Short Report

Ambient air pollution and incident bladder cancer risk: updated analysis of the Spanish Bladder Cancer Study

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Abbreviations used: Cancer Prevention Study-II (CPS-II), carbon monoxide (CO), confidence interval (CI), European Study of Cohorts for Air Pollution Effects ESCAPE), fine particulate matter ($PM_{2.5}$), hazard ratio (HR), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), odds ratio (OR), ozone (O_3), particles of 10 µm or less in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2)

Novelty and Impact: Outdoor air pollution and particulate matter in outdoor air have been linked with increased lung cancer risk, however the evidence for other cancer sites is limited. This study examined associations of ambient $PM_{2.5}$ and NO_2 concentrations based on European multi-city land-use regression models and bladder cancer risk in the

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large-scale Spanish Bladder Cancer Study. No clear associations with incident bladder cancer risk were observed. Further research in other large-scale population studies is needed.

ABSTRACT

Although outdoor air pollution and particulate matter in outdoor air have been consistently linked with increased lung cancer risk, the evidence for associations at other cancer sites is limited. Bladder cancer shares several risk factors with lung cancer and some positive associations of ambient air pollution and bladder cancer risk have been observed. This study examined associations of ambient air pollution and bladder cancer risk in the large-scale Spanish Bladder Cancer Study. Estimates of ambient fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) concentrations were assigned to the geocoded participant residence of 938 incident bladder cancer cases and 973 hospital controls based on European multi-city land-use regression models. Adjusted odds ratios (ORs) and 95% confidence intervals (CI) for associations of ambient air pollution and bladder cancer risk were estimated using unconditional logistic regression models. Overall, there was no clear association between either ambient $PM_{2.5}$ (OR per 5.9 μg/m^3 = 1.06, 95% CI 0.71-1.60) or NO_2 (OR per 14.2 μg/m^3 = 0.97, 95% CI 0.84-1.13) concentrations and incident bladder cancer risk. There was no clear evidence for effect modification according to age group, sex, region, education, cigarette smoking status, or pack-years. Results were also similar among more residentially stable participants and in two-pollutant models. Overall, there was no clear evidence for associations of ambient $PM_{2.5}$ and NO_2 concentrations and incident bladder cancer risk. Further research in other large-scale population studies is needed with detailed information on measured or modeled estimates of ambient air pollution concentrations and individual level risk factors.

INTRODUCTION

In 2013, the International Agency for Research on Cancer classified outdoor air pollution and particulate matter in outdoor air pollution as a Group 1 human carcinogen.[1] Although there was sufficient evidence in human studies for lung cancer, evidence for other cancer sites is limited. Bladder cancer shares several risk factors with lung cancer. Some positive associations in studies using different metrics of exposure to outdoor air pollution, traffic, or traffic fumes and urinary bladder cancer risk were observed.

Among workers' studies, positive associations of occupation as a taxi driver, truck driver, or holding another job with assumed higher levels of exposure to outdoor air pollution (i.e. urban police officers, street vendors) and bladder cancer risk were reported.[1] There were also positive associations with occupational exposure to diesel or polycyclic aromatic hydrocarbons specifically.[2-6]

Among general population studies, the Spanish Bladder Cancer Study reported a significant positive association of living > 40 years in a city of > 100,000 inhabitants and bladder cancer risk (odds ratio (OR) = 1.30, 95% confidence interval (CI) 1.04-1.63), but no association with having windows facing a street with traffic, number of traffic lanes, traffic intensity, or living in proximity to industry.[7] Other studies with either measured or modeled estimates of ambient air pollution concentrations have also reported positive associations with bladder cancer, though there are limitations in some studies including a lack of data on cigarette smoking history, small numbers of observed cases, or the use of fatal rather than incident disease.[8-10] In contrast, a recent analysis of the European Study of Cohorts for Air Pollution Effects project (ESCAPE) reported no evidence for an association.[11]

This study seeks to further examine the association between ambient air pollution and bladder cancer risk updating previous work based on city size and proximity to traffic in the Spanish Bladder Cancer Study by assigning estimates of ambient air pollution concentrations from a European land-use regression model developed as part of the ESCAPE project to the residential address of study participants. The Spanish Bladder Cancer Study is a large case-control study including data on 1,219 incident bladder cancer cases and 1,271 hospital controls.

