



Spatial variations in ambient ultrafine particle concentrations and the risk of incident prostate cancer: A case-control study

Scott Weichenthal^{a,b,*}, Eric Lavigne^{a,c}, Marie-France Valois^{f,g}, Marianne Hatzopoulou^d, Keith Van Ryswyk^a, Maryam Shekarzifard^d, Paul J. Villeneuve^e, Mark S. Goldberg^{f,g}, Marie-Elise Parent^h

^a Department of Epidemiology, Biostatistics, and Occupational Health and Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada

^b Health Canada, Air Health Science Division, Ottawa, Canada

^c Department of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Canada

^d Department of Civil Engineering, University of Toronto, Toronto, Canada

^e Department of Health Sciences, School of Mathematics and Statistics, Carleton University, Ottawa, Ontario, Canada

^f Department of Medicine, McGill University, Montreal, Canada

^g Division of Clinical Epidemiology, Research Institute of the McGill University Hospital Centre

^h INRS-Institut Armand-Frappier, University of Quebec, Montreal, Canada

ARTICLE INFO

Keywords:

Ultrafine particles
Prostate cancer
Case-control study
Diesel exhaust

ABSTRACT

Background: Diesel exhaust contains large numbers of ultrafine particles (UFPs, $< 0.1 \mu\text{m}$) and is a recognized human carcinogen. However, epidemiological studies have yet to evaluate the relationship between UFPs and cancer incidence.

Methods: We conducted a case-control study of UFPs and incident prostate cancer in Montreal, Canada. Cases were identified from all main Francophone hospitals in the Montreal area between 2005 and 2009. Population controls were identified from provincial electoral lists of French Montreal residents and frequency-matched to cases using 5-year age groups. UFP exposures were estimated using a land use regression model. Exposures were assigned to residential locations at the time of diagnosis/recruitment as well as approximately 10-years earlier to consider potential latency between exposure and disease onset. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated per interquartile range (IQR) increase in UFPs (approximately 4000 particles/cm³) using logistic regression models adjusting for individual-level and ecological covariates.

Results: Ambient UFP concentrations were associated with an increased risk of prostate cancer (OR = 1.10, 95% CI: 1.01, 1.19) in fully adjusted models when exposures were assigned to residences 10-years prior to diagnosis. This risk estimate increased slightly (OR = 1.17, 95% CI: 1.01, 1.35) when modeled as a non-linear natural spline function. A smaller increased risk (OR = 1.04, 95% CI: 0.97, 1.11) was observed when exposures were assigned to residences at the time of diagnosis.

Conclusions: Exposure to ambient UFPs may increase the risk of prostate cancer. Future studies are needed to replicate this finding as this is the first study to evaluate this relationship.

1. Introduction

Prostate cancer is the leading cause of cancer incidence in men worldwide, with an estimated 1.4 million new cases annually (Global Burden of Disease Cancer Collaboration, 2015). Age, family history, and race are the only recognized risk factors for this cancer (International Agency for Research on Cancer (IARC), 2014), as well as specific genetic determinants which explain a small portion of familial risk

(Eeles et al., 2014). The environment is suspected to play a role, as geographic variations in disease occurrence have been observed (Klassen and Platz, 2006). Exposure to environmental chemicals may explain some of these patterns. For example, pesticides, arsenic, cadmium, diesel engine emissions, and polycyclic aromatic hydrocarbons have been associated with increased risks of prostate cancer (Aronson et al., 1996; Rybicki, 2006; Koutros, 2013; Coglian et al., 2011), as have occupations potentially entailing chemical exposures

Abbreviations: IARC, International Agency for Research on Cancer; IQR, interquartile range; OR, odds ratio; UFPs, ultrafine particles

* Correspondence to: Department of Epidemiology, Biostatistics, and Occupational Health and Gerald Bronfman Department of Oncology, McGill University, 1020 avenue des Pins Ouest, Montreal, QC, Canada H3A 1A2.

E-mail address: scott.weichenthal@mcgill.ca (S. Weichenthal).

<http://dx.doi.org/10.1016/j.envres.2017.03.035>

Received 22 February 2017; Received in revised form 21 March 2017; Accepted 24 March 2017

0013-9351/ Crown Copyright © 2017 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1

Distributions of selected potential risk factors for prostate cancer and associated age-adjusted odds ratios (OR) and 95% confidence intervals (CI).

