Cancer Incidence Attributable to Oral Contraceptives and Hormone Replacement Therapy Use in Alberta, Canada in 2012

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

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
4. Cancer Measurement , Outcomes, Research and Evaluation (C-MORE), CancerControl Alberta, Alberta Health Services
5. Department of Agricultural, Food and Nutritional Science, Faculty of ALES, University of Alberta

*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

Running Title: Cancer Incidence Attributable to Oral Contraceptives and Hormone Replacement Therapy Use in Alberta

ABSTRACT

Background: Hormonal contraceptives and menopausal hormone replacement therapies are classified as carcinogenic to humans (Group 1) by the International Agency for Research on Cancer. The current study estimated the proportion and total number of cancers attributable to oral contraceptive (OC) and hormone replacement therapy (HRT) use in Alberta in 2012.

Methods: Population attributable risk calculations were used to estimate the proportion of attributable cases for each associated cancer site. Relative risk estimates used were obtained from most relevant and recent epidemiological literatures. Prevalence of OC and HRT use in Alberta were collected from Alberta's Tomorrow Project cohort. Specific cancer incidence data were obtained from the Alberta Cancer Registry for year 2012.

Results: Overall, 8% of breast cancers diagnosed in Alberta in 2012 were attributable to OC use and, conversely, OC use resulted in the reduction of approximately 57% of endometrial cancers and 29% of ovarian cancers. Approximately 15.5% of breast cancers and 9% of ovarian cancers were attributable to HRT use, whereas 11.2% of endometrial cancers were prevented by HRT use.

Interpretation: OCs and HRT are risk factors for breast cancer however they provide protective effect against endometrial cancer. For ovarian cancer, OC use provides long lasting protection, whereas HRT use poses a slight increase of risk. As OCs and HRT have both a positive and negative influence on cancer burden depending on the cancer site being considered, the risks and benefits of both of these medications should be carefully considered prior to their use.

INTRODUCTION

This manuscript is the ninth 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]

Hormones play a major role in the risk of breast, endometrial and ovarian cancers. The impact of oral contraceptives (OCs) and hormone replacement therapy (HRT) on the risk of these cancers has been researched extensively.[2] The 2007 International Agency for Research on Cancer (IARC) Monographs classified both combined estrogen-progestin hormonal contraceptives and menopausal therapy as carcinogenic to humans (Group 1).[2]

OCs are one of the most common methods of contraception used by women worldwide.[2] Globally, over 100 million women, approximately 10% of all women of reproductive age, use combined OCs.[2] In Canada, based on a 2006 national survey, the prevalence of OC use was estimated to be 43% among women who used contraception.[3] While many women continue to use OCs, they have been associated with increased risks of breast cancer especially among current and recent users [2]. A meta-analysis reported a significant 8% increase in breast cancer risk among OC users (OR, 1.08; 95% CI 1.00-1.17).[4] Given the relatively high incidence of breast cancers, even a slightly elevated risk caused by OCs could result in substantial number of incidences.[4] On the positive side, the 2007 Monograph determined that combined estrogen-progestin hormonal contraceptives decreases the risk of endometrial and ovarian cancers.[2] A recent quantitative review reported a near 50% reduction of endometrial cancer risk with OC use (OR, 0.57; 95% CI, 0.43-0.77).[4] A 2014 meta-analysis reported a significant 27% reduction in ovarian cancer risk (OR, 0.73; 95% CI 0.66-0.81) in ever users compared with never users [5] and the risk reduction persist for at least 20-25 years following cessation of use [6].

HRT is administered to peri- or postmenopausal women to reduce the symptoms of menopause and it has been associated with post-menopausal breast cancer as reported in the 2007 IARC Monograph.[2] Shah *et al*.[7] assessed the effect of combined HRT on breast cancer risk in a meta-analysis and pooled ORs of 1.39 (95% CI, 1.12-1.72) was reported.[7] Unopposed estrogen therapy was shown to substantially increase endometrial cancer risk, such that progestins were added to the therapy to mitigate the risk.[2] Women who used continuous combined HRT, where progestins were included in the therapy for >25 days/month, were reported to have up to 22% of reduced risk for endometrial cancer (RR, 0.78; 95% CI, 0.72-0.86).[8] For ovarian cancer, the Collaborative Group on Epidemiological Studies of Ovarian Cancer published a meta-analysis on 52 epidemiological studies in 2015 and concluded that the risk of developing ovarian cancer was 41% higher among current HRT users (RR, 1.41; 95% CI, 1.33-1.50) compared to never users and the estimated risk among ever users was also significantly elevated by as much as 20% (RR, 1.20; 95% CI, 1.15-1.26).[9]

Given the established associations between exogenous hormones and human cancer risks, this study aimed to quantify the proportions of breast, endometrial and ovarian cancer diagnosed in 2012 in Alberta that could be attributed to OC and HRT use.

METHODS

Oral Contraceptive Use

The prevalence of OC use in Alberta was estimated using data from Alberta's Tomorrow Project (ATP)[10]. This large population-based cohort study recruited 31,792 Albertan, including 18,836 women, aged 35 to 69, between 2000 and 2009. Information on ever use of OCs was collected in the cohort baseline questionnaire.[10]

Relative risks associated with OC use for breast, endometrial and ovarian cancers were obtained from a comprehensive literature review and are summarized in Table 1. ATP data did not allow current users of OCs to be distinguished from former users; therefore, the risk estimates comparing ever users

with never users were used. The population attributable risk associated with ever use of oral contraceptives for breast, endometrial and ovarian cancers were estimated using equation 1[11].

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

Where *Pe* is the prevalence of ever OC users, *RR* is the relative risk of cancer for ever vs. never OC users and (RR-1) is the excess relative risk for OC use.

