Preventive Medicine 122 (2019) 91–99

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Estimates of the current and future burden of lung cancer attributable to $PM_{2.5}$ in Canada

Priyanka Gogna[a], Tasha A. Narain[a], Dylan E. O'Sullivan[a], Paul J. Villeneuve[b], Paul A. Demers[c], Perry Hystad[d], Darren R. Brenner[e,f,g], Christine M. Friedenreich[e,f,g], Will D. King[a,*], on behalf of the ComPARe Study Team[1]

[a] Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada
[b] Department of Health Sciences, Carleton University, Ottawa, Ontario, Canada
[c] Occupational Cancer Research Centre, Toronto, Ontario, Canada
[d] College of Public Health and Human Sciences, Oregon State University, Corvallis, OR, USA
[e] Department of Cancer Epidemiology and Prevention Research, Cancer Control Alberta, Alberta Health Services, Calgary, Alberta, Canada
[f] Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[g] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

ARTICLE INFO

Keywords:
Cancer
$PM_{2.5}$
Population attributable risk
Air pollution
Potential impact fraction
Prevention

ABSTRACT

The International Agency for Research on Cancer has classified $PM_{2.5}$ (fine particulate matter, $PM_{2.5}$) as a lung cancer carcinogen in humans. We estimated the proportion of lung cancer cases attributable to $PM_{2.5}$ exposure in Canada in 2015, and future avoidable cancers over the period 2016–2042 under different future exposure scenarios. A meta-analysis was conducted to estimate the relative risk of lung cancer associated with $PM_{2.5}$ that was generalizable to Canada. A population-weighted Canadian distribution of residential $PM_{2.5}$ exposure was estimated annually using ecological-level, satellite-derived $PM_{2.5}$ data for the period 1990 to 2009. Population attributable risks (PAR) were estimated for $PM_{2.5}$ and applied to lung cancer incidence from the Canadian Cancer Registry. Potential impact fractions based on counterfactual scenarios for the year 2042 were estimated, along with cumulative preventable cases from 2016 to 2042. The relative risk of lung cancer associated with $PM_{2.5}$ was 1.09 (95% CI: 1.06–1.12) per an increase of 10 $\mu g/m^3$. The average population-weighted exposure to $PM_{2.5}$ corresponding to a 20-year exposure window from 1990 to 2009 was 8.3 $\mu g/m^3$. The PAR for $PM_{2.5}$ was estimated at 6.9%, accounting for 1739 attributable lung cancer cases in 2015. If patterns of decline in $PM_{2.5}$ continue, over 3000 lung cancer cases could be prevented between 2016 and 2042. Exposure to $PM_{2.5}$ contributes to a considerable burden of lung cancer in Canada and policies aimed at sustaining outdoor $PM_{2.5}$ declines are important for lung cancer prevention in Canada.

1. Introduction

Outdoor air pollution is a complex mixture containing a number of known carcinogens – several of which are classified by the International Agency of Research on Cancer (IARC) as group 1 (benzo[*a*]pyrene), group 2A (creosotes, cyclopenta(cd)pyrene, dibenz(a,j)acridine, dibenz (a,h)anthracene, 1-nitropyrene) and 2B (naphthalene, dibenzo(a,l) pyrene, indeno (1,2,3-cd)pyrene) carcinogens (IARC, 2016).

* Corresponding author at: Queen's University, Carruthers Hall, 62 Fifth Field Company Lane, 2nd floor, Kingston, Ontario K7L 3N6, Canada.
E-mail address: kingw@queensu.ca (W.D. King).

[1] Additional members of the ComPARe study team Stephen Walter, Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada; Eduardo Franco, Gerald Bronfman Department of Oncology, Division of Cancer Epidemiology, McGill University, Montréal, Québec, Canada; Prithwish De, Cancer Care Ontario, Toronto, Ontario, Canada; Leah Smith, Canadian Cancer Society, Toronto, Ontario, Canada; Abbey Poirier, Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Calgary, Alberta, Canada; Yibing Ruan, Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Calgary, Alberta, Canada; Xin Grevers, Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services, Calgary, Alberta, Canada; Elizabeth Holmes, Canadian Cancer Society, Toronto, Ontario, Canada; Karena Volesky, Gerald Bronfman Department of Oncology, Division of Cancer Epidemiology, McGill University, Montréal, Québec, Canada; Zeinab El-Masri, Cancer Care Ontario, Toronto, Ontario, Canada; Robert Nuttall, Canadian Cancer Society, Toronto, Ontario, Canada; Mariam El-Zein, Gerald Bronfman Department of Oncology, Division of Cancer Epidemiology, McGill University, Montréal, Québec, Canada.

https://doi.org/10.1016/j.ypmed.2019.03.010

Epidemiologic studies have reported associations between various measures of air pollution and lung cancer, including particulate matter ($PM_{2.5}$ and PM_{10} [particles with an aerodynamic diameter ≤ 2.5 μm and ≤ 10 μm, respectively]), nitrogen dioxide (NO_2), and other traffic-related air pollutants. Fine particulate matter ($PM_{2.5}$) consists of airborne particles resulting from chemical reactions in the atmosphere, and through fuel combustion. These particles can also carry metals and other carcinogens (Sarti et al., 2015), and are able to reach deep into lung tissue causing inflammation, oxidative stress, and alterations to the DNA methylome (Baccarelli et al., 2009; Buschini et al., 2001; Stuart, 1984). The most consistent air pollution exposure in relation to lung cancer risk has been with $PM_{2.5}$, and it has been classified as a carcinogen by IARC (Loomis et al., 2013).

The level and composition of $PM_{2.5}$ varies considerably across international studies examining the association between $PM_{2.5}$ and lung cancer risk (Loomis et al., 2013). A recent analysis by the World Health Organization (WHO) estimates the world average $PM_{2.5}$ exposure in 2016 at 39.6 $\mu g/m^3$. Average levels exceed 60 $\mu g/m^3$ in several African, Asian, and Eastern Mediterranean countries, including Niger, Chad, Nepal, India, Qatar, and Saudi Arabia. In contrast, both Canada and the United States consistently report average levels below 10 $\mu g/m^3$ (World Health Organization, 2018).

There is emerging evidence that the carcinogenic potential of air pollution is determined by its composition, so that differential risks in lung cancer mortality can occur at the same mass of $PM_{2.5}$ particles (Weichenthal et al., 2016). Consequently, the relative risks (RR) from studies conducted in other countries and published meta-analyses may not apply to exposures experienced in Canada (Hamra et al., 2014). All Canadians are exposed to some level of $PM_{2.5}$, and although exposure levels in Canada are typically lower than those in other countries, studies have shown that even at low levels $PM_{2.5}$ is associated with an increased risk of lung cancer (Hamra et al., 2014, 2015; Pope III et al., 2011).

Lung cancer is the most diagnosed, and the leading cause of cancer-related mortality in Canada. Projections show that approximately 28,600 Canadians were diagnosed with lung cancer in 2017, with slightly higher incidence in males compared to females. Incident rates of lung cancer in men and women have been declining since 2006. Although smoking is the strongest risk factor for lung cancer in Canada, occupational and environmental exposures have also been well established as lung cancer risk factors (Canadian Cancer Statistics Advisory Committee, 2018).

