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Title	**Cancer incidence attributable to red and processed meat consumption in Alberta, Canada in 2012**
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Reviewer 1	Dr. Katherine Grey-Donald
Institution	McGill University, School of Dietetics and Human Nutrition, Montréal, Que.
General comments (author response in bold)	This study examines the attributable risk of red meats and processed meats to colon cancer given previous RR estimates and dietary intake data from Alberta. The RR for the level of meat consumption was calculated based on an age-specific RR values. The attributable risk makes many presumptions. 1. One important assumption is that the method of measuring meat intake was similar in this study compared to the initial studies contributing to the risk estimates. In order to be credible one would like to know what variables were controlled for in the original studies as this is a somewhat controversial area where some RR values for colon cancer risk have shown that only very high intakes are associated with an elevated risk. **Response: As is described in Table 3 and as we have added in the text on p. 6 in response to a comment from reviewer #3, the RRs used in this study were obtained from the World Cancer Research Fund's Continuous Update Project on Colon Cancer published in 2011 (2). These relative risks were obtained from a systematic review and meta-analysis conducted by the Continuous Update Project group and it is indicated that the primary covariates for which RRs were controlled in addition to age and sex were smoking, alcohol consumption, body mass index and physical activity (2). As we have previously described in our methods document (1), we did not attempt to control for other exposures when we were estimating population attributable risks for Alberta. Specifically relevant to this comment is that while our estimates of the prevalence of each level of meat consumption were stratified by age and sex, they were not stratified by other colorectal cancer risk factors (ex. smoking). We have added a discussion of the potential impact of some other colorectal cancer risk factors to the limitations section on p. 9 – 10.** **With respect to the comment that only high intakes of meat are associated with an elevated risk of colorectal cancer, for this analysis we chose to use the same methods as Parkin (4), which assume that the increase in risk is a logarithmic function of meat intake. The choice to use the same methods in our study as were used by Parkin (4) has two main benefits. The first of these is that by using the same methodological framework to estimate population attributable risks, our Alberta population attributable risk results are directly comparable to the estimates from the United Kingdom, which provides important context to our findings. Given that there is very little literature in this area we believe that the ability to compare our Alberta findings to those from another jurisdiction is important to the interpretation of our work. Secondly, the use of the Parkin method (4), which assumes no safe level of meat consumption and that risk increases with increasing meat intake, allowed us to have a more nuanced exposure assessment than the alternative, which would have been choosing a cutoff for unsafe meat intake and assuming that everyone in the Alberta population above this cutoff had the same increased risk. The application of Parkin's method (4) to our data allows the RR of colorectal cancer to increase with increasing meat intake. For example among men in the 35 – 44 year age group for red meat consumption, according to Equation 2, the RR in quartile 1 is 0.0014, while in quartile 10 the RR is 0.25. As you can see, the chosen method allows for substantially greater relative risks among those with very high levels of meat intake, consistent with the literature. Given that the majority of published RR concerning the relationship between meat consumption and colorectal cancer risk conceptualize risk as the risk per excess X grams of meat intake, in our opinion our chosen method is most consistent with the way in which this association is described in the literature.** 2. It is also important to indicate how such important variables such as exercise and body weight and fruit and vegetable consumption were controlled for. **Response: As we mention in our response to comment 1, we have described in our published methodological framework (1) for our**

