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Title: Towards refining WCRF/AICR cancer prevention recommendations for red and processed meat intake: Insights from Alberta's Tomorrow Project cohort.

Short title: Association between processed meat intake and cancer risk

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Abbreviations:

ACR, Alberta Cancer Registry

AHR, Adjusted Hazard Ratio

ATP, Alberta's Tomorrow Project

CCHS, Canadian Community Health Survey

CDHQ-I, Canadian Diet History Questionnaire 1

CI, Confidence Interval

CRC, Colorectal Cancer

FFQ, Food Frequency Questionnaire

GI, Gastrointestinal

HLQ, Health and Lifestyle Questionnaire

IBD, Inflammatory Bowel Disease

PYTPAQ, Past-Year Total Physical Activity Questionnaire

WCRF/AICR, World Cancer Research Fund / American Institute for Cancer Research

WHO, World Health Organization

ABSTRACT

Current cancer prevention recommendations advise limiting red meat intake to <500g/week and avoiding consumption of processed meat, but do not differentiate the source of processed meat. We examined the associations of processed meat derived from red vs. non-red meats with cancer risk in a prospective cohort of 26,218 adults who reported dietary intake using the Canadian Diet History Questionnaire. Incidence of cancer was obtained through data linkage with Alberta Cancer Registry with median (IQR) follow-up of 13.3 (5.1) years. Multivariable Cox proportional hazards regression models were adjusted for covariates and stratified by age and gender. The median (IQR) consumption (g/week) of red meat, processed meat from red meat and processed meat from non-red meat were 267.9 (269.9), 53.6 (83.3), and 11.9 (31.8), respectively. High intakes (4^{th} Quartile) of processed meat from red meat was associated with increased risk of gastro-intestinal cancer Adjusted Hazard Ratio (AHR) (95% CI): 1.68 (1.09 – 2.57) and colorectal cancers AHR (95% CI): 1.90 (1.12 – 3.22), respectively in women. No statistically significant associations were observed for intakes of red meat or processed meat from non-red meat. Results suggests that the carcinogenic effect associated with processed meat intake may be limited to processed meat derived from red meats. The findings provide preliminary evidence toward refining cancer prevention recommendations for red and processed meat intake.

INTRODUCTION

In February 2018, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) released the Third Expert Report, *Diet, Nutrition, Physical Activity and cancer: a Global Perspective*.[1] Based on comprehensive evaluations of the global body of scientific evidence,[2] the Report provides the latest cancer prevention recommendations with an emphasis on a more holistic approach of maintaining a healthy body weight, being physically active and eating a healthy diet.[1] It has been estimated that nearly one-third of all cancers can be linked to factors that are modifiable, including the consumption of red and processed meats.[3]

Red meat refers to all types of unprocessed mammalian muscle meat, such as beef, veal, pork, lamb, mutton, horse and goat.[4,5] Processed meat (e.g. ham, salami, bacon, pastrami, and some sausages) refers to meat that is transformed through salting, curing, smoking, drying, fermentation or other processes to improve the flavour or the quality,[5] and may contain poultry, offal or meat by-products.[6] Evaluation of the evidence on red and processed meat consumption suggests that red meat is a *probable* human carcinogen while processed meat is *convincingly* carcinogenic;[1,6] when it comes to cancer risk there is no safe level of processed meat intake.[1,6]

Potential mechanisms underlying the carcinogenesis of red and processed meat have been identified in the IARC Monograph[2], and include N-nitroso compounds (NOC), heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH), which are mutagenic compounds that form during cooking of meat at high temperatures and processing of meats.[7–9] Pro-oxidants, including heme iron and N-glycolyneuraminic acid are also hypothesized to induce inflammation which may lead to tumorigenesis.[10,11] Epidemiological studies on dietary carcinogen intake have been challenging, due in part to difficulties in capturing levels of exposure to HCA or PAH by dietary assessment questionnaires.[12]

For those who eat meat, the WCRF/AICR recommendations are to limit red meat consumption to moderate amounts (<500 grams/week) and to eat little, if any, processed meat.[1] Published findings from the Alberta's Tomorrow Project (ATP) cohort participants have found that 35% of men and 11% of women reported consuming more than 500 grams/week of red meat, exceeding WCRF/AICR Cancer Prevention recommendations.[13] This has important public health and policy implications, and represents an opportunity to help those who exceed consumption recommendations to make informed choices to reduce their cancer risk. The WCRF/AICR recommendations for red and processed meat consumption are largely based on convincing and probable evidence of elevated colorectal cancer (CRC) risk,[1,2,6,14] however these recommendations intended to reduce overall cancer risk. Limited suggestive evidence of increased cancer risk has been identified in a variety of other subsites, including nasopharynx, esophagus, lung, stomach and pancreas.[1,2]

Cancer prevention recommendations are meant to work as whole and to be adopted as a lifestyle package to promote an overall healthy lifestyle for cancer prevention. Our previous work has shown that greater adherence to all six selected WCRF/AICR lifestyle recommendations for cancer prevention was associated with lower risk of cancer in this cohort.[15] The WCRF/AICR recommendations for red and processed meat consumption were not developed using evidence of a well-defined threshold exposure, but are intended to provide a balance between the advantages of consuming meat, which are sources of essential macronutrients and micronutrients, with the disadvantages of potential risk of carcinogenesis.[1] In effort to explore these relationships in greater detail, many epidemiological studies have examined dose-response relationships[16] and compared highest vs. lowest (tertiles, quartiles or quintiles) intakes[17–19], adjusting for a varying range of known risk factors for cancer[20,21], yet inconsistent associations across cancer subsites and between studies have prevented the refinement of current intake recommendations. Moreover, current evidence has yet to determine whether the carcinogenic effect of processed meat varies as a result of its origin. As a result, the current WCRF/AICR recommendations have not differentiated processed meat based on its source: from red meat vs. non-red meat. By analyzing processed meat from all origins combined, true carcinogenic associations with processed meat intake may be obscured. This knowledge gap limits our understanding processed meat carcinogenicity, particularly how the independent carcinogenic effects of processed meat production methods and meat redness interact.

Understanding cancer risk related to varying intakes of red meat and different sources of processed meat will provide useful information concerning the potential role of different dietary patterns with respect to cancer prevention and will likewise provide valuable evidence towards the refinement of cancer prevention recommendations. Thus, the aim of the current analysis was (i) to evaluate whether all processed meat confer equitable cancer risk and (ii) to explore the association between red meat and cancer risk, while adjusting for other known risk factors for cancer.

