www.alineanutrition.com

TABLE OF
CONTENTS

What We Know, Think We Know, or Are Starting to Know

The role of red meat in long-term disease risk, and the place of red meat in an overall healthy diet pattern, remains a point of ongoing debate. However, we can delineate that debate based on type of meat:

- Processed meat = less debate
- Unprocessed meat = more debate

The reason there is less debate for processed meat is based on the sizeable body that, per the International Agency for Research on Cancer [IARC] evidential criteria, demonstrates *"consistent associations...in different populations, which make chance, bias, and confounding unlikely as explanations..."* * [1]. The IARC conclusion in 2015 that processed meat was causal in carcinogenesis was corroborated in an analysis of research published subsequent to the decision, which demonstrated a dose response per 50g/d that was strongly associated with colorectal cancer incidence [2].

Unprocessed meat has been the subject of more debate, particularly because the IARC decision was largely based on mechanistic data which did not account for potential effect modifiers, including calcium, vegetables, and fruit. The epidemiological evidence for unprocessed meat is less consistent, and may reflect:

- A lack of sufficiently large cohorts to factor in measurement error in dietary assessment
- A lack of a sufficiently wide contrast in level of intake between 'high' and 'low' groups
- Populations were the 'high' group is not particularly high, i.e., <100g/d

Within these questions has been the fact that in most cohort studies demonstrating a risk for unprocessed meat consumption, meat intake tends to correlate with an overall unhealthy lifestyle. As a result, the question remains whether certain factors - like a healthy diet pattern and high intakes of vegetables and fruits - would modify the relationship between red meat and health outcomes. The present study investigated the associations with different levels of red meat intake based on different levels of vegetable and fruit, wholegrain, and fibre intakes.

*Geek Box: Confounders, Correlations, and Control

There is a tendency when it comes to interpreting epidemiological findings to dismiss any related factor between an exposure and and outcome as a "confounder". This ranges from over simplistic, to plain wrong. In order to be a confounder, a variable has to be associated with the exposure but not caused by it, and independently associated with the outcome. For example, an analysis looks at coffee as the exposure and heart disease as the outcome, and finds a strong association; but high coffee drinkers in the study are also heavy smokers. Coffee does not cause smoking, but they are related behaviours. In this case, controlling for smoking means the relationship between coffee and heart disease is not longer evident, i.e., smoking was the confounder. Many of the factors that we deem 'confounders' may in fact only be correlated behaviours or variables. The question to ask from a nutritional perspective is whether the dietary association is independent of non-dietary related lifestyle factors. We can determine this through appropriate control of known variables which may be correlated with diet, like socio-economic status, alcohol intake, or BMI. These variables are not inherently confounders; it depends on what the exposure-outcome relationship is that we're looking at. A common misconception reading such a list of covariates is to assume that all are confounders, however, this is incorrect; there are distinct differences between confounders [i.e., smoking], and moderating or mediating factors [i.e., fibre, fruit]. A general lack of understanding for the differences between such variables in widespread in discourse surrounding nutritional epidemiology. However, a fundamental difference is that a confounder may have direct relationship with the outcome, while a moderating factor may influence the size of the effect and the full operation of a cause-effect relationship, however, it does not invalidate that a relationship exists between the exposure and the outcome. If these were true confounders, then once they are adjusted for in the statistical analysis, the exposure-outcome relationship would no longer be evident. If the exposure-outcome relationship survives this adjustment, then it indicates that the effect of the exposure on the outcome is independent of these related non-dietary variables. While the caveat of epidemiology is always that "residual confounding cannot be ruled out", in reality it can't be ruled out in an RCT either, it's simply that randomisation is deemed to equally distribute unknown variables between an intervention and control group. The reality is that residual confounding implies there is something we don't know which could influence the results, which is always true; what is important to remember is that there is a lot we do know, and we can build that into an adjustment model to control for these variables. Remember: correlation does not imply confounding.

