Cancer Incidence Attributable to Red and Processed Meat Consumption in Alberta, Canada in 2012

Anne Grundy PhD[1], Abbey E. Poirier MSc[1], Farah Khandwala MSc[1], Alison McFadden BSc[1], Christine M. Friedenreich PhD[1,2,3], Darren R. Brenner PhD[1,2,3*]

Affiliations:

1. Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services
2. Department of Oncology, Cumming School of Medicine, University of Calgary
3. Department of Community Health Sciences, Cumming School of Medicine, University of Calgary

*To Whom Correspondence should be addressed.

Department of Cancer Epidemiology and Prevention Research
CancerControl Alberta, Alberta Health Services
Holy Cross Centre – Room 513C
Box ACB, 2210 – 2nd St. SW.
Calgary, Alberta
T2S 3C3
Darren.Brenner@albertahealthservices.ca

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ABSTRACT

Background: Red and processed meat consumption has been associated with an increased risk of colorectal cancer. The purpose of this study was to quantify the proportion and absolute number of cancers in Alberta that could be attributed to red and processed meat consumption in 2012.

Methods: The number and proportion of colorectal cancers in Alberta attributable to red and processed meat consumption were estimated using the population attributable risk.. Relative risks were obtained from the World Cancer Research Fund's 2011 Continuous Update Project on colorectal cancer and the prevalence of red and processed meat consumption 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: Among Tomorrow Project participants 41 - 61% of men and 14 - 25% of women consumed more than 500g of red and processed meat per week, exceeding World Cancer Research Fund cancer prevention guidelines. Population attributable risks for colorectal cancer were substantially higher in men (13.6-17.9%) than in women (1.6- 2.1%) for red meat consumption. For processed meat consumption the population attributable risk was also higher among men (3.2-4.8%) than women (1.5-2.1%). Overall approximately 12% of colorectal cancers or 1.5% of all cancers in Alberta in 2012 were attributable to red and processed meat consumption.

Interpretation: With an estimated population attributable risk of approximately 12%, decreasing red and processed meat consumption in Alberta has the potential to reduce to the provincial burden of colorectal cancer.

INTRODUCTION

This manuscript is the sixth 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 2007 the World Cancer Research Fund determined there was a 'convincing increased risk' for colorectal cancer associated with both red and processed meat consumption on the basis of data from both case-control and cohort studies that provided evidence of a dose-response relationship.[2] In 2011 the World Cancer Research Fund's Continuous Update Project evaluated updated evidence concerning this relationship and confirmed the 2007 classification.[3] The World Cancer Research Fund recommends limiting red meat consumption to 'less than 500g (18oz) per week, with very little if any to be processed' for the purposes of cancer prevention.[2] Most recently, in October of 2015, the International Agency for Research on Cancer classified processed meat consumption as a Group 1 carcinogen and red meat consumption as a Group 2 (probable) carcinogen as part of their Monograph program.[4]

Previous analyses from the United Kingdom estimated that 21.1% of colorectal cancers or 2.7% of all cancers in 2010 could be attributed to red and processed meat consumption.[5] However, to our knowledge, no similar estimates exist for Canada or more specifically, Alberta. Given that red and processed meat consumption is a modifiable cancer risk factor, understanding the burden of cancer in Alberta attributable to this dietary characteristic will provide useful information concerning the potential impact of changes in dietary patterns among Albertans with respect to cancer. Thus, the objective of this study was to quantify the proportion and absolute number of colorectal cancer cases in Alberta that could be attributed to red and processed meat consumption in 2012.

METHODS

An adaptation of the method used by Parkin [5] was used to estimate the population attributable risks for both red and processed meat with respect to colorectal cancer (as well as colon and rectal cancer individually) in Alberta. Information on consumption of both red and processed meat was obtained from data from Alberta's Tomorrow Project.[6] The Tomorrow Project is a population-based cohort study conducted in Alberta, Canada [6] and collection of the data used in the current analysis occurred between 2000 and 2009. Participation in Alberta's Tomorrow Project cohort involved completing a baseline study questionnaire and three months after enrollment into the study, participants completed a diet history questionnaire 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.[6] Alberta's Tomorrow Project variables taken from this questionnaire estimated the number of ounces of each of red (beef, pork, lamb, veal, venison, liver etc.) and processed (cold cuts, sausage, ham, hot dogs) meat consumed each day. These values were converted to grams per day for analysis. Overall, red and processed meat consumption was divided into deciles and the mean level of consumption, along with the proportion of the population in each decile was calculated for men and women in four age groups (35 – 44, 45 – 54, 55 – 64, ≥65 years), as shown in Tables 1 and 2.

The relative risks for colorectal cancer, as well as colon and rectal cancer individually, with respect to red and processed meat consumption were obtained from the World Cancer Research Fund's 2011 Continuous Update Project on Colon Cancer.[3] As in Parkin's analysis [5], the assumption was made that the increase in risk for both of these exposures was logarithmic relative to meat intake and as such, the risk per gram of meat intake was estimated using equation 1:

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

where x represents the exposure level in grams per day of the original relative risk. These values are summarized in Table 3.

As has been previously described [1], we considered the theoretical latency period to be the time between initiation of exposure and cancer diagnosis and the measured latency period to be the time between exposure measurement and cancer diagnosis. For the analyses concerning red and processed meat described in this paper, we attempted to quantify the measured latency period from existing high-quality cohort studies and subsequently refer to this simply as the latency period. This process revealed that average follow-up times between meat consumption and colorectal cancer incidence were between 10 and 14 years in previously conducted high-quality cohort studies.[7-9] However, data on meat consumption in Alberta was only available from Tomorrow Project data, collected between 2000 and 2009, such that at 8 years the average latency period examined in this analysis is slightly shorter than that suggested by cohort studies in the literature.

To estimate population attributable risks, the relative risk of meat consumption in each of the ten consumption categories was estimated according to equation 2:

$$Equation\ 2\text{: } RR_x = \exp(R_g \times G_x)$$

where R_g represents the risk per gram of meat consumption as shown in Table 3 and G_x represents the consumption of meat per day in consumption category x, as shown in Table 1 for red meat and Table 2 for processed meat. Population attributable risks were then estimated within each age-sex group according to equation 3:

$$Equation\ 3\text{: } PAR = \frac{\sum(p_x \times ERR_x)}{1 + \sum(p_x \times ERR_x)}$$

where p_x represents the proportion of the population in consumption category x as shown in Tables 1 and 2, while ERR_x represents the excess relative risk in consumption category x, calculated as RR_x - 1. To estimate the total number of cancers at each site overall and by age-group and gender attributable to red and processed meat consumption, population attributable risks were applied to cancer incidence data obtained from the Alberta Cancer Registry for 2012.

