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The current burden of cancer attributable to occupational exposures in Canada

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ABSTRACT

Exposure to occupational carcinogens is often overlooked as a contributor to the burden of cancer. To estimate the proportion of cancer cases attributable to occupational exposure in Canada in 2011, exposure prevalence and levels of 44 carcinogens were informed by data from the Canadian carcinogen exposure surveillance project (CAREX Canada). These were used with Canadian Census (between 1961 and 2011) and Labour Force Survey (annual surveys between 1976 and 2013) data to estimate the number of workers ever exposed to occupational carcinogens. Risk estimates of the association between each carcinogen and cancer site were selected mainly from published literature reviews. Population attributable risks were estimated using Levin's equation and applied to the 2011 cancer statistics from the Canadian Cancer Registry. It is estimated that 15.5 million Canadians alive in 2011 were exposed, during at least one year between 1961 and 2001, to at least one carcinogen in the workplace. Overall, we estimated that in 2011, between 3.9% (95% CI: 3.1%–8.1%) and 4.2% (95% CI: 3.3%–8.7%) of all incident cases of cancer were due to occupational exposure, corresponding to lower and upper numbers of 7700–21,800 cases. Five of the cancer sites – mesothelioma, non-melanoma skin cancer, lung, female breast, and urinary bladder – account for a total of 7600 to 21,200 cancers attributable to occupational exposures such as solar radiation, asbestos, diesel engine exhaust, crystalline silica, and night shift work. Our study highlights cancer sites and occupational exposures that need recognition and efforts by all stakeholders to avoid preventable cancers in the future.

1. Introduction

While numerous carcinogens have been discovered through the

study of exposures of working populations (Loomis et al., 2018), only a few attempts have been undertaken to quantify the contribution of occupational exposures to the burden of cancer (Purdue et al., 2015).

Abbreviations: CANJEM, CANadian job-exposure matrix; CAREX Canada, CARcinogen EXposure surveillance project in Canada; CI, Confidence interval; ICD-10, International classification of disease, 10th revision; IARC, International Agency for Research on Cancer; JEM, Job-exposure matrix; PAHs, Polychlorinated aromatic hydrocarbons; PAR, Population attributable risk; REP, Risk exposure period; RR, Relative risk

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Doll and Peto (1981) estimated that 4% of all cancer deaths in the United States were attributable to occupational exposures, mentioning that this estimate was unlikely to be off by more than a factor of two. More recent estimates indeed varied between 2.4% and 8.4% (Boffetta et al., 2010; Dreyer et al., 1997; Nurminen and Karjalainen, 2001; Rushton et al., 2012; Steenland et al., 2003). Some of these studies were restricted to a small number of relatively high-burden carcinogens and few associated cancer sites, such as the Driscoll et al. (2005) study based on the Global Burden of Disease project. Other studies have considered close to ten cancer sites related to definite or probable carcinogens (Boffetta et al., 2010; Dreyer et al., 1997; Steenland et al., 2003). Only two studies estimated population attributable risks (PARs) for > 20 cancer sites and attempted to provide more comprehensive estimates of the burden of cancer from occupational carcinogens. In Finland, Nurminen and Karjalainen (2001) estimated that, overall, 8.4% of cancer deaths (13.8% in men and 2.2% in women) were attributable to occupational exposure to definite and suspected carcinogens. A decade later, Rushton et al. (2012) estimated that 5.3% of cancer deaths (8.2% in men and 2.3% in women) were attributable to work-related exposure to known or probable carcinogens in Great Britain.

The objective of our current work, the Canadian Burden of Occupational Cancer study, was to estimate the number and proportion of cancer cases that were attributable, in 2011, to occupational exposure to carcinogens in Canada.

2. Methods

The burden estimation relied on PAR methods adapted from the Burden of Occupational Cancer in Britain study (Hutchings and Rushton, 2017; Hutchings and Rushton, 2012b; Rushton et al., 2012). The methods used in our study have been published elsewhere (Kim et al., 2018).

Briefly, the calculation of the PAR is based on Levin's equation (Levin, 1953), which requires an estimate of the relative risk (RR) of developing cancer due to an occupational exposure, and an estimate of the proportion of the population exposed (P_e) to that occupational exposure. Thus every PAR is specific to a cancer-exposure pair, in a given population, in a given year. Its general formula is:

$$\text{PAR} = \frac{P_e(\text{RR} - 1)}{1 + P_e(\text{RR} - 1)}$$

Census labour force data from 1961 to 2011 was used to estimate population exposure (see Section 2.3) and 2011 was chosen as the target year for burden estimation because it was the last available Canadian census year at the time the study was initiated.

2.1. Selection of agents and estimation of exposure

Exposures classified by the International Agency for Research on Cancer (IARC) as either definite (IARC Group 1) or probable (IARC Group 2A) human carcinogens were considered for inclusion in the current study. Of these, carcinogens deemed to be most pertinent to the Canadian context (Peters et al., 2015), and for which epidemiologic and exposure data were available, were retained. This resulted in the initial selection of 44 chemical agents or mixtures, physical exposures, occupations, work conditions or industries. Assessment of exposure was generally based on job-exposure matrices (JEMs) that were produced by the CAREX Canada project (Peters et al., 2015), and complemented by other JEMs such as the Canadian Job Exposure Matrix (CANJEM, Siemiatycki and Lavoué, 2018) as well as literature reviews on exposure levels by industry.

2.2. Selection of cancer sites and of risk estimates

All cancer sites associated in IARC monographs with sufficient or

limited human evidence to each selected exposure were retained for burden estimation, totalling 32 cancer sites (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2018). Specific literature searches for epidemiologic studies indexed in PubMed between January 2012 and January 2016 identified studies on the association between each occupational carcinogen and cancer site. These literature searches were completed with studies identified from the latest IARC evaluations on the concerned carcinogens (Kim et al., 2018). Priority was given to studies that applied to the Canadian context in terms of industrial activity, presented meta-analyses or pooled risk estimates, reported dose-response relations, and controlled for important potential confounders.

2.3. Calculation of the number exposed during the risk exposure period

Latency periods between first exposure and diagnosis were assumed to be 10 to 50 years for solid tumors, and 0 to 20 years for hematopoietic and lymphoid tumors. Thus the time windows inside which an exposure could contribute, within the assumed latency period, to the risk of a cancer being diagnosed in 2011 (our target year), were 1961 to 2001 for solid tumors and 1991 to 2011 for hematopoietic and lymphoid tumors. These time windows of exposure were called "risk exposure periods" (REPs).