The Study

The Alberta's Tomorrow Project [ATP] is a cohort recruited between 2001-2009 in Alberta, Canada. Participants were eligible if they were aged 35 to 60yrs at baseline and had no prior personal history of cancer. Diet was assessed using the Canadian Diet History Questionnaire I, 124-item semi-quantitative food-frequency questionnaire [FFQ] based on the US National Cancer Institute Diet History Questionnaire which has been extensively validated [3]. The FFQ was modified for use in Canada.

Dietary intakes of unprocessed meat, processed meat, fruits and vegetables [F&V], wholegrains, and fibre, were divided into tertiles - low, moderate, high - and stratified according to age and gender-specific dietary recommendations for intake.

Red meat tertiles were as follows [levels for women are in brackets]:

- Low: <250g [<150g] per week for unprocessed meat - <42g [<28g] per week for processed meat
- Moderate: 250-500g/wk [150-300g] for unprocessed meat - 42-168g/wk [28-112g] for processed meat
- High: >500g/wk [>300g] for unprocessed meat - >168g/wk [>112g] for processed meat

F&V, wholegrain, and fibre tertiles were [in that order]:

- Low: <3-4 servings F&V per day - <0.75 servings [<0.6] wholegrains per day - <117g fibre per week
- Moderate: 3-6/d servings F&V - 0.75-1.5/d wholegrains - 117-150g/wk fibre
- High: >5-6/d servings F&V - >1.5/d wholegrains - >150g/wk fibre

The exposure of interest was red and processed meat intake and co-consumption of F&V, wholegrains, and fibre. The outcome of interest was overall cancer incidence, and 15 specific cancers [analysed together as a composite endpoint] associated with red meat intake. Hazard ratios for risk were calculated together with 95% confidence intervals [CI], for different combinations of low, moderate, and high intakes of the exposures of interest.

Results: 26,218 participants with completed dietary assessments were included in the analysis. The average age was 50yrs, 60% women, 55% current/former smokers, 46% reported a personal history of at least one chronic disease, and 52% had a family history of cancer. The following are the main results, divided by sex:

Women:

- *Unprocessed Meat with F&V:* There was no significant association with cancer in women at any level of unprocessed red meat, at any level of F&V intake.

- *Processed Meat with F&V:* Both the moderate and high tertiles of processed meat were associated with significant increases in cancers risk at all levels of F&V intake. In the highest category of F&V, the highest processed meat was associated with a 32% higher risk, while in the lowest category of F&V this increased to 44% higher risk.

- *Unprocessed Meat with wholegrains:* There was no significant association with cancer in women at any level of unprocessed red meat, at any level of wholegrain intake.

- *Processed Meat with wholegrains:* The highest tertiles of processed meat were associated with significant increases in cancers risk at the lowest levels of wholegrain intake. In the highest category of wholegrain, there was no significant association with risk.

- *Unprocessed Meat with fibre:* There was no significant association with cancer in women at any level of unprocessed red meat, at any level of fibre intake.

- *Processed Meat with fibre:* Both the moderate and high tertiles of processed meat were associated with significant increases in cancers risk at all levels of fibre intake. In the highest category of fibre, the highest processed meat was associated with a 43% higher risk, while in the lowest category of F&V this increased to 50% higher risk.

Men:

- *Unprocessed Meat with F&V:* There was a significant 31% increase in risk at the highest level of red meat intake combined with the lowest level of F&V intake. There were no other significant associations at other levels of intake.

- *Processed Meat with F&V:* Every tertile of processed meat was associated with significant increases in cancers risk at all levels of F&V intake. In the highest category of F&V, the highest processed meat was associated with a 66% higher risk, while in the lowest category of F&V this increased to 91% higher risk.

- *Unprocessed Meat with wholegrains:* There was no significant association with overall cancers in men at any level of unprocessed red meat, at any level of F&V intake. However, at both moderate and high levels of wholegrain intake there was a significant 27% and 36% higher risk of the composite of 15 cancer sites in the highest red meat tertiles.

