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The current and future burden of cancer attributable to modifiable risk factors in Canada: Summary of results

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A R T I C L E I N F O

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A B S T R A C T

Nearly one in two Canadians are expected to be diagnosed with cancer in their lifetime. However, there are opportunities to reduce the impact of modifiable cancer risk factors through well-informed interventions and policies. Since no comprehensive Canadian estimates have been available previously, we estimated the proportion of cancer diagnosed in 2015 and the future burden in 2042 attributable to lifestyle and environmental factors, and infections. Population-based historical estimates of exposure prevalence and their associated risks for each exposure-cancer site pair were obtained to estimate population attributable risks, assuming the exposures were distributed independently and that the risk estimates were multiplicative. We estimated that between 33 and 37% (up to 70,000 cases) of incident cancer cases among adults aged 30 years and over in 2015 were attributable to preventable risk factors. Similar proportions of cancer cases in males (34%) and females (33%) were attributable to these risk factors. Tobacco smoking and a lack of physical activity were associated with the highest proportions of cancer cases. Cancers with the highest number of preventable cases were lung (20,100), colorectal (9800) and female breast (5300) cancer. If current trends in the prevalence of preventable risk factors continue into the future, we project that by 2042 approximately 102,000 incident cancer cases are expected to be attributable to these risk factors per year, which would account for roughly one-third of all incident cancers. Through various risk reduction interventions, policies and public health campaigns, an estimated 10,600 to 39,700 cancer cases per year could be prevented by 2042.

1. Introduction

Almost half of Canadians will be diagnosed with cancer in their lifetime and one-quarter are expected to die from it (*Canadian Cancer Statistics* 2017 [Internet], 2017). In 2017, there were an estimated 206,200 newly diagnosed cancer cases and 80,800 deaths due to cancer in Canada (*Canadian Cancer Statistics* 2017 [Internet], 2017). The four most common cancer types in adults (lung, colorectal, breast and

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prostate) together account for approximately half of all cases (*Canadian Cancer Statistics* 2017 [Internet], 2017). Besides the considerable impact of cancer on patients and their families (Canadian Partnership Against Cancer, 2018), the disease also has a significant impact on the Canadian economy, amounting to C$7.5 billion in 2012, which included direct and indirect costs associated with hospital-based care (e.g. acute inpatient care, cancer clinics, chemotherapy, radiation, etc.), healthcare provider services (e.g. fee-for-service), non-publicly funded drugs, and home care services (de Oliveira et al., 2018).

Population attributable risk (PAR) estimates associated with potentially preventable cancer risk factors differ by country due to variation in the prevalence of those factors. In light of this fact, country-specific PAR estimates for lifestyle and environmental factors are important and have recently been published for the United Kingdom, France, United States, Australia, China and Japan (Parkin et al., 2011; Whiteman et al., 2015; Boniol et al., 2008; Wang et al., 2012; Inoue et al., 2012; Schottenfeld et al., 2013). In a country with such a diverse population and regional heterogeneity of cancer risk factors as Canada, exposure distributions can also vary within the country. Therefore, it is informative to not only produce attributable burden estimates nationally, but also by region.

Identifying the relative impact of various exposures on cancer burden in Canada can help health planners and decision-makers prioritize cancer prevention initiatives and, subsequently inform resource planning. It can also help create targeted prevention messaging with the goal of influencing individual risk reduction behaviours. In this study, we estimated the proportions of cancer in 2015 in Canada and its provinces that were attributable to 20 risk factors: 1) lifestyle risk factors thatincluded tobacco smoking and exposure to second-hand smoke, alcohol, excess body weight, lack of physical activity, sedentary behaviour, consumption of red and processed meat, and low fruit and vegetable); 2) environmental risk factors that included ultraviolet radiation, outdoor air pollution, residential radon, and; 3) infections that included hepatitis B and C viruses, *Helicobacter pylori*, Epstein-Barr virus, human papillomavirus, human herpesvirus type 8, and human T-cell lymphotropic virus type 1.

Here, we focus on summary estimates for cancers attributable to all exposures combined in 2015. In addition, we report the projected proportion of cancer attributable to all exposures in 2042, and the estimated proportions of preventable cases using various intervention scenarios aimed at reducing risk factor prevalence.