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.[12, 13] Wherever possible and appropriate, these estimations were performed for individual sex and age groups

Hormone Replacement Therapy

Data from the ATP cohort [10] were also used to estimate population attributable risks associated with HRT use. Data were available on ever and current use of hormone therapies, but specific details concerning the preparations and regimens were not provided. Thus, RRs related to breast, endometrial and ovarian cancers for continuous estrogen-progestin combined hormone therapy were used, as this was the most commonly used formulation (Table 1). The risk of breast cancer associated with HRT use has been shown to vary by histological types [14], such that analyses for ductal, lobular and tubular breast cancers specifically were also conducted in association to current HRT use. Such analyses were not included for HRT ever use as RR estimates were not available. population attributable risks were estimated for all cancer types using equation 1. Where *Pe* is the prevalence of ever or current use of HRT, *RR* is the relative risk of cancer due to ever or current HRT use and (RR-1) is the excess relative risk for

HRT use. Ninety-five percent confidence intervals around population attributable risk estimates for HRT use were estimates as described above.

Excess Attributable Cancers

The numbers of cancer cases attributable to OC and HRT use were estimated by combining 2012 Alberta cancer incidence data with population attributable risk estimates calculated above. Cancer incidence data were obtained from Alberta Cancer Registry. Given that exposure data were collected between 2000 and 2009, a latency period of 8 years was estimated and age groups for cancer incidence data were lagged by 8 years (ex. exposure data for 35 – 44 year olds corresponded to incidence data for 43 – 52 year olds) to reflect cancers diagnosed in 2012 caused by previous hormone exposure.

RESULTS

Prevalence of OC and HRT use

The prevalence of OC and HRT use among Alberta women is presented in Table 2. Based on Alberta's Tomorrow Project (ATP) 2000-2009 survey results, over 90% of women between the ages of 35 and 54 used oral contraceptives at some point in their reproductive life and the prevalence of OC use declined with increasing age (Table 2). Approximately 60% of women aged 55 or older have used HRT (Table 2). As HRT is predominantly prescribed to peri- or postmenopausal women, much smaller proportions of women aged 54 or younger had ever used HRT (25.2% for age 45-54, 4.4% for age 35-44). Among current users, the proportion of HRT use peaked at the ages of 55-64, which involved 27.2% (95% CI = 25.9, 28.5) women in this age group.

Oral contraceptives

Table 3 illustrates the proportion and numbers of cancer cases attributed to OC and HRT use in Alberta in 2012. The 95% confidence intervals (CIs) for population attributable risk estimates are

presented in Supplementary Table 1. For breast cancer, 5.2% to 7.0% of cases were attributable to OC use across different age groups. In contrast to the increased breast cancer risk, OC use was inversely associated with the risk of endometrial cancer and ovarian cancer. The population attributable risks for endometrial cancer and ovarian cancer linked to ever use of OCs were in the negative ranges of 40.4-64.8% and 22.3-33.2%, respectively. The protective effect of OCs translates to potential reduction of 277 endometrial cancer cases and 52 ovarian cancer cases. Overall in Alberta in 2012, 2,128 breast cancer cases were diagnosed and among those 136 cases (6.4%) were attributable to OC use. A total of 661 cases were diagnosed for endometrial and ovarian cancers combined and approximately half (49.7%) of these cases (n = 329) could be prevented with ever use of OCs (Table 4).

Hormone Replacement Therapy

HRT use is associated with increased risks of postmenopausal breast and ovarian cancers, and decreased risk of endometrial cancer. The population attributable risks for breast cancer attributable to ever and current use of HRT were highest among older women (age of exposure ≥ 55) due to higher HRT prevalence rates for older age groups (Table 2 & 3). It was estimated that 258 and 199 breast cancer cases could be attributed to ever use of HRT and current use of HRT respectively. Population attributable risks for ovarian cancer were 4.8% to 10.8% for HRT ever use and 6.0% to 10.0 % for HRT current use. Due to the relatively low incidence of ovarian cancer, totals of 13 and 12 ovarian cancer cases were estimated to be associated with ever and current use of HRT respectively. Based on the population attributable risk estimates, the protective effect of HRT on endometrial cancer risk could benefit HRT ever users aged 45 or older the most (population attributable risk = -15.3%). In total, HRT ever use corresponds to a potential reduction of 48 out of 425 postmenopausal endometrial cancer cases diagnosed in Alberta in 2012. On the other hand, an excess of 279 out of 1,808 postmenopausal breast and ovarian cancers diagnosed in Alberta in 2012 were linked to HRT use (Table 4).

Among the dutal, lobular and tubular breast cancer histological types, the population attributable risks associated with HRT current use all exceed 30% for women aged 45 or older at the time of HRT exposure. The impact of HRT use on the risk of developing lobular and tubular breast cancers increased approximately 1.5 and 2 fold, respectively (Table 3). The story is much different when considering the absolute number of cases. Current HRT use was linked to 350 excess ductal breast cancer cases, the highest among the three subtypes due to its high prevalence rate whereas 11 tubular breast cancer diagnoses were estimated to be attributed to current HRT use.

INTERPRETATION

In this study we quantitatively assessed the risks of breast, endometrial and ovarian cancers associated with OC and HRT use among women aged 35 or older in Alberta, Canada. Overall, 6.4% of breast cancers and 1.8% of all cancers diagnosed in 2012 in Alberta were attributable to ever OC use. Conversely, reductions of 57.4% in endometrial cancer and 29.1% in ovarian cancer, together representing 4.3% of total cancer diagnoses in 2012 in Alberta, were linked with ever use of OCs. For breast and ovarian cancers, an estimated 15% of cases (n = 271) for these two sites were attributable to HRT use, corresponding to 3.5% of all cancer cases in 2012 in Alberta. Conversely, prevention of 48 postmenopausal endometrial cancers could be attributed to HRT use, representing 0.6% of all cancers.