	Cases		Controls		Age-adjusted OR	95% CI
	Number	%	Number	%		
Total	1240	100	1246	100		
Age (years)						
< 60	332	26.77	288	23.11	–	–
≥ 60 and < 65	299	24.11	283	22.71	–	–
≥ 66 and < 70	314	25.32	314	25.20	–	–
≥ 70	295	23.79	361	28.97	–	–
Annual family income						
< \$20,000	179	14.44	186	14.93	1	
\$20,000 to \$29,999	184	14.84	172	13.80	1.14	0.85, 1.52
\$30,000 to \$49,999	284	22.90	285	22.87	1.02	0.78, 1.32
\$50,000 to \$79,999	235	18.95	235	18.86	0.99	0.76, 1.31
\$80,000 and more	256	20.65	257	20.63	0.93	0.71, 1.22
Other (Prefer not to respond, Do not know)	102	8.23	111	8.91	0.97	0.69, 1.36
Ancestry						
European	1055	85.08	1030	82.66	1	
Black	101	8.15	66	5.30	1.45	1.05, 2.00
Asian	16	1.29	46	3.69	0.34	0.19, 0.60
Other	56	4.52	94	7.54	0.57	0.40, 0.80
Do not know	12	0.97	10	0.80	1.15	0.49, 2.68
Highest level of schooling						
Elementary school	297	23.95	259	20.79	1	
High school	384	30.97	352	28.25	0.88	0.71, 1.11
College	173	13.95	204	16.37	0.66	0.50, 0.86
University	384	30.97	430	34.51	0.70	0.56, 0.87
Other (Do not know or missing)	2	0.16	1	0.08	1.97	0.18, 21.88
First-degree relative with history of prostate cancer						
No	932	75.16	1087	87.24	1	
Yes	265	21.37	122	9.79	2.54	2.01, 3.20
Do not know	43	3.47	37	2.97	1.32	0.84, 2.07
Marital status						
Married, common law	852	68.71	885	71.03	1	
Separated, divorced, widower	246	19.84	236	18.94	1.09	0.89, 1.33
Single	134	10.81	118	9.47	1.13	0.86, 1.47
Member of religious order, other, or missing	8	0.65	7	0.56	1.28	0.46, 3.57
Maximum body mass index during their lives (kg/m ²)						
< 25.4	312	25.16	307	24.64	1	
≥ 25.4 and < 27.9	315	25.40	307	24.64	1.01	0.81, 1.26
≥ 27.9 and < 31.0	303	24.44	303	24.32	0.99	0.79, 1.24
≥ 31.0	302	24.35	318	25.52	0.93	0.75, 1.17
Unknown	8	0.65	11	0.88	0.78	0.31, 1.97
Smoking status						
Never	351	28.31	339	27.21	1	
Ever	884	71.29	902	72.39	0.95	0.79, 1.13
Missing	5	0.40	5	0.40	1.03	0.30, 3.60
Smoking (pack-years)						
0	351	28.31	339	27.21	1	
> 0 and < 13.75	291	23.47	255	20.47	1.09	0.87, 1.36
≥ 13.75 and < 39.63	272	21.94	349	28.01	0.74	0.60, 0.92
≥ 39.63 and ≤ 225	321	25.89	298	23.92	1.07	0.86, 1.33
Missing	5	0.40	5	0.40	1.04	0.30, 3.62
Per interquartile range of pack-years (39.63)					0.99	0.88, 1.10
Alcohol						
Never	146	11.77	151	12.12	1	
Ever	1056	85.16	1078	86.52	1.02	0.80, 1.30
Missing	38	3.06	17	1.36	2.44	1.32, 4.52
Alcohol consumption (drink-years)						
≥ 0 and < 8.37	300	24.19	308	24.72	1	
≥ 8.37 and < 38.28	294	23.71	313	25.12	0.95	0.76, 1.19
≥ 38.28 and < 96.36	294	23.71	314	25.20	0.95	0.76, 1.19
≥ 96.36 and ≤ 2656	314	25.32	294	23.60	1.14	0.91, 1.43
Missing	38	3.06	17	1.36	2.43	1.34, 4.41
Per interquartile range of drink-weeks (87.99)					1.02	0.97, 1.07
Frequency of fruit and vegetable consumption (per week)						
≤ 6	315	25.40	325	26.08	1	
> 6 and ≤ 9	354	28.55	325	26.08	1.13	0.91, 1.40
> 9 and ≤ 12	282	22.74	305	24.48	0.95	0.75, 1.18

(continued on next page)

Table 1 (continued)

	Cases		Controls		Age-adjusted OR	95% CI
	Number	%	Number	%		
> 12	281	22.66	288	23.11	1.00	0.80, 1.25
Do not know or missing	8	0.65	3	0.24	2.86	0.75, 10.91
Proxy respondent						
No	1200	96.77	1191	95.59	1	
Yes	40	3.23	55	4.41	0.77	0.51, 1.17
Diabetes						
No	1057	85.24	1009	80.98	1	
Yes	180	14.52	236	18.94	0.76	0.61, 0.94
Do not know or missing	3	0.24	1	0.08	2.86	0.30, 27.63
Physical activity						
Not very active	306	24.68	369	29.61	1	
Moderately active	284	22.90	290	23.27	1.18	0.94, 1.48
Very active	645	52.02	586	47.03	1.37	1.14, 1.66
Do not know or missing	5	0.40	1	0.08	6.99	0.81, 60.28
Ambient concentrations of NO ₂ (ppb) at recruitment address from a land use regression model						
NO ₂	IQ = 4.13				1.22	1.09, 1.38
Ambient concentrations of NO ₂ (ppb) at address 10 years prior to recruitment from a land use regression model						
NO ₂	IQ = 4.13				1.09	0.94, 1.26

2486 subjects with UFP assessments on the Island of Montreal; Age was included as a linear effect. ppb, parts per billion.

Table 2

Distribution of ambient concentrations of UFPs, by time since recruitment and by case status.

