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3 **A Protocol to Evaluate the Number of Cancers Attributable to Lifestyle and Environment in**
4 **Alberta, Canada**
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ABSTRACT

Background: Previous research to estimate population attributable risks for cancer in Alberta has been limited. Attributable burden estimates are important for planning and implementing population-based cancer prevention strategies. This manuscript describes a protocol 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. In order to address this need we set out to conduct a systematic estimation of the burden of cancer attributable to all accepted modifiable risk factors risk factors in Alberta. In this paper we describe the protocol 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.

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,

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3 water and soil contaminants and components), infectious agents, hormone therapies, dietary intake
4 characteristics and energy imbalance. The full list of exposures and cancer sites of interest for this project
5 is shown in Supplementary Table 1. A secondary consideration in the selection of exposures was the
6 expected range of population prevalence of the individual exposures, as those with very low prevalence
7 will not be of high value in population-based preventive efforts assuming moderate risk relationships.
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14 15 16 **Data Sources**

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

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31 A review of reports from International Collaborative Groups/Panels (e.g. International Agency
32 for Research on Cancer, World Cancer Research Fund), along with a review of the current published
33 peer-reviewed literature in PubMed, was conducted to extract estimates of risk for each exposure and
34 cancer site of interest for this project. Following this review, estimates of relative risk (RR), hazard ratio
35 (HR), odds ratio (OR) or incidence rate ratio (IRR) were selected according to the hierarchy shown in
36 Figure 1. This strategy assumed that the individual risk estimates reflect biological phenomena, such that
37 results from populations outside Alberta or Canada are applicable to the Alberta population. This process
38 produced a single risk estimate for each exposure/cancer site pair, stratified by gender where appropriate,
39 that was used in the estimation of population attributable risks.
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51 *Exposure Prevalence Data*

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53 Prevalence data for the exposures of interest were collected at the provincial level. Prevalence
54 data were obtained from a search of: 1) results from Statistics Canada surveys; 2) publically available
55 government databases; 3) published peer-reviewed literature; and 4) consultation with relevant experts.
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3 Data sources for estimation of exposure prevalence were selected according to the hierarchy shown in
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5 Figure 2.
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8 For all potential sources of exposure prevalence data, several characteristics of available data
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10 sources were considered. First, a theoretical minimum risk principle was used to characterize relevant
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12 measures of exposure.[11] This principle refers to the concept that for meaningful population attributable
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14 risk estimates, alternative population levels of exposure or exposure distributions must be compared.
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16 Under the theoretical minimum risk model, the exposure distribution that corresponds to the lowest level
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18 of population risk is used as the comparison.[11] To apply this concept to our analysis, for risk factors
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20 where complete lack of exposure is possible, those with any exposure to the risk factor were considered
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22 exposed and the prevalence of all potential levels of exposure (if more than one level is appropriate) was
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24 obtained for use in population attributable risk calculations. For example, with active tobacco exposure,
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26 both current and former smokers were considered to have some level of exposure, with never smokers
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28 used as a comparison (i.e. minimum risk) group. For risk factors where all individuals have some level of
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30 exposure such that zero is not a relevant value (e.g. body mass index), the level of exposure associated
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32 with the lowest degree of cancer risk was used as the comparison group and the prevalence of higher
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34 levels of exposure was used in population attributable risk calculations.
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38 Since the effect of exposure on cancer risk is assumed to be the product of a previous exposure
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40 we identified a biologically meaningful latency period for all exposures from the literature. We used the
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42 average time between exposure and cancer diagnosis obtained from high-quality cohort studies. The
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44 quality of cohort studies was evaluated based on the size of the cohort, methods of exposure assessment
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46 and follow-up time, where large cohorts with detailed exposure and longer follow-up were considered to
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48 be of highest quality. This latency information was then compared with the time period for which high-
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50 quality exposure prevalence data were available. Where possible, prevalence estimates corresponding to
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52 the midpoint of the range of potential latency periods identified from cohort studies were selected for
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54 analysis. For example, if cohort studies identified potential latency periods as between nine and 13 years,
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56 exposure prevalence data incorporating an 11 year latency period were selected for analysis if available.
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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 2.

