancers were well-reported in this cohort, we included any primary report re-confirmed by the participant where pathological reports were not available.

Exposure assessment

As part of the questionnaire mailing process, residential address information is updated every two years. All available addresses (1976, 1986-2010) have been geocoded to obtain the corresponding latitude and longitude. For women with a street segment level geocode (i.e. highest quality, 80-90% of the available addresses in each follow-up cycle), we calculated

distance to road at each address as a proxy for traffic-related exposures. Distance to the nearest road (in meters) was determined using geographic information system (GIS) software (ArcGIS, version 9.3; ESRI, Redlands, CA) and the ESRI Streetmap Pro2007 dataset. We calculated the shortest distances to the following road classes as defined by the US Census (US Census 2001): A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits), A2 (primary major, non-interstate highways and major roads without access restrictions), and A3 (smaller, secondary roads, usually with more than two lanes). Analyses were conducted using distance to the nearest of all three road types (A1-A3), distance to the two largest road types (A1, A2), and distance to the largest road type (A1). Based on the distribution of distance to road in this cohort and previous exposure studies showing approximately exponential decay in exposures to traffic-related air pollutants with increasing distance from a road, we divided distance to road into the following categories (0–50, 50–200, ≥ 200 m) (Adar and Kaufman 2007; Karner et al. 2010; Lipfert et al. 2006; Lipfert and Wyzga 2008; Lipfert et al. 2008; Sahlodin et al. 2007; Zhu et al. 2002) We also considered analyses of continuous distance to roads.

Ambient GIS-based spatio-temporal exposure model predictions of PM_{2.5} and PM₁₀ were available for all months between January 1988 and December 2007 for the continental US. These values were generated for each address from nationwide expansions of previously validated spatiotemporal models (Weuve et al. 2012; Yanosky et al. 2008; Yanosky et al. 2009). The models used monthly average PM_{2.5} and/or PM₁₀ data from the US Environmental Protection Agency's (EPA) Air Quality System, the IMPROVE network and various other sources (Spengler et al. 1996; Suh et al. 1997). Generalized additive mixed models with monthly penalized spline smooth spatial terms, penalized spline smooth terms of geospatial predictors

(listed below), and terms for time were used to create separate PM prediction surfaces for each month and each PM size fraction (Yanosky et al. 2009). The following geospatial predictors used by the models were generated using a GIS: distance to nearest A1-A4 roads, percent urban land use within 1 km, elevation, point sources of PM (PM_{2.5} emissions density within 7.5 km for PM_{2.5} models and PM₁₀ emissions density within 7.5 km for PM₁₀ models), smoothed county population density, tract population density (only for PM₁₀) and meteorological predictors: wind speed, total precipitation, temperature, and percent stagnant air days per month (Yanosky et al. 2009). Since monitoring data on PM_{2.5} is limited prior to 1999, PM_{2.5} in the period before 1999 was modeled using data on PM₁₀ (Yanosky et al. 2008). By subtraction of the monthly PM₁₀ and PM_{2.5} estimates, information was also obtained on PM_{2.5-10}. Cross-validation results demonstrated that the models had high predictive accuracy (cross-validation R² values of 0.59, 0.76, and 0.77 for PM₁₀, pre-1999 PM_{2.5}, and post-1999 PM_{2.5}, respectively).

Potential confounders and effect modifiers

We selected *a priori* a number of potential confounders or effect modifiers previously associated with lung cancer or exposure in this cohort. Information on the following time-varying variables was available every 2 or 4 years from the follow-up questionnaires: body mass index (BMI, kg/m³, continuous), physical activity in metabolic equivalent hours per week (MET hours/week; < 3, 3 - < 18, ≥ 18), overall diet quality (Alternative Health Eating Index, continuous) (Chiuve et al. 2012), alcohol consumption (dichotomized at 0 g/day), smoking status (current, former, never), months since quit for former smokers (continuous), and pack years (continuous). In 1982 a question was included on exposure to second hand smoke at home, work and during childhood. We considered Census tract median household income and median house value as measures of area level socioeconomic status. To account for differences in exposure and other unmeasured

regional factors, we also controlled for US geographic region of residence (Northeast, South, Midwest, West).