When comparing these findings to a similar study conducted in the United Kingdom (UK) by Parkin [11], the population attributable risks calculated for Alberta appears to be higher than the results published in the UK study. In Parkin's analysis, it was estimated that OC use contributed to approximately 1.1% of breast cancers and prevented 16.9% of the endometrial cancer and 9.3% of the ovarian cancers occurring in the UK in 2010. [11] Parkin also concluded that HRT use increase the risk of breast, endometrial and ovarian cancers and the estimated population attributable risks were 3.2%, 1.2% and 0.7%, respectively. The disparities in the estimated population attributable risks between the current study and Parkin's study were largely due to differences in hormone exposure prevalence rates between the two studies. In the current study, prevalence rates from the ATP study were used and the data showed

that 92.3% of female participants aged 35 to 44 years had ever used OCs. In Parkin's study only approximately 23-31% of women reported to have used female hormones, which include exposure to OC and HRT, for the same age group. [11] Further, 60.3% of ATP participants between the age of 55 and 64 reportedly have used HRT whereas, in the UK, less than 10% of women of the same age have ever used female sex hormones. [11] A 2006 Canadian cross-sectional national survey showed that 31.5-58.3% of women aged 20 to 39 years used OCs in the previous six months. [3] Parkin's prevalence results were comparable to a 2006-7 English national survey which reported the prevalence of OC use in England as 28-64% for women between the ages of 20-39. [11] This evidence indicates that the prevalence of OC use in Canada is similar to UK and the higher exposure rates in ATP were likely due to over estimation of exposure in this cohort. Parkin's prevalence data were abstracted from a large computerized database which contains anonymised longitudinal medical records from primary care. [11] The ATP OC and HRT exposure information were collected from self-reported baseline questionnaires. In addition, it is unclear of the ATP and Parkin's study use the same definition for hormone 'ever use' which could have further the disparity of hormone prevalence.

The current study estimated that the HRT use prevented 11.2% of endometrial cancers in Alberta in 2012. In the UK study, the comparable estimate was 1.2% [11], where the observed difference could have been due to the regimen of HRT investigated by the two studies. The ATP survey did not provide detailed information on how progestin is added to the HRT regimen, thus our analysis used the RR of endometrial cancer for a continuous oestrogen-progestin combined HRT regimen, as this was the most commonly used formulation. In contrast, in Parkin's study the investigators were able to examine oestrogen only, combined HRT and tibolone as separate HRT regimens. [11] Evidence has shown that unopposed estrogen therapy and tibolone substantially increase endometrial cancer risk [15], whereas women who used continuous combined hormone therapy have lowered endometrial cancer risk (RR = 0.78, 95% CI 0.72-0.86). [8]

The RRs used in the UK study were all from the Million Women Study, a large cohort study involving more than one million UK women between 1996 and 2001. For our analysis, we conducted a thorough literature review and selected relevant RRs from more recent literature that also included more current studies. Particularly for ovarian cancer risk, the evidence regarding HRT and ovarian cancer risk was inconclusive as stated in the 2007 IARC Monograph. [2] However, more recent studies provided stronger evidence on the carcinogenic effect of HRT on ovarian cancer. A 2008 meta-analysis [16], which included eight cohort and 19 case-control studies, reported that ever use of HRT was associated with increased risk of ovarian cancer. The summary RR was 1.24 (95% CI, 1.15-1.34) for cohort studies and 1.19 (95%CI, 1.02-1.40) for case-control studies. [16] Even stronger evidence of the adverse association between HRT use and ovarian cancer risk were recently published in a 2015 meta-analysis, which systematically reviewed and analyzed 52 epidemiologic studies. [9] The primary analyses, based on 17 prospective studies, reported that ever used of HRT elevated the risk of ovarian cancer by 20% (RR=1.20, 95% CI 1.15-1.26) and the risk was even greater among current short-term (<5 years) HRT users (RR=1.43, 95% CI 1.31-1.56). [9]

LIMITATIONS

The restricted prevalence data available on OC and HRT exposure in Alberta posed a number of limitations in this study. The prevalence data used in the current study was based on the available data from the ATP cohort project collected between 2000 and 2009. The ATP cohort population was geographically representative of Alberta population rather than socioeconomically representative, and as a results, the population had a higher proportion of individuals completed high school and had higher income compared to national average [10]. Higher income may allow women who participated in the cohort to have better access to treatment and more drug coverage. In addition, studies both in the US and Canada have found that women with less than post-secondary education are less likely to use contraception. [3, 17] As such, if women with lower education were differentially excluded from the ATP cohort as they were less likely to voluntarily participate in the cohort, the ATP data would overestimate

the true population prevalence of hormone use and thus lead to an overestimation of population attributable risks.

In addition, limited data availability posed a challenge in conducting sensitivity analysis to verify the impact of a longer latency period may have on population attributable risk estimates. The survey data used in the study were collected between 2000 and 2009 and the cancer incidence data used was abstracted for the year of 2012. Base on these numbers the midpoint of observed follow-up time between assessment and cancer incidence was 7.5 years. Since we did not have access to other data concerning OC and HRT use among Albertans with the same level of detail prior to 2000, we were unable to conduct sensitivity analyses to investigate whether the prevalence of OC and HRT exposure among Albertans would be different from what was reported if a different latency period was used.

