ORIGINAL ARTICLE

Traffic-related air pollution and prostate cancer risk: a case–control study in Montreal, Canada

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ABSTRACT

Objectives There is a paucity of information on environmental risk factors for prostate cancer. We conducted a case–control study in Montreal to estimate associations with exposure to ground-level nitrogen dioxide (NO_2), a marker for traffic-related air pollution.

Methods Cases were 803 men with incident prostate cancer, ≤75 years of age, and diagnosed across all French hospitals in Montreal. Concurrently, 969 controls were drawn from electoral lists of French-speaking individuals residing in the same electoral districts as the cases and frequency-matched by age. Concentrations of NO_2 were measured across Montreal in 2005–2006. We developed a land use regression model to predict concentrations of NO_2 across Montreal for 2006. These estimates were back-extrapolated to 1996. Estimates were linked to residential addresses at the time of diagnosis or interview. Unconditional logistic regression was used, adjusting for potential confounding variables.

Results For each increase of 5 parts per billion of NO_2, as estimated from the original land use regression model in 2006, the OR_{5ppb} adjusted for personal factors was 1.44 (95% CI 1.21 to 1.73). Adding in contextual factors attenuated the OR_{5ppb} to 1.27 (95% CI 1.03 to 1.58). One method for back-extrapolating concentrations of NO_2 to 1996 (about 10 years before the index date) gave the following OR_{5ppb}: 1.41 (95% CI 1.24 to 1.62) when personal factors were included, and 1.30 (95% CI 1.11 to 1.52) when contextual factors were added.

Conclusions Exposure to ambient concentrations of NO_2 at the current address was associated with an increased risk of prostate cancer. This novel finding requires replication.

INTRODUCTION

Prostate cancer has the highest incidence of all tumours among Canadian men, with an estimated 26 500 new cases in 2012.[1] Age-adjusted incidence rates have remained stable over the last decade, while mortality rates have declined somewhat. Similar patterns have been observed in several other countries.[2]

The incidence of prostate cancer increases exponentially with age, is higher among men with a first-degree relative affected by the disease, and varies by geography and ancestry.[3 4] There are no accepted modifiable risk factors for this cancer. Evidence from migrant studies suggests that environmental influences may be implicated in its aetiology.[5] In addition, diet, physical activity, anthropometric and sexual factors, occupational circumstances and smoking have been investigated, but no clear signal has emerged.[2]

Local vehicular traffic in urban areas is a primary contributor to air pollution. Vehicular emissions include gases, particles, volatile organic compounds and polycyclic aromatic hydrocarbons (PAHs). Some constituents are recognised carcinogens (eg, benzene) and may have hormone-modulating properties.[6] Little is known about the role of air pollution in prostate cancer. Two ecological studies of air pollution conducted in the USA in the 1960s, one in Erie County, New York[7] and the other in Nashville, Tennessee,[8] found positive associations with prostate cancer mortality, while a recent cohort study from Denmark found no association with the incidence of prostate cancer.[9]

Nitrogen dioxide (NO_2) has been shown to be a good marker for traffic-related pollution.[10–12] Similar to the approach used by us in another study,[13–15] our objective was to determine whether traffic-related air pollution was associated with incident prostate cancer.

METHODS

We restricted the population to French-speaking men living on the Island of Montreal and Nuns' Island, which have a population of approximately 1.8 million people.[16] Over 86% of the population on the Island of Montreal speak French.

Study population

The Prostate Cancer and Environment Study (PROtEuS) is a case–control study of environmental risk factors for prostate cancer. Study subjects were men, under 76 years of age at the time of diagnosis or selection, residents of the greater Montreal area, listed on the Province of Quebec's permanent electoral list (continually updated) and Canadian citizens. Cases were actively ascertained through pathology departments across all 11 French hospitals, of the total of 14 hospitals that diagnose prostate cancer in the Montreal area. We included all patients diagnosed with primary, histologically confirmed prostate cancer (International Classification of Diseases, 10th revision, code C61) between September 2005 and June 2008. Control subjects were selected concurrently from the population-based provincial electoral French-speaking list, and frequency-matched to cases by 5-year age groups. The electoral list is thought to represent a nearly complete listing of Canadian citizens residing in the province of Quebec. Controls were drawn randomly from an area comprising 39 electoral

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districts (about 40 000 electors each), corresponding to those of the case series. Subjects were still eligible if they had a history of cancer other than prostate cancer.

