Unprocessed red meat and processed meat consumption: dietary guideline recommendations

Bradley C. Johnston[1,2,3*], Dena Zeraatkar[2], Mi Ah Han[4], Robin W.M. Vernooij[1,5], Claudia Valli[6,7], Regina El Dib[1,8], Catherine Marshall[9], Patrick J. Stover[10], Susan Fairweather-Taitt[11], Grzegorz Wojcik[12], Faiz Bhatia[13], Russell de Souza[2,14-17], Carlos Brotons[18], Joerg J. Meerpohl[19,20], Chirag J. Patel[21], Benjamin Djulbegovic[22], Pablo Alonso-Coello[6,7], Malgorzata M. Bala[23], Gordon H. Guyatt[2,24]

1. Department of Community Health and Epidemiology, Dalhousie University, Centre for Clinical Research, 5790 University Avenue, Room 404, Halifax, Nova Scotia B3J 0E4, Canada.
2. Department of Health Research Methods, Evidence and Impact, McMaster University Health Sciences Center, 1280 Main Street West, Hamilton, Ontario, L8S-4L8, Canada.
3. Department of Nutrition and Food Science, Agriculture and Life Sciences Building, 600 John Kimbrough Boulevard, Suite 510, Texas A&M University, 2142 College Station, Texas, 77843-2142, USA.
4. Department of Preventive Medicine, College of Medicine, Chosun University, 309 Pilmun-daero, Dong-gu, Gwangju, 61452, Korea.
5. Department of Research, Netherlands Comprehensive Cancer Organisation, Godebaldkwartier 419, Utrecht, 3511DT, Netherlands.
6. Iberoamerican Cochrane Centre Barcelona, Biomedical Research Institute San Pau (IIB Sant Pau), Carrer de Sant Antoni Maria Claret, 167, Barcelona, 08025, Spain.
7. CIBER de Epidemiología y Salud Pública (CIBERESP), Carrer de Sant Antoni Maria Claret, 167, Barcelona, 08025, Spain.
8. Institute of Science and Technology, Unesp - Univ Estadual Paulista, Avenida Engenheiro Francisco José Longo, 777, Jardim São Dimas, São José dos Campos, Sao Paolo, 12245-000, Brazil.
9. Cochrane Consumer Group, 6 Horomona Road, Wellington, 5034, New Zealand.
10. Texas A&M AgriLife Research, College of Agriculture and Life Sciences, Agriculture and Life Sciences Building, 600 John Kimbrough Boulevard, Suite 510, Texas A&M University, 2142 College Station, Texas, 77843-2142, USA.
11. Norwich Medical School, University of East Anglia, Norwich Research Park, Floor 2, Bob Champion Research and Education Building, James Watson Road, NR4 7UQ, Norwich.
12. Department of Medical Sociology, Jagiellonian University Medical College, 7 Kopernika Street, Kraków, 31-034, Poland.
13. 1503-33 Shore Breeze Drive, Etobicoke, Ontario, M8V-0G1, Canada.
14. Population Health Research Institute (PHRI), 237 Barton Street East, Hamilton, Ontario, L8L-2X2, Canada.
15. Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, 5th Floor, Room 5253A, 1 King's College Circle, Toronto, Ontario, M5S-1A8, Canada.

16. Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, M5C-2T2, Canada.
17. Li Ka Shing Knowledge Institute, St. Michael's Hospital, 38 Shuter Street, Toronto, Ontario, M5B-1A6, Canada.
18. Sardenya Primary Health Care Centre, Biomedical Research Institute Sant Pau (IIB Sant Pau), Sardenya 466, Barcelona, 08025, Spain.
19. Institute for Evidence in Medicine, Medical Centre - University of Freiburg, Breisacher Strasse 153, Freiburg, 79110, Germany.
20. Cochrane Germany, Breisacher Strasse 153, Freiburg, 79110, Germany.
21. Department of Biomedical Informatics, Harvard University, 10 Shattuck Street., Room 302, Boston, Massachusetts, 02115, USA.
22. City of Hope, 1500 E Duarte Road, Duarte, California, 91010, USA.
23. Chair of Epidemiology and Preventive Medicine, Department of Hygiene and Dietetics, Jagiellonian University Medical College, 7 Kopernika Street, Kraków, 31-034, Poland.
24. Department of Medicine, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S-4K1, Canada.