While the proportion of lung cancer cases attributable to air pollution has been estimated for Alberta (Poirier et al., 2017), Ontario (Cancer Care Ontario, 2016), Europe (Vineis et al., 2007), and worldwide (Cohen et al., 2005), no study has estimated the related burden for all of Canada. We estimated the burden of lung cancer associated with $PM_{2.5}$ in Canada through population attributable risks (PARs) and potential impact fractions (PIFs). This work focused on established exposure-disease relationships supported by IARC, and therefore, only the burden of lung cancer attributable to $PM_{2.5}$ was assessed.

2. Methods

2.1. Overview

The ComPARe Study aims to assess the burden of cancer from several modifiable risk factors in the Canadian population. The general methods used in the estimation of PARs and PIFs for all modifiable exposures that are part of the ComPARe Study have been previously published (Brenner et al., 2018).

For our analyses, the RR of $PM_{2.5}$ exposures in relation to lung cancer were assumed to follow a log-linear, dose-response pattern for continuous exposures representing the population exposure distribution during a 20-year exposure window. The RR for $PM_{2.5}$ was estimated from a meta-analysis of Canadian studies. Satellite-derived measures were used to estimate $PM_{2.5}$ at the census subdivision level (Hystad et al., 2011; van Donkelaar et al., 2015). Census population data were used to obtain a population weighted exposure distribution for $PM_{2.5}$, and PAR and attributable cases were estimated for 2015 (Statistics Canada, 2002; Statistics Canada, 2007; Statistics Canada, 2012; Statistics Canada, 2017). PIFs and preventable cases were estimated for the time period 2016 to 2042 using several counterfactual scenarios. PARs, PIFs as well as attributable and preventable cases were estimated for Canada as a whole and by province.

2.2. Relative risk estimates

For our meta-analysis, we built on a previously conducted pooled analysis by Hamra et al. (2014). This analysis considered all published cohort and case-control studies on the relationship between $PM_{2.5}$ and lung cancer, and provided individual outcome information (Hamra et al., 2014). We updated their search in August 2018, using identical inclusion and search criteria, with the exception of limiting studies to those conducted in Canada. To be included, studies must have provided quantitative estimates of residential exposure to $PM_{2.5}$, and risk estimates for the relationship between residential $PM_{2.5}$ and lung cancer per 10 $\mu g/m^3$, or in units that would allow for conversion to these measures (Hamra et al., 2015). Studies in which there was implication of considerable overlap in study populations based on the period over which data was collected were assessed for inclusion. For these, the study with the highest number of events was selected.

Potentially relevant studies for $PM_{2.5}$ exposure were identified and consensus for inclusion was reached after independent review by PG and WK using the above described inclusion criteria. RR estimates that adjusted for the maximum number of individual-level and neighbourhood-level covariates were extracted. All studies adjusted for age, sex, occupation, smoking, education, and socio-economic status indicators, as well as several other lifestyle and ecological variables, depending on the study. Given the potential for colinearity between $PM_{2.5}$ and NO_2 exposures, risk estimates simultaneously adjusting for both exposures were not used.

Where required, RR estimates were converted to represent the change in lung cancer risk per 10 $\mu g/m^3$ increase in exposure to $PM_{2.5}$ (Hamra et al., 2014). Standard errors were estimated from confidence intervals, and studies included in meta-analyses were weighted by the inverse of the variance of the RR estimate. Heterogeneity was quantitatively assessed with the Q and I^2 statistics. If statistically significant heterogeneity was present, a random effects model was employed, otherwise a fixed effects model was assumed. Publication bias was assessed with Egger's weighted linear regression and Begg's rank correlation tests.

2.3. Statistical methods

2.3.1. Current cancer burden (2015)

2.3.1.1. Exposure prevalence. The use of an exposure window and latency period to assess relationships between $PM_{2.5}$ and lung cancer is heterogeneous, however, studies typically report a range between 20 and 30 years, often using “latency” or “lag” to describe the time from first exposure to diagnosis. We chose a 20-year exposure window with a five-year latency period to represent the relationship between $PM_{2.5}$ exposure and lung cancer risk, which is in accordance with previous descriptions of lung cancer exposure and latency periods (Finkelstein, 1991; Hu and Jiang, 2014; Hystad et al., 2013; Rothman, 1981; Siemes et al., 2006).

Canada-wide estimates for $PM_{2.5}$ were available from satellite-derived data by census subdivision for the years 1990 to 2009 (Hystad et al., 2011; van Donkelaar et al., 2015). Census subdivisions were used as the geographic unit for analysis because of their correspondence with Canadian municipalities, population data, and their relatively consistent definitions across census years. Considering the low variability

in $PM_{2.5}$ exposures compared to other pollutants in Canadian cities, use of census subdivisions as the geographic unit of analysis was deemed appropriate (Villeneuve et al., 2015). These estimates were averaged to represent 20-year exposure windows, and weighted to the population estimate closest to the midpoint of the exposure window (2001). Age- and sex-specific data on $PM_{2.5}$ exposure was not available.

2.3.1.2. Cancer incidence. Lung cancer incidence data for 2015 were obtained from the Canadian Cancer Registry at both the national and provincial level, and were used to estimate attributable cases for $PM_{2.5}$. Lung cancer incidence data were only available as a combined estimate for the three Canadian territories.

2.3.1.3. Population attributable risk (PAR). PARs were estimated using the following formula (Drescher and Becher, 1997; Murray et al., 2003).

$$PAR = \frac{\int_{x=0}^{m} RR(x)P(x)dx - 1}{\int_{x=0}^{m} RR(x)P(x)dx}$$

Where $RR(x)$ is the RR at exposure x; $P(x)$ is the population distribution of exposure; m is the maximum exposure level.

A simplified approach to estimate 95% CIs for the PAR of a continuous exposure was utilized (Daly, 1998). This approach involved calculating the upper and lower bound of the 95% CI for associated PARs by applying the lower and upper 95% CI from the pooled RR estimate.

2.3.2. Future cancer burden (2042)

2.3.2.1. Prevalence of exposure projections. Projection of future $PM_{2.5}$ distributions was based on the average exposure for the years 2010 to 2014, assuming that levels have stabilized and exposures would remain unchanged.

2.3.2.2. Cancer incidence projections. Cancer incidence data were available from 1983 to 2015, and were used to project cancer incidence for each year up to 2042 (Brenner et al., 2018). Province-specific incidence cases were projected to 2038. Sex-specific incidence for lung cancer was projected using Poisson-based age cohort models. Further details on model selection can be found elsewhere (Poirier et al., 2019).