Compare to other similar studies [11], being able to include 95% confidence intervals around the population attributable risk estimates is a strength of the current analysis as the confidence intervals quantify the precision of the estimates. However, for certain estimates, especially the ones associated with ever exposure of oral contraceptives and current exposure of hormone replacement therapies (Supplementary Table 1), the wide confidence intervals highlight the lack of precision around the population attributable risk estimates. For instance, while we estimated that 136 breast cancer cases are attributable to ever OC use, this estimate could range from 5 to 260 cases. In contrast, while we estimated that 52 ovarian cancer cases are prevented by ever OC use, when taking the 95% confidence interval into consideration, this estimate could range from 25 to 71 cases. This lack of precision in the population attributable risk estimates should certainly be taken into consideration when interpreting the proportion of cancer cases associated with the impact of OC and HRT use.

CONCLUSION

Oral contraceptive use increases the risk of breast cancer and substantially decreases the risk of endometrial and ovarian cancer. [2] Overall, 1.8% of cancers in Alberta were attributable to ever use of

OCs, while 4.3% were prevented by this same exposure. HRT is a risk factor for breast and ovarian cancers and 3.5% of cancers in Alberta in 2012 were attributable to ever use of HRT. Given that use of both OCs and HRT has been shown to have both a positive and negative influence on cancer burden depending on the cancer site being considered, the risks and benefits of both of these medications should be carefully considered prior to their use.

ACKNOWLEDGEMENTS

This project was funded by the Alberta Cancer Prevention Legacy Fund. Dr Christine Friedenreich is supported by an Alberta Innovates-Health Solutions Health Senior Scholar Award and the Alberta Cancer Foundation Weekend to End Women's Cancers Breast Cancer Chair at the University of Calgary. Dr. Darren Brenner is supported by a Career Development Award in Prevention from the Canadian Cancer Society Research Institute. We gratefully acknowledge Dr. Laura McDougall from the Alberta Cancer Prevention Legacy Fund for her support and guidance. We also thank Bethany Kaposhi and Lorraine Shack from the Alberta Cancer Registry for providing cancer incidence data, the department of Data Integration, Measurement and Reporting at Alberta Health Services for access to CCHS data and Eileen Shaw for critical review of this manuscript. This project was funded by the Alberta Cancer Prevention Legacy Fund. Dr Christine Friedenreich is supported by an Alberta Innovates-Health Solutions Health Senior Scholar Award and the Alberta Cancer Foundation Weekend to End Women's Cancers Breast Cancer Chair at the University of Calgary. Dr. Darren Brenner is supported by a Career Development Award in Prevention from the Canadian Cancer Society Research Institute. We gratefully acknowledge Dr. Laura McDougall from the Alberta Cancer Prevention Legacy Fund for her support and guidance. We also thank Bethany Kaposhi and Lorraine Shack from the Alberta Cancer Registry for providing cancer incidence data. We are grateful for the prevalence data from Alberta's Tomorrow Project. Alberta's Tomorrow Project is only possible due to the commitment of its research participants, its staff and its funders: Alberta Cancer Foundation, Canadian Partnership Against Cancer, Alberta Cancer Prevention Legacy Fund (administered by Alberta Innovates – Health Solutions) and substantial in kind funding from Alberta Health Services. The views expressed herein represent the views of the author(s) and not of Alberta's Tomorrow Project or any of its funders.

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. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer. 2007;91:1-528.

3. Black A, Yang Q, Wu Wen S, Lalonde AB, Guilbert E, Fisher W. Contraceptive use among Canadian women of reproductive age: results of a national survey. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2009;31(7):627-40.

4. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013;22(11):1931-43.

5. Havrilesky LJ, Moorman PG, Lowery WJ, Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstetrics and gynecology. 2013;122(1):139-47.

6. Bernstein L. The risk of breast, endometrial and ovarian cancer in users of hormonal preparations. Basic & clinical pharmacology & toxicology. 2006;98(3):288-96.

7. Shah NR, Borenstein J, Dubois RW. Postmenopausal hormone therapy and breast cancer: a systematic review and meta-analysis. Menopause (New York, NY). 2005;12(6):668-78.

8. Brinton LA, Felix AS. Menopausal hormone therapy and risk of endometrial cancer. The Journal of steroid biochemistry and molecular biology. 2014;142:83-9.

9. Collaborative Group On Epidemiological Studies Of Ovarian C. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 2015.

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

11. Parkin DM. 10. Cancers attributable to exposure to hormones in the UK in 2010. British journal of cancer. 2011;105 Suppl 2:S42-8.

12. 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.

13. 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.

14. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. The Lancet Oncology. 2006;7(11):910-8.

15. Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2005;365(9470):1543-51.

16. Zhou B, Sun Q, Cong R, Gu H, Tang N, Yang L, et al. Hormone replacement therapy and ovarian cancer risk: a meta-analysis. Gynecologic oncology. 2008;108(3):641-51.

17. Frost JJ, Singh S, Finer LB. Factors associated with contraceptive use and nonuse, United States, 2004. Perspectives on sexual and reproductive health. 2007;39(2):90-9.

18. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003;362(9382):419-27.