Data collection

As part of face-to-face interviews, participants provided information about socio-demographic characteristics, a wide range of lifestyle-related factors, a prostate cancer screening history and detailed occupational histories. The degree of aggressiveness of prostate cancers, as defined by the Gleason score (http://gleasonscore.net/), was extracted from pathology reports. Ethics committees at all participating institutions approved the protocol and subjects provided informed consent.

Assessment of exposure to traffic-related air pollution

Findings from our sampling survey of ambient concentrations of NO_2 conducted in Montreal in 2005 and 2006 were reported previously.[14] NO_2 is recognised as a marker of traffic-related pollution due in part to its co-locational association with other pollutants.[10–12] NO_2 is a near-source exhaust dilution pollutant that is formed within seconds and metres of emission from vehicles, and so can be used as a marker of traffic-related air pollution. It correlates with elemental carbon (a product of combustion) and with distance from roadways, and studies of areas with high traffic density show some of the highest levels of NO_2 compared to other locations where there is no traffic.[11] Although NO_2 has a regional component, measurement close to the surface of roads will measure mostly traffic-related sources. A number of Dutch studies have shown correlations with elemental carbon and with distance from roadways.[11] NO_2 is the most widely used marker for traffic-related air pollution: in a review paper, Hoek *et al*[12] showed that in 18 cities where it has been measured, roadways, traffic, and truck routes were all important predictors.[12]

Briefly, the locations for the samplers were selected using a location-allocation model that placed samplers in areas likely to have high spatial variability in traffic-related pollution and high population densities.[17] Samplers were deployed at 133 locations on roadside utility poles, approximately 3 m above the ground, across the Island of Montreal on three occasions (spring, summer, winter) to obtain 2-week integrated samples. We used Ogawa passive diffusion samplers that use triethanolamine-impregnated filters as an absorbent. Valid observations at 129 locations were obtained from all three sampling periods.

We used these observations to develop a land use regression model to predict concentrations of mean annual NO_2 for 2005–2006, at a resolution of 5 m^2 across the Island of Montreal.[14] We modelled the natural logarithm of NO_2 on land use and traffic-related variables to generate an exposure surface (R^2 = 0.80). We found that the most important predictors were traffic counts, major roads, and other land use associated with traffic. In addition, the highest values were found along the major roadways and highways in the city.

Residential addresses, at the time of diagnosis for cases and at the time of interview for controls, were then linked to the exposure surface. Eighty-seven per cent of subjects included in the present analysis were geocoded to the x,y coordinates of their home address and 13% were geocoded to the centroid of the area represented by the six-character postal code, which in Montreal usually refers to a block face or to a large apartment complex.

Historical estimates of exposure

We developed three separate but related methods[15] to back-extrapolate our exposure surface to 1996 using measurements of ambient NO_2 from 12 fixed-site monitoring stations of Environment Canada's National Air Pollution Surveillance network. These measurements of NO_2 were used to produce location-specific ratios that would scale the 2006 surface, using three related back-extrapolation methods[15]: for method 1, we used inverse distance weighting on the mean annual concentrations at the fixed-site stations to interpolate the spatial surfaces, while for methods 2 and 3 we made use of land use regression models to produce the surfaces.

Method 1

For method 1, we divided the interpolated surface from the fixed-site monitors in 1996 by the interpolated surface for 2006. We then multiplied our original land use regression model by this ratio to produce a surface of estimated annual mean concentrations of NO_2 for 1996.

Method 2

For method 2, we used land use regression models to create two surfaces to form the ratio. The numerator was computed by regressing the observed annual concentrations of NO_2 at the 12 fixed-site monitors in 1996 against a reduced set of spatial variables that were used in the land use regression model of 2006. For the denominator, we used as the dependent variable predicted concentrations at the 12 fixed-site monitors from the land use regression model of 2006, and then regressed these predicted values against the same covariates that were selected for the numerator. We then formed the ratio of the 1996 to the 2006 newly developed surfaces and multiplied by the land use regression surface of 2006.