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Corresponding author:
*Bradley C. Johnston, PhD
Department of Community Health & Epidemiology, Dalhousie University
Centre for Clinical Research, Room 404, 5790 University Avenue
Halifax, Nova Scotia, Canada, B3H 1V7
Tel: 902-494-1659, Fax: 902-494-1597
Email: bjohnston@dal.ca

Description: Dietary guideline recommendations require consideration of the certainty in the evidence, the magnitude of potential benefits and harms, and explicit consideration of peoples' values and preferences. We produced a set of recommendations regarding red meat and processed meat consumption based on five de novo systematic reviews that included consideration of all these issues.

Methods: We developed recommendations following the NutriRECS guideline development process that includes rigorous systematic review methodology, and the use of GRADE methods to rate the certainty of evidence for each outcome, and to move from evidence to recommendations. A panel including 14 members from seven countries, including three community members, voted on the final recommendations. Strict criteria limited the conflicts of interest among panel members. Considerations of environmental impact or animal welfare did not bear on the recommendations. We conducted four systematic reviews addressing the health effects associated with red meat and processed meat consumption, and one systematic review addressing people's health-related values and preferences regarding meat consumption.

Recommendations: The panel suggests that adults continue current unprocessed red meat consumption (weak recommendation, low certainty evidence). Similarly, the panel suggests adults continue current processed meat consumption (weak recommendation, low certainty evidence).

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Introduction

Contemporary dietary guidelines recommend limiting consumption of unprocessed red meat and processed meat. For example, the 2015 Dietary Guidelines for Americans have recommended limiting red meat intake, including processed meat, to approximately one serving/day (1). Similarly, the UK dietary guidelines have endorsed limiting the intake of both red and processed meat to 70 g/day (2) while the World Cancer Research Fund/American Institute for Cancer Research have recommended limiting red meat consumption to moderate amounts and consuming very little processed meat (3). The World Health Organization International Agency for Research on Cancer has indicated that consumption of red meat is "probably carcinogenic" to humans while processed meat is considered "carcinogenic" to humans (4).

These recommendations are, however, primarily based on observational studies that are at high risk of confounding and thus are limited in establishing causal inferences nor do they report the absolute magnitude of any possible effects. Further, the organizations that produce guidelines have failed to conduct or access rigorous systematic reviews of the evidence, have been limited in addressing conflicts of interest, and have failed to explicitly address population values and preferences, raising questions regarding adherence to trustworthiness guideline standards (5-9).

A potential solution for the limitations of contemporary nutrition guidelines is for an independent group with clinical and nutritional content expertise and skilled in the methodology of systematic reviews and practice guidelines, methods that include careful management of conflicts of interest, to produce trustworthy recommendations based on the values and preferences of guideline users. We have developed the Nutritional Recommendations (NutriRECS) (7) international consortium to produce rigorous evidence-based nutritional recommendations adhering to trustworthiness standards (10-12).

To support our recommendations, we performed four parallel systematic reviews that focused both on randomized trials and observational studies addressing the possible impact of unprocessed red meat and processed meat consumption on cardiometabolic and cancer outcomes (13-16), and a fifth review addressing people's

health-related values and preferences related to meat consumption (17). Based on these reviews, we developed recommendations for unprocessed red meat and processed meat consumption specific to health outcomes.

Methods

Guideline Development Process

We developed our recommendations following the NutriRECS guideline development process (7) that includes the use of GRADE methodology (18-20). To inform our guideline recommendations, systematic reviews were conducted based on a priori methods (21, 22).

Guideline team structure

This work involved three teams:

1. A core NutriRECS leadership team was responsible for supervision and coordination of the project, and for drafting of the research questions, guideline protocol and manuscripts;
2. A guideline panel included experts in health research methodology, nutritional epidemiology, dietetics, basic and translational research, family medicine, and general internal medicine. The panel included three members from outside the medical and health care communities. Panelists resided in high income countries (Canada, England, Germany, New Zealand, Poland, USA, Spain);
3. A literature review team drafted the protocols for the systematic reviews, completed the literature search and eligibility review, abstracted data and conducted data analysis and produced narrative and tabular summaries of the results.