To estimate 95% confidence intervals related to 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.[10, 11] Wherever possible and appropriate, these estimations were performed for individual sex and age groups.

RESULTS

The World Cancer Research Fund recommends consumption of less than 500g per week of red meat, with little of this in a processed form.[2] Among Alberta's Tomorrow Project cohort participants, levels of red and processed meat consumption were substantially higher among men than women in all age groups, although consumption did appear to decrease with age in both genders (Figure 1). The proportions of individuals consuming >500g/week of red and processed meat were highest amongst 35 – 44 year olds (men: 61%, women: 25%) and lowest among individuals aged 65 and greater (men: 41%, women: 14%).

The higher prevalence of red and processed meat consumption among men compared to women translated to elevated estimates of population attributable risk among men, particularly for red meat (Tables 4 and 5). Among men, population attributable risks for colorectal cancer related to red meat consumption ranged from 13.6% to 17.9% across age groups, where comparable estimates among women ranged from 1.6% to 2.1% (Table 4). When colon and rectal cancers were considered separately, for both men and women population attributable risk estimates were consistently higher for rectal cancer (Table 4). Differences between men and women were less pronounced when considering population attributable risks associated with processed meat consumption (Table 5), although estimated population attributable risk values remained higher among men (range 3.2% to 4.2%) than among women (range 1.5% to 2.1%) for colorectal cancer. In contrast to the pattern observed for red meat, when colon and rectal cancers were

considered separately, estimated population attributable risk values were higher for colon compared to rectal cancer for both men and women (Table 5).

Overall 9.5% of colorectal cancers were attributable to red meat consumption and 5.9% to processed meat consumption (Table 6). This translates to 181 excess colorectal cancer cases due to red meat consumption and 54 excess cases due to processed meat consumption. There were substantial differences in the number of excess colorectal cancer cases for men and women, where among men 166 excess cases were due to red meat consumption and 41 excess cases due to processed meat consumption, while comparable values for women were 15 excess cases attributable to red meat consumption and 13 cases attributable to processed meat consumption (Table 6). Overall we estimate that 1.1% of all cancers in Alberta can be attributed to red meat consumption and 0.3% to processed meat consumption.

DISCUSSION

Overall 181 colorectal cancer cases were attributable to red meat consumption and 54 to processed meat consumption, which corresponds to approximately 1.5% of all cancers in Alberta. The most comparable previous estimate of population attributable risk for colorectal cancer related to red and processed meat consumption was that completed by Parkin for cancer in the United Kingdom in 2010.[5]

Parkin's analysis estimated that 3.5% of cancers in men and 1.9% of cancers in women (2.7% overall) diagnosed in the United Kingdom in 2010 could be attributed to red and processed meat consumption.[5] These estimates are substantially higher than those we estimated for cancer in Alberta and there are several possible explanations for these differences. First, the reported levels of meat consumption among Tomorrow Project participants in Alberta are substantially lower than those reported in the United Kingdom in Parkin's analysis.[5] These differences could reflect real differences in meat consumption between Alberta and the United Kingdom, but could also be the result of differences in the populations in which the dietary data were measured in the two studies. In Parkin's analysis, data on red and processed meat consumption were obtained from the National Diet and Nutrition Survey, a cross-sectional population survey designed to be representative of all four countries in the United Kingdom and Parkin included data

from ages 19 - 64.[5, 12] In contrast, our analysis used Alberta's Tomorrow Project data which only included individuals aged 35 and older. Given that in the United Kingdom data the mean red and processed meat consumption levels were highest for individuals aged 19 – 34, particularly in men, the exclusion of younger individuals in our analysis could have led to underestimates of overall levels of meat consumption in Alberta and thus partially account for observed differences in estimated Population Attributable Risks.

Limitations

In addition to including only individuals over the age of 35, participants in Alberta's Tomorrow Project are volunteers, such that the ability of the participants in this cohort to accurately represent red and processed meat consumption levels in Alberta needs to be considered. Specifically, while Tomorrow Project participants are geographically representative of the province of Alberta, there may be differences in dietary patterns between participants and non-participants, presenting a risk of volunteer bias. For example, if individuals who eat more red and processed meats systematically chose not to enroll in the cohort, consumption levels estimated in Tomorrow Project data would represent an underestimate of true consumption levels in Alberta. Data published by Cancer Care Ontario from the Canadian Health Measures Survey estimated that the proportions of both men and women exceeding the 500 g/week guideline for red and processed meat consumption were much lower in Canada as a whole than as estimated for Alberta's Tomorrow Project participants.[13] This could indicate that Albertans consume much more red and processed meats than the general Canadian population, or could be due to differences in the techniques used to quantify consumption across these two surveys. Where dietary data for Alberta's Tomorrow Project participants were obtained from a food-frequency questionnaire and intake of red and processed meat in grams per day was converted to grams per week, the Canadian Health Measures Survey used three questions on the number of times per year that individuals consumed different types of red and processed meat with the total number of times per year converted to times per week, where one occasion of consumption was considered as one serving or 75g.[13] As such, estimates of red and processed meat consumption from Tomorrow Project and Canadian Health Measures Survey data are not directly comparable and Canadian Health Measures Survey data cannot be used to reasonably examine the

potential for either over or under estimation of red and processed meat consumption in Alberta's Tomorrow Project.

Our population attributable risk estimates represent the first such estimates for Alberta, making our contribution novel. As well, the use of 95% confidence intervals around our population attributable risk estimates to quantify the precision of these estimates is a strength of our analysis, particularly in comparison to other similar studies that have not estimated 95% confidence intervals.[5] However, these 95% confidence intervals also highlight the lack of precision around our population attributable risk estimates (Tables 4 and 5). Specifically, while we estimate that 181 cases of colorectal cancer are attributable to red meat consumption, this estimate could range from 0 to 759. Similarly, for processed meat, while we estimate 54 colorectal cancer cases are attributable to processed meat consumption, this estimate could range from 0 to 157. These upper estimates would correspond to up to 4.8% of cancers attributable to red meat consumption and 1.0% to processed meat consumption. As such, the lack of precision of our population attributable risk estimates is a limitation of this analysis and should be considered when interpreting the proportion of colorectal cancers in Alberta attributable to red and processed meat consumption.