	No. subjects	Mean	Standard deviation	Minimum	Median	Maximum	Interquartile range
UFPs assigned to recruitment residence							
All subjects	2486	24,263	5256	10,288	23,226	91,056	4140
Prostate cancer cases	1240	24,349	5935	10,288	23,172	91,056	4304
Population controls	1246	24,177	4480	15,964	23,306	77,176	4041
UFPs assigned to residence ~10 years before diagnosis							
All subjects	1625	24,187	5311	14,779	23,058	91,056	4051
Prostate cancer cases	858	24,378	5741	14,779	23,094	91,056	4237
Population controls	767	23,792	4779	15,968	23,021	80,292	3899

(Parent, 2001; Doolan, 2014; Sauvé, 2016). However, other studies have failed to observe associations between occupational exposures to diesel exhaust and prostate cancer (Boers et al., 2005).

More recently, three epidemiological studies examined the association between traffic-related air pollution and prostate cancer incidence. Raaschou-Nielsen et al. (2011) modeled concentrations of nitrogen oxides and the amount of traffic at the residence of participants as indicators of traffic-related air pollution, and reported no association with the incidence of prostate cancer. In contrast, Cohen et al. (2017) noted that exposure to traffic-related air pollution (measured as nitric oxide) was associated with an increased risk of lung, bladder, kidney, and prostate cancer (analyzed as a combined group of cancers) among men in Israel. In Canada, we reported an increased risk of incident prostate cancer with increased exposure to nitrogen dioxide around the residence (Parent et al., 2013).

In this study, we determined the relationship between concentrations of ambient ultrafine particles (UFPs, < 0.1 µm in diameter) and incident prostate cancer in Montreal, Canada. In Canadian metropolitan areas, diesel vehicles are a major source of ambient UFPs (Weichenthal et al., 2015); therefore, spatial differences in UFP concentrations may provide important information on population exposures to diesel exhaust. This is an important point as IARC classifies both diesel engine exhaust (Benbrahim-Tallaa et al., 2012) and outdoor air pollution (Loomis et al., 2013) as Group 1 carcinogens (i.e., carcinogenic to humans); thus, exposure surfaces of outdoor UFP concentrations may provide a useful means of evaluating the long-term health effects of diesel emissions on a population-level.

2. Methods

2.1. Study design

We conducted a population-based case-control study of incident prostate cancer during the years 2005–2009 (referred to as Prostate Cancer and Environment Study; PROtEuS) as described previously (Parent et al., 2013; Blanc-Lapierre, 2015). Briefly, cases included 1933 men (under 76 years of age) identified across the main Franco-phone hospitals that diagnose prostate cancer in the greater Montreal area (Montreal Island as well as the North and South Shores). Cases were all patients newly diagnosed with primary prostate cancer, actively ascertained through pathology departments across French-speaking hospitals in the Montreal area between September 2005 and December 2009. According to the Quebec Cancer Registry, these hospitals covered over 80% of all prostate cancer cases diagnosed in the Montreal region during the study period. A total of 1994 population controls were selected concurrently from the continually updated population-based provincial electoral lists of French-speaking residents of Montreal, and controls were frequency-matched to cases by 5-year age groups. Controls with a history of prostate cancer were excluded. This resulted in an approximate 1:1 case to control ratio. Response rates were 79% for cases and 57% for controls.

In Montreal, citizens have free access to healthcare including prostate cancer screening. At the time of study, prostate cancer screening occurred for most subjects on a yearly basis and information was available on screening practices. We do not have information on

