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Ambient air pollution and lung cancer risk among never-smokers in the Women's Health Initiative

Shilpa N. Gowda[a,b], Anneclaire J. DeRoos[c], Rebecca P. Hunt[d], Amanda J. Gassett[a], Maria C. Mirabelli[e], Chloe E. Bird[f], Helene G. Margolis[g], Dorothy Lane[h], Matthew R. Bonner[i], Garnet Anderson[d], Eric A. Whitsel[j], Joel D. Kaufman[a], Parveen Bhatti[k,l*]

Background: Ambient air pollution is classified as a human carcinogen by the International Agency for Research on Cancer (IARC). However, epidemiologic studies supporting this classification have focused on lung cancer mortality rather than incidence, and spatial and temporal resolutions of exposure estimates have varied considerably across studies.

Methods: We evaluated the association of outdoor air pollution and lung cancer incidence among never-smoking participants of the Women's Health Initiative (WHI) study, a large, US-based cohort of postmenopausal women (N = 65,419; 265 cases). We used geospatial models to estimate exposures to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) based on residential addresses at baseline and throughout follow-up. We also characterized exposures to traffic-related air pollution by proximity to major roadways. We estimated hazard ratios (HRs) for the risk of lung cancer in association with these exposure metrics using Cox proportional hazards regression models.

Results: No compelling associations of $PM_{2.5}$ and NO_2 exposures with lung cancer risk were observed. An increased risk of lung cancer was observed when comparing those individuals with residences <50 versus ≥200 meters from a primary limited access highway (HR = 5.23; 95% confidence interval = 1.94, 14.13).

Conclusions: Our results do not exclude lung cancer risk estimates observed in association with $PM_{2.5}$ and NO_2 exposures identified in previous studies. Our results suggest that residential proximity to major roadways may be a proxy for carcinogenic exposures not correlated with $PM_{2.5}$ or NO_2 levels. New studies of air pollution and lung cancer incidence should characterize additional aspects of proximity to major roadways.

Keywords: Adenocarcinoma; Air pollution; Distance to roadway; Lung cancer

Introduction

In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution in general, and particulate matter ($PM_{2.5}$) specifically, as Group 1 carcinogens for their role in lung cancer pathogenesis.[1] This classification is supported by a meta-analysis of 14 studies of lung cancer, which found a meta-relative risk of 1.09 (95% confidence interval [CI] = 1.04, 1.14) in association with each 10 μg/m^3 increase in $PM_{2.5}$ pollution (i.e., air pollution particles measuring less than 2.5 μm in diameter).[2] Studies have also evaluated distance to roadway and nitrogen dioxide (NO_2) exposures as markers of traffic-related air pollution in association with lung cancer risk. In a review of seven studies that evaluated traffic exposure (e.g., distance to roadway), only one demonstrated a statistically significant association with lung cancer.[3] However, a meta-analysis of 15 studies found a meta-relative risk of 1.04 (95% CI = 1.00, 1.09) for lung cancer in association with each 10 μg/m^3 increase in exposure to NO_2.[3]

The bulk of previous studies have focused on cancer mortality rather than incidence, and the quality of exposure assessment, in terms of spatial and temporal resolutions of exposure, have varied considerably.[2] Although multiple studies have examined distinct effects among women,[4–6] there have been few studies of adequate sample size to restrict these analyses to never-smokers, a useful strategy given the strong confounding effects of smoking. New studies addressing these limitations can further our understanding of the carcinogenic effects of air pollution. As such, we evaluated the association of various high-quality metrics of air pollution exposure and lung cancer incidence among never-smokers in the Women's Health Initiative (WHI), a large US-based cohort of postmenopausal women.