METHODS

Cohort Design and Data Collection

ATP is a longitudinal prospective cohort of ~ 55,000 Albertans established in 2000 to facilitate studies into the etiology of cancer and other chronic diseases. A full description of study feasibility, design and enrollment is presented elsewhere.[22,23] Briefly, Albertans aged 35–69 years, with no history of cancer except non-melanoma skin cancer, were recruited throughout the province. Participants enrolled between 2000 and 2008 completed the Health and Lifestyle Questionnaire (HLQ), the Canadian Diet History Questionnaire (CDHQ-I) and the Past-Year Total Physical Activity Questionnaire (PYTPAQ). The HLQ collected information on personal and family health history, reproductive history, smoking habits, anthropometric variables and sociodemographic characteristics. CDHQ-I is a 257-item past-year food frequency questionnaire (FFQ) of foods, beverages, and dietary supplements, based on the US National Cancer Institute's Diet History Questionnaire, modified for use in Canada.[24,25] The validated PYTPAQ assessed the frequency, duration, and intensity of physical activities performed over the previous year.[26] As part of the informed consent process, participants consented to ongoing data linkage with administrative health data including the Alberta Cancer Registry (ACR) and provided valid Personal Health Numbers to facilitate linkage.

Inclusion in the current study was restricted to participants who completed all three self-report baseline questionnaires (HLQ, CDHQ-I and PYTPAQ). Participants were excluded from this analysis if they were: deemed as residing outside of Alberta at enrollment (n=29), recruited as second individual from the same household (n=342), had a prior cancer diagnosis, except for non-melanoma skin cancer, assessed via ACR linkage (n=71), outside of the age range of 35 – 69 years at enrolment (n=46), reported indeterminate gender (n=3), or did not consent for linkage to administrative health data (n=180). The final sample size was n=26,218 adults (median age (IQR), 50.0 (14.0) years, 37.5% men). Ethical approval for baseline data collection in ATP was obtained from the former Alberta Cancer Board's Research Ethics Committee and the University of Calgary Conjoint Health Research Ethics Board, Certification file number HREBA.CC-17-0461 (baseline data collection), while ethics approval for the current study was obtained from the Health Research Ethics Board of Alberta – Cancer Committee, Certification file number HREBA.CC-17-0099.

Dietary Intake Assessment

Past year dietary intake data was collected using CDHQ-I.[24,25] CDHQ-I data were analysed using Diet*Calc software for Windows (version 1.4.2; National Cancer Institute, MD, USA). The CDHQ-I nutrient database was used to estimate average daily intakes of energy, nutrients, foods, beverages, and dietary supplements. Red meat and processed meat were defined following the WCRF/AICR criteria (**Supplementary Material A: Table SA1**).

We focused on selected food items recommended for cancer prevention (red meat, processed meat, non-starchy vegetables and fruits (excluding juices), pulses, and wholegrains)[1] and further differentiated the source of processed meat (derived from red vs. non-red meats) (**Supplementary Material A: Table SA1**). Adherence to the WCRF/AICR recommendations for red meat and processed meat consumption was based on 500 grams/week[1] and 50 grams/week, respectively. We used 50 grams/ week as the cut-off for processed meat intake since it is considered the standard serving size equivalent to approximately 1 hot dog or 4 strips of bacon.[27,28] In order to explore whether a dose-response relationship exists between processed meat derived from red vs. non-red meat sources and cancer risk, we also categorized processed meat intake into quartiles.

Sociodemographic, Health Characteristics, and Assessment of Physical Activity

Age, gender, educational attainment, annual household income, family (father, mother, brothers and sisters) history of cancer, personal history of health conditions (high blood pressure, high blood cholesterol, angina, heart attack, stroke, emphysema, chronic bronchitis, diabetes, polyps in colon or rectum, inflammatory bowel diseases ((IBD): which includes ulcerative colitis and Crohn's disease) hepatitis, and liver cirrhosis), personal history of bowel condition which includes IBD and/or a history of polyps in colon or rectum, smoking status (current smoker, former smoker, never smoked), body weight, standing height and geographical location of residence. The above were self-reported at enrollment using the HLQ. Each participant's past year physical activity was also self-reported at enrollment using the PYTPAQ.

Assessment of Cancer Incidence

All participants included in this study were cancer-free at enrollment, as confirmed by linkage with the ACR. Primary incident cancer cases following enrollment were ascertained through data linkage with the ACR in June 2018. Primary malignant cancers, excluding non-melanoma skin cancer, were grouped into four outcomes of cancer incidence, based on cancer type:

1. All cancers combined.
2. Fifteen cancers combined - previously linked with red and/or processed meat intakes as identified in the IARC Monographs:[2,3,6,29] colorectal (colon, rectum and rectosigmoid junction), stomach, pancreas, prostate, breast, bronchus and lung, esophagus, kidney, bladder, ovary, endometrium, non-Hodgkin lymphoma, liver and intrahepatic bile ducts, leukemia, and others (thyroid, gallbladder, testis, brain).
3. Gastrointestinal (GI) cancers, based on the World Health Organization (WHO) classification of digestive system cancers:[30] esophagus, stomach, small intestine, colorectal (colon, rectum and rectosigmoid junction), anus, anal canal and anorectum, liver and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts, and exocrine pancreas.
4. CRC: colon, rectum and rectosigmoid junction.

Statistical Analyses

To investigate the association between red meat and processed meat intakes with cancer incidence (all cancers combined, fifteen cancers combined, GI cancers, and CRC), Cox proportional hazard (Cox PH) models were used. Person-years of follow-up were calculated from the date of enrollment to the date of cancer diagnosis or date of case ascertainment through the ACR linkage, whichever came first. To account for the effect of participant who passed away during the study on person-years follow-up, we conducted a sensitivity analysis using vital statistics data obtained from administrative databases. In these participants, follow-up time was calculated from age at enrollment to age at death. Competing risk analysis was performed, with the standard multivariable Cox PH regression model applied to the cause-specific hazard of interest and competing events treated as censored observations.[31]

For all cancers combined and fifteen cancer combined incidences, the PH assumption (e.g. constant relative hazard) was not met. Thus, adjusted hazard ratios (AHR) and 95%

confidence intervals (CI) were estimated separately for men and women using multivariable Cox PH models and stratified on age at enrollment in 5-year age categories.

For the outcomes of GI cancers and CRC incidence, the PH assumption was met. Thus, AHR and 95% CI were estimated for men and women separately without any age stratified adjustment. However, for GI and CRC cancers, the Firth penalized estimation method[32] was used in the multivariable Cox regression to account for the small number of cancer cases in these subgroups.

In all models, red and processed meat intakes were the exposure variables of interest and were modelled using two categorization schemes. The first scheme was based on categories created using quartiles and the second scheme was based on the WCRF/AICR recommendations, evaluated separately for men and women. Two models were run for each cancer outcome with different covariate adjustments. Covariates were chosen based on personal recommendations for cancer prevention published by the WCRF/AICR for cancer research (2018)[5] and univariate analysis to determine significant sociodemographic variables. AHRs were estimated in comparison to the association of the lowest category of red or processed meat consumption with cancer outcomes. Analyses were conducted using SAS Enterprise Guide version 9.4 (SAS Institute Inc., Cary, NC, USA), and statistical significance was set as alpha ≤0.05 (two-tailed).