Method 3

For method 3, we applied the regression coefficients of an alternative land use regression model for 2006 (R^2=0.65) to land use and traffic variables measured in 1996. This alternative model was developed because not all spatial variables used in 2006 were available for 1996. As in method 2, we then multiplied this alternative model by the ratio of two additional models: for the numerator we used as dependent variables observed values at the 12 stations in 1996, and for the denominator we used predicted values from the alternative land use regression model at the same 12 locations.

Using back-extrapolation methods similar to those for 1996, we also developed a set of historical exposure estimates for 1985 based on 10 fixed-site monitors. Considering the unknown proportion of subjects who would have lived in 1985 at an address other than the one they had in 2006, as well as the probable lower reliability of estimates for 1985, the latter are treated here as sensitivity analyses.

Statistical analysis

Our main analyses focused on the recent exposure estimates (2006) and the back-extrapolated estimates of exposure 10 years earlier (1996). We used unconditional logistic regression to estimate OR and 95% CI between exposure to NO_2 and the risk of developing prostate cancer. We included continuous covariates as linear terms or as natural cubic spline functions if the response was non-linear. Individual-level covariates considered included age, first-degree family history of prostate cancer, ancestry, family income, body mass index and attained level of education, but not all of these were included in the final models, as some variables did not show associations.

We postulated that neighbourhood deprivation, a contextual factor, may be associated with prostate cancer and may

confound associations with air pollution because deprived populations often live in areas that are characterised by higher concentrations of air pollution.[18 19] There is no information, however, as to whether these variables are causally associated with prostate cancer or are surrogates for other causal factors. We made use of Canadian census tract data from 1996 to describe the socio-economic characteristics of Montreal's neighbourhoods according to the address at the index date. Variables describing median household income and percentage of adults who did not complete high school were compiled for the 350 census tracts that included addresses of subjects (heretofore referred to as neighbourhood ecologic covariates).

Standard regression diagnostics were applied to identify possible influential subjects and to ensure that the models did not violate the assumptions of the logistic models. Potential effect-modification according to all of the covariates was evaluated.

We included NO_2 as a continuous, linear variable after verifying this assumption through the use of b-spline functions (2 degrees of freedom) and visual inspection of the fitted exposure–response curves. ORs are presented for each increase in exposure to NO_2 of 5 parts per billion (ppb), referred to as OR_{5ppb}.

Sensitivity analyses

We conducted analyses using estimates back-extrapolated to 1985. In addition, we considered the potential confounding effects of smoking and alcohol consumption where we assessed the effect of status (never smoked/drank, ex-smoker/drinker, current smoker/drinker) as well as indices of cumulative smoking and alcohol consumption. We also compared the results for subjects who were geo-coded to x,y coordinates and those who were geocoded to the centroid of the area represented by the six-character postal code. Separate analyses were carried out among those subjects for whom we had information on duration of residence, restricting to those who had been residents at the same address for 10 or more years prior to interview. We also investigated whether severity of prostate cancer, and whether restricting subjects to those who had been screened for prostate cancer, affected the estimates. Lastly, we determined whether response patterns had any substantial effect on the findings.

RESULTS

Although 1260 prostate cancer cases and 1535 controls from the Greater Montreal area had been interviewed at the time of analysis, we had spatial estimates of air pollution only for the Island of Montreal and Nuns' Island. We thus excluded 457 prostate cases and 566 controls who lived in outlying regions, thereby leaving 803 cases and 969 controls for the present analyses. The mean (SD) age of cases and controls was 65 (7) years. Response rates were 86% for cases and 63% for controls. Reasons for non-participation among cases were refusal (94%), unable to trace (3%), death with no proxy available (2%) and language barrier (1%). Among eligible controls, non-participation was attributable to refusal (86%), unable to trace (11%), language barrier (1%), death with no proxy available (1%) and too sick with no proxy available (1%). Proxy respondents provided information for 3% and 5% of cases and controls, respectively. Table 1 shows the distributions of recognised and selected potential risk factors for prostate cancer and associated age-adjusted ORs and 95% CIs. A first-degree family history of prostate cancer conferred a twofold increase in risk. Compared to men of French ancestry, men of African descent had higher risks, while men of Asian descent had lower risks of developing prostate cancer. Men who only completed primary school had higher risks than all others. There was little difference between groups on body mass index, smoking, alcohol intake, proxy responses and annual family income.