Materials and methods

Study population

The WHI is a prospective study of 161,808 postmenopausal women (ages 50–79 at enrollment) recruited across the United States from 1993 to 1998.[7] The two arms of the WHI, the

[a]*Department of Environmental & Occupational Health Sciences, School of Public Health, University of Washington, Seattle, Washington;* [b]*Workplace Health and Wellness, MaineGeneral Health, Augusta, Maine;* [c]*Department of Environmental and Occupational Health, Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania;* [d]*Women's Health Initiative Clinical Coordinating Center, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington;* [e]*Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia;* [f]*RAND Corporation, Santa Monica, California;* [g]*Department of Internal Medicine, School of Medicine, University of California, Davis, California;* [h]*Department of Family, Population & Preventive Medicine, School of Medicine, Stony Brook University, Stony Brook, New York;* [i]*Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, New York;* [j]*Department of Epidemiology, Gillings School of Global Public Health and Department of Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina;* [k]*Cancer Control Research, BC Cancer, Vancouver, British Columbia, Canada; and* [l]*Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington.*

**Corresponding Author. Address: Cancer Control Research, BC Cancer, 675 West 10 Ave., Vancouver, British Columbia, Canada, V5Z 1L3. E-mail: pbhatti@bccrc.ca (P. Bhatti).*

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clinical trials (CTs) study and the observational study (OS), included 68,132 and 93,676 women, respectively. The CT, which involved concurrent randomized controlled trials of hormone therapy, dietary modification, and calcium/vitamin D, ended in 2005. Those not able or willing to participate in the CTs were asked to participate in the OS. After 2005, WHI participants were invited to enroll in the WHI Extension Studies, which tracked health outcomes for another 10 years.

Lung cancer case ascertainment

Cancers were identified as part of medical update questionnaires administered at least annually to participants. Participants reporting a cancer were contacted by mail or phone to get more detailed information about the cancer diagnosis, and then copies of pathology/cytology reports, operative reports, and hospital discharge summaries were provided to centrally-trained Surveillance, Epidemiology, and End Results (SEER) Program coders, who were blinded to exposure status, to confirm or deny the diagnosis, using standardized SEER Program criteria. For deceased participants (deaths identified via proxy report, returned mail marked deceased, newspaper obituary, etc.), WHI staff contacted participant families and care providers to retrieve information on cause of death and document any cancer diagnoses. For any cancer diagnoses ascertained through linkage with the National Death Index, date of death was used as date of diagnosis.

Covariate data

Data for factors known or suspected to be associated with lung cancer were obtained from the WHI baseline questionnaires, interviews, and clinical measures. Smoking history was assessed as smoking status (never/former/current). For OS participants only, secondhand smoking was assessed as living with a smoker as a child, worked with a smoker (yes/no), number of years worked with a smoker, currently living with a smoker, and living with a smoker after the age of 18. Additional covariates considered in the analyses included age at baseline, history of asthma, history of emphysema, ethnicity, US region of residence, and body mass index (BMI). A previously constructed variable reflecting neighborhood socioeconomic status (NSES) was also available for the study.[8] The NSES variable is a composite of six factors as follows: (1) percent of adults ≥25 years old with less than a high school education, (2) percent male unemployment, (3) percent of households with income below the poverty line, (4) percent of households receiving public assistance, (5) percent of households with children headed only by a female, and (6) median household income. As previously described, the factors were each standardized and summed to create the composite NSES score variable, with higher values indicating higher socioeconomic levels.[9] Each factor was assessed at the census tract level, which are defined by the US Census Bureau. In general, the population sizes in a census tract are between 1,200 and 8,000 people, with spatial size depending on population density.[10]

Air pollution data

We obtained estimates of exposure to ambient air pollution as follows: $PM_{2.5}$ in $\mu g/m^3$, NO_2 in parts per billion (ppb) and residential distance to major roadways in meters. Regionalized national universal kriging models that included over 200 geographic covariates (1999–2013) were used to generate likelihood-based ambient point-specific $PM_{2.5}$ and NO_2 predictions at geocoded participant residences.[11,12] This approach resulted in a high level of cross-validated accuracy of prediction with an overall R^2 of 0.88 for $PM_{2.5}$ and 0.85 for NO_2.[11,12] Using these models, we assigned each subject in our study annual estimates of exposure for their residential address during each year of follow-up. Participant addresses were updated as new address information became available (e.g., participant reported new address on follow-up questionnaire, field center called participant for new address in response to returned questionnaire, etc.) and annual exposure estimates were generated for these new addresses. Annual estimates were used to derive a cumulative average of exposure for the duration of follow-up (i.e., until lung cancer diagnosis or censoring). We explored the impact of including a 5-year exposure lag period on our results. Since air pollution exposures have generally decreased over time in the United States, participants with more years of follow-up, and, presumably, higher cumulative exposures, may actually be assigned lower cumulative averages. To ascertain potential for bias in our results due to this issue, we conducted a sensitivity analyses in which each participant's year 2000 air pollution estimates were assigned to each subsequent year of follow-up to derive a cumulative average exposure.