Table 1 Risk risks of cancers associated with oral contraceptive and hormone replacement therapy use

Exposure	Cancer Site	Detailed Exposure	Risk Estimate	95% CI[a]	Source (first author, year)
Oral Contraceptives	Breast	Ever Use	1.08	(1.00 – 1.17)	Gierisch, 2013[4]
	Endometrium	Ever Use	0.57	(0.43 – 0.77)	Gierisch, 2013
	Ovary	Ever Use	0.73	(0.66 – 0.81)	Havrilesky, 2013[5]
Hormone Replacement Therapy[b]	Breast	Ever Use	1.39	(1.12 – 1.72)	Shah, 2005[7]
	Breast	Current Use	1.66	(1.58 – 1.75)	Beral, 2003[18]
	Breast – Ductal	Current Use	1.76	(1.68 – 1.85)	Reeves, 2006[14]
	Breast – Lobular	Current Use	2.51	(2.27 – 2.77)	Reeves, 2006
	Breast – Tubular	Current Use	3.57	(2.93 – 4.36)	Reeves, 2006
	Endometrium	Ever Use	0.78	(0.72 – 0.86)	Brinton, 2014[8]
	Endometrium	Current Use	0.75	(0.58 – 0.97)	Beral, 2005[16]
	Ovary	Ever Use	1.20	(1.15 – 1.26)	CGESOC[c], 2015[9]
	Ovary	Current Use	1.41	(1.32 – 1.50)	CGESOC, 2015

[a] CI, confidence interval
[b] Continuous estrogen-progestin combined hormone therapy (progestins were included in the therapy for >25 days/month).
[c] CGESOC, Collaborative Group on Epidemiological Studies of Ovarian Cancer.

Table 2 Prevalence of oral contraceptive and hormone replacement therapy use in Alberta (Alberta's Tomorrow Project, 2000-2009)

Exposure	Age (years)	Prevalence (95% CI)[a]
Oral Contraceptives – Ever Use	35-44	92.3 (91.7,93.0)
	45-54	91.1 (90.4,91.8)
	55-64	85.5 (84.5,86.6)
	≥ 65	67.6 (65.3,69.9)
Hormone Replacement Therapy – Ever Use	35-44	4.4 (3.9,4.9)
	45-54	25.2 (24.2,26.3)
	55-64	60.3 (58.9,61.7)
	≥ 65	60.5 (58.1,62.9)
Hormone Replacement Therapy – Current Use	35-44	2.8 (2.4,3.3)
	45-54	15.5 (14.7,16.4)
	55-64	27.2 (25.9,28.5)
	≥ 65	19.6 (17.6,21.5)

[a] CI, confidence interval

Table 3 Observed cancer cases in Alberta (2012) and proportions attributable to oral contraceptive and hormone replacement therapy use

Age at Exposure	Age at Outcome	Breast			Breast – Ductal			Breast - Lobular			Breast - Tubular			Endometrium			Ovary		
		Obs. Cases[a]	PAR[b] (%)	EAC[c]	Obs. Cases	PAR (%)	EAC	Obs. Cases	PAR (%)	EAC	Obs. Cases	PAR (%)	EAC	Obs. Cases	PAR (%)	EAC	Obs. Cases	PAR (%)	EAC
Oral Contraceptives – Ever Use																			
35-44	43-52	463	7.0	32										57	-64.8	-37	36	-33.2	-12
45-54	53-62	584	6.9	40										183	-63.4	-116	46	-32.6	-15
55-64	63-72	559	6.5	36										152	-57.3	-87	46	-30.0	-14
≥ 65	≥ 73	522	5.2	27										90	-40.4	-36	51	-22.3	-11
Total		2128		135										482		-276	179		-52
Hormone Replacement Therapy – Ever Use																			
35-44	43-52																		
45-54	53-62	584	9.0	52										183	-5.9	-11	46	4.8	2
55-64	63-72	559	19.0	106										152	-15.3	-23	46	10.8	5
≥ 65	≥ 73	522	19.1	100										90	-15.3	-14	51	10.8	6
Total		1665		258										425		-48	143		13
Hormone Replacement Therapy – Current Use																			
35-44	43-52																		
45-54	53-62	584	9.3	54	499	16.1	80	47	27.6	13	8	39.3	3	183	-4	-7	46	6.0	3
55-64	63-72	559	15.2	85	458	31.4	144	62	47.7	30	6	60.8	4	152	-7.3	-11	46	10.0	5
≥ 65	≥ 73	522	11.4	60	401	31.5	126	69	47.7	33	7	60.8	4	90	-5.1	-5	51	7.4	4
Total		1665		199	1358		350	178		76	21		11	425		-23	143		12

[a] Obs. Cases, observed cases. The values represent the total number of cases of each cancer type diagnosed in 2012. For HRT, only post menopausal cancer cases (cancers diagnosed at age 53 or older) are included.

[b] PAR, population attributable risk (%). It represents the proportion (%) of cancer cases attributable to OC ever use or HRT ever use or HRT current use. The negative values represent preventable proportions of cancer cases due to protective effect.

[c] EAC, excess attributable risk due to exposure. It represents the number of cases attributable to OC ever use or HRT ever use or HRT current use. The negative values represent preventable cancer cases attributable to protective effect.

Table 4 Summary of cases and proportions of cancer in Alberta in 2012 attributable to oral contraceptive and hormone replacement therapy use [a]

Cancer Site	Oral Contraceptive – Ever Use			Hormone Replacement Therapy – Ever Use			Hormone Replacement Therapy – Current Use		
	Observed Cases[b]	Excess Attributable Cases[c]	% Attributable[d]	Observed Cases	Excess Attributable Cases	% Attributable	Observed Cases	Excess Attributable Cases	% Attributable
Breast	2128	136	6.4	1665	258	15.5	1665	199	12.0
Endometrium	482	-277	-57.4	425	-48	-11.2	425	-23	-5.4
Ovary	179	-52	-29.1	143	13	8.9	143	11	7.8
All Attributable Cancers[e]	2128	136	6.4	1808	271	15.0	1808	210	11.6
All Cancers[f]	7681	136	1.8	7681	271	3.5	7681	210	2.7
All Preventable Cancers[g]	661	-329	-49.7	425	-48	-11.3	425	-23	-5.4
All Cancers	7681	-329	-4.3	7681	-48	-0.6	7681	-23	-0.3

