

HUMAN NUTRITION

Title: Systematic review of red and processed meat consumption and cancer –
NPB #15-149

Investigator: Shalene McNeill, PhD, RD

Institution: National Cattlemen's Beef Association

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Industry Summary:

1. **Objectives:** National Cattlemen's Beef Association and National Pork Board jointly funded a project for Dr. Dominik Alexander, PhD, MSPH (Principal Epidemiologist, EpidStat Institute) to conduct a thorough review of the science on red and processed meat consumption and cancer risk.
2. **How research was conducted:** Dr. Alexander performed a comprehensive review (in the form of meta-analyses) of the epidemiologic and mechanistic studies surrounding red meat and processed meat and risk of several cancer types. Dr. Alexander extracted, analyzed and interpreted the relevant qualitative and quantitative information from each study.
3. **Research findings:** The researchers observed some weak positive associations, which were generally slightly more elevated for processed meat; but 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.
4. **What these findings mean to the industry:** Despite billions of research dollars and decades of research, few, if any, foods have been clearly demonstrated to cause an increase or decrease of cancer risk. Red meat is no exception. The potential role that red meat or processed meat intake plays on cancer risk has been widely debated in scientific communities with no clear evidence that its consumption (on its own) causes cancer. Red meat consumption fits into a complex paradigm creating challenges including the inability to disentangle effects from other dietary and lifestyle factors; when evaluating its role (or lack of role) in cancer risk or development. This should not take away the fact that red meat and processed meats have a role in a healthful dietary pattern and thus should not be justification for consumers to reduce their intake of red meat.
5. **Include your contact information.**
Shalene McNeill, PhD, RD
smcneill@beef.org
830-569-0046

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These research results were submitted in fulfillment of checkoff-funded research projects. This report is published directly as submitted by the project's principal investigator. This report has not been peer-reviewed.

For more information contact:

National Pork Board • PO Box 9114 • Des Moines, IA 50306 USA • 800-456-7675 • Fax: 515-223-2646 • pork.org

Scientific Abstract:

Introduction: National Cattlemen's Beef Association and National Pork Board jointly funded a project for Dr. Dominik Alexander, PhD, MSPH (Principal Epidemiologist, EpidStat Institute) to conduct a systematic review of the scientific evidence on red and processed meat consumption and cancer risk.

Objectives: The primary objective of this project is to conduct a systematic review, including quantitative meta-analyses where relevant, of the scientific evidence on red and processed meat consumption and cancer. The researchers will summarize epidemiologic and mechanistic studies, as well as animal studies where appropriate. Several cancer types will be summarized in the context of red and processed meat intake. In addition, multiple manuscripts for publication in peer-reviewed journals will be developed, including a manuscript on the International Agency for Research on Cancer methodological and review process.

Materials & Methods: The researchers 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.

Results: 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 some weak positive associations were observed, 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

Discussion: The potential role that red meat or processed meat intake plays on cancer risk has been widely debated in scientific communities. 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 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.

The researchers' 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, 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 colorectal cancer 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, Dr. Alexander and colleagues state "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 observed associations between meat intake and chronic disease incidence and mortality outcomes from nutritional epidemiologic studies."