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Cover Letter

Re: Red Meat and Processed Meat and Cancer: A Summary of the Epidemiology

September 8, 2015

Dear IARC Working Group,

As an epidemiologist who received a doctorate under a National Cancer Institute Fellowship in Cancer Prevention and Control, I am deeply grateful for the opportunity to submit epidemiologic summaries and commentaries for your consideration prior to the IARC Red and Processed Meat meeting in October, 2015. I appreciate the extensive time and effort that the IARC committee has spent on comprehensively examining this important, yet challenging, area of research.

The potential role that red meat or processed meat intake plays on cancer risk has been widely debated in scientific communities. Indeed, interpreting findings from epidemiologic studies of dietary factors, such as individual foods or food groups, involves numerous methodological considerations. These include, but are not limited to: clearly and specifically defining the food variables (i.e., exposure) and outcomes of interest, accurately measuring food intake (a foremost challenge in nutritional epidemiology), accounting for dietary pattern differences across populations, understanding the role of bias and confounding within and across studies, isolating the effects of a single food or food group from the countless foods and dietary constituents that individuals consume on a daily basis, assessing potential (and relevant) biological mechanisms and genetic variation in metabolizing enzymes, and interpreting results based on varying analytical metrics and statistical testing parameters. What makes interpretation even more challenging is the fact that prospective cohort studies generate associations between foods and cancer that are very weak in magnitude, with most relative risks ranging between 0.8 and 1.25. Given the considerable degree of exposure misclassification from self-reported dietary intake, correlation of certain foods with other dietary and lifestyle factors, and the impact of bias and confounding, there is significant uncertainty surrounding the epidemiologic evidence for foods and cancer. In fact, despite billions of research dollars and decades of research, few, if any, foods have been clearly causally associated with increasing or decreasing the risk of cancer. Red meat



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consumption fits into this methodologically complex paradigm because of the inherent challenges of interpretation; many of which are more pronounced when evaluating red meat because of the high colinearity with other dietary and lifestyle factors.

As mentioned, I am a trained cancer epidemiologist, and my expertise is in the area of systematic review methodology, meta-analysis, and disease causation. I serve on the editorial board of the American Journal of Clinical Nutrition and I am an associate editor for Frontiers in Nutrition Methodology. Over the past decade, I have performed extensive research on red meat consumption and cancer. Specifically, I have applied systematic meta-analysis methodology and disease causation principles to red meat intake, including processed meat intake, and numerous types of cancer, such as colorectal, prostate, and breast. I've published 10 first-author papers on this topic in peer-reviewed journals, and have given over 25 presentations on the complexity and interpretation of epidemiologic studies of red meat intake and cancer to a wide variety of professional audiences, including registered dietitians, epidemiologists, nutrition scientists, toxicologists, computational biologists, and governmental health leaders in Australia, New Zealand, Norway, Mexico, and Canada. In addition, I was asked to comment on the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) methodological protocol for their Continuous Updates project. This was largely a result of the methodological and analytical errors that my research team (including other research groups) identified after reviewing the 2007 WCRF/AICR report, Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.

I am very active in the field in epidemiology, and I serve as principal investigator on a wide variety of research projects, such as studies of occupational and environmental factors, pharmacoepidemiology, cancer survival, and dietary factors. I receive research funding from numerous organizations, including the National Institutes of Health, and public and private organizations. All of my research projects, regardless of funding support, are conceptualized, designed, conducted, and interpreted independently. Because of my expertise in the epidemiology of red meat and cancer, EpidStat Institute was commissioned by the National



Cattlemen's Beef Association (NCBA), a contractor to the Beef Checkoff, to provide a comprehensive summary of the epidemiologic evidence pertaining to red meat and processed meat consumption and all types of cancer. In addition, the epidemiology on cooking methods and meat preparation, heterocyclic amines, heme iron, n-nitroso compounds, and polycyclic aromatic hydrocarbons (exposure from meat preparation only) was summarized. Our submission summarizes the epidemiologic evidence based on a critical examination of the published peer-reviewed literature. All work was performed objectively and transparently in accordance with well-established guidelines for performing systematic reviews of the evidence, including the PRISMA statement and MOOSE guidelines.