Major roads were identified by census code class features A1 through A3.[11] A1 roadways are primary highways with limited access, A2 roadways are primary roads without limited access, and A3 roadways are secondary and connecting roads. We started by assigning each subject running averages of distance to nearest A1 roadway. We then created an additional variable that assigned the subject a running average of distance to nearest A1 or A2 roadway (e.g., if an A2 roadway was more proximal than A1, then distance to A2 was assigned). Finally, we created a variable that assigned a running average of distance to nearest A1, A2, or A3 roadway.

Statistical analyses

All statistical analyses were completed using the proportional hazards regression procedure in SAS version 9.4 (SAS Institute, Inc., Cary, NC). We calculated hazard ratios for the association of air pollution exposure metrics with lung cancer incidence using Cox proportional hazards regression; length of follow-up was the basic time variable. We examined $PM_{2.5}$ and NO_2 exposure concentrations as continuous variables and quartile categories based on exposure distributions in the entire cohort. $PM_{2.5}$ and NO_2 were included in the regression models as time-varying cumulative average exposures. Distance to roadways were categorized as follows: ≥200 meters, 50 to <200 meters, and <50 meters. Proximities to these roadway categories were included in the regression models as time-varying running averages. All statistical models were adjusted for age at baseline (continuous), race/ethnicity (White, Black, Hispanic, American Indian, Asian Pacific Islander, Unknown), BMI (continuous), US region of residence (Northeast, South, Midwest, West), history of emphysema (yes/no), history of asthma (yes/no), and NSES (continuous). NSES was included as at time-varying factor over the follow-up period. We stratified the baseline hazard rate by study/trial arm participation. We explored potential histology-specific effects by examining adenocarcinomas separately; there were too few cases of the other histologic subtypes to conduct meaningful analyses. We also explored the potential impact of secondhand smoke exposure on our results by conducting analyses restricted to the OS that were adjusted and unadjusted for having lived with a smoker as a child (yes/no) and having lived with a smoker after age 18 (yes/no).

Results

A total of 81,430 never-smokers were identified. We excluded 10,198 participants with a history of any cancer diagnosis (or missing cancer history) at baseline, except nonmelanoma skin cancer, 596 participants missing BMI, 2,966 participants missing history of emphysema, 822 participants missing history of asthma, 2,412 participants missing NSES, 311 participants with no follow-up time (did not complete any follow-up

questionnaires), and 2,388 participants missing air pollution data (because residential addresses were either missing, located outside the United States, part of the US military, within a US protectorate, in Hawaii or in Alaska, all of which precluded estimation of exposures), leaving a total of 265 lung cancer cases and 65,154 noncases (follow-up from October 1993 to April 2012). Mean (standard deviation) follow-up time for participants was 14.1 years (4.8 yr). Distributions of demographic and study-related factors by case status are presented in Table 1. Cases were older at baseline than noncases. In addition, greater proportions of cases were of white race/ethnicity, resided in the Northeast region of the United States, and had lower BMI than noncases.