2. Methods

Details of the methods we used in the Canadian Population Attributable Risk of Cancer (ComPARe) study havebeen published previously (Brenner et al., 2018) and are described in detail in the first article of this Special Issue. Theoretical minimum risks for cancer thresholds and data sources for each exposure are presented in Table 1 of that article. Cancer-risk factor pairs were included in this analysis if they were classified as having a probable association by the International Agency for Research on Cancer (IARC) (International Agency for Research on Cancer, 2018) or the World Cancer Research Fund (WCRF) (World Cancer Research Fund/American Institute for Cancer Research, 2018). As a secondary analysis, we included all cancer-risk factor pairs with probable and suggestive associations to estimate an upper limit of the overall PAR.

We applied the following equation to estimate the summary PAR of multiple lifestyle, environmental, and infectious risk factors for each cancer site by sex, assuming the exposures are independently distributed and that their associated relative risks (RRs) act multiplicatively (Steenland and Armstrong, 2006):

$$PAR_{combined,c,s} = 1 - \prod (1 - PAR_{c,s,i}).$$

where $PAR_{c,\ s,\ i}$, is the PAR for cancer site *c* in sex *s* (male or female) for risk factor *i*.

The number of cases of a cancer attributable to all associated risk factors was estimated by multiplying the number of incident cases in 2015 by its summary PAR. When risk factors were associated with more than one subtype of a given cancer (e.g., cardia- or non-cardia gastric cancer), a summary PAR was estimated for each subtype. The attributable cases were then estimated for each subtype and the sum of the attributable cases of all subtypes was used to estimate the summary PAR for that cancer as a whole.

To estimate the number of future preventable cancer cases under various intervention scenarios, we estimated the summary potential impact fraction (PIF) of all associated risk factors for each cancer by sex, also assuming that the exposures are independently distributed and the relative risks act multiplicatively (Soerjomataram et al., 2010):

$$\mathrm{PIF}_{\mathrm{combined,c,s}} = 1 - \prod (1 - \mathrm{PIF}_{\mathrm{c,s,i}})$$

in which $PIF_{c,\ s,\ i}$, is the PIF for cancer site *c* in sex *s* (male or female) for risk factor *i*. The PIF estimate was then multiplied by the projected number of cancer cases in 2042. Details of the methods used to project cancer incidence to 2042 have been published previously (Poirier et al., 2019a). The year 2042 was used for future burden estimates to allow enough time (25 years from 2018) for potential interventions to be implemented and changes in risk factor prevalence to be obseverd, taking the latency period between exposure and cancer incidence into consideration. We considered modest, moderate and aspirational intervention scenarios for the included cancer risk factors to estimate a range of the number of cancer cases that could be prevented in the future.

To account for the uncertainty in our assumptions, we also estimated the proportion of cancer cases attributable to all associated risk factors for an expanded list of cancer sites with a probable or suggestive association with the risk factor as classified by the IARC (International Agency for Research on Cancer, 2018) or the WCRF (World Cancer Research Fund/American Institute for Cancer Research, 2018). In a sensitivity analysis, we used alternative PAR estimation methods to account for self-report bias for body mass index (BMI) and we used an alternative approach to quantify cancer risk associated with residential radon exposure. Detailed methods for these two exposures are included in this Special Issue (Gogna et al., 2019a; Brenner et al., 2019b). Occupational exposures were not included in this summary analysis since these were estimated in a separate project. The PAR estimates for occupational exposures in Canada are, however, presented in a separate manuscript in this Special Issue (Labrèche et al., 2019).

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. Estimated current burden

Detailed sex- and age-specific results for individual risk factors are presented in separate articles in this Special Issue. Among adults in Canada in 2015, there were 187,070 incident cancer cases. There were more cases in males (94,910) than females (92,160). We estimated that 33.3% (62,320 cases) of those cases were attributable to lifestyle and environmental factors, and infections (Table 1), with several lifestyle risk factors accounting for the highest proportions of preventable cases, namely tobacco smoking (17.5%), lack of physical activity (4.9%), and excess body weight (3.1%). The proportion of cancer attributable to other exposures ranged from 0.1% to 2.3%.

All lifestyle risk factors were associated with 28.0% (52,316 cases) of cancers, environmental factors (ultraviolet radiation, outdoor air pollution and residential radon) for 4.1% (7636 cases) of cancers, and

Table 1
Estimated percentages of incident cancer cases in Canadians in 2015 attributable to established risk factors.

