



Towards refining World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations for red and processed meat intake: insights from Alberta's Tomorrow Project cohort

Ala Al Rajabi^{1,2,3}, Geraldine Lo Siou¹, Alianu K. Akawung¹, Kathryn McDonald¹, Tiffany R. Price⁴, Grace Shen-Tu^{1*}, Paula J. Robson⁵, Paul J. Veugeliers⁶ and Katerina Maximova^{7,8}

¹Alberta's Tomorrow Project, Cancer Research & Analytics, Cancer Care Alberta, Alberta Health Services, Calgary, AB, Canada

²Department of Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

³Health Sciences Department, College of Natural and Health Sciences, Zayed University, Abu Dhabi, UAE

⁴Chronic Disease Prevention & Oral Health, Provincial Population and Public Health, Alberta Health Services, Calgary, AB, Canada

⁵Cancer Research & Analytics, Cancer Care Alberta, Alberta Health Services, Edmonton, AB, Canada

⁶School of Public Health, University of Alberta, Edmonton, AL, Canada

⁷MAP Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada

⁸Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

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Abstract

Current cancer prevention recommendations advise limiting red meat intake to <500 g/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 *v.* 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 follow-up of 13.3 (interquartile range (IQR) 5.1) years. Multivariable Cox proportional hazards regression models were adjusted for covariates and stratified by age and sex. The median consumption (g/week) of red meat, processed meat from red meat and processed meat from non-red meat was 267.9 (IQR 269.9), 53.6 (IQR 83.3) and 11.9 (IQR 31.8), respectively. High intakes (4th Quartile) of processed meat from red meat were associated with increased risk of gastrointestinal cancer adjusted hazard ratio (AHR): 1.68 (95% CI 1.09, 2.57) and colorectal cancers AHR: 1.90 (95% CI 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 suggest that the carcinogenic effect associated with processed meat intake may be limited to processed meat derived from red meats. The findings provide preliminary evidence towards refining cancer prevention recommendations for red and processed meat intake.

Key words: Alberta's Tomorrow Project; Cancer incidence; Cancer prevention recommendations; Dietary intakes; Processed meat; Red meat

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

Abbreviations: ACR, Alberta Cancer Registry; AHR, adjusted hazard ratios; ATP, Alberta's Tomorrow Project; CDHQ-I, Canadian Diet History Questionnaire; CRC, colorectal cancer; GI, gastrointestinal; IQR, interquartile range; PH, proportional hazard; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

* **Corresponding author:** Grace Shen-Tu, email: grace.shentu@albertahealthservices.ca

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, heterocyclic amines and polycyclic aromatic hydrocarbons, which are mutagenic compounds that form during cooking of meat at high temperatures and processing of meats^(7–9). Pro-oxidants, including haem Fe and N-glycolyneuraminic acid, are also hypothesised 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 heterocyclic amines or polycyclic aromatic hydrocarbons by dietary assessment questionnaires⁽¹²⁾.

For those who eat meat, the WCRF/AICR recommendations are to limit red meat consumption to moderate amounts (<500 g/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 g/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, oesophagus, 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 *v.* 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 *v.* non-red meat. By analysing processed meat from all origins combined, true carcinogenic associations with processed meat intake may be obscured. This knowledge gap limits our understanding

on 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 meats 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 about 55 000 Albertans established in 2000 to facilitate studies into the aetiology of cancer and other chronic diseases. A full description of study feasibility, design and enrolment 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, the Canadian Diet History Questionnaire (CDHQ-I) and the Past-Year Total Physical Activity Questionnaire. The Health and Lifestyle Questionnaire 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 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 Past-Year Total Physical Activity Questionnaire 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 (Health and Lifestyle Questionnaire, CDHQ-I and Past-Year Total Physical Activity Questionnaire). Participants were excluded from this analysis if they were: deemed as residing outside of Alberta at enrolment (*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 sex (*n* 3) or did not consent for linkage to administrative health data (*n* 180). The final sample size was 26 218 adults (median age, 50.0 (interquartile range (IQR) 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 were collected using CDHQ-I^(24,25). CDHQ-I data were analysed using Diet*Calc software for Windows (version 1.4.2; National Cancer Institute). 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 *v.* 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 g/week⁽¹⁾ and 50 g/week, respectively. We used 50 g/week as the cut-off for processed meat intake since it is considered the standard serving size equivalent to approximately one hot dog or four strips of bacon^(27,28). In order to explore whether a dose-response relationship exists between processed meat derived from red *v.* non-red meat sources and cancer risk, we also categorised processed meat intake into quartiles.

Sociodemographic, health characteristics and assessment of physical activity

Age, sex, 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 (which includes ulcerative colitis and Crohn's disease), hepatitis and liver cirrhosis), personal history of bowel condition which includes inflammatory bowel diseases 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 were obtained. The above were self-reported at enrolment using the Health and Lifestyle Questionnaire. Each participant's past-year physical activity was also self-reported at enrolment using the Past-Year Total Physical Activity Questionnaire.

Assessment of cancer incidence

All participants included in this study were cancer-free at enrolment, as confirmed by linkage with the ACR. Primary incident cancer cases following enrolment 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, oesophagus, kidney, bladder, ovary, endometrium, non-Hodgkin lymphoma, liver and intrahepatic bile ducts, leukaemia and others (thyroid, gallbladder, testis, brain).