We estimated age-adjusted ORs for the three ecological covariates acting as possible confounding variables; that is, median household income, percentage of recent immigrants and percentage of adults who did not complete high school (the first two were modelled as natural cubic splines on 2 degrees of freedom). We observed an inverse association with median household income and found higher risks as the proportion of individuals without a high school education increased. Higher risks were found amongst men in the third quartile of the distribution of recent immigrants.

Associations with estimates of concentrations of ground-level NO_2

Concentrations of NO_2 decreased from a mean of 43.2 $\mu g/m^3$ in 1985 to 25.7 $\mu g/m^3$ in 2009, a 41% reduction. Table 2 shows that the mean concentrations of NO_2 estimated from our original land-use regression (2006) were 12.4 ppb amongst cases and 11.8 ppb amongst controls. Making use of our three back-extrapolation methods, mean concentrations in 1996 were between 17.5 ppb and 17.8 ppb amongst cases and between 16.4 ppb and 16.9 ppb amongst controls.

The surfaces that we used also reflected a narrowing of the distributions of NO_2 over time. We found positive correlations between 1000 randomly sampled locations on the different exposure surfaces (Pearson correlation coefficients: 0.96–0.99) and observed annual mean concentrations of NO_2 at the fixed-site stations for 1985, 1996 and 2006 suggesting that the spatial patterns of NO_2 did not vary importantly during the 20-year period between 1985 and 2006. Furthermore, the observed concentrations at the locations of the fixed-site monitoring stations in 2006 were correlated with those in 1996 (r=0.89, 95% CI 0.60 to 0.97) and in 1985 (r=0.72, 95% CI 0.12 to 0.94; see online supplementary eTable 1 and eFigure 1). Table 3 shows OR_{5ppb} for prostate cancer adjusted for age only, adjusted for age and personal covariates, and adjusted for these variables and the three ecological variables. Personal covariates included age (linear), first-degree family history of prostate cancer (yes, no, don't know), ancestry (French, African, Asian, other, unknown) and attained level of education (six categories). Family income and body mass index were not retained in the models as they were not associated with the risk of prostate cancer. There were no influential observations in these or any other analyses.

We did not find any evidence of non-linearity in the response functions for NO_2 (see online supplementary eFigure 2) and we thus present ORs for each increase of 5 ppb in NO_2 making use of the land use regression map developed in 2005–2006 (essentially the index date period) as well as the three methods of back-extrapolation to 1996. There were minimal differences between OR_{5ppb} adjusted only for age and those also adjusted for selected personal factors. The OR_{5ppb} using NO_2 evaluated in 2006 using our original land use regression model was 1.44 (95% CI 1.21 to 1.73). It was attenuated to 1.27 (95% CI 1.03 to 1.58) when the three ecological factors were included. Median household income was the only ecological factor that attenuated the ORs and inclusion of personal income did not affect the risk estimates (data not shown). For the period about 10 years before the index date (1996), the range of the fully-adjusted OR_{5ppb} was between 1.23 and 1.38, attenuated from those of 2006.

Table 1 Selected characteristics among prostate cancer cases and controls and associated age-adjusted ORs and 95% CIs in a French-speaking population, Montreal, Canada, 2005–2008