The CAREX Canada JEMs provided the proportion of workers exposed by industry and occupation; for exposures thought to have changed over the REP, an adjustment was made using prevalence trends derived from the CANJEM data (Sauvé et al., 2018).

The method to estimate the total number of workers ever exposed to carcinogens during the REP (N_{eREP}) was the same for all types of cancers, except for the number of years that varied according to the assumed latency periods mentioned above. The number of men and women in each intersection of industry and occupation was obtained from the national census data (censuses held in 1961, 1971, 1981, 1991, and 2001 for solid tumors), with linear interpolation to estimate numbers for each year of the REP between the census years. Industry-specific age-distribution and new-hire rates were obtained from all available years of Labour Force Survey data during the REP (1976–2001); men and women exposed from the first REP year and new hires in each subsequent year of the REP constituted the theoretical cohort. Finally, the survival of these workers from entry into the REP until the 2011 target year was calculated based on Canadian sex-specific life tables (1960–2000) (Statistics Canada, 2019) relevant to the year at entry into the exposed cohort, resulting in the number of ever-exposed workers during the REP still alive in 2011 (N_{eREP}).

2.4. Calculation of the population attributable risks

Across the included > 100 exposure-cancer site pairs, there was variation in the level of available quantitative exposure data and exposure-response relationships. This variation shaped our approach for estimating the PAR, which we grouped into three scenarios. The simplest scenario (Scenario A) was applied when only an assessment of presence/absence of exposure was available and/or for which there were limited epidemiologic data, e.g. a single summary RR for a never/ever exposure. Scenario B was applied to exposure-cancer pairs for which it was possible to categorize exposure data into two or more groups (e.g. high/low/unexposed, quartiles of cumulative exposure, etc.), and the corresponding semi-quantitative RR estimates were available from the literature. Finally, scenario C was applied to situations where the exposure data were sufficiently detailed to assign quantitative mean values, using exposure duration, level or cumulative exposure, to groups of exposed workers, and a continuous exposure-response relationship was available for the exposure-cancer pairs from the literature. Table 1 presents, by cancer site and for selected occupational carcinogens, the associated level of human and animal evidence of carcinogenicity according to the IARC classifications, the

Table 1
 Characteristics of occupational carcinogens^a by cancer site, scenario of exposure and risk estimate selected, number of workers exposed during the risk exposure period and risk estimates selected (with level of exposure if applicable). Canada, 1961–2001.

Cancer site	Carcinogen	Evidence of carcinogenicity in humans (H) and animals (A) ^b	PAR scenario and exposure information	Number exposed during the REP	Relative risk or risk model			Source of relative risk estimate	Reference
					Estimate	Confidence interval			
						Min	Max		
Skin (all non-melanoma) [ICD-10: C44.x1, 44.x2] Creosotes	H: Limited A: Sufficient	H: Limited A: Sufficient	A – Overall RR assigned to ever-exposed groups	5,215	2.37	1.08	4.50	Cohort study (9 cases/929 exposed)	Karlehagen et al. (1992)
			A – Overall RR assigned to ever-exposed groups ^d	66,816	1.74	1.07	2.65	Meta-analysis (20 studies)	Partanen and Boffetta (1994)
PAHs and related exposures ^c	H: Limited A: Sufficient	H: Sufficient A: Sufficient	B – Semi-quantitative by outdoor work • low, mostly indoor • mixed and outdoor work	255,144 2,316,720	1.00 (ref) 1.43	– 1.23	– 1.66	Meta-analysis (23 studies)	Bauer et al. (2011)
			B – Semi-quantitative by outdoor work • low, mostly indoor • mixed and outdoor work	255,144 2,316,720	1.00 (ref) 1.77	– 1.40	– 2.22	Meta-analysis (18 studies)	Schmitt et al. (2011)
Skin (squamous cell carcinoma) [ICD-10: C44.x2] Solar radiation	H: Sufficient A: Sufficient	H: Sufficient A: Sufficient	A – Overall RR ^{e,f} assigned to ever-exposed groups	61,749	1.65	1.05	2.58	Case-control study (2853 cases)	t Mannetje et al. (2011)
			Another scenario, excess lung cancer to mesothelioma ratio : 4.67 (95% CI = 2.87–7.61) C – RR ^g assigned from dose-response based on cumulative exposure	N/A	–	–	–	Meta-analysis (53 cohort studies)	Demers et al. (to be published)
Lung - [ICD-10: C34] Arsenic	H: Sufficient A: Sufficient	H: Sufficient A: Sufficient	• Low	104,035	1.07	1.00	1.28	Quantitative risk assessment RR = 1 + 1.44x, where x = cumulative exposure to CrO ₃ (mg/m ³ -yrs)	Park et al. (2004)
			• Medium	7,037	1.42	1.02	2.65		
Asbestos	H: Sufficient A: Sufficient	H: Sufficient A: Sufficient	• High	5,267	2.69	1.06	7.09	ln(RR) = 0.08813 + 0.000982x, where x = cumulative exposure to elemental carbon (µg/m ³ -years)	Vermeulen et al. (2014)
			C – RR assigned from dose-response based on cumulative exposure						
Chromium VI	A: Sufficient H: Sufficient	H: Sufficient A: Sufficient	• Low	1,356,639	1.14	1.10	1.20	Cohort study (267 cases/5297 exposed)	Grimsrud et al. (2003)
			• Medium	199,414	1.24	1.11	1.47		
Diesel engine exhaust	H: Sufficient A: Sufficient	H: Sufficient A: Sufficient	• High	55,844	3.01	1.36	3.20	Meta-analysis (27 studies)	Guha et al. (2010)
			B – Semi-quantitative ^e by exposure groups						
Nickel compounds	H: Sufficient A: Sufficient	H: Sufficient A: Sufficient	• Low	44,699	1.2	0.6	2.4	Meta-analysis (3-13 studies)	Rota et al. (2014)
			• Medium	56,980	2.1	1.1	3.9		
Painting ^g	H: Sufficient A: N/A	H: Sufficient A: N/A	• High	9,534	2.4	1.3	4.5	Meta-analysis (2-10 studies)	Bosetti et al. (2007)
			A – Overall RR ^g assigned to ever-exposed groups	263,337	1.35	1.21	1.51		
PAHs and related exposures	H: Limited (sufficient mechanistic) A: Sufficient	H: Limited (sufficient mechanistic) A: Sufficient	B – Semi-quantitative by industry	253,189	1.07	0.93	1.23	Meta-analysis (2-10 studies)	Bosetti et al. (2007)
			Aluminum Production						
PAHs and related exposures	H: Limited (sufficient mechanistic) A: Sufficient	H: Limited (sufficient mechanistic) A: Sufficient	Iron/Steel Foundry		1.31	1.07	1.61	Meta-analysis (2-10 studies)	Bosetti et al. (2007)
			Carbon Black Manufacturing		1.52	0.91	2.52		
PAHs and related exposures	H: Limited (sufficient mechanistic) A: Sufficient	H: Limited (sufficient mechanistic) A: Sufficient	Coal Gasification		2.29	1.98	2.64	Meta-analysis (2-10 studies)	Bosetti et al. (2007)
			Coke Production		1.58	1.47	1.69		
PAHs and related exposures	H: Limited (sufficient mechanistic) A: Sufficient	H: Limited (sufficient mechanistic) A: Sufficient	Tar Distillation		1.21	0.95	1.55	Meta-analysis (2-10 studies)	Bosetti et al. (2007)
			Roofers		1.51	1.28	1.78		
PAHs and related exposures	H: Limited (sufficient mechanistic) A: Sufficient	H: Limited (sufficient mechanistic) A: Sufficient	Asphalt Workers		1.14	1.07	1.22	Meta-analysis (2-10 studies)	Bosetti et al. (2007)
			Carbon Electrode Manufacturing		1.00	0.82	1.23		