Exposure	Lung	Colorectum	Liver	Oral cavity & pharynx	Larynx	Esophagus	Melanoma	Stomach	Non-Hodgkin's lymphoma	Pancreas	Kidney	Bladder	Female breast	Cervix	Prostate[b]	All
Active tobacco smoking	71.8%	10.4%	24.1%	40.3%	73.6%	42.0%		19.7%		16.6%	17.1%	39.0%	4.6%	25.8%		17.5%
Passive tobacco smoke exposure	1.7%	2.4%											1.3%	10.5%		0.8%
Physical inactivity	11.7%	5.7%				9.2%		11.9%			7.8%	12.5%	7.4%			4.9%
Excess weight		5.9%	9.2%			14.0%		3.7%		5.1%	11.9%		4.1%		3.8%	3.1%
Sedentary behaviour		7.0%											2.8%			1.7%
Alcohol consumption		5.5%	3.6%	17.9%	11.1%	5.7%		1.9%		1.6%			3.2%			1.8%
Low vegetable consumption		2.2%														0.3%
Low fruit consumption		6.1%														0.7%
Red meat consumption		5.3%														0.6%
Processed meat consumption		4.3%						2.6%								0.6%
Ultraviolet radiation[a]							62.3%									2.3%
Outdoor air pollution ($PM_{2.5}$)	6.9%															0.9%
Residential radon	6.9%															0.9%
Epstein-Barr virus				4.4%												0.3%
Helicobacter pylori								49.8%								1.1%
Hepatitis B virus			6.8%													0.1%
Hepatitis C virus			16.5%						0.3%							0.2%
Human papillomavirus				27.4%	12.4%									100%		2.0%
All of the above	79.7%	43.2%	48.3%	66.2%	79.4%	57.4%	62.3%	68.1%	0.3%	22.1%	32.7%	46.6%	21.4%	100%	3.8%	33.3%
Incident cases	25,235	22,610	2205	4425	1145	1960	6865	3475	8290	4405	5930	9870	24,555	1250	3872	187,070
Attributable cases	20,118	9762	1064	2931	910	1126	4276	2368	29	972	1938	4603	5263	1250	146	62,320

Footnote: Risk factors included in estimating the overall summary PAR but not shown in the table include human herpesvirus type 8 and human T-cell lymphotropic virus type 1. Cancers included in estimating the overall summary PAR but not shown in the table include ovarian cancer, endometrial cancer, ureter cancer, gallbladder cancer, thyroid cancer, acute myeloid leukemia, myeloma, Burkitt lymphoma, extranodal NK/T-cell lymphoma, nasal type, Hodgkin lymphoma, gastric mucosa-associated lymphoid tissue lymphoma, primary effusion lymphoma, adult T-cell leukemia/lymphoma, Kaposi sarcoma, cancer of anus, penis, vagina, and vulva.

[a] Included sunburn, sunbathing and indoor tanning.

[b] Advanced cases only.