	Cases		Controls		Age-adjusted	
	Number	%	Number	%	OR	95% CI
Age at interview (quartiles)					–	–
<60	171	21.3	219	22.6	–	–
≥60 and <66	226	28.1	260	26.8	–	–
≥66 and <71	197	24.5	242	25.0	–	–
≥71	209	26.0	248	25.6	–	–
Annual family income						
$C30000–49999	234	24.1	195	24.3	1	–
<$C10000	38	3.9	35	4.4	1.11	0.67 to 1.82
$C10000–19999	107	11.0	86	10.7	0.96	0.68 to 1.36
$C20000–29999	133	13.7	121	15.1	1.09	0.80 to 1.49
$C50000–79999	173	17.9	153	19.1	1.06	0.80 to 1.42
$C80000–100000	77	7.9	55	6.8	0.86	0.58 to 1.28
>$C100000	123	12.7	101	12.6	0.99	0.71 to 1.38
Preferred not to respond	78	8.0	51	6.4	0.78	0.52 to 1.17
Don't know	6	0.6	6	0.7	1.20	0.38 to 3.78
Ancestry						
French	505	52.1	566	70.5	1	–
African	52	5.4	72	9.0	1.24	0.85 to 1.81
Asian	30	3.1	9	1.1	0.27	0.13 to 0.57
Other	372	38.4	146	18.2	0.35	0.28 to 0.44
Don't know	10	1.0	10	1.2	0.90	0.37 to 2.17
Attained educational level						
Primary school	214	22.1	220	27.4	1	–
High school	274	28.3	236	29.4	0.83	0.64 to 1.07
College	152	15.7	103	12.8	0.65	0.47 to 0.89
University, undergraduate	191	19.7	121	15.1	0.60	0.45 to 0.82
University, graduate	137	14.1	122	15.2	0.85	0.62 to 1.16
Don't know	1	0.1	1	0.1	0.99	0.06 to 15.94
First-degree family history of prostate cancer						
No	830	85.7	617	76.8	1	–
Yes	107	11.0	162	20.2	2.04	1.56 to 2.66
Don't know	32	3.3	24	3.0	1.01	0.59 to 1.73
Body mass index (kg/m^2)						
<24.06	196	24.4	226	23.3	1	–
≥24.06 and <26.20	204	25.4	248	25.6	0.95	0.73 to 1.24
≥26.20 and <28.73	196	24.4	235	24.3	0.96	0.73 to 1.26
>28.73	203	25.3	251	25.9	0.93	0.71 to 1.22
Unknown	4	0.5	9	0.9	0.51	0.15 to 1.68
Smoking						
Never	226	28.1	266	27.5	1	–
Ex-smokers	417	51.9	515	53.1	0.95	0.76 to 1.19
Current smokers	160	19.9	188	19.4	1.00	0.76 to 1.32
Per IQR of pack-years (787.5)					0.97	0.85 to 1.10
Alcohol						
Never	99	12.3	120	12.4	1	–
Ex-drinkers	118	14.7	153	15.8	0.93	0.65 to 1.33
Current drinkers	586	73.0	696	71.8	1.02	0.76 to 1.36
Per IQR of drink-weeks (628)					1.02	0.96 to 1.08
Ecological covariates						
Percentage of adults who did not complete high school						
≥6.00 and <41.35	165	20.5	271	28.0	1.00	–
≥41.35 and <56.15	203	25.3	241	24.9	1.38	1.06 to 1.81
≥56.15 and <66.63	209	26.0	232	23.9	1.48	1.13 to 1.94
≥66.63 and ≤96.76	221	27.5	221	22.8	1.64	1.26 to 2.15
Missing	5	0.6	4	0.4	NA	

Continued

Table 1 Continued

	Cases		Controls		Age-adjusted	
	Number	%	Number	%	OR	95% CI
Median household income						
≥$C12900 and <$C29905	237	29.5	203	20.9	1.00	–
≥$C29905 and <$C37412	203	25.3	236	24.4	0.74	0.57 to 0.96
≥$C37412 and <$C48015	210	26.2	232	23.9	0.78	0.60 to 1.01
≥$C48015 and ≤$C164570	148	18.4	294	30.3	0.43	0.33 to 0.57
Missing	5	0.6	4	0.4	NA	
Percentage of recent immigrants						
≥0.00 and <1.81	187	23.3	249	25.7	1.00	–
≥1.81 and <3.36	187	23.3	254	26.2	0.98	0.75 to 1.28
≥3.36 and <5.82	228	28.4	213	22.0	1.42	1.09 to 1.86
≥5.82 and ≤25.79	196	24.4	249	25.7	1.05	0.80 to 1.37
Missing	5	0.6	4	0.4	NA	

Sensitivity analyses

For 1985, the fully-adjusted OR_{5ppb} varied between 1.11 and 1.17 (see online supplementary eTable 3). The OR_{5ppb} tended to be somewhat higher when analyses were restricted to cases with a Gleason score <7, as compared to those with a Gleason score ≥7 (considered to indicate aggressive cancer), but CIs overlapped. For example, the fully-adjusted OR_{5ppb} associated with our original land use model (2006) were 1.41 (95% CI 1.07 to 1.86) and 1.23 (95% CI 0.95 to 1.58) for non-aggressive and aggressive cancers, respectively.

