Long-term Residential Exposure to Air Pollution and Lung Cancer Risk

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Background: There is accumulating evidence that air pollution causes lung cancer. Still, questions remain about exposure misclassification, the components of air pollution responsible, and the histological subtypes of lung cancer that might be produced.

Methods: We investigated lung cancer incidence in relation to long-term exposure to three ambient air pollutants and proximity to major roads, using a Canadian population-based case-control study. We compared 2,390 incident, histologically confirmed lung cancer cases with 3,507 population controls in eight Canadian provinces from 1994 to 1997. We developed spatiotemporal models for the whole country to estimate annual residential exposure to fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) over a 20-year exposure period. We carried out a subanalysis in urban centers, using exposures derived from fixed-site air pollution monitors, and also examined traffic proximity measures. Hierarchical logistic regression models incorporated a comprehensive set of individual and geographic covariates.

Results: The increase in lung cancer incidence (expressed as fully adjusted odds ratios [ORs]) was 1.29 (95% confidence interval = 0.95–1.76) with a ten-unit increase in $PM_{2.5}$ ($\mu g/m^3$), 1.11 (1.00–1.24) with a ten-unit increase in NO_2 (ppb), and 1.09 (0.85–1.39) with a ten-unit increase in O_3 (ppb). The urban monitor-based subanalyses generally supported the national results, with larger associations for NO_2 (OR = 1.34; 1.07–1.69) per 10 ppb increase. No dose-response trends were observed, and no clear relationships were found for specific histological cancer subtypes. There was the suggestion of increased risk among those living within 100 m of highways, but not among those living near major roads.

Conclusions: Lung cancer incidence in this Canadian study was increased most strongly with NO_2 and $PM_{2.5}$ exposure. Further investigation is needed into possible effects of O_3 on development of lung cancer.

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Evidence is accumulating for a causal association between exposure to ambient air pollution and lung cancer;[1–5] however, several uncertainties remain. Air pollution exposure misclassification is a particular concern, due to the long latency period for lung cancer, temporal changes in air pollution levels, and the likelihood of substantial residential mobility during biologically relevant exposure periods. To date, few studies of lung cancer have incorporated historical exposure assessments[4,6–9] or examined different air pollutants and emission sources[6–9] beyond urban settings.[9,10] In addition, little research has examined air pollution exposure and lung cancer risk by histological subtypes,[11–14] due to the need for large sample sizes. Given the variation in risks associated with cigarette smoking and lung cancer histology,[15] as well as evidence from occupational[16] and animal studies,[17] it is probable that risks associated with air pollution also vary by histological subtype.

The present study builds upon prior work to partially address these uncertainties by identifying associations between three ambient air pollutants and proximity to traffic emissions, and lung cancer incidence. Specifically, we use a Canadian population-based case-control study that includes comprehensive individual and geographic information on potential confounding factors such as cigarette smoking, second-hand smoke exposure, occupational hazards, and residential radon exposures, as well as complete 20-year residential histories from 1975 to 1994. Spatiotemporal models were developed and applied to annual residential histories in both urban and rural locations to estimate long-term exposures to fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3).[18] An urban subanalysis was also conducted using exposures derived from the nearest fixed-site air pollution monitors within 50 km, as well as proximity measures to highways and major roads.

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METHODS

Study Design

The National Enhanced Cancer Surveillance System is a population-based, multicancer-site case-control study that includes 3,280 histologically confirmed lung cancer cases, and 5,073 population controls collected between 1994 and 1997 in eight of Canada's ten provinces. Johnson et al[19] describe the recruitment methodology and study design of the overall National Enhanced Cancer Surveillance System project. Between 1994 and 1997 cases were identified and randomly sampled for inclusion in the study by provincial cancer registries within 1–3 months of initial diagnosis. Population controls were selected from a random sample of people within each province, frequency matched on sex and 5-year age categories to the overall collection of National Enhanced Cancer Surveillance System cancer cases (~20,000 cases including 19 types of cancer). Recruitment methods for controls depended on data availability and accessibility by province and included provincial health insurance plans in five provinces, random digit dialing in two, and property assessment data in one. A research questionnaire was mailed to selected cases and controls and active follow-up was conducted. The response rate was 62% for contacted lung cancer cases and 67% for population controls. The research questionnaire collected comprehensive information regarding personal characteristics, lifetime occupational exposures, and residential histories. Residential histories were geo-coded to 6-digit postal codes and are the basis of the air pollution exposure assessment. Due to residential mobility, postal codes were located in all provinces of Canada, requiring national-level exposure assessment.

National Air Pollution Exposure Assessment

Long-term exposures to ambient $PM_{2.5}$, NO_2, and O_3, and proximity to highways and major roads, were estimated from residential histories from 1975 to 1994. Residential histories were available before 1975; however, few air pollution measurements and geographic data were available for these years, and recall bias was present for residential histories before 1975 (cases tended to report more residences than controls).[18] To ensure reliable exposure assessment, only persons with complete 20-year residential histories in Canada during this period were included in the final analysis, which reduced the study to 2,390 cases and 3,507 controls. Various exposure periods were examined (eg, 1975–1980/85/90), but ambient pollution exposures for all periods were highly correlated with the 1975–1994 period ($r \geq 0.96$).

The spatiotemporal air pollution exposure assessment approach is described in detail elsewhere.[18] Briefly, a multistaged approach was used to assign annual concentrations of $PM_{2.5}$ and NO_2, and summer (May to September) O_3, to residential histories. First, national spatial surface estimates of each pollutant were created from recent satellite-based estimates at a 10x10 km resolution (for $PM_{2.5}$[20] and NO_2[21]) and from a 25x25 km resolution chemical transport model (for O_3[22]). Next, all fixed-site National Air Pollution Surveillance monitoring data were formatted to annual averages for the study period. Since $PM_{2.5}$ measurements were not available before 1984, a random effects linear regression model was used to estimate pre-1986 $PM_{2.5}$ based on total suspended particulate (TSP) measurements (as these were measured beginning in 1974) and metropolitan variables (Model R^2 = 0.67, root mean square error = 2.31 $\mu g/m^3$). This approach is similar to others studies that have estimated $PM_{2.5}$ from TSP.[2,23] Finally, yearly calibration of the national spatial pollutant surfaces was conducted by calculating a ratio of measured to surface estimates at each National Air Pollution Surveillance monitoring station. Smoothed inverse distance–weighted interpolation was conducted using the ratios, and the resulting surface applied to adjust the spatial pollutant surface for each year in the 1975–1994 study period.