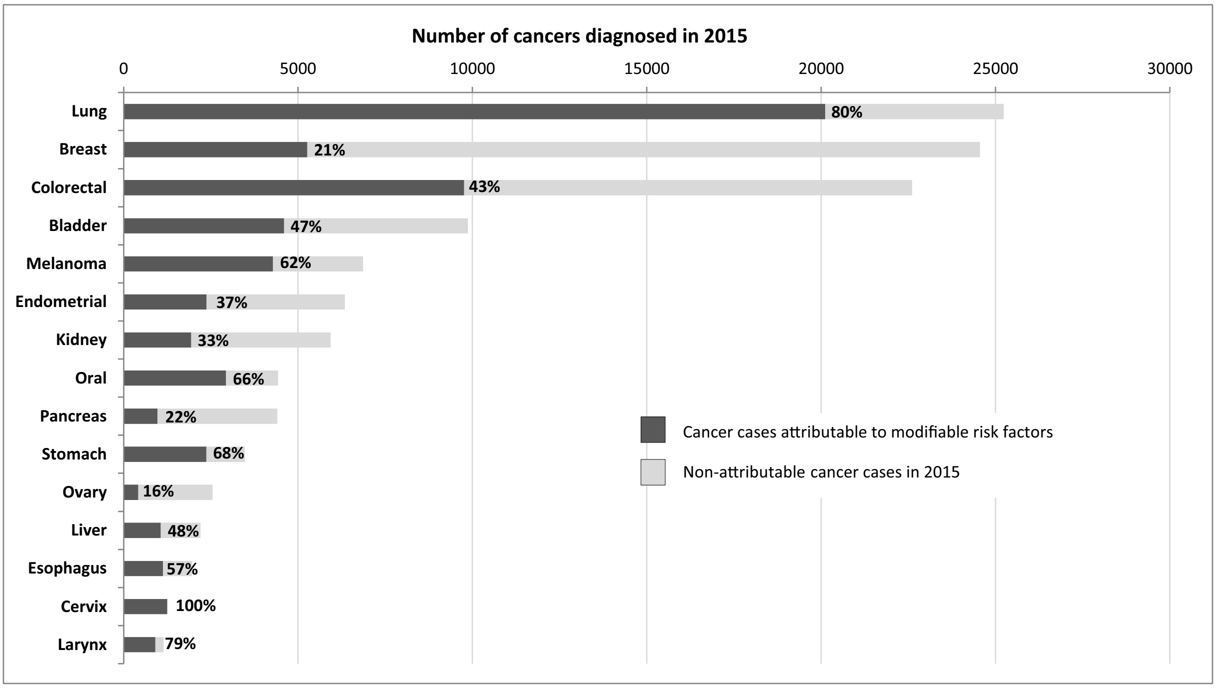

Fig. 1. Number of incident cancer cases in Canada in 2015 and percentages attributable to lifestyle and environmental risk factors, and infections.

infections (hepatitis B and C virus, *Helicobacter pylori*, Epstein-Barr virus, human herpesvirus type 8, human T-cell lymphotropic virus type 1 and human papillomavirus) for 3.7% (6971 cases) of cancers.

In total, 79.7% of lung cancer, 46.6% of bladder cancer, 43.2% of colorectal cancer, 3.8% of prostate cancer and 21.4% of femake breast cancer and were attributable to the risk factors that we considered, these being four of the most common cancer types (*Canadian Cancer Statistics* 2017 [Internet], 2017) (Table 1, Fig. 1).

In males, 33.9% (32,141 cases) of cancers diagnosed in 2015 was attributable to the risk factors examined here (Supplementary Table 1) and were led by tobacco smoking (20.1%), a lack of physical activity (4.0%), and excess body weight (2.6%). A total of 81.6% of lung, 47.9% of bladder, and 47.8% of colorectal cancers were attributable to modifiable factors in males.

In females, 32.7% (30,180 cases) of incident cancers were attributable to the considered risk factors (Supplementary Table 2) and were led by the same risk factors as in males, namely tobacco smoking (14.7%), a lack of physical activity (6.0%), and excess body weight (3.6%). A total of 77.7% of lung, 42.5% of bladder, 37.3% of colorectal and 21.4% of breast cancer were attributable to modifiable risk factors in females.

When risk factors with a probable or suggestive association to cancer were considered together with established risk factors, we estimated that 37.4% (69,990 cases) were attributable to all 20 exposures combined (Table 2). Approximately 17.5% of incident cancer cases was still attributable to active tobacco smoking but 6.4% was now attributable to a lack of physical activity and 3.9% was attributable to excess body weight.

3.2. Esimated future burden

Future cancer burden estimates are presented by individual risk factor and grouped for infections in this Special Issue. We projected that if trends in exposure prevalence continue into the future, about 49,000 cancer cases in males and 53,000 cancer cases in females will occur due to modifiable risk factors in 2042. These numbers amount to about one-third (31%) of the total cancer incidence expected in 2042–170,000 in males and 160,000 in females (Table 3). The PARs due to preventable risk factors for lung cancer are projected to decrease from 79.7% in 2015 to 76.4% in 2042 and for bladder cancer from 46.6% in 2015 to 44.5% in 2042. In contrast, the PAR for colorectal cancer is projected to increase slightly from 43.2% in 2015 to 47.9% in 2042.

3.3. PAR reductions under various intervention scenarios

We estimate that approximately 11,000 cancer cases could be prevented in 2042, under the modest scenario in which current estimates of excess weight are reduced by 5%; average daily intake of processed meat and red meat is reduced by 0.2 and 0.5 servings, respectively; all residential radon exposures above 200 Bq/m^3 are mitigated to 50 Bq/m^3; overall $PM_{2.5}$ levels continue to decrease to a population-weighted average of 5.2 μg/m^3; HPV vaccination direct coverage is maintained at 72.4%; and active and passive smoking, alcohol consumption, inadequate physical activity, sedentary behaviour, low fruit and vegetable consumption, and UV radiation are reduced by 10%, and a 10% population-wide reduction in the current prevalence of HBV, HCV, and *Helicobacter pylori* (Table 4).