Statistical analysis

Time-varying Cox proportional hazards models were used to assess the relationship of incident lung cancer with residential distance to road and exposure to PM_{2.5}, PM₁₀, or PM_{2.5-10}. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each category of roadway proximity compared to the furthest category. We examined the linearity of the association with distance to road using cubic splines, and considered models examining the linear dose-response with distances from 0-499 m, compared to values 500 m or more. For the metrics of PM we calculated HRs and 95% CIs for a 10 µg/m³ increase in each size fraction, after assessing linearity of the dose response. Since the appropriate averaging period is unknown, yet assumed to be more chronic than short-term, we considered 24, 48, 72, 96, and 120 month cumulative averages. We used Akaike's information criterion (AIC) (Akaike 1974) to determine the best fit cumulative average for PM_{2.5} among individuals with at least 120 months of exposure, so that the AIC criteria were evaluated among a single population. In sensitivity analyses we considered the consistency of results for other possible averaging times. A p-value of 0.05 was used to determine statistical significance.

In the Cox models, person-months were calculated from the start of disease follow-up until June 2010, the end of follow-up, censoring at event, death from another cause, or loss to follow-up, whichever occurred first. We determined the start of disease follow-up based on the selected cumulative average. All models were based on a biennial time scale, were stratified by age in months and time period, and adjusted for geographic region. Separate models were run for the distance to road types and for each size fraction of PM. Potential confounders (or sets of

confounders) were entered separately into the basic model to determine their influence on the association of the exposure with lung cancer. We included variables in the final models that changed the effect estimate for PM_{2.5} and lung cancer at least 10%. For comparability, we used the same confounders across the different size fractions and distance to road models.

To examine effect modification by smoking status, we performed stratified models and created multiplicative interaction terms. Due to small numbers of cases among never smokers, we also considered effect modification combining never smokers with former smokers who had quit at least 10 years ago (“long-term former smokers”). Sensitivity analyses were performed restricted to non-movers, defined as women who remained at the same address between 1976 and the start of follow-up. SAS version 9.2 was used for all analyses.

Results

Based on the assessment of averaging times described in the methods, the 72 month average was identified as the optimal cumulative average, and therefore we began disease follow-up for all analyses in 1994. A total of 103,650 participants were available for analysis of PM exposures (4,548 died prior to 1994, 10,710 had a previous diagnosis of cancer, and an additional 2,753 had no information on air pollution).

Age-adjusted characteristics during follow-up are presented overall and by smoking status in Table 1. The average age was 67.0 years (SD: 8.3), the age-adjusted mean BMI was 25.6 (SD: 7.5) and about 39% reported between 3 and 18 MET hours per week of physical activity. About half of the women lived in the Northeast, and 52% of participants reported second hand smoke exposure at work and from their parents and about 35% at home. More never smokers were non-drinkers and were less exposed to second hand smoke, while more current smokers reported less

than 3 MET hours per week of physical activity. Distributions of the three size fractions of PM overall and by region and correlations between the three size fractions within and across cumulative averages are presented in Supplemental Material, Tables S1 and S2, respectively.

All of our *a priori* potential confounders met our definition of confounding and were included in the final multivariable adjusted models. Physical activity, diet, and Census tract median income and median home value attenuated the effect estimate when added to the basic models, while estimates increased after control for alcohol consumption and BMI. We considered a number of combinations of smoking variables, including smoking status and pack years; smoking status, pack years, and months since quit; smoking status, cigarettes per day and duration of smoking; and smoking status, number of cigarettes per day, duration and months since quitting. Adjustment for any of these combinations led to similar elevated effect estimates (data not shown); therefore we included smoking status, pack years, and months since quitting in all multivariable models.