	population attributable risk work that we did not attempt to control for other exposures when estimating population attributable risks for meat consumption or any other exposures. Consequently, it is possible that some of the cancer cases we identify as attributable to excess red and processed meat consumption in this analysis may in fact be attributable to the interaction of excess meat consumption with other colorectal cancer risk factors. However, we do not discuss the impact of fruit and vegetable consumption specifically as the independent relationship between fruit and vegetable consumption and colorectal cancer is less established (evidence considered limited in 2011 WCRF Continuous Update Project) (2). As such, while there is potential for interaction between red and processed meat consumption and other colorectal cancer risk factors, we do not believe that it is necessary to discuss fruit and vegetable consumption specifically in this context. 3. The data from a FFQ provides data on grams of intake to 2 decimal places which seems exaggerated as the portions were just presumed to be 75 g. Using the same cut-off for men and women will obviously show a higher risk for men as they eat more of everything than women as they are bigger. **Response: As we state in the methods on p. 5, meat intake from the FFQ in Alberta's Tomorrow Project data estimated the number of ounces of each of red and processed meat consumed each day and the ounces were converted into grams for analysis. Conversely, we describe in the limitations section on p. 9 assessments of red and processed meat intake for Canada as a whole from the Canadian Health Measures Survey (CHMS) where each 'time' of reported meat consumption was estimated as 1 serving or 75g. To clarify, we did not use CHMS data in our population attributable risk analyses and discuss the CHMS data in the limitations section only as they relate to attempting to quantify the potential volunteer bias from estimating the prevalence of meat consumption in Alberta using data from the volunteers who participated in Alberta's Tomorrow Project, a prospective cohort study. We have added to the text in the limitations on p. 8 – 9 in attempt to clarify our discussion of CHMS data.** 4. In table 3 there are no confidence intervals on the RR. Is there really a linear relationship of colorectal cancer and red meat or as is evident in some publications only the highest quintile of meat consumption is associated with an elevated RR. In order to make the argument more convincing I think it is important to mention what primary studies have found in terms of risk instead of using a recommendation that is the same for men and women. This seems to be a recommendation and not a level derived from the best studies in this area. **Response: As we describe in response to comment 1 from this reviewer, the method chosen to estimate the population attributable cancer risks associated with red and processed meat consumption in our analysis developed by Parkin (4) assumes a dose-response relationship between meat consumption and colorectal cancer risk, rather than assigning a specific risk to consumption over a certain threshold. This choice is consistent with the findings of the World Cancer Research Fund in both their 2007 Second Expert Report on Food, Nutrition, Physical Activity and Cancer (5) and their 2011 Continuous Update Project on Colorectal Cancer (2), where they identify substantial evidence of a dose-response relationship for both red and processed meat consumption. While we cite the World Cancer Research Fund recommendation of 'less than 500g (18oz) per week, with very little if any to be processed' for red and processed meat consumption for context (5) in our introduction section, this cutpoint was not used in our estimations of population attributable risk.** 5. All of the PAR values have a CI that goes down to 0. Given this broad range it is not very clear what the findings really show us about the importance of limiting red meats in Alberta any more than general caution in the literature that this may be a risk factor for high red meat consumers. It is hard to quantify red meat as well given the emergence of sausages etc. without beef or pork. **Response: We agree with the reviewer that the wide confidence intervals associated with our population attributable risk estimates are a limitation of this analysis and discuss this in the limitations section on p. 9. While we agree that the width of these confidence intervals highlights that the number of excess attributable cases could be as low as 0 for both red and processed**

	meats, they also suggest that true values could be much higher than our estimates. As we discuss in the limitations section on p. 8 – 9, the use of meat consumption data from a sample of volunteers in Alberta's Tomorrow Project means that the values concerning the prevalence of meat consumption in Alberta used in our analysis may not be truly representative of levels in Alberta. It is clear from the wide confidence intervals that future research that is more precisely able to quantify meat consumption levels in Alberta is needed. 6. Some information on the best studies and what they found would be more enlightening than using a recommendation. **Response: As we describe in our response to comment #1 from this reviewer, the "guideline" of 500g per week was not specifically used in our population attributable risk estimations, rather we assumed an increasing risk with increasing levels of meat consumption. We cite the 500g per week guideline simply to provide some context to the overall prevalence of meat consumption in Alberta in the context of existing public health recommendations.**
Reviewer 2	Dr. Paul G. Ritvo
Institution	Cancer Care Ontario, Toronto, Ont.
General comments (author response in bold)	This project represents efforts to better estimate and represent colorectal cancer risks due to red and processed meat consumption into proportions and absolute numbers of cancers in Alberta in 2012. This effort is laudable as the more personalized these risks are represented, the more individuals will take them seriously in making lifestyle choices. The lifestyle choice factor is represented in the finding that, amongst the Tomorrow Project participants, 41-61% of men vs. 14-25% of women consumed > 500 g of red and processed meat per week. Roughly put, compared to females, ~ 2 x's or more males are exceeding World Cancer Research Fund cancer prevention guidelines. This involves conscious choice, albeit influenced by advertising and, to some degree, 'male' traditions. Certainly, these male excesses could be modified if they got the 'point' that such excesses are raising risks of real consequence. This article adds momentum to the awareness-raising process. 1. A key question is whether their quantification (of proportions and absolute numbers of cancer in Alberta) is accurate. It is, to be fair, an approximate quantification. For several different dietary exposures, prevalence was estimated using data from Alberta's Tomorrow Project, a volunteer cohort that might be expected, based on cohort participation, to reflect more cautious, conscious behaviour than present in the true population of Alberta. Furthermore, cancer relevant exposures that occur in the occupational setting were not considered in this study to prevent a duplication of work on occupational exposures currently being completed at Cancer Care Ontario. Last, but not least, given the multi-causal nature of cancer, some of the cancer cases investigated may have been caused by an interaction of factors. The cases that resulted from a combination of factors, may have been counted twice, as caused by individual factors, in the analyses undertaken. This point is carefully detailed in the manuscript, citing the unavailability of exposure data with estimations of joint distributions of risk factors on a consistent basis. There was also an estimate of the period between exposure and cancer incidence (i.e. diagnosis), referred to as the latency period, and approximated as the midpoint of observed follow up times between exposure assessment and cancer incidence in existing large cohort studies. Sensitivity analyses aimed at evaluating the impact of this estimation by modeling its impact on changes in exposure prevalence (across of range of differing latency periods) and population attributable risk were not done. All of these approximations/limitations are carefully identified in the paper. This is 'work in progress' and the locale in the trajectory of progress is carefully demarcated. Altogether, I would say this is a worthwhile publication for CMAJ that highlights risks in such a way that physicians in practice could implement these data in advising patients. I don't have any major critiques or suggestions for revision. **Response: We thank the reviewer for his kind comments concerning our work.**

