Cancer Incidence Attributable to Insufficient Fibre Consumption in Alberta, Canada in 2012

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ABSTRACT

Background: Insufficient fibre consumption has been associated with a decreased risk of colorectal cancer. The purpose of this study was to estimate the proportion and absolute number of cancers in Alberta that could be attributed to insufficient fibre consumption in 2012.

Methods: The number and proportion of colorectal cancers in Alberta attributable to insufficient fibre consumption were estimated using population attributable risk calculations. Relative risks were obtained from the World Cancer Research Fund's 2011 Continuous Update Project on colorectal cancer and the prevalence of insufficient fibre consumption (<23g/day) was estimated using dietary data from Alberta's Tomorrow Project cohort. Age and sex specific colorectal cancer incidence data for 2012 were obtained from the Alberta Cancer Registry.

Results: In the Tomorrow Project cohort, 66 – 67% of men and 73 – 78% of women reported a diet with insufficient fibre consumption. Population attributable risks for colorectal cancer were marginally higher in men (6.3 – 6.8%) than in women (5.0 – 5.5%) and overall 6.0% of colorectal cancers or 0.7% of all cancers in Alberta in 2012 were attributable to insufficient fibre consumption.

Interpretation: With an estimated population attributable risk of 6.0%, as a modifiable exposure, increasing fibre consumption in Alberta has the potential to reduce to the future burden of colorectal cancer in the province.

INTRODUCTION

This manuscript is the seventh in a series of exposure-specific manuscripts concerning the proportion of cancer attributable to modifiable lifestyle and environmental risk factors in the general population of Alberta. The methodologic framework for this series methods has been previously described.[1]

In a follow up from their 2007 analysis (WCRF, 2007), in 2011 the World Cancer Research Fund Continuous Update Project focusing on colorectal cancer identified 12 new cohort studies addressing associations with dietary fibre and determined that the evidence for a fibre-colorectal cancer relationship could be classified as convincing for a decreased risk of colorectal cancer.[2] While the exact mechanism through which fibre consumption influences colorectal cancer risk is not entirely clear, several plausible biological pathways have been hypothesized and investigated. Specifically, increased fibre consumption is thought to increase fecal bulk, diluting carcinogens and decreasing transit time through the bowel, reducing the opportunity for said carcinogens to interact with the intestinal lumen.[3] Further, both alterations to bile acid metabolism and the fermentation of fibre by microflora present in the colon leading to an increase in apoptosis are also considered potential mechanisms that could link fibre consumption with a decreased risk of colorectal cancer.[3, 4]

Previous work has estimated that 12.2% of colorectal cancers diagnosed in the United Kingdom in 2010 were attributable to insufficient fibre consumption, which translated to a population attributable risk of 1.5% for all cancers.[5] However, to our knowledge, no similar estimates exist for Canada and more specifically, the province of Alberta. The purpose of this study was to estimate the proportion and number of colorectal cancers in Alberta in 2012 that could be attributed to insufficient intake of dietary fibre.

METHODS

A similar approach to Parkin and Boyd [5] was employed to evaluate population attributable risks of colorectal cancer related to insufficient fibre consumption, as well as population attributable risks for colon and rectal cancers individually. Levels of fibre consumption in Alberta were obtained from data from Alberta's Tomorrow Project.[6] As described in our previous study on meat consumption, the Tomorrow Project is a population-based cohort study conducted in Alberta, Canada that includes a diet history questionnaire as part of baseline data collection.[6] The diet history questionnaire was composed of a cognitive-based food-frequency questionnaire developed by the United States National Cancer Institute as a tool to assess diet over the preceding 12 months.(Bryant, 2006) Data used in this analysis was collected between 2000 and 2009, where data derived from the diet history questionnaire was used to estimate total dietary fibre intake in grams per day. We used a guideline of 23 g/day of fibre intake to evaluate attributable risks related to colorectal cancer in line with previous estimations.[5] This is within the range of 21 – 38 g/day of both dietary and functional fibre intake recommended for general health by Health Canada. Total dietary fibre intake from Tomorrow Project data was divided into deciles using all data and the mean level of consumption, the deficit between this mean and the 23 g/day guideline and proportion of the population in each decile, was estimated for men and women in four age groups (35 – 44, 45 – 54, 55 – 64, ≥65), as shown in Table 1.

Relative risks linking fibre intake to colorectal cancer, as well as colon and rectal cancers individually, were obtained from the World Cancer Research Fund Continuous Update Project publication on colorectal cancer from 2011.[2] As fibre intake is considered protective for colorectal cancer, the risk associated with a decrease of 1 gram per day of fibre intake was estimated according to equation 1:

$$Equation\ 1: Risk\ per\ gram = \frac{\ln\left(\frac{1}{RR_x}\right)}{x}$$

where x represents the exposure level in grams per day of the original relative risk. These values for colorectal, colon and rectal cancer are summarized in Table 2.

As previously described [1], follow up times from cohort studies in the existing peer-reviewed literature were examined to determine the most appropriate latency period between fibre consumption and colorectal cancer development. Specifically, we distinguish between the theoretical latency period (time between initiation of exposure and cancer diagnosis) and the measured latency period (time between exposure measurements and cancer diagnosis), where we attempted to quantify the measured latency period from high-quality cohort studies and refer to it simply as the latency period. Follow up times from assessment of fibre consumption at baseline to case ascertainment in published cohort studies ranged from 6 to 20 years.[7-9] As detailed information on fibre consumption in Alberta by both sex and age group was only available from the Tomorrow Project data, this data source was selected setting the average latency period at 8 years, for data collected between 2000 and 2009.

As in Parkin and Boyd [5], the excess relative risk (ERR) in each fibre consumption category was estimated using equation 2:

$$Equation\ 2: ERR = \{\exp(R_g \times G_x) - 1\}$$

where R_g represents the increase in risk associated with a 1 gram decrease in fibre consumption per day and G_x represents the deficit in consumption (< 23 g/day) of fibre in consumption category x. Population attributable risks were then estimated using equation 3:

$$Equation\ 3: PAR = \frac{(p_1 \times ERR_1) + (p_2 \times ERR_2) + \ldots\ldots + (p_x \times ERR_x)}{1 + [(p_1 \times ERR_1) + (p_2 \times ERR_2) + \ldots\ldots + (p_x \times ERR_x)]}$$

where p_x represents the proportion of the population in consumption category x and ERR_x is the excess relative risk for consumption category x, as described above. To estimate the total number of cancers attributable to insufficient fibre consumption at each site overall, as well as by age-group and gender, population attributable risks were applied to cancer incidence data obtained from the Alberta Cancer Registry for 2012.

Monte Carlo methods were used to construct 95% confidence intervals around population attributable risk point estimates.[10] Prevalence and risk estimates and their associated confidence intervals were used to parameterize a probability distribution from which 10,000 random samples were drawn. A binomial probability distribution was assumed for the prevalence of exposure, a lognormal distribution for risk, and a Poisson distribution for cancer incidence. The 95% confidence intervals were then determined by the 2.5 and 97.5 percentiles of the distribution of simulated population attributable risk and excess attributable cases estimates. Similar techniques were used by two previous studies that estimated population attributable risk.[11, 12] All analyses were conducted in RStudio (version 0.98.1080, R Studio, Inc.).