There were a total of 1,510,027 person-years of follow-up and 2,155 lung cancer cases (1,930 definite) among the 103,650 women with information on 72 month cumulative average PM. Models of associations between lung cancer and 72 month average exposures to the different size fractions of PM are presented in Table 2. There were no statistically significant deviations from linearity; therefore, we present linear exposure-response functions. In basic models adjusted for age, calendar time, and region of the country, each $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} , $\text{PM}_{2.5}$, and $\text{PM}_{2.5-10}$ was associated with positive, but non-statistically significant, HRs in the full cohort. The HRs from the multivariable models were similar to those from the basic models for PM_{10} and $\text{PM}_{2.5}$; however, the HRs in multivariable models for $\text{PM}_{2.5-10}$ were attenuated compared to the basic models. For all size fractions, the magnitude of the HRs increased in models restricted to never

smokers. There was a suggestion of effect modification comparing never smokers and former smokers who had quit at least 10 years prior to current smokers or former smokers who had quit less than 10 years prior (p for interaction: PM₁₀ 0.09; PM_{2.5} 0.09; PM_{2.5-10} 0.26). For example, for each 10 µg/m³ increase in PM_{2.5}, among never smokers and former smokers who had quit at least 10 years prior, the HR = 1.37; 95% CI: 1.06, 1.77, while among current and recent former smokers the HR = 0.94; 95% CI: 0.76-1.15.

Among all lung cancer cases, 44% were adenocarcinoma, 14% were squamous, 14% were small cell, 16% were other histologies (large cell and non-small cell carcinoma, carcinoid, or papillary, mixed sarcoma), and 12% were unknown histology. There were only sufficient numbers of adenocarcinomas to perform subtype-specific analyses. In general, HRs for associations with adenocarcinomas were stronger than corresponding HRs for all lung cancer subtypes combined (Table 2).

In sensitivity analyses, the HRs for PM_{2.5} and all lung cancers, the HRs for associations with adenocarcinomas specifically, and the HRs based on models restricted to never or long-term former smokers were slightly stronger when analyses were restricted to 66,051 women who did not move between 1976 and 1994 (986,370 person years, 1,441 total cases) (Supplemental Material, Table S3). Furthermore, our conclusions were unchanged when we used the 24, 48, 96, or 120 month cumulative averages for PM (data not shown).

There were a total of 1,291,229 person-years of follow-up and 1,841 lung cancer cases (1,654 definite) among the 88,596 women with information on distance to road in 1994 (i.e. with a street segment level geocode). Results from basic and multivariable adjusted models of associations with distance to road are presented in Table 3 for each of the different roadway

size/distance category combinations. Living within 50 m of an A1 road versus > 200 m from an A1 road was positively associated with lung cancer, though estimates were very unstable due to the small number of cases (n = 10).. When distance to road was modeled continuously, there was no apparent association with decreasing distance. In sensitivity analyses restricted to women who did not move between 1976 and 1994, results were similar (Supplemental Material, Table S4).

Discussion

In this large prospective cohort study of women living in the contiguous US, we observed positive associations between long-term exposures to ambient air pollution (PM₁₀, PM_{2.5} and PM_{2.5-10}) and incident lung cancer after adjusting for time-varying information on known risk factors, including lifetime smoking history, diet, and physical activity. In the full cohort, a 10 µg/m³ increase in the 72 month cumulative average of all three size fractions was associated with modest increases in risk [PM₁₀: HR = 1.04 (95% CI: 0.95, 1.14); PM_{2.5}: HR = 1.06 (95% CI: 0.91, 1.25); PM_{2.5-10}: HR = 1.05 (95% CI: 0.92, 1.20)]. However, associations were stronger when the cohort was restricted to never smokers and former smokers who had quit at least 10 years prior to diagnosis, particularly for PM_{2.5} [PM₁₀: HR =1.15 (95% CI: 1.00,1.32); PM_{2.5}: HR = 1.37 (95% CI: 1.06,1.77); PM_{2.5-10}: HR =1.11 (95% CI: 0.90,1.37)]. In addition, associations were stronger when only the most common lung cancer subtype, adenocarcinoma, was considered. We also assessed distance to major roadways as a proxy for overall traffic exposures. Living within 50m of an A1 road (versus >200m from an A1 road) was positively associated with lung cancer risk, but numbers of exposed participants were small and there was no evidence of an association with distance from a road modeled as a continuous variable.