Conclusions

Overall red and processed meat consumption account for just over 12% of cases of colorectal cancer and around 1.5% of all cancers in Alberta. Further, about half of the men and a quarter of the women participating in Alberta's Tomorrow Project cohort exceed the World Cancer Research Fund's 500g/week recommendation for red and processed meat consumption.[2] If the consumption levels reported among Alberta's Tomorrow Project participants are representative of Alberta as a whole, reducing red and processed meat consumption in the Alberta population could reduce the incidence of colorectal cancer, one of the most common cancer types in Alberta.

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REFERENCES

1. Grundy A, Frienenreich CM, Poirier AE, Brenner DR. The number of cancers attributable to lifestyle and environment in Alberta, Canada: methods and series overview. CMAJ Open. 2016;Under review.
2. Research WCRFAIfC. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007.
3. Research WCRFAIfC. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011.
4. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al. Carcinogenicity of consumption of red and processed meat. The Lancet Oncology. 2015;16(16):1599-600.
5. Parkin DM. 5. Cancers attributable to dietary factors in the UK in 2010. Br J Cancer. 2011;105(s2):s24-S6.
6. Bryant H, Robson PJ, Ullman R, Freidenreich C, Dawe U. Population-based cohort development in Alberta, Canada: a feasibility study. Chronic Diseases in Canada. 2006;27(2):51 - 9.
7. Ruder EH, Thiebaut AC, Thompson FE, Potischman N, Subar AF, Park Y, et al. Adolescent and mid-life diet: risk of colorectal cancer in the NIH-AARP Diet and Health Study. Am J Clin Nutr. 2011;94(6):1607-19.
8. Ollberding NJ, Wilkens LR, Henderson BE, Kolonel LN, Le Marchand L. Meat consumption, heterocyclic amines and colorectal cancer risk: The Multiethnic Cohort Study. International Journal of Cancer. 2012;131(7):E1125-E33.
9. Egeberg R, Olsen A, Christensen J, Halkjaer J, Jakobsen MU, Overvad K, et al. Associations between red meat and risks for colon and rectal cancer depend on the type of red meat consumed. J Nutr. 2013;143(4):464-72.
10. Renehan AG, Soerjomataram I, Tyson M, Egger M, Zwahlen M, Coebergh JW, et al. Incident cancer burden attributable to excess body mass index in 30 European countries. International journal of cancer Journal international du cancer. 2010;126(3):692-702.
11. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. The Lancet. 2012;380(9838):219-29.
12. Agency FS. National Diet and Nutrition Survey. Available from: http://tna.europarchive.org/20110116113217/http://www.food.gov.uk/science/dietarysurveys/ndnsdocuments/.
13. Cancer Care Ontario. Cancer Risk Factors in Ontario: Healthy Weight, Healthy Eating and Active Living. Toronto, Ontario: Cancer Care Ontario, 2015.

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

Meat Consumption Category (grams	**35 – 44**		**45 – 54**		**55 – 64**		**≥ 65**	
	Grams per day	*%*	*Grams per day*	*%*	*Grams per day*	*%*	*Grams per day*	*%*

per day)								
					MEN			
1: < 14.5	8.52	2.66	8.67	3.77	9.13	4.67	8.98	5.89
2: 14.5 – 21.4	18.27	4.00	18.09	4.36	17.97	6.31	17.94	9.11
3: 21.5 – 27.9	25.06	4.92	24.58	5.52	24.80	7.53	24.92	11.58
4: 28.0 – 34.2	31.04	6.56	31.10	6.90	31.09	7.25	31.38	7.61
5: 34.3 – 41.3	37.53	7.48	37.65	7.86	37.58	8.94	38.05	9.97
6: 41.4 – 49.2	45.54	8.40	45.60	9.43	45.00	10.20	45.51	9.75
7: 49.3 – 59.2	54.26	11.31	54.17	11.07	54.16	10.82	53.59	9.65
8: 59.3 – 73.3	65.57	14.14	65.98	13.21	65.88	12.16	65.95	13.72
9: 73.4 – 100.3	85.31	16.77	85.73	16.28	85.92	15.14	86.82	10.93
10: ≥ 100.4	154.29	23.74	154.03	21.60	144.21	16.98	149.84	11.79
Mean grams per day	77.22		73.81		65.00		57.04	
					WOMEN			
1: < 14.5	9.28	10.22	8.95	13.57	9.31	14.86	9.07	19.20
2: 14.5 – 21.4	18.05	11.48	18.07	12.17	17.92	15.03	18.02	15.79
3: 21.5 – 27.9	24.86	12.01	24.71	12.22	24.66	12.34	24.87	14.67
4: 28.0 – 34.2	30.97	11.40	30.98	11.27	30.85	11.10	30.98	11.50
5: 34.3 – 41.3	37.54	12.33	37.59	11.49	37.72	10.76	37.44	10.19
6: 41.4 – 49.2	45.07	10.46	45.22	10.28	45.28	10.71	44.69	8.70
7: 49.3 – 59.2	54.21	10.66	53.81	9.77	53.69	8.24	53.87	8.02
8: 59.3 – 73.3	65.65	9.11	65.58	7.97	65.82	7.83	65.72	5.66
9: 73.4 – 100.3	84.45	7.80	84.19	7.03	85.00	5.87	84.47	4.10
10: ≥ 100.4	131.99	4.53	132.78	4.22	134.37	3.27	129.22	2.18
Mean grams per day	43.20		40.90		38.41		33.81	

Table 2 Processed meat consumption in grams per day and the proportion of the population (%) and corresponding 95% confidence intervals in each of ten consumption categories by age/sex group, Alberta.