A more optimistic estimate of 40,000 cancers could be prevented under the scenario in which excess weight is reduced by 25%; daily intake of processed meat and red meat is reduced by 1 and 2 servings, respectively; all residential radon exposures above 100 Bq/m3 are mitigated to 50 Bq/m3; HPV vaccination direct coverage is increased to 80% among girls and boys; and all other aforementioned risk factors are reduced by 50% at population level (Table 4).

4. Discussion

In 2015, 33.3% of all incident cancer cases in Canada were estimated to be attributable to lifestyle, environmental and infectious agent risk factors. When both probable and suggestive exposure-cancer site pairs were considered together with established risk factors, our estimate increased to 37.4%. If the current trend in the prevalence of these risk factors continues unchanged into the future, 102,000 cancer cases attributed to preventable risk factors are expected to occur by 2042. However, we estimate that by 2042, between 11,000 and 40,000 cancer cases could be prevented per year based on modest and aspirational

Table 2
Estimated percentages of incident cancer cases with established and probable or suggestive associations to the listed risk factors in Canadians in 2015 attributable to modifiable exposures.

Exposure	Lung	Colorectum	Liver	Oral cavity & pharynx	Larynx	Esophagus	Melanoma	Stomach	Non-Hodgkin lymphoma	Pancreas	Kidney	Bladder	Female breast	Cervix	Prostate[d]	All
Active tobacco smoking	71.8%	10.4%	24.1%	40.3%	73.6%	42.0%		19.7%		16.6%	17.1%	39.0%	4.6%	25.8%		17.5%
Passive tobacco smoke exposure	1.7%	2.4%											1.3%	10.5%		0.8%
Physical inactivity	11.7%	8.4%	12.7%	9.9%	9.9%	9.2%		11.9%	3.8%		7.8%	12.5%	7.4%			6.4%
Excess weight[a]		7.4%	11.4%			17.1%		4.7%		6.4%	14.9%		5.3%		4.7%	3.9%
Sedentary behaviour		7.0%											2.8%			1.7%
Alcohol consumption		5.5%	3.6%	17.9%	11.1%	5.7%		1.9%		1.6%			3.2%			1.8%
Low vegetable consumption	5.3%	2.2%	6.9%	9.5%	9.9%	8.4%				7.2%		4.2%				1.9%
Low fruit consumption	11.1%	6.1%				11.0%		2.8%		9.1%		4.1%	5.8%			3.6%
Red meat consumption		5.3%						5.4%		6.7%						1.2%
Processed meat consumption		4.3%				2.6%		2.6%		3.0%						0.9%
Ultraviolet radiation[b]							62.3%									2.3%
Outdoor air pollution ($PM_{2.5}$)	6.9%															0.9%
Residential radon[c]	11.3%															1.5%
Epstein-Barr virus				4.4%												0.3%
Helicobacter pylori								49.8%								1.1%
Hepatitis B virus			6.8%													0.1%
Hepatitis C virus			16.5%						0.3%							0.2%
Human papillomavirus				27.4%	12.4%											2.0%
All of the above	83.7%	45.6%	61.8%	72.4%	83.2%	68.3%	62.3%	71.3%	6.2%	40.9%	34.9%	51.0%	26.9%	100%	4.7%	37.4%
Incident cases	25,235	22,610	2205	4425	1145	1960	6865	3475	8290	4405	5930	9870	24,555	1250	3872	187,070
Attributable cases	21,119	10,314	1362	3205	953	1338	4276	2479	518	1803	2070	5029	6614	1250	182	69,990

Footnote: Risk factors included in estimating the overall summary PAR but not shown in the table include human herpesvirus type 8 and human T-cell lymphotropic virus type 1. Cancers included in estimating the overall summary PAR but not shown in the table include ovarian cancer, endometrial cancer, ureter cancer, gallbladder cancer, small intestine cancer, thyroid cancer, acute and chronic myeloid leukemia, myeloma, Burkitt lymphoma, extranodal NK/T-cell lymphoma, nasal type, Hodgkin lymphoma, gastric mucosa-associated lymphoid tissue lymphoma, primary effusion lymphoma, adult T-cell leukemia/lymphoma, Kaposi sarcoma and cancer of the anus, penis, vagina, and vulva.

[a] Adjusted for self-report bias.
[b] Included sunburn, sunbathing and indoor tanning.
[c] Estimated using the BEIR VI risk model.
[d] Advanced cases only.