2.3.2.3. Counterfactual scenarios. Counterfactual air pollution scenarios were applied at the census subdivision level, prior to population weighting, assuming that counterfactual scenarios represent changes in $PM_{2.5}$ and not population distributions. To estimate the number of lung cancer cases that could be avoided by 2042, we considered two counterfactual scenarios for $PM_{2.5}$ exposure. The first counterfactual was based on a 50% reduction in exposure by 2036. The second counterfactual was a continued decline in exposure from 2015 to 2036 based on trends observed to date. Trends in $PM_{2.5}$ were examined using data available for the years 1980–2014 (Hystad et al., 2011; van Donkelaar et al., 2015). Spline curve modelling (degree = 1 and knots = 2) indicated an inflection point at 1993 and therefore data from 1993 to 2014 was used to model $PM_{2.5}$ trends. A linear model of the effect of log(year) and census subdivision on $PM_{2.5}$ levels was generated.

For both counterfactual exposure distributions, estimates were averaged to represent 20-year exposure windows and weighted to the population estimate at the midpoint of the exposure window using population data by census subdivision from Statistics Canada for years 2001, 2006, 2011, and 2016 (Statistics Canada, 2002; Statistics Canada, 2007; Statistics Canada, 2012; Statistics Canada, 2017). Yearly populations between census years were estimated using weighted averages from census data surrounding the year.

2.3.2.4. Potential impact fraction. PIFs were estimated for different counterfactual exposure distributions for $PM_{2.5}$ using the following formula (Drescher and Becher, 1997; Murray et al., 2003).

$$PIF = \frac{\int_{x=0}^{m} RR(x)P(x)dx - \int_{x=0}^{m} RR(x)P'(x)dx}{\int_{x=0}^{m} RR(x)P(x)dx}$$

Where $RR(x)$ is the RR at exposure x; $P(x)$ is the population distribution of exposure; $P'(x)$ is the counterfactual distribution of exposure; m is the maximum exposure level.

Ethics approval was granted for this project by the Health Research Ethics Board of Alberta - Cancer Committee (HREBA.CC-14-0220_REN4) and the Queen's University Health Sciences Research Ethics Board (File # 6015362).

3. Results

3.1. Relative risk estimates for air pollution exposures

The meta-analysis for $PM_{2.5}$ incorporated one Canadian study reported by Hamra et al. prior to 2014 (Hystad et al., 2013). Table 1 summarizes this study along with seven $PM_{2.5}$ studies based on large Canadian populations published since the Hamra et al., 2014 review. This list includes two studies from the Canadian National Breast Screening Study (Tomczak et al., 2016; Villeneuve et al., 2015), three studies from the Canadian Census Health and Environment Cohort (Crouse et al., 2015; Pinault et al., 2017; Weichenthal et al., 2016), one study each from the National Enhanced Surveillance System (Hystad et al., 2013), Canadian Community Health Survey (Pinault et al., 2016), and the Ontario Population and Environment Cohort (Weichenthal et al., 2017). To maintain population independence, previously defined criteria were used to exclude studies by Tomczak et al., 2016, and Weichenthal et al., 2016 (Table 1). Cohorts used by Crouse et al., 2015 and Pinault et al., 2017 were examined to determine potential for overlap, however, due to relatively distinct time periods of data collection, both were included in the final pooled RR estimate. Six studies met the inclusion criteria (Crouse et al., 2015; Hystad et al., 2013; Pinault et al., 2016, 2017; Villeneuve et al., 2015; Weichenthal et al., 2017), and were used to derive the Canada-specific pooled RR estimate for the relationship between $PM_{2.5}$ and lung cancer. Three of six studies included in the meta-analysis were based on large national cohort (Crouse et al., 2015; Pinault et al., 2016, 2017) or case-control (Hystad et al., 2013) studies, and a fifth based on a large population based Ontario cohort (Weichenthal et al., 2017). The study by Villeneuve et al. used information on the participants in a randomized controlled trial (women only) and participants were recruited from 15 Canadian urban centers (Villeneuve et al., 2015).

Fig. 1 shows a meta-analysis of the six included Canadian studies. RR estimates are presented for the risk of lung cancer associated with a 10 $\mu g/m^3$ increase in $PM_{2.5}$. The pooled RR estimate for lung cancer associated with $PM_{2.5}$ was 1.09 per 10 $\mu g/m^3$ (95% CI: 1.06–1.12). There was no evidence of heterogeneity and a fixed effects model was used to pool relative risk estimates (Q-test p-value = 0.12). There was no evidence of publication bias in the Canadian studies (Egger's linear regression test p-value = 0.20, Begg's Rank Correlation test p-value = 1.00).

Table 1
Summary of studies considered for inclusion in meta-analysis of lung cancer risk associated with exposure to $PM_{2.5}$ in Canadian populations.

Reference	Study population (study type)	No. of events/total population	Study period[a]	Exposure assessment method	Mean exposure (SD) μg/m^3	Inclusion
Hystad et al. (2013)	National Enhanced Cancer Surveillance System (Case-Control)	2390 (incidence)/5897	1994–1997	Spatiotemporal model	11.9 (3.0)	Yes
Villeneuve et al. (2015)	Canadian National Breast Screening Study (Cohort nested within RCT)	1011 (mortality)/89,248	1980–2005	Spatiotemporal model	9.5 (3.5)	Yes
Crouse et al. (2015)	Canadian Census Health and Environment (Cohort)	30,545 (mortality)/2,521,525	1991–2006	Spatiotemporal model	8.9	Yes
Pinault et al. (2016)	Canadian Community Health Survey (Cohort)	2700 (mortality)/299,500	2000–2011	Spatiotemporal model	6.3 (2.5)	Yes
Tomczak et al. (2016)	Canadian National Breast Screening Study (Cohort nested within RCT)	932 (incidence)/89,234	1980–2004	Spatiotemporal model	9.5 (3.5)	No[b]
Weichenthal et al. (2016)	Canadian Census Health and Environment Cohort (Cohort)	3200 (mortality)/193,300	1991–2009	Fixed site monitor	9.8 (1.6)	No[c]
Pinault et al. (2017)	Canadian Census Health and Environment (Cohort)	23,900 (mortality)/2,448,500	2001–2011	Spatiotemporal model	7.4 (2.6)	Yes
Weichenthal et al. (2017)	Ontario Population Health and Environment Cohort (Cohort)	12,908 (incidence)/1,105,258	1996–2012	Land-use Regression	10.9 (2.10)	Yes

[a] Lung cancer mortality/incidence assessment period.
[b] Overlap with larger Villeneuve et al. (2015) study.
[c] Overlap with larger Crouse et al. (2015) study.

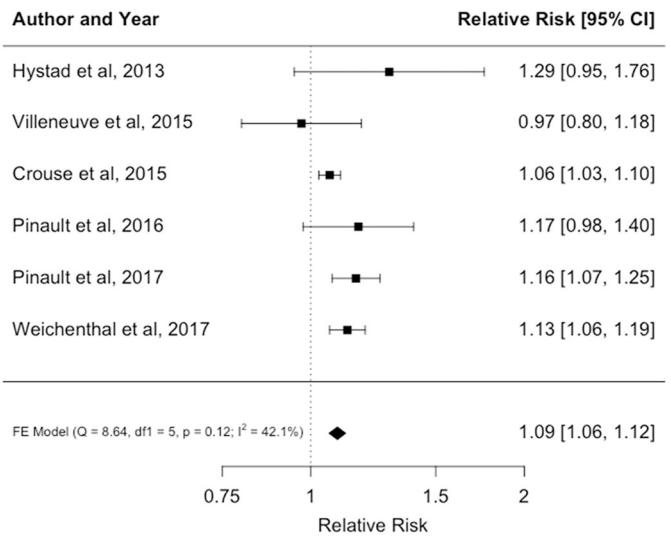

Fig. 1. Canadian estimates for lung cancer risk associated with a 10 μg/m^3 increase in $PM_{2.5}$ using a fixed-effects model.