RESULTS

Fibre intake was characterized using data from the diet history questionnaire included in baseline data collection in Alberta's Tomorrow Project.[6] A greater proportion of women (73.5 – 78.2%) than men (66.2 – 67.3%) in the Tomorrow Project cohort consumed less than 23 g/day of fibre, which was classified as insufficient (Figure 1). The proportions of individuals with insufficient fibre intake were similar across age groups for both men and women and consistently higher for women than men. However, women in the Tomorrow Project cohort had lower overall caloric intake compared to men (1,640 kcal vs 2,237 kcal), which may partially explain the lower levels of fibre consumption.

Population attributable risks and 95% confidence intervals around these population attributable risk estimates for colorectal, as well as colon and rectal cancers separately, are shown in Table 3. As the relative risks of colorectal and colon cancers associated with insufficient fibre consumption are higher for men than women (Table 2), population attributable risks for colorectal cancer were slightly higher in men (6.3 – 6.7%) than in women (5.0 – 5.5%), a pattern also observed for colon cancer (7.4 – 8.0% in men, 3.7 – 4.1% in women). However, for rectal cancer, where the relative risks for men and women are much more similar, the estimated population attributable risks due to insufficient fibre consumption were marginally higher among women (5.6 – 6.2%) than among men (5.2 – 5.6%). Among men and women

combined, 6.0% of colorectal cancers or 0.7% of all cancers diagnosed in Alberta in 2012 were attributable to insufficient fibre intake (Table 4). These estimates translated to an excess 114 cases of colorectal cancer (approximately 71 in men, 42 in women) diagnosed in Alberta in 2012.

INTERPRETATION

Approximately 0.7% of all cancer cases in Alberta in 2012 were attributable to insufficient fibre consumption. Our estimate of the proportion of cancers attributable to insufficient fibre consumption is lower than a comparable estimate produced by Parkin and Boyd for cancer in the United Kingdom in 2010, where 1.5% of cancers were attributable to low fibre intake.[5] There are several important methodological differences that should be considered when comparing the results from the United Kingdom analysis to ours. First, Parkin utilized data from the National Diet and Nutrition Surveys in the United Kingdom, a population-based survey including data from individuals aged 19 – 64 to estimate fibre consumption.[5] In comparison, the data from Alberta's Tomorrow Project used in the current analysis only included individuals aged 35 – 70. In the United Kingdom data, fibre consumption levels were lower in the younger age groups [5] and the exclusion of the younger component of the adult population in Alberta could partially explain the lower observed population attributable risk estimates. In addition, different estimates of relative risk were used for the United Kingdom and Alberta analyses.(Parkin, 2011 fibre) When converted to risk per decrease of 1 gram per day of fibre intake, the RR used by Parkin and Boyd was 0.029 while the comparable estimate from the World Cancer Research Fund Continuous Update Project used in the Alberta analysis was 0.011.[2] The difference between these two estimates of relative risk likely explains a large portion of the observed difference in population attributable risks between the United Kingdom analysis and ours.

Limitations

As information on the prevalence of insufficient fibre consumption was taken from Alberta's Tomorrow Project, the ability of this cohort to accurately represent fibre consumption in the Alberta population needs to be considered. Specifically, as the Tomorrow Project cohort is composed of volunteers, although it is geographically representative of the population of Alberta, the potential for volunteer bias and systematic differences in dietary patterns between participants and non-participants is a possibility. Data on mean fibre consumption in Alberta was available from the Canadian Community Health Survey Cycle 2.2 (Nutrition) conducted in 2004, where equivalent values from the Tomorrow

Project cohort and 2004 Canadian Community Health Survey showed that means for comparable age groups were consistently lower in Canadian Community Health Survey data.[13] Consequently, the Tomorrow Project data may somewhat overestimate fibre consumption levels in Alberta, leading to an underestimation of the proportion of colorectal cancers attributable to insufficient fibre consumption. Further, the use of Tomorrow Project cohort data to estimate fibre consumption levels meant that the longer latency periods suggested by large cohort studies between fibre consumption and colorectal cancer incidence could not be explored.[7-9] As such, if a longer latency period represented a more biologically relevant time window for exposure and fibre consumption levels in Alberta in the more distant past were higher or lower than those captured among Tomorrow Project cohort members, estimates of population attributable risk could have been either over or under estimated.

A strength of this analysis was the use of Monte Carlo methods that incorporated variation associated with estimates of RR and exposure prevalence to produce 95% confidence intervals to quantify the precision of population attributable risk estimates. However, these confidence intervals are relatively wide and indicate that while we estimate an excess 114 cases of colorectal cancer in Alberta due to insufficient fibre consumption, the true number could be as low as 11 or as high as 146. As such, this lack of precision in our population attributable risk estimates needs to be considered when interpreting the results of our analysis.

Conclusions

In conclusion, we estimate that approximately 6.0% of colorectal cancers or 0.7% of all cancers in Alberta in 2012 can be attributed to insufficient consumption of fibre. Although the individual population attributable risks associated with fibre intake are relatively small (<10%), as colorectal cancer is the second most common cancer in Alberta, just under 1% of all cancers in the province can be considered attributable to low fibre intake. Fibre consumption is a modifiable exposure and thus represents a strong target for continued cancer prevention initiatives.

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Table 1. Fibre consumption in grams per day and the proportion of the population in each of ten consumption categories by age/sex group