Figure 1 illustrates the average spatiotemporal pollutant surfaces from 1975 to 1994 and the location of study participants' residential histories (sum of residential postal code locations within a 50-km grid). These maps represent pollution concentrations that would be assigned if there were no residential mobility; in practice, the exposure assessment was conducted using yearly pollutant concentrations and residential histories.

Urban Fixed-site Monitor Exposure Assessment

An urban subanalysis was conducted using air pollution exposures derived solely from fixed-site National Air Pollution Surveillance measurements. As mentioned, the spatial and temporal coverage of $PM_{2.5}$ monitors is limited before 1986, and TSP measurements and modeled $PM_{2.5}$ are thus examined in the urban analysis. Annual average pollutant concentrations were calculated for postal codes using the nearest National Air Pollution Surveillance monitor (within 50 km) with at least 6 months of complete measurements and 1 month per season for TSP and NO_2 and at least 3 summer months for O_3. Cumulative averages were calculated for people with at least 18 years of complete monitor coverage from 1975 to 1994.

Proximity Measures to Highways and Major Roads

Proximity measures to major roads were used to estimate exposure to vehicle emissions. The 1996 (DMTI Spatial, Inc.) road network was applied to derive proximity measures for all residential years, due to the lack of historical national road networks. We calculated the number of years residing within 50, 100, and 300 m of a highway or major road. Because emissions from vehicles have decreased significantly over the study period, proximity indicators were weighted to account for these changes using annual motor vehicle emission estimates.[18] Analyses of proximity to highways and major roads were also restricted to participants residing in urban areas (defined as >30,000 residents) due to large spatial errors associated with rural postal code locations.

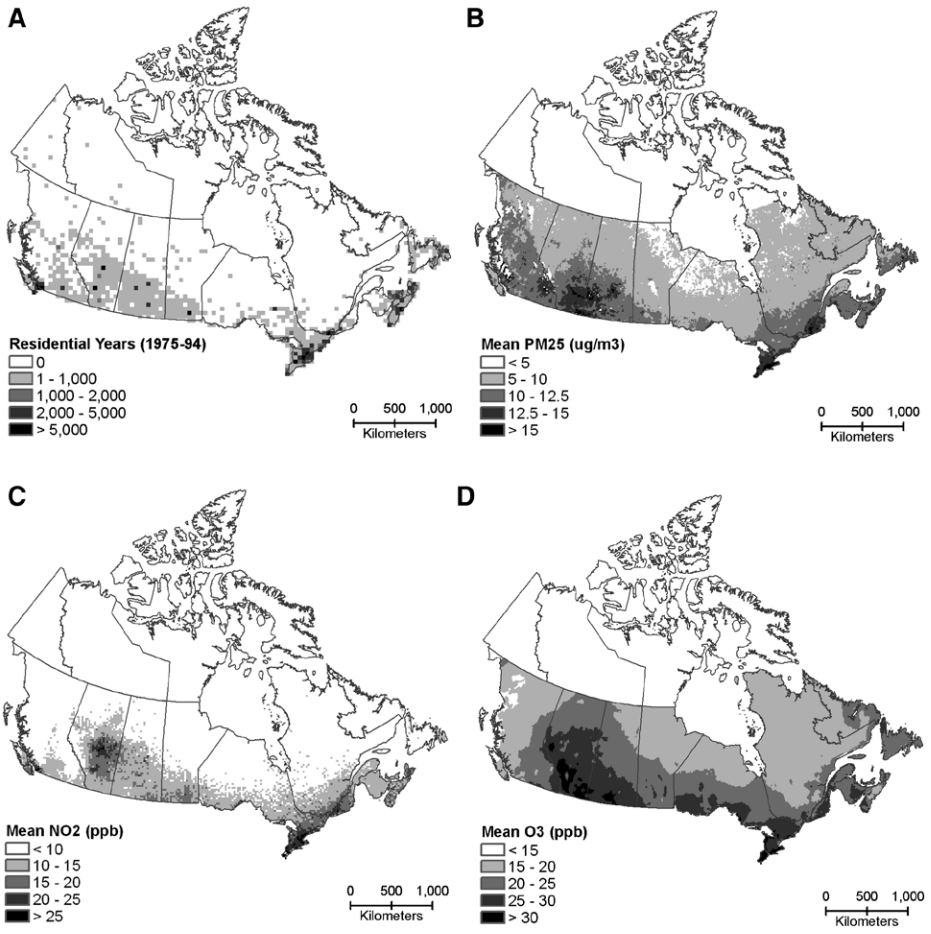

FIGURE 1. Location of study participant (A) residential histories and average (B) $PM_{2.5}$ (μg/m^3), (C) NO_2 (ppb), and (D) O_3 (ppb) concentrations for the period 1975 to 1994.

Outcomes

Histologically confirmed lung cancer incidence is the primary outcome variable of this study. We also examined specific histological subtypes, which for the 2,390 lung cancer cases with complete residential histories included: 669 (28%) squamous cell carcinoma, 756 (32%) adenocarcinoma, 363 (15%) small cell carcinoma, 213 (9%) large cell carcinoma, and 389 (16%) other or unspecified carcinomas (which are not included in subsequent analyses due to the heterogeneity of this category).