Table 3
Estimated percentages of incident cancer cases in Canadians in 2042 attributable to modifiable exposures.

Exposure	Lung	Colorectum	Liver	Oral cavity & pharynx	Larynx	Esophagus	Melanoma	Stomach	Pancreas	Kidney	Bladder	All
Active tobacco smoking	69.7%	10.5%	23.9%	35.4%	72.8%	41.7%		19.0%	15.3%	16.1%	37.9%	14.2%
Passive tobacco smoke exposure	0.6%	0.8%										0.2%
Physical inactivity	9.7%	4.5%				10.0%		9.9%		6.4%	10.5%	3.8%
Excess weight		9.1%	14.5%			22.1%		6.0%	8.1%	19.1%		5.3%
Sedentary behaviour		9.5%										2.6%
Alcohol consumption		9.1%	6.7%	27.6%	17.9%	4.6%		3.2%	3.0%			3.1%
Low vegetable consumption		6.9%										1.0%
Low fruit consumption		2.9%										0.4%
Red meat consumption		5.3%										0.8%
Processed meat consumption		4.3%						2.6%				0.7%
Ultraviolet radiation[a]							29.3%					0.9%
Outdoor air pollution ($PM_{2.5}$)	5.4%											0.6%
Residential radon	6.9%											0.7%
Helicobacter pylori								45.2%				1.3%
Hepatitis B virus			7.0%									0.1%
Hepatitis C virus			11.9%									0.2%
Human papillomavirus				27.0%	12.4%							1.6%
All of the above	76.4%	47.9%	50.3%	65.5%	80.4%	60.9%	29.3%	64.7%	24.4%	36.5%	44.5%	31.0%
Projected incident cases	34,009	49,158	4251	5277	1416	3731	10,349	6712	7468	11,027	14,056	330,104
Attributable cases	25,982	23,564	2140	3456	1139	2272	3032	4345	1823	4021	6248	102,415

Footnote: The cancer incidence projections were described elsewhere (Poirier et al., 2019a); the estimation of future burden of each risk factor were described in individual articles in this Special Issue, with the exception of Epstein-Barr virus, human herpesvirus type 8 and human T-cell lymphotropic virus type 1, which were excluded in the future burden analysis due to a lack of a feasible intervention.

[a] Included sunburn, sunbathing and indoor tanning.

prevention scenarios, respectively. To our knowledge, these projection estimates are the first of their kind for Canada.

In 2015, the proportions of attributable cancer were similar for males (34%) and females (33%). Active tobacco smoking (17.5%), a lack of physical activity (4.9%), and excess body weight (3.1%) were the greatest preventable contributors to cancer burden. These Canadian results are slightly lower than in a previous analysis for Alberta, Canada, where it was estimated that 40.8% of incident cancer in 2012 was attributable to modifiable lifestyle and environmental risk factors, and infections (Grundy et al., 2017). Tobacco smoking (15.7%), physical inactivity (7.2%) and excess body weight (4.3%) were also the greatest contributors to the burden of cancer in Alberta. The difference in the estimate for Canada (33%) compared to Alberta (41%) is likely due to the inclusion of additional cancer sites and exposures with

Table 4
Projected percentages and number of cases of cancer preventable in 2042 based on modest, moderate and aspirational intervention scenarios.

Intervention scenario[a]	Estimate	Lung	Colorectum	Bladder	Oral cavity & pharynx	Larynx	Esophagus	Stomach	Pancreas	Liver	Kidney	Melanoma	All
	Projected cases	34,009	49,158	14,056	5277	1416	3731	6712	7468	4251	11,027	10,349	330,104
Modest	Combined PIF	4.3%	5.1%	3.1%	4.8%	3.0%	2.6%	14.1%	7.7%	5.2%	3.8%	3.4%	3.2%
	Preventable cases	1618	3196	270	391	43	275	513	188	243	553	218	10,687
Moderate	Combined PIF	8.8%	11.3%	7.8%	9.9%	6.5%	5.7%	19.5%	14.8%	10.9%	7.0%	7.0%	6.6%
	Preventable cases	3357	6838	669	743	101	499	1177	377	490	1011	570	21,876
Aspirational	Combined PIF	15.2%	21.3%	15.5%	18.3%	12.3%	11.1%	31.3%	26.6%	20.9%	13.4%	12.9%	12.0%
	Preventable cases	5729	12,525	1322	1301	197	850	2200	705	891	1801	1242	39,716

PIF, potential impact fraction.