3. Gastrointestinal (GI) cancers, based on the WHO classification of digestive system cancers⁽³⁰⁾: oesophagus, 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 (PH) models were used. Person-years of follow-up were calculated from the date of enrolment 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 enrolment 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 % CI were estimated separately for men and women using multivariable Cox PH models and stratified on age at enrolment 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 cancer and CRC, the Firth penalised 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 categorisation 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 socio-demographic variables. AHR were estimated in comparison with 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.), and statistical significance was set as $\alpha \leq 0.05$ (two-tailed).

Results

Participants' characteristics

Participant characteristics at enrolment and cancer incidence during follow-up are presented in [Table 1](#). The median consumption (g/week) of red meat, processed meat from red meat and processed meat from non-red meat was 267.9 (IQR 269.9), 53.6 (IQR 83.3), and 11.9 (IQR 31.8), respectively. Having a family history of all cancers combined, fifteen cancers combined, GI cancers, and CRC was 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 enrolment, 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 (BMI \geq 25 kg/m²) (65.7%). Greater proportions of women than men had normal BMI (18.5 \geq BMI < 25 kg/m²; 40.5% *v.* 23.1%), reported consuming <500 g/week of red meat (90.4% *v.* 66.8%), <50 g/week of processed meat derived from red meat (59.2% *v.* 28.3%), processed meat from non-red meat (86.8% *v.* 76.1%) and processed meat from red and non-red meat combined (44.6% *v.* 17.8%). Lower proportions of women than men were diagnosed with all cancers combined (8.9% *v.* 11%), fifteen cancers combined (7.6% *v.* 9.4%), GI cancers (1.4% *v.* 2.1%) and CRC (0.9% *v.* 1.2%).

Associations of high red and processed meat intakes with incidence of all cancers combined

For incidence of all cancers combined, the median follow-up time was 13.4 (IQR 5.1) and 13.3 (IQR 5.1) years (total of 129 105.7 and 214 164.8 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: 1.22 (95% CI 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: 1.20 (95% CI 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 gastrointestinal cancers

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

Association of high red and processed meat intakes with incidence of colorectal cancer

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

When the analysis was repeated using adherence *v.* 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 *v.* low intakes, and also a secondary analysis using the current WCRF/AICR recommendations for red meat intake cut-offs (500 g/week) and a 50 g/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 with both red meat and processed meat from non-red meat, but these were not observed in all cancers and fifteen 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 that 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 with other studies using different study designs and methodology, a Japanese cohort of men and women aged 35 years 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 aged 27–75 years, which also used an FFQ, examined the effect of red meat, processed meat, chicken



Table 1 Participants' characteristics at enrolment to Alberta's Tomorrow Project and cancer incidence at follow-up, stratified by sex* (Numbers and percentages; median and interquartile range (IQR))

	Men		Women		Total	
	<i>n</i> 9825		<i>n</i> 16 393		<i>n</i> 26 218	
Age (years)†	50.0	15.0	50.0	14.0	50.0	14.0
Marital status						
	8164	83.1	12 442	75.9	20 606	78.6
	635	6.5	879	5.4	1514	5.8
	1025	10.4	3070	18.7	4095	15.6
Educational level						
	2456	25.0	4878	29.8	7334	28.0
	3987	40.6	6365	38.8	10 352	39.5
	3381	34.4	5149	31.4	8530	32.5
Employment status						
	8028	81.7	11 018	67.2	19 046	72.6
	550	5.6	3093	18.9	3643	13.9
	1243	12.7	2276	13.9	3519	13.4
Annual household income (\$CAD)II,§,‡						
	2342	23.8	5742	35.0	8084	30.8
	4349	44.3	6377	38.9	10 726	40.9
	2999	30.5	3803	23.2	6802	25.9
Family history of cancer¶I,§						
	4936	50.2	8827	53.9	13 763	52.5
	4013	40.8	7032	42.9	11 045	42.1
	1346	13.7	2469	15.1	3815	14.6
	740	7.5	1478	9.0	2218	8.5
Personal history of health conditions§						
	4975	50.6	7305	44.6	12 280	46.8
Geographic location***,§ ‡						
	603	6.1	990	6.0	1593	6.1
	7610	77.5	12 440	75.9	20 050	76.5
	2215	22.5	3953	24.1	6168	23.5
Smoking status§,‡						
	1780	18.1	2813	17.2	4593	17.5
	3914	39.8	5948	36.3	9862	37.6
	4126	42.0	7620	46.5	11 746	44.8
BMI (kg/m ²) †††,§,‡						
	2272	23.1	6645	40.5	8917	34.0
	4820	49.1	5438	33.2	10 258	39.1
	2710	27.6	4259	26.0	6969	26.6
Recreational physical activity (MET-h/week) †††, †,‡	12.0	28.9	8.2	22.5	9.5	25.0
Total energy intake (kcal/d)†,‡	2062	1050	1536	754	1702	918
Red meat§,‡						
	6563	66.8	14 824	90.4	21 387	81.6
	3262	33.2	1569	9.6	4831	18.4
Processed meat from red meat§,‡						
	2778	28.3	9707	59.2	12 485	47.6
	7047	71.7	6686	40.8	13 733	52.4
Processed meat from non-red meat§,‡						
	7478	76.1	14 231	86.8	21 709	82.8
	2347	23.9	2162	13.2	4509	17.2
Processed meat from red meat and non-red meat combined§,‡						
	8080	82.2	9085	55.4	17 165	65.5
Non-starchy vegetable and fruit (servings/d) §§§,†,‡	3.6	3.2	4.2	3.5	4.0	3.4
Pulses (servings/d) †,‡	0.1	0.1	0.04	0.1	0.04	0.1
Wholegrains (servings/d) †,*	1.1	1.2	0.8	0.9	0.9	1.0
Alcohol (drinks/d)†,‡	0.5	1.1	0.2	0.4	0.2	0.7
Cancer incidence¶IIII,§						
	1078	11.0	1457	8.9	2535	9.7
	926	9.4	1245	7.6	2171	8.3
	209	2.1	228	1.4	437	1.7
	119	1.2	147	0.9	265	1.0