(continued on next page)

Table 1 (continued)

Cancer site Carcinogen	Evidence of carcinogenicity in humans (H) and animals (A) ^b	PAR scenario and exposure information	Number exposed during the REP	Relative risk or risk model		Source of relative risk estimate	Reference	
				Estimate	Confidence interval			
					Min			Max
Radon	H: Sufficient A: Sufficient	C – RR assigned from exposure-age-concentration risk model	15,476,800			BEIR VI exposure-age-concentration risk model	National Research Council Committee on Health Risks of Exposure to Radon (1999)	
		Low – indoor		1.01	1.00			1.02
		> 50 – 100 Bq/m ³		1.02	1.00			1.05
		> 100 – 150 Bq/m ³		1.04	1.01			1.08
		> 150 – 200 Bq/m ³		1.05	1.01			1.11
> 200 – 400 Bq/m ³	1.09	1.01	1.18					
> 400 – 800 Bq/m ³	1.19	1.03	1.36					
> 800 Bq/m ³	1.42	1.05	2.25					
Second-hand smoke (among non-smokers)	H: Sufficient A: Sufficient	High – certain occupations	26,100	1.60	1.08	Meta-analysis (22 studies)	Stayner et al. (2007)	
		C – RR assigned from dose-response based on exposure duration		RR = 1 + 0.011x, where x = exposure duration (years)				
		1 – 5 years						
		5 – 10 years						
Silica	H: Sufficient A: Sufficient	C – RR assigned from dose-response based on cumulative exposure	1,925,152 3,453,109 1,640,220 198,720	ln(RR) = 0.062*ln(x+1), where x = cumulative exposure to silica (mg/m ³ -days)		Cohort studies (1272 cancers/ 65,980 exposed)	Steenland et al. (2001)	
		• Low		1.36	1.17			1.50
		• Medium		1.46	1.25			1.60
		• High		1.56	1.34			1.72
Welding fumes	H: Sufficient A: Limited	B – Semi-quantitative ^c by occupation	222,195 828,815	1.19	1.10	Case-control study (568 cases)	Kendzia et al. (2013)	
		• Occasional welder		1.44	1.25			1.67
		• Ever welder						
Breast (female) - [ICD-10: C50]	H: Limited A: Sufficient	A – Overall RRs ^b assigned to ever-exposed groups	1,505,849	1.15-1.40	1.05-1.13	Meta-analysis (9 studies)	Jia et al. (2013)	
Mesothelium [ICD-10: C45]	H: Sufficient A: Sufficient	A – Sex-specific overall % ^d of all diagnoses	N/A	–	–	Large case-control studies	Lacourt et al. (2014); Rake et al. (2009); Spirtas et al. (1994)	
		• Men: 85%						
		• Women: 40% (60% including para-occupational exposure)						
Urinary bladder - [ICD-10: C67]	H: Limited A: Inadequate	B – Semi-quantitative by exposure group	543,021 523,319 545,870	1.14	0.95	Case-control study (1062 cases)	Richardson et al. (2007)	
		• Low		1.17	0.97			1.40
		• Medium		1.25	1.04			1.49
		• High						

(continued on next page)

Table 1 (continued)

Cancer site Carcinogen	Evidence of carcinogenicity in humans (H) and animals (A) ^b	PAR scenario and exposure information	Number exposed during the REP	Relative risk or risk model		Source of relative risk estimate	Reference	
				Estimate	Confidence interval			
					Min			Max
PAHs	H: Limited A: Sufficient	B – Semi-quantitative by industry	253,489			Meta-analysis (2-10 studies)	Rota et al. (2014)	
		Aluminum Production		1.28	0.98	1.68		
		Iron/Steel Foundry		1.38	1.00	1.91		
		Carbon Black Manufacturing		1.10	0.61	2.00		
		Coal Gasification		2.39	1.36	4.21	Bosetti et al. (2007)	
		Roofers		1.57	0.96	2.56		
		Asphalt Workers		1.02	0.85	1.23		
		Carbon Electrode Manufacturing		1.35	0.83	2.20		

A, animals; EC, elemental carbon; H, Humans; PAHs, polycyclic aromatic hydrocarbons; N/A, Non applicable; PAR, population attributable risk; REP, risk exposure period.

^a Carcinogens associated with at least 50 cancer cases for the stated cancer site.

^b Source: volumes 1-122 of the IARC Monographs (<https://monographs.iarc.fr/list-of-classifications-volumes/>).

^c Among PAHs, benzo[a]pyrene has been classified as group 1 carcinogen, whereas several other individual PAHs are group 2A and 2B. Related exposures are found in several industrial operations (see supplementary table 1).

^d Workers who may be exposed to coal tar and pitches, bitumen, and asphalt.

^e Smoking-adjusted risk estimate.

^f Relative risk adjusted for age, sex, smoking, asbestos, silica, wood dust, welding fumes, chromium, nickel, cadmium.

^g Professional building/industrial painters.

^h A lower and a higher risk estimates were selected to convey the uncertainty of limited evidence.