- *Processed Meat with wholegrains:* The highest tertiles of processed meat were associated with significant increases in cancers risk at each levels of wholegrain intake.

- *Unprocessed Meat with fibre:* Both the low and moderate levels of unprocessed red meat intake were associated with significant 39% and 28% higher risk, respectively, at the lowest level of fibre intake and 18% [both] higher risk at the moderate fibre intake level. However, in the highest red meat tertile there was no significant association with overall cancers in men at any level of fibre intake.

- *Processed Meat with fibre:* Every tertile of processed meat was associated with significant increases in cancers risk at all levels of fibre intake. In the highest category of fibre, the highest processed meat was associated with a 62% higher risk, while in the lowest category of fibre this increased to 65% higher risk.

Adjusting for total fat, dairy, calcium, folate, other plant foods, and sodium, did not alter the associations.

The Critical Breakdown

Pros: The thresholds for the various tertiles were based on established current recommendations from different bodies, e.g., the World Cancer Research Fund and Global Burden of Disease for red meat, and Canadian and US national guidelines for fruit and vegetable, wholegrain, and fibre intake. The effect of red and processed meat was examined across tertiles of intake, relative to the co-consumption of different levels of plant-food intakes. This allowed for a more refined comparison of the potential interaction than an adjustment model including, for example, fruit and vegetable intake. The cohort sample size was moderately large and balanced for factors like education, income, smoking status, and BMI.

Cons: No upper limits on the highest tertile of meat intake were defined. The highest tertile for unprocessed red meat was >500g/d in men, yet the mean intake was 461g/wk with a standard deviation of 347g/wk - it would have been helpful to know what the upper limit of 'high' was in grams per week. The fibre thresholds appear to be a mistake: >161g/week as the highest in women but >150g in men, whereas usually recommendations for men are higher in grams/day. Servings for wholegrains were based on actual consumption due to very low levels of wholegrain intake in the overall cohort, which makes the co-consumption comparisons with red meat potentially lacking a full contrast in effect of wholegrains.

Key Characteristic

The analysis relative to defined levels of plant-based food intake, rather than simply adjust for these foods in a multivariate analysis, allowed for a more refined evaluation of the relationship between meat intake and these potential modifying factors. In a multivariate analysis, the variable - for example F&V intake - is adjusted for as a whole category of exposure along with other categories, e.g., BMI, smoking, etc. The aim of such an analysis is to eliminate potential variables associated with the outcome by demonstrating that they have no independent relationship with the outcome, and the association with the primary exposure of interest remains [4]. In the present study, however, hazard ratios were calculated for each level of meat intake relative to each level of F&V, wholegrain, and fibre intake, providing a more nuanced analysis of the relationship between meat and cancer with these additional protective foods included.

Interesting Finding

There are a few in this study. The first is that in the high tertile of red meat intake, those with the highest F&V had a trend toward reduced risk [HR 0.78, 95% CI 0.57 to 1.05]. Much has been made of this finding, suggesting that once F&V are eaten in large enough quantities, unprocessed red meat is not an issue - indeed the low F&V category in this red meat tertile had a 31% higher risk for cancers. However, this finding was not observed for wholegrains or for fibre. This may simply mean F&V are that protective, but the confidence intervals are quite wide and this is something that remains to be repeated. It may not mean reduced risk as much as substantially attenuated risk.

The second interesting finding is the difference in overall risk for unprocessed red meat intake between women and men, wherein women had no associations that were statistically significant. The weekly intake in women was on average 262g, or 37g/d: this is a similar range of daily intake observed in cohorts in Asia, which have not found associations between red meat and increased disease risk [5]. Sex differences have been shown before in the Adventist Health Study 2, where compared to meat the reductions in mortality among vegetarian women have not been significant [6]. One potential explanation emerged from the EPIC-InterAct cohort [7], which assessed outcomes associated with red meat intake relative to iron status, suggesting that differences in iron status between men and women may in some part explain the divergent associations between sexes [7]. This potential factor warrants further investigation.