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.

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

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.

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

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]

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

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.

$$\text{Equation 4: } PAR = P_c$$

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

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3 method used for each exposure included in the full population attributable risk project is shown in Table
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8 Monte Carlo simulation techniques (n = 10,000 simulations) were used to estimate 95%
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10 confidence intervals around population attributable risk estimates, similar to techniques used by two
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12 previous studies that estimated population attributable risk.[16,17] The distribution assumed for the
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14 exposure distribution and log of the risk estimate varied across exposure-cancer groups and will be
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16 described in the exposure-based manuscripts. Wherever possible and appropriate, these estimations were
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18 performed for individual sex and age groups.
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21 These different methods for estimating population attributable risks resulted in a set of
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23 proportions of cases by cancer site that can be attributed to these selected exposures. To estimate the
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25 specific number of cases of cancer in Alberta that could be attributed to individual exposures, we applied
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27 these proportions to the 2012 the Alberta Cancer Registry cancer incidence data. Where possible, these
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29 calculations were also performed for age and sex specific groups.
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32 33 34 **INTERPRETATION**

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36 The estimation of population attributable risks for cancer for modifiable lifestyle and
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38 environmental risk factors for Alberta will allow the proportion of cancer diagnosed in the province that is
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40 theoretically preventable to be quantified. This knowledge has implications for cancer prevention since it
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42 will identify the modifiable characteristics for which changes in the provincial risk profile are likely to
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44 have the greatest impact on Alberta's cancer burden. To our knowledge no effort to systematically
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46 quantify the cancer burden attributable to modifiable lifestyle and environmental risk factors has
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48 previously been conducted in Canada.
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51 The most comparable project to ours was conducted by Parkin *et al.* to estimate population
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53 attributable risks for cancer risk factors in the United Kingdom in 2010.[13,18-32] The general approach
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55 that was used by Parkin *et al.*[13] has been adopted for our project and adapted for several of the
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57 exposure-specific methods to apply to the population of Alberta. These similarities will allow the results
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3 from our project and Parkin *et al.* to be directly comparable. Our analysis has also been informed by
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5 previous studies of population attributable cancer risk for the individual exposures included in our project,
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7 particularly from studies conducted in Canada. In 2014, Brenner estimated that 3.5% and 7.9% of cancers
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9 in Canada could be attributed to overweight/obesity and physical inactivity respectively.[4] The methods
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11 we chose to assess the impact of these exposures in Alberta will be identical and thus our estimates will
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13 be directly comparable to those of the Brenner study. Cancer Care Ontario also published population
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15 attributable risk estimates to estimate the cancer burden attributable to tobacco [5], alcohol [33] and
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17 obesity [34] in Ontario and similar methods to those that we propose were used. Several studies have also
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19 attempted to quantify the proportion of lung cancer attributable to residential radon exposure for Canada
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21 as a whole [7, 8, 35], as well as for Ontario specifically.[6] Our estimation of the impact of residential
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23 radon on lung cancer incidence in Alberta will utilize the method developed by Brand *et al.* [7] and will
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25 use the same data source used in previous analyses for Canada [8] and Ontario.[6] Given that no previous
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27 estimates of the population attributable cancer risk in Alberta have been conducted, the ability to compare
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29 our estimates to others in a Canadian context will assist in interpreting our findings.
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36 **Limitations**