Footnote: Epstein-Barr virus, human herpesvirus type 8 and human T-cell lymphotropic virus type 1 were excluded in the future burden analysis due to a lack of feasible intervention.

[a] **Modest**: active and passive smoking, alcohol consumption, inadequate physical activity, sedentary behaviour, low fruit and vegetable consumption, UV radiation, HBV, HCV, and *Helicobacter pylori* infection are each reduced by 10% of the prevalence used for the 2015 burden estimates at the population level; excess weight are reduced by 5%; daily intake of processed meat and red meat is reduced by 0.2 and 0.5 serving, respectively; all radon exposures above 200 Bq/m^3 are mitigated to 50 Bq/m^3; $PM_{2.5}$ continues to decrease to 5.2 $\mu g/m^3$; and HPV vaccination direct coverage is maintained at 72.4%, with herd immunity at 85% among girls and 68% among boys.

Moderate: active and passive smoking, alcohol consumption, inadequate physical activity, sedentary behaviour, low fruit and vegetable consumption, UV-irradiation risk behaviours, HBV, HCV, and *Helicobacter pylori* infection are reduced by 25% of the prevalence used for the 2015 burden estimates at the population level; excess weight is reduced by 10%; daily intake of processed meat and red meat is reduced by 0.5 and 1 serving, respectively; all radon exposures above 100 Bq/m^3 are mitigated to 50 Bq/m^3; $PM_{2.5}$ is decreased by 50%; and HPV vaccination direct coverage is maintained at 72.4%, with herd immunity at 85% among girls and 68% among boys.

Aspirational: active and passive smoking, alcohol consumption, inadequate physical activity, sedentary behaviour, low fruit and vegetable consumption, UV-irradiation risk behaviours, HBV, HCV, and *Helicobacter pylori* infection are reduced by 50% of the prevalence used for the 2015 burden estimates at population level; excess weight is reduced by 25%; daily intake of processed meat and red meat is reduced by 1 and 2 servings, respectively; all radon exposures above 100 Bq/m^3 are mitigated to 50 Bq/m^3; $PM_{2.5}$ is decreased by 50%; and HPV vaccination direct coverage is increased to 80% among boys and girls, with herd immunity increased to 93% among girls and 83% among boys.

probable or suggestive of an association with modifiable risk factors in the Alberta analysis. This reasoning is supported by our sensitivity analysis, which included cancer sites with limited evidence, in which our upper summary estimate was 37%.

The overall PAR estimate of 33.3% for Canada is similar to estimates in some countries. Parkin et al. estimated that in 2010, 42.7% of incident cancers in the UK were attributable to modifiable lifestyle and environmental risk factors, and infections (Parkin et al., 2011). The majority of the risk factors identified in the UK analysis were in common with our analysis. However, Parkin et al. included occupational exposures, breastfeeding, hormone use and dietary fibre and salt intake, and did not include outdoor air pollution or sedentary behaviour. In addition, the study included both probable and suggestive exposure-cancer site pairs. Consistent with our findings, the overall PAR for males (45%) was higher than for females (40%) in the UK. There were also differences in the greatest contributors to cancer burden between Canada and the UK. In our study, tobacco smoking, a lack of physical activity, and excess body weight contributed to the largest proportion of cancer, whereas in the UK, tobacco smoking (19.4%) and excess weight (5.5%) were followed by inadequate fruit and vegetable consumption (4.7%) and a lack of physical activity only accounted for 1.0% of cancer (Parkin et al., 2011).

In Australia, the overall PAR of cancer in 2010 attributable to modifiable risk factors was 31.9% (Whiteman et al., 2015), which is slightly lower than our Canadian estimates. The Australian study included insufficient breastfeeding and fibre intake as risk factors but did not include outdoor air pollution or residential radon exposure. Similar to Canada, tobacco smoking was responsible for the highest proportion of cancer cases in Australia (13.4%), however, the second highest PAR estimate was for ultraviolet radiation (6.2%), followed by overweight and obesity (3.4%) (Whiteman et al., 2015). A lack of physical activity accounted for 1.6% of cancer in the Australian study.

The difference in the order of risk factors contributing to cancer burden in Australia, the UK and Canada highlights the role that cultural differences relating to lifestyle and behaviours can have in PAR estimates across different populations. In general, the difference in PAR estimates between geographic regions are due to differences in exposure prevalence and, to a lesser extent, the use of different risk estimates in the PAR analyses. Variations in the methods used for PAR estimations for specific risk factors based on the data available are also a source of variation between studies.