Framework for panel construction and guideline recommendations

The core leadership team applied safeguards against competing interests (7). After generating a list of potential panel members without perceived vested interests, we contacted prospective candidates from North America, Western Europe and New Zealand. Those who expressed interest completed a detailed form enumerating potential financial or intellectual conflicts during the previous three years. If important competing issues were identified (one interested individual had financial conflicts), they

were not invited to participate. **Table 1** includes a summary of the conflict of interest forms, with full competing interests available upon request.

Prior to our initial guideline panel meeting, the methods editor and panel chair contacted panelists, shared the draft questions, and received and incorporated feedback. At the initial meeting, the guideline panel discussed the scope of the project, and agreed on the research questions and subgroups of interest. The panel focused on health outcomes thought to be associated with unprocessed red meat and processed meat and chose not to consider animal welfare and environmental issues related to meat consumption in making recommendations. The panel chose to exclusively focus on health outcomes because environmental and animal welfare concerns are very different issues, extremely challenging to integrate with health concerns, possibly more societal rather than personal issues, and with extreme variability in the extent to which people find these issues a priority. Finally, to consider these issues rigorously would require systematic reviews that we were not resourced to undertake. The panel also chose to make separate recommendations for unprocessed red meat and processed meat given the potential for differential health effects, and differing values and preferences members of the public may have to unprocessed meat versus processed meat.

Target audience for recommendations

The target audience for our guidance statement was individuals who consume unprocessed red meat or processed meat as part of their diet. The panel took the perspective of individual decision-making rather than a public health perspective.

Key principles for PICO question and study eligibility criteria

Each NutriRECS project addresses a single nutrition question or topic, in this case guidance regarding the potential harms, benefits and health-related values and preferences related to consuming unprocessed red meat and processed meat. We conducted a series of systematic reviews to inform our recommendations addressing the following questions: i) *Among adults, what is the impact of diets and dietary patterns lower in red or processed meat versus diets higher in red or processed meat intake on the risk of outcomes important to community members?* and ii) *What are their health-related values and preferences for red and processed meat consumption?*

The panel considered all-cause mortality, major cardiometabolic outcomes (e.g. cardiovascular mortality, stroke, myocardial infarction, diabetes), cancer incidence and mortality (i.e. gastrointestinal, prostate, female cancers), quality of life and willingness to change unprocessed red or processed meat consumption as *critically important* for developing recommendations. *Important* outcomes included surrogate outcomes (weight, body mass index, blood lipids, blood pressure, hemoglobin, anemia) and reasons for eating unprocessed red meat and processed meat.

Methods for systematic reviews

In consultation with an expert librarian, we searched the major literature databases to identify all relevant studies on harms, benefits and health-related values and preferences on unprocessed red meat and processed meat. Each database was searched from inception until July 2018 without restrictions on language or date of publication (see respective systematic reviews in this issue (13-17)).

For harms and benefits, we included any randomized trial, as well as cohort studies including 1,000 or more adults assessing diets with varying quantities of unprocessed red meat (e.g., servings or times/week, g/day) and/or processed meat (meat preserved by smoking, curing, salting, or by the addition of preservatives) (23) for a duration of six months or more. Studies in which more than 20% of the sample was pregnant or had cancer or a chronic health condition, other than cardiometabolic diseases, were excluded. The review articles report our methods for screening, data abstraction, risk of bias assessment and data analysis (13-17).

Panelists considered 3 servings per week as a realistic reduction in meat consumption (e.g. moving from 7 to 4, or 4 to 1 servings) based on the average intake of 2 to 4 servings per week in North America and Western Europe (24-28). We therefore framed the evidence regarding the potential reduced risks associated with a decrease of 3 servings per week of both unprocessed red meat and processed meat.