[a] Data on prevalence of oral contraceptive and hormone replacement therapy use are from the Alberta's Tomorrow Project (ATP).
[b] Number of observed cancer cases in Alberta in 2012 at individual cancer sites. Cancer incidence data obtained from the Alberta Cancer Registry. For HRT, only post menopausal cancer cases (cancers diagnosed at age 53 or older) are included.
[c] Number of cancer cases at individual cancer sites that can be attributed to OC ever use or HRT ever use or HRT current use. Negative values represent preventable cancer cases due to the protective effect of OC ever use or HRT ever use or HRT current use.
[d] Proportion of cancers at individual cancer sites attributable to OC ever use, HRT ever use or HRT current use. Calculated as excess attributable cases/observed cases.
[e] Represents all cancers with a known association with OC ever use, HRT ever use or HRT current use, as listed in table.
[f] Represents all incident cancers in Alberta in 2012 in all age groups.
[g] Represents all preventable cancer cases associated with OC ever use, HRT ever use or HRT current use, as listed in table.

Supplementary Table 1 Observed cancer cases in Alberta (2012) and population attributable risks associated to oral contraceptive and hormone replacement therapy use

Age at Exposure	Age at Outcome	Cancer Site	Observed Cases	PAR[a] (%) (95% CI)		
				Oral Contraceptive - Ever Use	Hormone Replacement Therapy - Current Use	Hormone Replacement Therapy - Ever Use
35-44	43-52	Breast	463	7.0 (0.3,13.3)		
		Breast – Ductal	418			
		Breast - Lobular	25			
		Breast - Tubular	<5			
		Endometrium	57	-64.8 (-111.5,-27.9)		
		Ovary	36	-33.2 (-46.0,-21.4)		
45-54	53-62	Breast	584	6.9 (0.2,13.1)	9.3 (8.2,10.5)	9.0 (3.0,15.6)
		Breast – Ductal	499			16.1 (14.5,17.7)
		Breast - Lobular	47			27.6 (24.3,31.1)
		Breast - Tubular	8			39.3 (32.5,45.9)
		Endometrium	183	-63.4 (-108.2,-26.9)	-4.0 (-7.0,-0.4)	-5.9 (-7.8,-3.9)
		Ovary	46	-32.6 (-45.2,-21.5)	6.0 (4.8,7.3)	4.8 (3.6,6.1)
55-64	63-72	Breast	559	6.5 (0.2,12.4)	15.2 (13.5,17.0)	19.0 (6.9,30.2)
		Breast – Ductal	458			31.4 (28.9,33.9)
		Breast - Lobular	62			47.7 (43.4,51.7)
		Breast - Tubular	6			60.8 (53.9,66.8)
		Endometrium	152	-57.3 (-95.1,-24.6)	-7.3 (-13.0,-0.7)	-15.3 (-20.9,-9.7)
		Ovary	46	-30.0 (-41.1,-19.4)	10.0 (8.1,12.2)	10.8 (8.1,13.4)
≥ 65	≥ 73	Breast	522	5.2 (0.3,10.1)	11.4 (9.8,13.1)	19.1 (6.5,30.2)
		Breast – Ductal	401			31.5 (28.9,34.0)
		Breast - Lobular	69			47.7 (43.5,51.9)
		Breast - Tubular	7			60.8 (53.8,67.1)
		Endometrium	90	-40.4 (-62.8,-18.7)	-5.1 (-9.0,-0.6)	-15.3 (-21.0,-9.8)
		Ovary	51	-22.3 (-30.0,-14.9)	7.4 (5.7,9.1)	10.8 (8.1,13.4)

[a] PAR, population attributable risk (%). It represents the proportion (%) of cancer cases attributable to OC ever use or HRT ever use or HRT current use. The negative values represent preventable proportions of cancer cases due to protective effect.

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

Abstract Word Count: 227
Manuscript Word Count: 3,001
Running Title: Methods for Estimating Cancer Incidence Attributable to Lifestyle and Environment in Alberta
Keywords: population attributable risk; cancer; lifestyle; environment; Alberta; methods

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.

ACKNOWLEDGEMENTS

This project was funded by the Alberta Cancer Prevention Legacy Fund. Dr Christine Friedenreich is supported by an Alberta Innovates-Health Solutions Health Senior Scholar Award and the Alberta Cancer Foundation Weekend to End Women's Cancers Breast Cancer Chair at the University of Calgary. Dr. Darren Brenner is supported by a Career Development Award in Prevention from the Canadian Cancer Society Research Institute. We gratefully acknowledge Dr. Laura McDougall from the Alberta Cancer Prevention Legacy Fund for her support and guidance. We also thank Bethany Kaposhi and Lorraine Shack from the Alberta Cancer Registry for providing cancer incidence data, the department of Data

Integration, Measurement and Reporting at Alberta Health Services for access to CCHS data and Eileen Shaw for critical review of this manuscript.

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.