It is possible that the Canadian PAR due to modifiable exposures will increase beyond our upper estimate of 37%, because the scientific evidence base continues to identify new risk factor and cancer associations. This expansion and progress can be observed between versions of the IARC monographs and WCRF reports, where additional cancer sites have moved up the evidence hierarchy when additional data become available. Furthermore, new and emerging risk factors will undoubtedly be discovered For example, sedentary behaviour as a new risk factor for cancer has only recently been identified, and now has a growing evidence base for multiple cancer sites (World Cancer Research Fund/American Institute for Cancer Research, 2018).

Based on our estimates, if interventions targeting modifiable cancer risk factors were implemented today, 10,600 to 39,700 cases of cancer could be prevented each year by 2042. This number of prevented cancers would be a substantial reduction in the future burden of cancer in Canada and highlights the importance of prioritizing the development and implementation of cancer prevention strategies at the population level.

4.1. Limitations

Our approach to estimating summary PAR for multiple risk factors relies on the assumptions that the risk factor exposures are independently distributed and the risk measures act multiplicatively (Steenland and Armstrong, 2006). When these assumptions are not met, this approach might over- or under-estimate the summary PAR (Walter, 1983). We attempted to quantify this bias by modeling joint exposure distributions in more detail for some risk factors (Poirier et al., 2019b). Unfortunately we were unable to account for their interactions and the associations between risk factors in our analysis. Information on the risk interactions between any two factors is rare. Although our summary estimates do account for the fact that some cancers are caused by multiple factors, a single source of prevalence data for all risk factors, including all their joint distributions, was not available, and therefore a PAR analysis including joint exposure interactions was not feasible. Hence, these results should be interpreted with caution, since the summary PAR estimates may have been associated with more than one risk factor, and thus the results could be biased.

PAR estimates are only as valid as the prevalence data and risk estimates upon which they are based. We used the most robust data available in Canada (and for infections – data from the United States and Western Europe). For most exposures, we were able to obtain data from representative population-based surveys of provincial and national populations. However, for some exposures (e.g. infections, and ultraviolet radiation) we had to rely on prevalence estimates from cohort studies (Gogna et al., 2019a; Volesky et al., 2019; O'Sullivan et al., 2019; Gogna et al., 2019b). Details about the limitations associated with exposure prevalence data for each of the exposures included here can be found in the exposure-specific manuscripts in this Special Issue. In addition, our projection estimates should be interpreted with caution, since both the prevalence projections and cancer incidence projections rely on assumptions (e.g. trends assumed to stay constant, increase or decrease in the future) and thereby involve some degree of uncertainty (Poirier et al., 2019a).

We used a systematic approach for the inclusion of exposure-cancer site pairs (Brenner et al., 2018; Brenner et al., 2019a). However, we acknowledge that the strength of causal evidence differs by exposure and cancer site and therefore, some of the associations with weaker evidence could lead to mis-estimated PARs. As part of a sensitivity analysis, we estimated the overall proportions of cancer attributable to modifiable risk factors deemed to be probable or suggestive causes of specific cancers by the WCRF or IARC (International Agency for Research on Cancer, 2018; World Cancer Research Fund/American Institute for Cancer Research, 2018). When probable and suggestive exposure-cancer site pairs were included, the overall PAR estimate was 37% compared to 33% when only well-established pairs were included. This difference demonstrates that including exposure-cancer site pairs based on suggestive evidence could lead to a mis-estimation if the exposure-cancer site pairs with weaker evidence are, in fact, not true associations. Conversely, if the associations between these potential exposure-cancer site pairs are true, then our PAR of 33% would be an underestimate.

We acknowledge that our analyses do not incorporate several key components of individual and population-level cancer risk. Factors such as individual germline genetics, family history of cancer and screening uptake were beyond the scope of our project, but merit consideration in future cancer burden modeling strategies

4.2. Conclusion

Our estimates suggest that between 33% and 37% of cancer diagnosed in Canada in 2015 was attributable to one or more of 20 modifiable lifestyle and environmental risk factors, and infections. These comprehensive results can help inform and prioritize policy and interventions targeting these risk factors, with the potential to reduce the future burden of cancer in Canada substantially.

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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.ypmed.2019.04.007.

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