RESULTS

Participants' Characteristics

Participant characteristics at enrollment and cancer incidence during follow-up are presented in **Table 1**. The median (IQR) consumption (g/week) of red meat processed meat from red meat and processed meat from non-red meat were 267.9 (269.9), 53.6 (83.3), and 11.9 (31.8), respectively. Having a family history of all cancers combined, fifteen cancers combined, GI cancers, and CRC were reported by 52.5%, 42.1%, 14.6% and 8.5% of participants, respectively. Whereas 46.8% and 6.1% of participants reported personal history of at least one health condition and bowel condition, respectively. At enrollment, most participants lived in urban regions (76.5%), had attained or completed post-secondary education (72%), were non-smokers (82.4%), and were overweight or obese (body mass index (BMI) ≥ 25) (65.7%). Greater proportions of women than men had normal BMI (18.5 ≥ BMI <25; 40.5% vs 23.1%), reported consuming <500 grams/week of red meat (90.4% vs. 66.8%), <50 grams/week of processed meat derived from red meat (59.2% vs. 28.3%), processed meat from non-red meat (86.8% vs. 76.1%), and processed meat from red and non-red meat combined (44.6% vs. 17.8%). Lower proportions of women than men were diagnosed with all cancers combined (8.9% vs. 11%), fifteen cancers combined (7.6% vs. 9.4%), GI cancers (1.4% vs. 2.1%) and CRC (0.9% vs. 1.2%).

Associations of High Red and Processed Meat Intakes with Incidence of All Cancers Combined

For incidence of all cancers combined, the median (IQR) follow-up time was 13.4 (5.1) and 13.3 (5.1) years (total of 129105.7 and 214164.8 person-years follow-up) for men and women, respectively.

Women with a mild intake (i.e., 1st quartile) of processed meat derived from red meats had an increased risk of all cancers combined (AHR (95% CI): 1.22 (1.05 - 1.42). No significant associations were observed in men (**Table 2 – Model 2**).

Association of High Red and Processed Meat Intakes with Incidence of Fifteen Cancers Combined

Women with a mild intake (i.e., 1st quartile) of processed meat derived from red meats had an increased risk of fifteen cancers combined (AHR (95% CI): 1.20 (1.02 – 1.41). No significant associations were found in men (**Table 3 = Model 2**).

Associations of High Red and Processed Meat Intakes with Incidence of GI Cancers

Women with a high intake (i.e., 4th quartile) of processed meat derived from red meat t had an increased risk of GI cancer (AHR (95% CI): 1.68 (1.09 – 2.57). Mild intakes (2nd Quartile) of processed meat from red and non-red meat combined was also associated with increased risk of GI cancers in women AHR (95% CI): 1.45 (1.01 – 2.11). (**Table 4 – Model 2**).

Association of High Red and Processed Meat Intakes with Incidence of CRC

Women with high intake (i.e., 4th quartile) of processed meat derived from red meat had an increased risk of CRC AHR (95% CI): 1.90 (1.12 – 3.22). This association persisted even after adjustment for covariates (**Table 5 – Model 2**).

When the analysis was repeated using adherence vs. non-adherence to the WCRF/AICR recommendations, there were no significant associations observed after covariate adjustment (**Supplementary Material B: Table SB1, SB2, SB3, SB4**). Interaction terms between BMI and red and processed meat intakes were not significant indicating that BMI does not modify the association between meat intake and cancer risk. Thus, these interaction terms were excluded from all the models.

Competing risk analysis to account for deaths before ACR linkage date in participants who were cancer-free during follow-up did not significantly change the observed hazard ratios (Data not shown).

DISCUSSION

In the present study, we evaluated associations between reported meat intake and cancer risk using two methods; quartiles to explore potential dose response relationships, comparing high vs. low intakes, and also a secondary analysis using the current WCRF/AICR recommendations for red meat intake cut-offs (500 grams/week) and a 50 grams/week intake cut-off for processed meat. Although no dose-response relationships were observed, we identified considerable differences in cancer risk conferred from the *source* of processed meat intake. Processed meat from red meat resulted in stronger associations with GI and CRC cancer outcomes compared to both red meat and processed meat from non-red meat, but these were not observed in all cancers and 15 cancers combined. This may be the first time that a differential risk related to the *source* of processed meat has been identified.

Our findings build on an extensive body of research on the association between red and processed meat intake and cancer risk. In 2018, the WCRF/AICR Continuous Update Project report stated there was strong evidence linking high red and processed meat consumption with an increased risk of cancer[(1)] and other cohort studies, systematic reviews and meta-analyses provide evidence for a positive association, especially for CRC.[(19,27,33–44)] Compared to other studies using different study designs and methodology, a Japanese cohort of men and women aged 35 and older, which used an FFQ, examined associations of total meat consumption, and intake of red meat and processed meat with risk of colorectal, colon and rectal cancer. [(45)] The authors reported that the highest intake (4th Quartile) of processed meat was significantly associated with colon cancer among men.[(45)] Moreover, the highest intake (4th Quartile) of red meat was significantly associated with colorectal and rectal cancers among men. No significant associations were observed among women.[45] Similarly, an Australian cohort study of men and women ages 27-75, which also used an FFQ, examined the effect of red meat, processed meat, chicken and fish consumption on risk of colorectal cancer.[44] The authors reported that intakes of processed meat were significantly associated with colorectal cancers (2nd and 4th Quartile) and rectal cancers (2nd, 3rd and 4th Quartiles).[44] High intake of fresh red meat (4th Quartile) was also significantly associated with colorectal cancer.[44] Despite both the Japanese and Australian studies using similar prospective cohort study designs, dietary assessment tools, and analysis methodology, neither differentiated the carcinogenic effects of processed meat based on the source (i.e., processed from red meat vs. non-red meat). We identified similar significant positive associations between intake of processed meat, particularly from red meat sources, and risk of GI cancers, and CRC, even after adjustment for covariates (Model-1 vs. Model-2). We also observed that intake of red meat was associated with risk of GI cancer, but only in men. This could be attributable to the fact that on average, men consume more red meat than women.[46] However, this effect was attenuated after covariate adjustment.