Meat Consumption Category (grams per day)	35 – 44		45 – 54		55 – 64		≥ 65	
	Grams per day	% (95% CI)	Grams per day	% (95% CI)	Grams per day	% (95% CI)	Grams per day	% (95% CI)
				MEN				
1: < 1.7	0.88	2.7 (2.1,3.3)	0.92	3.9 (3.2,4.5)	0.93	5.4 (4.5,6.3)	0.97	6.3 (4.8,7.9)
2: 1.7 – 3.1	2.40	2.7 (2.1,3.2)	2.45	3.0 (2.5,3.6)	2.45	5.5 (4.6,6.4)	2.45	6.3 (4.8,7.9)
3: 3.1 – 4.5	3.67	4.7 (3.9,5.4)	3.72	5.7 (5.0,6.5)	3.71	8.5 (7.4,9.6)	3.66	8.0 (6.3,9.8)
4: 4.5 – 6.2	5.25	6.1 (5.2,7.0)	5.24	7.6 (6.7,8.5)	5.23	9.5 (8.4,10.7)	5.24	9.7 (7.8,11.5)
5: 6.2 – 8.2	7.23	9.3 (8.2,10.3)	7.17	9.7 (8.8,10.7)	7.25	10.4 (9.2,11.6)	7.21	12.2 (10.1,14.3)
6: 8.2 – 11.0	9.59	9.7 (8.7,10.8)	9.53	8.8 (7.8,9.7)	9.55	10.0 (8.8,11.1)	9.61	10.6 (8.6,12.6)
7: 11.1 – 15.0	12.90	12.0 (10.8,13.2)	12.79	11.9 (10.8,12.9)	12.76	11.5 (10.3,12.8)	12.95	13.0 (10.8,15.1)
8: 15.0 – 21.5	17.96	13.9 (12.7,15.2)	18.11	14.4 (13.3,15.6)	18.11	12.2 (11.0,13.5)	18.23	11.5 (9.4,13.5)
9: 21.5 – 32.6	26.51	16.8 (15.4,18.1)	26.83	14.6 (13.4,15.8)	26.41	13.0 (11.7,14.3)	26.81	11.2 (9.2,13.3)
10: ≥ 32.6	56.94	22.1 (20.6,23.6)	56.57	20.4 (19.0,21.7)	54.45	13.9 (12.5,15.2)	50.70	11.2 (9.1,13.2)
Mean grams per day	7.19		6.92		6.27		6.02	
				WOMEN				
1: < 1.7	0.97	9.7 (8.8,10.5)	0.99	13.7 (12.8,14.5)	1.02	16.8 (15.7,18.0)	0.96	20.0 (18.1,22.0)
2: 1.7 – 3.1	2.43	8.3 (7.5,9.0)	2.41	10.9 (10.1,11.7)	2.38	13.2 (12.1,14.2)	2.37	14.7 (12.9,16.4)
3: 3.1 – 4.5	3.68	10.4 (9.5,11.2)	3.65	12.7 (11.8,13.5)	3.66	13.6 (12.6,14.6)	3.68	13.6 (11.9,15.3)
4: 4.5 – 6.2	5.24	11.1 (10.2,11.9)	5.21	12.6 (11.7,13.4)	5.25	12.2 (11.2,13.2)	5.17	11.9 (10.3,13.4)
5: 6.2 – 8.2	8	12.6 (11.7,13.5)	7.16	11.9 (11.1,12.8)	7.23	11.7 (10.7,12.7)	7.17	9.1 (7.7,10.5)
6: 8.2 – 11.0	9.57	10.8 (10.0,11.7)	9.50	9.2 (8.4,9.9)	9.56	8.1 (7.3,8.9)	9.60	7.6 (6.3,8.9)
7: 11.1 – 15.0	12.69	10.9 (10.0,11.7)	12.83	9.3 (8.5,10.0)	12.80	7.7 (6.9,8.6)	12.89	6.0 (4.9,7.2)
8: 15.0 – 21.5	17.85	10.9 (10.0,11.7)	17.93	8.0 (7.3,8.7)	17.90	6.7 (5.9,7.4)	17.63	6.7 (5.5,7.9)
9: 21.5 – 32.6	24.94	9.2 (8.4,10.1)	26.30	7.5 (6.8,8.2)	26.11	5.4 (4.7,6.1)	26.09	6.1 (4.9,7.3)
10: ≥ 32.6	49.80	6.2 (5.5,6.9)	47.89	4.3 (3.8,4.8)	46.11	4.5 (3.9,5.2)	47.36	4.2 (3.2,5.2)
Mean grams per day	5.38		4.78		4.42		4.22	

Table 3 Estimated Risks with Consumption of Red and Processed Meat and Latency Periods for PAR Calculations

Cancer Site	Gender	RR Estimate	Units	Risk per gram per day	Source	Latency Period
Red Meat						
Colorectal	All	1.17	100 g/day	0.0016	WCRF, 2011	8 years
Colorectal	Men	1.28	100 g/day	0.0025	WCRF, 2011	8 years
Colorectal	Women	1.05	100 g/day	0.00049	WCRF, 2011	8 years
Colon	All	1.12	100 g/day	0.0011	WCRF, 2011	8 years
Colon	Men	1.00	100 g/day	0	WCRF, 2011	8 years
Colon	Women	1.06	100 g/day	0.00058	WCRF, 2011	8 years
Rectum	All	1.18	100 g/day	0.0017	WCRF, 2011	8 years
Processed Meat						
Colorectal	All	1.18	50 g/day	0.0033	WCRF, 2011	8 years
Colorectal	Men	1.11	50 g/day	0.0021	WCRF, 2011	8 years
Colorectal	Women	1.09	50 g/day	0.0017	WCRF, 2011	8 years
Colon	All	1.24	50 g/day	0.0043	WCRF, 2011	8 years
Colon	Men	1.38	50 g/day	0.0064	WCRF, 2011	8 years
Colon	Women	1.64	50 g/day	0.0099	WCRF, 2011	8 years
Rectum	All	1.12	50 g/day	0.0023	WCRF, 2011	8 years

Table 4 Cancer cases and proportions attributable to red meat intake in Alberta in 2012

Age at Exposure (years)	Age at Outcome (years)	Colorectal			Colon			Rectum		
		Total Observed Cases	PAR % (95% CI)[a]	EAC[b]	Total Observed Cases	PAR % (95% CI)[a]	EAC[b]	Total Observed Cases	PAR % (95% CI)[a]	EAC[b]
Men										
35 - 44	43 - 52	96	17.9 (0-67.3)	17	38	8.5 (0-18.5)	3	58	12.3 (0-24.7)	7
45 - 54	53 - 62	280	17.2 (0-65.6)	48	139	8.2 (0-17.8)	11	141	11.8 (0-23.7)	17
55 - 64	63 - 72	320	15.3 (0-60.4)	49	177	7.2 (0-15.8)	13	143	10.4 (0-21.1)	15
≥ 65	≥ 73	383	13.6 (0-56.1)	52	260	6.4 (0-14.1)	17	123	9.2 (0-19.2)	11
Total	Total	1079		166	614		44	465		50
Women										
35 - 44	43 - 52	81	2.1 (0-14.4)	2	42	4.8 (0-10.7)	2	39	7 (0-14.5)	3
45 - 54	53 - 62	181	2.0 (0-13.4)	4	105	4.6 (0-10.2)	5	76	6.6 (0-13.9)	5
55 - 64	63 - 72	202	1.9 (0-13.0)	4	125	4.3 (0-9.5)	5	77	6.3 (0-13.0)	5
≥ 65	≥ 73	356	1.6 (0-11.5)	6	265	3.8 (0-8.4)	10	91	5.5 (0-11.5)	5
Total	Total	820		15	537		22	283		18
Total[c]										
35 - 44	43 - 52	177	10.7	19	80	6.6	5	97	10.2	10
45 - 54	53 - 62	461	11.2	52	244	6.6	16	217	10	22
55 - 64	63 - 72	522	10.1	53	302	6	18	220	9	20
≥ 65	≥ 73	739	7.8	58	525	5.1	27	214	7.6	16
Total	Total	1899		181	1151		66	748		68

a. PAR, population attributable risk
b. EAC, excess attributable cases. Numbers rounded to nearest case.
c. Values for 'Total' (Men and Women combined) may not match individual totals for Men and Women.