Covariates

We include a comprehensive set of individual and geographic-level variables in the multivariate models. Individual-level covariates include age, sex, educational attainment, average household income during the 5 years before study interview, smoking pack years, years since quitting smoking, person-years of residential and occupational second-hand smoke exposure (defined by the number of smokers in the home multiplied by number of residential years and the number of smokers in the immediate work environment multiplied by number of occupational years), average alcohol and meat consumption per week, years working with daily or weekly exposure to dust, odors, and hazardous substances, and exposure to specific occupational lung hazards (arsenic, asbestos, asphalt, benzene, mustard gas, welding, and wood dust). Geographic covariates included study province (to account for the study design), ecological radon risk (defined using mean residential radon concentrations by Health Regions),[24] and neighborhood contextual deprivation variables (described in the eAppendix; http://links.lww.com/EDE/A678). Coding for all individual and geographic variables is provided in the eAppendix, eTable 1 (http://links.lww.com/EDE/A678).

Statistical Analyses

Analyses were conducted using two-level random intercept logistic regression models (GLIMMIX, SAS version 9.3; SAS Institute, INC, Cary, NC). The random intercept was defined from Statistics Canada 1986 census division boundaries (n = 188), representing regional areas in Canada, and assigned to each person's longest residential location to account for residual geographic patterns. We report odds ratios (ORs) and 95% confidence intervals (95% CIs) for ten-unit increases in ambient pollutant concentrations and for exposure quintiles. Only the national models were stratified by major lung cancer histological subtypes, given the reduced sample sizes for the urban subset analysis. National models were also stratified to examine pollutant interactions by a

priori variables (smoking status, education, and sex) that may modify the relationship between air pollution and lung cancer.[4,10,25,26]

RESULTS

Characteristics of Case and Control Subjects

Table 1 provides descriptive statistics and ORs (adjusted for age, sex, and study province) for selected subject characteristics (descriptive statistics for all individual and geographic variables are shown in eAppendix, eTable 1; http://links.lww.com/EDE/A678). Study subjects were approximately evenly divided by sex, and lung cancer cases were slightly older than population controls. Cases had a higher number of smoking pack years, less education, lower income, higher alcohol and meat consumption, higher residential and occupational second-hand smoke exposures, and more occupational exposures to dust, odors, and hazardous substances. Only 130 (6%) of lung cancer cases were never smokers compared with 1,337 (38%) of population controls. Cases lived in regions with higher average indoor radon measurements and resided longer in the most socioeconomic-deprived neighborhoods. Table 2 summarizes study participant air pollution exposures from the national spatiotemporal models and correlations between pollutants.

TABLE 1. Descriptive Statistics and ORs for the Association Between Lung Cancer Incidence and Select Subject Characteristics

Variable	Cases (n = 2,390) No. (%)	Controls (n = 3,507) No. (%)	OR[a] (95% CI)
Age; mean (standard deviation)	63.5 (8.2)	59.0 (12.6)	NE[b]
Sex			
Female	1,152 (48)	1,719 (49)	NE[b]
Male	1,238 (52)	1,788 (51)	NE[b]
Smoking pack years			
Nonsmoker	130 (6)	1,337 (38)	1.00
1–19	319 (14)	1,169 (34)	3.3 (2.6–4.2)
20–29	467 (20)	392 (11)	15.1 (12.0–19.1)
30–39	519 (22)	247 (7)	27.9 (21.7–35.7)
40–49	446 (19)	149 (4)	39.3 (28.9–51.8)
50–59	205 (9)	69 (2)	40.6 (28.8–57.4)
≥60	235 (10)	79 (2)	44.4 (31.9–61.8)
Years since cessation of smoking			
Nonsmoker	130 (6)	1,337 (38)	1.00
>35	29 (1)	177 (5)	1.3 (0.8–2.0)
26–35	70 (3)	312 (9)	2.0 (1.4–2.7)
16–25	158 (7)	383 (11)	4.4 (3.3–5.7)
11–15	168 (7)	223 (6)	7.5 (5.7–10.0)
6–10	268 (11)	208 (6)	13.6 (10.4–17.8)
2–5	276 (12)	143 (4)	23.1 (17.4–30.8)
Current smoker	1,273 (54)	715 (20)	22.6 (18.3–28.0)
Median household income			
>$100,000	47 (2)	137 (4)	1.00
$50,000–$99,999	283 (12)	630 (18)	1.3 (0.0–1.9)
$30,000–49,000	474 (20)	840 (24)	1.4 (1.0–2.1)
$20,000–29,999	398 (17)	548 (16)	1.7 (1.2–2.4)
$10,000–19,999	366 (15)	363 (10)	2.6 (1.6–3.3)
<$10,000	133 (6)	100 (3)	3.2 (2.1–5.0)
Prefer not to report	689 (29)	889 (25)	1.8 (1.2–2.5)
Education			
More than high school	590 (25)	1,373 (39)	1.00
High school	406 (17)	607 (17)	1.5 (1.3–1.8)
Less than high school	1,379 (58)	1,514 (43)	1.8 (1.6–2.1)

[a]OR adjusted for age, sex, and study province.
[b]Not estimated, frequency matched to all cancer cases in National Enhanced Cancer Surveillance System study.

National Analyses

Table 3 summarizes lung cancer OR with exposure to $PM_{2.5}$, NO_2, and O_3 derived from the national spatiotemporal models. Adjusted for all individual and geographic variables, the OR for a 10 μg/m^3 increase in $PM_{2.5}$ was 1.29 (95% CI = 0.95–1.76), and for a 10 ppb increase in NO_2 and O_3 was 1.11 (1.00–1.24) and 1.09 (0.85–1.39), respectively. For NO_2, all exposure quintiles were elevated relative to the lowest (<7.1 ppb), but there was no dose-response relationship. Although variance inflation factors for all three pollutant exposures were less than 2.5, the high positive correlation between $PM_{2.5}$ and NO_2 exposures (r = 0.73) and the complex spatial patterns of these pollutant relationships limit the interpretation of joint models. We did, however, examine joint models for NO_2 and O_3 to explore the independent associations between each pollutant and lung cancer incidence because O_3 is typically decreased in high NO_2 locations. In the joint national model, the NO_2 OR was slightly increased to 1.14 (1.02–1.28) and the O_3 OR doubled to 1.20 (0.92–1.56).