We used GRADEpro software to formulate GRADE summary of findings (SoF) tables for each PICO question (29). The overall certainty of evidence was evaluated using the GRADE approach (18). For estimates of risk with current levels of meat consumption we used population estimates from the Emerging Risk Factors

Collaboration study for cardiometabolic outcomes (30), and we used population estimates from Globocan for cancer outcomes (31). Using these resources, our estimates for cardiometabolic mortality and incidence outcomes are based on an average of 10.8 years of follow-up, while for cancer mortality and incidence our estimates are for the overall lifetime risk.

Complementing existing GRADE standards and to determine if we should rate up for a dose-response effect, we assessed the plausibility of a causal relationship between meat and adverse health outcomes contrasting results from two bodies of evidence (7, 22): cohort studies specifically addressing red meat and processed meat intake, and cohort studies addressing dietary patterns associated with varying red meat and processed meat consumption. We hypothesized that if red meat and processed meat were indeed causally related to adverse health outcomes, we would find stronger associations in studies that specifically addressed red meat and processed meat intake versus studies addressing dietary patterns (7).

To address health-related values and preferences related to red meat and processed meat, we included qualitative (e.g. interviews, focus groups) and quantitative (e.g. cross-sectional survey) studies conducted in adults. We independently screened, abstracted data and assessed risk of bias (17) and synthesized the data into narrative themes and tabulated summaries, and again assessed the certainty of evidence using GRADE (18, 32).

To assist our three public panel members without health science backgrounds, the method's editor conducted electronic meetings with them prior to the guideline panel meetings to explain the systematic review results and the GRADE approach for assessing the certainty of evidence and for moving from evidence to recommendations. During the guideline panel meetings, the leads of each of the systematic reviews shared the summary data and certainty of evidence for each of our outcomes with the guideline panel, and the panel chair answered any questions as necessary.

Moving from evidence to recommendations

Prior to our final guideline panel meeting, we asked each panellist to complete a GRADE Evidence to Decision (EtD) framework. The purpose of EtD frameworks is to help

panelists use the evidence summaries in a structured and transparent way to develop the final recommendations. In doing so the panellists considered evidence summaries for health effects, values and preferences, and also considered the cost, acceptability, and feasibility of a recommendation to decrease meat consumption (33). During the final meeting, the panel reviewed the results of the EtD survey and considered the implications of those judgments for their recommendations.

Recommendation for unprocessed red meat

For adults 18 years of age or older, we suggest continuing current unprocessed red meat consumption (weak recommendation, low certainty evidence). Eleven of 14 panelists voted for a continuation of current unprocessed red meat consumption, while three voted for a weak recommendation to reduce red meat consumption.

Recommendation for processed meat

For adults 18 years of age or older, we suggest continuing current processed meat consumption (weak recommendation, low certainty evidence). Again, eleven of fourteen panel members voted for a continuation of current processed meat consumption, and three voted for a weak recommendation to reduce processed meat consumption.

Summary evidence for harms and benefits for unprocessed red meat

For our review of randomized trials on harms and benefits (12 unique trials enrolling 54 thousand participants), we found low to very low certainty evidence that diets lower in unprocessed red meat may have little or no effect on the risk for major cardiometabolic outcomes and cancer mortality and incidence (15). Dose-response meta-analysis results from 23 cohorts studies with 1.4 million participants provided low to very low certainty evidence that decreasing unprocessed red meat intake may result in a very small reduction in the risk for major cardiovascular outcomes (cardiovascular disease, stroke, myocardial infarction) and type 2 diabetes (range 1 fewer to 6 fewer events per 1000 with a 3 serving/week decrease), with no statistically significant differences in 2 additional outcomes (all-cause mortality, cardiovascular mortality) (16). Dose-response meta-analysis results from 17 cohorts with 2.2 million participants provided low certainty evidence that decreasing unprocessed red meat intake may

result in a very small reduction of overall lifetime cancer mortality (7 fewer events per 1000 with a 3 serving/week decrease), with no statistically significant differences for 8 additional cancers observed (prostate cancer mortality, and the incidence of overall, breast, colorectal, esophageal, gastric, pancreatic and prostate cancer) (13). Similar to studies directly addressing red meat, cohort studies assessing dietary patterns (70 cohort studies with just over 6 million participants) provided mostly uncertain evidence for the risk of adverse cardiometabolic and cancer outcomes. Although statistically significant, low to very low certainty evidence indicates that adherence to dietary patterns lower in red or processed meat is associated with a very small absolute risk reduction in 9 major cardiometabolic and cancer outcomes (range 1 fewer to 18 fewer events per 1000), with no statistically significant differences for 21 additional outcomes observed (14). See **Appendix 1** for the GRADE summary of finding tables.