GI, gastrointestinal; CRC, colorectal cancer.

* A total of 711 participants (169 men, 542 women) had missing sociodemographic data.

† Values are presented as median (IQR).

‡ *P*-value < 0.05 men v. women (Pearson χ^2 tests for categorical variables; Wilcoxon rank-sum tests for continuous variables).

§ Values are presented as frequency (column percentage).

¶ Education attainment and annual household income were treated as continuous variables.

¶¶ Family includes father, mother, brothers and sisters.

** Primary malignant cancers, excluding non-melanoma skin cancer.

†† Fifteen cancers combined previously linked to red and processed meat intakes: colorectal (colon, rectum and rectosigmoid junction), stomach, pancreas, prostate, breast, bronchus and lung, oesophagus, kidney, bladder, ovary, endometrium, non-Hodgkin lymphoma, liver and intrahepatic bile ducts, leukaemia and others (thyroid, gallbladder, testis, brain).

‡‡ Oesophagus, 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.

§§ Colon, rectum and rectosigmoid junction.

¶¶¶ 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 inflammatory bowel disease (IBD; includes ulcerative colitis and Crohn's disease) and/or a history of polyps in colon or rectum.

*** Geographic location was determined using postal codes, where '0' as the second digit corresponded to rural regions.

††† Calculated from self-reported height and weight.

‡‡‡ Total metabolic equivalent of task (MET)-h/week spent performing recreational physical activities at moderate (>3 to ≤6 MET) or vigorous (>6 MET) intensity.

§§§ Excluding juices.

¶¶¶¶ Primary incident cancer cases were ascertained on November 2017 through data linkage with the Alberta Cancer Registry (ACR).



Table 2 Multivariable Cox proportional hazard (PH) models for the association of red and processed meat intake with incidence cases of all cancers combined*, separated by sex (Adjusted hazard ratios (AHR) and 95 % confidence intervals)

	Cancer cases*	Men			Cancer cases*	Women		
		AHR	95 % CI	P		AHR	95 % CI	P
Model 1†	1078				1457			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		1.07	0.90, 1.27	0.476		1.29	1.12, 1.48	0.001
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		1.15	0.97, 1.36	0.119		1.13	0.97, 1.32	0.105
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.05	0.89, 1.24	0.592		0.98	0.85, 1.13	0.813
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.12	0.94, 1.32	0.207		1.01	0.87, 1.18	0.857
Q4 (Men: >48, Women: >26) g/week		1.03	0.87, 1.23	0.735		1.03	0.89, 1.19	0.724
Processed meat from red meat and non-red meat combined								
Q1 (Men: ≤64, Women: ≤30) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		1.13	0.96, 1.34	0.148		1.16	1.02, 1.34	0.042
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		1.22	1.03, 1.45	0.022		1.09	0.94, 1.27	0.268
Q4 (Men: >224, Women: >109) g/week		1.15	0.96, 1.39	0.136		1.22	1.05, 1.43	0.011
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		0.94	0.80, 1.12	0.496		0.95	0.83, 1.10	0.524
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.11	0.94, 1.32	0.221		1.05	0.91, 1.22	0.495
Q4 (Men: >587, Women: >341) g/week		1.04	0.85, 1.27	0.705		0.98	0.83, 1.15	0.765
Model 2‡	1054				1397			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		1.03	0.86, 1.23	0.741		1.22	1.05, 1.42	0.008
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		1.10	0.92, 1.31	0.293		1.07	0.91, 1.26	0.407
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.06	0.89, 1.25	0.517		1.00	0.87, 1.16	0.999
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.11	0.94, 1.32	0.229		1.01	0.86, 1.18	0.907
Q4 (Men: >48, Women: >26) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		1.10	0.92, 1.30	0.303		1.13	0.97, 1.31	0.108
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		1.18	0.99, 1.41	0.074		1.03	0.88, 1.21	0.695
Q4 (Men: >224, Women: >109) g/week		1.11	0.91, 1.35	0.306		1.15	0.97, 1.36	0.106
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		0.93	0.78, 1.10	0.401		0.91	0.78, 1.05	0.201
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.08	0.90, 1.28	0.426		1.01	0.86, 1.17	0.955
Q4 (Men: >587, Women: >341) g/week		0.99	0.80, 1.22	0.889		0.88	0.74, 1.05	0.161

* Incidence primary malignant cancers, excluding non-melanoma skin cancer.