Additional analyses excluded proxy subjects and included smoking (pack-years) and alcohol (drink-years) in the models, entered as continuous covariates using natural cubic splines on 4 and 2 degrees of freedom, but this did not alter the results (data not shown). There was no evidence of effect modification according to any of the covariates (data not shown).

We conducted analyses restricting to subjects who reported that they had been screened for prostate cancer within the previous 5 years (prostate-specific antigen (PSA) test and/or a digital rectal examination), in order to reduce the possibility of undiagnosed prostate cancer in the control series (see online supplementary eTable 4). There were few differences from the main analyses.

A separate analysis restricted subjects to those who lived at the same address for 10 or more years at the time of diagnosis for cases and at the time of interview for controls. This analysis is limited because we did not start asking this question until well into the data collection, and it is based on only 71 cases and 223 controls. About 70% of subjects for whom duration of residency at the current address was collected had lived there for at least 10 years. For the original land use model, we found among those subjects who had lived in their homes for 10 years an OR_{5ppb} of 1.36 (95% CI 0.76 to 2.45) and adding in the ecological covariates attenuated this to 1.13 (95% CI 0.56 to 2.29), compatible with our main findings (see online supplementary eTable 5).

Analyses comparing whether the address was geocoded directly to x,y coordinates (1522 subjects) or to the centroid of the six-character postal code (250 subjects) generated fairly similar results (see online supplementary eTable 6).

Table 2 Distributions of concentrations of NO_2 (parts per billion, ppb) at street level using different exposure surfaces, Montreal, Canada*

Estimated ambient exposures to NO_2 (ppb)				Percentiles			
25th	Mean	SD	Minimum	50th	75th	100th	
Estimates for 2006							
Original land use model							
Cases	12.39	2.79	5.76	10.27	11.89	14.44	22.75
Controls	11.81	2.70	5.53	9.91	11.34	13.47	22.75
Estimates back-extrapolated to 1996							
Method 1†							
Cases	17.45	3.81	8.09	14.55	16.84	20.25	31.07
Controls	16.41	3.63	7.91	13.91	15.88	18.58	31.07
Method 2‡							
Cases	17.78	3.91	8.12	15.02	17.25	20.41	32.44
Controls	16.77	3.81	8.03	14.20	16.48	19.12	32.44
Method 3§							
Cases	17.71	2.93	9.09	15.73	17.65	19.88	26.23
Controls	16.94	3.03	7.87	14.86	16.96	19.07	24.63

*Using the methods described in the Methods section, from Crouse *et al*[14] and Chen *et al*.[15] Based on data from 803 cases and 969 controls.
†Method 1: extrapolated using predicted concentrations of NO_2 derived from the inverse distance weighting in 2006 at each fixed-site monitoring station.
‡Method 2: extrapolated using predicted concentrations of NO_2 derived from the land use regression model in 2006 at each fixed-site monitoring station.
§Method 3: extrapolated using predicted concentrations of NO_2 derived from the alternate land use regression model in 2006 at each fixed-site monitoring station.

Table 3 ORs and 95% CIs between ambient concentrations of nitrogen dioxide (NO_2) and the risk of developing prostate cancer in a French-speaking population, Montreal, Canada, 2005–2008

	803 Cases and 969 controls					
	Model 1		Model 2		Model 3	
	Adjusted for age		Adjusted for age and personal covariates*		Adjusted for age, personal and ecological covariates†	
Exposure surface	OR per increase of 5 ppb	95% CI	OR per increase of 5 ppb	95% CI	OR per increase of 5 ppb	95% CI
Estimates for 2006						
Original land use model	1.47	1.24 to 1.75	1.44	1.21 to 1.73	1.27	1.03 to 1.58
Estimates back-extrapolated to 1996						
Method 1‡	1.45	1.28 to 1.65	1.41	1.24 to 1.62	1.30	1.11 to 1.52
Method 2§	1.40	1.24 to 1.59	1.35	1.19 to 1.54	1.23	1.04 to 1.45
Method 3¶	1.54	1.31 to 1.81	1.49	1.26 to 1.77	1.38	1.12 to 1.69