Mean (standard deviation) year 2000 $PM_{2.5}$ exposures were 13.1 (2.9) and 13.3 (3.1) $\mu g/m^3$ for cases and controls, respectively. Mean (standard deviation) year 2000 NO_2 exposures were 15.7 (5.7) and 15.8 (6.8) ppb for cases and controls, respectively. No statistically significant associations were observed between overall lung cancer risk and yearly cumulative average $PM_{2.5}$ or NO_2 exposures (Table 2). Inclusion of a 5-year exposure lag period did not materially impact the results (results not shown). Results were generally consistent with those from the analysis of year 2000 cumulative average exposures (Table 2). Although a statistically significant elevated risk of lung cancer was observed with the third quartile of year 2000 cumulative average NO_2 exposure, there was no elevated risk in the highest quartile. Residing an average distance of <50 meters from an A1 roadway was associated with a 5.23 (95% CI = 1.94, 14.13) fold increased risk of lung cancer as compared to residing an average distance ≥200 meters from an A1 roadway. No evidence for an increased risk of lung cancer was observed among those living 50 to <200 meters from an A1 roadway. When considering distance to nearest A1 or A2 roadway and distance to nearest A1, A2, or A3 roadway, no associations with lung cancer were observed (Table 2).

Of the 265 lung cancer cases, 168 were adenocarcinoma cases, five were small-cell lung cancer cases, 34 were large cell lung cancer cases, 35 were unspecified nonsmall cell lung cancer cases, 10 were squamous cell carcinoma cases, and 10 were other lung cancer cases. No statistically significant associations of adenocarcinoma risk with yearly cumulative average $PM_{2.5}$ or NO_2 exposures were observed (Table 2). Although a statistically significant elevated risk of adenocarcinoma was observed with the third quartile of year 2000 cumulative average NO_2 exposure, there was no evidence for an elevated risk in the highest quartile. Residing an average distance of <50 meters from an A1 roadway was associated with a 6.10 (95% CI = 1.93, 19.27) fold increased risk of adenocarcinoma compared to residing an average distance ≥200 meters from an A1 roadway. No evidence for an increased risk of adenocarcinoma was observed among those living 50 to <200 meters from an A1 roadway. When considering multiple roadway types (distance to nearest A1 or A2 and distance to nearest A1, A2, or A3), no associations with adenocarcinoma were observed.

When restricting to OS participants with data on secondhand smoke exposures, an average residential distance of <50 meters from an A1 roadway was associated with a 2.21 (95% CI = 0.31, 15.80) fold increased risk of lung cancer as compared to residing an average residential distance ≥200 meters from an A1 roadway. This association remained unchanged when adjusting for secondhand smoke exposures (results not shown).

Table 1

Demographic, lifestyle, and clinical factors by lung cancer case status

Characteristic	Noncases, N = 65,154, n (%)	Cases, N = 265, n (%)
WHI study arm		
Clinical trials	28,205 (43.0)	100 (37.9)
Observational study	36,949 (56.7)	165 (62.3)
Age at baseline		
50–54	8,185 (12.6)	22 (8.3)
55–59	12,692 (19.5)	38 (14.3)
60–64	14,864 (22.8)	57 (21.5)
65–69	14,264 (21.9)	72 (27.2)
70–74	10,493 (16.1)	58 (21.9)
75–79	4,656 (7.1)	18 (6.8)
Race/ethnicity		
White	53,745 (82.5)	228 (86.0)
Black	5,882 (9.0)	20 (7.5)
Hispanic	3,195 (4.9)	5 (1.9)
American Indian	271 (0.4)	2 (0.8)
Asian/Pacific Islander	1,222 (1.9)	7 (2.6)
Unknown	839 (1.3)	3 (1.1)
US region		
Northeast	14,115 (21.7)	73 (27.5)
South	17,869 (27.4)	63 (23.8)
Midwest	15,299 (23.5)	55 (20.8)
West	17,871 (27.4)	74 (27.9)
Lived with smoker as child		
No	15,019 (23.0)	68 (25.7)
Yes	21,113 (32.4)	94 (35.4)
Missing	29,022 (44.5)	103 (38.9)
Lived with smoker after age 18		
No	14,066 (21.6)	62 (23.4)
Yes	22,567 (34.6)	103 (38.9)
Missing	28,521 (43.8)	100 (37.7)
History of emphysema		
No	63,626 (97.7)	258 (97.4)
Yes	1,528 (2.3)	7 (2.6)
History of asthma		
No	60,412 (92.7)	240 (90.6)
Yes	4,742 (7.3)	25 (9.4)
Body mass index (kg/m^2), baseline		
<18.5	558 (0.9)	2 (0.8)
18.5–24.9	22,191 (34.1)	107 (40.4)
25 to <30	22,509 (34.5)	97 (36.6)
30.0–34.9	12,362 (19.0)	41 (15.5)
35.0–39.9	4,961 (7.6)	13 (4.9)
≥40	2,573 (3.9)	5 (1.9)