Fibre Consumption Category (grams per day)	Age											
	35 – 44			**45 – 54**			**55 – 64**			**≥ 65**		
	Grams per day	*Deficit from 23 g/day*	*%*	*Grams per day*	*Deficit from 23 g/day*	*%*	*Grams per day*	*Deficit from 23 g/day*	*%*	*Grams per day*	*Deficit from 23 g/day*	*%*
						MEN						
1: < 9.38	7.35	15.65	6.70	7.29	15.71	7.83	7.28	15.72	8.08	7.49	15.51	8.04
2: 9.38 – 11.84	10.69	12.31	8.03	10.66	12.34	8.11	10.77	12.23	9.57	10.46	12.54	8.47
3: 11.85 – 13.89	12.85	10.15	8.85	12.83	10.17	8.67	12.84	10.16	9.10	12.91	10.09	9.43
4: 13.90 – 15.73	14.83	8.17	9.02	14.82	8.18	9.72	14.91	8.09	9.02	14.78	8.22	7.93
5: 15.74 – 17.63	16.68	6.32	9.05	16.74	6.26	10.28	16.67	6.33	9.18	16.67	6.33	8.90
6: 17.64 – 19.75	18.63	4.36	10.59	18.63	4.37	9.55	18.67	4.33	9.37	18.69	4.31	10.72
7: 19.76 – 22.17	20.87	2.13	10.59	20.92	2.08	10.48	20.94	2.06	10.04	20.93	2.07	10.18
8: 22.18 – 25.47	23.71	0	11.21	23.74	0	10.56	23.79	0	11.14	23.61	0	10.61
9: 25.48 – 30.68	27.77	0	11.62	27.80	0	11.74	27.90	0	11.73	27.84	0	14.15
10: ≥ 30.69	40.10	0	14.35	38.97	0	13.07	38.22	0	12.78	38.98	0	11.58
Mean grams per day	21.14			20.54			20.32			20.45		
						WOMEN						
1: < 9.38	7.29	15.71	12.11	7.08	15.92	11.32	7.19	15.81	11.12	7.17	15.83	10.57
2: 9.38 – 11.84	10.66	12.34	11.30	10.70	12.30	11.56	10.66	12.34	9.60	10.70	12.30	10.32
3: 11.85 – 13.89	12.94	10.06	11.77	12.89	10.11	10.71	12.92	10.08	9.65	13.01	9.99	9.88
4: 13.90 – 15.73	14.82	8.18	11.18	14.82	8.18	10.59	14.82	8.18	9.79	14.83	8.17	10.01
5: 15.74 – 17.63	16.66	6.34	9.97	16.69	6.31	10.38	16.62	6.38	10.47	16.69	6.31	10.25
6: 17.64 – 19.75	18.72	4.28	9.93	18.68	4.31	9.95	18.70	4.30	9.43	18.74	4.26	12.00
7: 19.76 – 22.17	20.87	2.13	9.27	20.95	2.05	9.41	20.97	2.03	10.13	20.88	2.12	12.24
8: 22.18 – 25.47	23.72	0	8.87	23.70	0	9.42	23.73	0	10.81	23.86	0	7.96
9: 25.48 – 30.68	27.75	0	8.50	27.74	0	8.64	27.73	0	9.69	27.73	0	8.76
10: ≥ 30.69	39.03	0	7.11	38.62	0	8.02	37.99	0	9.31	37.88	0	8.02
Mean grams per day	17.96			18.28			18.94			18.51		

Table 2. Estimated risks associated with decreased fibre consumption and latency periods for estimation of population attributable risk

Cancer Site	Gender	RR Estimate	Units	Risk per decrease of 1 gram per day fibre intake	Source	Latency Period
Colorectal	All	0.90	10 g/day	0.011	WCRF, 2011	8 years
	Men	0.88	10 g/day	0.013	WCRF, 2011	8 years
	Women	0.92	10 g/day	0.0083	WCRF, 2011	8 years
Colon	All	0.89	10 g/day	0.012	WCRF, 2011	8 years
	Men	0.86	10 g/day	0.015	WCRF, 2011	8 years
	Women	0.94	10 g/day	0.0062	WCRF, 2011	8 years
Rectum	All	0.91	10 g/day	0.0094	WCRF, 2011	8 years
	Men	0.90	10 g/day	0.011	WCRF, 2011	8 years
	Women	0.91	10 g/day	0.0094	WCRF, 2011	8 years

Table 3. Cancer cases and proportions attributable to insufficient fibre intake in Alberta in 2012

Age at Exposure (years)	Age at Outcome (years)	Colorectal			Colon			Rectum		
		Total Observed Cases[a]	PAR % (95% CI)[b]	EAC[c]	Total Observed Cases[a]	PAR % (95% CI)[b]	EAC[c]	Total Observed Cases[a]	PAR % (95% CI)[b]	EAC[c]
Men										
35 - 44	43 - 52	96	6.3 (0.1-7.1)	6	38	7.4 (0.7-7.8)	3	58	5.2 (0-12.2)	3
45 - 54	53 - 62	280	6.6 (0.2-8.1)	19	139	7.8 (0.9-9.1)	11	141	5.5 (0-13.9)	8
55 - 64	63 - 72	320	6.7 (0.3-8.6)	22	177	8.0 (0.9-9.4)	14	143	5.6 (0-14.3)	8
≥ 65	≥ 73	383	6.6 (0.2-8.5)	25	260	7.8 (0.9-9.3)	20	123	5.4 (0-14.1)	7
Total	Total	1079		71	614		48	465		25
Women										
35 - 44	43 - 52	81	5.5 (1.2-7.5)	4	42	4.1 (0-10.8)	2	39	6.2 (0-14.6)	2
45 - 54	53 - 62	181	5.3 (1.1-7.1)	10	105	4.0 (0-10.4)	4	76	6.0 (0-14.3)	5
55 - 64	63 - 72	202	5.0 (1.0-6.3)	10	125	3.7 (0-9.1)	5	77	5.6 (0-12.3)	4
≥ 65	≥ 73	356	5.1 (1.1-6.9)	18	265	3.8 (0-9.7)	10	91	5.8 (0-13.5)	5
Total	Total	820		42	537		21	283		17
Total										
35 - 44	43 - 52	177	5.9	11	80	5.7	5	97	5.6	5
45 - 54	53 - 62	461	6.1	28	244	6.2	15	217	5.7	12
55 - 64	63 - 72	522	6.1	32	302	6.2	19	220	5.6	12
≥ 65	≥ 73	739	5.9	43	525	5.8	30	214	5.6	12
Total	Total	1899		114	1151		68	748		42

a. Represents total number of incident cancer cases in 2012 from the Alberta Cancer Registry
b. PAR: Population attributable risk. Represents the proportion (%) of cancer cases attributable to insufficient fruit and vegetable consumption. 95% CI represents the 95% confidence intervals around each PAR estimate.
c. EAC: Excess attributable risk. Numbers rounded to nearest case. Values for 'Total' (Men and Women combined) may not match totals for Men and Women.

Table 4: Summary of cases and proportions of cancer in Alberta in 2012 attributable to insufficient fibre consumption

Cancer Site	Total			Men			Women		
	Observed Cases[a]	Excess Attributable Cases[b]	% Attributable[c]	Observed Cases[a]	Excess Attributable Cases[b]	% Attributable[c]	Observed Cases[a]	Excess Attributable Cases[b]	% Attributable[c]
Colorectum	1899	114	6.0	1079	71	6.6	820	42	5.2
Colon	1151	68	6.0	614	48	7.8	537	21	3.8
Rectum	748	42	5.6	465	25	5.4	283	17	5.9
All Associated Cancers[d]	1899	114	6.0	1079	71	6.6	820	42	5.2
All Cancers[e]	15836	114	0.7	8155	71	0.9	7681	42	0.5

a. Represents total number of incident cancer cases in 2012 from the Alberta Cancer Registry
b. Number of cancer cases at individual cancer sites that can be attributed to insufficient fibre consumption.
c. Proportion of cancers at individual cancer sites attributable to insufficient fibre consumption. Calculated as excess attributable cases/observed cases.
d. Represents all cancers with a known association with insufficient fibre consumption, as listed in table. Here this represents colorectal cancer, as colon and rectal cancers are subsets of this.
e. Represents all incident cancers in Alberta in 2012 in all age groups.