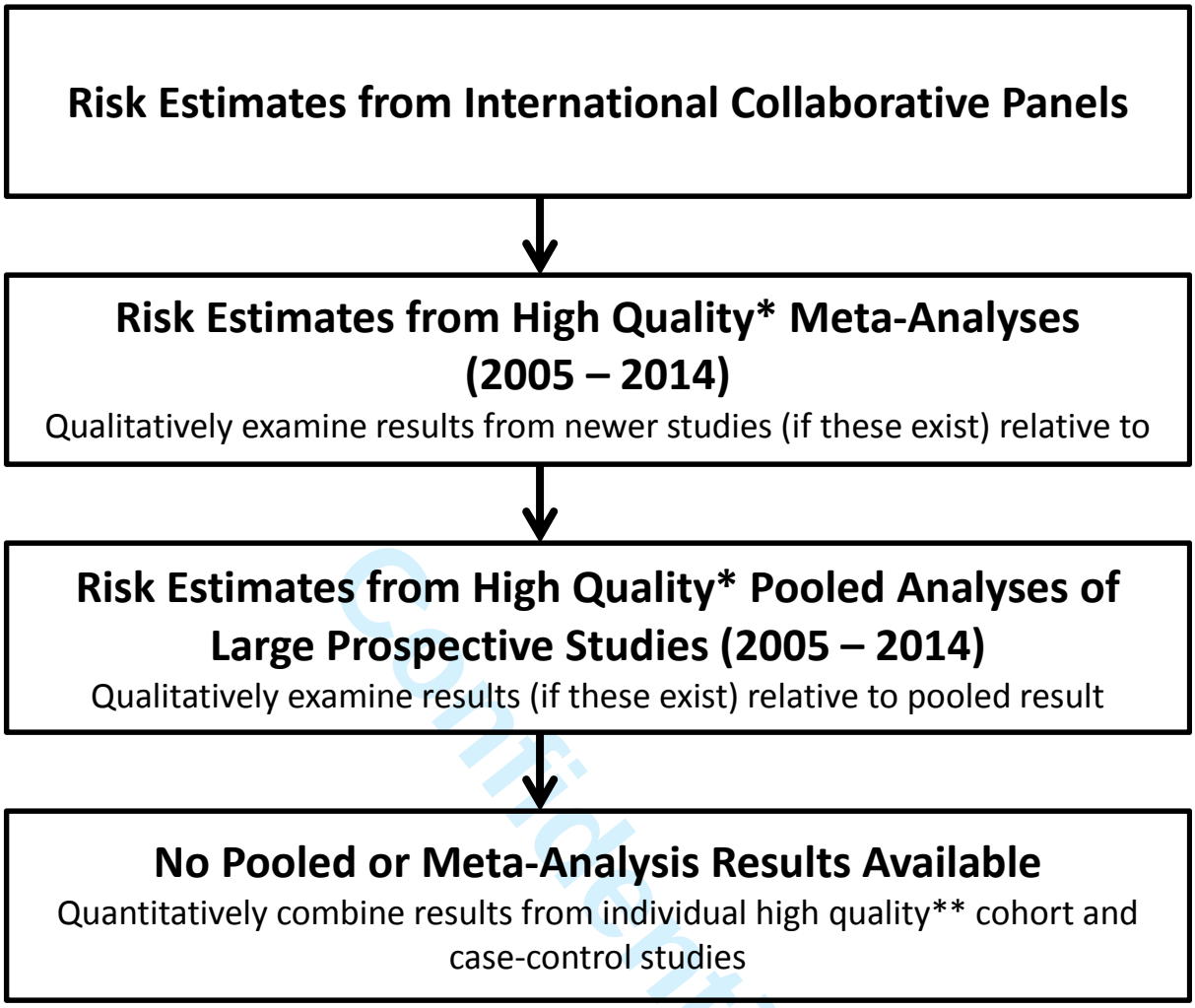
Table 1. The population attributable risk estimation methods employed for the for individual exposures of interest in this Series

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

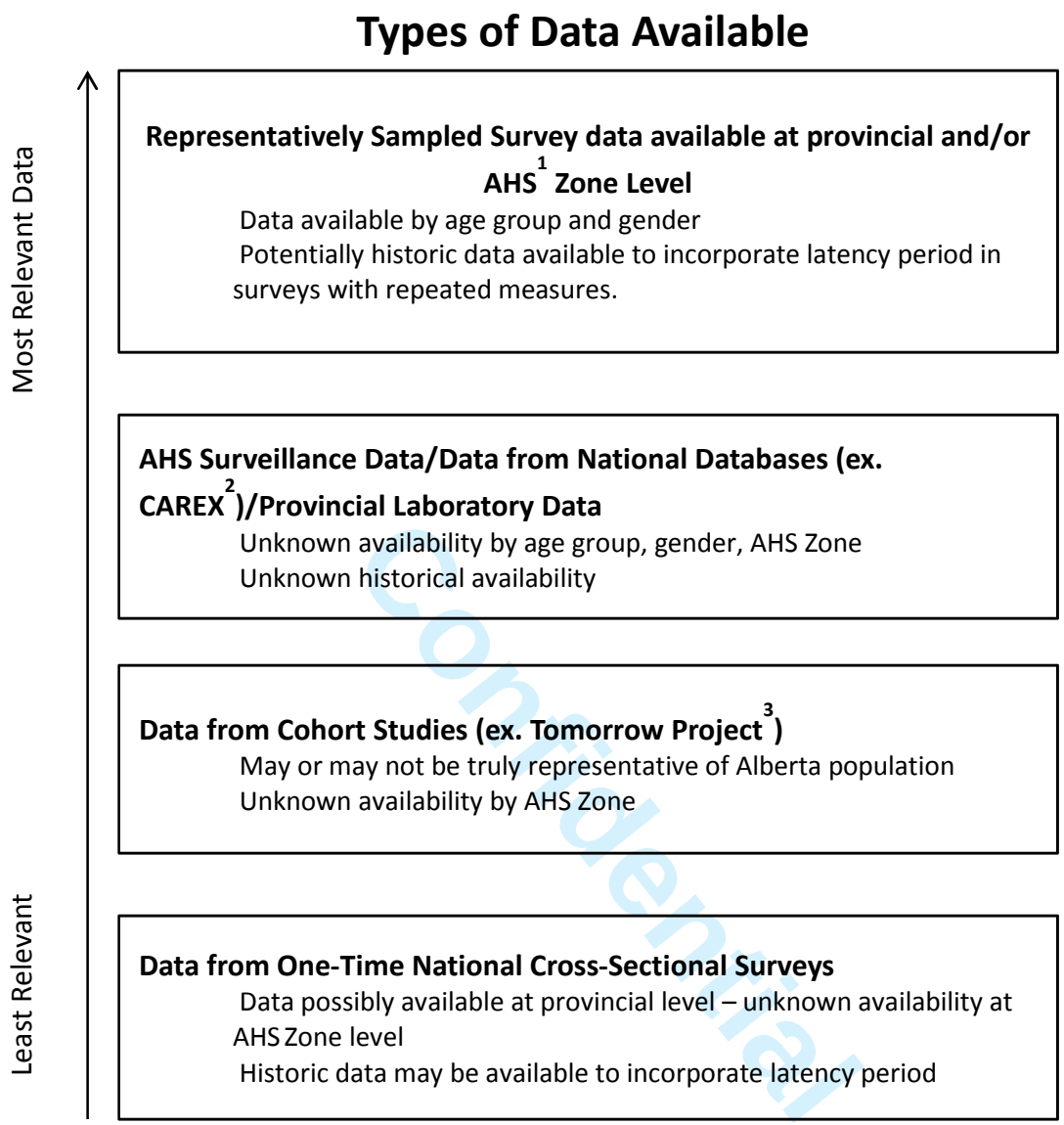
Manuscript	Exposure	Cancer types consistently associated with exposure
1	Active Tobacco Exposure	Lung
		Oral cavity and pharynx
		Oesophagus
		Stomach
		Liver
		Pancreas
		Colorectum
		Larynx
		Cervix
		Ovarian (mucinous)
		Urinary bladder
		Kidney
		Acute myeloid leukemia
	Passive Tobacco Exposure	Lung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