*Model 2 adjusted for age, personal covariates including first-degree family history of prostate cancer, ancestry and attained level of education.
†Model 3 adjusted for age, personal covariates in model 2, and three ecological variables from the 1996 Canadian census: percentage of adults who did not complete high school, median household income and percentage of recent immigrants. Based on 1763 subjects.
‡Method 1: extrapolated using predicted concentrations of NO_2 derived from the inverse distance weighting in 2006 at each fixed-site monitoring station.
§Method 2: extrapolated using predicted concentrations of NO_2 derived from the land use regression model in 2006 at each fixed-site monitoring station.
¶Method 3: extrapolated using predicted concentrations of NO_2 derived from the alternate land use regression model in 2006 at each fixed-site monitoring station.

Non-participants were generally similar to participants, with a slight trend towards non-participants living in areas with a greater proportion of recent immigrants within the previous 10 years, with a higher unemployment rate, with a greater proportion of adults without a high school diploma, and with a lower median household income (data not shown). These findings are consistent with the absence of major socio-economic disparities between subjects who participated in the study and those who did not. We also carried out an analysis that included all eligible cases and controls, including non-participants, to evaluate the potential impact of non-participation. While we had no information on personal covariates for non-participants, we found similar results when adjusting only for age and slightly attenuated ORs after including the ecological variables (data not shown).

DISCUSSION

Our findings showed increased risks of incident prostate cancer among men exposed to higher concentrations of NO_2, a marker of traffic-related air pollution. These findings are novel and surprising. As discussed below, associations persisted when we considered potential alternate explanations and sensitivity analyses, but we are cautious in interpreting the results.

Local, national and international geographical variations in patterns of occurrence of prostate cancer are one of its most puzzling characteristics. Identification of modifiable risk factors for this disease has remained largely unsuccessful and the use of spatially referenced data represents a potentially fruitful avenue for research.[20]

Combustion engines produce thousands of compounds, including fine particulate matter, nitrogen oxides, carbon monoxide, PAHs and volatile organic compounds.[21] The magnitude of the risk estimates varied somewhat when estimates of exposure from different time periods were used. We found the highest risks for recent estimates of pollution but also found slightly increased risks for more remote estimates. It is likely that the back-extrapolated estimates of exposure entailed more misclassification than the original land use model, and this may explain the observed reductions in relative risks.

Long-term exposure to ambient air pollution entails potential exposure to a wide range of chemicals or compounds and it has been associated with several health effects.[22 23] With respect to cancer, there is strong evidence of an association with lung cancer.[23] For prostate cancer, only a few studies have been conducted. In two ecological studies conducted on suspended particles in the USA in the 1960s, one by Winkelstein and Kantor[7] in Erie County, New York and the other by Hagstrom *et al*[8] in Nashville, Tennessee, associations were observed with prostate cancer mortality. In one other study, increased mortality from prostate cancer was found to be associated with residential proximity to metal industrial facilities,[24] while in another investigation, a slightly higher incidence of prostate cancer was reported among men living near a major airport.[25] More recently, Raaschou-Nielsen *et al*[9] as part of the Diet, Cancer and Health cohort study in Denmark, made use of modelled concentrations of NO_x at residences and reported associations with cervical and brain cancer incidence but not with prostate cancer (HR of 0.96 per an increase of 100 $\mu g/m^3$ of NO_x; 673 cases).

There is clearly insufficient information to make any informed judgments regarding whether air pollution causes prostate cancer, and our findings could be due to chance. The prostate cancer carcinogenesis process is poorly understood and we believe that it is premature to speculate at length on potential mechanisms. A number of occupational studies have provided some information on occupational circumstances that may increase the risk of developing prostate cancer. In two reviews, the following occupational factors were identified as possibly associated with this cancer: farming, pesticides and herbicides, cadmium, mineral oils, metal working-related exposures, and PAHs and engine emissions.[26 27] In a few studies using substance-based exposure assessment protocols, increased risks of prostate cancer have been observed among men occupationally exposed to PAHs from coal[28] and diesel fumes,[29] but these findings have not been replicated in other studies.[30 31] While several chemicals may cause endocrine disruption or modulation[32 33] and might relate to the development of prostate cancer,[6] the hormonal hypothesis remains unconfirmed. Of course, many of the compounds in ambient air, such as PAHs, may act directly as carcinogens.