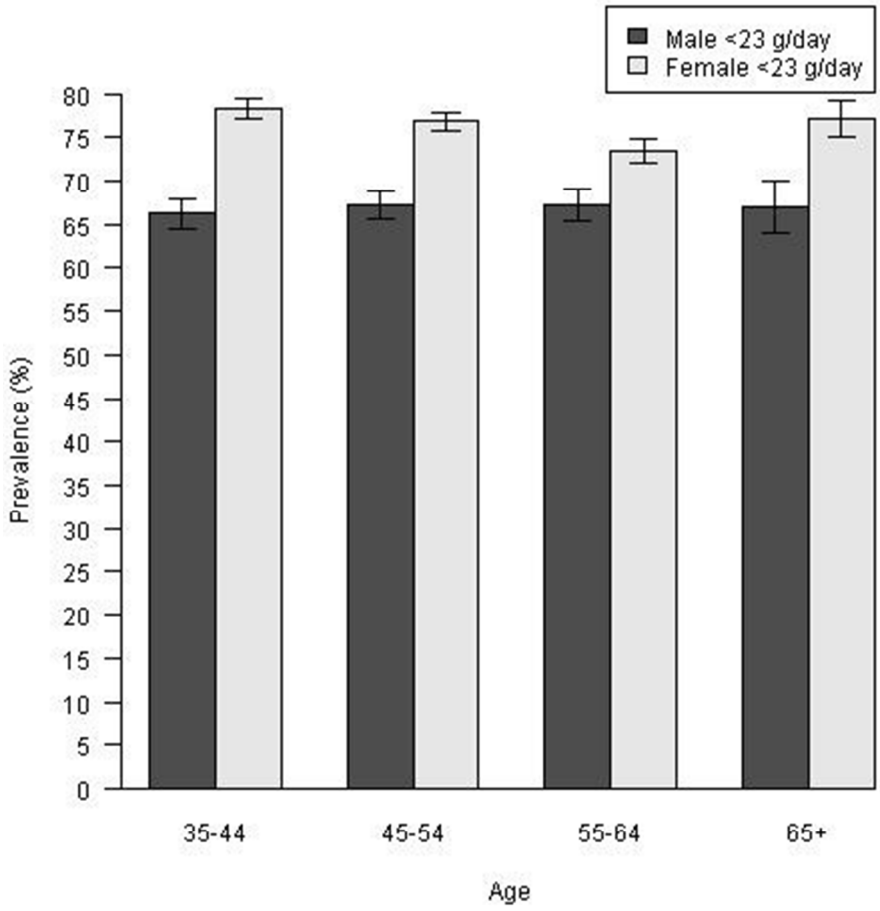

Figure 1 Proportion of men and women in Alberta with insufficient fibre intake (<23 g/day) by age group

A Methodologic Framework to Evaluate the Number of Cancers Attributable to Lifestyle and Environment in Alberta, Canada

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ABSTRACT

Background: Previous research to estimate population attributable risks for cancer in Alberta has been limited. Attributable burden estimates are important for planning and implementing population-based cancer prevention strategies. This manuscript describes a methodologic framework to estimate the number of incident cancers attributable to modifiable lifestyle and environmental risk factors in Alberta, Canada.

Methods: Population attributable risks for cancer were estimated for exposures to 24 established cancer risk factors. These included: tobacco consumption and environmental tobacco exposure, environmental factors, infectious agents, hormone therapies, dietary intake, obesity and physical inactivity. Risk estimates, to quantify the association between individual exposures and cancer sites, as well as prevalence estimates for individual exposures in Alberta were used to estimate the proportion of cancer in Alberta that could be attributed to each exposure. These estimations were conducted in the context of a theoretical minimum risk principle, where exposures corresponding to the lowest levels of population risk were used as the comparisons for alternate exposure levels.

Interpretation: Herein we outline the main methodological principles for the protocol used in evaluating population attributable risks for modifiable lifestyle and environmental risk factors for cancer in Alberta. The findings from this work will be disseminated to the scientific community through publications in peer-reviewed journals and conference presentations, as well as to the general public and public health professionals in collaboration with the Alberta Cancer Prevention Legacy Fund.

BACKGROUND

Population attributable risks provide an estimate of the proportion of a given disease that can be attributed to exposure to an individual risk factor.[1] These estimates inform public health planning and disease prevention programs by identifying exposures that have the greatest impact on disease incidence.

To date, limited research effort has focused on estimating these population attributable risks for modifiable risk factors and cancer in Canada and more specifically in Alberta. A 2009 analysis of the economic burden of occupational cancers in Alberta [2] did not include any population-based estimates of attributable fractions of cancer for non-occupational exposures. Additionally, while there have been a number of efforts in recent years to address the population attributable risks of individual risk factors for either Canada or other provinces individually [3-9], no systematic estimations of attributable cancer incidence across the spectrum of modifiable lifestyle and environmental risk factors have been completed in Canada. Since information concerning the fraction of cancer attributable to individual risk factors is essential for both resource allocation and implementation of population-based cancer prevention strategies, additional research that identifies priorities for modifiable cancer risk factors in Alberta is needed. To address this need, we conducted a systematic estimation of the burden of cancer attributable to all accepted modifiable risk factors in Alberta. In this paper we describe the methodologic framework that was used to identify relevant exposure-cancer associations and systematically estimate the proportion of incident cancer cases attributable to previous exposure to modifiable risk factors among Albertans. As the first in a series of manuscripts that will be presented concerning population attributable cancer risks in Alberta, this paper provides an overview of the general methodologic principles used for all exposures. Exposure-specific manuscripts will provide greater details related to exposure-specific methods.

METHODS

Modifiable lifestyle and environmental risk factors for cancer were selected for inclusion in this project on the basis of a literature search of three main sources: 1) the International Agency for Research on Cancer Monograph Series; 2) the World Cancer Research Fund Report [10]; and 3) recent meta-analyses, large prospective cohort studies and/or the current epidemiologic literature. Selected exposures can be classified in the categories of: tobacco consumption and exposure, environmental factors (air, water and soil contaminants and components), infectious agents, hormone therapies, dietary intake characteristics and energy imbalance. The full list of exposures and cancer sites of interest for this project is shown in Table 2. A secondary consideration in the selection of exposures was the expected range of population prevalence of the individual exposures, since those with very low prevalence are not of high value in population-based preventive efforts assuming moderate risk associations.

Data Sources

Three main types of data are required for the estimation of population attributable risks. These are: 1) the magnitude of the risk association between individual exposures and cancer sites; 2) estimates of the population prevalence of individual exposures; and 3) current age and sex specific cancer incidence data for the associated cancer sites. These data were obtained and used in the analyses for each exposure/cancer site pair of interest.