Our estimated HRs for a 10 µg/m³ increase in PM_{2.5} and PM₁₀ in the full cohort are at the lower end of the distribution of associations observed in the majority of previous equivalent studies

(Beelen et al. 2008a; Beelen et al. 2008b; Beeson et al. 1998; Cao and Gao 2012; Carey et al. 2013; Cesaroni et al. 2013; Hales et al. 2013; Hart et al. 2011; Heinrich et al. 2013; Hystad et al. 2013; Jerrett et al. 2013; Katanoda et al. 2011; Krewski et al. 2009; Lepeule et al. 2012; Lipsett et al. 2011; McDonnell et al. 2000; Naess et al. 2007; Nafstad et al. 2003; Nyberg et al. 2000; Pope et al. 2002; Raaschou-Nielsen et al. 2010; Raaschou-Nielsen et al. 2011; Raaschou-Nielsen et al. 2013; Turner et al. 2011). These studies have reported associations ranging from 0.95-1.40 for PM_{2.5} and 0.93-2.40 for PM₁₀ when estimated for increments of 10 µg/m³. To our knowledge, to date, only one other study has presented assessment of PM_{2.5-10} (Raaschou-Nielsen et al. 2013) and the HR was 1.19 (95% CI: 0.77, 1.82), if expressed as a 10 µg/m³ increase.

In its recent assessment of the carcinogenicity of outdoor air pollution in general and particulate matter in particular, IARC determined that the evidence was remarkably consistent in epidemiological studies from Europe, North America and Asia, studies of experimental animals, and across a wide range of mechanisms related to cancer (Loomis et al. 2013). IARC determined that for lung cancer the most informative epidemiologic studies were the European Study of Cohorts for Air Pollution Effects (ESCAPE) and the American Cancer Society Study (ACS). ESCAPE combined data from 17 cohort studies based in nine European countries, including 312,944 individuals and 2,095 incident lung cancer cases over 12.8 years of follow-up. Using land-use regression models incorporating data from 2008-2011, they predicted PM exposures at the participants' baseline address (in the 1990s for most cohorts). They observed associations of lung cancer with PM₁₀ (HR 1.22; 95% CI 1.03,1.45 per 10 µg/m³), PM_{2.5} (HR 1.18; 95%CI 0.96,1.46 per 5 µg/m³), and PM_{2.5-10} (HR 1.09; 95%CI 0.88,1.33 per 5 µg/m³) after adjusting for sex, smoking variables, SHS, occupational variables, fruit intake and area level SES (Raaschou-Nielsen et al. 2013). The most recent updates of the full ACS Cancer Prevention Study II (CPS-

II) study included ~500,000 individuals residing in metropolitan statistical areas (MSAs) throughout the US with information on air pollution (Krewski et al. 2009; Pope et al. 2002). The investigators estimated MSA-level average baseline exposures to PM_{2.5} 1979-1983 and towards the end of the follow-up 1999-2000. HRs were adjusted for sex, age, race, and baseline information on smoking, education, marital status, BMI, alcohol consumption, occupational exposure and diet. With follow-up from 1982-1998, the adjusted HRs for a 10 µg/m³ increase in PM_{2.5} using the baseline average, the 1999-2000 average, or the average of the two time periods were 1.08 (95%CI 1.01,1.16), 1.13 (95%CI 1.04,1.22), and 1.14 (95%CI 1.04,1.23), respectively (Pope et al. 2002). The adjusted HR per 28.8 µg/m³ for exposure to PM₁₀ averaged from 1987-1996 was not elevated (HR 0.94; 95%CI 0.86, 1.02) (Krewski et al. 2009). An additional 2 years of follow-up and extensive consideration of additional individual level and ecological level covariates, as well as assessment of autocorrelation, did not materially change these results (Krewski et al. 2009).

There is no clear evidence in the literature of sex differences in the relation of PM with lung cancer. To date, only two other studies have focused specifically on women. In the California Teachers Study, a prospective cohort of 133,479 female public school professionals (age 20-80 at baseline) residential level cumulative exposures to PM_{2.5} and PM₁₀ were quantified. From 1997 through 2005, 234 and 275 participants with PM_{2.5} and PM₁₀ exposure information, respectively, died from lung cancer. Adjusted analyses showed no association with a 10 µg/m³ change in PM_{2.5} (HR 0.95; 95%CI 0.70-1.28) or PM₁₀ (HR 0.93; 95%CI 0.81-1.07) (Lipsett et al. 2011). In a German cohort study of 4800 women air pollution exposure was assessed for up to 18 years using air-monitoring station data to calculate yearly averages of PM₁₀. Adjusted analysis showed an increase of 7 µg/m³ PM₁₀ was associated with an increased HR for lung cancer

mortality (HR 1.84; 95%CI 1.23, 2.74)(Heinrich et al. 2013). In other studies that presented results stratified by sex, no clear patterns of effect modification emerged (Abbey et al. 1999; Cesaroni et al. 2013; Katanoda et al. 2011; Naess et al. 2007; Pope et al. 2002).