ⁱ Average proportions of cases attributed to work were derived from French, British and American mesothelioma panel studies.

calculation scenario used in this study and the risk estimates reported in the relevant reference. Scenarios A and B used the available risk estimate itself (column labelled “estimate” in Table 1), whereas Scenario C made use of the published dose-response models (e.g. see Table 1 for the diesel and lung cancer dose-response model and its application in Kim et al., 2018). The 95% confidence intervals (CI) for the PAR values were estimated by Monte Carlo simulations. Ten thousand random samples were drawn from the distributions of RR and P_e (the two components in Levin's equation). For the RR component, the variance was estimated based on its point estimate and 95% CI, as reported in the selected meta-analysis or study. The uncertainty around the proportion of the population exposed (P_{exp}) was assumed to follow a log-normal distribution with a constant geometric standard deviation of 2.7 (Buringh and Lanting, 1991). The PARs and their 95% CIs were estimated for the entire Canadian population alive in 2011 and of working age (15 to 65 years old) at any point during the REP, and by age group, sex and province, and then applied to the number of incident cancer cases diagnosed in 2011 in Canadians aged 25 years and over for solid tumors, and 15 years and over for hematopoietic and lymphoid tumors, by cancer site, using data from the Canadian Cancer Registry.

2.5. Special situations for PAR calculation

Due to the limitations in availability of historical exposure data, a different approach for PAR estimation was used for asbestos. For mesothelioma, attributable risks of 85% in men, and 60% in women (occupational and para-occupational cases), were derived from the results of three large case-control studies (Lacourt et al., 2014; Rake et al., 2009; Spirtas et al., 1994), and applied to all diagnosed cases. For asbestos-related lung cancers, an “excess lung cancer to mesothelioma ratio” was calculated based on a systematic review and meta-analysis of 15 North American cohort studies specifically conducted for this study and not yet published. The resulting meta-ratio of 4.67 (95% CI = 2.87–7.61) was used to derive the number of attributable lung cancers.

Night shift work associated with circadian disruption was classified a “probable carcinogen” (Group 2A) based on limited human evidence and indirect animal evidence based on exposure to light at night (and not shift work per se). After a systematic review of meta-analyses (Pahwa et al., 2018), a lower and an upper risk estimates were selected from a meta-analysis (Jia et al., 2013), producing a low and a high risk estimates instead of a single PAR, to account for the uncertainty in the human evidence. This approach was not deemed necessary for the other exposure to a probable carcinogen (creosotes and non-melanoma skin cancer) because the direct animal evidence was sufficient (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010a).

2.6. Estimating combined PARs across different exposures

Since more than one carcinogen can target the same organ (most commonly the lung), it was appropriate to estimate a combined PAR for a few cancer-site specific exposures. Two methods were used to do these estimations.

For a cancer site with little overlap of carcinogens within industries (carcinogens deemed to occur with independent probabilities), the overall combined PAR was estimated using the “complement of the product of complements” formula suggested by Steenland and Armstrong (2006) and by Miettinen (1974):

$$\text{Overall PAR} = 1 - [(1 - PAR_1)(1 - PAR_2)...(1 - PAR_x)]$$

where PAR₁, PAR₂, PAR₃... PAR_x are the PARs estimated for each of the 1 to x carcinogens considered. This method was used to estimate the combined PAR for skin cancers (exposures to solar radiation and to creosotes and PAHs).

For lung and bladder cancers, combined PARs were estimated in

two steps. First the industry and occupation groups where co-exposures to the associated carcinogens occurred were identified by merging all of the CAREX Canada JEMs for these carcinogens. Within these groups, the proportions of workers exposed to each possible combination of two or more overlapping carcinogens were calculated, assuming statistical independence of these exposures. Workers were then considered exposed to the carcinogen associated with the highest RR among the overlapping exposures. Next, the overall combined PARs were estimated for lung and bladder cancers with the complement of the product of complements formula described above, using the individual exposure-specific PARs, now adjusted for concurrent exposures.

3. Results

Available exposure and epidemiologic data allowed the estimation of PARs for a total of 64 exposure-cancer site pairs from 31 occupational carcinogens and 24 cancer sites. We estimated that between 5.0% (95% CI: 4.0%–10.3%) and 5.4% (95% CI: 4.2%–11.2%) of incident cases of these 24 sites were attributable to occupational exposure to carcinogens, which translates to 9700–10,400 cases (this range of PAR estimates results from using low and high estimates for breast cancer and shift work). The top six cancer sites in terms of proportions caused by all site-specific occupational carcinogens considered here were: mesothelioma (80.6%), lung cancer (14.9%), non-melanoma skin cancer (6.5%), eye melanoma (5.4%; less than 50 cases), breast (2.0–5.2%) and nasopharynx (4.7%) (Fig. 1). In terms of the number of attributable cases, the five cancer sites with the highest occupational cancer burden were: non-melanoma skin cancer (4700 cases), lung (3500), female breast (470 to 1200) mesothelioma (430) and urinary bladder (320). These cancers were associated with a total of 23 occupational exposures. Results for other cancer sites with < 50 attributable cases to occupational exposures can be found in the supplementary material (Table S-1).

Overall in 2011, we estimated that between 3.9% (95% CI: 3.1%–8.1%) and 4.2% (95% CI: 3.3%–8.7%) of incident cases of cancer diagnosed in Canadians aged 25 years and over (solid tumors) or 15 years and over (hematopoietic and lymphoid tumors) were due to occupational exposure, corresponding to a minimum estimate of 7700

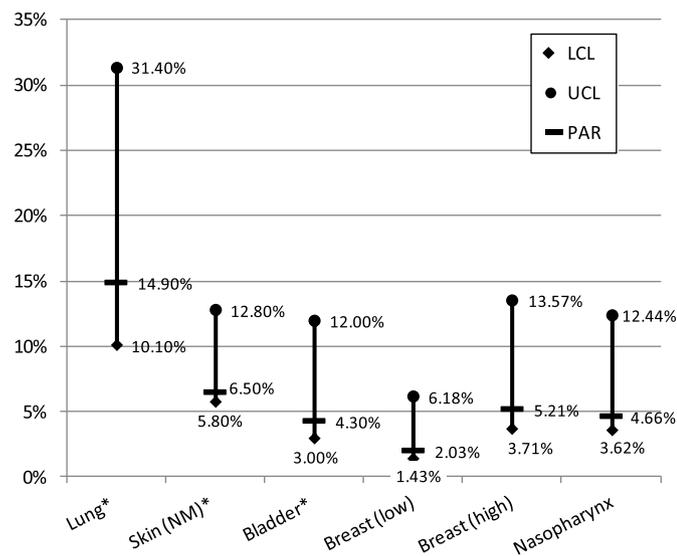


Fig. 1. Combined exposures (*) and single exposure population attributable risk estimates for the five cancer sites with the highest proportions attributable to occupational exposures (excluding mesothelioma, PAR = 80.6%). Overall population, Canada, 2011. (Breast (high), high PAR estimate for breast cancer; Breast (low), low PAR estimate for breast cancer; LCL, lower confidence limit; UCL, upper confidence limit; *, PAR estimate combined for more than one carcinogen; NM, non-melanoma).

cases (lower overall PAR confidence limit estimated with the low estimate of night shift work-breast cancer PAR, see Table 2) and a maximum estimate of 21,800 attributable cases (upper overall PAR confidence limit estimated with the high estimate of night shift work-breast cancer PAR).