The final interesting finding relates to processed meat. Although the title of the study may lead you to think otherwise, closer scrutiny of the findings for processed meat and this results are fairly damning for the risk associated with processed meat intake. Processed meat intake was associated with increased almost across the board, an effect which was observed even at low weekly levels of processed meat intake in men. Even if we confined our interpretation of the study to only the very highest tertile of processed meat intake, it is important to recall that they study quantified weekly intake: the highest tertile would correspond to an daily average of 24g in men and 16.5g in women. Factors like the high concentrations of nitrates, exogenous N-nitroso compounds [NOCs], sodium, and fat content of processed meats would appear to define the difference in risk between processed and unprocessed meats, resulting in a more consistent relationship with increased risk from processed meat [2]. The dose-response for processed meat appears to be strongest with over 50g/d [2]. The Global Burden of Disease recommendation for processed meat intake is 28g/wk, which was used as the lowest tertile in the present study: the findings suggest this risk may be evident beyond this threshold.

Relevance

The findings in relation to processed meat are largely consistent with the IARC finding designating processed meat as carcinogenic to humans, and current mechanistic understanding of why processing of meats may significantly increase their carcinogenic potential [1,2]. A 2017 paper [8] from the NIH-AARP cohort found a 26% relative risk increase for processed meat intake, but also examined mediating factors which indicated:

- Heme iron mediated 22.8% of the effect between processed meat and cancer
- Nitrates mediated 37.0% of the effect between processed meat and cancer

Of greater interest are the findings in relation to unprocessed red meat, as on the face of these findings it appears that the attenuating effect of protective foods is new. However, it is not necessarily a novel finding. In the Swedish Mammography Cohort and the Cohort of Swedish Men [9], a combined analysis of 74,645 men and women, unprocessed meat at a median intake of 88g/d was not significantly associated with mortality at high [>4/d servings] levels of fruit and vegetable intake, albeit the overall direction of effect was toward higher risk [a HR of 1.10 and 95% CI of 0.99 to 1.22]. A median of 62g/d processed meat intake was still associated with a significant 15% increase in mortality risk in the highest category of F&V intake.

Similarly, the European Prospective Investigation into Cancer [EPIC] cohort found that a median of 51g/d unprocessed meat was not significantly associated with cancer, while processed meat was associated with a significant 30% increase in risk per 50g/d, after adjusting for F&V intake [10].

The major US cohorts have, however, consistently found statistically significant associations between unprocessed red meat intake and cancer after adjusting for F&V [8,11]. These cohorts do, however, uniformly exhibit substantially higher average daily red meat intakes. For example, the highest level of intake in the NIH-AARP cohort is 156g/d for 2,500kcal/d diet, the Nurses Health Study is 184g/d, and the Health Professionals Follow-Up study is 176g/d [8,11]. In the present study, the highest category would correspond to an average of 71g/d in men and 42g/d in women. It is not possible to conclude that higher levels of fruits, vegetables, fibre, etc., would protect against potential adverse effects of red meat at levels of intake observed in the major US cohorts.

Graphical illustration of the conceptual risk associated with red meat and effect modification by fruits and vegetables. On the left, it may be that at average daily doses of unprocessed red meat under a threshold of <100g, high F&V intake may inhibit any potential carcinogenic interactions from red meat [illustrated by the black bar from F&V inhibiting red meat carcinogens]. On the right, it may be that doses similar to those observed in US cohorts of >150g/d contain sufficient related carcinogens such that any effect of F&V is negated [illustrated by the black bar from meat inhibiting F&V anti-carcinogenic activity].

This study is almost bound to be misinterpreted in terms of the direction of overall effect. Out of 48 hazard ratios calculated for unprocessed meat in mean, 41 were positively associated and 14 were statistically significant. Findings in women were weaker overall, which may also reflect the difference in dose of exposure. In effect, the findings present the same dilemma as previous attempts to synthesis the evidence for unprocessed meat intake faced. For example, the 2017 WCRF report on unprocessed red meat relied primarily on the overall direction of effect, which was positive, but not statistically significant overall in included cohort studies or three included pooled analyses [12].