We acknowledge that the present analysis provides only partial information on personal exposure to air pollution. Total personal exposure is related to a number of factors, including daily activity patterns and amount of time spent indoors and outdoors, among others. Two limitations of using the home

address as a surrogate of exposure are thus related to population mobility: people do not necessarily live in the same home over the course of their lifetime nor do they spend all of their time at home. While it is true that many subjects may spend their days away from home, a study by Leech *et al*[34] found that Canadian adults spend on average ~67–68% of their time at home (indoors and outdoors combined). Our analysis restricted to subjects who lived for 10 or more years at the current address were compatible with our primary results.

Given some imprecision associated with geocoded addresses and other geographical data, as well as the fact that we used spatially derived exposures as surrogates for personal exposures, the risk estimates presented here are clearly misclassified. Thus, our results may underestimate the true estimates of the relative risk of prostate cancer associated with exposure to air pollution in this population.

We could not assess associations with early life exposures, nor do we know what age periods may be critical in the induction of cancer. However, sensitivity analyses suggested that risks were slightly elevated using exposure estimates pertaining to 25 years before interview. Further work is needed to verify whether these results represent true associations or whether they are due to chance or to undetected bias. Our findings should not be interpreted as meaning that NO_2 might be a causal factor; should the association with NO_2 be confirmed, it would more likely reflect an association with the complex mixture that is derived from the combustion of hydrocarbons.[35]

This study focuses on the majority French-speaking population in Montreal. Cases were ascertained across all French hospitals, covering over 80% of all cases in the region. In order to reduce the potential for referral bias, we selected French-speaking controls who came from the same areas of the city as the cases. A comparison of the distribution of residential postal codes amongst cases and controls indeed confirmed that both groups resided in the same geographical areas. Access to medical care is entirely free across all Montreal hospitals, and it is reasonable to assume that French-speaking controls would be referred to the French-speaking hospitals where the cases arose.

Response rates were relatively high among cases (86%) and lower among controls (63%). Our analysis based on all eligible subjects suggests that differential response rates did not substantially alter the risks. Inflated estimates of risk may be expected if, for example, controls with higher educational levels responded more frequently than the target population and if higher concentrations of air pollution are inversely associated with higher educational levels.[18]

Cancer screening practices are an important issue in studies of prostate cancer. In this study population, prostate cancer screening was widespread. In the 5 years preceding the index date, about 40% of cases and the same proportion of controls had been PSA-tested between one and four times, and 36.0% of cases and 47.1% of controls had had five PSA tests, what could be considered to be the equivalent of about one routine PSA test each year, on average, which corresponds to common practice in Montreal. Nearly all (98.8%) cases reported being screened (PSA test and/or digital rectal examination), while 75.2% of controls reported being screened in the 2 years before the index date. It may well be that some of the recent screening tests reported by cases were in fact diagnostic tests based on symptoms, but we have no information to verify this. Sub-analyses restricting controls to those men who reported having been screened for prostate cancer in the previous 5 years yielded results similar to those from the main analyses.

We observed associations previously confirmed in population-based studies, such as higher risks among men of African descent, lower risks among those of Asian descent, and an excess risk with a first-degree family history of prostate cancer.[36 37] It is possible that the observed associations reflect a role for an aetiological factor correlated with traffic-related pollution and unaccounted for in our analyses.

CONCLUSIONS

Exposures to ambient concentrations of NO_2 at the current address were associated with an increased risk of incident prostate cancer. Should traffic-related air pollution prove to be causal, it could explain a large proportion of new cases. It is thus essential that other independent studies be conducted.

What this paper adds

- Geographical variations in the occurrence of prostate cancer are one of its most puzzling characteristics.
- Using a survey conducted in Montreal, Canada, of concentrations of nitrogen dioxide (NO_2) in ambient air, which is a marker for traffic-related air pollution, we developed a spatial map of these concentrations and linked them to the addresses of men with prostate cancer.
- While a handful of studies have examined this relationship, ours is the first to observe an association between exposure to traffic-related air pollution and prostate cancer incidence.

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Notes