3.1. Estimation of exposure and selection of risk estimates

Occupational carcinogens estimated to be associated with at least 50 cancer cases are presented, by cancer site, in Table 1, together with their associated level of human and animal evidence of carcinogenicity according to the IARC classifications for the selected cancer sites (information for the other carcinogens can be found in supplementary Table S-1). Among these, three carcinogens are associated with more than one cancer site: asbestos, diesel engine exhaust and polycyclic aromatic hydrocarbons and related exposures (PAHs). The numbers of Canadian workers estimated to be exposed to some point to these carcinogens during the REP, and alive in 2011 (N_{eREP}), varied between 5000 (exposed to creosotes), and > 15 million (exposed to radon; Table 1).

Table 1 also presents the PAR-calculation scenario that was applied for each exposure-cancer pair, with the selected risk estimates.

3.2. Population attributable risk estimates

The PAR estimates are illustrated with their 95% CI in Fig. 2 for lung cancer and Fig. 3 for the four other cancer sites, for each carcinogen included in Table 1. The largest PARs were associated with exposure to asbestos, estimated to be responsible for up to 80.6% of mesothelioma cases and 8% of lung cancers. The next most important exposures were solar radiation for both basal cell and squamous cell carcinomas (5% and 9% respectively), night shift work for female breast cancer (2–5%), diesel engine exhaust (a little above 2%) for lung and bladder cancers, and crystalline silica dust (about 2%) for lung cancer.

The exposures associated with the greatest number of cases were solar radiation (> 4500 non melanoma skin cancers; Table 2), asbestos (about 1900 lung cancers and 430 mesothelioma cases), night shift work among women (between 470 and 1200 breast cancer cases), and diesel engine exhaust and crystalline silica (approximately 500 lung cancer cases each). All PARs were larger for men than for women (Table 2), but the difference between sexes was smaller for exposure to second-hand smoke and lung cancer (PAR for men of 0.59%, and for women of 0.51%; Table 2), and for low indoor radon exposure and lung cancer (PAR for men, 0.75%, and for women, 0.69%).

3.3. Estimation of combined PARs

Table 3 presents the combined PARs estimated for the three cancer sites associated with more than one carcinogen. More than 6% of non-melanoma skin cancers were attributed to occupational exposure to three carcinogens in 2011 (approximately 4700 new diagnoses). Concurrent exposures to 17 lung carcinogens were estimated to be responsible for 15% of annual lung cancer cases, which amounted to approximately 3500 lung cancers. The burden is particularly elevated in men for whom 16 to 49% of lung cancer cases (2000–6200 cases) are estimated to be attributable to occupational exposures. Finally, a combined PAR of 4% for bladder cancer was attributed to exposures to seven carcinogens.

4. Discussion

The overall burden of cancer attributable to occupational exposures among Canadians in 2011 was estimated to range between 3.9% and 4.2% of all incident cases (9700 and 10,400 attributable cases). In comparison, Rushton et al. (2012) reported for Great Britain that

Table 2

Total number of Canadian incident cancer cases^a, and population attributable risks and number of attributable cases by cancer site and associated carcinogen^b, by sex. Canada, 2011.

Cancer site	Number of cancers in 2011 ^a			Carcinogen ^b	Total		Men		Women	
	Total	Men	Women		PAR	Attributable	PAR	Attributable	PAR	Attributable
					%	cases	%	cases	%	cases
Skin (non-melanoma)	72,245	39,715	32,529	Creosotes	0.14	98	0.24	96	0.01	2
					(0.10–0.55)	(74–400)	(0.18–1.00)	(70–3978)	(0.00–0.02)	(1–7)
				PAH and related exposures	0.07	51	0.13	50	0.00	1
Skin (BCC)	53,695	28,387	25,308	Solar radiation	5.30	2845	8.99	2551	1.16	295
					(4.18–11.77)	(2245–6321)	(6.38–20.35)	(1811–5777)	(0.85–3.71)	(216–938)
Skin (SCC)	18,549	11,329	7220	Solar radiation	9.22	1710	14.03	1589	1.67	121
Lung	23,735	12,540	11,195	Arsenic	0.25	59	0.44	56	0.03	3
					(0.18–0.94)	(43–223)	(0.30–1.74)	(38–218)	(0.02–0.10)	(2–11)
				Asbestos	8.01	1904	13.76	1727	1.58	177
					(4.92–13.05)	(1168–3101)	(8.44–22.41)	(1059–2812)	(0.97–2.58)	(109–289)
				Chromium VI	0.20	48	0.36	45	0.03	3
					(0.13–0.76)	(32–180)	(0.22–1.39)	(27–174)	(0.02–0.12)	(2–13)
				Diesel engine exhaust	2.37	563	4.31	540	0.21	23
					(1.60–6.60)	(380–1567)	(2.75–12.22)	(345–1532)	(0.13–0.75)	(15–83)
				SHS (among non-smokers)	0.55	131	0.59	74	0.51	57
					(0.46–0.74)	(110–174)	(0.41–0.71)	(51–89)	(0.40–0.86)	(45–96)
				Nickel compounds	0.70	167	1.22	153	0.12	13
					(0.52–2.64)	(123–627)	(0.82–4.77)	(102–598)	(0.08–0.54)	(9–61)
				PAHs and related exposures	0.56	132	0.93	116	0.14	16
					(0.43–1.89)	(101–447)	(0.62–3.34)	(78–419)	(0.09–0.54)	(10–60)
				Painting	0.31	74	0.55	69	0.05	5
					(0.22–1.09)	(52–259)	(0.36–1.99)	(45–249)	(0.03–0.18)	(3–20)
				Radon	0.81	188	0.90	110	0.72	78
					(0.70–2.25)	(166–534)	(0.66–2.91)	(83–365)	(0.44–2.43)	(50–272)
				Radon – Low indoor exposures	0.73	172	0.75	94	0.69	78
					(0.59–2.12)	(141–504)	(0.48–2.69)	(60–337)	(0.44–2.43)	(49–271)
				Radon - high exposures	0.07	16	0.13	16	0.0	0.4
					(0.05–0.25)	(11–60)	(0.08–0.48)	(10–60)	(0.00–0.01)	(0.3–2)
				Silica	2.41	573	4.38	549	0.21	24
					(1.67–6.47)	(396–1536)	(2.85–11.96)	(357–1499)	(0.14–0.78)	(15–88)
				Welding	1.32	314	2.43	305	0.08	8
					(0.88–3.65)	(208–866)	(1.56–6.81)	(195–853)	(0.05–0.29)	(6–33)
Breast (female)	23,210	–	23,210	Shift work – Low estimate	2.03	471	–	–	2.03	471
					(1.43–6.18)	(333–1433)			(1.43–6.18)	(333–1433)
				Shift work – High estimate	5.21	1209	–	–	5.21	1209
					(3.71–13.57)	(862–3150)			(3.71–13.57)	(862–3150)
Mesothelium	530	435	95	Asbestos	80.6	427	85.00	370	60.00	57
Urinary bladder	7510	5680	1830		(–)	(–)	(–)	(–)	(–)	(–)
				Diesel engine exhaust	2.66	200	3.46	197	0.17	3
					(1.79–6.63)	(135–498)	(2.28–8.68)	(130–493)	(0.12–0.62)	(2–11)
				PAHs	1.08	81	1.36	77	0.23	4
					(0.79–3.57)	(59–268)	(0.93–4.60)	(53–261)	(0.16–0.86)	(3–16)

