

SECTION **10**
**RED AND PROCESSED
 MEAT AND CANCER:
 INTERPRETATION**

Collectively, hundreds of epidemiologic studies have been published that reported findings for red meat and processed meat intake and cancer.

Although the majority of epidemiologic data comes from case-control studies, large-scale prospective cohort studies are being conducted with increased frequency, thereby facilitating a more accurate and comprehensive understanding of the relationship between meat consumption and many types of cancer.

Answering the question of whether intake of red meat or processed meat is associated with increasing the risk of cancer is complex, involving biological mechanisms, food definitions, intake measurements, outcome classifications, statistical testing, colinearity of red meat intake with other food items, and many lifestyle and behavior characteristics. Moreover, cancer commonly takes several years to progress and comprises a heterogeneous array of specific types of cancer, each with their own set of etiological factors. With consideration of these 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.

The pendulum swings on the positive side for certain cancers, such as colorectal, esophageal, lung, and stomach, as the majority of associations across epidemiologic studies have been greater than 1.0. However, findings across studies are heterogeneous and are likely affected by lifestyle and behavioral confounding factors, such as other dietary choices, smoking, body mass, and physical activity. Furthermore, most associations are weak in magnitude (i.e., RRs < 1.5) and are not statistically significant, and patterns of associations tend to vary among these cancer types by certain characteristics, such as gender, anatomic location of the tumor, specific type of meat, and cooking practices.

Other cancers for which the majority of associations are in the positive direction are pancreatic cancer and ovarian cancer. Because these are rare types of cancer with a high case-fatality rate, the majority of scientific evidence comes from case-control studies, which are prone to certain types of biases (e.g., information bias, recall bias) that may affect reported associations. Furthermore, smoking is associated with these cancer types; thus, parsing out the independent effects of meat consumption is difficult and reported associations may be unreliable.

Overall, most associations for breast cancer and prostate cancer, two of the most common types of cancer and for which an abundance of literature on red/processed meat intake exist, have been approximately null, indicating no relationship with red meat or processed meat intake.

Other types of cancer for which there is a large enough volume of literature to make a comprehensive assessment of the epidemiologic findings are kidney cancer and bladder cancer. In total, the epidemiologic data are not suggestive of increased risks of kidney or bladder cancer among consumers of red meat or processed meat.

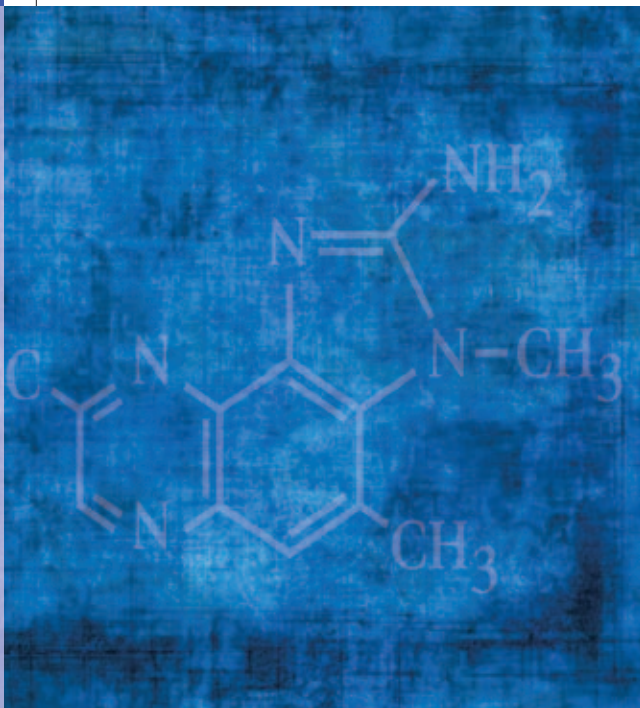
Although limited by relatively sparse data, the currently available epidemiologic evidence does not appear to support an independent positive association between red/processed meat consumption and liver cancer, endometrial cancer, skin cancer, or non-Hodgkin's lymphoma. Interpretation for the remaining cancer types are limited to data from few studies, suggesting that red meat or processed meat have not been purported as contributing to increasing cancer risk.

POSTULATED MECHANISMS

There are several postulated mechanisms as to why or how meat consumption may contribute to carcinogenesis, although no mechanism has been established as being responsible for increasing the risk of cancer in human studies. Of the hypothesized mechanisms, mutagenic compounds have been the most heavily studied. Dietary mutagens (i.e., physical or chemical agents that are capable of genetically altering an organism; commonly referred to as carcinogens) include chemical compounds that are not naturally present in foods, but may develop during cooking or food preservation. There are three major groups of potential dietary carcinogens: heterocyclic amines, polycyclic aromatic hydrocarbons (PAHs), and nitrosamines.