Risk Estimate Data

As the objective of this work was to produce population attributable cancer risk estimates representative of the general Alberta population, risk estimates applicable to this population were sought from several sources of epidemiologic data. A review of reports from International Collaborative Groups/Panels (e.g. International Agency for Research on Cancer, World Cancer Research Fund), along with a review of the current published peer-reviewed literature in PubMed, was conducted to extract estimates of risk for each exposure and cancer site of interest for this project. Following this review, estimates of relative risk (RR), hazard ratio (HR), odds ratio (OR) or incidence rate ratio (IRR) were

selected according to the hierarchy shown in Figure 1. This strategy assumed that the individual risk estimates reflect biological phenomena, such that results from populations outside Alberta or Canada are applicable to the Alberta population. For individual exposures, risk estimates corresponding to the highest available rank on the hierarchy were used in exposure-specific analyses. For example, if risk estimates were available from both international collaborative panels and recent meta-analyses, the estimate from an international collaborative panel was used since it corresponded to a higher rank on the hierarchy presented in Figure 1. This process produced a single risk estimate for each exposure/cancer site pair, stratified by gender where appropriate, that was used in the estimation of population attributable risks.

Exposure Prevalence Data

Prevalence data for the exposures of interest were collected at the provincial level. Prevalence data were obtained from a search of: 1) results from Statistics Canada surveys; 2) publically available government databases; 3) published peer-reviewed literature; and 4) consultation with relevant experts. Data sources for estimation of exposure prevalence were selected according to the hierarchy shown in Figure 2, were data from the highest ranking available source from the hierarchy were used. Where available, exposure prevalence data were age and sex-specific measures of exposure prevalence were obtained.

For all potential sources of exposure prevalence data, several characteristics of available data sources were considered. First, a theoretical minimum risk principle was used to characterize relevant measures of exposure.[11] This principle refers to the concept that for meaningful population attributable risk estimates, alternative population levels of exposure or exposure distributions must be compared. Under the theoretical minimum risk model, the exposure distribution that corresponds to the lowest level of population risk is used as the comparison.[11] To apply this concept to our analysis, for risk factors where complete lack of exposure is possible, those with any exposure to the risk factor were considered exposed and the prevalence of all potential levels of exposure (if more than one level is appropriate) was obtained for use in population attributable risk calculations. For example, with active tobacco exposure, both current and former smokers were considered to have some level of exposure, with never smokers

used as a comparison (i.e. minimum risk) group. For risk factors where all individuals have some level of exposure such that zero is not a relevant value (e.g. body mass index), the level of exposure associated with the lowest degree of cancer risk was used as the "unexposed" group and the prevalence of higher levels of exposure (ex. overweight and obese for body mass index) was used in population attributable risk calculations.

Since the effect of exposure on cancer risk is assumed to be the product of a previous exposure, we identified a biologically meaningful latency period for all exposures from the literature. To quantify this latency period, we distinguish between the theoretical latency period (the time between initiation of exposure and cancer diagnosis) and the measured latency period (the time between exposure measurement and cancer diagnosis), as shown in Figure 3. For these analyses and the selection of appropriate exposure prevalence data, we attempted to quantify the measured latency period and subsequently refer to this simply as the "latency period" for simplicity. To quantify the measured latency period we used the average time between exposure measurement and cancer diagnosis obtained from high-quality cohort studies. The quality of cohort studies was evaluated based on the size of the cohort, methods of exposure assessment and follow-up time, where large cohorts with detailed exposure and longer follow-up were considered to be of highest quality. This information concerning the latency period was then compared with the time period for which high-quality exposure prevalence data were available. Where possible, prevalence estimates corresponding to the midpoint of the range of potential latency periods identified from cohort studies were selected for analysis. For example, if cohort studies identified potential latency periods as between nine and 13 years, exposure prevalence data incorporating an 11 year latency period were selected for analysis if available. When high-quality exposure prevalence data within the range of latency periods for a given exposure could not be identified, the closest available estimates were used.

The availability of exposure data in units or measures reflective of the selected risk estimates were also evaluated such that, where possible, an exposure data source with similar units to the selected risk estimate was identified. In instances where a less representative exposure data source was utilized

(e.g. cohort instead of survey data), sensitivity analyses were performed where possible to characterize the potential impact of this choice on estimates of population attributable risk.

Cancer Incidence Data

Data on current cancer incidence levels in Alberta were needed to quantify the number of current incident cancer cases that could be attributed to individual exposures. Data on cancer incidence in 2012 (the most recent year for which complete data were available) were obtained from the Alberta Cancer Registry. Cases were classified using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) and the International Agency for Research on Cancer rules for determining multiple primary sites. The complete list of cancer sites and ICD-O-3 codes used for this request are found in Supplementary Table 1.

Analytic Methods

The formula of Levin [12], shown in Equation 1, was used as the basis to estimate most population attributable risk values. This method uses information on the prevalence of a given exposure in the Alberta population in combination with a relative risk measure to estimate population attributable risk.

$$Equation\ 1: PAR = \frac{Pe\ (RR - 1)}{1 + [Pe\ (RR - 1)]}$$

PAR = Population attributable risk
Pe = Prevalence of exposure
RR = Relative Risk

For risk factors with multiple levels of exposure (i.e.. low, medium, high) a variant of this formula, similar to that used by Parkin [13] was used (Equation 2). In this formula, estimates of prevalence in each exposure category (P_{ex}) and excess relative risk (ERR), where ERR=RR-1, are substituted into the Levin formula.

$$Equation\ 2: PAR = \frac{(p_{e1} \times ERR_1) + (P_{e2} \times ERR_2) + \ldots + (P_{ex} \times ERR_x)}{1 + \left((p_{e1} \times ERR_1) + (P_{e2} \times ERR_2) + \ldots + (P_{ex} \times ERR_x)\right)}$$

Equation 1 was used to estimate population attributable risk for exposure to UV; disinfection by-products; oral contraceptives and hormone replacement therapy. The variant approach from Equation 2 was used for tobacco (both active and passive); intake of fruits/vegetables, red/processed meat, alcohol and fibre; overweight/obesity; and physical inactivity.

Population attributable risks associated with infectious disease exposures were evaluated using one of two formulae, similar to the methods of de Martel *et. al.*[14] Population attributable risk is estimated retrospectively in Equation 3, using the prevalence of exposure among cases as a substitute for prevalence of exposure in the population.[15]

$$Equation\ 3: PAR = p_c \frac{(RR - 1)}{RR}$$

p_c = prevalence of exposure among cases

Equation 3 was used for *Helicobacter Pylori*, Epstein-Barr Virus, Hepatitis B and Hepatitis C. Further, as the value of the RR increases, the quantity (RR – 1)/RR approaches a limit of 1, hence population attributable risk can be approximated using Equation 4.

$$Equation\ 4: PAR = p_c$$

Equation 4 was used for HPV and all cancer sites except cervical cancer, as mechanistic information suggests the presence of infection is likely to cause cancer for these infections. In situations where infection is considered a necessary cause of cancer (i.e. HPV and cervical cancer), 100% of cases were considered to be attributed to infection and therefore no population attributable risk estimations were done. Exposure-specific methods that will be described in more detail in individual manuscripts were used for air pollution, radon, and consumption of salt, dietary calcium and vitamin D. A summary of the method used for each exposure included in the full population attributable risk project is shown in Table 1.