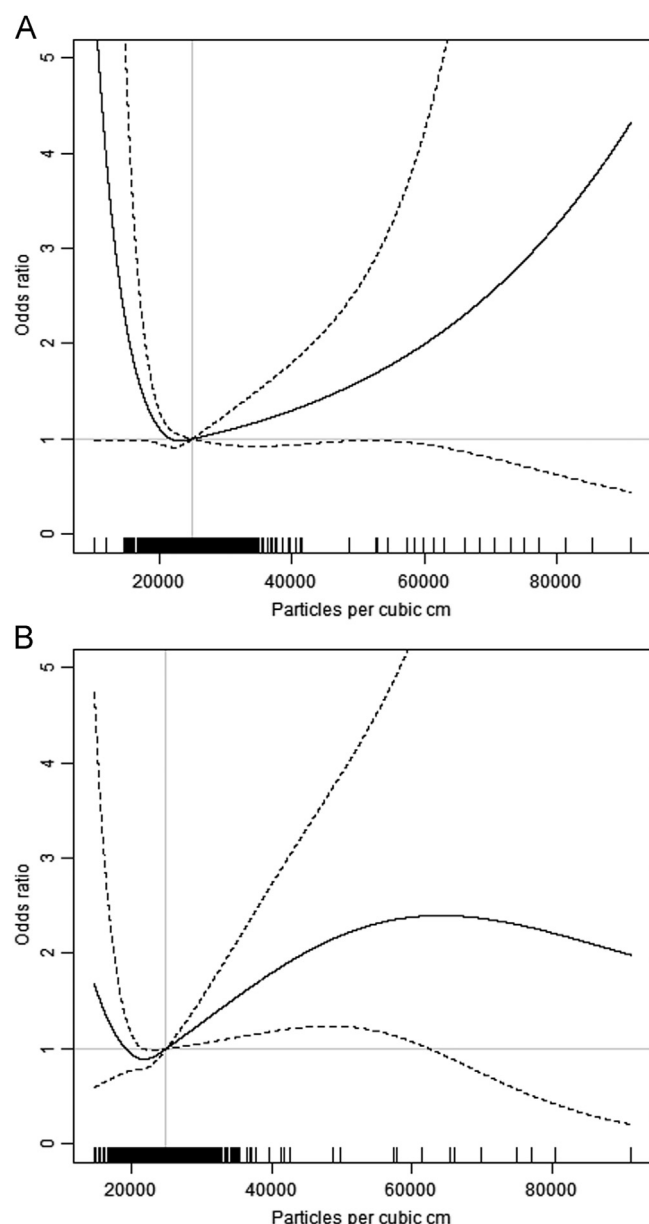


Fig. 1. Concentration-response relationship between ambient UFPs and prostate cancer using concentrations assigned to residences at time of interview (panel A) and 10-years prior to recruitment (panel B), both modeled as a natural cubic spline with 3 degrees of freedom. Models are adjusted for age, personal covariates, and ecological variables from the 1996 Canadian census. The reference concentration is 25,000/cm³ (vertical line). The maximum likelihood estimate is shown as the solid line and the broken lines represent the upper and lower 95% confidence limits.

race for non-participants although most of our sample was of European descent; there were marginal differences in SES indicators between participants and non-participants. The study was approved by the institutional review board of the Institut National de la Recherche Scientifique, along with the ethics committees from the following hospitals: Hôpital Notre-Dame, Hôpital St-Luc, Hôtel-Dieu de Montréal, Hôpital Maisonneuve-Rosemont, Hôpital Jean-Talon, Hôpital Charles-Lemoyne, Hôpital de Fleury, Hôpital du Sacré-Coeur de Montréal, Hôpital Santa Cabrini.

Residential addresses at the time of diagnosis for cases were extracted from hospital records; those of controls were obtained from electoral lists at the time of recruitment. Lifetime residential addresses were elicited through follow-up telephone interviews and geocoded with the ArcGIS geographic information system (GIS, ESRI, Redlands,

CA). Home addresses and geographic coordinates at the index date (diagnosis/interview) were available for all 3927 subjects. Information on home address in 1996 was collected at re-contact for 2891 (74%) subjects; 2646 (92%) of these could be geocoded.

To evaluate the potential for selection bias in the study, we conducted analyses comparing study participants to non-participants in terms of four ecological variables derived from census tract data in 2006 for the address at recruitment. The percentage of subjects living in areas with a greater proportion of recent immigrants within the previous 5 years were 5.2% and 6.0%, for participants and non-participants, respectively. Corresponding values were 6.6% and 7.2% for higher unemployment rate, 19.6% and 20.5% of adults without a high school diploma, and 22.9% and 25.3% for the lowest quintile of household income. These observations suggest that there were small differences between participants and non-participants, with non-participants showing slightly less favourable socio-economic indicators. Mean UFP exposures were also similar among participant cases (24,349/cm³) and non-participant cases (24,267/cm³) as well as participant controls (24,177/cm³) and non-participant controls (24,196/cm³).

Using in-depth, face-to-face interviews, participants provided information on socio-demographic characteristics, lifestyle factors, prostate cancer screening history, detailed occupational histories, and residential address at time of diagnosis for cases or time of interview for controls. In addition, addresses at time of interview were available for all participants and addresses of 88% of participants were available in 1996, corresponding to about 10 years prior to recruitment.

2.2. Exposure assessment

A land use regression model (Weichenthal et al., 2016) was used to estimate ambient concentrations of UFPs at participants' residences across the island of Montreal. Briefly, this model was derived from data collected during a mobile monitoring campaign conducted between 2011 and 2012, and it included information from 414 road segments across Montreal. Model parameters included variables for park space (200-meter buffer), open space (100-meter buffer), local roads (100-meter buffer), length of rail (100-meter buffer), and annual NO_x emissions (100-meter buffer) as well as parameters for long-term average temperature and wind speed in Montreal. The R² value from the land-use regression model was 0.62 and the cross-validation R² was 0.60. This model was used to assign UFP exposures to geocoded addresses or centroids of six-character postal codes. A six-character postal code in urban areas represents a block face or a large apartment complex. Exposures were assigned to addresses at the time of enrollment as well as to addresses in 1996 (approximately 10-years prior to enrollment), to account for potential latency between exposure and disease onset.

2.3. Statistical analysis

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) describing the relationship between interquartile range (IQR) increases in ambient UFP concentrations and the risk of developing prostate cancer. Three separate models were developed in the main analyses with UFP exposures assigned to the recruitment address or the address approximately 10-years prior to recruitment (65% of subjects had the same address at recruitment and 10-years prior to recruitment). We show the results of three models in which different covariates were included. Model 1 adjusted only for age (continuous, linear). Model 2 included additional parameters for personal covariates including ancestry (European, Black, Asian, Other), first-degree relative with history of prostate cancer (Yes, No), highest level of schooling (Elementary, High School, College, University), annual family income (5 categories), marital status (Married or Common Law, Separated, Divorced or Widower, Single,

Table 3

Associations between ambient concentrations of UFPs and the incidence of prostate cancer in Montreal, Canada, 2005–2009.