† Models 1: AHR were estimated using a Cox PH model stratified on age at enrolment in 5-year categories and adjusted only for total daily energy intake, separated by sex.

‡ Models 2: AHR were estimated using a Cox PH model stratified on age at enrolment in 5-year categories and adjusted for smoking status, BMI, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, whole grains, family history of all cancer types, alcohol consumption (drinks/d), 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 sex.

§ Reference category.

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 Quartiles) 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 *v.* 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 *v.* 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 indicates 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



Table 3 Multivariable Cox proportional hazard (PH) models for the association of red and processed meat intake with incidence cases of fifteen cancers combined*, separated by sex (Adjusted hazard ratios (AHR) and 95 % confidence intervals)

	Cancer cases*	Men			Cancer cases*	WWomen		
		AHR	95 % CI	P		AHR	95 % CI	P
Model 1†	926				1245			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		1.03	0.85, 1.24	0.767		1.27	1.08, 1.48	0.003
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		1.12	0.94, 1.35	0.215		1.14	0.97, 1.35	0.104
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.07	0.89, 1.28	0.467		0.99	0.85, 1.15	0.887
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.13	0.94, 1.36	0.180		1.01	0.85, 1.19	0.933
Q4 (Men: >48, Women: >26) g/week		1.00	0.82, 1.20	0.964		1.03	0.88, 1.21	0.708
Processed meat from red meat and non-red meat combined								
Q1 (Men: ≤64, Women: ≤30) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		1.14	0.95, 1.36	0.172		1.17	1.00, 1.36	0.052
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		1.20	1.00, 1.45	0.053		1.14	0.97, 1.34	0.112
Q4 (Men: >224, Women: >109) g/week		1.11	0.90, 1.36	0.324		1.24	1.05, 1.47	0.011
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		0.97	0.81, 1.17	0.779		0.93]	0.79, 1.08	0.329
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.15	0.96, 1.39	0.134		1.12	0.95, 1.31	0.174
Q4 (Men: >587, Women: >341) g/week		1.05	0.85, 1.31	0.641		0.98	0.82, 1.17	0.794
Model 2‡	903				1186			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		1.00	0.82, 1.21	0.976		1.20	1.02, 1.41	0.025
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		1.07	0.89, 1.30	0.475		1.08	0.91, 1.28	0.381
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.08	0.90, 1.30	0.387		1.00	0.86, 1.17	0.999
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.13	0.94, 1.35	0.212		1.00	0.84, 1.18	0.959
Q4 (Men: >48, Women: >26) g/week		1.02	0.84, 1.24	0.821		1.02	0.87, 1.20	0.813
Processed meat from red meat and non-red meat combined								
Q1 (Men: ≤64, Women: ≤30) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		1.10	0.91, 1.32	0.332		1.14	0.97, 1.34	0.109
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		1.15	0.95, 1.39	0.154		1.08	0.91, 1.28	0.386
Q4 (Men: >224, Women: >109) g/week		1.05	0.85, 1.31	0.632		1.17	0.98, 1.41	0.083
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		0.96	0.79, 1.16	0.652		0.88	0.75, 1.03	0.113
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.12	0.92, 1.36	0.248		1.07	0.91, 1.26	0.420
Q4 (Men: >587, Women: >341) g/week		1.00	0.80, 1.26	0.999		0.87	0.72, 1.06	0.163

* 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, oesophagus, kidney, bladder, ovary, endometrium, non-Hodgkin lymphoma, liver and intrahepatic bile ducts, leukaemia and others (thyroid, gallbladder, testis, brain).

† Models 1: AHR were estimated using a Cox PH model stratified on age at enrolment in 5-year categories and adjusted only for total daily energy intake, separated by sex.

‡ Models 2: AHR were estimated using a Cox PH model stratified on age at enrolment in 5-year categories and adjusted for smoking status, BMI, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, whole grains, family history of all cancer types, alcohol consumption (drinks/d), 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 sex.

§ Reference category.

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

Table 4 Multivariable cox proportional hazard (PH) models for the association of red and processed meat intake with incidence cases of gastrointestinal cancers*, separated by sex (Adjusted hazard ratios (AHR) and 95 % confidence intervals)