To estimate 95% confidence intervals around population attributable risk estimates, Monte Carlo simulation methods were used wherein the relative risk estimates were drawn from a log normal

distribution, prevalence estimates were drawn from a binomial distribution, and incidence estimates were drawn from a Poisson distribution. Parameters for the distributions were defined by reported point estimates and confidence intervals. 10,000 samples were drawn and the 2.5th and 97.5th percentiles of the resulting population attributable risk distribution used as the lower and upper limits of a 95 % confidence interval. Similar techniques were used by two previous studies that estimated population attributable risk.[16,17] Wherever possible and appropriate, these estimations were performed for individual sex and age groups.

These different methods for estimating population attributable risks resulted in a set of proportions of cases by cancer site that can be attributed to these selected exposures. To estimate the specific number of cases of cancer in Alberta that could be attributed to individual exposures, we applied these proportions to the 2012 Alberta Cancer Registry cancer incidence data. Where possible, these estimations were also performed for age and sex specific groups.

INTERPRETATION

The estimation of population attributable risks for cancer for modifiable lifestyle and environmental risk factors for Alberta will allow the proportion of cancer diagnosed in the province that is theoretically preventable to be quantified. This knowledge has implications for cancer prevention since it will identify the modifiable characteristics for which changes in the provincial risk profile are likely to have the greatest impact on Alberta's cancer burden. To our knowledge no systematic effort to quantify the cancer burden attributable to modifiable lifestyle and environmental risk factors has previously been conducted in Canada.

The project most comparable to ours was conducted by Parkin *et al.* to estimate population attributable risks for cancer risk factors in the United Kingdom in 2010.[13,18-32] The general approach used by Parkin *et al.*[13] has been adopted for our project and adapted for several of the exposure-specific methods to apply to the population of Alberta. These similarities will allow the results from our project and Parkin *et al.* to be directly comparable. Our analysis has also been informed by previous

studies of population attributable cancer risk for the individual exposures included in our project, particularly from studies conducted in Canada. In 2014, Brenner estimated that 3.5% and 7.9% of cancers in Canada could be attributed to overweight/obesity and physical inactivity respectively.[4] The methods we chose to assess the impact of these exposures in Alberta will be identical and thus our estimates will be directly comparable to those of the Brenner study. Cancer Care Ontario also published population attributable risk estimates to estimate the cancer burden attributable to tobacco [5], alcohol [33] and obesity [34] in Ontario and similar methods to those that we propose were used. Several studies have also attempted to quantify the proportion of lung cancer attributable to residential radon exposure for Canada as a whole [7, 8, 35], as well as for Ontario specifically.[6] Our estimation of the impact of resedential radon on lung cancer incidence in Alberta uses the method developed by Brand *et al.* [7] and will use the same data source used in previous analyses for Canada [8] and Ontario.[6] The implementation of methods that have previously been used to evaluate population attributable cancer risks in general [13] and for individual exposures [4-8,33,34,35] makes our estimates directly comparable to these previous efforts. Given that no previous estimates of the population attributable cancer risk in Alberta have been conducted, the ability to compare our estimates to others, particularly in a Canadian context, will assist in interpreting our findings.

Limitations

While the systematic evaluation of the population attributable cancer in Alberta described in our protocol will provide novel information about the main causes of cancer in the province, there are some limitations to our approach. First, our protocol does not consider the influence of exposures that occur in an occupational setting in order to prevent duplication of work currently being completed by the Occupational Cancer Research Centre at Cancer Care Ontario concerning the burden of occupational cancer in Canada. [36] Further, the accuracy of the estimates of population attributable risk that will be produced will necessarily be limited by the extent to which the prevalence estimates for individual exposures are representative of the true exposure levels in Alberta. For example, for several dietary

exposures, exposure prevalence was estimated using data from Alberta's Tomorrow Project, a population-based cohort study.[37] Participants in Alberta's Tomorrow Project are volunteers [37] and the potential for volunteer bias (systematic differences between those who volunteer for the study and those who do not) will need to be considered when evaluating whether the prevalence of individual exposures in the cohort is representative of exposure levels in the general Alberta population.

Our analyses are further limited by the fact that we were unable to account for potential interactions between risk factors when quantifying population attributable risks. As many cancers have multiple causes, it is reasonable to suspect some cancer cases may have been caused by interactions between risk factors investigated in our project. In our analysis each risk factor was considered individually, such that cancers that may have been the result of a combination of risk factors would have been counted twice. However, in order to accurately account for these potential interactions in our population attributable risk estimates, exposure data with estimations of the joint distribution of risk factors that may interact are required and these were not consistently available for Alberta across the range of exposures included in our project. We also estimated that the period between exposure and cancer incidence (referred to in the analyses as latency period) would be the midpoint of observed follow-up times between exposure assessment and cancer incidence in large cohort studies. We did not conduct subsequent sensitivity analyses to examine the impact of this choice by modeling the extent to which changes in exposure prevalence across a range of different latency periods would have influenced estimates of population attributable risk.

Through a national collaborative partnership project funded by the Canadian Cancer Society (Grant Number 703106) we will be conducting a similar series of estimations at the national level in Canada. We will be working to address the methodological limitations listed above with a series of statistical advancements that will include joint risk factor considerations and projection of future avoidable disease burden.

Conclusion

The results from the analyses described in this manuscript will estimate population attributable cancer risks for modifiable lifestyle and environmental risk factors for cancer in Alberta. Each of the exposure-specific manuscripts outlined in Table 2 will follow in this journal. The data produced by this project will provide important information concerning which known cancer risk factors are responsible for the largest proportions of cancer in Alberta and could inform future cancer prevention strategies.