Reviewer 3	Neela Guha
Institution	WHO-IARC, IARC Monographs, Lyon, France
General comments (author response in bold)	This manuscript estimates the fraction of colorectal cancer incidence in Alberta, Canada that are attributable to red and processed meat consumption. The manuscript is very well written and proper methods were used for the statistical analyses. This manuscript provides scientific basis for guidelines that could be introduced to limit red and processed meat consumption to decrease colorectal cancer burden in Alberta. I have a few minor points: Introduction 1. Define red meat and processed meat. Use the WCRF or IARC definitions **Response: This definition has been added to the beginning of the introduction on p.3.** 2. pg 4. line 29. specify that 'consumption of red meat' is a Group 2A carcinogen and colorectal cancer was the target organ identified. **Response: This clarification has been added to the final sentence of the first paragraph on p. 3.** METHODS 3. p5, line 5 and throughout - you mention the method by Parkin was used to estimate PAF. You should probably mention Levin's formula **Response: A mention of the relation between the formula used by Parkin (4) and the fact that it is a derivative of Levin's formula has been added to the description of Equation 3 in the methods section on p. 5.** 4. Perhaps mention that dietary data were collected prospectively. In this discussion, you could add prospecitive exposure assessment as a strength. **Response: We agree with the reviewer that if we were conducting a study specifically to quantify the association between meat consumption and colorectal cancer the prospective nature of the collection of data concerning meat consumption would be a strength we would want to highlight. However, in this analysis we are utilizing the data from Alberta's Tomorrow Project (ATP) to capture the prevalence of meat consumption in baseline data and are not** utilizing the prospective component of the ATP data. We chose to use ATP data for our population attributable risk analyses as we believed it was the best available data to represent meat consumption levels in the Alberta population as Alberta-specific data on meat consumption from population survey data were not available. We highlight the geographic representativeness of these data in the first paragraph of the limitations section on p. 8. 5. p6, line17: Why do you only cite the canadian cohorts? **Response: We cite three cohort studies that were used to establish the appropriate latency period and these were: the NIH-AARP Diet and Health Study (USA), The Multiethnic Cohort Study (USA) and the Danish Diet, Cancer and Health Study (Denmark). In the following sentence we state that data on meat consumption in Alberta was only available from Alberta's Tomorrow Project data. For the purpose of establishing the prevalence of red and processed meat consumption in order to generate Alberta-specific data on population attributable risk, we focused on data sources that could help us estimate the prevalence of meat consumption within the province of Alberta. We did not consider national Canadian data (that would include other provinces) or data from outside of Canada to establish the prevalence of red and processed meat consumption in Alberta as we did not believe these would be representative sources. As such, in the last sentence of the paragraph concerning latency on p. 5 we sought to explain that the latency period we would be able to evaluate using this Alberta-specific data (only available from data collected between 2000 and 2009) for cancers diagnosed in 2012 would be shorter than the 10 – 14 years suggested by cohort studies.** 6. pg, line 25. Mention again theat relative risk of meat consumption for colorectal cancer was obtained from the CUP project. **Response: We have added this detail to the text on p. 5 just after equation 2.**