	Cancer cases*	Men			Cancer cases*	WWomen		
		AHR	95 % CI	P		AHR	95 % CI	P
Model 1†	209				228			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		0.88	0.59, 1.33	0.553		1.79	1.24, 2.59	0.002
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		0.91	0.61, 1.35	0.639		1.23	0.82, 1.86	0.317
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.32	0.89, 1.96	0.174		0.89	0.62, 1.29	0.548
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.51	1.02, 2.24	0.039		1.35	0.94, 1.95	0.109
Q4 (Men: >48, Women: >26) g/week		1.16	0.76, 1.75	0.492		0.96	0.66, 1.40	0.825
Processed meat from red meat and non-red meat combined								
Q1 (Men: ≤64, Women: ≤30) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		1.18	0.80, 1.75	0.400		1.54	1.08, 2.21	0.017
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		1.19	0.80, 1.77	0.388		1.03	0.69, 1.55	0.875
Q4 (Men: >224, Women: >109) g/week		1.13	0.74, 1.73	0.559		1.42	0.95, 2.10	0.085
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		1.11	0.74, 1.66	0.623		0.93	0.64, 1.34	0.695
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.09	0.72, 1.66	0.675		1.13	0.79, 1.63	0.508
Q4 (Men: >587, Women: >341) g/week		1.55	1.02, 2.38	0.046		0.92	0.60, 1.40	0.686
Model 2‡	204				220			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		0.79	0.52, 1.20	0.275		1.69	1.16, 2.47	0.007
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		0.81	0.54, 1.22	0.306		1.14	0.74, 1.76	0.556
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.34	0.90, 1.99	0.156		0.92	0.63, 1.34	0.658
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.49	1.00, 2.22	0.051		1.35	0.92, 1.96	0.125
Q4 (Men: >48, Women: >26) g/week		1.16	0.76, 1.77	0.493		0.99	0.67, 1.46	0.964
Processed meat from red meat and non-red meat combined								
Q1 (Men: ≤64, Women: ≤30) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		1.04	0.70, 1.55	0.854		1.45	1.01, 2.11	0.049
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		1.05	0.70, 1.59	0.800		0.98	0.64, 1.50	0.918
Q4 (Men: >224, Women: >109) g/week		0.94	0.60, 1.47	0.774		1.33	0.87, 2.03	0.184
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		1.07	0.71, 1.62	0.739		0.85	0.59, 1.24	0.408
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.04	0.68, 1.59	0.865		1.06	0.73, 1.53	0.776
Q4 (Men: >587, Women: >341) g/week		1.29	0.81, 2.04	0.283		0.75	0.48, 1.18	0.209

* Incidence primary malignant gastrointestinal cancers: cancers oesophagus, 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.

† Models 1: AHR were estimated using a Cox PH model and adjusted only for total daily energy intake, separated by sex.

‡ Models 2: AHR were estimated using a Cox PH model and adjusted for smoking status, BMI, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, wholegrains, family history of all cancer types, alcohol consumption (drinks/d), 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 sex.

§ Reference category.

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 *v.* low intake risk analyses categorise intakes (i.e. 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 utilising larger intake cut-offs, such as adherence to the WCRF/AICR cut-off for red meat consumption (500 g/week)^(5,54), may lack the sensitivity to identify associations, particularly with smaller numbers of events⁽⁵⁵⁾. This was noted in the current analysis;

Table 5 Multivariable cox proportional hazard (PH) models for the association of red and processed meat intake with incidence cases of colorectal cancers*, separated by sex (Adjusted hazard ratios (AHR) and 95 % confidence intervals)

	Cancer cases*	Men			Cancer cases*	WWomen		
		AHR	95 % CI	P		AHR	95 % CI	P
Model 1†	118				147			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		0.56	0.31, 1.01	0.055		1.60	1.02, 2.53	0.042
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		0.76	0.45, 1.28	0.298		1.17	0.70, 1.95	0.546
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.30	0.76, 2.22	0.333		0.84	0.53, 1.32	0.439
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.58	0.94, 2.66	0.084		1.34	0.85, 2.09	0.205
Q4 (Men: >48, Women: >26) g/week		1.17	0.67, 2.03	0.579		0.91	0.57, 1.45	0.679
Processed meat from red meat and non-red meat combined								
Q1 (Men: ≤64, Women: ≤30) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		0.92	0.54, 1.58	0.767		1.54	0.98, 2.41	0.059
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		1.07	0.63, 1.81	0.803		1.15	0.70, 1.90	0.575
Q4 (Men: >224, Women: >109) g/week		1.32	0.78, 2.26	0.305		1.53	0.94, 2.51	0.091
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		1.17	0.68, 2.02	0.567		0.96	0.61, 1.51	0.855
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.13	0.64, 1.98	0.677		1.18	0.75, 1.86	0.486
Q4 (Men: >587, Women: >341) g/week		1.70	0.96, 3.03	0.069		1.03	0.61, 1.76	0.903
Model 2‡	116				141			
Processed meat from red meat								
Q1 (Men: ≤46, Women: ≤20) g/week§		ref		ref		ref		ref
Q2 (Men: >46–≤89, Women: >20–≤40) g/week		0.48	0.26, 0.87	0.015		1.60	1.00, 2.56	0.049
Q3 (Men: >89–≤169, Women: >40–≤77) g/week		0.62	0.36, 1.06	0.079		1.08	0.63, 1.87	0.774
Q4 (Men: >169, Women: >77) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >6–≤20, Women: >2–≤10) g/week		1.31	0.77, 2.24	0.323		0.81	0.51, 1.29	0.379
Q3 (Men: >20–≤48, Women: >10–≤26) g/week		1.54	0.91, 2.61	0.108		1.26	0.80, 2.00	0.324
Q4 (Men: >48, Women: >26) g/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) g/week§		ref		ref		ref		ref
Q2 (Men: >64–≤123, Women: >30–≤58) g/week		0.80	0.46, 1.38	0.421		1.39	0.88, 2.21	0.163
Q3 (Men: >123–≤224, Women: >58–≤109) g/week		0.89	0.52, 1.54	0.697		1.05	0.62, 1.77	0.863
Q4 (Men: >224, Women: >109) g/week		1.02	0.57, 1.81	0.951		1.45	0.86, 2.46	0.163
Red meat								
Q1 (Men: ≤232, Women: ≤133) g/week§		ref		ref		ref		ref
Q2 (Men: >232–≤377, Women: >133–≤221) g/week		1.12	0.65, 1.95	0.676		0.89	0.56, 1.43	0.640
Q3 (Men: >377–≤587, Women: >221–≤341) g/week		1.04	0.58, 1.84	0.904		1.12	0.70, 1.79	0.624
Q4 (Men: >587, Women: >341) g/week		1.40	0.75, 2.60	0.292		0.86	0.49, 1.53	0.613

* Incidence primary malignant colorectal cancers: colon, rectum and rectosigmoid junction.