MATERIALS & METHODS

Study Population

The Spanish Bladder Cancer Study was conducted from 1998-2001 and recruited participants from 18 hospitals in five regions (Alicante, Asturias, Barcelona, Tenerife, Valles/Bages).[7] Incident cases were histologically-confirmed, aged between 21-80 years. Completeness of case ascertainment was verified through regular verification of hospital registries, clinical records and pathology lists. Controls were patients admitted to the hospital for conditions unrelated to the exposures under study including hernia (37%), fracture (23%), hydrocele (12%), and other abdominal surgery (11%) and were individually-matched to cases by hospital, 5-year age at diagnosis/interview, sex, ethnicity, and region of residence. Other orthopedic, circulatory (varicose veins, hemorrhoids), dermatological, and ophthalmologic conditions represented the remainder of control diagnoses. The response rates were 84% for cases and 88% for controls.

Study participants completed an in-person computer-assisted interview in the hospital that captured data on a range of sociodemographic, lifestyle, occupational, personal and family characteristics, as well as lifetime residential history and several self-reported surrogate measures of ambient air pollution exposure for each residence held for more than one year including proximity to industry (i.e. presence of an industry within 1 km of the residence) and windows facing a street with traffic (including number of traffic lanes and traffic intensity). A total of 20% of participants completed an abbreviated version of the study interview that did not capture the self-reported surrogate measures of ambient air pollution (above). City size (for the year 2000) was obtained from the National Institute of Statistics, Spain. Ethics approval was obtained from all participating institutions. Written informed consent was obtained from all participants prior to interview.

Ambient Air Pollution Concentrations

Estimated annual average ambient fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) concentrations from European multi-city land-use regression models developed as part of the ESCAPE study were used here. Briefly, the ESCAPE study sought to examine the long-term health effects of air pollution exposure in cohort studies in 36 areas of Europe using a common approach.[12] Ambient air pollution concentrations were estimated using standardized methods for measurements, GIS variable collection, and land-use regression model development in individual study areas.[13,14] Land-use regression models are based on a combining of data across 17 ESCAPE study areas for $PM_{2.5}$ and 23 for NO_2 (including Barcelona) across 14 countries.[15] Monitoring data were collected at the street, urban background, and regional background locations from October 2008-May 2011 in three 2-week sampling periods in different seasons (warm, cold, intermediate) at 356 sites for $PM_{2.5}$ and 960 sites for NO_2. Annual average concentrations were estimated taking into account temporal trends from continuous reference monitors. Following a supervised stepwise regression procedure, the final $PM_{2.5}$ land-use regression model included regional background concentration, traffic load between 50 m and 1,000 m, traffic load in 50 m, and road length in 100 m (overall model $R^2 = 0.86$). For NO_2, the final model included regional background concentration, traffic load in 50 m, road length in 1,000 m, natural and green in 5,000 m, and traffic intensity on the nearest road (overall model $R^2 = 0.56$). Models had good prediction ability for transferability to independent study areas excluded from model building (median $R^2 = 0.42$ for $PM_{2.5}$ and 0.59 for NO_2) supporting their application to other European areas with common predictors and geographies. Annual average air pollutant concentrations were linked to the geocoded participant residence address at enrollment.

Statistical Analysis

Associations of either ambient $PM_{2.5}$ or NO_2 concentrations and incident bladder cancer risk were estimated using unconditional logistic regression models adjusting for 5-year age group, sex, region, pack-years of cigarette smoking, and previously holding any high risk occupation (metal workers, hairdressers and barbers, painters, and chemical, leather, transport, and rubber industry workers) in both single and two-pollutant models.[7] Sensitivity analysis adjusting for: exposure to disinfection by-products in drinking water (mean trihalomethane levels), fruit and vegetable consumption, education, passive smoking, income, marital status, and body mass index resulted in virtually no change in findings (<10% change in regression coefficients) (not presented here). Potential effect modification by age group, sex, region, education, cigarette smoking status and pack-years of smoking was examined on the multiplicative scale with two-sided *p* values assessed according to the likelihood ratio statistic. Finally, additional sensitivity analyses according to tumour histology, interview quality, previous cancer history, and number of years lived in the current residence was also performed. Statistical analysis was conducted using R version 3.3.[16]

RESULTS

A total of 938 incident bladder cancer cases and 973 controls were retained for analysis following exclusions due to unreliable geocoding (n = 278 cases and 297 controls) or for the small number of non-white participants recruited (n= 3 cases and 1 control). Table 1 presents the distribution of selected participant characteristics. Cases had a mean (SD) age of 65.8 (9.7) years and controls 64.7 (9.8) years. The majority were male (88% cases, 87% controls). The largest study regions were Asturias and Barcelona. Cases reported smoking for a greater number of pack-years and more often ever holding a high risk occupation.