We summarize the benefits of eating meat below in a section on values and preferences: in short, omnivores enjoy eating meat, and consider meat an essential component of a healthy diet. There is also evidence of possible health benefits of omnivorous versus vegetarian diets on outcomes such as muscle development and anemia (34, 35), but we did not systematically review this literature.

Evidence summary for harms and benefits for processed meat

No randomized trials directly assessed processed meat for our target outcomes. With respect to cohorts addressing adverse cardiometabolic outcomes (10 cohort studies with 778 thousand participants providing dose-response meta-analysis), we found low to very low certainty evidence that a decreased intake of processed meat was associated with a very small reduced risk for major morbid cardiometabolic outcomes including all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, and type 2 diabetes (range 1 fewer to 12 fewer events per 1000 with a 3 serving/week decrease), with no statistically significant difference in 1 additional outcome (cardiovascular disease) (16). For cohort studies addressing adverse cancer outcomes (31 cohorts with 3.5 million participants providing data for our dose-response analysis), we also found low to very low certainty evidence that a decreased intake of processed meat was associated with a very small absolute risk reduction in overall lifetime cancer

mortality, prostate cancer mortality, and the incidence of esophageal, colorectal, and breast cancer (range 1 fewer to 8 fewer events per 1000 with a 3 serving/week decrease), with no statistically significant differences in incidence or mortality for 12 additional cancers (colorectal, gastric, pancreatic mortality; overall, endometrial, gastric, hepatic, small intestinal, oral, ovarian, pancreatic, prostate cancer incidence)(13). For cohort studies assessing dietary patterns (70 cohort studies with over 6 million participants), although statistically significant, we found low to very low certainty evidence that adherence to dietary patterns lower in red or processed meat was associated with a very small absolute risk reduction in 9 major cardiometabolic and cancer outcomes (range 1 fewer to 18 fewer events per 1000), with no statistically significant differences for 21 additional outcomes observed (14). Again, we assessed the risk of adverse cardiometabolic outcomes based on an average of 10.8 years follow-up, and adverse cancer outcomes over a lifetime.

In our assessment of etiologic causal inferences on unprocessed red meat and processed meat and adverse health outcomes, we found that the absolute effect estimates for red meat and processed meat intake (13, 16) were smaller than those from dietary pattern estimates (14), indicating that meat consumption is unlikely to be a causal factor of adverse health outcomes (**Table 2**). We anticipated that, if unprocessed red meat or processed meat was indeed a causal factor in raising the risk of adverse outcomes, the observed association between unprocessed red and processed meat and adverse outcomes would be greater in studies directly addressing the lowest versus highest intake of unprocessed red or processed meat versus studies in which meat was only one component of a dietary pattern (7, 22). Using our findings, in our assessment of the certainty of evidence, we did not rate up for dose-response, given the potential for residual confounding (36). See **Appendix 1** for the GRADE summary of finding tables.

Evidence summary of health-related values and preferences for meat

Our systematic review on health-related values and preferences yielded 54 articles from Australia, Canada, Europe and the United States, including 41 quantitative and 13 qualitative studies (17). Omnivores reported enjoying eating meat, consider meat an essential component of a healthy diet and often felt they had limited culinary

skills to prepare satisfactory meals without meat. Participants tended to be unwilling to change their meat consumption. The certainty of evidence was low for "reasons for meat consumption", and low for "willingness to reduce meat consumption" in the face of undesirable health effects due to issues of risk of bias (e.g. unvalidated surveys), imprecision (small number of participants in qualitative studies), and indirectness (failure to specifically ask about the health benefits that would motivate a reduction in meat consumption) (**Table 3**).