Our findings of stronger associations when we restricted to never smokers and participants who had quit at least ten years before diagnosis are consistent with the majority of the literature. After 26 years of follow-up in the ACS study, the adjusted HR for lung cancer mortality risk among never smokers was 1.27; 95%CI 1.03,1.56 for a 10 $\mu\text{g}/\text{m}^3$ change in $\text{PM}_{2.5}$ 1999-2000 (Turner et al. 2011). In ESCAPE, the HRs for a 10 $\mu\text{g}/\text{m}^3$ change in PM_{10} increased to 1.39 (95%CI 0.94, 2.06) and for a 5 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ to 1.21 (95%CI 0.61, 2.40) (Raaschou-Nielsen et al. 2013). Although no association between PM and lung cancer mortality was observed in the California Teachers Study, when the population was restricted to never smokers the adjusted HR for a 10 $\mu\text{g}/\text{m}^3$ change in $\text{PM}_{2.5}$, but not PM_{10} , showed an increased risk ($\text{PM}_{2.5}$ HR 1.62; 95%CI 0.83, 3.16; PM_{10} HR 1.00; 95%CI 0.75, 1.31) (Lipsett et al. 2011). In the Harvard Six Cities Study (n=8,096), adjusted HRs increased from 1.37 (95%CI 1.07, 1.75) for a 10 $\mu\text{g}/\text{m}^3$ change overall, to 1.96 (95%CI 1.29, 2.99) among former smokers. However, HRs for never and current smokers were 1.25 (95%CI 0.54, 2.89) and 1.25 (0.95, 1.64), respectively (Lepeule et al. 2012). Similarly, in a case-control study in Canada, adjusted HRs for the whole study were 1.29 (95% CI 0.95, 1.76) per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$, but HRs among never, former and current smokers were 0.95 (95%CI 0.38, 2.34), 1.45 (95%CI 0.96, 2.19) and 1.17 (95%CI 0.75, 1.84), respectively (Hystad et al. 2013). In a Japanese cohort of 63,520 participants, all never smokers were female. The adjusted HR for a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was 1.16 (95%CI 1.02, 1.33) in the never smokers, while the HR for all females was 1.17 (95%CI 0.98, 1.39) (Katanoda et al. 2011). With the exception of the ACS study (1,100 cases), in each individual study the numbers

of lung cancer cases who had never smoked was quite small (<200). Overall, however, since they reduce the potential for residual confounding by smoking, these analyses among never and former smokers increase our confidence that exposure to air pollution is independently associated with lung cancer.

Very few studies have estimated associations of air pollution with histological subtypes of lung cancer. Hystad and colleagues reported increased risk for adenocarcinoma for each 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ (OR: 1.27, 95%CI: 0.84, 1.90) (Hystad et al. 2013). Similar to our study, in ESCAPE results were stronger when the case definition was restricted to adenocarcinomas (5 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ HR: 1.55; 95%CI: 1.05, 2.29 and 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} exposure HR: 1.51; 95%CI: 1.10, 2.08) (Raaschou-Nielsen et al. 2013). In a hospital-based case control study of over 1,200 patients in Northern Spain, with residential area as a proxy for air pollution levels, residents in urban areas showed significantly increased risks for adenocarcinoma (OR: 1.92, 95%CI: 1.09, 3.38) compared to rural areas (Lopez-Cima et al. 2011). Adenocarcinomas are the lung cancer sub-type most commonly observed among non-smokers (Schuller 2002), and time-trend and geographic studies have also suggested associations of this sub-type with ambient air pollution (Chen et al. 2007; Chen et al. 2009).