The WCRF/AICR indicate that the *type* of meat consumed is important and may influence exposure to certain known carcinogens (including nitrites and nitrates), especially with respect to processed meat.[1,47,48] In studies that have examined the effects of red meat and processed meat separately, associations between cancer risk and processed meat were often stronger than associations with red meat, and were more consistent across various studies, particularly for CRC risk.[34,43,49] However, differences in the intake amounts of processed meat and red meat reported by participants may affect these outcomes. Similar to current findings, many studies have observed no association or only a weak association between red meat intake and cancer risk, despite finding significant associations between processed meat consumption and cancer risk.[50–53]

While other studies have separated out *type* of meat (processed meat or red meat), few have explored the effect of the *source* of processed meat (i.e. processed from red meat or processed from other sources) on cancer risk. A recent pooled analysis of six cohort studies in Japan explored differences in CRC risk across red meat and processed meat from red meat sources, and chicken.[17] The authors did not identify significant associations with high intakes of red meat and risk of CRC, however, processed meat from red meat sources was associated with an increased risk of CRC and colon cancer in women but not in men. Many studies evaluating processed meat have provided limited definitions of the source of processed meat, making it difficult to ascertain whether the observed associations are a result of intake of only processed red meat, or of processed meat from any source. In our study, there was an overall association with cancer risk for processed meat from red meat and from non-red meat combined, but this association was stronger for processed meat derived from red meats. This finding provides reasonable support for potential biological mechanisms, in which the combined carcinogenic effects attributable to red meats and also to production methods involved in processing meat have together resulted in more significant cancer associations.[7–11] Processed meat from non-red meat sources was only borderline significantly associated with risk of GI cancers in men providing some evidence that processed meat production methods may have a carcinogenic effect that is independent of the *source* of meat, however, this was not a dose-response relationship, as only the 3rd Quartile was borderline significantly associated with GI cancer risk.[1]

There is a lot of variability in the way studies performing high vs. low intake risk analyses categorize intakes (ie., by tertiles, quartiles or quintiles), and as a result, associations with cancer may vary depending on the range of processed and red meat intake within the sample and the size of the study sample.[17–19] Other studies performing dose-response analyses have applied different increments of exposure which may also contribute to variability in cancer associations.[16] Studies utilizing larger intake cut-offs, such as adherence to the WCRF/AICR cut-off for red meat consumption (500 grams/per week)[5,54] may lack the sensitivity to identify associations, particularly with smaller numbers of events.[55] This was noted in the current analysis; using the current WCRF/AICR recommendations as cut-offs resulted in few statistically significant associations, compared to the dose-response approach. Additionally, methodological differences in the assessment of the red and processed meat intake assessment, covariate adjustment and limited statistical power to examine certain cancers may, at least in part, explain some of the inconsistencies in the significance of cancer associations observed in different studies. We observed that adjustment for a greater range of known risk factors for cancer (Model 2) attenuated many significant associations which had been identified in the unadjusted model (Model 1), particularly for all cancers combined, and 15 cancers combined. These differences in associations demonstrate the importance of adjustment for all known risk factors to ensure more meaningful interpretations. Moreover, differences observed between cancer outcome categories may be due to site-specific carcinogenic effects which are not evenly shared across all cancers included in these outcome categories. Studies which use different dietary assessment tools may capture data on red and processed meat intakes with different levels of sensitivity. For example, the classifications used to define red meat and processed meat food groups and dishes, and definitions of portion sizes may influence the calculations of total dietary intake.[2] Compared to an FFQ, 24-hour dietary recalls have been found to provide more comprehensive data including details on eating occasions and foods consumed in combination, however, 24-hour recalls are infrequently used as primary dietary assessment tools in large cohort studies.[56] Technological advances have made 24-hour recalls increasingly feasible in these settings, and future research on the carcinogenic effects of red and processed meat may benefit from these tools.[57]

This study made use of an existing cohort with a large sample size and a long median (IQR) follow-up time of 13.3 (5.1) years, compared to that of other studies which have reported shorter follow-up periods.[38,39,50,58–68] Short follow-up periods may result in issues with sub-clinical disease or insufficient numbers of incident cancer cases resulting in low or inadequate statistical power to identify the associations of interest. Additionally, this study utilized a large dataset which included a wide range of lifestyle, environmental and dietary components and risk factors and adjusted for a wide range of baseline covariates and well-known risk factors for cancer. To assess dietary habits, we used an FFQ tool which has been validated in other large studies to assess meat intake, and captures a comprehensive list of foods enabling the separation of *type* and *source* of meat.[69] However, processed meat production methods and *sources* of processed meat differ largely worldwide, and the FFQ tool used in this analysis may not have captured all meat intakes. A limitation of our study is the possibility of measurement error due to misreporting of dietary intake data, which could result in attenuated risk estimates for cancer.[70] To partially deal with the influence of misreporting we adjusted for total energy intake in all of the statistical models,[71] a method which has been utilized in other large cohort studies.[38] As with all observational studies, there is potential for residual confounding by unknown risk factors. For example, the WCRF/AICR Third Expert Report mentions that certain cooking methods confer carcinogenic risk.[1] We were unable to adjust for this aspect due to insufficient data on cooking methods. We were likewise unable to adjust for menopausal status and hormone replacement therapy as these variables were characterized by a high degree of missingness in ATP data. We also did not adjust for race because the ATP cohort consists of >90% Caucasian ethnicity thus any adjustment would have negligible impact on the cancer outcomes.

Despite these limitations, in this large informative cohort study we considered both red meat and processed meat separately, captured a variety of associated and well-known cancers and cancer groups. This was made possible by linkage with Alberta Cancer Registry, which is Gold Certified by the North American Association of Central Cancer Registries.[72] Linkage was facilitated using validated Personal Health Numbers to determine cancer incidence. We employed the totality of quantitative dietary data and lifestyle components obtained from validated questionnaires and adjusted for well-known cancer risk factors and confounders, which is a notable advantage compared to other existing studies which utilized only aspects or single components of diet and lifestyle factors.

Future Directions

This analysis did not inquire about the variability in the co-current consumption of other foods, such as (specific) vegetables, fruit, and fibre intake, which may modify the effects of processed and red meat consumption on cancer risk at various sites. It is recognized in the field, that individuals who consume large amounts of red and processed meat also tend to consume less fish, poultry and vegetables.[5] A previous study conducted using ATP data reported that low vegetables and fruit intake with high processed meat intake was associated with higher cancer incidence, compared to high vegetables and fruit intake with low processed meat intake.[73] However, more large studies are required to understand the potential synergies of food co-occurrence which may result in a combination of influences on several pathways involved in carcinogenesis. Thus, future work of this nature could allow researchers to better capture the attributable cancer risk associated with specific dietary habits. Moreover, the prevalence of modifiable risk factors is also thought to be strongly socioeconomically patterned. Future studies would do well to explore whether socioeconomic disparities exist in the associations between dietary intake and cancer. Additionally, we found that existing data on the percentage of Canadians whose red meat consumption exceeds cancer prevention recommendation limits is scarce and more accurate and available estimates of these indicators are needed. Finally, more research is needed to evaluate whether all processed meat confer equitable risk and to determine what are the attributable risks by *source* and dose of processed meat.

CONCLUSION

In this study, we observed that cancer risk differs according to the *source* of processed meat consumed. Specifically, the carcinogenic effect associated with red and processed meat intake may be limited to processed meat derived from red meats. The finding that not all processed meats confer equitable risk and *type* of processed meat (i.e., processed from red meat vs. processed from other) are meaningful aspects to consider when evaluating cancer risk is novel. These findings provide initial evidence toward developing and refining cancer prevention recommendations for red and processed meat intake.

Supplementary Materials: Supplementary Materials A (Definitions for red and processed meat) Supplementary Materials B (Secondary Analysis using current WCRF/AICR recommendations), Supplementary Materials C (Competing Risk Analysis).