Analyses	Model 1 ^a		Model 2 ^b		Model 3 ^c	
	OR	95% CI	OR	95% CI	OR	95% CI
UFPs assigned to recruitment residence						
From 3df natural cubic spline, OR evaluated from the 25th–75th percentile	0.98	0.88, 1.09	1.01	0.90, 1.12	1.00	0.89, 1.12
Linear model, evaluated for an increase equal to the interquartile range (4140 cm ⁻³)	1.03	0.97, 1.10	1.04	0.97, 1.11	1.04	0.97, 1.11
UFPs assigned to residence ~10 years before diagnosis						
From 3df natural cubic spline, OR evaluated from the 25th–75th percentile	1.11	0.97, 1.27	1.16	1.01, 1.34	1.17	1.01, 1.35
Linear model, evaluated for an increase equal to the interquartile range (4051 cm ⁻³)	1.06	0.98, 1.15	1.09	1.01, 1.19	1.10	1.01, 1.19

^a Model 1 is adjusted for age.^b Model 2 is adjusted for age as well as personal covariates: ancestry, first-degree relative with history of prostate cancer, highest level of schooling, annual family income, marital status, number of cigarette pack-years during lifetime, drinking status, frequency of fruit and vegetable consumption, proxy status, diabetes, level of physical activity and maximum BMI.^c Model 3 is adjusted for age, personal covariates, and four ecological variables from the 1996 (or 2006) Canadian census: percentage of adults who did not complete high school, median household income, percent of recent immigrants, and unemployment rate.

Member of religious order, Other), cigarette pack-years (quartiles), drink-years (quartiles), frequency of fruit and vegetable consumption (quartiles), proxy status (Self, Other), diabetes (Yes, No), overall physical activity level (Very, Moderately, Not very active), and maximum body mass index during their lifetime (BMI, in kg/m²) (as a natural spline with 2 degrees of freedom). Model 3 included additional contextual variables from the 2006 (or 1996 for addresses 10-years prior to recruitment) Canadian Census (within a 1000-meter radius): percentage of adults who did not complete high school (as a linear effect), median household income (as a linear effect), percent of recent immigrants (as a linear effect), and unemployment rate (as a linear effect). Missing values were included as their own category. Continuous covariates were modeled as natural cubic spline functions (Cao et al., 2006), using 2 or 3 degrees of freedom (df), with linear terms used if there was no evidence of non-linearity. For continuous variables, missing values resulted in the subject being dropped from the analysis.

As sensitivity analyses we included smoking and alcohol consumption using natural cubic splines instead of as categorical variables and we also developed models that additionally adjusted for ambient NO₂ (natural spline, 2 df) using a land use regression model developed by Crouse et al. (2010). Further sensitivity analyses were conducted limiting the control population only to those subjects who were screened for prostate cancer by prostate specific antigen and/or digital rectal exam (and tested negative) in the 2-years prior to the interview to reduce the likelihood of undiagnosed cancers. Finally, we created separate models for more aggressive cancers (Gleason score > 7, or 7 with primary pattern of 4 and secondary pattern of 3) and less aggressive cancers (Gleason score < 7, or 7 with primary pattern of 3 and secondary pattern of 4). Statistical interactions were evaluated by including first-order interaction terms and through stratified analyses.

3. Results

Our analysis included 1240 prostate cases and 1246 controls. As expected, race and family history of prostate cancer were identified as independent risk factors for prostate cancer but few of the other individual-level covariates were associated with the risk of developing the disease (Table 1). Ambient NO₂ concentrations at recruitment addresses were associated with an increased risk of prostate cancer (Table 1). Ambient concentrations of UFPs varied substantially across the Island, ranging from approximately 10,000/cm³ to more than 90,000/cm³ (Table 2). Mean concentrations of UFPs were similar among participants and non-participants for both cases (participants: 24,249/cm³; non-participants: 24,479/cm³) and controls (participants: 24,177/cm³; non-participants: 24,196/cm³). The Spearman correlation coefficients between ambient UFPs and NO₂ were 0.19 for exposures assigned to the recruitment address and 0.22 for exposures assigned 10-years prior to enrollment.

Fig. 1 shows the fully-adjusted (i.e. Model 3) exposure response functions for concentrations of UFPs evaluated at their residence at time of interview (Panel A) and approximately 10 years prior to enrollment (Panel B). Both curves show a j-shaped relationship, although the 95% CIs were wide at low concentrations (< 20,000/cm³). These somewhat large confidence intervals were a result of relatively few numbers of cases and controls exposed; e.g., for current address, the number of cases and controls exposed at concentrations 20,000/cm³ and less were 92 and 80, respectively (for address 10 years before interview, 61 cases and 53 controls). For larger values of UFPs, both response curves were consistent with a linear response between approximately 25,000 and 60,000 particles/cm³, and with greater model uncertainty outside this exposure range.

Table 3 shows the detailed results for UFP exposures assigned at the time of interview and approximately 10 years prior to enrollment using the fitted non-linear response function as well as those assuming a linear relationship throughout the entire range of UFP values. For exposures assigned at time of interview there was little increase in risk observed between the 25th and 75th percentiles in non-linear models; increases in risk of about 3–4% per IQR were observed if a linear relationship was assumed. Stronger associations were observed for UFP exposures assigned 10 years before time of interview. Notably, as suggested by the increase in the response curve shown in Panel B of Fig. 1, the risks for a change in concentrations of UFPs from the 25th to the 75th percentiles were much higher than for an assumed linear relationship. Specifically, the OR from the 25th and 75th percentiles was 1.17 (95% CI: 1.01–1.35) as compared to an OR of 1.10 (95% CI: 1.01–1.19) for the linear model. The lower risks for the linear model are due to the j-shaped form at lower concentrations and the convex curve at high concentrations.