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38 While the systematic evaluation of the population attributable cancer in Alberta described in our
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40 protocol will provide novel information about the main causes of cancer in the province, there are some
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42 limitations to our approach. First, our protocol does not consider the influence of exposures that occur in
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44 an occupational setting in order to prevent duplication of work currently being completed by the
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46 Occupational Cancer Research Centre at Cancer Care Ontario concerning the burden of occupational
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48 cancer in Canada (P. Demers, personal communication). Further, the accuracy of the estimates of
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50 population attributable risk that will be produced will necessarily be limited by the extent to which the
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52 prevalence estimates for individual exposures are representative of the true exposure levels in Alberta.
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54 For example, for several dietary exposures, exposure prevalence was estimated using data from Alberta's
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56 Tomorrow Project, a population-based cohort study.[36] Participants in Alberta's Tomorrow Project are
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3 volunteers [36] and the potential for volunteer bias (systematic differences between those who volunteer
4 for the study and those who do not) will need to be considered when evaluating whether the prevalence of
5 individual exposures in the cohort is representative of exposure levels in the general Alberta population.
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10 Our analyses are further limited by the fact that we were unable to account for potential
11 interactions between risk factors when quantifying population attributable risks. As many cancers have
12 multiple causes, it is reasonable to suspect some cancer cases may have been caused by interactions
13 between risk factors investigated in our project. In our analysis each risk factor was considered
14 individually, such that cancers that may have been the result of a combination of risk factors would have
15 been counted twice. However, in order to accurately account for these potential interactions in our
16 population attributable risk estimates, exposure data with estimations of the joint distribution of risk
17 factors that may interact are required and these were not consistently available for Alberta across the
18 range of exposures included in our project. We also estimated that the period between exposure and
19 cancer incidence (referred to in the analyses as latency period) would be the midpoint of observed follow-
20 up times between exposure assessment and cancer incidence in large cohort studies. We did not conduct
21 subsequent sensitivity analyses to examine the impact of this choice by modeling the extent to which
22 changes in exposure prevalence across a range of different latency periods would have influenced
23 estimates of population attributable risk.
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40 Through a national collaborative partnership project funded by the Canadian Cancer Society
41 (Grant Number 703106) we will be conducting a similar series of estimations at the national level in
42 Canada. We will be working to address the methodological limitations listed above with a series of
43 statistical advancements that will include joint risk factor considerations and projection of future
44 avoidable disease burden.
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53 **Conclusion**