Author Contributions: Formulating the research question: A.A.R., T.R.H., G.L.S., P.J.R., J.E.V., K.M; designing the study: A.A.R., G.L.S., T.R.H., P.J.R., and K.M; analyzing the data: G.L.S and A.K.A.; writing and/or revising the manuscript: A.K.A., K.L.M., G.L.S., T.R.H., A.A.R., K.M., P.J.R., and J.E.V.

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Ethics of Human Participation: This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the former Alberta Cancer Board's Research Ethics Committee and the Health Research Ethics Board of Alberta Cancer Committee (ID: HREBA.CC-17-0099). Written informed consent was obtained from all participants.

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Table 1. Participants' characteristics at enrollment to Alberta's Tomorrow Project and cancer incidence at follow-up, stratified by gender. [†]

		Men n=9,825	Women n=16,393	Total n=26,218
Age (years) [€]		50.0 (15.0)	50.0 (14.0)	50.0 (14.0)
Marital status	Married/living with a partner	8164 (83.1)	12442 (75.9)	20606 (78.6)
	Single (never married)	635 (6.5)	879 (5.4)	1514 (5.8)
	Divorced/separated/widowed	1025 (10.4)	3070 (18.7)	4095 (15.6)
Educational level	≤ High school	2456 (25.0)	4878 (29.8)	7334 (28.0)
	Some post-secondary	3987 (40.6)	6365 (38.8)	10352 (39.5)
	Post-secondary completed	3381 (34.4)	5149 (31.4)	8530 (32.5)
Employment status	Employed	8028 (81.7)	11018 (67.2)	19046 (72.6)
	Not employed	550 (5.6)	3093 (18.9)	3643 (13.9)
	Retired	1243 (12.7)	2276 (13.9)	3519 (13.4)
Annual household income ($CAD) [a, ¥, *]	<50,000	2342 (23.8)	5742 (35.0)	8084 (30.8)
	50, 000 - <100, 000	4349 (44.3)	6377 (38.9)	10726 (40.9)
	≥100, 000	2999 (30.5)	3803 (23.2)	6802 (25.9)
Family history of cancer [b, ¥]	All cancer types [c, *]	4,936 (50.2)	8,827 (53.9)	13,763 (52.5)
	15 cancers [d, *]	4,013 (40.8)	7,032 (42.9)	11,045 (42.1)
	GI cancers [e, *]	1,346 (13.7)	2,469 (15.1)	3,815 (14.6)
	CRC [f, *]	740 (7.5)	1,478 (9.0)	2,218 (8.5)
Personal history of health conditions [¥]	At least one health condition [g, *]	4,975 (50.6)	7,305 (44.6)	12,280 (46.8)
	Bowel condition [h]	603 (6.1)	990 (6.0)	1,593 (6.1)
Geographic location [i, ¥, *]	Urban	7,610 (77.5)	12,440 (75.9)	20,050 (76.5)
	Rural	2,215 (22.5)	3,953 (24.1)	6,168 (23.5)
Smoking Status [¥, *]	Current smoker	1,780 (18.1)	2,813 (17.2)	4,593 (17.5)
	Former smoker	3,914 (39.8)	5,948 (36.3)	9,862 (37.6)
	Never smoked	4,126 (42.0)	7,620 (46.5)	11,746 (44.8)
BMI (kg/m^2) [j, ¥, *]	<25 (Healthy)	2,272 (23.1)	6,645 (40.5)	8,917 (34.0)
	≥25 and < 30 (Overweight)	4,820 (49.1)	5,438 (33.2)	10,258 (39.1)
	≥ 30 (Obese)	2,710 (27.6)	4,259 (26.0)	6,969 (26.6)

Recreational physical activity (MET-hours/week) [k, €, *]		12.0 (28.9)	8.2 (22.5)	9.5 (25.0)
Total energy intake (kcal/day) [€, *]		2,062 (1,050)	1,536 (754)	1,702 (918)
Red meat [¥, *]	<500 grams/week	6,563 (66.8)	14,824 (90.4)	21,387 (81.6)
	≥500 grams/week	3,262 (33.2)	1,569 (9.6)	4,831 (18.4)
Processed meat from red meat [¥, *]	<50 grams/week	2,778 (28.3)	9,707 (59.2)	12,485 (47.6)
	≥50 grams/week	7,047 (71.7)	6,686 (40.8)	13,733 (52.4)
Processed meat from non-red meat [¥, *]	<50 grams/week	7,478 (76.1)	14,231 (86.8)	21,709 (82.8)
	≥50 grams/week	2,347 (23.9)	2,162 (13.2)	4,509 (17.2)
Processed meat from red meat & non-red meat combined [¥, *]	<50 grams/week	1,745 (17.8)	7,308 (44.6)	9,053 (34.5)
	≥50 grams/week	8,080 (82.2)	9,085 (55.4)	17,165 (65.5)
Non-starchy vegetable & fruit (servings/day) [l, €, *]		3.6 (3.2)	4.2 (3.5)	4.0 (3.4)
Pulses (servings/day) [€, *]		0.1 (0.1)	0.04 (0.1)	0.04 (0.1)
Wholegrains (servings/day) [€, *]		1.1 (1.2)	0.8 (0.9)	0.9 (1.0)
Alcohol (drinks/day) [€, *]		0.5 (1.1)	0.2 (0.4)	0.2 (0.7)
Cancer incidence [m, ¥]	All cancers combined [c, *]	1078 (11.0)	1457 (8.9)	2535 (9.7)
	Fifteen cancers combined [d, *]	926 (9.4)	1245 (7.6)	2171 (8.3)
	GI cancers [e, *]	209 (2.1)	228 (1.4)	437 (1.7)
	CRC [f, *]	119 (1.2)	147 (0.9)	265 (1.0)

BMI, body mass index; GI, gastrointestinal; CRC, colorectal cancer.

a- Education attainment and annual household income were treated as continuous variables.
b- Family includes father, mother, brothers, and sisters.
c- Primary malignant cancers, excluding non-melanoma skin cancer.
d- Fifteen cancers combined previously linked to red and processed meat intakes: colorectal (colon, rectum and rectosigmoid junction), stomach, pancreas, prostate, breast, bronchus and lung, esophagus, kidney, bladder, ovary, endometrium, non-Hodgkin lymphoma, liver and intrahepatic bile ducts, leukemia, and others (thyroid, gallbladder, testis, brain).

e- Esophagus, stomach, small intestine, colorectal (colon, rectum and rectosigmoid junction), anus, anal canal and anorectum, liver and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts, and exocrine pancreas.
f- Colon, rectum and rectosigmoid junction.
g- High blood pressure, high blood cholesterol, angina, heart attack, stroke, emphysema, chronic bronchitis, diabetes, polyps in colon or rectum, inflammatory bowel diseases (IBD, which includes ulcerative colitis and Crohn's disease) hepatitis, and liver cirrhosis.
h- Personal history of bowel condition which includes inflammatory bowel disease (IBD; includes ulcerative colitis and Crohn's disease) and/or a history of polyps in colon or rectum.
i- Geographic location was determined using postal codes, where "0" as the second digit corresponded to rural regions.
j- Calculated from self-reported height and weight.
k- Total metabolic equivalent of task (MET)-hours per week spent performing recreational physical activities at moderate (>3 to ≤6 MET) or vigorous (>6 MET) intensity.
l- Excluding juices.
m- Primary incident cancer cases were ascertained on November 2017 through data linkage with the Alberta Cancer Registry (ACR).
† A total of 711 participants (169 men, 542 women) had missing sociodemographic data.
* P-value < 0.05 men vs. women (Pearson chi-square tests for categorical variables; Wilcoxon rank-sum tests for continuous variables).
€- Values are presented as median (IQR).
¥- Values are presented as frequency (column percentage).

