# EXECUTIVE SUMMARY

Evaluating the question, "Is there scientific evidence that dietary intake of red meat or processed meat has an effect on developing cancer?" is a complex and methodologically challenging undertaking. It not only involves factors related to the composition of meat or methods of meat processing and preparation, but also involves accounting for other dietary choices, lifestyle characteristics, and genetic traits that may impact the risk of cancer, such as a balanced diet, obesity, physical activity, smoking, family history of cancer, and adherence to cancer screening recommendations. In addition, the scientific methodology used to address the relationship between meat consumption and cancer may have a profound impact on the reported associations across the published literature.

The genesis of the hypothesis that meat consumption may contribute to increasing the risk of cancer dates back to the 1960s, at which time ecologic studies correlated per capita intake levels of animal fat with population rates of cancer, particularly colorectal cancer and breast cancer. Even without scientific consensus, this "animal fat hypothesis" evolved into a hypothesis that animal protein or meat intake may contribute to carcinogenesis. Over time, early correlational or descriptive studies gave way to more advanced and scientifically rigorous designs, such as analytical epidemiologic case-control and prospective cohort studies. Despite significant improvements in research methodology, technological advances in statistical computing, an increased understanding of the biological aspects of carcinogenesis, and an abundance of data from hundreds of published studies, a lack of a clear scientific consensus regarding meat consumption and cancer remains today.

The purpose of this technical report is to summarize the currently available epidemiologic studies of red meat and processed meat consumption and cancer. The fundamental basis of the science of epidemiology, including study designs, research methodology, data evaluation, and scientific interpretation is also discussed.

Cancer is the second leading cause of death in the United States, behind heart disease, and approximately one in every three Americans will be diagnosed with some type of cancer during their lifetime. The specific etiology, or cause(s), of the majority of cancers is unknown, although researchers have determined that cancer is multifactorial, involving a complex interaction of genetic, lifestyle, infectious, and environmental factors that usually take several years or decades to progress.

Nutritional epidemiology, especially as it relates to cancer, is faced with a multifarious set of challenges to understand the relationship between dietary factors and disease outcomes. Although randomized double-blind controlled clinical trials are considered the gold standard in evaluating cause and effect, these experimental designs are not typically conducted for food groups, such as red meat intake, because they are cost-prohibitive. The development of cancer usually takes several years, and it is not practical for participants and researchers to be "blinded" to receive or be assigned to a food item, such as beef or pork. Therefore, the large majority of analytical study designs used to evaluate meat intake and cancer are observational prospective cohort studies and case-control studies.

Prospective cohort studies are considered to be more informative in evaluating dietary factors because exposure (i.e., intake) is measured prior to the onset of disease, thereby minimizing the potential for certain types of methodological bias that will affect the interpretation of results. For example, in a case-control study, past dietary history is ascertained after the disease has been diagnosed; thus, these designs may be affected by information bias (the accuracy of dietary information may be different for cases and controls) and selection bias (healthier controls may be more likely to participate). Meta-analyses are useful in synthesizing a large volume of epidemiologic data to estimate summary associations across studies. In addition, a meta-analysis can facilitate the identification of potential sources of between-study variation and estimate patterns of associations among population sub-groups.

When considering data from published epidemiologic studies, associations between red meat and processed meat have commonly been in the positive direction for certain cancers, such as colorectal, esophageal, lung, and stomach. However, across these studies:

- Most associations are weak in magnitude (i.e., RR $<$ 1.4)
- Many associations are null or inverse
- Most associations are not statistically significant
- Patterns of associations vary by gender and anatomic location of the tumor
- Red and processed meat definitions are heterogeneous across studies
- Measures of intake and the analytical comparisons are variable

- Confounding and residual confounding, such as that for physical activity, body mass index, alcohol intake, or adherence to screening recommendations, may impact associations

Other cancers for which the majority of associations are in the positive direction are pancreatic cancer and ovarian cancer, although most data comes from case-control studies, which may be more susceptible to bias. Overall, most associations from large prospective cohort studies of breast cancer and prostate cancer, two of the most common types of cancer, have been approximately null, indicating no relationship with red meat or processed meat intake. Similarly, epidemiologic data are not suggestive of increased risks of kidney or bladder cancer among consumers of red meat or processed meat. Although limited by relatively sparse data, the currently available epidemiologic evidence does not appear to support an independent positive association between red or processed meat consumption and liver cancer, endometrial cancer, skin cancer, or non-Hodgkin's lymphoma. Interpretation for the remaining cancer types are limited to data from few studies, particularly few cohort studies, suggesting that red meat or processed meat have not been purported as contributing to increasing cancer risk.

Of note, meat intake is commonly evaluated as part of a large collection of dietary factors (e.g., over 100 food items on a food frequency questionnaire); thus, if red meat was not found to be associated with cancer in a particular analysis, the researchers may not report the results (i.e., null associations) for red meat in a peer-reviewed journal. However, researchers may focus on associations for the factors that were positively or inversely associated with the outcome, such as fruits, vegetables, or fiber.

Over time, several postulated mechanisms have been suggested as to why or how meat consumption may contribute to carcinogenesis. Of the hypothesized mechanisms, mutagenic compounds, such as heterocyclic amines and polycyclic aromatic hydrocarbons (PAHs), have been the most heavily studied, although results have been inconsistent across epidemiologic investigations. Dietary mutagens include chemical compounds that are not naturally present in foods, but may develop during cooking or food preservation. Nitrates and nitrites, commonly used in processed meats for preservation, color, and flavoring agents, and N-nitroso compounds, have been suggested to increase the risk of cancer.

The role that these chemicals, via the processed meat pathway, may play in carcinogenesis is unclear, however, as exposure is not specific to processed meat intake. In fact, greater exposure may occur through consumption of other dietary sources such as vegetables or cereal products. Many researchers have suggested that iron, particularly heme iron, may play a role in cancer development. Heme iron is found naturally in meat as part of hemoglobin and myoglobin. Although red meat is a primary source of heme iron, few epidemiologic studies have investigated the potential role that this factor may play in cancer risk, and of the studies that have reported data, associations have been inconsistent.

Based upon a comprehensive assessment of associations across the epidemiologic literature, and in consideration of the complex methodological, analytical, and biological challenges, the totality of the available scientific evidence is not supportive of an independent association between red meat or processed meat and the types of cancer reported in this technical summary. Although positive associations have been reported in several epidemiologic studies for certain types of cancer, namely colorectal cancer, taken together, results have been relatively weak in magnitude and most associations are not statistically significant. Furthermore, there are some apparent differences in the patterns of results by gender, as associations from some of the largest and most well-conducted cohort studies have been null or inverse among women; an observation not readily explained by level of intake or biological or hormonal differences.

Diet as it relates to chronic diseases, such as cancer, is an ever-expanding area of research. A comprehensive and continuously updated state of knowledge is necessary to understand the evolving patterns of associations and to identify population sub-groups who may be at higher risk of developing cancer. Discoveries of new methods, such as efficient methods for genotyping large populations, and refinements of existing methods, such as better ascertainment of diet using visual stimuli and biomarkers, will continue to enhance current methodological approaches in conducting studies of diet and cancer. Science is a dynamic field of study and it is essential to continually appraise nutritional epidemiology research in an effort to provide perspective to consumers of advances in the understanding of diet and health outcomes. Accordingly, this technical summary serves to provide a comprehensive overview of the epidemiology surrounding red meat and processed meat and cancer.