Conclusions from studies specifically assessing the association of lung cancer with traffic exposures have been inconclusive. Six previous studies in Europe and Canada have looked at measures of distance to roadway or traffic intensity (Beelen et al. 2008a; Beelen et al. 2008b; Cesaroni et al. 2013; Hystad et al. 2013; Raaschou-Nielsen et al. 2011; Raaschou-Nielsen et al. 2013; Vineis et al. 2006). Similar to our findings, the results have been suggestive of a modest association, however, the different metrics are difficult to compare and no results are statistically significant. Four studies, all in Europe, have modeled NO_2 or NO_x specifically from traffic

sources (Nafstad et al. 2003; Nyberg et al. 2000; Raaschou-Nielsen et al. 2010; Raaschou-Nielsen et al. 2011). Overall, these studies indicate a possible contribution from traffic, but again they are difficult to compare due to differences in exposure assessment.

Our study has a number of limitations. We used a spatio-temporal model to assign monthly residential level PM exposures for each participant. However, we do not account for differences in time activity patterns, time spent outdoors, or time spent at the residence. Additionally, due to paucity of monitoring for PM_{2.5} prior to 1999, our models for PM_{2.5} and PM_{2.5-10} in the earlier years are less precise than our models in the later years. Although we had detailed residential history information during the course of the study when the women were all at least 58 years old, we were unable to assess exposures throughout the life course. Another source of exposure measurement error is the temporal mismatch of our road layer with the address information used in the distance to road analyses, which may partially explain our generally null results. Even though our study was conducted within a large cohort of women with a large number of total cases, we were limited by the small number of cases among certain subgroups of particular interest, including never smokers, people living close to roadways or histological subtypes other than adenocarcinomas. As with all studies, residual confounding, particularly by active and passive smoking is of concern. We controlled for secondhand smoke exposures; however, this information was only available at one time point and was not available for a large number of participants. Though modification by educational attainment has been reported (Raaschou-Nielsen et al. 2011) this cohort of predominantly Caucasian nurses allows very limited exploration of the influence of socioeconomic status or race, although controlling for individual- and area-level SES along with other risk factors made little difference to the results.

This study also has a number of strengths, including our ability to control for time-varying exposures after baseline. Additionally, we were able to examine the effects of adjusting for a number of different parameterizations of smoking, incorporating time since quit as well as duration and intensity. We were also able to adjust for exposures to secondhand smoke. Although the survival rate of lung cancer is low, we assessed lung cancer incidence as opposed to mortality. Finally, we had sufficient adenocarcinomas to be able to specifically examine this subtype of interest.

Conclusions

In the largest study of incident lung cancers among women to date, positive associations were observed with average PM exposures in the previous 72 months. Associations were stronger when analyses were restricted to adenocarcinomas, or to never and long-term former smokers. This study provides additional support of an association of air pollution exposure and lung cancer, particularly among non-smokers.

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Table 1. Age-adjusted descriptive characteristics averaged over follow-up (1994-2010) among 103,650 participants in the Nurses' Health Study overall and stratified by smoking status.

Characteristics	All Participants	Never Smokers	Former Smokers	Current Smokers
Person-years (%) ^a	1,510,027 (100)	668,581 (44)	663,062 (44)	175,563 (12)
Age [years (mean ± SD)] ^a	67.0 ± 8.3	67.1 ± 8.5	67.4 ± 8.2	64.8 ± 7.9
BMI [kg/m ² (mean ± SD)]	25.6 ± 7.5	25.8 ± 7.4	26.4 ± 6.8	22.1 ± 9.4
Pack-years of smoking (mean ± SD)	13.4 ± 20.0	0.0 ± 0.0	19.3 ± 18.5	43.0 ± 23.0
Months since quit smoking (mean ± SD)	123.9 ± 178.8	0.0 ± 0.0	279.2 ± 167.4	0.0 ± 0.0
Alternative Healthy Eating Index (mean ± SD)	180.4 ± 108.5	182.8 ± 108.0	190.6 ± 106.5	129.4 ± 102.1
Census Tract Median household income (mean ± SD)	63,518 ± 24,491	62,648 ± 23,194	64,849 ± 24,978	61,954 ± 23,644
Census Tract Median home value (mean ± SD)	170,126 ± 125,261	166,431 ± 123,720	176,055 ± 128,455	161,998 ± 118,139
Move Between 1976 and 1994 (%) ^a				
No	65.4	66.1	64.1	67.4
Yes	34.6	33.9	35.9	32.6
Region (%)				
Northeast	51.1	48.0	53.2	54.6
Midwest	17.3	19.4	15.4	16.4
West	13.7	14.5	13.3	11.4
South	18.0	18.1	18.1	17.7
Alcohol Category (%)				
Non-drinker (0 g/day)	15.0	22.1	9.3	9.7
Drinker	71.4	63.3	80.3	68.5
Missing	13.6	14.6	10.4	21.8
Physical Activity (%)				
<3 MET hr/week	21.5	20.5	21.2	26.0
3 to < 18 MET hr/week	38.8	39.7	39.4	33.2
18+ MET hr/week	30.7	31.2	33.0	20.3
Missing	9.0	8.5	6.5	20.5
Second Hand Smoke During Childhood (%)				
None	25.1	30.9	21.8	15.7
From Mother	3.8	3.1	4.4	3.8
From Father	33.9	34.1	34.9	29.1
From Both Parents	14.7	11.2	17.5	17.0
Missing	22.6	20.7	21.4	34.4