Table 2. AHR and 95% CI from multivariable Cox PH models for the association of red and processed meat intake with incidence cases of all cancers combined [a], separated by gender.

	MEN			WOMEN		
	Cancer cases [a]	AHR [95% CI]	P-value	Cancer cases[a]	AHR [95% CI]	P-value
Model 1 [b]	1,078			1,457		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		1.07 [0.90, 1.27]	0.476		**1.29 [1.12, 1.48]**	**0.001**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		1.15 [0.97, 1.36]	0.119		1.13 [0.97, 1.32]	0.105
Q4(Men: >169, Women: >77) grams/week		**1.25 [1.05, 1.50]**	**0.015**		**1.21 [1.04, 1.41]**	**0.016**
Processed meat from non-red meat						
Q1(Men:≤6, Women:≤2) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week		1.05 [0.89, 1.24]	0.592		0.98 [0.85, 1.13]	0.813
Q3(Men:>20-≤48, Women:>10-≤26) grams/week		1.12 [0.94, 1.32]	0.207		1.01 [0.87, 1.18]	0.857
Q4(Men: >48, Women: >26) grams/week		1.03 [0.87, 1.23]	0.735		1.03 [0.89, 1.19]	0.724
Processed meat from red meat & non-red meat combined						
Q1(Men:≤64, Women:≤30) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week		1.13 [0.96, 1.34]	0.148		**1.16 [1.02, 1.34]**	**0.042**
Q3(Men:>123-≤224, Women:>58-≤109) grams/week		**1.22 [1.03, 1.45]**	**0.022**		1.09 [0.94, 1.27]	0.268
Q4(Men: >224, Women: >109) grams/week		1.15 [0.96, 1.39]	0.136		**1.22 [1.05, 1.43]**	**0.011**
Red meat						
Q1(Men:≤232, Women:≤133) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week		0.94 [0.80, 1.12]	0.496		0.95 [0.83, 1.10]	0.524
Q3(Men:>377-≤587, Women:>221-≤341) grams/week		1.11 [0.94, 1.32]	0.221		1.05 [0.91, 1,22]	0.495
Q4(Men: >587, Women: >341) grams/week		1.04 [0.85, 1.27]	0.705		0.98 [0.83, 1.15]	0.765
Model 2 [c]	1,054			1,397		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		1.03 [0.86, 1.23]	0.741		**1.22 [1.05, 1.42]**	**0.008**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		1.10 [0.92, 1.31]	0.293		1.07 [0.91, 1.26]	0.407
Q4(Men: >169, Women: >77) grams/week		1.18 [0.98, 1.44]	0.088		1.10 [0.93, 1.31]	0.269

Processed meat from non-red meat				
Q1(Men:≤6, Women:≤2) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week	1.06 [0.89, 1.25]	0.517	1.00 [0.87, 1.16]	0.999
Q3(Men:>20-≤48, Women:>10-≤26) grams/week	1.11 [0.94, 1.32]	0.229	1.01 [0.86, 1.18]	0.907
Q4(Men: >48, Women: >26) grams/week	1.05 [0.88, 1.26]	0.561	1.02 [0.88, 1.19]	0.773
Processed meat from red meat & non-red meat combined				
Q1(Men:≤64, Women:≤30) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week	1.10 [0.92, 1.30]	0.303	1.13 [0.97, 1.31]	0.108
Q3(Men:>123-≤224, Women:>58-≤109) grams/week	1.18 [0.99, 1.41]	0.074	1.03 [0.88, 1.21]	0.695
Q4(Men: >224, Women: >109) grams/week	1.11 [0.91, 1.35]	0.306	1.15 [0.97, 1.36]	0.106
Red meat				
Q1(Men:≤232, Women:≤133) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week	0.93 [0.78, 1.10]	0.401	0.91 [0.78, 1.05]	0.201
Q3(Men:>377-≤587, Women:>221-≤341) grams/week	1.08 [0.90, 1.28]	0.426	1.01 [0.86, 1.17]	0.955
Q4(Men: >587, Women: >341) grams/week	0.99 [0.80, 1.22]	0.889	0.88 [0.74, 1.05]	0.161

Abbreviations: CI, confidence interval; AHR, adjusted hazard ratio; Cox PH, Cox proportional hazards;

a- Incidence primary malignant cancers, excluding non-melanoma skin cancer.
b- Models 1: AHRs were estimated using a Cox PH model stratified on age at enrollment in 5-year categories and adjusted only for total daily energy intake, separated by gender
c- Models 2: AHRs were estimated using a Cox PH model stratified on age at enrollment in 5-year categories and adjusted for smoking status, body mass index, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, whole grains, family history of all cancer types, alcohol consumption (drinks/day), annual household income, marital status, employment status, education level, geographic location, personal history of at least one health condition, red meat, and all processed meat, separated by gender.

λ- Reference category.

Table 3. AHR and 95% CI from multivariable Cox PH models for the association of red and processed meat intake with incidence cases of fifteen cancers combined[a], separated by gender.