Application to Practice

Unprocessed red meat intake is likely to remain the subject of debate. However, a number of cohorts in different populations have found that levels on average <100g per day do not appear to be associated with adverse health outcomes, particularly in populations with higher fruit and vegetable intake [e.g., EPIC]. Although the highest tertile in the present study was stated as >500g/wk, the median intake suggests in men the daily average likely did not exceed 100g/d. While the study will no doubt be cited to the tune of "just eat your vegetables and the meat will take of itself", that isn't an entirely accurate representation of the overall findings. With regard to unprocessed meat, the weight of data continues to suggest that the dose makes the poison.

References

1. Bouvard V, Loomis D, Guyton K, Grosse Y, Ghissassi F, Benbrahim-Tallaa L et al. Carcinogenicity of consumption of red and processed meat. The Lancet Oncology. 2015;16(16):1599-1600.

2. Domingo J, Nadal M. Carcinogenicity of consumption of red meat and processed meat: A review of scientific news since the IARC decision. Food and Chemical Toxicology. 2017;105:256-261.

3. Subar A, Thompson F, Kipnis V, Midthune D, Hurwitz P, McNutt S et al. Comparative Validation of the Block, Willett, and National Cancer Institute Food Frequency Questionnaires. American Journal of Epidemiology. 2001;154(12):1089-1099.

4. Willett W. Nutritional epidemiology. New York [etc.]: Oxford University Press; 2013.

5. Lee JE, McLerran DF, Rolland B, Chen Y, Grant EJ, Vedanthan R, Inoue M, Tsugane S, Gao YT, Tsuji I, Kakizaki M, Ahsan H, Ahn YO, Pan WH, Ozasa K, Yoo KY, Sasazuki S, Yang G, Watanabe T, Sugawara Y, Parvez F, Kim DH, Chuang SY, Ohishi W, Park SK, Feng Z, Thornquist M, Boffetta P, Zheng W, Kang D, Potter J, Sinha R. Meat intake and cause-specific mortality: a pooled analysis of Asian prospective cohort studies. Am J Clin Nutr. 2013 Oct;98(4):1032-41.

6. Orlich MJ, Fraser GE. Vegetarian diets in the Adventist Health Study 2: a review of initial published findings. Am J Clin Nutr. 2014 Jul;100 Suppl 1(1):353S-8S.

7. The InterAct Consortium. Association between dietary meat consumption and incident type 2 diabetes: the EPIC-InterAct study. Diabetologia. 2013;56:47–59.

8. Etemadi A, Sinha R, Ward M, Graubard B, Inoue-Choi M, Dawsey S et al. Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP Diet and Health Study: population based cohort study. BMJ. 2017;:j1957.

9. Bellavia A, Stilling F, Wolk A. High red meat intake and all-cause cardiovascular and cancer mortality: is the risk modified by fruit and vegetable intake?. The American Journal of Clinical Nutrition. 2016;104(4):1137-1143.

10. Rohrmann S, Overvad K, Bueno-de-Mesquita H, Jakobsen M, Egeberg R, Tjønneland A. Meat consumption and mortality — Results from the European prospective investigation into cancer and nutrition. BMC Medicine. 2013;11(S. Rohrmann, K. Overvad, H.B. Bueno-de-Mesquita, M.U. Jakobsen, R. Egeberg, A. Tjønneland,):63.

11. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Stampfer MJ, Willett WC, Hu FB. Red meat consumption and mortality: results from 2 prospective cohort studies. Arch Intern Med. 2012 Apr 9;172(7):555-63.

12. World Cancer Research Fund. Diet, Nutrition, Physical Activity and Colorectal Cancer. World Cancer Research Fund/American Institute for Cancer Research; 2017.