† Models 1: AHR were estimated using a Cox PH model and adjusted only for total daily energy intake, separated by sex.

‡ Models 2: AHR were estimated using a Cox PH model and adjusted for smoking status, BMI, recreational physical activity, total daily energy intake, non-starchy vegetables and fruits, pulses, wholegrains, family history of all cancer types, alcohol consumption (drinks/d), 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 sex.

§ Reference category.

using the current WCRF/AICR recommendations as cut-offs resulted in few statistically significant associations, compared with 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 fifteen 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 with an FFQ, 24-h dietary recalls have been found to provide more comprehensive data including details on eating occasions and foods consumed in combination; however,

24-h recalls are infrequently used as primary dietary assessment tools in large cohort studies⁽⁵⁶⁾. Technological advances have made 24-h 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 follow-up time of 13.3 (IQR 5.1) years, compared with 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 utilised a large data set 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 utilised 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 characterised 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 with other existing studies which utilised 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 recognised 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 with 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 socio-economically patterned. Future studies would do well to explore whether socio-economic 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 meats 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 *v.* processed from other) is meaningful aspects to consider when evaluating cancer risk is novel. These findings provide initial evidence towards developing and refining cancer prevention recommendations for red and processed meat intake.

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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.

References

- World Cancer Research Fund/American Institute for Cancer Research (2018) Diet, nutrition, physical activity and cancer: a global perspective. Continuous update project expert report 2018. <http://www.dietandcancerreport.org> (accessed December 2019).
- International Agency for Research on Cancer (2018) *Red Meat and Processed Meat*. Lyon, France: IARC Monographs.
- World Cancer Research Fund International: Continuous Update Project Report (2015) Cancer prevention and survival: Summary of global evidence on diet, weight, physical activity & what increases or decreases your risk of cancer. <https://wp.ufpel.edu.br/renatabib/files/2016/03/WCRFI-dieta-e-atividade-fisica.pdf> (accessed December 2015).
- McAfee AJ, McSorley EM, Cuskelly GJ, *et al.* (2010) Red meat consumption: an overview of the risks and benefits. *Meat Sci* **84**, 1–13.
- World Cancer Research Fund/American Institute for Cancer Research (2018) Continuous update project expert report 2018. Meat, fish and dairy products and the risk of cancer. <https://www.wcrf.org/sites/default/files/Meat-Fish-and-Dairy-products.pdf> (accessed December 2019).
- Bouvard V, Loomis D, Guyton KZ, *et al.* (2015) Carcinogenicity of consumption of red and processed meat. *Lancet Oncol* **16**, 1599–1600.
- Lauber SN & Gooderham NJ (2007) The cooked meat derived genotoxic carcinogen 2-amino-3-methylimidazo[4,5-b]pyridine has potent hormone-like activity: mechanistic support for a role in breast cancer. *Cancer Res* **67**, 9597–9602.
- Sanz Alaejos M & Afonso AM (2011) Factors that affect the content of heterocyclic aromatic amines in foods. *Compr Rev Food Sci Food Saf* **10**, 52–108.
- Alomirah H, Al-Zenki S, Al-Hooti S, *et al.* (2011) Concentrations and dietary exposure to polycyclic aromatic hydrocarbons (PAHs) from grilled and smoked foods. *Food Control* **22**, 2028–2035.
- Casella M, Bimonte S, Barbieri A, *et al.* (2018) Dissecting the mechanisms and molecules underlying the potential carcinogenicity of red and processed meat in colorectal cancer (CRC): An overview on the current state of knowledge. *Infect Agent Cancer* **13**, 1–8.