Rationale for recommendations for red meat and processed meat

The rationale for our recommendation to continue rather than reduce unprocessed red meat or processed meat consumption is based on: 1) low to very low certainty evidence for potential adverse health outcomes associated with meat consumption (13-16), supported by the similar effect estimates for red meat and processed meat consumption from dietary pattern studies as from studies directly addressing red meat and processed meat intake (13, 14, 16), 2) a very small absolute risk reduction based on a realistic decrease of 3 servings of red or processed per week, 3) if the very small exposure effect is true, given peoples' attachment to their meat based diet (17), the associated risk reduction is not likely to provide sufficient motivation to reduce red meat or processed meat in fully informed individuals, 4) the weak, rather than strong recommendation is based on the large variability in peoples' values and preferences related to meat (17), 5) the panel's exclusive focus on health outcomes associated with meat, and our decision not to consider animal welfare and environmental issues. Taken together, these observations warrant a weak recommendation to continue current levels of red meat and processed meat consumption.

Other considerations

The panel judged that though for some people in some circumstances, issues of cost, acceptability, feasibility and equity may be relevant, these issues were not major considerations in making their judgements. Considerations of animal welfare, and particularly of environmental impact will certainly be important to some individuals; the latter might be of particular importance from a societal perspective (37-41). The panel,

at outset, decided that issues of animal welfare, and potential environmental impact were outside the scope of this guideline.

Discussion

Summary

We developed recommendations for unprocessed red meat and processed meat following the NutriRECS guideline development process that adheres to the Institute of Medicine and GRADE working group standards. Based on four systematic reviews assessing the harms and benefits associated with red meat and processed meat consumption, and one systematic review assessing people's health-related values and preferences on meat consumption, we suggest that individuals continue their current consumption of both unprocessed red meat and processed meat (both weak recommendations, low certainty evidence).

Our weak recommendation that people continue their current meat consumption highlights both the uncertainty associated with possible harmful effects, and very small magnitude of effect, even if the best estimates represent true causation, which we believe to be implausible. Despite our findings from our assessment of intake studies versus dietary pattern studies that suggest that unprocessed red meat and processed meat are unlikely to be causal factors for adverse health outcomes (13, 14, 16), this does not preclude the possibility that meat has a very small causal effect. Taken together with other potential casual factors (e.g. preservatives such as sodium, nitrates and nitrites) (42) among dietary patterns with very small effects, this may explain the larger reductions among dietary patterns high in red meat and processed meat (14). The guideline panel's assessment was based on the available evidence regarding values and preferences suggesting that the majority of individuals, when faced with a very small and uncertain absolute risk reduction in cardiometabolic and cancer outcomes would choose to continue their current meat consumption. People considering decreasing their meat consumption should be aware of this evidence.

Strengths

We conducted five separate rigorous systematic reviews addressing both evidence from randomized trials and observational studies regarding the impact of

unprocessed red meat and processed meat on cardiovascular and cancer outcomes (13-16), and community values and preferences regarding red meat and processed meat consumption (17). Using the GRADE approach, our reviews explicitly addressed the uncertainty of the underlying evidence. We have presented results focusing on absolute estimates of effects associated with realistic decreases in meat consumption of three servings per week (See **Appendix 1**), and these estimates informed our recommendations. Our panel included nutrition content experts, methodologists, health care practitioners, and members of the public, and we minimized conflicts of interest through pre-screening panel members for financial, intellectual and personal conflicts of interest; providing a full account of potential competing interests (panel member conflict of interest forms available upon request).

Limitations

Our guideline is limited in that we considered issues of animal welfare and potential environmental impact outside the scope of our recommendations. These guidelines may therefore be of limited relevance to individuals for whom these issues are of major importance. Related to this, we took an individual rather than a societal perspective. Decision makers considering broader environmental issues may reasonably consider evidence regarding the possible contribution of meat consumption to global warming, and suggest policies limiting meat consumption on that basis.