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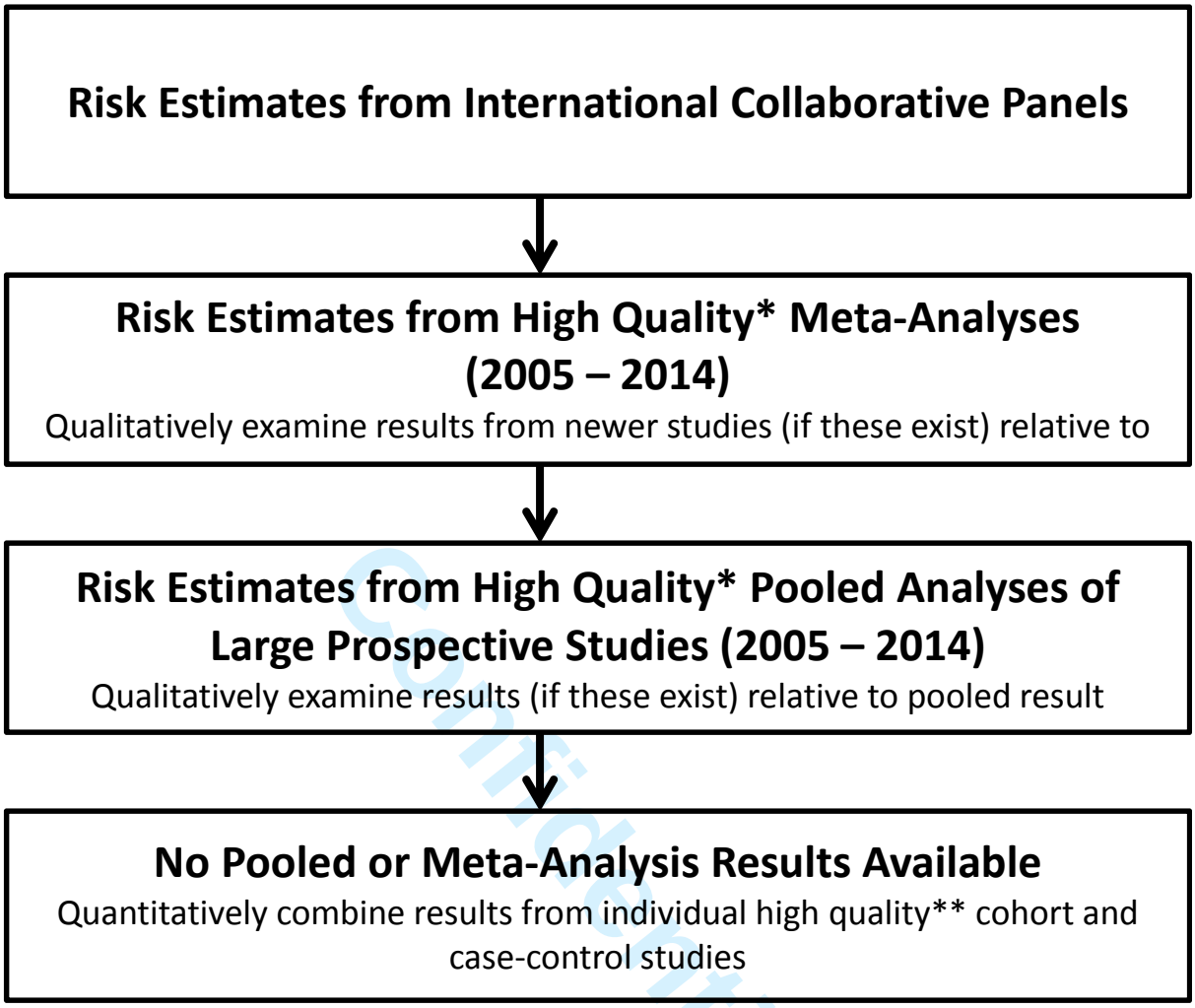
Table 1. The population attributable risk estimation methods employed for the for individual exposures of interest in this Series

Formula for PAR Estimation	Exposure
$Formula\ 1: PAR = \frac{Pe\ (RR-1)}{1+[Pe\ (RR-1)]}$	• tobacco (passive exposure) • UV exposure • disinfection by-products • low vitamin D • high salt intake • low dietary calcium intake
$Formula\ 2: PAR = p_c \frac{(RR-1)}{RR}$	• *Helicobacter Pylori* • EBV • hepatitis B • hepatitis C
$Formula\ 3: PAR = P_c$	• HPV for all cancer sites except the cervix
$Formula\ 4: PAF = \frac{(p_{e1} \times ERR_1) + (P_{e2} \times ERR_2) + \ldots + (P_{ex} \times ERR_x)}{1 + \left((p_{e1} \times ERR_1) + (P_{e2} \times ERR_2) + \ldots + (P_{ex} \times ERR_x)\right)}$	• Tobacco (active exposure) • oral contraceptives • hormone replacement therapy • overweight/obesity • low fruit and vegetable intake • red meat/processed meat intake • high alcohol intake • low dietary fibre intake • physical activity/inactivity
Individualized Methods	• air pollution • radon • insufficient fruit and vegetable intake • red/processed meat intake • insufficient fibre intake • alcohol consumption

Table 2: Exposure and Cancer Site Associations of Interest to be Included in this Project

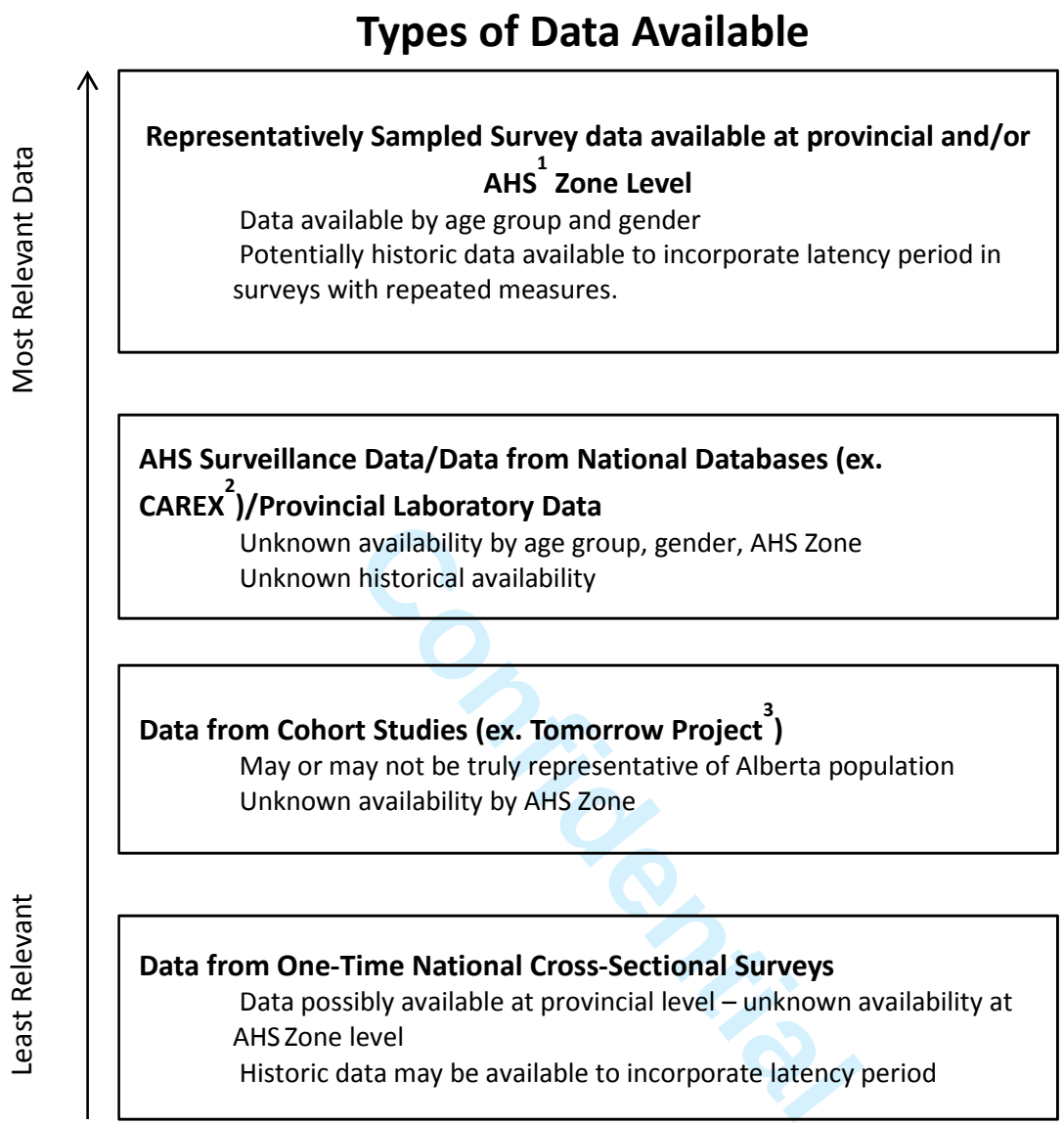
Manuscript	Exposure	Cancer types consistently associated with exposure
1	Active Tobacco Exposure	Lung
		Oral cavity and pharynx
		Oesophagus
		Stomach
		Liver
		Pancreas
		Colorectum
		Larynx
		Cervix
		Ovarian (mucinous)
		Urinary bladder
		Kidney
		Acute myeloid leukemia
	Passive Tobacco Exposure	Lung
		Oral cavity and pharynx
		Oesophagus
		Larynx
2	High Alcohol Intake	Mouth
		Pharynx
		Larynx
		Liver
		Colorectum
		Breast (pre & post-menopause)
3	Overweight/Obesity (>25 kg/m^2)	Breast (post-menopausal)
		Colorectum
		Oesophagus (adenocarcinoma)
		Kidney
		Endometrium
		Gall bladder
		Pancreas
4	Physical inactivity	Breast (post-menopausal)
		Colorectum
		Endometrium
		Lung
		Ovary
		Prostate
5	Low vegetable intake (non-starchy)	Oral cavity and pharynx
		Oesophagus