Characteristics	All Participants	Never Smokers	Former Smokers	Current Smokers
Home Second Hand Smoke (%)				
None	33.2	38.6	31.8	17.7
Occasional	18.6	18.7	19.6	14.0
Regular	17.1	11.4	19.5	29.6
Missing	31.2	31.3	29.1	38.8
Occupational Second Hand Smoke(%)				
None	15.0	16.9	14.5	9.5
Occasional	29.3	33.0	28.6	17.7
Regular	22.6	19.2	24.5	28.1
Missing/Not working	33.1	30.9	32.4	44.7

BMI – Body Mass Index; MET – Metabolic Equivalent

^aNot age-adjusted.

Note: Women can be in multiple smoking status categories throughout follow-up.

Table 2. Hazard ratios and 95% confidence intervals of the association of incident lung cancer 1994-2010 per 10 $\mu\text{g}/\text{m}^3$ increase in 72-month cumulative Average particulate matter exposures among 103,650 members of the Nurses' Health Study.

Case Definition/Cohort	Cases	Person-Years	PM ₁₀ : Basic ^a	PM ₁₀ : Adjusted ^b	PM _{2.5} : Basic ^a	PM _{2.5} : Adjusted ^b	PM _{2.5-10} : Basic ^a	PM _{2.5-10} : Adjusted ^b
All Cases								
Full Cohort	2,155	1,510,027	1.06 (0.98, 1.16)	1.04 (0.95, 1.14)	1.05 (0.90, 1.23)	1.06 (0.91, 1.25)	1.12 (0.98, 1.27)	1.05 (0.92, 1.20)
Never Smokers	176	668,581	1.12 (0.85, 1.46)	1.11 (0.85, 1.46)	1.24 (0.74, 2.05)	1.25 (0.75, 2.07)	1.13 (0.75, 1.70)	1.11 (0.74, 1.68)
Never or Quit Smoking at Least 10 Yrs	828	1,203,946	1.11 (0.97, 1.28)	1.15 (1.00, 1.32)	1.22 (0.95, 1.57)	1.37 (1.06, 1.77)	1.11 (0.91, 1.37)	1.11 (0.90, 1.37)
Current or Smoked in the Last 10 Yrs	1,327	306,081	0.97 (0.86, 1.08)	0.99 (0.88, 1.12)	0.88 (0.72, 1.08)	0.94 (0.76, 1.15)	1.01 (0.85, 1.21)	1.03 (0.86, 1.24)
Adenocarcinomas								
Full Cohort	847	1,510,027	1.15 (0.95, 1.39)	1.18 (0.97, 1.45)	1.28 (0.89, 1.83)	1.33 (0.92, 1.93)	1.18 (0.87, 1.59)	1.23 (0.89, 1.70)
Never or Quit Smoking at Least 10 Yrs	425	1,203,946	1.18 (0.83, 1.67)	1.41 (0.95, 2.09)	1.41 (0.73, 2.72)	1.66 (0.81, 3.42)	1.14 (0.69, 1.86)	1.49 (0.85, 2.63)

^aModels adjusted for age, time period, and geographic region. ^bAdditionally adjusted for BMI, alcohol consumption, physical activity, overall diet quality, smoking status (when not stratified by status) and pack years, months since quit smoking, second hand smoke exposure at home, work and during childhood, and Census tract median home value and median income.