$PM_{2.5}$ concentrations ranged from 7.0 to 25.6 µg/m^3 with a mean (SD) of 15.8 µg/m^3 (3.89) (Supplemental Table 1). NO_2 concentrations ranged from 1.1 to 58.6 µg/m^3 with a mean (SD) of 28.6 µg/m^3 (10.2). The correlation between the two pollutants was r = 0.64. Participants from Barcelona had the highest concentrations of both $PM_{2.5}$ and NO_2 followed by Elche and Valles (Table 2). Men with the largest number of smoking pack-years tended to have somewhat higher ambient $PM_{2.5}$ and NO_2 concentrations compared with never smokers whereas the opposite was observed for women.

Overall, there was no clear association of either ambient $PM_{2.5}$ or NO_2 concentrations and bladder cancer risk and there was no evidence for a trend (Table 3). The OR (95% CI) in the highest (vs lowest) tertile of $PM_{2.5}$ concentrations (>18.6 µg/m^3) was 1.00 (95% CI 0.64-1.56) and per each 5.9 µg/m^3 (IQR) was 1.06 (95% CI 0.71-1.60). For

NO_2 the OR (95% CI) in the highest (vs lowest) tertile (>34.3 μg/m^3) was 1.04 (95% CI 0.80-1.34) and per each 14.2 μg/m^3 was 0.97 (95% CI 0.84-1.13). Results were also similar in a two-pollutant model. There were some elevated ORs for both $PM_{2.5}$ and NO_2 among both female participants and never smokers, though results are based on small numbers (interaction *p*-values > 0.05) (Supplemental Table 2). There was also no clear evidence for effect modification according to age group, region, education, or pack-years of smoking (not shown) (interaction *p*-values > 0.05).

There was no association of either ambient $PM_{2.5}$ or NO_2 concentrations and bladder cancer risk upon analysis of participants with either a reliable or high quality interview as determined by the interviewer (92% of cases and 90% of controls), upon exclusion of participants with a previous or unknown history of cancer (6% of cases and 7% of controls), or those living for atleast 5 years in the current residence (86% of both cases and controls) (not shown). There was also no clear association of ambient $PM_{2.5}$ or NO_2 and urothelial carcinoma only.

DISCUSSION

Our analysis indicated no clear association between ambient $PM_{2.5}$ and NO_2 concentrations and bladder cancer risk. In contrast, a previous analysis in the same study population based on surrogate indicators of ambient air pollution reported a significant positive association of living > 40 years in a city of > 100,000 inhabitants, but no association with windows facing a street with traffic, number of lanes, traffic intensity, or living in proximity to industry.[7] The correlation between estimated ambient air pollution concentrations and city size here was moderate (*r*'s = 0.39 and 0.41 for $PM_{2.5}$ and NO_2, respectively).

In contrast, positive associations have been reported in several other studies, including in a death certificate–based case-control study in Taiwan, with significant positive associations of particles of 10 µm or less in aerodynamic diameter (PM_{10}), NO_2, and sulfur dioxide (SO_2) observed, but not with carbon monoxide (CO) or ozone (O_3) (n = 680 cases and 680 controls).[8] An analysis of the Danish Diet Cancer and Health cohort reported a positive though non-significant association of nitrogen oxides (NO_x) and bladder cancer risk (n = 221).[9] There was a significant positive association of ambient $PM_{2.5}$ concentrations, but not NO_2 or O_3, and bladder cancer mortality in an analysis of the American Cancer Society Cancer Prevention Study-II (CPS-II) (hazard ratio (HR) per 4.4 $\mu g/m^3$ = 1.13 (95% CI 1.03-1.23), n = 1,324 bladder cancer deaths).[10] In contrast, in ESCAPE, no association of various modeled estimates of ambient air pollution concentrations, including ambient $PM_{2.5}$ and NO_2, and incident bladder cancer risk (n = 943) was observed.[11] There was also no association of residential $PM_{2.5}$ concentrations and mortality due to malignant neoplasms of the urinary tract (n = 155) in a cohort of elderly Hong Kong residents.[17]