Table 5 Cancer cases and proportions attributable to processed meat intake in Alberta in 2012

Age at Exposure (years)	Age at Outcome (years)	Colorectal			Colon			Rectum		
		Total Observed Cases	PAR % (95% CI)[a]	EAC[b]	Total Observed Cases	PAR % (95% CI)[a]	EAC[b]	Total Observed Cases	PAR % (95% CI)[a]	EAC[b]
Men										
35 - 44	43 - 52	96	4.8 (0-16.0)	5	38	9.9 (5.7-13.9)	4	58	5.2 (0-11.2)	3
45 - 54	53 - 62	280	4.5 (0-15.5)	13	139	9.3 (5.3-13.3)	13	141	4.9 (0-10.5)	7
55 - 64	63 - 72	320	3.6 (0-12.7)	12	177	7.5 (4.2-10.7)	13	143	3.9 (0-8.4)	6
≥ 65	≥ 73	383	3.2 (0-11.0)	12	260	6.6 (3.8-9.5)	17	123	3.5 (0-7.4)	4
Total	Total	1079		41	614		47	465		20
Women										
35 - 44	43 - 52	81	2.1 (0-6.9)	2	42	5.1 (2.8-7.4)	2	39	2.7 0-5.7)	1
45 - 54	53 - 62	181	1.7 (0-5.9)	3	105	4.3 (2.4-6.1)	4	76	2.2 (0-4.9)	2
55 - 64	63 - 72	202	1.5 (0-5.2)	3	125	3.9 (2.2-5.6)	5	77	2.0 (0-4.4)	2
≥ 65	≥ 73	356	1.5 (0-5.1)	5	265	3.7 (2.1-5.4)	10	91	2.0 (0-4.2)	2
Total	Total	820		13	537		21	283		6
Total										
35 - 44	43 - 52	177	3.6	6	80	7.4	6	97	4.2	4
45 - 54	53 - 62	461	3.4	16	244	7.1	17	217	4	9
55 - 64	63 - 72	522	2.8	15	302	6	18	220	3.3	7
≥ 65	≥ 73	739	2.4	18	525	5.1	27	214	2.8	6
Total	Total	1899		54	1151		68	748		26

a. PAR, population attributable risk
b. EAC, excess attributable cases. Numbers rounded to nearest case.
c. Values for 'Total' (Men and Women combined) may not match individual totals for Men and Women.

Table 6 Summary of cases and proportions of cancer in Alberta adults in 2012 attributable to red and processed meat intake[a]

Cancer Site[b]	Total			Men			Women		
	Observed Cases[c]	Excess Attributable Cases[d]	% Attributable[e]	Observed Cases[c]	Excess Attributable Cases[d]	% Attributable[e]	Observed Cases[c]	Excess Attributable Cases[d]	% Attributable[e]
Red Meat									
Colorectum	1899	181	9.5	1079	166	15.4	820	15	1.8
Colon	1151	66	5.7	614	44	7.1	537	22	4.1
Rectum	748	68	9	465	50	10.7	283	18	6.2
All Associated Cancers[f]	1899	181	9.5	614	166	15.4	537	15	1.8
All Cancers[g]	15836	181	1.1	8155	166	2.0	7681	15	0.2
Processed Meat									
Colorectum	1899	54	2.9	1079	41	3.8	820	13	1.6
Colon	1151	68	5.9	614	47	7.6	537	21	4.0
Rectum	748	26	3.5	465	20	4.3	283	6	2.2
All Associated Cancers[f]	1899	54	2.9	1079	41	3.8	537	13	1.6
All Cancers[g]	15836	54	0.3	8155	41	0.5	7681	13	0.2

a. Red and processed meat consumption data for Alberta from Alberta's Tomorrow Project cohort. In this cohort diet history questionnaire estimated the number of ounces of each of red (beef, pork, lamb, veal, venison, liver etc.) and processed (cold cuts, sausage, ham, hot dogs) meat consumed each day

b. Cancer incidence data obtained from the Alberta Cancer Registry. Data from 2012 was used for observed cancer cases for all cancer sites.

c. Number of observed cancer cases in Alberta in 2012 at individual cancer sites.

d. Number of cancer cases at individual cancer sites that can be attributed to red and processed meat consumption.

e. Proportion of cancers at individual cancer sites attributable to red and processed meat consumption. Calculated as excess attributable cases/observed cases.

f. Represents all cancers with a known association with red and processed meat consumption as listed in table. In this cases these values represent colorectal cancer, as colon and rectal cancers are subsets of this type.

g. Represents all incident cancers in Alberta in 2012 in all age groups.