Table 2
Population-weighted $PM_{2.5}$ exposure distribution (2015; Exposure Window 1990–2009).

Region	$PM_{2.5}$ μg/m^3			
	Mean	SD	Median	IQR
Canada	8.3	1.9	8.3	4.0
British Columbia	7.1	2.1	8.0	2.1
Alberta	7.0	1.3	7.2	2.1
Saskatchewan	6.2	2.1	5.8	1.6
Manitoba	5.5	0.8	6.3	1.3
Ontario	9.2	1.9	9.7	4.3
Quebec	8.9	1.6	9.2	3.7
New Brunswick	5.5	1.4	5.5	1.7
Nova Scotia	5.5	0.8	5.5	1.7
Prince Edward Island	3.9	0.3	3.8	0.9
Newfoundland and Labrador	4.3	0.8	4.1	2.4
Territories	4.5	1.5	3.7	4.3

Abbreviations: SD-standard deviation, IQR-interquartile range.

Table 3
Incidence lung cancer cases and proportions attributable to $PM_{2.5}$ in Canada (2015).

Region	Lung cancer cases Obs.[a]	PAR	95% CI of PAR	AC
Canada	25,235	6.9%	4.7%–9.0%	1739
British Columbia	3175	6.0%	4.1%–7.8%	189
Alberta	2085	5.9%	4.0%–7.7%	123
Saskatchewan	690	5.3%	3.6%–6.9%	36
Manitoba	855	4.6%	3.2%–6.0%	40
Ontario	8380	7.9%	5.4%–10.3%	662
Quebec	7715	7.4%	5.1%–9.6%	570
New Brunswick	710	4.7%	3.2%–6.1%	33
Nova Scotia	950	4.6%	3.2%–6.0%	43
Prince Edward Island	160	3.3%	2.2%–4.4%	5
Newfoundland and Labrador	460	3.6%	2.5%–4.8%	17
Territories	55	3.9%	2.6%–5.0%	2

Abbreviations: PAR = population attributable risk, AC = attributable cases, CI = confidence interval.
[a] Obs. = observed lung cancer cases.

3.2. Current cancer burden (2015)

3.2.1. Exposure prevalence

A population-weighted Canadian average exposure distribution for $PM_{2.5}$ was estimated for the period 1990 to 2009; the mean and median

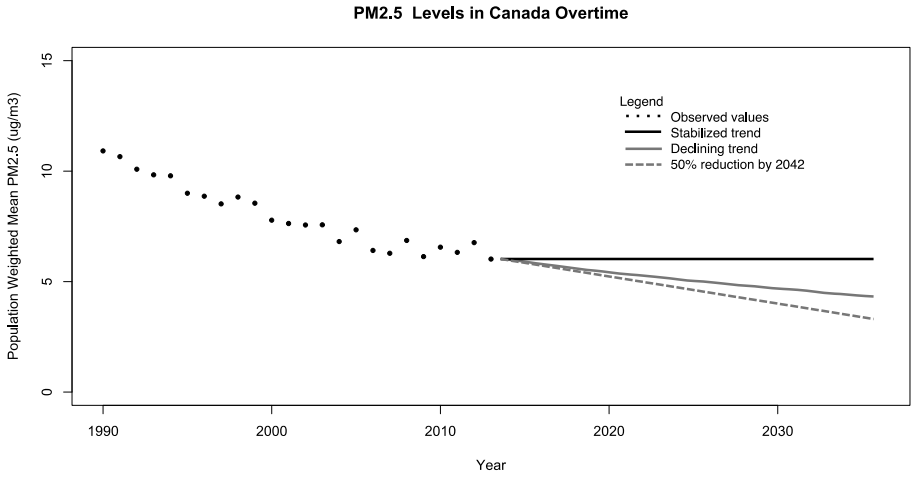

Fig. 2. Population-weighted changes in $PM_{2.5}$ levels in Canada from 1990 to 2036.

were 8.3 μg/m^3 (Table 2).

3.2.2. Population attributable risk (PAR) and attributable cases

Table 3 presents Canadian and province-specific PARs for 2015, and attributable lung cancer case estimates in relation to $PM_{2.5}$ exposure between 1990 and 2009. The PAR estimate was 6.9%, accounting for 1739 lung cancer cases. Province-specific PARs were highest in Ontario, Quebec, and British Columbia (7.9%, 7.4%, 6.2%, respectively).

3.3. Future cancer burden (2042)

Average population-weighted $PM_{2.5}$ levels in Canada have been declining from 1980 to 2014 (Fig. 2). PAR and PIF calculations up to 2042 were estimated based on the assumption of stabilized $PM_{2.5}$ levels equivalent to the average of observed data from 2010 to 2014 (population-weighted average of 6.4 μg/m^3). This estimate along with province-specific stabilized values is presented in Table 4. The estimated PAR for $PM_{2.5}$ for the year 2042 based on these levels was 5.4%, corresponding to 1820 attributable cases (Table 5).

The consideration of a counterfactual distribution based on a 50% decrease relative to the stabilized value by 2036 resulted in a population-weighted estimate of 4.7 μg/m^3 for $PM_{2.5}$, while the average population-weighted estimated distribution based on a declining trend was 5.2 μg/m^3 (Table 6). After population weighting, the projected declining trend in $PM_{2.5}$ did not result in consistent reductions in $PM_{2.5}$ (Table 6).

PIFs and preventable case estimates for counterfactual scenarios corresponding to a 50% reduction in exposure levels by 2036, and a continuation of the declining trend in $PM_{2.5}$ levels are presented in Table 6. Projecting a 50% reduction in exposure levels by 2036 compared to current levels, the PIF for $PM_{2.5}$ would be 1.4%, with 476 estimated preventable cases in 2042, (3686 cumulative cases) (Figs. 3 & 4). Based on a declining trend in exposure levels, the PIF for $PM_{2.5}$ was estimated at 1% with 333 estimated preventable cases in 2042 (2863 cumulative cases) (Figs. 3 & 4).

Table 4
Population-weighted $PM_{2.5}$ exposure distribution (2042)[a].