We found no evidence of interactions with any of the variables (results not shown). In sensitivity analyses including additional adjustment for NO₂ in the models (over the same time frame as UFPs), UFP exposures 10-years prior to enrollment remained associated with prostate cancer (linear model, OR = 1.11, 95% CI: 2.0, 22) with a smaller risk observed for exposures assigned to residences at enrollment (linear model, OR = 1.03, 95% CI: −0.96, 1.10). Similarly, results did not change when analyses were limited to controls who were screened for prostate cancer in the 2-years prior to recruitment (results not shown).

Finally, analyses according to Gleason score classifications suggested stronger associations with less aggressive cancers although confidence intervals overlapped considerably between low- and high-grade categories. Specifically, each interquartile change in UFP exposures 10-years prior to enrollment was associated with an increased risk of less aggressive prostate cancers (OR = 1.12, 95% CI: 1.02, 1.23) whereas a smaller risk was observed for more aggressive cancers (OR = 1.05, 95% CI: 0.93, 1.19).

4. Discussion

Prostate cancer is one of the most common cancers among men but uncertainty remains with respect to environmental exposures that may impact the likelihood of disease onset. In this population-based case-control study in Montreal, Canada, we determined the relationship between ambient UFPs near participants' residences and the incidence of prostate cancer. Our findings suggest that ambient UFP exposures may contribute to increased prostate cancer incidence. Although the chronic health effects of UFPs have not been evaluated in many epidemiological studies, these pollutants are an important component of diesel exhaust (a known human carcinogen) and thus may contribute to the development of cancer in exposed populations.

Oxidative stress is one of the primary mechanisms thought to play an important role in air pollution health effects including carcinogenicity (Li et al., 2003; Khandrika et al., 2009; Reuter et al., 2010; Weichenthal et al., 2013). Since UFPs are known to reach the systemic circulation soon after exposure (Nemmar et al., 2002), and increase systemic inflammation and oxidative stress (Traboulsi et al., 2017), this may be one mechanism through which UFPs increase the risk of prostate cancer. Alternatively, the spatial distribution of UFPs may serve as a marker for a complex mixture of traffic pollutants including metals or PAHs which may also increase oxidative stress and cancer risk (Kooiman et al., 2000; Valko et al., 2006). New assays are currently available to characterize the oxidative potential of particulate air pollution (Ayres et al., 2008) and future studies should evaluate if particle oxidative potential metrics are more strongly associated with cancer risk than tradition mass or number-based exposure metrics.

The j-shaped response function observed in this study is rather counter-intuitive in terms of carcinogenic exposures, as one would expect a monotonically-increasing association. The j-shaped response function, which was less apparent when evaluated 10 years before interview, persisted throughout most of our sub-analyses. We had the opportunity to evaluate whether there could be some selection effects at low concentrations, as our response rates were not high and there was a difference in response between cases and controls. As part of the identification of all subjects, we obtained current addresses of all possible participants and, thus, we were able to evaluate an unadjusted response function for UFPs. The fitted curve at time of identification for all non-participants and participants combined was consistent with linearity (results not shown) especially at low concentrations. Thus, it is likely that the true response in this target population is linear and that the j-shaped part of the curve was an artifact due to sampling or perhaps residual confounding. Of importance was that concentrations of UFPs were similar for participants and non-participants among cases and controls and our comparison of participants and non-participants in terms of socio-demographic indicators (income, unemployment, education, % of recent immigrants) derived from census data suggested minimal differences, arguing against selection bias. In addition, known risk factors (race and family history) were associated with increased prostate cancer incidence in our population (as expected) and this too supports the validity of our observations.

To our knowledge, this is the first study to determine the potential association between UFPs and the incidence of prostate cancer. In the present study, we observed positive associations between UFPs and prostate cancer and found that this association was independent of NO₂, suggesting that these two measures of traffic-related air pollution may capture different aspects of the overall air pollution mixture. Indeed, outdoor concentrations of UFPs and NO₂ estimated using land use regression models were only weakly correlated (~0.2) and this correlation is consistent with data previously reported for personal UFP and NO₂ exposures in Montreal (Weichenthal et al., 2014a, 2014b). In Canada, we have repeatedly observed that UFPs are strongly associated with emissions from diesel vehicles (Weichenthal et al., 2014b, 2015); therefore, our results may primarily reflect the impact of diesel emissions on prostate cancer risk. More generally, our findings

are also consistent with two previous studies that reported positive associations between traffic-related air pollution (measured as NO or NO₂) and prostate cancer (Parent et al., 2013; Cohen et al., 2017).

Studies of risk factors for prostate cancer typically explore differences by disease aggressiveness. Not only are aggressive cancers of greater clinical significance, there is also evidence that risk factors or predictors differ between less and more aggressive cancers (Demoury, 2016). In this study, positive associations between exposure to UFPs and prostate cancer were observed for both high-grade and low-grade cancers; point estimates were somewhat higher for the latter but confidence intervals overlapped.