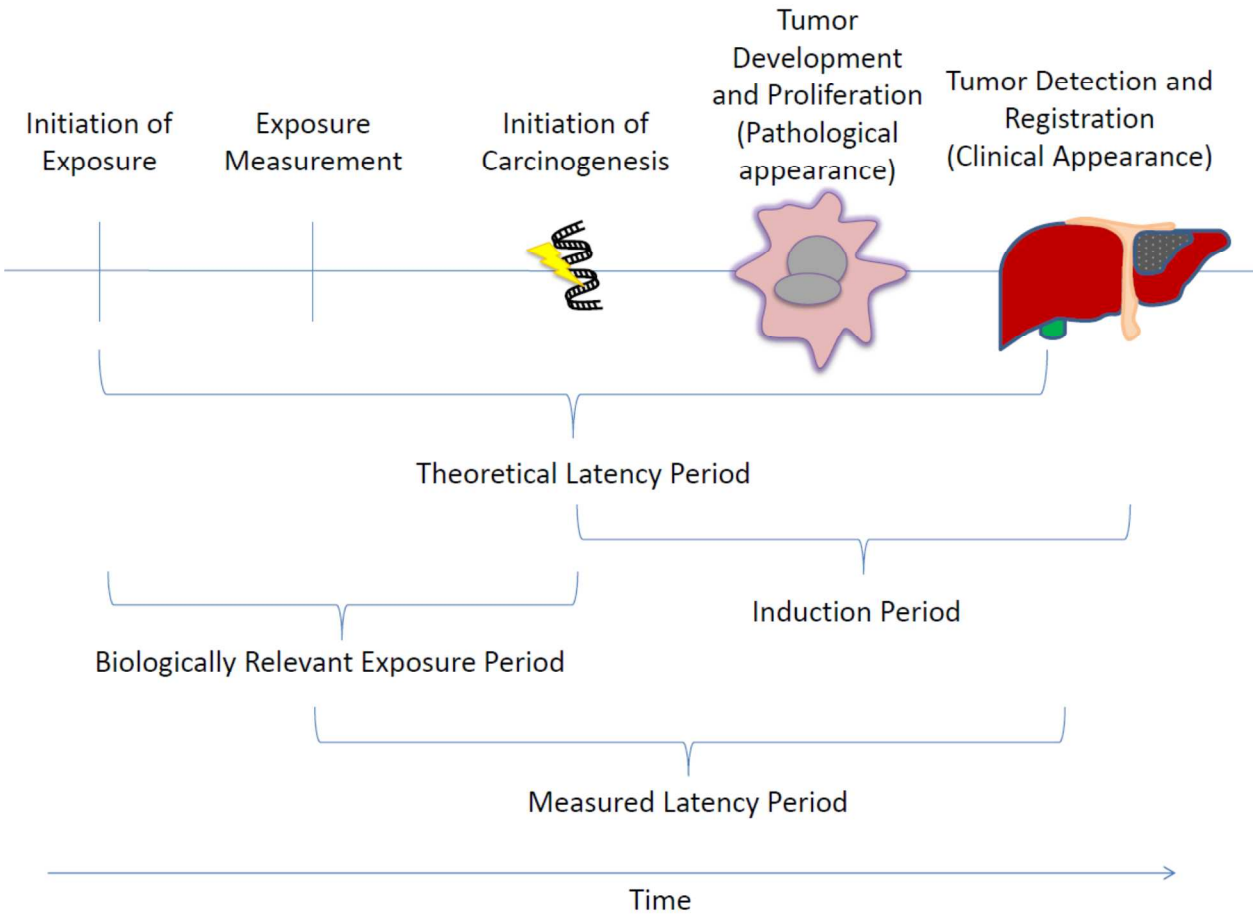


Figure 3. Proposed model of carcinogenesis related to the adverse exposure of interest. The measured latency period is referred to as the latency period for the purposes of estimating population attributable cancer risks in Alberta.