BCC, basal cell carcinoma skin cancer; CI, confidence interval; PAR, population attributable risk; PAHs, polychlorinated aromatic hydrocarbons; SCC, squamous cell carcinoma skin cancer; SHS, second-hand smoke.

^a Cancer cases aged 25 years and over for solid tumors, and aged 15 years and over for hematopoietic and lymphoid tumors.

^b Carcinogens associated with at least 50 cancer cases for the stated cancer site.

overall 4.0% (2.7%–5.9%) of incident cases occurring after age 24 years (solid cancers) or age 15–84 (hematopoietic and lymphoid tumors; based on 24 cancer sites and 41 definite or probable carcinogens) were attributable to occupational exposures. In Finland, Nurminen and Karjalainen (2001) reported an overall PAR of 8% for deaths occurring after 24 years of age (based on 28 cancer sites and exposure to definite and suspected carcinogens). Interestingly, in 1981 Doll and Peto estimated (based on deaths from about 20 cancer sites before the age of 65 years) that 4% of all cancer deaths were attributable to occupational carcinogens in the United States. Although these PARs were not estimated with identical methods, because of differences in selected cancer sites, in age at diagnosis and in considered carcinogens, these overall figures are of the same order of magnitude.

It is also very likely that occupational exposures primarily impact a limited number of cancer sites and thus comparisons by cancer site are probably more relevant. PAR estimates calculated in other countries

also vary for the same cancer sites, depending on the selected carcinogens. However the estimates from our study are generally consistent with the ones calculated with the same selection of carcinogens (Supplementary Table S-2) (Boffetta et al., 2010; Doll and Peto, 1981; Nurminen and Karjalainen, 2001; Rushton et al., 2012; Steenland et al., 2003).

The top five cancers based on the number of cases were those of the skin (non-melanoma), lung, female breast, mesothelium and urinary bladder, contributing to a total of 9420 to 10,160 cancer cases diagnosed annually, based on the incidence of these cancers in 2011.

4.1. Cancer sites

Non-melanoma skin cancers are the most numerous occupational cancers (Fartasch et al., 2012) and are largely due to exposure to solar radiation. Several studies have shown increased risks with both

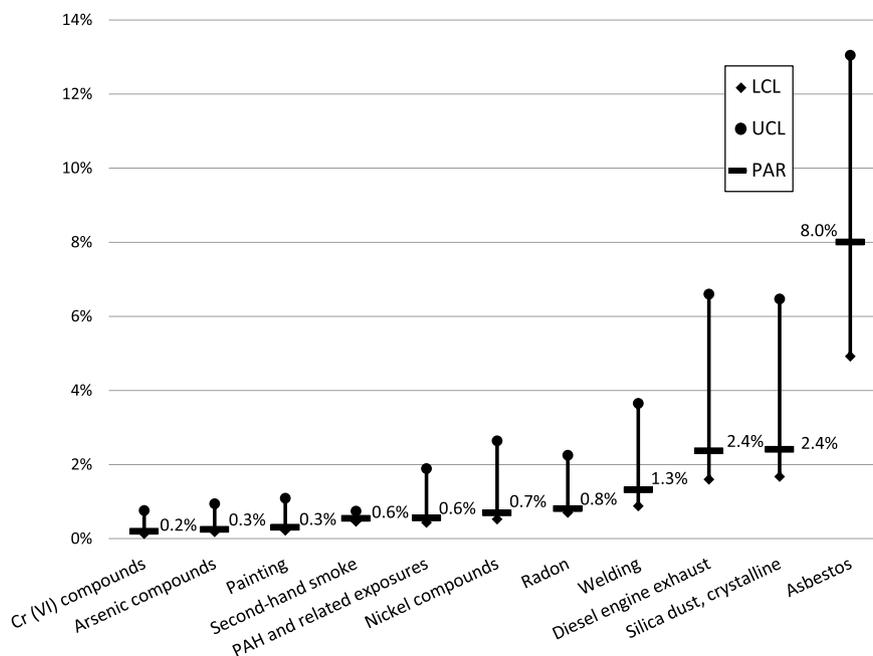


Fig. 2. Population attributable risks of lung cancers attributable to selected occupational exposures (with lower and upper confidence limits). Overall population. Canada, 2011. (Cr (VI), chromium VI; LCL, lower confidence limit; PAR, population attributable risk; UCL, upper confidence limit).

sunburns and intermittent high exposures such as those encountered in outdoor work (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012b; John et al., 2016), and with total lifetime ultraviolet (UV) exposure score (Savoie et al., 2018). Close to 2.32 million Canadian workers experienced medium (defined as mixed indoor and outdoor work) or high (working outdoors during at least 75% of their workday) levels of sun exposure during the REP; most of the burden is attributable to the high exposure of these workers.