Region	$PM_{2.5}$ μg/m^3			
	Mean	SD	Median	IQR
Canada	6.4	1.7	6.3	2.3
British Columbia	5.4	2.1	5.6	1.1
Alberta	6.0	1.4	5.9	0.7
Saskatchewan	4.7	0.8	5.3	2.0
Manitoba	4.3	0.6	4.8	1.2
Ontario	6.6	1.4	6.6	1.9
Quebec	7.7	1.8	8.2	1.8
New Brunswick	4.6	0.9	4.6	1.3
Nova Scotia	5.6	1.2	6.0	1.0
Prince Edward Island	4.3	0.5	4.2	1.5
Newfoundland and Labrador	4.0	0.6	3.8	2.1
Territories	3.9	1.2	2.9	2.8

Abbreviations: SD = standard deviation, IQR = interquartile range.
[a] Exposure window of 2017–2036 for Canada, and 2013–2032 for provinces.

Table 5
Lung cancer cases and proportions attributable to $PM_{2.5}$ in Canada (2042).

Region	Lung cancer cases	$PM_{2.5}$	
	Obs.[a]	PAR[b]	AC[c]
Canada	34,027	5.4%	1820
British Columbia	3601	4.5%	163
Alberta	3943	5.1%	202
Saskatchewan	947	4.0%	38
Manitoba	1350	3.7%	50
Ontario	10,745	5.5%	594
Quebec	12,261	6.4%	785
Atlantic Provinces	2890	4.1%	117

Abbreviations: PAR = population attributable risk, AC = attributable cases, Atlantic Provinces: New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island.
[a] Obs. = observed lung cancer cases.
[b] PAR estimate for 2042 for Canada, and 2038 for provinces.
[c] Attributable case estimates use data from 2042 for Canada and 2038 for provinces.

4. Discussion

This study estimated the proportion of lung cancer cases attributable to $PM_{2.5}$ exposure in Canada in 2015 and future avoidable cancers over the period 2016–2042 under different future exposure scenarios. A pooled RR estimate for the relationship of $PM_{2.5}$ with lung cancer from Canadian studies was 1.09 per 10 μg/m^3. For 2015, we estimated that 6.9% of lung cancer cases were attributable to $PM_{2.5}$ exposure. $PM_{2.5}$ levels in Canadian municipalities declined between 1990 and 2014. However, the impact of these declines on PAR and PIF estimates are somewhat mitigated by increasing populations in urban areas with higher $PM_{2.5}$. The PAR attributable to $PM_{2.5}$ in 2042 was estimated at 5.4%. Over 3000 lung cancer cases could be prevented between 2016 and 2042 if declining trends in $PM_{2.5}$ continue.

Seven observational studies based on Canadian populations have been published in the past five years, collectively supporting an

Table 6
Projected cancer cases, proportions attributable to $PM_{2.5}$, and the number of cancer cases that could be prevented in 2042 for two counterfactual scenarios.

Region	Obs	$PM_{2.5}$				
		Counterfactual scenario[a]	Projected distribution (μg/m^3)	PIF[b] (%)	Preventable cases[c]	Cumulative preventable cases[d]
Canada	34,027	1	4.7	1.4	476	3686
		2	5.2	1.0	333	2863
British Columbia	3601	1	4.4	0.8	29	184
		2	4.5	0.5	18	148
Alberta	3943	1	5.0	1.0	39	212
		2	4.6	1.3	49	381
Saskatchewan	947	1	3.9	0.7	7	42
		2	3.6	1.0	9	73
Manitoba	1350	1	3.6	0.7	9	55
		2	2.9	1.1	15	131
Ontario	10,745	1	5.4	1.0	107	662
		2	6.5	0.0	4	0
Quebec	12,261	1	6.3	1.1	135	859
		2	6.3	1.1	135	1078
Atlantic Provinces	2890	1	4.0	0.7	20	132
		2	2.9	1.6	46	412

Abbreviations: PIF = potential impact fraction; Obs. = observed lung cancer cases. Atlantic provinces: New Brunswick, Nova Scotia, Newfound and Labrador, Prince Edward Island.

[a] Counterfactual scenarios: 1 = 50% reduction off stabilized value, 2 = declining trend.

[b] PIF estimate for 2042 for all of Canada and 2038 for all provinces.

[c] Total preventable lung cancer cases for 2042 for all of Canada, and 2038 for province specific estimates.

[d] Cumulative preventable cases uses years 2016–2042 for Canada-wide estimates, and 2016–2038 for provincial estimates.

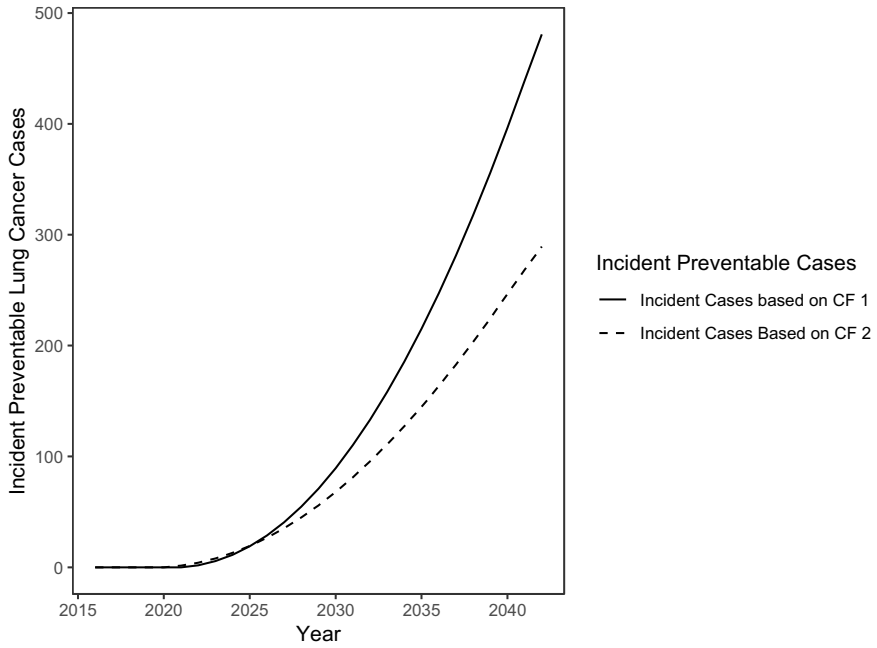

Fig. 3. Incident preventable lung cancer cases in Canada due to $PM_{2.5}$ exposure.
CF (counterfactual) 1 = 50% reduction off stabilized levels by 2036.
CF (counterfactual) 2 = declining trend.

increased risk in lung cancer in relation to $PM_{2.5}$ exposure (Tomczak et al., 2016; Villeneuve et al., 2015). A Canadian specific RR was deemed important because $PM_{2.5}$ levels in Canada are generally lower than in locations where previous epidemiologic studies have been conducted, and because the composition of $PM_{2.5}$ can vary by country (Hamra et al., 2015). We followed the methodology of a recent high quality meta-analysis of $PM_{2.5}$ and lung cancer risk published by Hamra et al. Our pooled RR estimate (1.09) was identical to that reported in the Hamra et al. meta-analysis (Hamra et al., 2015).

Our PAR estimates were higher than those recently published for Alberta (Poirier et al., 2017) and Ontario (Cancer Care Ontario, 2016). Among major differences in the methodologic approaches was our focus on a longer exposure window (20 years) and lag period (5 years), such that the exposure distribution used in our PAR for 2015 reflected past $PM_{2.5}$ levels that were higher than more recent levels.