- Turesky RJ (2018) Mechanistic evidence for red meat and processed meat intake and cancer risk: a follow-up on the International Agency for Research on Cancer Evaluation of 2015. *Chim* **72**, 718–724.
- Sinha R, Peters U, Cross AJ, *et al.* (2005) Meat, meat cooking methods and preservation, and risk for colorectal adenoma. *Cancer Res* **65**, 8034–8041.
- Whelan HK, Xu J-Y, Vaseghi S, *et al.* (2017) Alberta's Tomorrow Project: adherence to cancer prevention recommendations pertaining to diet, physical activity and body size. *Public Health Nutr* **20**, 1143–1153.
- Diallo A, Deschasaux M, Latino-Martel P, *et al.* (2018) Red and processed meat intake and cancer risk: Results from the prospective NutriNet-Santé cohort study. *Int J Cancer* **142**, 230–237.
- Xu JY, Vena JE, Whelan HK, *et al.* (2019) Impact of adherence to cancer-specific prevention recommendations on subsequent risk of cancer in participants in Alberta's Tomorrow Project. *Public Health Nutr* **22**, 235–245.
- Crippa A, Larsson SC, Discacciati A, *et al.* (2018) Red and processed meat consumption and risk of bladder cancer: a dose-response meta-analysis of epidemiological studies. *Eur J Nutr* **57**, 689–701.
- Islam Z, Akter S, Kashino I, *et al.* (2019) Meat subtypes and colorectal cancer risk: a pooled analysis of 6 cohort studies in Japan. *Cancer Sci* **110**, 3603–3614.
- McCullough ML, Jacobs EJ, Shah R, *et al.* (2018) Meat consumption and pancreatic cancer risk among men and women in the Cancer Prevention Study-II Nutrition Cohort. *Cancer Causes Control* **29**, 125–133.
- Keszei AP, Schouten LJ, Goldbohm RA, *et al.* (2012) Red and processed meat consumption and the risk of esophageal and gastric cancer subtypes in The Netherlands Cohort Study. *Ann Oncol* **23**, 2319–2326.
- Zhao Z, Yin Z & Zhao Q (2017) Red and processed meat consumption and esophageal cancer risk: a systematic review and meta-analysis. *Oncotarget* **8**, 30563–30575.
- Zhao Z, Yin Z, Pu Z, *et al.* (2017) Association between consumption of red and processed meat and pancreatic cancer risk: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* **15**, 486–493.
- Bryant H, Robson PJ, Ullman R, *et al.* (2006) Population-based cohort development in Alberta, Canada: a feasibility study. *Chronic Dis Can* **27**, 51–59.
- Robson PJ, Solbak NM, Haig TR, *et al.* (2016) Design, methods and demographics from phase I of Alberta's Tomorrow Project cohort: a prospective cohort profile. *C Open* **4**, E515–E527.
- Csizmadia I, Kahle L, Ullman R, *et al.* (2007) Adaptation and evaluation of the National Cancer Institute's Diet History Questionnaire and nutrient database for Canadian populations. *Public Health Nutr* **10**, 88–96.
- National Cancer Institute (2005) Diet History Questionnaire: Canadian Version. <https://epi.grants.cancer.gov/DHQ/forms/canadian/index.html> (accessed March 2020).
- Friedenreich CM, Courneya KS, Neilson HK, *et al.* (2006) Reliability and validity of the past year total physical activity questionnaire. *Am J Epidemiol* **163**, 959–970.
- Chan DSM, Lau R, Aune D, *et al.* (2011) Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One* **6**, e20456.
- Nomura SJO, Inoue-Choi M, Lazovich D, *et al.* (2016) WCRF/AICR recommendation adherence and breast cancer incidence among postmenopausal women with and without non-modifiable risk factors. *Int J Cancer* **138**, 2602–2615.
- Grunst J, Fateh A, Lamerz R, *et al.* (1976) Metabolic changes in human partial hepatectomy. *Verh Dtsch Ges Inn Med* **82**, 331–334.
- Bosman F, Carneiro F, Hruban R, *et al.* (2010) *World Health Organization Classification of Tumours of the Digestive System*, 4th ed. Lyon, France: IARC Press.
- Prentice RL, Kalbfleisch JD, Peterson AV, *et al.* (1978) The analysis of failure times in the presence of competing risks. *Biom* **34**, 541–554.
- Firth D (1993) Bias reduction of maximum likelihood estimates. *Biometrika* **80**, 27–38.
- Huxley RR, Ansary-Moghaddam A, Clifton P, *et al.* (2009) The impact of dietary and lifestyle risk factors on risk of colorectal