Strengths of the study include the assignment of ambient $PM_{2.5}$ and NO_2 concentrations based on European multi-city land-use regression models specifically developed and validated for transferability to other geographical areas,[15] addressing a major limitation of previous work based on surrogate self-reported indicators of ambient air pollution with high likelihood of misclassification.[7] Though land-use regression models predicted variability in areas excluded from model building reasonably well (median R^2's ranging from 0.42-0.59), there are also other more locally developed models in Barcelona, Catalunya, and Asturias, with model R^2's ranging from 62-83% for $PM_{2.5}$ (Barcelona and Catalunya) and 71-75% for NO_2.[13,14] However, results based on local models here were similar and based on smaller numbers of study participants (Supplemental Table 1 and 3). The correlation between concentrations assigned using the European or local models was strong for NO_2 (r = 0.79) but weaker for $PM_{2.5}$ (r = 0.28). We were unable to examine $PM_{2.5}$ absorbance here (an indicator of diesel exhaust) based on the European models, as it required a regional value in the study area which could not be obtained, though results for $PM_{2.5}$ absorbance based on local models also showed no evidence for an association.

This work was also based on a large number (n=938) of included incident bladder cancer cases overall as well as detailed data on potentially confounding or modifying factors. Although some previous studies noted stronger air pollution-lung cancer associations in either never or former smokers,[18-20] there was no clear evidence for effect modification by cigarette smoking status here, though there was a tendency for

ORs to be somewhat larger among never smokers as well as among men with fewer pack-years of cigarette smoking. There was also no clear evidence for effect modification by cigarette smoking status in either the ESCAPE study or in CPS-II, though in CPS-II the HR for never smokers was also somewhat larger (HR per 4.4 $\mu g/m^3$ = 1.21 (95% CI 1.01-1.44)) than that for current or former smokers.[10] Participation rates were high for both cases and controls (>80%).

Limitations of the current work include the assignment of recent (2008-2011 average) estimates of ambient $PM_{2.5}$ and NO_2 concentrations from European land-use regression models to the participant residence at enrollment in 1998-2001. However, study participants were residentially stable with a mean (SD) length of time in the enrollment residence of 27.8 (17.2) years. Results were also similar in sensitivity analyses with atleast 5, 10, or 20 years in the current residence, both overall and in never smokers (not shown). It is also unclear the most relevant exposure time window of interest here which may extend for several decades prior to enrollment. We also required assumptions regarding the temporal stability of the spatial distribution of ambient air pollution concentrations over time. $PM_{2.5}$ concentrations, and to a lesser extent NO_2, generally exhibited a gradual similar decline during the recent decade from 2001-2012 in Spain in both urban and regional background sites, with a sharper decline observed during 2007-2008.[21] Studies in other areas in Europe have also documented the spatial stability of the exposure contrast over time.[22-24] Finally, there was limited variability in $PM_{2.5}$ concentrations within each study region as compared to between study regions, in both the European and local models (not shown), thereby limiting our ability to detect associations with bladder cancer incidence here and leading to imprecision in relative risk estimates.

The hospital-based nature of the study design may also result in some form of bias if control diagnoses were somehow related with ambient air pollution exposure, which is unlikely here with hernias and fractures comprising the majority of the control population. Participating hospitals captured study participants from broad geographical areas and none was a cancer referral centre. Though there may be some degree of overmatching on air pollution exposure based on enrollment address, matching by region of residence was based on wide geographic zones, balanced for case and control participants.

In summary, this large case-control study examining ambient $PM_{2.5}$ and NO_2 concentrations and bladder cancer risk observed no clear evidence for associations. Further research in other large-scale population studies of cancer incidence is needed with detailed information on measured or modeled estimates of ambient air pollution concentrations, particularly with detailed data on more historical estimates of exposure, and individual level risk factor data.

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Spanish Bladder Cancer Study data are protected to ensure to confidentiality of study participants. Interested colleagues are encouraged to contact MK.

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Table 1. Distribution of selected participant characteristics, Spanish Bladder Cancer Study, 1998-2001.

	Cases (n=938) %	Controls (n=973) %	*p*
Age group (years)			
<60	23	27	
60-69	36	37	
70+	41	36	*0.01*
Sex			
Male	88	87	
Female	12	13	*0.46*
Region			
Barcelona	21	22	
Valles	18	17	
Elche	8	8	
Tenerife	15	17	
Asturias	38	36	*0.66*
Education			
Less than primary school	45	45	
Primary school	38	39	
High school/higher education	16	14	
Other	1	1	
Missing	0	1	*0.60*
Cigarette smoking status			
Never	13	29	
Former	42	41	
Current	40	22	
Missing	5	8	*<0.001*
Pack-years (Male)			
Never smoker	5	20	
0-25	17	23	
>25-51	35	24	
>51	37	22	
Missing	6	11	*<0.001*
Pack-years (Female)			
Never smoker	73	84	
0-14	4	6	
>14	11	4	
Missing	12	6	*0.07*
High risk occupations (Any)			