	Low fruit intake	Stomach Larynx Oral cavity and pharynx Oesophagus Stomach Larynx Lung
6	High red meat intake High process meat intake	Colorectum Colorectum
7	Low fibre intake	Colorectum
8	Low vitamin D High salt intake Low dietary calcium intake	Colorectum Breast Stomach Colorectum
9	**Hormone therapies**	
	Oral contraceptive use	Breast Endometrium Ovary
	Hormone Replacement Therapy	Breast Endometrium Ovary
10	**Infectious agents**	
	Human papillomavirus	Cervix Vagina Penis Anus Vulva Oropharynx
	Helicobacter Pylori	Stomach
	Epstein Barr Virus	Non-Hodgkin lymphoma Hodgkin lymphoma Burkitt's lymphoma Nasopharyngeal carcinoma
	Hepatitis B Virus	Liver
	Hepatitis C Virus	Liver
11	UV Exposure	Melanoma
12	Radon	Lung
13	Air pollution PM 2.5	 Lung



*Quality determined using STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for cohort and case-control studies and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analysis

Figure 1. The process flow used for selecting risk estimates used in this project.



[1] Alberta Health Services
[2] CARcinogen Exposure (CAREX)– a multi-institution research project dedicated to generating evidence based carcinogen surveillance in Canada (www.carexcanada.ca)
[3] The Tomorrow Project is a large prospective cohort study currently being conducted in Alberta to study health outcomes including cancer. The project, which began in 2000, is recruiting adults aged 35 – 69 who will be followed for up to 50 years.

Figure 2. The hierarchy for selection of exposure prevalence estimates

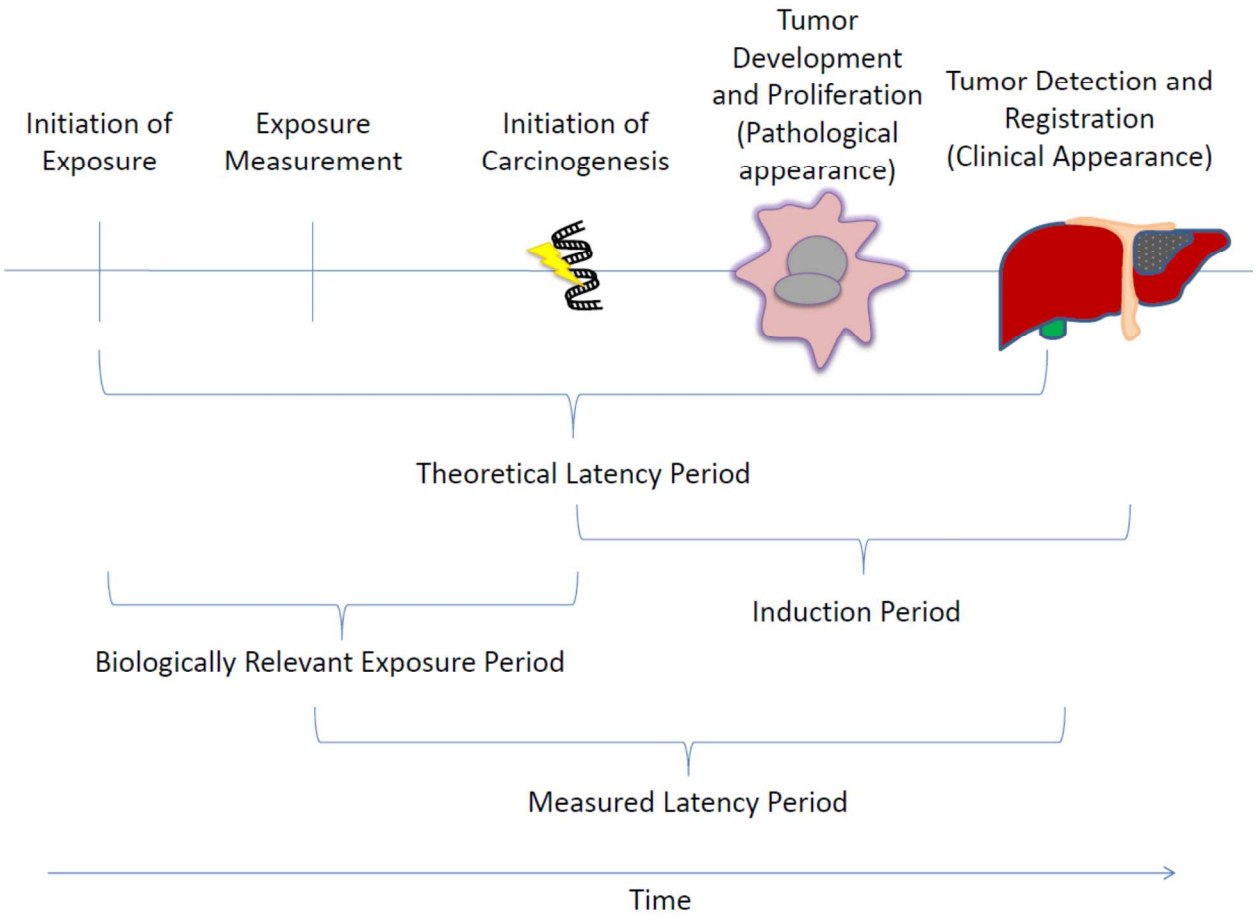


Figure 3. Proposed model of carcinogenesis related to the adverse exposure of interest. The measured latency period is referred to as the latency period for the purposes of estimating population attributable cancer risks in Alberta.