Regarding the uncertainty of the evidence - randomized trials were limited by the small differences in meat consumption between the intervention and control groups, while observational studies were limited in the accuracy of dietary measurement and possible residual confounding related both to aspects of diet other than red meat and processed meat and non-dietary confounders – making decisions regarding meat consumption particularly value and preference dependent. With respect to our review on dietary patterns, studies did not typically report data separately for red and processed meat. Moreover, although all dietary patterns discriminated between participants with low and high red and processed meat intake, other food and nutrient characteristics of dietary patterns varied widely across studies (14). Evidence was also limited in that we found information insufficient to conduct planned subgroup analyses

regarding the method of meat preparation (e.g. grilling vs. boiling) based on possible carcinogenic compounds from grilling such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) (43). Finally, our panel was not unanimous in its recommendation: three of 14 panel members favoured a weak recommendation in favour of decreasing red meat consumption.

Comparison with other guidelines

As noted in our introduction, other dietary guidelines and position statements suggest limiting consumption of red and processed meat because of the reported association with cancer (1, 2, 44-46). There are three major explanations for these discrepancies. First, other guidelines have not used the GRADE approach to rating certainty of evidence that highlight the low or very low certainty of evidence supporting the causal nature of the association between meat consumption and health outcomes. As a result, we are less convinced of meat consumption as a cause of cancer. Because of the likelihood of residual confounding (i.e. confounding that exists after adjustment for known prognostic factors) the GRADE approach we used for assessing causation considers that – in the absence of a large effect or a compelling dose-response gradient – observational studies provide only low or very low certainty evidence for causation (47, 48). Second, even if one assumes causation, other guidelines have not calculated, or if calculated have not highlighted, the very small magnitude of the absolute adverse impacts over long periods of time associated with meat consumption. Third, other guidelines have paid little or no attention to the reasons people eat meat, and the extent to which they would choose to reduce meat consumption given small and uncertain health benefits. Indeed, no prior guideline has attended with care to evidence bearing on values and preferences, and in particular has not conducted a systematic review addressing the issue.

Nutritional guidelines are challenging because each potential source of evidence has substantial limitations. Randomized trials are limited by sample size, duration of follow-up, and difficulties participants have adhering to prescribed diets. These limitations make showing an intervention effect very challenging. Observational studies are limited in the inevitable residual confounding (unmeasured differences in prognosis

that remain after adjusted analyses). These limitations in randomized trials and observational studies are evident in studies addressing meat consumption and health outcomes. Studies focusing on intermediate outcomes (e.g. cholesterol and triglycerides) suffer from additional limitations in that changes in biomarkers often fail to deliver the anticipated benefits in patient-important health outcomes. Therefore, our reviews focused only on those outcomes important to patients. Nutritional recommendations must therefore, acknowledge the low quality evidence and avoid strong "just do it" recommendations that can, as evidenced by the many low fat recommendations worldwide (49), be very misleading.

How to interpret the recommendations

A weak recommendation indicates that the panel believed that for the majority of individuals, the desirable effects (a potential lowered risk of cancer and cardiometabolic outcomes) associated with reducing meat consumption probably do not outweigh the undesirable effects (impact on quality of life, burden associated with modifying cultural and personal meal preparation and eating habits). The weak recommendation reflects the panel's awareness that values and preferences differ widely, and that as a result a minority of fully informed individuals will choose to reduce meat consumption.

Implications for future research

Generating higher quality evidence regarding the impact of red meat and processed meat on health outcomes would be, were it possible, both desirable and important. It may not, however, be possible. Randomized trials will always face challenges with participants complying with diets that differ sufficiently in meat consumption, adhering to these diets for very long periods of time, and being available for follow-up over these long periods. These challenges are all the more formidable because results of observational studies may well represent the upper boundary of causal effects of meat consumption on adverse health outcomes, and the estimated effects are very small. Observational studies will continue to be limited by challenges of accurate measurement of diet, the precise and accurate measurement of known

confounders (50), and the likelihood of residual confounding after adjusted analyses (13, 14, 16).

This assessment may be excessively pessimistic; indeed, we hope that is the case. What is certain is that generating higher quality evidence regarding the magnitude of any causal effect of meat consumption on health outcomes will test the ingenuity and imagination of health science investigators.

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