No	74	83	
Yes	23	13	
Missing	3	4	*<0.001*

Table 2. Mean (SD) of ambient $PM_{2.5}$ and NO_2 concentrations by selected participant characteristics, Spanish Bladder Cancer Study, 1998-2001.

	n	$PM_{2.5}$		NO_2	
		Mean	SD	Mean	SD
Age group (years)					
<60	478	16.2	3.7	29.3	9.9
60-69	703	15.4	3.8	27.8	10.2
70+	730	15.9	3.9	28.8	10.3
Sex					
Male	1,673	15.8	3.8	28.5	10.2
Female	238	16.0	3.7	28.9	10.2
Region					
Barcelona	408	20.2	1.4	34.9	6.9
Valles	333	18.6	1.9	31.1	9.1
Elche	153	18.8	0.7	34.2	11.2
Tenerife	312	10.2	1.7	21.3	9.5
Asturias	705	13.8	0.9	25.7	9.2
Education					
Less than primary school	859	15.7	4.2	27.9	10.8
Primary school	731	15.9	3.5	28.3	9.7
High school/higher education	285	15.9	3.4	31.0	9.3
Other	25	14.3	2.5	27.6	8.2
Missing	11	17.3	3.4	32.4	10.3
Cigarette smoking status					
Never	401	15.7	3.7	28.1	10.4
Former	791	15.7	3.9	28.6	10.4
Current	598	16.0	3.7	28.8	10
Missing	121	16.1	3.7	29.1	8.9
Pack-years (Male)					
Never smoker	213	15.4	3.7	27.4	10.5
0-25	332	15.6	3.9	28.0	11.2
>25-51	498	15.9	3.8	28.9	9.8
>51	489	16.0	3.9	29.2	10.0
Missing	141	15.7	3.7	27.8	9.1
Pack-years (Female)					
Never smoker	188	16.0	3.8	28.8	10.4
0-14	12	16.6	3.3	30.7	9.1
>14	17	14.1	2.8	24.9	9.6
Missing	21	16.8	3.3	31.3	9.0
High risk occupations (Any)					

No	1,502	15.8	3.8	28.8	10.1
Yes	339	16.0	3.9	27.9	10.7
Missing	70	15.2	3.6	26.6	8.8

Table 3. Associations of ambient $PM_{2.5}$ and NO_2 concentrations and incident bladder cancer risk, Spanish Bladder Cancer Study, 1998-2001.

	$PM_{2.5}$ Cases (n)	Controls (n)	OR[a] (95% CI)		NO_2 Cases (n)	Controls (n)	OR[a] (95% CI)
Single Pollutant Model							
7.0-13.7[b]	288	321	1.00 (Ref)	1.1-24.2[b]	288	321	1.00 (Ref)
>13.7-18.6	341	321	1.22 (0.90-1.64)	>24.2-34.3	327	321	1.13 (0.89-1.44)
>18.6-25.6	309	331	1.00 (0.64-1.56)	>34.3-58.6	323	331	1.04 (0.80-1.34)
p trend			*0.85*	*p* trend			*0.79*
per 5.9 μg/m³	938	973	1.06 (0.71-1.60)	per 14.2 μg/m³	938	973	0.97 (0.84-1.13)
Two-Pollutant Model							
7.0-13.7[b]	288	321	1.00 (Ref)	1.1-24.2[b]	288	321	1.00 (Ref)
>13.7-18.6	341	321	1.17 (0.83-1.63)	>24.2-34.3	327	321	1.11 (0.85-1.44)
>18.6-25.6	309	331	0.95 (0.56-1.60)	>34.3-58.6	323	331	1.05 (0.77-1.43)
p trend			*0.96*	*p* trend			*0.85*
per 5.9 μg/m³	938	973	1.20 (0.71-2.01)	per 14.2 μg/m³	938	973	0.93 (0.77-1.13)

[a] adjusted for age group, sex, region, smoking pack years, high risk occupations where appropriate
[b] tertiles of exposure among controls overall

Novelty and Impact:

Novelty and Impact: Outdoor air pollution and particulate matter in outdoor air have been linked to increased lung cancer risk. However, evidence for other cancer sites is limited. In this study, the authors examined associations between ambient $PM_{2.5,}$ NO_2 concentrations based on European multi-city land-use regression models, and bladder cancer risk in the large-scale Spanish Bladder Cancer Study. They found no clear associations with incident bladder cancer risk. Further research in other large-scale population studies is needed to confirm these results.