While this study had several advantages including detailed spatial scale estimates of ambient UFPs concentrations, past residential history, and individual-level information on confounding factors it is important to note several limitations. First, our exposure model for UFPs was developed in 2011–2012 and thus reflects spatial patterns in ambient UFP concentrations slightly after the identification of incident cases/controls. As spatial patterns in ambient UFP concentrations depend largely on patterns of diesel traffic (which tend to be concentrated on major roadways), spatial differences over time have likely remained stable. However, overall air pollution concentrations have decreased over time and thus our estimated UFP concentrations likely underestimate absolute exposure levels in the past owing to improvements in vehicle efficiency and emissions regulations. In addition, our exposure model did not account for other combustion sources of air pollution (e.g. residential wood burning) and thus non-differential exposure measurement error almost certainly had an impact on our results. In addition, since UFP exposures were assigned to residential locations we do not have information on exposures away from the home. This is an important consideration as UFP have high spatial variability and this measurement error likely biased our risk estimates toward the null. Future studies should aim to capture additional combustion sources of air pollution and integrate mobility information into the exposure assessment process in order to reduce exposure misclassification.

5. Conclusions

Our findings suggest that exposure to ambient UFPs may increase the risk of incident prostate cancer. This is the first study to examine the relationship between ambient UFPs and prostate cancer and our findings require replication.

Competing financial interest

The authors declare no conflict of interest.

Acknowledgements

Analyses for this study were funded by Health Canada. Dr. Weichenthal received support from a GRePEC salary award funded by the Cancer Research Society, the Quebec Ministry of Economy, Science and Innovation, and FRQS (Fonds de Recherche du Québec - Santé). The prostate cancer study was funded through grants from the Canadian Cancer Society (grant numbers 13149, 19500, 19864 and 19865) and the Cancer Research Society in partnership with the FRQS and the Ministère de l'enseignement supérieur, recherche, science et technologie du Québec. Marie-Élise Parent held a career award from the FRQS.

References

- Aronson, K.J., Siemiatycki, J., Dewar, R., Gerin, M., 1996. Occupational risk factors for prostate cancer: results from a case-control study in Montreal, Quebec, Canada. *Am. J. Epidemiol.* 143 (4), 363–373.
- Ayres, J.G., Borm, P., Cassee, F.R., Castranova, V., Donaldson, K., Ghio, A., Harrison, R.M., Hider, R., Kelly, F., Kooter, I.M., 2008. Evaluating the toxicity of airborne particulate matter and nanoparticles by measuring oxidative stress potential - a workshop report and consensus statement. *Inhal. Toxicol.* 20, 75–99.