	MEN			WOMEN		
	Cancer cases [a]	AHR [95% CI]	P-value	Cancer cases[a]	AHR [95% CI]	P-value
Model 1 [b]	926			1,245		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		1.03 [0.85, 1.24]	0.767		**1.27 [1.08, 1.48]**	**0.003**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		1.12 [0.94, 1.35]	0.215		1.14 [0.97, 1.35]	0.104
Q4(Men: >169, Women: >77) grams/week		**1.24 [1.02, 1.50]**	**0.032**		**1.23 [1.04, 1.45]**	**0.017**
Processed meat from non-red meat						
Q1(Men:≤6, Women:≤2) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week		1.07 [0.89, 1.28]	0.467		0.99 [0.85, 1.15]	0.887
Q3(Men:>20-≤48, Women:>10-≤26) grams/week		1.13 [0.94, 1.36]	0.180		1.01 [0.85, 1.19]	0.933
Q4(Men: >48, Women: >26) grams/week		1.00 [0.82, 1.20]	0.964		1.03 [0.88, 1.21]	0.708
Processed meat from red meat & non-red meat combined						
Q1(Men:≤64, Women:≤30) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week		1.14 [0.95, 1.36]	0.172		**1.17 [1.00, 1.36]**	**0.052**
Q3(Men:>123-≤224, Women:>58-≤109) grams/week		**1.20 [1.00, 1.45]**	**0.053**		1.14 [0.97, 1.34]	0.112
Q4(Men: >224, Women: >109) grams/week		1.11 [0.90, 1.36]	0.324		**1.24 [1.05, 1.47]**	**0.011**
Red meat						
Q1(Men:≤232, Women:≤133) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week		0.97 [0.81, 1.17]	0.779		0.93 [0.79, 1.08]	0.329
Q3(Men:>377-≤587, Women:>221-≤341) grams/week		1.15 [0.96, 1.39]	0.134		1.12 [0.95, 1.31]	0.174
Q4(Men: >587, Women: >341) grams/week		1.05 [0.85, 1.31]	0.641		0.98 [0.82, 1.17]	0.794
Model 2 [c]	903			1,186		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		1.00 [0.82, 1.21]	0.976		**1.20 [1.02, 1.41]**	**0.025**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		1.07 [0.89, 1.30]	0.475		1.08 [0.91, 1.28]	0.381
Q4(Men: >169, Women: >77) grams/week		1.16 [0.94, 1.42]	0.172		1.12 [0.93, 1.35]	0.223

Processed meat from non-red meat				
Q1(Men:≤6, Women:≤2) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week	1.08 [0.90, 1.30]	0.387	1.00 [0.86, 1.17]	0.999
Q3(Men:>20-≤48, Women:>10-≤26) grams/week	1.13 [0.94, 1.35]	0.212	1.00 [0.84, 1.18]	0.959
Q4(Men: >48, Women: >26) grams/week	1.02 [0.84, 1.24]	0.821	1.02 [0.87, 1.20]	0.813
Processed meat from red meat & non-red meat combined				
Q1(Men:≤64, Women:≤30) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week	1.10 [0.91, 1.32]	0.332	1.14 [0.97, 1.34]	0.109
Q3(Men:>123-≤224, Women:>58-≤109) grams/week	1.15 [0.95, 1.39]	0.154	1.08 [0.91, 1.28]	0.386
Q4(Men: >224, Women: >109) grams/week	1.05 [0.85, 1.31]	0.632	1.17 [0.98, 1.41]	0.083
Red meat				
Q1(Men:≤232, Women:≤133) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week	0.96 [0.79, 1.16]	0.652	0.88 [0.75, 1.03]	0.113
Q3(Men:>377-≤587, Women:>221-≤341) grams/week	1.12 [0.92, 1.36]	0.248	1.07 [0.91, 1.26]	0.420
Q4(Men: >587, Women: >341) grams/week	1.00 [0.80, 1.26]	0.999	0.87 [0.72, 1.06]	0.163

Abbreviations: CI, confidence interval; AHR, adjusted hazard ratio; Cox PH, Cox proportional hazards;

a- Incidence primary malignant fifteen cancers combined previously linked to red and processed meat intakes: colorectal (colon, rectum and rectosigmoid junction), stomach, pancreas, prostate, breast, bronchus and lung, esophagus, kidney, bladder, ovary, endometrium, non-Hodgkin lymphoma, liver and intrahepatic bile ducts, leukemia, and others (thyroid, gallbladder, testis, brain).

b- Models 1: AHRs were estimated using a Cox PH model stratified on age at enrollment in 5-year categories and adjusted only for total daily energy intake, separated by gender.

c- Models 2: AHRs were estimated using a Cox PH model stratified on age at enrollment in 5-year categories and adjusted for smoking status, body mass index, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, whole grains, family history of all cancer types, alcohol consumption (drinks/day), annual household income, marital status, employment status, education level, geographic location, personal history of at least one health condition, red meat, and all processed meat, separated by gender.

λ- Reference category.

Table 4. AHR and 95% CI from multivariable Cox PH models for the association of red and processed meat intake with incidence cases of gastro-intestinal cancers[a], separated by gender.

	MEN			WOMEN		
	Cancer cases [a]	AHR [95% CI]	P-value	Cancer cases[a]	AHR [95% CI]	P-value
Model 1 [b]	209			228		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		0.88 [0.59, 1.33]	0.553		**1.79 [1.24, 2.59]**	**0.002**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		0.91 [0.61, 1.35]	0.639		1.23 [0.82, 1.86]	0.317
Q4(Men: >169, Women: >77) grams/week		1.32 [0.90, 1.95]	0.158		**1.79 [1.21, 2.66]**	**0.004**
Processed meat from non-red meat						
Q1(Men:≤6, Women:≤2) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week		1.32 [0.89, 1.96]	0.174		0.89 [0.62, 1.29]	0.548
Q3(Men:>20-≤48, Women:>10-≤26) grams/week		**1.51 [1.02, 2.24]**	**0.039**		1.35 [0.94, 1.95]	0.109
Q4(Men: >48, Women: >26) grams/week		1.16 [0.76, 1.75]	0.492		0.96 [0.66, 1.40]	0.825
Processed meat from red meat & non-red meat combined						
Q1(Men:≤64, Women:≤30) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week		1.18 [0.80, 1.75]	0.400		**1.54 [1.08, 2.21]**	**0.017**
Q3(Men:>123-≤224, Women:>58-≤109) grams/week		1.19 [0.80, 1.77]	0.388		1.03 [0.69, 1.55]	0.875
Q4(Men: >224, Women: >109) grams/week		1.13 [0.74, 1.73]	0.559		1.42 [0.95, 2.10]	0.085
Red meat						
Q1(Men:≤232, Women:≤133) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week		1.11 [0.74, 1.66]	0.623		0.93 [0.64, 1.34]	0.695
Q3(Men:>377-≤587, Women:>221-≤341) grams/week		1.09 [0.72, 1.66]	0.675		1.13 [0.79, 1.63]	0.508
Q4(Men: >587, Women: >341) grams/week		**1.55 [1.02, 2.38]**	**0.046**		0.92 [0.60, 1.40]	0.686
Model 2 [c]	204			220		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		0.79 [0.52, 1.20]	0.275		**1.69 [1.16, 2.47]**	**0.007**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		0.81 [0.54, 1.22]	0.306		1.14 [0.74, 1.76]	0.556
Q4(Men: >169, Women: >77) grams/week		1.09 [0.72, 1.66]	0.678		**1.68 [1.09, 2.57]**	**0.018**