After skin cancer, lung cancer is the most common cancer worldwide (Fitzmaurice et al., 2018), thus even a small proportion of attributable lung cancers conveys an important population burden. As the major entry route of air contaminants, the lung is subjected to multiple concurrent exposures and > 25 occupational exposures or working circumstances are considered to be lung carcinogens (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2018). After

removing overlapping exposures, the combined overall PAR for lung cancer in Canada for 17 carcinogens was estimated to be 14.9% (24.4% in men and 3.4% in women). Doll and Peto (1981) estimated that 15% and 5%, respectively for men and women, of lung cancer deaths in the United States could be attributable to occupational exposures. Occupational exposure to asbestos is the largest contributor to the burden of lung cancer in Canadians, with a PAR of 8.0% (13.8% for men and 1.6% for women). Doll and Peto (1981) reported that 5% of lung cancers could be attributed to past asbestos exposures. In Finland, Nurminen and Karjalainen (2001) reported lung cancer PARs of 14.0% for men and 0.6% for women due to occupational asbestos exposure. In Great Britain, asbestos was estimated to be responsible for 8.9% of lung cancers in men and 1.7% in women (Brown et al., 2012a); a ratio of excess lung cancer to mesothelioma cases of 1:1 was used to estimate the PAR, whereas we used a ratio of 4.67:1 based on our internal meta-

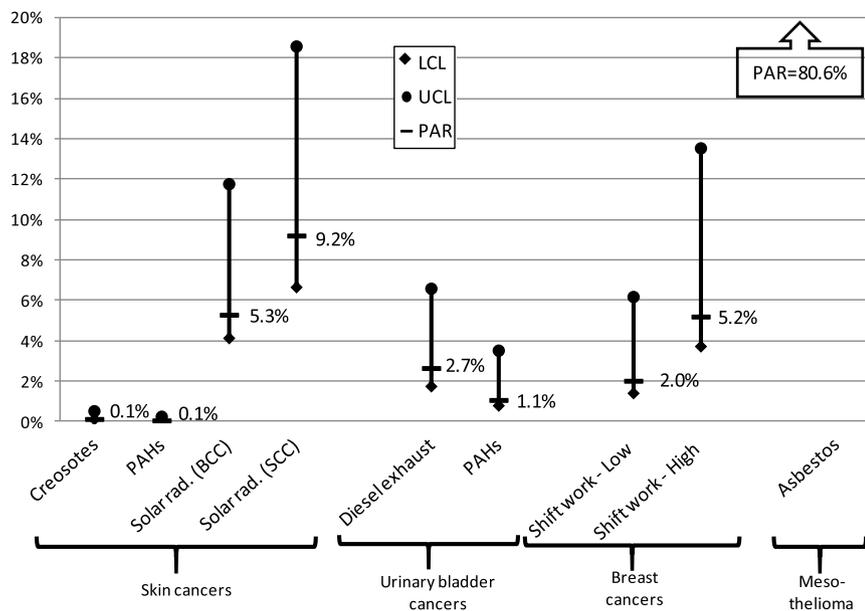


Fig. 3. Population attributable risks of other cancers attributable to selected occupational exposures (with lower and upper confidence limits). Overall population. Canada, 2011. BCC, basal cell carcinoma; LCL, lower confidence limit; PAHs, polycyclic aromatic hydrocarbons; PAR, population attributable risk; SCC, squamous cell carcinoma; Shift work – High, shift work high estimate; Shift work – Low, shift work low estimate; Solar rad., solar radiation; UCL, upper confidence limit.

Table 3

Combined population attributable risk estimates of three occupational cancers sites across different exposures to site-specific carcinogens, by sex. Canada, 2011.

	Total		Men		Women	
	PAR (95%CI)	Attributable cases (95%CI)	PAR (95%CI)	Attributable cases (95%CI)	PAR (95%CI)	Attributable cases (95%CI)
Non-melanoma skin cancer ^a	6.5% (5.8%–12.8%)	4700 (4200–9200)	10.8% (9.0%–21.1%)	4300 (3600–8500)	1.3% (1.1%–3.6%)	420 (370–1200)
Lung ^b	14.9% (10.1%–31.4%)	3500 (2400–7500)	24.4% (16.0%–49.4%)	3100 (2000–6200)	3.4% (2.2%–8.2%)	380 (250–920)
Bladder ^c	4.3% (3.0%–12.0%)	320 (230–900)	5.4% (3.6%–15.2%)	310 (210–860)	0.9% (0.6%–3.2%)	15 (10–60)

CI, confidence interval; PAR, population attributable risk.

^a Non melanoma skin cancer carcinogens included exposure to solar radiation, creosotes and polycyclic aromatic hydrocarbons.^b Lung carcinogens included exposure to acid mist, asbestos, arsenic, beryllium, cadmium, chromium, diesel engine exhaust, second-hand smoke, ionizing radiation, nickel, polycyclic aromatic hydrocarbons, radon, silica, welding fumes; exposures as a painter; exposures in industries of art glass manufacturing and rubber manufacturing.^c Bladder carcinogens included exposure to aromatic amines, diesel engine exhaust, polycyclic aromatic hydrocarbons, tetrachloroethylene; exposures as a painter, a hairdresser or barbers and in rubber manufacturing.

analysis of 15 North American cohort studies (not yet published). Crystalline silica and diesel engine exhaust exposures follow with a similar PAR (2.4%).

Breast cancer is the leading cause of cancer deaths in women globally (Fitzmaurice et al., 2018). Shift work involving circadian disruption is classified as a probable carcinogen for the female breast (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010b). In 2005, an average of 17% of Europeans and 15% of Americans were working shifts that entailed night work, with large variation between industrial sectors (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010b). In Canada, approximately 12% of the working population did shift work in 2005 (Peters et al., 2015). Studies that estimated a PAR associated with shift work in Great Britain (Rushton et al., 2012) and the United States (Purdue et al., 2015) obtained estimates similar to our own of 2–5%.

Mesothelioma is a rare cancer with a global mortality rate estimated to be 9.9 per million people per year, based on statistics from 59 countries (Odgerel et al., 2017). The main recognized risk factor is exposure to asbestos (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012a). The estimated proportion of occupational and para-occupational mesothelioma cases used in our study (85.0% for men and 60.0% for women), derived from three pertinent large case-control studies (including cases retrieved from a French mesothelioma registry (Lacourt et al., 2014)), is consistent with proportion of cases for which an occupational history of exposure to asbestos could be found in the Italian mesothelioma registry (86% for men and 60% for women) (Corfiati et al., 2015).

Urinary bladder cancer is ranked 13th in terms of incident cancers worldwide, but stands between the sixth and the ninth ranks in most European countries and in Canada (Fitzmaurice et al., 2018). Most urinary bladder carcinogens are of occupational origin (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2018). The proportion of bladder cancers attributable to seven carcinogens (5.4% for men and 0.9% for women) is lower than the estimates from other burden estimates (that range between 5.5% and 19% for men and 0.6 and 19% for women) (Boffetta et al., 2010; Brown et al., 2012b; Doll and Peto, 1981; Nurminen and Karjalainen, 2001; Steenland et al., 2003). These differences can be explained by very diverse parameters used in the PAR calculations (different carcinogens, risk estimates) and in variations in industrial sectors across countries (for example, in 1972, Canada was the 4th largest producer of aluminum – a major source of PAHs –, after the USA and ahead of France and the UK (Nappi, 2013)).