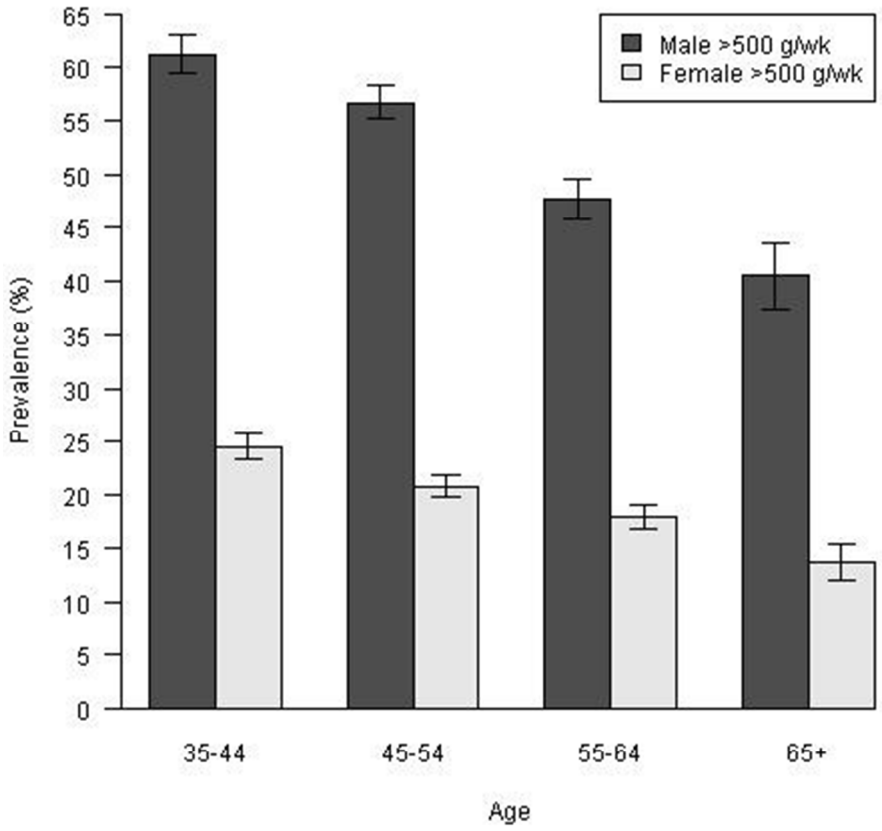

Figure 1 Proportion of men and women in Alberta's Tomorrow Project cohort consuming >500. g/week of red and processed meat by age group

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

Anne Grundy PhD[1], Christine M. Friedenreich PhD[1,2,3], Abbey E. Poirier MSc[1], Farah Khandwala MSc[1], Darren R. Brenner PhD[1,2,3]*

1. Department of Cancer Epidemiology and Prevention Research, Alberta Health Services-CancerControl Alberta, Calgary, Alberta, Canada
2. Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
3. Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
4. Alberta Cancer Prevention Legacy Fund, Division of Population, Public and Aboriginal Health, Alberta Health Services, Calgary, Alberta, Canada

*Corresponding Author:
Darren R. Brenner
Darren.Brenner@albertahealthservices.ca
Department of Cancer Epidemiology and Prevention Research
CancerControl Alberta, Alberta Health Services
Holy Cross Centre – Room 513C
Box ACB, 2210 – 2nd St. SW.
Calgary, AB.
T2S 3C3

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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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REFERENCES

1. Walter SD. Local estimates of population attributable risk. J Clin Epidemiol. 2010;63(1):85-93.
2. Orenstein M, Chen J, Dall T, Curley P. The economic burden of occupational cancers in Alberta. Calgary: 2009.
3. Neutel CI, Morrison H. Could recent decreases in breast cancer incidence really be due to lower HRT use? Trends in attributable risk for modifiable breast cancer risk factors in Canadian women. Can J Public Health. 2010;101(5):405-9.
4. Brenner DR. Cancer incidence due to excess body weight and leisure-time physical inactivity in Canada: Implications for prevention. Preventive Medicine. 2014;66(0):131-9.
5. Cancer Care Ontario. Cancer Risk Factors in Ontario: Tobacco. Toronto, Ontario: 2014.
6. Peterson E, Aker A, Kim J, Li Y, Brand K, Copes R. Lung cancer risk from radon in Ontario, Canada: how many lung cancers can we prevent? Cancer Causes & Control. 2013;24(11):2013-20.
7. Brand KP, Zielinski JM, Krewski D. Residential Radon in Canada: An Uncertainty Analysis of Population and Individual Lung Cancer Risk. Risk Analysis. 2005;25(2):253-69.
8. Chen J, Moir D, Whyte J. Canadian population risk of radon induced lung cancer: a re-assessment based on the recent cross-Canada radon survey. Radiation Protection Dosimetry. 2012;152(1-3):9-13.
9. Cancer Care Ontario. Cancer Risk Factors in Ontario: Evidence Summary. Toronto, Canada: 2013.
10. Research WCRFAIfC. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007.
11. Murray CJ, Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S. Comparative quantification of health risks conceptual framework and methodological issues. Popul Health Metr. 2003;1(1):1.
12. Levin M. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9:531-41.
13. Parkin DM. 1. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105 Suppl 2:S2-5.
14. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. The Lancet Oncology. 2012;13(6):607-15.
15. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. American Journal of Epidemiology. 1974;99(5):325-32.

16. Renehan AG, Soerjomataram I, Tyson M, Egger M, Zwahlen M, Coebergh JW, et al. Incident cancer burden attributable to excess body mass index in 30 European countries. International Journal of Cancer. 2010;126(3):692-702.

17. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. The Lancet. 2012; 380(9838):219-29.

18. Parkin DM. 2. Tobacco-attributable cancer burden in the UK in 2010. Br J Cancer. 2011;105(S2):S6-S13.

19. Parkin D. 3. Cancers attributable to consumption of alcohol in the UK in 2010. British Journal of Cancer. 2011;105:S14-S8.

20. Parkin DM, Boyd L. 4. Cancers attributable to dietary factors in the UK in 2010. Br J Cancer. 2011;105(S2):S19-S23.

21. Parkin DM. 5. Cancers attributable to dietary factors in the UK in 2010. Br J Cancer. 2011;105(s2):s24-S6.

22. Parkin DM, Boyd L. 6. Cancers attributable to dietary factors in the UK in 2010. Br J Cancer. 2011;105(S2):S27-S30.

23. Parkin DM. 7. Cancers attributable to dietary factors in the UK in 2010. Br J Cancer. 2011;105(S2):S31-S3.

24. Parkin DM, Boyd L. 8. Cancers attributable to overweight and obesity in the UK in 2010. Br J Cancer. 2011;105(S2):S34-S7.

25. Parkin DM. 9. Cancers attributable to inadequate physical exercise in the UK in 2010. Br J Cancer. 2011;105(S2):S38-S41.

26. Parkin DM. 10. Cancers attributable to exposure to hormones in the UK in 2010. Br J Cancer. 2011;105(S2):S42-S8.

27. Parkin DM. 11. Cancers attributable to infection in the UK in 2010. Br J Cancer. 2011;105(S2):S49-S56.

28. Parkin DM, Darby SC. 12. Cancers in 2010 attributable to ionising radiation exposure in the UK. Br J Cancer. 2011;105(S2):S57-S65.

29. Parkin DM, Mesher D, Sasieni P. 13. Cancers attributable to solar (ultraviolet) radiation exposure in the UK in 2010. Br J Cancer. 2011;105(S2):S66-S9.

30. Parkin DM. 14. Cancers attributable to occupational exposures in the UK in 2010. Br J Cancer. 2011;105(S2):S70-S2.

31. Parkin DM. 15. Cancers attributable to reproductive factors in the UK in 2010. Br J Cancer. 2011;105(S2):S73-S6.

32. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105 Suppl 2:S77-81.