We also examined the influence of urban residence using a community-size category based on the longest residence during the exposure period. A community-size variable was not included in the national models due to high correlation with NO_2 (r = 0.73) and to a lesser degree with $PM_{2.5}$ (r = 0.55). When the urban-size category was included in the national models, the fully adjusted OR per 10 unit increase in NO_2 was 1.14 (0.99–1.31) and for $PM_{2.5}$ was 1.26 (0.90–1.77). No change was seen when average population density within 5 and 10 km of residential postal codes (over the 20-year exposure period) was added. There were weak associations between population density within 5 and 10 km and lung cancer incidence (ORs of 1.06 [0.83–1.15] and 1.10 [0.86–1.40] for the highest vs. lowest population density categories).

Table 4 presents stratified models for smoking status, smoking pack years, educational attainment, and sex. No consistent patterns were observed for any of the national $PM_{2.5}$, NO_2, and O_3 exposures. For example, compared with current smokers, larger ORs for lung cancer were seen among former

TABLE 2. Distribution of Ambient Air Pollution Exposures and Pollutant Exposure Correlations

Pollutant	Mean (Standard Deviation)	Median	Interquartile Range	Range	Spearman Correlation		
					$PM_{2.5}$	NO_2	O_3
$PM_{2.5}$ (μg/m³)	11.9 (3.0)	12.1	4.5	3.8–19.6	1.00	—	—
NO_2 (ppb)	15.4 (9.0)	13.8	14.3	1.1–44.9	0.73	1.00	—
O_3 (ppb)	20.3 (4.9)	21.2	6.2	6.6–33.8	0.25	0.11	1.00

smokers for $PM_{2.5}$ and O_3, but smaller ORs for NO_2. The small number of never smokers in this study makes interpretation of these models difficult. For all three pollutants, higher ORs were seen in men.

Urban Fixed-site Monitor Subanalyses

The urban analyses, based on exposures derived from the closest monitor within 50 km, are summarized in Table 5. In the fully adjusted model, a 10 μg/m³ increase in TSP was associated with an OR of 1.04 (0.95–1.13). The largest difference from the national analysis was seen for NO_2: a 10 ppb increase in the monitor-based analysis was associated with an OR of 1.34 (1.07–1.69). It is likely that NO_2 exposures derived for the urban monitors are also capturing a component of $PM_{2.5}$, due to the correlation between the two pollutants. Figure 1 in the eAppendix (http://links.lww.com/EDE/A678) illustrates the relationship between exposures derived from measured NO_2 and TSP (as $PM_{2.5}$ measurements were available only after 1984 and had poor spatial coverage).

Proximity to Vehicle Emissions

Table 6 summarizes ORs per 10 years living in proximity (50, 100, or 300 m) to a highway or major road, as well as weighted proximity measures that capture the decrease in vehicle emissions over the exposure period. Few study participants lived within 50 m of highways, but increased ORs were observed for these participants, as well those living within 100 m of highways. No associations were seen for those residing near major roads.

DISCUSSION

The present study aimed to enhance current understanding of the risks posed by air pollution to lung cancer incidence. We attempted to reduce exposure misclassification by conducting extensive spatiotemporal air pollution exposure assessments that incorporate long-term residential histories, and we examined associations with various pollutants and sources of exposure. We were also able to control for a comprehensive set of potential individual and geographic confounding factors.

Overall, our results support previous literature showing that ambient $PM_{2.5}$ air pollution is associated with increased lung cancer risk. In our national analysis, we found that a 10 μg/m³ increase in $PM_{2.5}$ was associated with an OR of 1.29 (0.95–1.76). This estimate is similar to the effect size reported in a 2008 meta-analysis, with a pooled relative risk (RR) of 1.21 (1.10–1.32) per 10 μg/m³ increase in $PM_{2.5}$.[1] An extended follow-up of the Harvard six cities study from 1974 to 2009 also found a 37% (7–75%) increase[5] and a recent analysis of never smokers in the Cancer Prevention Study-II cohort based on 26 years of follow-up found a RR of 1.19 (0.97–1.47) (both for a 10 μg/m³ increase in $PM_{2.5}$).[27]

Unlike the relatively robust literature on $PM_{2.5}$ and lung cancer, there are fewer studies on the associations of the gaseous pollutants NO_2 and O_3 with lung cancer. We found an OR for a ten-unit increase in NO_2 of 1.11 (1.00–1.24) in the national analysis and a substantially larger OR [1.34 (1.07–1.69)] in the urban monitor-based analysis. This higher estimate may be due to restricting the study to large urban areas, more accurate exposure assessment, or exposure assessment that captured both NO_2 and $PM_{2.5}$ influences (due to the high correlation between $PM_{2.5}$ and NO_2 and the lack of $PM_{2.5}$ monitoring data before 1984). Studies of NO_2 and lung cancer risk generally show positive associations ranging from 5 to 30% increases in risk per 10 ppb increases in NO_2,[2,8,9,26] however, negative associations have also been observed (RR 0.86 [0.70–1.07] per 30 μg/m³).[10]

In addition to NO_2, a number of studies have examined NO_x air pollution (primarily as a marker of traffic air pollution) with most reporting positive associations with lung cancer.[4,7,8,28] When we considered proximity to highways and major roads as a surrogate for traffic air pollution exposure, we found elevated risk of lung cancer incidence associated with living within 100 m of highways (OR 1.10 [0.83–1.46] per 10-year residence), but not for major roads. Our results are similar to those from a Danish cohort (incidence rate ratio of 1.21 [0.95–1.55] for lung cancer associated with living within 50 m of a major road [>10,000 vehicles per day])[4] as well as those from a Dutch cohort (RR of 1.10 [0.74–1.62] for living within 100 m of a motorway or 50 m of a road with >10,000 vehicles/day).[10] Major roads in urban locations of Canada have similar traffic volumes; however, we did not see any associations between living near major roads and lung cancer incidence.