4.2. Combined population attributable risks

Concurrent exposures to different occupational carcinogens may occur in some industries or occupations (Supplementary Table S-3). For example, construction workers may be exposed to solar radiation, asbestos, diesel engine exhaust, silica, second-hand smoke and wood dust; metal fabrication workers may be exposed to asbestos, chromium, nickel, other metals, diesel engine exhaust and welding fumes; healthcare workers may experience exposures to night shift work, antineoplastic drugs and ionizing radiation; and agricultural workers may be exposed to diesel engine exhaust, solar radiation, and pesticides. (Hutchings and Rushton, 2012a; Labrèche et al., 2013; Peters et al., 2015). Summing up the PARs from exposures targeting the same organ will overestimate results (Steenland and Armstrong, 2006). Using the complement of the product of the complements to combine PARs has been recommended when the different exposures are statistically independent (Miettinen, 1974; Steenland and Armstrong, 2006). However, co-exposures can occur in a sizeable proportion of occupations (Bertin et al., 2018) and thus probably do not meet the independence assumption. Removal of overlapping lung carcinogens lowered our overall lung cancer PAR estimate by 1.6%, a small but appreciable amount, representing 300 to 400 lung cancer cases.

4.3. Methodologic considerations

The methodologic assumptions and decisions made, together with limited exposure data available, may have produced both underestimations and overestimations of the true burden of occupational cancer. However, specific efforts were made towards reducing the main sources of potential biases and uncertainties associated with the estimation of population attributable risks. In particular, the choice of relative risk estimates and the calculation of employment turnover, identified as the largest contributors to the overall PAR estimates in the British Burden of Cancer project (Hutchings and Rushton, 2017), were subjected to intense scrutiny in order to increase their precision. For the selection of risk estimates, we tried to alleviate the lack of Canadian epidemiologic data by selecting studies that applied the most closely to the Canadian context, presented pooled risk estimates, reported dose-response relationships, and controlled for major potential confounders (notably smoking for lung and bladder cancers).

In addition, precision of exposure assessment was increased by the use of several data sources (primarily CAREX Canada data) that allowed the integration of exposure-response models for about a third of the

carcinogens. This detailed approach to industry and occupation-specific exposure assessment, an important strength of our study, was tailored by agent and specific to the Canadian context. It facilitated the adoption of several scenarios to match the level of detail of both exposure data and risk estimates used to calculate the PARs. Additionally, this more precise exposure assessment gave us the possibility to take into account overlapping exposures in estimating the combined PARs for cancer sites associated with more than one carcinogen, reducing the bias of the estimates compared to the ones that would have been obtained from only applying the complement of the product of complements formula (Miettinen, 1974; Steenland and Armstrong, 2006).

We refined the estimation of the turnover rate and of the occupationally-exposed population by taking advantage of several reliable data sources on the Canadian labour force that accounted for sex, province and industrial context. Matching exposure estimates with risk estimates by occupation was also challenging. In order to avoid mismatches, one of three scenarios was generally adopted, and this allowed us to use the most detailed available exposure data and risk estimates. However in some cases, we had to aggregate exposure levels into broader categories or even a binary variable (exposed vs. non-exposed) to match exposure with available risk estimates, thus possibly increasing non-differential misclassification and increasing uncertainty (Wacholder et al., 1994).

One of the assumptions of a valid PAR estimation is of a causal relationship between exposure and cancer (Rockhill et al., 1998). Most exposures selected for study were agents or exposure circumstances classified as carcinogenic to humans (IARC Group 1) in 2018, and only two were probable carcinogens (IARC Group 2A: creosotes and night shift work). The number of recognized occupational carcinogens increased from 28 to 47 agents between 2004 and 2018, following the availability of additional human evidence (Loomis et al., 2018). As the number of known occupational carcinogens will only increase in the future, our use of an incomplete list of occupational carcinogens almost certainly resulted in an underestimated overall cancer burden attributable to occupational exposure.

The latency of most cancers caused by occupational exposures is not well known, and we presumed the same latency for all solid tumors (10–50 years), as was done in previous studies (Hutchings and Rushton, 2012b; Hutchings and Rushton, 2017). This assumption affects the estimate of the N_{REP} , which in turn affects the PAR. A sensitivity analysis presented by Kim et al. (2018) showed that an increase of 20% in the N_{REP} augmented the PAR for lung cancer associated with diesel exhaust by 14%.

4.4. Preventive interventions

Even with an overall PAR of about 4%, the economic burden is large. For non-melanoma skin cancer due to occupational exposure to solar radiation, the combined annual direct and indirect costs is 28.9 million Canadian dollars (Mofidi et al., 2018), whereas the total cost is 1.87 billion Canadian dollars for lung cancer due to occupational and para-occupational exposure to asbestos (Tompa et al., 2017), and 171 million Canadian dollars for occupational urinary bladder cancers (Jung et al., 2018).

Regarding exposure control, aside from elimination and substitution, which are the most effective methods to reduce occupational carcinogen exposure (Jahn et al., 2015), lowering occupational exposure limits and improving compliance with these limits was reported to be the most effective to reduce the attributable burden of occupational cancers in Great Britain (Hutchings et al., 2012). Additional efforts have to be devoted to exposures that are not currently regulated, such as solar radiation and night shift work. Protective methods can be implemented for solar radiation (e.g. shade provision, clothing, large brim-hat, sunscreen use), but night shift work cannot be totally eliminated (for example in sectors of health care, protective services or hospitality); there are however several promising avenues, such as

better shift scheduling (e.g. shorter periods of consecutive nights, organized in a forward pattern (Neil-Sztramko et al., 2014)) or controlled lighting (Lunn et al., 2017; Rahman et al., 2011). Complex mixtures, such as welding fumes or diesel engine exhaust, for which occupational exposure limits exist for single components but may not protect from long term carcinogenic effects of the mixture (Henschler, 1991) pose a particular problem that requires further methodological development (Kienzler et al., 2016).

5. Conclusion

Methodologic efforts are still warranted to better consider competing causes of cancer, to explore the sensitivity of burden estimates and to reflect on assumptions and their impact on correctly interpreting the PARs. However, the present results highlight several occupational exposures and their associated cancer sites that already need recognition and preventive efforts. As stated by Doll and Peto (1981), "... [occupational] risks can usually be reduced, or even eliminated, once they have been identified. The detection of occupational hazards should therefore have a higher priority in any program of cancer prevention than their proportional importance might suggest." p. 1245.

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Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpmed.2019.03.016>.

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