33. Cancer Care Ontario. Cancer Risk Factors in Ontario: Alcohol. Toronto, Ontario: 2014.

34. Cancer Care Ontario. Cancer Risk Factors in Ontario: Healthy Weights, Healthy Eating and Active Living. Toronto, Ontario: 2015.

35. Chen J, Tracy BL. Canadian Population Risk of Radon Induced Lung Cancer. Canadian Journal of Respiratory Therapy. 2005;41:19-27.

36. Jardine K, Pahwa M, Kramer D, Demers P. Preventing the Burden of Occupational Cancer in Canada: Stakeholder Meeting Summary. Toronto, Ontario: 2015.

37. Bryant H, Robson PJ, Ullman R, Freidenreich C, Dawe U. Population-based cohort development in Alberta, Canada: a feasibility study. Chronic Diseases in Canada. 2006;27(2):51 - 9.

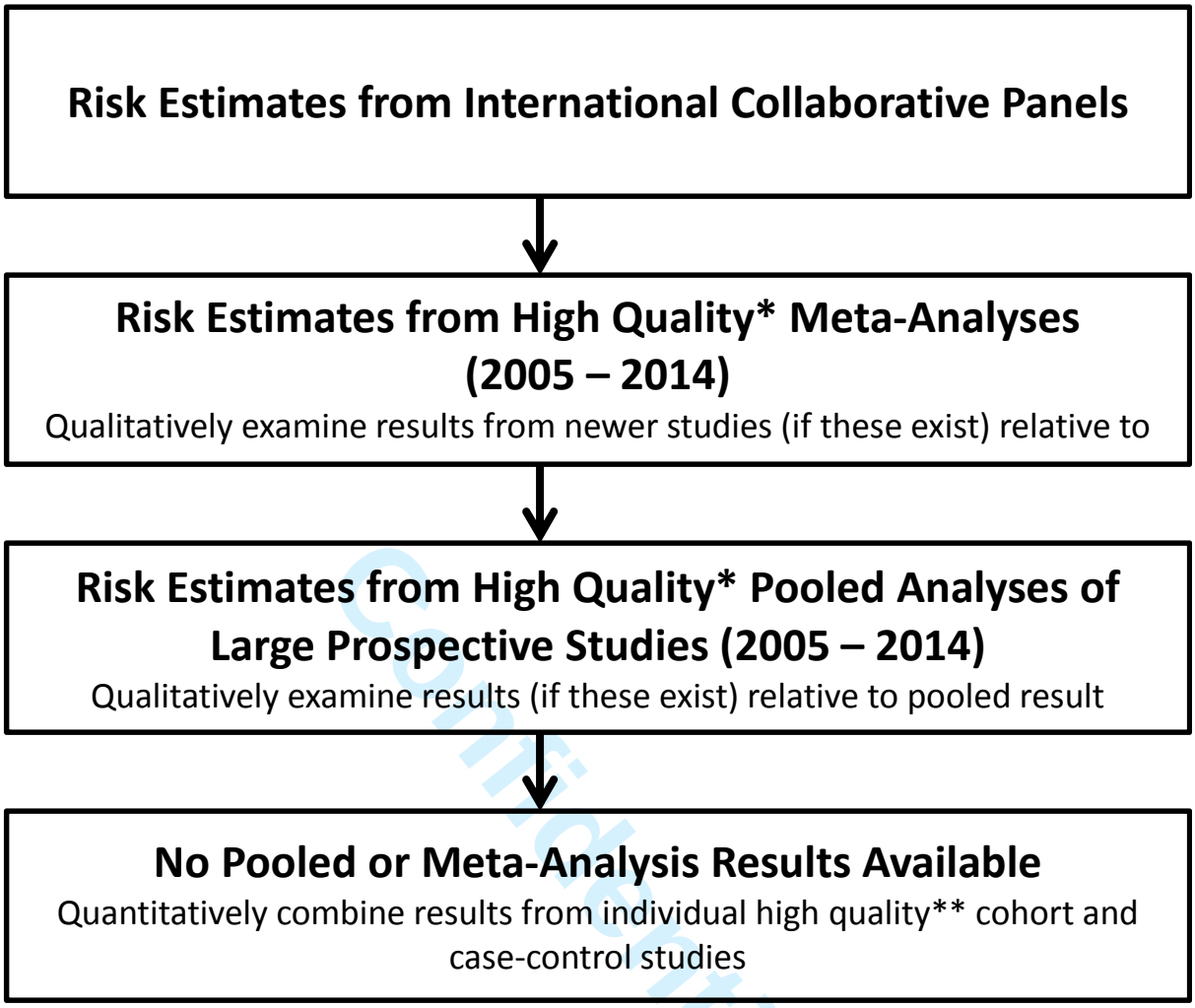
Table 1. The population attributable risk estimation methods employed for the for individual exposures of interest in this Series