- cancer: a quantitative overview of the epidemiological evidence. *Int J Cancer* **125**, 171–180.
34. Larsson SC & Wolk A (2006) Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* **119**, 2657–2664.
 35. Sandhu MS, White IR & McPherson K (2001) Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev* **10**, 439–446.
 36. Berndt SI, Platz EA, Fallin MD, *et al.* (2006) Genetic variation in the nucleotide excision repair pathway and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* **15**, 2263–2269.
 37. Key TJ, Schatzkin A, Willett WC, *et al.* (2004) Diet, nutrition and the prevention of cancer. *Public Health Nutr* **7**, 187–200.
 38. Norat T, Bingham S, Ferrari P, *et al.* (2005) Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst* **97**, 906–916.
 39. Cross AJ, Leitzmann MF, Gail MH, *et al.* (2007) A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med* **4**, e325.
 40. Flood A, Rastogi T, Wirfält E, *et al.* (2008) Dietary patterns as identified by factor analysis and colorectal cancer among middle-aged Americans. *Am J Clin Nutr* **88**, 176–184.
 41. Larsson SC & Wolk A (2012) Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. *Br J Cancer* **106**, 603–607.
 42. Fung TT, Hu FB, Holmes MD, *et al.* (2005) Dietary patterns and the risk of postmenopausal breast cancer. *Int J Cancer* **116**, 116–121.
 43. Norat T, Lukanova A, Ferrari P, *et al.* (2002) Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer* **98**, 241–256.
 44. English DR, MacInnis RJ, Hodge AM, *et al.* (2004) Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* **13**, 1509–1514.
 45. Wada K, Oba S, Tsuji M, *et al.* (2017) Meat consumption and colorectal cancer risk in Japan: the Takayama study. *Cancer Sci* **108**, 1065–1070.
 46. Canadian Meat Council (2007) Red Meat Intake: a Canadian Perspective. <https://www.cmc-cvc.com/sites/default/files/files/MeatIntakeFactSheetENG.pdf> (accessed November 2007).
 47. Cross AJ & Sinha R (2004) Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen* **44**, 44–55.
 48. Cross AJ, Pollock JRA & Bingham SA (2003) Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res* **63**, 2358–2360.
 49. Chao A, Thun MJ, Connell CJ, *et al.* (2005) Meat consumption and risk of colorectal cancer. *JAMA* **293**, 172–182.
 50. Wie G-A, Cho Y-A, Kang H, *et al.* (2014) Red meat consumption is associated with an increased overall cancer risk: a prospective cohort study in Korea. *Br J Nutr* **112**, 238–247.
 51. Bernstein AM, Song M, Zhang X, *et al.* (2015) Processed and unprocessed red meat and risk of colorectal cancer: analysis by tumor location and modification by time. *PLoS One* **10**, e0135959.
 52. Parr CL, Hjartåker A, Lund E, *et al.* (2013) Meat intake, cooking methods and risk of proximal colon, distal colon and rectal cancer: the Norwegian Women and Cancer (NOWAC) cohort study. *Int J Cancer* **133**, 1153–1163.
 53. Anderson JJ, Darwis NDM, Mackay DF, *et al.* (2018) Red and processed meat consumption and breast cancer: UK Biobank cohort study and meta-analysis. *Eur J Cancer* **90**, 73–82.
 54. Hastert TA & White E (2016) Association between meeting the WCRF/AICR cancer prevention recommendations and colorectal cancer incidence: results from the VITAL cohort. *Cancer Causes Control* **27**, 1347–1359.
 55. Biau DJ, Kernéis S & Porcher R (2008) Statistics in brief: the importance of sample size in the planning and interpretation of medical research. *Clin Orthop Relat Res* **466**, 2282–2288.
 56. Subar AF, Freedman LS, Tooze JA, *et al.* (2015) Addressing current criticism regarding the value of self-report dietary data. *J Nutr* **145**, 2639–2645.
 57. Shim J-S, Oh K & Kim HC (2014) Dietary assessment methods in epidemiologic studies. *Epidemiol Health* **36**, 1–8.
 58. Oba S, Shimizu N, Nagata C, *et al.* (2006) The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. *Cancer Lett* **244**, 260–267.
 59. Fraser GE (1999) Associations between diet and cancer, ischemic heart disease, and all-cause mortality in Non-Hispanic white California Seventh-Day Adventists. *Am J Clin Nutr* **70**, 532S–538S.
 60. Pietinen P, Malila N, Virtanen M, *et al.* (1999) Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* **10**, 387–396.
 61. Thun MJ, Calle EE, Namboodiri MM, *et al.* (1992) Risk factors for fatal colon cancer in a large prospective study. *J Natl Cancer Inst* **84**, 1491–1500.
 62. Brink M, Weijenberg MP, de Goeij AFPM, *et al.* (2005) Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Br J Cancer* **92**, 1310–1320.
 63. Goldbohm RA, van den Brandt PA, van 't Veer P, *et al.* (1994) A prospective cohort study on the relation between meat consumption and the risk of colon cancer. *Cancer Res* **54**, 718–723.
 64. Cross AJ, Ferrucci LM, Risch A, *et al.* (2010) A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res* **70**, 2406–2414.
 65. Giovannucci E, Rimm EB, Stampfer MJ, *et al.* (1994) Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* **54**, 2390–2397.
 66. Lee S-A, Shu XO, Yang G, *et al.* (2009) Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer* **61**, 194–205.
 67. Lichtenborg M, Weijenberg MP, de Goeij AFPM, *et al.* (2005) Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: a prospective cohort study (The Netherlands). *Cancer Causes Control* **16**, 1041–1054.
 68. Kim J, Park S & Nam B-H (2011) The risk of colorectal cancer is associated with the frequency of meat consumption in a population-based cohort in Korea. *Asian Pac J Cancer Prev* **12**, 2371–2376.
 69. Norat T, Vierira A, Chan D, *et al.* (2013) World Cancer Research Fund International Systematic Literature Review. The Associations between Food, Nutrition and Physical Activity and the Risk of Prostate Cancer. <https://www.wcrf.org/sites/default/files/prostate-cancer-slr.pdf> (accessed January 2021).
 70. Kaaks R, Riboli E & van Staveren W (1995) Calibration of dietary intake measurements in prospective cohort studies. *Am J Epidemiol* **142**, 548–556.
 71. Willett W (2001) Commentary: dietary diaries versus food frequency questionnaires—a case of undigestible data. *Int J Epidemiol* **30**, 317–319.
 72. Alberta Health Services (2012) Alberta Cancer Registry 2009 Annual Report of Cancer Statistics. <https://www.albertahealthservices.ca/assets/healthinfo/poph/hi-poph-surv-cancer-alta-cancer-registry-2009.pdf>
 73. Maximova K, Moez EK, Dabravolskaj J, *et al.* (2020) Co-consumption of vegetables and fruit, whole grains, and fiber reduces the cancer risk of red and processed meat in a large prospective cohort of adults from Alberta's tomorrow project. *Nutrients* **12**, 1–21.