We found a trend of increasing lung cancer incidence with increasing O_3 concentrations (OR 1.09 [0.85–1.39]) for a 10 ppb increase in the national models) with similar results in the urban analysis. In multipollutant models incorporating

TABLE 3. ORs for the Association Between Lung Cancer Incidence and $PM_{2.5}$, NO_2, and O_3 Exposures, as Derived from National Spatiotemporal Models

Pollutant	Cases[a]	Controls[a]	Partially Adjusted OR[b]	OR Adjusted for Individual Covariates[c]	OR Adjusted for Individual and Geographic Covariates[d]
$PM_{2.5}$					
All lung (per 10 µg/m^3)	2,154	3,264	0.82 (0.66–1.02)	1.24 (0.92–1.67)	1.29 (0.95–1.76)
Q1 [<9.0]	378	718	1.00	1.00	1.00
Q2 [9.0–10.9]	470	598	1.25 (1.05–1.50)	1.26 (1.00–1.59)	1.26 (0.99–1.59)
Q3 [11.0–12.8]	462	619	1.13 (0.94–1.35)	1.32 (1.04–1.67)	1.35 (1.06–1.71)
Q4 [12.9–14.7]	445	646	1.05 (0.87–1.26)	1.35 (1.05–1.72)	1.39 (1.08–1.79)
Q5 [>14.7]	399	683	0.86 (0.70–1.05)	1.14 (0.87–1.49)	1.19 (0.90–1.57)
Histology (per 10 µg/m^3)					
Squamous cell	643	3,264	0.64 (0.46–0.89)	1.24 (0.91–1.68)	1.09 (0.70–1.70)
Adenocarcinoma	816	3,264	0.91 (0.67–1.24)	1.22 (0.81–1.83)	1.27 (0.84–1.90)
Small cell	383	3,264	0.98 (0.64–1.51)	1.56 (0.87–2.81)	1.70 (0.92–3.13)
Large cell	226	3,264	0.89 (0.52–1.51)	1.08 (0.48–2.44)	1.11 (0.48–2.54)
NO_2					
All lung (10 ppb)	2,154	3,264	0.97 (0.92–1.02)	1.09 (0.99–1.21)	1.11 (1.00–1.24)
Q1 [<7.1]	373	720	1.00	1.00	1.00
Q2 [7.1–11.4]	454	604	1.36 (1.12–1.65)	1.57 (1.22–2.01)	1.64 (1.28–2.11)
Q3 [11.4–16.0]	455	631	1.20 (1.00–1.48)	1.54 (1.19–2.00)	1.63 (1.26–2.12)
Q4 [16.0–25.5]	452	649	1.11 (0.91–1.35)	1.66 (1.27–2.15)	1.79 (1.37–2.36)
Q5 [>25.5]	420	660	1.06 (0.87–1.30)	1.49 (1.13–1.97)	1.59 (1.19–2.13)
Histology (per 10 ppb)					
Squamous cell	653	3,264	0.88 (0.78–0.98)	1.00 (0.87–1.15)	0.99 (0.85–1.16)
Adenocarcinoma	828	3,264	1.03 (0.94–1.14)	1.13 (0.99–1.30)	1.17 (1.01–1.35)
Small cell	390	3,264	0.98 (0.84–1.14)	1.07 (0.88–1.3)	1.10 (0.89–1.37)
Large cell	230	3,264	0.96 (0.80–1.15)	1.03 (0.77–1.37)	1.08 (0.79–1.46)
O_3					
All lung (per 10 ppb)	2,154	3,264	1.15 (0.96–1.37)	1.09 (0.86–1.38)	1.09 (0.85–1.39)
Q1 [<15.3]	455	615	1.00	1.00	1.00
Q2 [15.3–20.2]	421	659	1.19 (0.98–1.46)	1.13 (0.86–1.47)	1.10 (0.84–1.45)
Q3 [20.3–22.0]	417	686	0.99 (0.77–1.26)	0.93 (0.68–1.29)	0.90 (0.65–1.25)
Q4 [22.0–24.4]	427	660	1.07 (0.83–1.38)	1.00 (0.72–1.40)	0.97 (0.69–1.37)
Q5 [>24.4]	434	644	1.10 (0.85–1.43)	1.15 (0.81–1.62)	1.13 (0.79–1.61)
Histology (per 10 ppb)					
Squamous cell	653	3,264	1.21 (0.91–1.62)	1.13 (0.80–1.62)	1.19 (0.82–1.71)
Adenocarcinoma	828	3,264	1.03 (0.79–1.34)	1.07 (0.77–1.48)	1.04 (0.74–1.44)
Small cell	390	3,264	1.14 (0.80–1.63)	1.07 (0.68–1.71)	1.07 (0.65–1.75)
Large cell	230	3,264	1.09 (0.70–1.70)	0.92 (0.49–1.71)	0.89 (0.57–1.38)

[a]Case and control numbers are for the final models including all individual and geographic characteristics.

[b]Unadjusted model includes age, sex, and study province.

[c]Unconditional logistic regression model with random effect for census division lived in the longest, adjusted for age, sex, cigarette smoking pack years, years since quitting smoking, educational attainment, household income, average weekly alcohol and meat consumption, residential and occupational second-hand smoke exposure, years working in occupations with dust or odors from industry, and years working with potential lung hazards.

[d]Unconditional logistic regression model with random effect for census division lived in the longest, adjusted for all individual variables, study province (to account for study design), ecological radon exposure, and years living in the lowest quintile of neighborhood median household income, percent without a high school diploma percent of households >30 years old dwellings.

NO_2 and O_3, the O_3 OR increased substantially to 1.20 (0.92–1.56), suggesting that accounting for areas with low O_3 but high NO_2 may be important to further understand the association between long-term O_3 exposure and lung cancer risk. There are no other large studies we are aware of to compare with these findings.