We conducted comprehensive literature searches using PubMed, EMBASE, the Cochrane Library, and hand searches of individual articles to identify prospective cohort studies that reported data for red meat or processed meat intake and all types of cancer. In addition, we identified epidemiologic studies of cooking methods, mutagenic by-products from cooking, heme iron, and n-nitroso compounds. Each study was reviewed critically and information for qualitative study characteristics and quantitative data were extracted for all included studies. If data across studies were amenable to harmonization, quantitative meta-analysis modeling was performed to estimate the relative strength of summary associations, and the consistency of findings across studies. In addition, dose-response was evaluated using categorical intake stratifications and meta-regression methodology. Bias, namely misclassification bias, is a global concern in studies of dietary factors and cancer, and was considered in the assessment of findings. Confounding, which can be evaluated more quantitatively because of the reporting of covariates in each study, was appraised in the evaluation of the epidemiologic studies. The epidemiologic evidence was then examined critically in terms of three primary components of the Sir Bradford Hill criteria for judging causality, which were the strength of association, potential dose-response patterns, and consistency of findings within and across studies. Importantly, an association should be established before causal criteria are applied. However, upon review of the epidemiologic evidence, an independent association (i.e., free from chance, bias, and confounding) is lacking for the red meat – cancer relationships. Despite this, the



epidemiologic evidence was interpreted in the context of strength, dose, and consistency, while the role of chance, bias, and confounding were carefully considered.

Collectively, most relative risks at the individual study level and after pooling data across studies, indicates null to weakly elevated positive associations for red and processed meat, including cooking methods and mutagenic by-products, and cancer. Although we observed some weak positive associations, which were generally slightly more elevated for processed meat, the evidence is limited and relatively inconsistent. Thus, the totality of the epidemiologic evidence on red meat and processed meat, including cooking methods and mutagenic by-products, are not supportive of causal relationship with cancer. Importantly, there is a major distinction between observing associations and whether or not an exposure causes a disease outcome. Some of the primary reasons why the epidemiology is not sufficient to make a causal inference between red meat consumption and cancer are as follows:

- Statistical summary associations are weak in magnitude, making it difficult to differentiate an association that is not impacted by chance, bias, or confounding.
- There is no clear pattern of a dose-response relationship when coalescing different ways of evaluating potential trends, such as by categorical intake groupings, meta-regression, and continuous linear and/or non-linear patterns.
- Results between studies (and even within studies in many cases) are relatively inconsistent.
- A relatively small proportion of individual study relative risks, as well as summary relative risks, are statistically significant.
- Heterogeneity is present across the literature, and several sources of between-study variation have been identified, such as by gender, study country, and tumor site.
- Definitions of red and processed meat vary considerably in the literature, rendering it difficult to harmonize exposure categories.
- The role of bias, namely misclassification bias, and confounding, coupled with the high degree of colinearity between red meat intake and other dietary and lifestyle



factors, warrants a cautious interpretation of the epidemiologic literature.

- There is a limited volume of human epidemiologic studies to make an informed decision for many red meat – cancer relationships. In particular, there is limited evidence for red meat cooking methods, heterocyclic amines, heme iron, and n-nitroso compounds and cancer.
- Carcinogenesis may take decades. The majority of epidemiologic studies analyze participants over an insufficient duration to adequately account for cancer induction and latency.

Our interpretation is generally in concert with the 2007 WCRF/AICR report and the Continuous Update projects, except for colorectal cancer. Aside from colorectal cancer, WCRF/AICR has concluded that the evidence for red and processed meat intake is limited and/or inconsistent and/or of low quality to support a causal relationship with cancer. Regarding colorectal cancer, we have published comprehensive and systematic reviews and meta-analyses on red meat and processed meat, and have concluded that, “the state of the epidemiologic science on red meat consumption and CRC is best described in terms of weak associations, heterogeneity, an inability to disentangle effects from other dietary and lifestyle factors, lack of a clear dose-response effect, and weakening evidence over time.” As mentioned, summary associations for processed meat are modestly stronger in magnitude, but a causal relationship is not supported by the current state of the science.

In summary, and as stated in my editorial in the *American Journal of Clinical Nutrition* (Alexander 2013) “Making sense of the relation between diet and disease is complicated by the difficult problems of interpretation that arise from a combination of the well-known limitations of observational studies and the complexity of understanding and generalizing results across diverse study populations. The entanglement of the exposure under study with other dietary and lifestyle factors, socioeconomic characteristics, clinical variables, and genetic traits makes it difficult to isolate the independent effects of a specific food or food group, such as meat intake, on disease risk. It may be this constellation of “other” factors that weigh in most heavily in



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observed associations between meat intake and chronic disease incidence and mortality outcomes from nutritional epidemiologic studies.”

With gratitude, I look forward to being an observer at your upcoming meeting. I earnestly and genuinely want to better understand and contribute to clarification of the scientific debate of any potential relationship between red meat or processed meat and cancer.

Sincerely,  
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