- Benbrahim-Tallaa, L., Baan, R.A., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., Bouvard, V., Guha, N., Loomis, D., Straif, K., 2012. on behalf of the IARC Monograph working Group. carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. *Lancet Oncol.* 13, 663–664.
- Blanc-Lapierre, A., Spence, A., Karakiewicz, P.I., Aprikian, A., Saad, F., Parent, M.É., 2015. Metabolic syndrome and prostate cancer risk in a population-based case-control study in Montreal, Canada. *BMC Public Health* 15, 913.
- Boers, D., Zeegers, M.P.A., Swaen, G.M., Kant, I.J., van den Brandt, P.A., 2005. The influence of occupational exposures to pesticides, polycyclic aromatic hydrocarbons, diesel exhaust, metal dust, metal fumes, and mineral oil on prostate cancer: a prospective cohort study. *Occup. Environ. Med.* 62, 531–537.
- Cao, J., Valois, M.F., Goldberg, M.S., 2006. An S-Plus function to calculate relative risks for regression models using natural splines. *Comput. Methods Prog. Biomed.* 84, 58–62.
- Cogliano, V.J., Baan, R., Straif, K., Grosse, Y., Lauby-Secretan, B., Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Freeman, C., Balichet, L., Wild, C.P., 2011. Preventable exposures associated with human cancers. *J. Natl. Cancer Inst.* 103, 1827–1839.
- Cohen, G., Levy, I., Yuval, Kark J.D., Levin, N., Broday, D.M., Steinberg, D.M., Gerber, Y., 2017. Long-term exposure to traffic-related air pollution and cancer among survivors of myocardial infarction: a 20-year follow-up study. *Eur. J. Prev. Cardiol.* 24, 92–102.
- Crouse, D.L., Goldberg, M.S., Ross, N.A., Chen, H., Labreche, F., 2010. Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case-control study. *Environ. Health Perspect.* 118, 1578–1583.
- Demoury, C., Karakiewicz, P., Parent, M.E., 2016. Association between lifetime alcohol consumption and prostate cancer risk: a case-control study in Montreal, Canada. *Cancer Epidemiol.* 45, 11–17.
- Doolan, G., Benke, G., Giles, G., 2014. An update on occupation and prostate cancer. *Asian Pac. J. Cancer Prev.* 15, 501–516.
- Eeles, R., Goh, C., Castro, E., Bancroft, E., Guy, M., Olama, A.A.A., et al., 2014. The genetic epidemiology of prostate cancer and its clinical implications. *Nat. Rev. Urol.* 11, 18–31.
- Global Burden of Disease Cancer Collaboration, 2015. The global burden of cancer 2013. *JAMA Oncol.* 1, 505–527.
- International Agency for Research on Cancer, 2014. *World Cancer Report: Chapter 5.11 Cancers of the Male Reproductive Organs*. In: Steward, Bernard W., Wild, Christopher P. (eds.).
- Khandrika, L., Kumar, B., Koul, S., Maroni, P., Koul, H.K., 2009. Oxidative stress in prostate cancer. *Cancer Lett.* 282, 125–136.
- Klassen, A.C., Platz, E.A., 2006. What can geography tell us about prostate cancer? *Am. J. Prev. Med.* 30 (Suppl. 2), S7–S15.
- Kooiman, G.G., Martin, F.L., Williams, J.A., Grover, P.L., Phillips, D.H., Muir, G.H., 2000. The influence of dietary and environmental factors on prostate cancer risk. *Prostate Cancer Prostatic Dis.* 3, 256–258.
- Koutros, S., Beane Freeman, L.E., Lubin, J.H., Heltshe, S.L., Andreotti, G., Barry, K.H., et al., 2013. Risk of total and aggressive prostate cancer and pesticide use in the agricultural health study. *Am. J. Epidemiol.* 177 (1), 59–74.
- Li, N., Hao, M., Phalen, R.F., Hinds, W.C., Nel, A.E., 2003. Particulate air pollution and asthma: a paradigm for the role of oxidative stress in PM-induced adverse health effects. *Clin. Immunol.* 109, 250–265.
- Loomis, D., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Baan, N., Mattock, H., Straif, K., 2013. on behalf of the IARC Monograph working Group. The carcinogenicity of outdoor air pollution. *Lancet Oncol.* 14, 1262–1263.
- Nemmar, A., Hoet, P.H., Vanquickenborne, B., Dinsdale, D., Thomeer, M., Hoylaerts, M.F., Vanbilloen, H., Mortelmans, L., Nemery, B., 2002. Passage of inhaled particles into the blood circulation in humans. *Circulation* 105, 411–414.
- Parent, M.E., Siemiatycki, J., 2001. Occupation and prostate cancer. *Epidemiol. Rev.* 23, 138–143.
- Parent, M.E., Goldberg, M., Crouse, D.L., Ross, N.A., Chen, H., Valois, M.F., Liautaud, A., 2013. Traffic-related air pollution and prostate cancer risk: a case-control study in Montreal, Canada. *Occup. Environ. Med.* 70, 511–518.
- Raaschou-Nielsen, O.I., Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Sørensen, M., Hansen, J., Loft, S., Overvad, K., Tjønneland, A., 2011. Air pollution from traffic and cancer incidence: a Danish cohort study. *Environ. Health* 10, 67.
- Reuter, S., Gupta, S.C., Chaturvedi, M.M., Aggarwal, B.B., 2010. Oxidative stress, inflammation, and cancer: how are they linked? *Free Rad. Biol. Med.* 49, 1603–1616.
- Rybicki, B.A., Neslund-Dudas, C., Nock, N.L., Schultz, L.R., Eklund, L., Rosbalt, J., Bock, C.H., Monaghan, K.G., 2006. Prostate cancer risk from occupational exposure to polycyclic aromatic hydrocarbons interacting with the GSTP1 Ile105Val polymorphism. *Cancer Detect. Prev.* 30, 412–422.
- Sauvé, J.F., Lavoué, J., Parent, M.E., 2016. Occupation, industry, and the risk of prostate cancer: a case-control study in Montréal, Canada. *Environ. Health* 15, 100.
- Traboulsi, H., Guerrina, N., Lu, M., Maysinger, D., Ariya, P., Bagloli, C.J., 2017. Inhaled pollutants: the molecular scene behind respiratory and systemic diseases associated with ultrafine particulate matter. *Int. J. Mol. Sci.* 18, 243.
- Valko, M., Rhodes, C.J., Moncol, J., Izakovic, M., Mazur, M., 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem. Biol. Interact.* 160, 1–40.
- Weichenthal, S., Godri-Pollitt, Villeneuve, P.J., 2013. PM2.5 oxidant defence and cardiorespiratory health: a review. *Environ. Health* 12, 40.
- Weichenthal, S., Hatzopoulou, M., Goldberg, M., 2014a. Exposure to traffic-related air pollution during physical activity and acute changes in blood pressure, autonomic and micro-vascular function in women: a cross-over study. *Part. Fibre Toxicol.* 11, 70.
- Weichenthal, S., Farrell, W., Goldberg, M., Joseph, L., Hatzopoulou, M., 2014b. Characterizing the impact of traffic and the built environment on near-road ultrafine particle and black carbon concentrations. *Environ. Res.* 132, 305–310.
- Weichenthal, S., Van Ryswyk, K., Kulka, R., Sun, L., Wallace, L., Joseph, L., 2015. In-vehicle exposures to particulate air pollution in Canadian metropolitan areas: the urban transportation exposure study. *Environ. Sci. Technol.* 49, 597–605.
- Weichenthal, S., Ryswyk, K.V., Goldstein, A., Bagg, S., Shekharizfard, M., Hatzopoulou, M., 2016. A land use regression model for ambient ultrafine particles in Montreal, Canada: a comparison of linear regression and a machine learning approach. *Environ. Res.* 146, 65–72.