Overall, analysis of trends overtime revealed declines in $PM_{2.5}$ exposures, suggesting the potential for a reduced lung cancer burden in Canada without direct intervention. However, the change in provincial exposure estimates between 2015 and 2042 do not consistently follow Canadian trends due to different patterns of urbanization and trends in $PM_{2.5}$ by province. The Clean Air Act (Government of Canada, 2006), End of Coal Action Plan (Harris et al., 2015), and revised Canadian Ambient Air Quality Standards for Fine Particulate Matter (CCME, 2012) represent a small selection of the considerable economic and

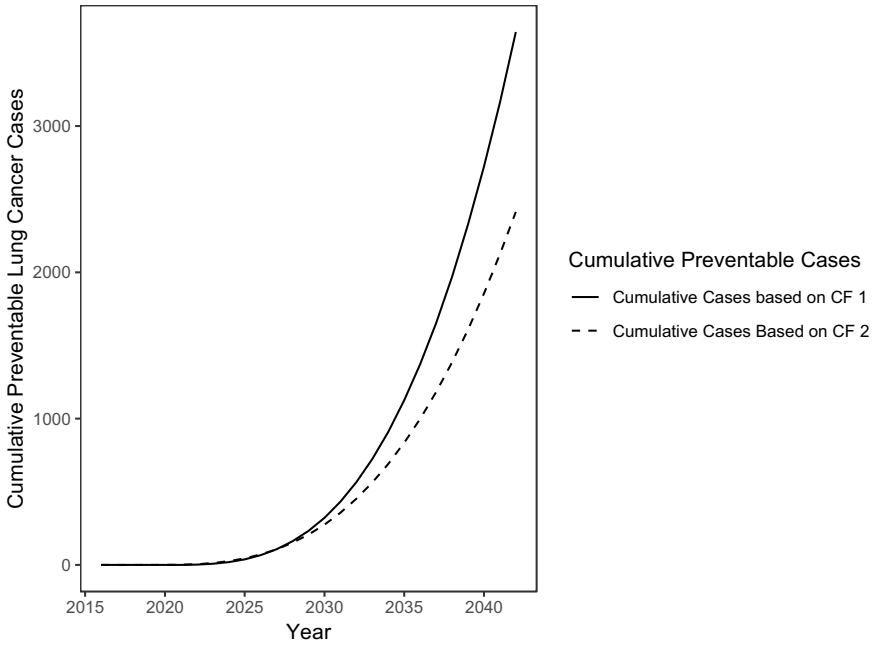

Fig. 4. Cumulative preventable lung cancer cases in Canada due to $PM_{2.5}$ exposure.
CF (counterfactual) 1 = 50% reduction off stabilized levels by 2036.
CF (counterfactual) 2 = declining trend.

policy changes that have occurred in Canada in recent decades that have likely contributed to the overall declines (El-Keib et al., 1994; Harris et al., 2015). However, there are several other sources of air pollution in Canada, including the oil and gas industries and diesel-powered vehicles, where targeted efforts could contribute to the reduction of the burden of lung cancer associated with air pollution (Walji and Flegel, 2015).

In addition, although the projected trends based on these declines suggest promising decreases in $PM_{2.5}$, the effect of these declines is somewhat mitigated by larger populations in high exposure areas, and the long exposure and latency period associated with the relationship of interest. For example, the PAR and PIF for 2042 take into account exposures occurring in 2017, diluting the effect of reduced exposures in years leading up to 2042. For exposures with long exposure windows and lag, changes in PAR and PIFs require changes occurring over substantial time periods.

There are limitations to this analysis with respect to RR and exposure distribution inputs to PAR and PIF estimates. The pooled RR estimate obtained in this study is subject to the same potential biases inherent to the individual studies contributing to this estimate, including misspecification of the dose-response relationship. Several previous analyses support a log-linear dose response between $PM_{2.5}$ exposure and lung cancer risk (Hystad et al., 2013; Lepeule et al., 2012; Puett et al., 2014; Turner et al., 2011), while two studies included in the meta-analysis reported some deviation from a log-linear relationship (Crouse et al., 2015; Pinault et al., 2017).

Exposure distribution is a product of $PM_{2.5}$ measurements and population distribution. For estimates of predicted exposure distribution, we assumed that the average level over the past five years would continue and that the population distribution would correspond to that in the 2016 Canadian Census. For counterfactual scenarios, we varied the exposure distribution but not the population distribution. $PM_{2.5}$ levels in Canadian municipalities declined between 1990 and 2014. However, the impact of these declines on PAR and PIF estimates are somewhat mitigated by an increase in the percentage of the population residing in urban areas with higher $PM_{2.5}$.

In the context of this study, PAR quantifies the total lung cancer burden from $PM_{2.5}$ exposures in Canada. These estimates are relevant in terms of a comparison to previous PAR estimates for Canada, the provinces, and internationally. However, considering that a proportion of $PM_{2.5}$ exposure in Canada is due to natural background levels (Vingarzan, 2004), the PARs presented represent an unrealistic exposure scenario and are therefore limited in their interpretation. The use of PIFs provided valuable information regarding the expected decreases in the Canadian lung cancer burden that can be achieved through realistic exposure mitigation scenarios. These PIFs were chosen for their ease of interpretation, and potential feasibility in future decades.

In addition, our PAR confidence intervals were estimated using a simplified approach that did not take into account sampling variation or measurement error in $PM_{2.5}$ observations, leading to artificially narrower CIs (Daly, 1998; Newcombe, 1999).

This paper provides up-to-date pooled RR estimates for $PM_{2.5}$ that are generalizable to exposures in Canada. We also acquired high-resolution Canada-wide exposure data, allowing us to calculate mean exposures for the appropriate time-window for the outcome of interest, and predict trends in air pollution in Canada over two decades. Importantly, this study provides the only current PAR estimate for the burden of lung cancer attributable to $PM_{2.5}$ in Canada, and presents novel estimates of the future burden of lung cancer in relation to $PM_{2.5}$.

5. Conclusion

Lung cancer remains a large public health concern in Canada, accounting for 26% of all cancer deaths (Canadian Cancer Statistics, 2018). This analysis provides up-to-date information on the burden of lung cancer in Canada attributable to $PM_{2.5}$. Although this study reveals promising declines in $PM_{2.5}$ in recent decades, this work highlights the importance of continued efforts by policy makers to reduce air pollution exposures across Canada. Our analysis suggested that > 3000 lung cancer cases could be prevented due to $PM_{2.5}$ exposure if the current decreasing trends in exposures are sustained. Quantifying the current and future burden of lung cancer attributable to $PM_{2.5}$ can directly inform policy makers and the development of targeted initiatives aimed at reducing the lung cancer burden in Canada.

Acknowledgments

Dylan O'Sullivan is supported by a Queen Elizabeth II Scholarship and an Empire Life Fellowship. Darren Brenner holds a Canadian Cancer Society Prevention Capacity Development Award (#703917). Christine Friedenreich was supported by an Alberta Innovates Health Senior Scholar Award and by the Alberta Cancer Foundation Weekend to End Women's Cancers Breast Cancer Chair.