	7. p.6, line 20 - an 8 years average latency, from the time of dietary assessment, is mentioned. You may wish to mention if there is any evidence on the stability of meat consumption over time **Response: In our opinion the stability of meat consumption over time is not directly relevant to our investigation of population attributable risks. Specifically, as we describe in the first full paragraph on p. 5 in the methods section, our analytic strategy is based on a theoretical latency period between time of exposure and time of cancer diagnosis, which is the rationale for the use of historical data from Alberta's Tomorrow Project to estimate the proportion of cancer diagnosed in 2012 that is attributable to past meat consumption. In our opinion, cancers diagnosed in 2012 are conceptually the result of past rather than current dietary exposures and as such, if we wish to estimate the proportion of cancer in 2012 in Alberta that could be attributable to meat consumption, we must estimate the prevalence meat consumption at an appropriate time in the past rather than in 2012. To incorporate this idea we included the concept of latency periods in our analysis and as we describe on p. 5 we attempted to identify an appropriate latency period based on the follow-up times observed in published cohort studies. As such, while we agree that dietary patterns may change over time, under the theoretical model where past exposures are responsible for current cancer diagnoses, we do not believe these potential changes are directly relevant to the analyses presented in our manuscript.** RESULTS 8. p8, line8: When presenting the cases attributable to meat consumption, perhaps it is better to present in the context that colorectal cancer is multifactorial and correlated with other factors that are associated with meat consumption (e.g fruit and vegetable intake). You may also want to discuss this and indicate in the methods if the RRs from CUP included studies that were adjusted for fruit and vegetable intake. **Response: Documentation for the systematic literature review upon which the RRs from the Continuous Update Project were based indicates that most studies included in the meta-analysis adjusted results for smoking, alcohol consumption, BMI and physical activity in addition to age and sex (2). In reviewing studies included in the meta-analysis for the Continuous Update Project it appears that control for fruit and vegetable consumption was inconsistent when evaluating associations between meat consumption and colorectal cancer risk. While the WCRF classifies the evidence for an association between fruit and vegetable consumption and colorectal cancer risk as only limited (2), if there is a real association between fruit and vegetable consumption and colorectal cancer risk and if fruit and vegetable consumption is related to meat consumption (ex. if those who eat more meat eat less fruits and vegetables) then some of the burden of colorectal cancer identified as attributable to meat consumption might more appropriately be attributable to fruit and vegetable consumption, such that our population attributable risk estimates represent overestimates of the true cancer burden. However, as we describe in response to comment #2 from Reviewer 1, while we have included a general discussion of the impact of interactions on our population attributable risk estimates on p. 9 – 10, we have chosen not to discuss fruits and vegetables specifically.** DISCUSSION 9. p8, lines 49-53 are unclear. Both halves of the sentence state that there could be real differences in meat consumption between the two populations **Response: We have attempted to clarify the language in this sentence at the bottom of p. 7 to better convey our ideas. Specifically, we were trying to explain that observed differences in meat consumption between Alberta and the United Kingdom could be due to real differences in the meat consumption habits between the two locations (i.e. that people in the United Kingdom actually eat more red and processed meat than people in Alberta). Alternatively, the lower meat consumption levels we observe in Alberta might be due to the exclusion of younger individuals (who in the UK are the age group with the highest levels of meat consumption) from our Alberta data, such that the exclusion of the youngest portion of the adult population from the Alberta analysis is the real reason our estimates of population attributable risk are lower than in the UK.**

10. p9: It would be more informative to present a comparison of the exposure assessment techniques between the different surveys in your paper somewhere and how this could affect the various prevalence estimates.
Response: We attempted to make the comparison between methods of assessment of red and processed meat consumption between Alberta's Tomorrow Project and the Canadian Health Measures Survey (CHMS) in the limitations section to address the potential for volunteer bias that arose through the use of data from Alberta's Tomorrow Project to quantify red and processed meat consumption levels in Alberta in a sample of volunteers. There is no other population survey data available at the Alberta level with which to make direct comparisons and comparisons with national data (that includes other provinces) are further complicated by the differences in data collection methods described in the limitations on p. 9 – 10 between Alberta's Tomorrow Project and the CHMS. Our description of these differences is meant to explain why we cannot use CHMS data to estimate the potential for volunteer bias in our Alberta specific data. Given that the CHMS represents a different population base (Canada-wide rather than Alberta-specific) it would also be misleading to present numerical comparisons to attempt to quantify the impact of exposure assessment techniques on estimates of population attributable risks. Namely, it is impossible to separate the impact of different population bases and differing exposure assessment techniques on prevalence estimates and in our opinion renders comparisons of population attributable risk from Alberta's Tomorrow Project and CHMS prevalence data inappropriate. We have attempted to clarify the language in the paragraph describing volunteer bias in the limitations section on p. 8 – 9 in order to make clear that we discuss CHMS data only in the sense of explaining why it cannot be used to make further inferences about potential volunteer bias in the Alberta's Tomorrow Project data.

11. Table 4 - Why are CIs not presented for the 'total' category?
Response: Confidence intervals are not presented for the 'total' category as population attributable risks were estimated based on excess attributable cases from the separate men and women analyses, not from population attributable risk models directly. As such, the information used in our Monte Carlo simulations to estimate confidence intervals for men and women was not available for the total category and as such, neither were confidence intervals. A notation regarding this issue has been added to the footnotes for Tables 4 and 5 to clarify this issue for readers.

References:

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2. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and Prevention of Colorectal Cancer. 2011.
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4. Parkin DM. 5. Cancers attributable to dietary factors in the UK in 2010. II. Meat consumption. Br J Cancer 2011;S24-26.

5. World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007.