Heterocyclic amines are potentially carcinogenic chemicals produced by cooking meats at high temperatures. Specifically, heterocyclic amines are formed when amino acids and creatine (a chemical found in muscles) react during cooking meat, including beef, poultry and fish, at high temperatures. To date, more than 17 different heterocyclic amines resulting from the cooking of muscle meats have been identified, with 2-amino-1-methyl-6-phenylimidazo (4,5-b) pyridine (PhIP) and 2-amino-3,8-dimethylimidazo [4,5-f] quinoxaline (MeIQx) being the most abundant in cooked meat (Cross and Sinha 2004; WCRF/AICR 2007).

The formation of heterocyclic amines has been suggested to be influenced by four factors: type of food, cooking method, temperature, and cooking time (NCI 2007; NCI CHARRED). Temperature is considered to be the most important factor in the formation of these chemicals, and frying, broiling, and barbecuing meats likely produce heterocyclic amines in the largest quantities because of high temperature cooking methods (NCI 2007; NCI CHARRED).



Structure of Heterocyclic Amines

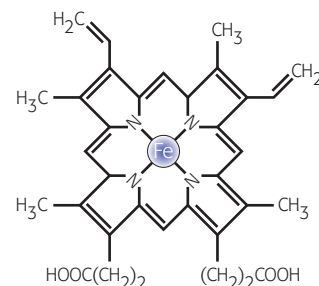
More than 100 PAHs exist, with benzo(a)pyrene (BaP) being the most extensively studied of these chemicals (Cross and Sinha 2004). Exposure to BaP occurs occupationally among coke oven workers. Environmentally, exposure may occur from cigarette smoke or from cooking meat over a direct flame (Cross and Sinha 2004). Nitrosamines are chemical carcinogens, and their carcinogenicity has been examined in experimental animal models, however, the understanding of these chemicals in the diet as related to human cancer is limited.

Several methodological challenges are intrinsic in examining the effects of dietary mutagens related to meat consumption and risk of cancer. First, heterocyclic amines and other potential carcinogenic chemicals are not included in food composition databases, since they are not a natural component of food and have no nutritional value. Second, measurement errors are likely to arise because dietary exposure is commonly based on indirect measures, such as chemically analyzing selected meat dishes that the study population may have consumed. Third, although diet is the primary source of exposure, mutagenic chemicals, resulting from tobacco smoke and other sources, are also present in the environment and ambient air. Thus, controlling for the effects of these potential sources of exposure is difficult.

In addition to potential limitations in exposure assessment, the available evidence pertaining specifically to mutagenic compounds from red/processed meat consumption and cancer is relatively limited. Moreover, the majority of associations across human studies of meat-related mutagenic compounds and cancer have been inconsistent. Because of the variability in mutagenic exposure assessment among dietary factors (e.g., type of cooking method, type of meat, methods used to estimate chemical exposures, etc.) and the sheer number of identified mutagenic compounds, additional well-conducted studies are needed before conclusions can be made regarding the nature of potential associations between dietary mutagenicity and cancer. Since certain dietary mutagens are produced by cooking meat at high temperatures (e.g., pan-frying, grilling, barbecuing, etc.), methods of cooking are commonly used as surrogate measures of mutagen exposure. Nevertheless, findings across studies that evaluated cooking methods or consumption preferences are variable.