Lastly, we did not observe clear patterns between air pollution exposures and specific histological subtypes. Generally, $PM_{2.5}$ exposure was most strongly associated with small cell and adenocarcinoma; NO_2 with adenocarcinoma; and O_3 with squamous cell carcinoma. The most persuasive association was for NO_2 and adenocarcinoma (OR 1.17

TABLE 4. Stratification of Lung Cancer and National Pollutant Models by Smoking Status, Education, and Sex

Stratification Variable	Cases No.	Controls No.	National Exposure ORs		
			$PM_{2.5}$	NO_2	O_3
Smoking status[a]					
Never smoker	120	1,261	0.95 (0.38–2.34)	0.98 (0.72–1.34)	1.24 (0.59–2.59)
Former	885	1,351	1.45 (0.96–2.19)	1.11 (0.96–1.28)	1.10 (0.79–1.52)
Current	1,149	652	1.17 (0.75–1.84)	1.20 (1.03–1.39)	0.85 (0.59–1.23)
Smoking pack years[a]					
Never smoker	120	1,261	0.95 (0.38–2.34)	0.98 (0.72–1.34)	1.24 (0.59–2.59)
1–20	296	1,121	1.53 (0.85–2.76)	1.33 (1.09–1.63)	0.91 (0.55–1.50)
20–40	928	599	1.24 (0.76–2.01)	1.07 (0.91–1.27)	1.23 (0.84–1.80)
>40	810	283	1.66 (0.84–3.28)	1.11 (0.87–1.41)	1.06 (0.63–1.80)
Education[b]					
More than high school	1,223	1,388	1.49 (0.96–2.31)	1.04 (0.89–1.22)	1.30 (0.91–1.85)
High school	381	567	1.97 (0.86–4.51)	1.66 (1.28–2.16)	0.77 (0.40–1.49)
Less than high school	550	1,309	0.99 (0.54–1.83)	1.07 (0.86–1.32)	1.00 (0.62–1.63)
Sex[b]					
Male	1,117	1,654	1.59 (1.05–2.40)	1.22 (1.06–1.40)	1.12 (0.80–1.58)
Female	1,037	1,610	1.12 (0.69–1.81)	1.02 (0.87–1.21)	1.08 (0.73–1.60)

[a]Adjusted for all individual variables and geographic variables (below) except other smoking variables.

[b]Adjusted for all individual variables and geographic variables (age, sex, cigarette smoking pack years, years since quitting smoking, educational attainment, household income, average weekly alcohol and meat consumption, residential and occupational second-hand smoke exposure, years working in occupations with dust or odors from industry, years working with potential lung hazards, study province, ecological radon exposure, and years living in the lowest quintile of neighborhood median household income, percent without a high school diploma and percent of households >30 years old dwellings).

[1.01–1.35]). Adenocarcinoma is the most common histological subtype among never smokers, but there is no consensus in the literature as to whether air pollution is associated more strongly with adenocarcinoma or other histological subtypes. Some studies have found air pollution to be more strongly associated with adenocarcinoma,[12,14,29] whereas others have found the strongest associations with other histological subtypes.[11,13,28]

This study relies on the accuracy of historical exposure assessments. A number of sensitivity analyses were conducted to examine how the ORs change with different historical exposure assessment methods (summarized in Figure 2). These methods included the spatiotemporal models (used in national models and described in methods); spatiotemporal models developed with a national ratio of historical pollutant concentrations to current levels (for $PM_{2.5}$ only); historical regression models that use satellite data, population density, and a time trend to predict historical concentrations;[18] the satellite or chemical transport model spatial surfaces without temporal adjustments; and exposures estimated only from fixed-site monitoring data within 50 km. Figure 2 demonstrates a relatively small degree of variability in the $PM_{2.5}$ and O_3 OR estimates, whereas the NO_2 urban monitor exposure assessment has a higher OR than the two national NO_2 models incorporating spatial and temporal variability. For all pollutant models, the a priori national spatiotemporal exposure assessments had the smallest standard errors.

Strengths and Limitations

This study has a number of strengths that address important limitations in the current air pollution and lung cancer literature. First, we estimated long-term historical air pollution levels at six-digit residential postal codes. To reduce exposure misclassification, exposures were derived from 20 years of residential histories. This time-period was selected because, before 1975, cases tended to report more addresses than population controls, which would have incorporated bias into the study.[18] To further reduce bias, only people with complete 20-year residential histories were included in the final analyses. We were able to examine the influence of residential history completeness and found that including study subjects with missing residential histories resulted in substantial attenuation of the OR estimates. For example, including subjects with 18 years (90%) of complete exposures in the national models resulted in ORs per 10 unit increase in $PM_{2.5}$, NO_2, and O_3 of 1.23 (0.92–1.65), 1.11 (1.00–1.22), and 1.05 (0.83–1.33). Attenuation was greater when subjects with 15 years (75%) of complete exposures were included. Unlike other studies that assume participants have lived at their home residence for a certain amount of time, missing data in this study likely represent substantial exposure error as study participants self-reported their addresses and missing periods represent addresses they could not recall or residential locations outside of Canada.

Second, unlike most studies, which are restricted to single pollutants and city locations, we developed national

TABLE 5. ORs for the Association Between Lung Cancer Incidence and $PM_{2.5}$, NO_2, and O_3 Exposure, as Derived from National Air Pollution Surveillance Monitors Within 50 km of Residential Postal Codes