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55 The results from the analyses described in this manuscript will estimate population attributable
56 cancer risks for modifiable lifestyle and environmental risk factors for cancer in Alberta. Each of the
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3 exposure-specific manuscripts outlined in Table 1 will follow in this journal. The data produced by this
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5 project will provide important information concerning which known cancer risk factors are responsible
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7 for the largest proportions of cancer in Alberta and will inform future cancer prevention strategies.
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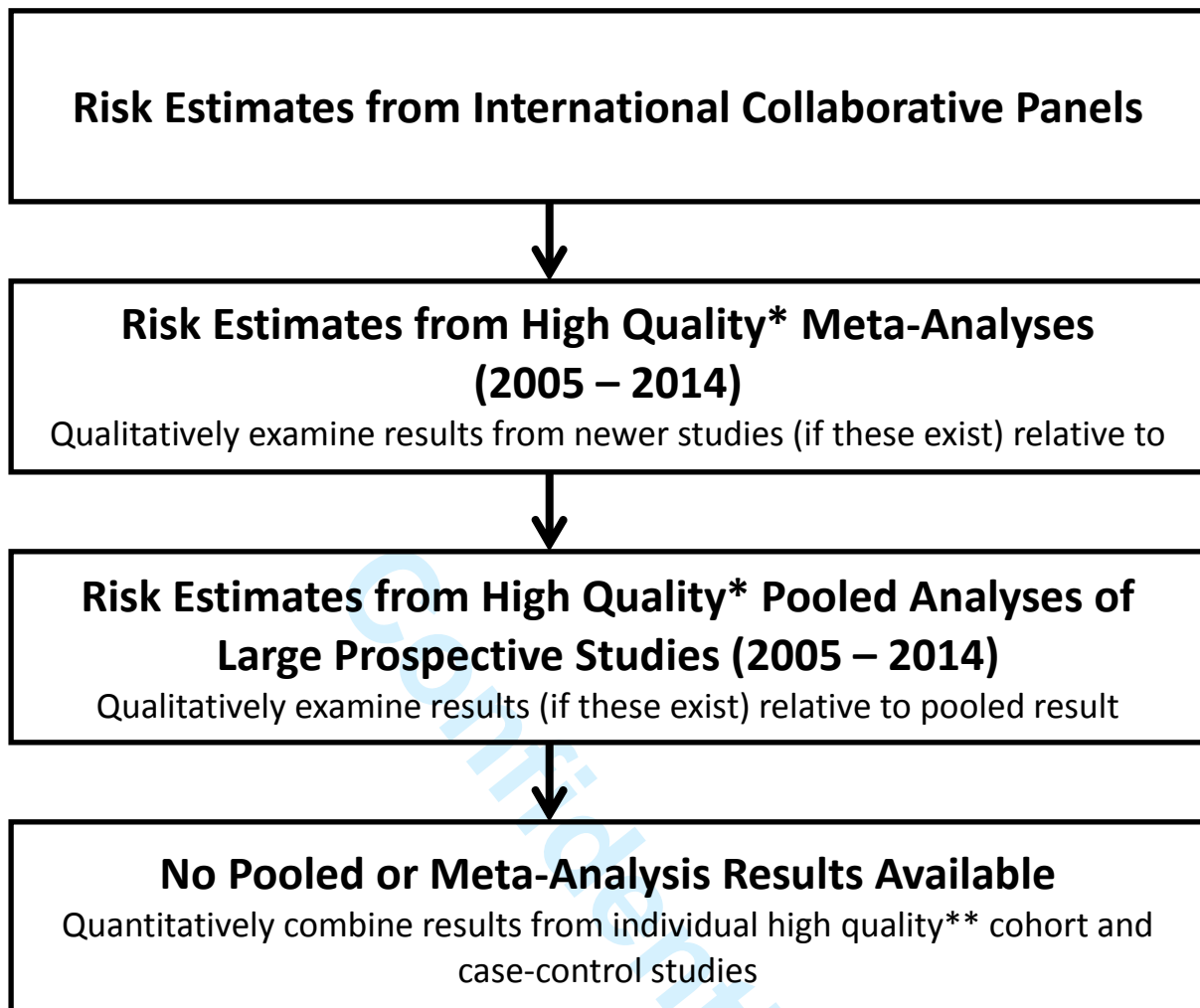
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Table 1. The population attributable risk estimation methods employed for the for individual exposures of interest in this Series