Processed meat from non-red meat				
Q1(Men:≤6, Women:≤2) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week	1.34 [0.90, 1.99]	0.156	0.92 [0.63, 1.34]	0.658
Q3(Men:>20-≤48, Women:>10-≤26) grams/week	**1.49 [1.00, 2.22]**	**0.051**	1.35 [0.92, 1.96]	0.125
Q4(Men: >48, Women: >26) grams/week	1.16 [0.76, 1.77]	0.493	0.99 [0.67, 1.46]	0.964
Processed meat from red meat & non-red meat combined				
Q1(Men:≤64, Women:≤30) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week	1.04 [0.70, 1.55]	0.854	**1.45 [1.01, 2.11]**	**0.049**
Q3(Men:>123-≤224, Women:>58-≤109) grams/week	1.05 [0.70, 1.59]	0.800	0.98 [0.64, 1.50]	0.918
Q4(Men: >224, Women: >109) grams/week	0.94 [0.60, 1.47]	0.774	1.33 [0.87, 2.03]	0.184
Red meat				
Q1(Men:≤232, Women:≤133) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week	1.07 [0.71, 1.62]	0.739	0.85 [0.59, 1.24]	0.408
Q3(Men:>377-≤587, Women:>221-≤341) grams/week	1.04 [0.68, 1.59]	0.865	1.06 [0.73, 1.53]	0.776
Q4(Men: >587, Women: >341) grams/week	1.29 [0.81, 2.04]	0.283	0.75 [0.48, 1.18]	0.209

Abbreviations: CI, confidence interval; AHR, adjusted hazard ratio; Cox PH, Cox proportional hazards;

a- Incidence primary malignant gastrointestinal cancers: cancers Esophagus, stomach, small intestine, colorectal (colon, rectum and rectosigmoid junction), anus, anal canal and anorectum, liver and intrahepatic bile ducts, gallbladder and extrahepatic bile ducts, and exocrine pancreas

b- Models 1: AHRs were estimated using a Cox PH model and adjusted only for total daily energy intake, separated by gender.

c- Models 2: AHRs were estimated using a Cox PH model and adjusted for smoking status, body mass index, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, whole grains, family history of all cancer types, alcohol consumption (drinks/day), annual household income, marital status, employment status, education level, geographic location, personal history of at least one health condition, red meat, and all processed meat, separated by gender.

λ- Reference category.

Table 5. AHR and 95% CI from multivariable Cox PH models for the association of red and processed meat intake with incidence cases of colorectal cancers[a], separated by gender.

	MEN			WOMEN		
	Cancer cases [a]	AHR [95% CI]	P-value	Cancer cases[a]	AHR [95% CI]	P-value
Model 1 [b]	118			147		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		0.56 [0.31, 1.01]	0.055		**1.60 [1.02, 2.53]**	**0.042**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		0.76 [0.45, 1.28]	0.298		1.17 [0.70, 1.95]	0.546
Q4(Men: >169, Women: >77) grams/week		1.33 [0.81, 2.18]	0.258		**1.89 [1.16, 3.06]**	**0.010**
Processed meat from non-red meat						
Q1(Men:≤6, Women:≤2) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week		1.30 [0.76, 2.22]	0.333		0.84 [0.53, 1.32]	0.439
Q3(Men:>20-≤48, Women:>10-≤26) grams/week		1.58 [0.94, 2.66]	0.084		1.34 [0.85, 2.09]	0.205
Q4(Men: >48, Women: >26) grams/week		1.17 [0.67, 2.03]	0.579		0.91 [0.57, 1.45]	0.679
Processed meat from red meat & non-red meat combined						
Q1(Men:≤64, Women:≤30) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week		0.92 [0.54, 1.58]	0.767		1.54 [0.98, 2.41]	0.059
Q3(Men:>123-≤224, Women:>58-≤109) grams/week		1.07 [0.63, 1.81]	0.803		1.15 [0.70, 1.90]	0.575
Q4(Men: >224, Women: >109) grams/week		1.32 [0.78, 2.26]	0.305		1.53 [0.94, 2.51]	0.091
Red meat						
Q1(Men:≤232, Women:≤133) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week		1.17 [0.68, 2.02]	0.567		0.96 [0.61, 1.51]	0.855
Q3(Men:>377-≤587, Women:>221-≤341) grams/week		1.13 [0.64, 1.98]	0.677		1.18 [0.75, 1.86]	0.486
Q4(Men: >587, Women: >341) grams/week		1.70 [0.96, 3.03]	0.069		1.03 [0.61, 1.76]	0.903
Model 2 [c]	116			141		
Processed meat from red meat						
Q1(Men:≤46, Women:≤20) grams/week [λ]		ref	ref		ref	ref
Q2(Men:>46-≤89, Women:>20-≤40) grams/week		**0.48 [0.26, 0.87]**	**0.015**		**1.60 [1.00, 2.56]**	**0.049**
Q3(Men:>89-≤169, Women:>40-≤77) grams/week		0.62 [0.36, 1.06]	0.079		1.08 [0.63, 1.87]	0.774
Q4(Men: >169, Women: >77) grams/week		0.98 [0.58, 1.68]	0.952		**1.90 [1.12, 3.22]**	**0.017**

Processed meat from non-red meat				
Q1(Men:≤6, Women:≤2) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>6-≤20, Women:>2-≤10) grams/week	1.31 [0.77, 2.24]	0.323	0.81 [0.51, 1.29]	0.379
Q3(Men:>20-≤48, Women:>10-≤26) grams/week	1.54 [0.91, 2.61]	0.108	1.26 [0.80, 2.00]	0.324
Q4(Men: >48, Women: >26) grams/week	1.13 [0.64, 1.99]	0.673	0.90 [0.56, 1.46]	0.669
Processed meat from red meat & non-red meat combined				
Q1(Men:≤64, Women:≤30) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>64-≤123, Women:>30-≤58) grams/week	0.80 [0.46, 1.38]	0.421	1.39 [0.88, 2.21]	0.163
Q3(Men:>123-≤224, Women:>58-≤109) grams/week	0.89 [0.52, 1.54]	0.697	1.05 [0.62, 1.77]	0.863
Q4(Men: >224, Women: >109) grams/week	1.02 [0.57, 1.81]	0.951	1.45 [0.86, 2.46]	0.163
Red meat				
Q1(Men:≤232, Women:≤133) grams/week [λ]	ref	ref	ref	ref
Q2(Men:>232-≤377, Women:>133-≤221) grams/week	1.12 [0.65, 1.95]	0.676	0.89 [0.56, 1.43]	0.640
Q3(Men:>377-≤587, Women:>221-≤341) grams/week	1.04 [0.58, 1.84]	0.904	1.12 [0.70, 1.79]	0.624
Q4(Men: >587, Women: >341) grams/week	1.40 [0.75, 2.60]	0.292	0.86 [0.49, 1.53]	0.613

Abbreviations: CI, confidence interval; AHR, adjusted hazard ratio; Cox PH, Cox proportional hazards;

a- Incidence primary malignant colorectal cancers: colon, rectum and rectosigmoid junction.
b- Models 1: AHRs were estimated using a Cox PH model and adjusted only for total daily energy intake, separated by gender.
c- Models 2: AHRs were estimated using a Cox PH model and adjusted for smoking status, body mass index, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, whole grains, family history of all cancer types, alcohol consumption (drinks/day), annual household income, marital status, employment status, education level, geographic location, personal history of at least one health condition, red meat, and all processed meat, separated by gender.

λ- Reference category.