Pollutant	Cases[a] No.	Controls[a] No.	Partially Adjusted OR[b]	OR Adjusted for Individual Covariates[c]	OR Adjusted for Individual + Geographic Covariates[d]
PM25[e] (10 μg/m^3)					
All lung	1,200	1,862	1.10 (0.88–1.39)	1.29 (0.80–2.07)	1.33 (0.82–2.15)
Q1 [<12.6]	219	385	1.00	1.00	1.00
Q2 [12.6–14.2]	246	370	1.06 (0.85–1.34)	1.28 (0.93–1.76)	1.17 (0.80–1.72)
Q3 [14.2–15.0]	247	366	1.09 (0.85–1.39)	1.00 (0.71–1.41)	0.96 (0.66–1.39)
Q4 [15.0–15.8]	254	356	0.85 (0.66–1.10)	0.92 (0.64–1.31)	1.03 (0.72–1.46)
Q5 [>15.8]	234	385	0.95 (0.74–1.24)	1.17 (0.81–1.71)	1.29 (0.94–1.78)
TSP (10 μg/m^3)					
All lung	1,196	1,859	1.06 (0.99–1.12)	1.05 (0.97–1.14)	1.04 (0.95–1.13)
Q1 [<43]	268	346	1.00	1.00	1.00
Q2 [43–52.8]	208	407	1.07 (0.81–1.42)	0.96 (0.64–1.42)	0.98 (0.65–1.47)
Q3 [52.8–61.4]	258	362	1.39 (1.01–1.91)	1.21 (0.78–1.87)	1.23 (0.79–1.90)
Q4 [61.4–67.3]	245	355	1.05 (0.75–1.46)	0.95 (0.60–1.49)	0.98 (0.62–1.55)
Q5 [>67.3]	217	389	1.37 (1.00–1.89)	1.33 (0.86–2.06)	1.29 (0.83–2.02)
NO_2 (10 ppb)					
All lung	983	1,550	1.05 (0.89–1.24)	1.34 (1.08–1.67)	1.34 (1.07–1.69)
Q1 [<19.1]	209	295	1.00	1.00	1.00
Q2 [19.1–22.8]	194	321	1.18 (0.89–1.56)	1.41 (0.92–2.14)	1.45 (0.95–2.22)
Q3 [22.8–24.6]	189	344	0.91 (0.65–1.27)	1.31 (0.87–1.99)	1.37 (0.90–2.08)
Q4 [24.6–28.8]	207	284	1.03 (0.76–1.39)	1.34 (0.87–2.05)	1.40 (0.91–2.16)
Q5 [>28.8]	184	306	1.04 (0.76–1.41)	1.63 (1.04–2.56)	1.60 (1.01–2.54)
O_3 (10 ppb)					
All lung	1,015	1,478	1.15 (0.9–1.48)	1.11 (0.80–1.55)	1.11 (0.79–1.54)
Q1 [<17.8]	219	283	1.00	1.00	1.00
Q2 [17.8–19.4]	168	322	1.30 (0.99–1.71)	1.34 (0.94–1.90)	1.27 (0.89–1.81)
Q3 [19.4–21.8]	211	294	1.22 (0.91–1.63)	1.26 (0.87–1.83)	1.22 (0.84–1.78)
Q4 [21.8–23.8]	221	278	1.02 (0.75–1.39)	0.89 (0.59–1.34)	0.88 (0.58–1.33)
Q5 [>23.8]	196	301	1.33 (0.99–1.80)	1.36 (0.92–2.01)	1.33 (0.90–1.98)

[a]Case and control numbers are for the final models including all individual and geographic characteristics.

[b]Unadjusted model includes age, sex, and study province.

[c]Unconditional logistic regression model with random effect for census division lived in the longest, adjusted for age, sex, cigarette smoking pack years, years since quitting smoking, educational attainment, household income, average weekly alcohol and meat consumption, residential and occupational second-hand smoke exposure, years working in occupations with dust or odors from industry, and years working with potential lung hazards.

[d]Unconditional logistic regression model with random effect for census division lived in the longest, adjusted for all individual variables, study province (to account for study design), ecological radon exposure, and years living in the lowest quintile of neighborhood median household income, percent without a high school diploma percent of households >30 years old dwellings.

[e]Measured and modeled.

models for multiple pollutants and were able to include participants in all areas of Canada. This type of exposure assessment has also been used in a recent national Canadian cohort analysis of $PM_{2.5}$ and nonaccidental and cardiovascular mortality.[30] Third, unlike many prior studies, we had a large sample size (n = 2,390 incident lung cancer cases and 3,507 population controls), which allowed us to examine the associations between air pollution and lung cancer histology. Fourth, a comprehensive set of individual and geographic-level information was available for modeling important confounding variables. The inclusion of smoking information in particular had a large influence on study results. Smoking variables in the adjusted models substantially increased ORs, due to the small negative spatial association between smoking prevalence and air pollution exposures.[31] The inclusion of ecological radon exposures was also important, specifically in the NO_2 and $PM_{2.5}$ models, as high radon concentrations in Canada are located in areas that generally have lower NO_2 and $PM_{2.5}$ concentrations.

A number of study limitations also need to be considered. First, although this study has a relatively high response rate for cases (62%) and population controls (67%), response and recall bias cannot be ruled out. No difference in the completeness of self-reported residential histories was present between cases and controls when restricted to the 1975–1994 exposure period. Second, it is essential to note that populations are not distributed evenly across geographic communities, and

TABLE 6. Adjusted ORs for Lung Cancer Incidence Per 10 Years Living in Proximity to a Highway or Major Road for Study Participants Residing in Urban Areas of Canada

Exposure Measure	Exposed: Cases (n = 1,265) No.	Exposed: Controls (n = 1,868) No.	OR Adjusted for Individual Characteristics[a]	OR Additionally Adjusted for Geographic Characteristics[b]	OR Additionally Adjusted for Ambient Pollutants[c]
Highways					
Years ≤50 m	59	58	1.21 (0.76–1.94)	1.19 (0.74–1.91)	1.23 (0.76–1.98)
Years ≤50 m (w)[d]	59	58	1.12 (0.80–1.58)	1.11 (0.78–1.56)	1.13 (0.80–1.60)
Years ≤100 m	123	137	1.08 (0.82–1.43)	1.07 (0.81–1.42)	1.10 (0.83–1.46)
Years ≤100 m (w)[d]	123	137	1.05 (0.86–1.29)	1.04 (0.85–1.28)	1.06 (0.87–1.31)
Years ≤300 m	320	416	0.97 (0.83–1.13)	0.94 (0.81–1.10)	0.95 (0.82–1.12)
Years ≤300 m (w)[d]	320	416	0.97 (0.87–1.09)	0.96 (0.86–1.07)	0.97 (0.86–1.08)
Major roads					
Years ≤50 m	331	427	1.05 (0.90–1.23)	1.00 (0.85–1.18)	1.00 (0.85–1.17)
Years ≤50 m (w)[d]	331	427	1.04 (0.92–1.16)	1.00 (0.89–1.13)	1.00 (0.89–1.12)
Years ≤100 m	507	717	1.02 (0.90–1.16)	0.99 (0.87–1.12)	0.98 (0.87–1.12)
Years ≤100 m (w)[d]	507	717	1.01 (0.93–1.11)	0.99 (0.90–1.08)	0.99 (0.90–1.08)
Years ≤300 m	1,040	1,485	0.99 (0.90–1.10)	0.96 (0.87–1.07)	0.96 (0.86–1.07)
Years ≤300 m (w)[d]	1,040	1,485	0.99 (0.47–2.12)	0.97 (0.90–1.05)	0.97 (0.90–1.05)

[a]Unconditional logistic regression model, adjusted for age, sex, cigarette smoking pack years, years since quitting smoking, educational attainment, household income, average weekly alcohol and meat consumption, residential and occupational second-hand smoke exposure, years working in occupations with dust or odors from industry, and years working with potential lung hazards.