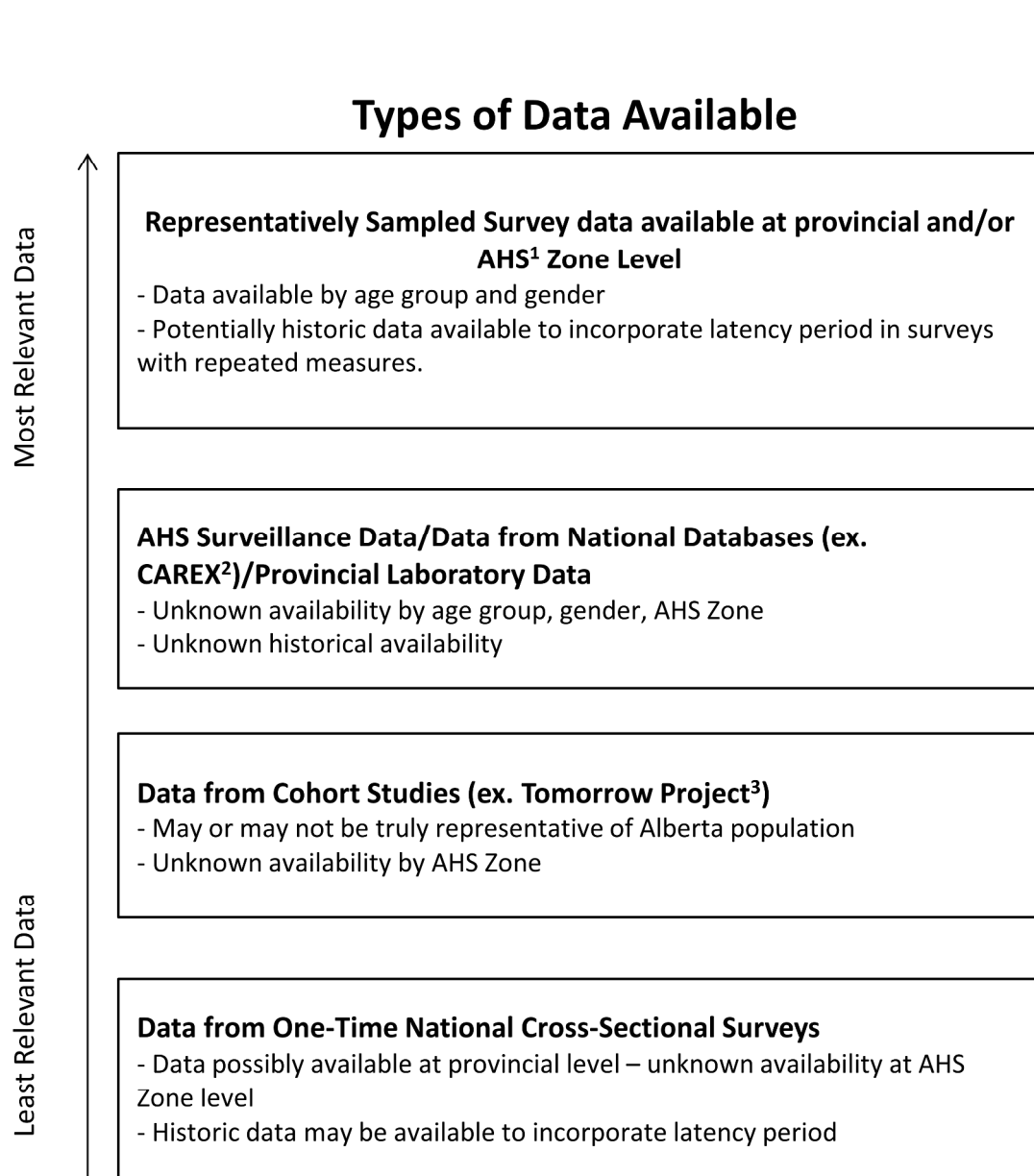
Formula for PAR Estimation	Exposure
$\text{Formula 1: } PAR = \frac{Pe (RR - 1)}{1 + [Pe (RR - 1)]}$	<ul style="list-style-type: none"> • tobacco (passive exposure) • UV exposure • disinfection by-products • low vitamin D • high salt intake • low dietary calcium intake
$\text{Formula 2: } PAR = p_c \frac{(RR - 1)}{RR}$	<ul style="list-style-type: none"> • <i>Helicobacter Pylori</i> • EBV • hepatitis B • hepatitis C
$\text{Formula 3: } PAR = P_c$	<ul style="list-style-type: none"> • HPV for all cancer sites except the cervix
$\text{Formula 4: } PAF = \frac{(p_{e1} \times ERR_1) + (p_{e2} \times ERR_2) + \dots + (p_{ex} \times ERR_x)}{1 + ((p_{e1} \times ERR_1) + (p_{e2} \times ERR_2) + \dots + (p_{ex} \times ERR_x))}$	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • air pollution • radon • insufficient fruit and vegetable intake • red/processed meat intake • insufficient fibre intake • alcohol consumption



*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

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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