Discussion

Among postmenopausal, never-smoking women, we observed no evidence for associations of lung cancer risk with exposures to $PM_{2.5}$ or NO_2. However, we cannot exclude the elevated risk estimates that have been identified in other large-scale studies.[2] We did observe a statistically significant elevated risk of lung cancer among those residing <50 meters from A1 roadways. Although the risk estimate was imprecise and an exposure-response relationship was not apparent, the results may suggest that close residential distance to A1 roadways is a proxy for one or more carcinogenic exposures not correlated with $PM_{2.5}$ or NO_2 levels.

Distance to roadway results are consistent with those from The Nurse's Health Study, which observed a 3.26 (95% CI = 1.17, 9.11) fold increased risk of lung cancer among never-smokers and former smokers who had quit for at least 10 years (mean age ~67 yr) when comparing those residing less than 50 meters from an A1 roadway to those residing 200 or more meters from such a roadway (587 lung cancer cases)[6] Similar to our results, no exposure-response relationship was apparent across distance categories, and no associations were observed in analyses of distance to A1 or A2 and distance to A1, A2, or A3 roadways. Six other studies examining traffic exposures observed no significant association with lung cancer risk.[3] Comparison of results across these studies is difficult, given the varied metrics of traffic exposure that were used.

Table 2

Risk of lung cancer in association with metrics of air pollution exposure among nonsmokers in the WHI

Exposure	All lung cancer HR[a] (95% CI)	Adenocarcinoma HR[a] (95% CI)
$PM_{2.5}$ ($\mu g/m^3$)		
Yearly cumulative average		
≤11.03	Reference	Reference
>11.03–12.96	1.12 (0.80, 1.57)	1.12 (0.74, 1.69)
>12.96–14.86	1.18 (0.83, 1.67)	1.11 (0.72, 1.72)
>14.86	0.96 (0.66, 1.41)	0.87 (0.54, 1.42)
Per 10 $\mu g/m^3$ increase	0.85 (0.53, 1.36)	0.78 (0.43, 1.42)
Year 2000 cumulative average		
≤11.13	Reference	Reference
>11.13–13.14	1.04 (0.75, 1.45)	0.86 (0.56, 1.31)
>13.14–15.35	1.16 (0.83, 1.61)	1.27 (0.86, 1.89)
>15.35	1.09 (0.77, 1.55)	0.95 (0.61, 1.46)
Per 10 $\mu g/m^3$ increase	1.09 (0.74, 1.61)	0.87 (0.53, 1.42)
NO_2 (ppb)		
Yearly cumulative average		
≤10.40	Reference	Reference
>10.40–14.64	1.18 (0.83, 1.68)	1.02 (0.65, 1.59)
>14.64–19.13	1.32 (0.93, 1.89)	1.36 (0.88, 2.10)
>19.13	0.96 (0.64, 1.44)	0.93 (0.56, 1.55)
Per 10 ppb increase	0.92 (0.74, 1.15)	0.93 (0.71, 1.23)
Year 2000 cumulative average		
≤10.75	Reference	Reference
>10.75–15.17	1.08 (0.76, 1.55)	1.04 (0.67, 1.63)
>15.17–19.53	**1.57 (1.12, 2.20)**	**1.51 (1.00, 2.30)**
>19.53	1.01 (0.68, 1.48)	0.89 (0.55, 1.45)
Per 10 ppb increase	1.04 (0.86, 1.26)	1.00 (0.78, 1.27)
Distance to A1 (m)		
≥200	Reference	Reference
50 to <200	0.82 (0.34, 1.98)	0.78 (0.25, 2.44)
<50	**5.23 (1.94, 14.13)**	**6.10 (1.93, 19.27)**
Distance to A1–A2 (m)		
≥200	Reference	Reference
50 to <200	1.05 (0.62, 1.77)	0.88 (0.43,1.80)
<50	1.54 (0.68, 3.47)	2.07 (0.85, 5.06)
Distance to A1–A3 (m)		
≥200	Reference	Reference
50 to <200	0.93 (0.71, 1.23)	1.03 (0.73, 1.44)
<50	0.91 (0.63, 1.31)	0.96 (0.60, 1.52)