[b]Unconditional logistic regression model with random effect for census division lived in the longest, adjusted for all individual variables, study province (to account for study design), ecological radon exposure, and years living in the lowest quintile of neighborhood median household income, percent without a high school diploma percent of households >30 years old dwellings.

[c]Unconditional logistic regression model with random effect for census division lived in the longest, adjusted for all individual and geographic variables, and $PM_{2.5}$, NO_2, and O_3 exposures.

[d]Weighted by vehicle emissions to account for emission changes from 1975 to 1994.

thus, a random sample of the population may not be a random sample of all places. The national enhanced cancer surveillance system was designed so each provincial cancer agency would sample and recruit study participants. A province variable was therefore included in the fully adjusted models to capture any differences between sampling strategies (health insurance plans were used in five provinces, random digit dialing in two, and property assessment data in one). This is not ideal, in that the province variable likely captured a portion of the air pollution variance. The province variable also had a large influence on histology results, suggesting possible classification or recruitment differences by province. In addition,

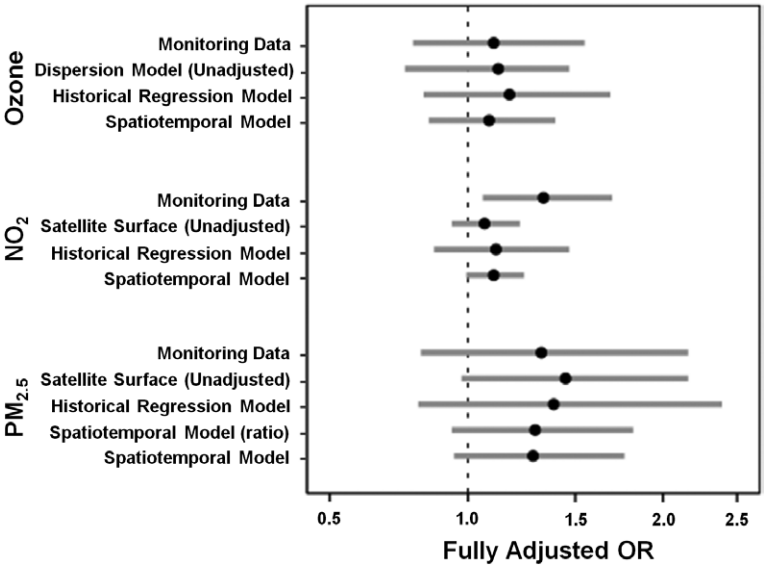

FIGURE 2. Fully adjusted ORs (per ten-unit increase in pollutants) from sensitivity analyses using various exposure assessment approaches.

a large portion of our study population was located in and around Toronto, Ontario (see Figure 1A), which had the highest $PM_{2.5}$ exposures. Any response bias or exposure assessment error in this geographic area would have a large influence on our study results. A sensitivity analysis including all provinces but Ontario (1,399 cases and 2,050 controls) indicated that results changed only slightly for NO_2 (OR 1.12 [0.97–1.31] per 10 ppb increase) and O_3 (OR 1.12 [0.80–1.56] per 10 ppb increase), but were reduced for $PM_{2.5}$ (OR 1.15 [0.77–1.72] per 10 $\mu g/m^3$ increase). The reduction for $PM_{2.5}$ is presumably due to the exclusion of the highest exposed (those living in Southern Ontario), which greatly reduced exposure variation in the analysis. The sensitivity to geographic variables is not as pronounced for NO_2 because those with the highest NO_2 exposure quintile lived in various large cities across Canada, rather than clustered in one region. We also included a random effect based on the census division of longest residence to account for unmeasured spatial structure in the data.

Third, the models were sensitive to subanalyses, as seen with the monitor-based exposure assessment results, which were substantially higher than the national NO_2 results. The difference in NO_2 results may be due to the various exposure assessment approaches, with the national models capturing inter- and intraurban variation and the urban monitor-based assessment capturing predominantly intraurban differences. NO_2 exposures derived from urban monitors may also be capturing a component of $PM_{2.5}$ because monitoring data for $PM_{2.5}$ were not available before 1984. Fourth, the OR estimates, primarily for $PM_{2.5}$, changed slightly with various coding schemes for smoking variables. For example, when a continuous smoking-pack-years-squared variable was included in the national model to account for nonlinear associations between smoking and lung cancer, the OR associated with a 10 unit increase in $PM_{2.5}$ decreased to 1.23 (0.91–1.67). Fifth, all model results did not show dose-response gradients. This may have been due to the relatively small sample size and range of exposures for study participants, particularly in the urban monitor-based analyses. Sixth, due to privacy concerns, residential history locations were limited to six-digit postal codes, which are accurate in urban areas but can cover much larger regions in rural areas. Proximity analyses were therefore restricted to urban areas of Canada. Lastly, although we were able to estimate exposure from residential history, no information was available for other important microenvironments such as work locations.

In sum, we found increased risks of lung cancer incidence with residential exposures to ambient $PM_{2.5}$, NO_2, and O_3, as well as living within 100 m of highways. Results were most robust for NO_2 and $PM_{2.5}$. More research is needed to establish whether O_3 exposure is an independent risk factor for lung cancer.

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