Funding sources

This research is supported by a Canadian Cancer Society Partner Prevention Research Grant (#703106).

Conflict of interest

None declared.

References

Baccarelli, A., Wright, R.O., Bollati, V., Tarantini, L., Litonjua, A.A., Suh, H.H., Zanobetti, A., Sparrow, D., Vokonas, P.S., Schwartz, J., 2009. Rapid DNA methylation changes after exposure to traffic particles. Am. J. Respir. Crit. Care Med. 179, 572–578.

Brenner, D.R., Poirier, A.E., Walter, S.D., King, W.D., Franco, E.L., Demers, P.A., Villeneuve, P.J., Ruan, Y., Khandwala, F., Grevers, X., 2018. Estimating the current and future cancer burden in Canada: methodological framework of the Canadian population attributable risk of cancer (ComPARe) study. BMJ Open 8, e022378.

Buschini, A., Cassoni, F., Anceschi, E., Pasini, L., Poli, P., Rossi, C., 2001. Urban airborne particulate: genotoxicity evaluation of different size fractions by mutagenesis tests on microorganisms and comet assay. Chemosphere 44, 1723–1736.

Canadian Cancer Statistics Advisory Committee, 2018. Canadian Cancer Statistics 2018. Canadian Cancer Society, Toronto, ON Available at: cancer.ca/Canadian-Cancer-Statistics-2018-EN, Accessed date: 3 December 2018.

Cancer Care Ontario, 2016. Environmental Burden of Cancer in Ontario 1–44.

CCME (Canadian Council for Ministers of the Environment), 2012. Guidance Document on Achievement Determination Canadian Ambient Air Quality Standards for Fine Particulate Matter and Ozone. https://www.ccme.ca/files/Resources/air/aqms/pn_1483_gdad_eng.pdf, Accessed date: 12 November 2019.

Cohen, A.J., Ross Anderson, H., Ostro, B., Pandey, K.D., Krzyzanowski, M., Künzli, N., Gutschmidt, K., Pope, A., Romieu, I., Samet, J.M., Smith, K., 2005. The global burden of disease due to outdoor air pollution. J. Toxic. Environ. Health A 68, 1301–1307. https://doi.org/10.1080/15287390590936166.

Crouse, D.L., Peters, P.A., Hystad, P., Brook, J.R., van Donkelaar, A., Martin, R.V., Villeneuve, P.J., Jerrett, M., Goldberg, M.S., Pope, C.A., Brauer, M., Brook, R.D., Robichaud, A., Menard, R., Burnett, R.T., 2015. Ambient PM 2.5, O_3, and NO_2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ. Health Perspect. 123, 1–7. https://doi.org/10.1289/ehp.1409276.

Daly, L.E., 1998. Confidence limits made easy: interval estimation using a substitution method. Am. J. Epidemiol. 147, 783–790.

Drescher, K., Becher, H., 1997. Estimating the generalized impact fraction from case-control data. Biometrics 1170–1176.

El-Keib, A.A., Ma, H., Hart, J.L., 1994. Economic dispatch in view of the clean air act of 1990. IEEE Trans. Power Syst. 9, 972–978.

Finkelstein, M.M., 1991. Use of "time windows" to investigate lung cancer latency intervals at an Ontario steel plant. Am. J. Ind. Med. 19, 229–235.

Government of Canada, 2006. Canada's Clean Air Act. Accessed Nov 12th. pp. 2019. http://publications.gc.ca/collections/Collection/En84-46-2006E.pdf.

Hamra, G.B., Guha, N., Cohen, A., Laden, F., Raaschou-Nielsen, O., Samet, J.M., Vineis, P., Forastiere, F., Saldiva, P., Yorifuji, T., Loomis, D., 2014. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ. Health Perspect. 122, 906–911. https://doi.org/10.1289/ehp.1408092.

Hamra, G.B., Laden, F., Cohen, A.J., Raaschou-Nielsen, O., Brauer, M., Loomis, D., 2015. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. Environ. Health Perspect. 123, 1107–1112. https://doi.org/10.1289/ehp.1408882.

Harris, M., Beck, M., Gerasimchuk, I., 2015. The End of Coal: Ontario's Coal Phase-Out. International Institute for Sustainable Development.

Hu, D., Jiang, J., 2014. $PM_{2.5}$ pollution and risk for lung cancer: a rising issue in China. JEP 5, 731.

Hystad, P., Setton, E., Cervantes, A., Poplawski, K., Deschenes, S., Brauer, M., van Donkelaar, A., Lamsal, L., Martin, R., Jerrett, M., Demers, P., 2011. Creating national air pollution models for population exposure assessment in Canada. Environ. Health Perspect. 119, 1123–1129.

Hystad, P., Demers, P.A., Johnson, K.C., Carpiano, R.M., Brauer, M., 2013. Long-term residential exposure to air pollution and lung cancer risk. Epidemiology 24, 762–772. https://doi.org/10.1097/EDE.0b013e3182949ae7.

IARC, 2016. Outdoor Air Pollution 1–454.

Lepeule, J., Laden, F., Dockery, D., Schwartz, J., 2012. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. Environ. Health Perspect. 120, 965–970. https://doi.org/10.1289/ehp.1104660.

Loomis, D., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., Guha, N., Baan, R., Mattock, H., Straif, K., 2013. The carcinogenicity of outdoor air pollution. Lancet Oncol. 14, 1262–1263.

Murray, C.J., Ezzati, M., Lopez, A.D., Rodgers, A., Vander Hoorn, S., 2003. Comparative quantification of health risks: conceptual framework and methodological issues. Popul. Health Metrics 1, 1.

Newcombe, R.G., 1999. Re: "confidence limits made easy: interval estimation using a substitution method". Am. J. Epidemiol. 149, 884–885.

Pinault, L., Tjepkema, M., Crouse, D.L., Weichenthal, S., van Donkelaar, A., Martin, R.V., Brauer, M., Chen, H., Burnett, R.T., 2016. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. Environ. Health 15 (1). https://doi.org/10.1186/s12940-016-0111-6.

Pinault, L.L., Weichenthal, S., Crouse, D.L., Brauer, M., Erickson, A., van Donkelaar, A., Martin, R.V., Hystad, P., Chen, H., Finès, P., Brook, J.R., Tjepkema, M., Burnett, R.T., 2017. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environ. Res. 159, 406–415. https://doi.org/10.1016/j.envres.2017.08.037.

Poirier, A.E., Grundy, A., Khandwala, F., Friedenreich, C.M., Brenner, D.R., 2017. Cancer incidence attributable to air pollution in Alberta in 2012. CMAJ Open 5, E524–E528. https://doi.org/10.9778/cmajo.20160040.

Poirier, A.E., Ruan, R., Walter, S.D., Franco, F.L., King, W.D., Villeneuve, P., Volesky, K., O'Sullivan, D.E., Qiou, W., et al., 2019. The future burden of cancer in Canada: long-term cancer incidence projections 2013–2042. Cancer Epidemiol. 59, 199–207.