[a]Hazard ratio calculated from Cox proportional hazards regression; baseline hazard rate stratified by study arm and models adjusted for age at baseline, race, BMI, US region, history of emphysema, history of asthma, and NSES.
Bold indicates Statistical significance.

The methods we used to generate the exposure data have been validated,[11,12] and exposure to $PM_{2.5}$ in the WHI has been previously associated with cardiovascular events and hypertension.[13–15] Although using yearly cumulative average as the exposure metric could lead to bias in risk estimates given the general trend of decreasing air pollution exposures over time, results were consistent with those from a sensitivity analysis that assigned year 2000 exposure estimates to each year of follow-up. In addition to the high-quality exposure data, strengths of our study of cancer incidence include a large, well-characterized prospective cohort of never-smoking women with detailed covariate data. Limitations of the study include a lack of data on air pollution exposures prior to baseline, insufficient case numbers to conduct detailed histology-specific analyses and a lack of secondhand smoking data for the entire cohort. In sensitivity analyses, however, adjustment for secondhand smoke exposure among the substantial fraction of the cohort with those data had minimal impact on risk estimates. Data on the individual level socioeconomic factors education level and family income were also examined, but income data were missing for 7.1% of the cohort, including 20 of the 265 cases. In analyses restricted to those with complete data, inclusion of education and income in the regression models along with NSES had very little impact on risk estimates (results not shown).

The association with distance to A1 roadway, but not with $PM_{2.5}$ or NO_2 estimates, suggests that there may be other aspects of living near major roadways responsible for an association with lung cancer that may not strictly correlate with $PM_{2.5}$ and NO_2 levels. Research has demonstrated that $PM_{2.5}$ is not a specific indicator of exposure to traffic-related air pollution, but NO_2 levels, along with ultrafine particles, volatile organic compounds (VOCs), and particle-bound polycyclic aromatic hydrocarbons (PPAHs) are typically elevated near major roadways.[16] However, a study of 36 homes in Amsterdam demonstrated that PPAHs and VOCs were significantly better indicators of traffic intensity than NO_2.[17] In our data, based on year 2000 exposure data, we observed that distance to A1 roadway was weakly correlated with $PM_{2.5}$ ($r = -0.3$) and moderately correlated with NO_2 ($r = -0.5$) exposure levels. Although exposure to PPAHs and VOCs, to a lesser degree, have been linked to increased risks of lung cancer,[18,19] research examining the health impacts of ultrafine particles, which have great potential to cause biologic harm due to their extremely small size, is in its infancy.

Given that traffic volume is highest on A1 roadways, proximity to A1 roadways is likely associated with much higher levels of exposure to traffic-related air pollutants as compared to proximity to A2 and A3 roadways. A recent study, however, demonstrated that the fraction of larger, heavy-duty vehicles traveling on roadways may be an especially critical factor in explaining variability in pollutant levels.[20] Differences in traffic volume and fraction of heavy-duty vehicles could explain the lack of associations observed in the combined analysis of proximity to A1 or A2 and A1, A2, or A3 roadways.

Although we did not observe compelling associations between ambient $PM_{2.5}$ exposure or NO_2 exposure and risk of lung cancer in a cohort of never-smoking, postmenopausal women, our results do not exclude elevated risk estimates observed in previous studies. We did observe associations of close residential proximity to major roadways and lung cancer, suggesting that one or more others aspect of living near major roadways may contribute to increased risks of lung cancer. Future studies should focus on generating high-quality data for other components of traffic-related air pollution such as VOCs, PPAHs, and ultrafine particles that can be evaluated for impacts on cancer risk.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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