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

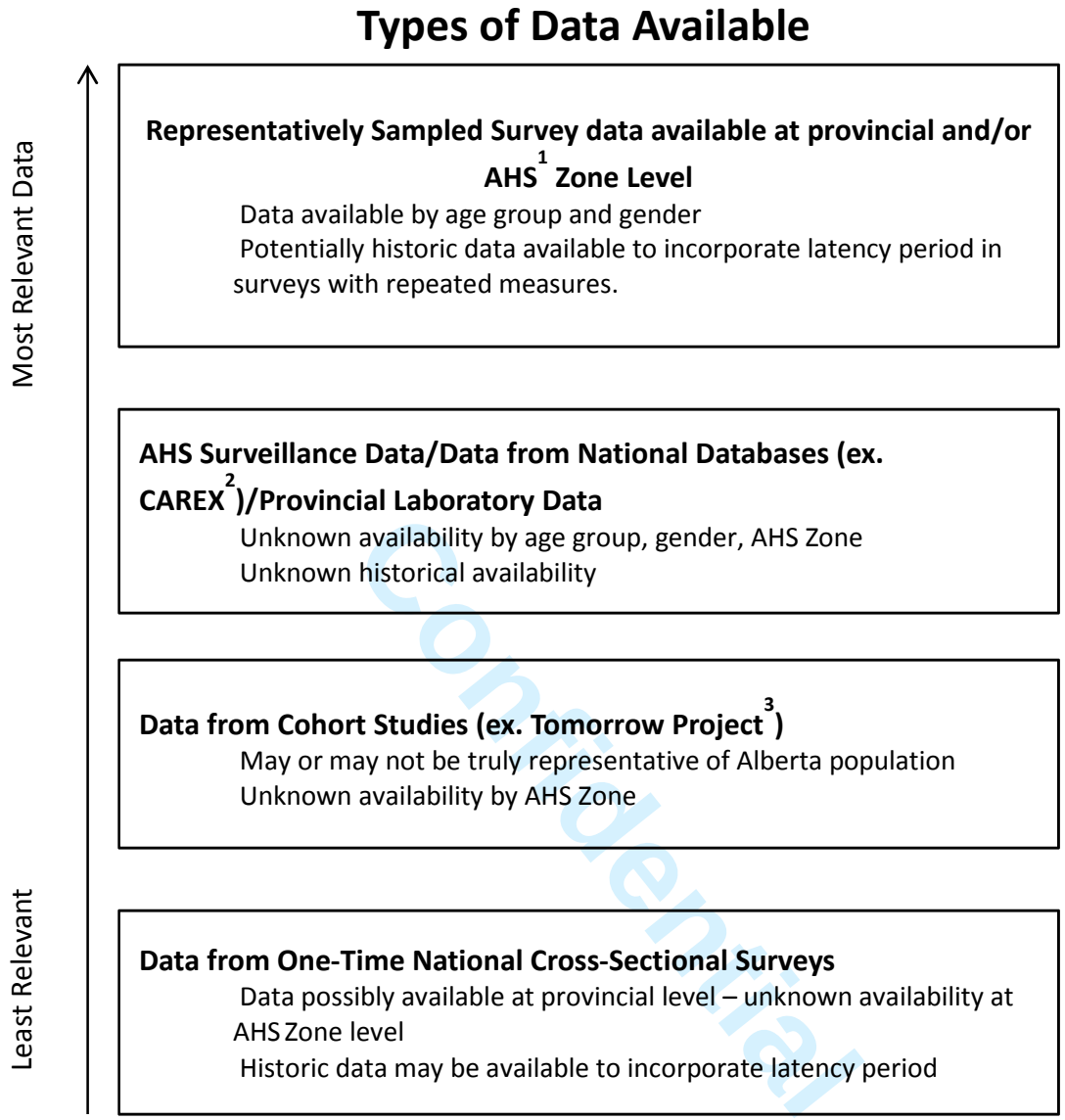
Manuscript	Exposure	Cancer types consistently associated with exposure
1	Active Tobacco Exposure	Lung
		Oral cavity and pharynx
		Oesophagus
		Stomach
		Liver
		Pancreas
		Colorectum
		Larynx
		Cervix
		Ovarian (mucinous)
		Urinary bladder
		Kidney
		Acute myeloid leukemia
	Passive Tobacco Exposure	Lung
		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

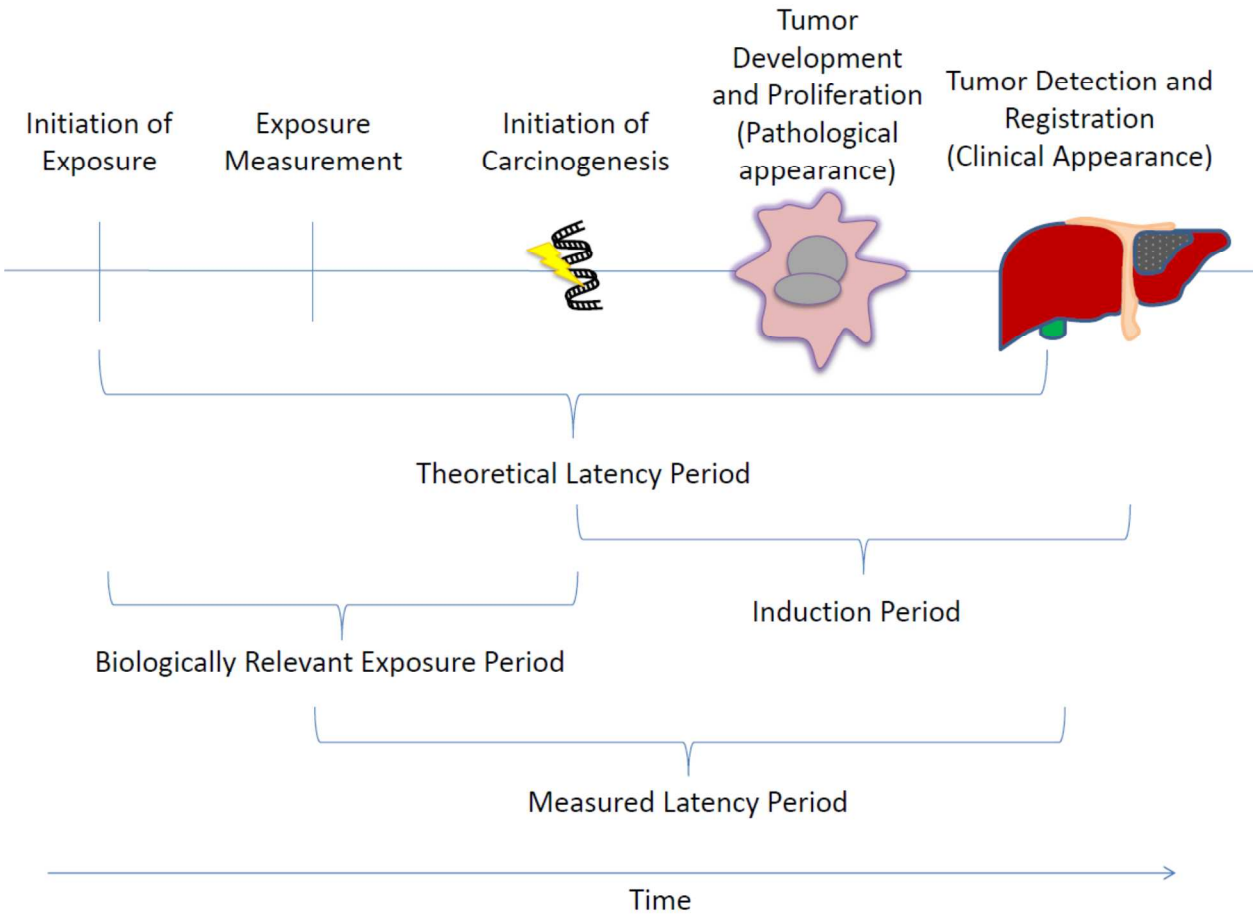


Figure 3. Proposed model of carcinogenesis related to the adverse exposure of interest. The measured latency period is referred to as the latency period for the purposes of estimating population attributable cancer risks in Alberta.