Pope III, C.A., Burnett, R.T., Turner, M.C., Cohen, A., Krewski, D., Jerrett, M., Gapstur, S.M., Thun, M.J., 2011. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure–response relationships. Environ. Health Perspect. 119, 1616.

Puett, R.C., Hart, J.E., Yanosky, J.D., Spiegelman, D., Wang, M., Fisher, J.A., Hong, B., Laden, F., 2014. Particulate matter air pollution exposure, distance to road, and incident lung cancer in the nurses' health study cohort. Environ. Health Perspect. 1–8. https://doi.org/10.1289/ehp.1307490.

Rothman, K.J., 1981. Induction and latent periods. Am. J. Epidemiol. 114, 253–259.

Sarti, E., Pasti, L., Rossi, M., Ascanelli, M., Pagnoni, A., Trombini, M., Remelli, M., 2015. The composition of PM1 and PM2.5 samples, metals and their water soluble fractions in the Bologna area (Italy). Atmos. Pollut. Res. 6, 708–718.

Siemes, C., Visser, L.E., Coebergh, J.-W.W., Splinter, T.A.W., Witteman, J.C.M., Uitterlinden, A.G., Hofman, A., Pols, H.A.P., Stricker, B.H.C., 2006. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam study. J. Clin. Oncol. 24, 5216–5222. https://doi.org/10.1200/JCO.2006.07.1381.

Statistics Canada. 2002. Census Profile – comprehensive download files for a selected geographic level, 100% data (table). "Population and Dwelling Counts, 2002 Census." Census. Statistics Canada Catalogue no. 93F0053XIE-301. Ottawa, Ontario. https://www12.statcan.gc.ca/census-recensement/2011/dp-pd/prof/details/download-telecharger/comprehensive/comp-csv-tab-dwnld-tlchrgr.cfm?Lang=E#tabs2011 (accessed October 3rd, 2018).

Statistics Canada. 2007. Census Profile – comprehensive download files for a selected geographic level, 100% data (table). "Population and Dwelling Counts, 2006 Census." Census. Statistics Canada Catalogue no. 92-591-XE-301. Ottawa, Ontario. https://www12.statcan.gc.ca/census-recensement/2011/dp-pd/prof/details/download-telecharger/comprehensive/comp-csv-tab-dwnld-tlchrgr.cfm?Lang=E#tabs2011 (accessed October 3rd, 2018).

Statistics Canada. 2012. Census Profile – comprehensive download files for a selected geographic level, 100% data (table). "Population and Dwelling Counts, 2011 Census." Census. Statistics Canada Catalogue no. 98-316-XWE2011001-301. Ottawa, Ontario. https://www12.statcan.gc.ca/census-recensement/2011/dp-pd/prof/details/download-telecharger/comprehensive/comp-csv-tab-dwnld-tlchrgr.cfm?Lang=E#tabs2011 (accessed October 3rd, 2018).

Statistics Canada. 2017. Census Profile – comprehensive download files for a selected geographic level, 100% data (table). "Population and dwelling counts, 2017 Census." Census. Statistics Canada Catalogue no. 98-401-X2016055. Ottawa, Ontario. https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/download-telecharger/comp/page_dl-tc.cfm?Lang=E (accessed October 3rd, 2018).

Stuart, B.O., 1984. Deposition and clearance of inhaled particles. Environ. Health Perspect. 55, 369–390. https://doi.org/10.1289/ehp.8455369.

Tomczak, A., Miller, A.B., Weichenthal, S.A., To, T., Wall, C., van Donkelaar, A., Martin, R.V., Crouse, D.L., Villeneuve, P.J., 2016. Long-term exposure to fine particulate matter air pollution and the risk of lung cancer among participants of the Canadian National Breast Screening Study. Int. J. Cancer 139, 1958–1966. https://doi.org/10.1002/ijc.30255.

Turner, M.C., Krewski, D., Pope III, C.A., Chen, Y., Gapstur, S.M., Thun, M.J., 2011. Long-term ambient fine particulate matter air pollution and lung cancer in a large cohort of never-smokers. Am. J. Respir. Crit. Care Med. 184, 1374–1381. https://doi.org/10.1164/rccm.201106-1011OC.

van Donkelaar, A., Martin, R.V., Spurr, R.J., Burnett, R.T., 2015. High-resolution satellite-derived PM2. 5 from optimal estimation and geographically weighted regression over North America. Environ. Sci. Technol. 49, 10482–10491.

Villeneuve, P.J., Weichenthal, S.A., Crouse, D., Miller, A.B., To, T., Martin, R.V., van Donkelaar, A., Wall, C., Burnett, R.T., 2015. Long-term exposure to fine particulate matter air pollution and mortality among Canadian women. Epidemiology 26, 536–545. https://doi.org/10.1097/EDE.0000000000000294.

Vineis, P., Hoek, G., Krzyzanowski, M., Vigna-Taglianti, F., Veglia, F., Airoldi, L., Overvad, K., Raaschou-Nielsen, O., Clavel-Chapelon, F., Linseisen, J., Boeing, H., Trichopoulou, A., Palli, D., Krogh, V., Tumino, R., Panico, S., Bueno-de-Mesquita, H.

B., Peeters, P.H., Lund E, E., Agudo, A., Martinez, C., Dorronsoro, M., Barricarte, A., Cirera, L., Quirós, J.R., Berglund, G., Manjer, J., Forsberg, B., Day, N.E., Key, T.J., Kaaks, R., Saracci, R., Riboli, E., 2007. Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. Environ. Health 6, 980–7. doi:https://doi.org/10.1186/1476-069X-6-7.

Vingarzan, R., 2004. Ambient Particulate Matter Concentrations in Canada and Background Levels. Environment Canada. Environmental Conservation Branch, Aquatic and Atmospheric Sciences Division. pp. 201–401.

Walji, M., Flegel, K., 2015. Adopting global guidelines for air pollution: protecting the health of Canadians. CMAJ 187, 788. https://doi.org/10.1503/cmaj.150722.

Weichenthal, S., Crouse, D.L., Pinault, L., Godri-Pollitt, K., Lavigne, E., Evans, G., van Donkelaar, A., Martin, R.V., Burnett, R.T., 2016. Oxidative burden of fine particulate air pollution and risk of cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC). Environ. Res. 146, 92–99. https://doi.org/10.1016/j.envres.2015.12.013.

Weichenthal, S., Bai, L., Hatzopoulou, M., Ryswyk, K., Kwong, J.C., Jerrett, M., Donkelaar, A., Martin, R.V., Burnett, R.T., Lu, H., Chen, H., 2017. Long-term Exposure to Ambient Ultrafine Particles and Respiratory Disease Incidence in in Toronto, Canada: A Cohort Study. pp. 1–11. https://doi.org/10.1186/s12940-017-0276-7.

World Health Organization, 2018. World Health Statistics data visualizations dashboard-Clean Cities. In: Concentrations of Fine Particulate Matter, by WHO Region (2016), . http://apps.who.int/gho/data/node.sdg.11-6-viz?lang=en, Accessed date: 5 February 2019.