Table 3. Hazard Ratios and 95% CIs for incident lung cancer 1994-2010 in association with residential proximity to roads in 1994 among 88,596 members of the Nurses' Health Study.

Exposure Category	Cases	Basic^a	Adjusted^b
Full Cohort			
Distance to A1 (m)			
200+	1,799	1.00	1.00
50-199	32	0.70 (0.49, 0.99)	0.73 (0.51, 1.04)
0-49	10	2.38 (1.27, 4.44)	2.01 (1.06, 3.80)
Continuous (per 100 m)	1,841	1.01 (0.95, 1.08)	1.01 (0.95, 1.07)
Distance to A1-A2 (m)			
200+	1,699	1.00	1.00
50-199	105	0.93 (0.76, 1.13)	0.93 (0.76, 1.14)
0-49	37	1.14 (0.82, 1.58)	1.02 (0.73, 1.42)
Continuous (per 100 m)	1,841	1.00 (0.96, 1.04)	1.01 (0.97, 1.04)
Distance to A1-A3 (m)			
200+	971	1.00	1.00
50-199	558	1.07 (0.96, 1.19)	1.05 (0.94, 1.17)
0-49	312	1.10 (0.97, 1.25)	1.05 (0.92, 1.19)
Continuous (per 100 m)	1,841	0.98 (0.95, 1.00)	0.99 (0.96, 1.02)
Current or Smoked in the Last 10 Yrs			
Distance to A1 (m)			
200+	1,212	1.00	1.00
50-199	19	0.79 (0.48, 1.31)	0.86 (0.52, 1.42)
0-49	6	2.74 (1.19, 6.32)	2.48 (1.04, 5.90)
Continuous (per 100 m)	1,237	1.00 (0.91, 1.09)	0.98 (0.89, 1.07)
Distance to A1-A2 (m)			
200+	1,142	1.00	1.00
50-199	69	0.96 (0.73, 1.28)	0.99 (0.75, 1.33)
0-49	26	1.01 (0.62, 1.62)	0.95 (0.58, 1.15)
Continuous (per 100 m)	1,237	1.02 (0.96, 1.08)	1.02 (0.96, 1.08)
Distance to A1-A3 (m)			
200+	647	1.00	1.00
50-199	370	1.10 (0.94, 1.28)	1.10 (0.94, 1.29)
0-49	220	1.10 (0.91, 1.33)	1.11 (0.92, 1.34)
Continuous (per 100 m)	1,237	0.98 (0.94, 1.02)	0.97 (0.93, 1.01)
Never or Quit Smoking at Least 10 Yrs			
Distance to A1 (m)			
200+	587	1.00	1.00
50-199	13	0.86 (0.49, 1.49)	0.90 (0.52, 1.57)
0-49	4	3.15 (1.16, 8.50)	3.26 (1.17, 9.11)
Continuous (per 100 m)	604	0.98 (0.88, 1.09)	0.98 (0.88, 1.09)
Distance to A1-A2 (m)			
200+	557	1.00	1.00
50-199	36	0.99 (0.71, 1.39)	1.03 (0.73, 1.45)
0-49	11	1.05 (0.58, 1.91)	1.07 (0.59, 1.96)
Continuous (per 100 m)	604	0.98 (0.91, 1.04)	0.97 (0.90, 1.03)

Exposure Category	Cases	Basic^a	Adjusted^b
Distance to A1-A3 (m)			
200+	324	1.00	1.00
50-199	188	1.10 (0.91, 1.31)	1.09 (0.91, 1.31)
0-49	92	1.00 (0.79, 1.26)	1.03 (0.81, 1.30)
Continuous (per 100 m)	604	1.00 (0.95, 1.04)	0.99 (0.95, 1.04)

^aModels adjusted for age, time period, and geographic region. ^bAdditionally adjusted for BMI, alcohol consumption, physical activity, overall diet quality, smoking status (when not stratified by status) and pack years, months since quit smoking, second hand smoke exposure at home, work, and during childhood, and Census tract median home value and median income