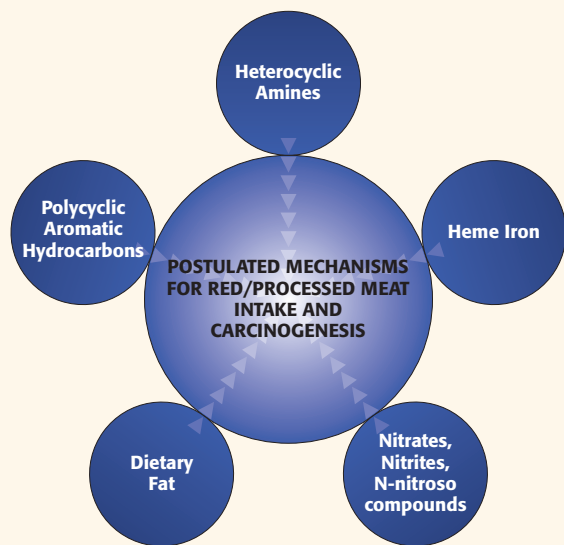
Nitrates and nitrites are commonly used in processed meats for preservation, color, and as flavoring agents. These environmentally ubiquitous chemicals are naturally occurring ions that are part of the global nitrogen cycle (IARC 2006). Exposure to nitrates and nitrites typically occurs through ingestion of water and food, such as vegetables, baked and processed cereal products, and cured meat. Exposure to nitrites also occurs endogenously when ingested nitrate is excreted in the saliva and reduced to nitrite mainly by oral bacteria, then re-ingested (Grosse et al. 2006). Endogenous nitrite and nitrate are also derived from metabolism of the neurotransmitter nitric oxide, which is synthesized from arginine. Nitrosating agents arising from nitrites under acidic gastric conditions may react with amines or amides to form N-nitroso compounds, several of which have been identified as potential carcinogens (IARC 2006; Grosse et al. 2006). Although few human studies have analytically isolated these chemicals, consumption of processed meats may be used to estimate exposure to nitrates, nitrites, or N-nitroso compounds. 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.

On average, associations across epidemiologic studies have been stronger in magnitude for red meat compared with white meat, leading researchers to suggest that iron, particularly heme iron, may play an important role in cancer. A significant difference between red meat and white meat is that there is a considerably higher amount of iron in red meat (Sinha et al. 2005). There are two primary forms of dietary iron: non-heme iron and heme iron. Non-heme iron is found mainly in iron-fortified cereals, vegetables, and meat, whereas heme iron is found primarily in meat as part of hemoglobin and myoglobin (Sinha et al. 2005). It has been suggested that free iron, a pro-oxidant, may contribute to carcinogenesis (primarily in studies



Structure of Heme Iron

FIGURE 10.1
POSTULATED MECHANISMS



of colorectal cancer) by promoting free radical production and lipid peroxidation (Kabat et al. 2007; Huang et al. 2004).

Although red meat is a primary source of heme iron, very 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. More prospective studies are needed before a comprehensive assessment of the scientific evidence can be conducted. Despite a few positive associations reported in some studies, the available epidemiologic data, albeit sparse, are not suggestive of a significant role of heme iron in cancer risk.

Even before meat consumption was hypothesized as contributing to carcinogenesis, fat from animal sources was implicated as increasing the risk of cancer. The "animal fat hypothesis," first introduced in the 1960s, was based largely on international correlation data in which rates of cancer, particularly colon and breast cancer, were shown to increase concurrently with increasing per capita consumption of animal fat (Armstrong and Doll 1975; Wynder and Shigematsu 1967). Since these early ecologic studies, extensive epidemiologic and experimental investigations have been conducted. However, fat intake, whether from animal sources or non-animal sources, has not been shown consistently to increase the risk of cancer. The preponderance of epidemiologic evidence surrounding animal fat intake comes from studies of colorectal, breast, and prostate cancer.

Several studies have examined the complex relationship between meat consumption, genetic characteristics, and certain types of cancer, particularly colorectal cancer, although there has been little consistency of results across studies. The study of gene-environment interactions can be useful in strengthening the association between an etiologic factor and disease by examining the role of an enzyme involved in the factor's metabolism as well as in identifying susceptible sub-populations of individuals for whom exposure to a factor may confer increased risk.

Many studies have evaluated the role of common genetic sequence variation (genetic polymorphisms) in genes for enzymes involved in carcinogen metabolism. Several genetic polymorphisms have been studied as main predictors of cancer and as effect modifiers of risk. Genes coded for enzymes in the cytochrome p450 (CYP), n-acetyltransferases (NAT), and glutathione s-transferases (GST) families have been the most commonly studied. N-acetyltransferase (Nat) 1 and 2 are metabolic enzymes involved in the metabolism of potential carcinogenic heterocyclic amines, such as those produced from heavily cooked meat and tobacco smoke. Fast (rapid) acetylator phenotype of Nat2 may confer increased susceptibility to colorectal cancer because of potentially rapid activation of heterocyclic amines or other possible carcinogens to more potent forms. Several functional polymorphisms in Nat2 have been identified that correlate with differential rates of enzymatic activity, and individuals have been commonly categorized as fast, slow, or intermediate acetylators in epidemiologic studies. Nat1, while not as well characterized as Nat2, is believed to have functional polymorphisms as well that may confer different acetylation rates.

Although an intriguing area of research, lack of knowledge of the functional relevance of various polymorphisms, differences in allele frequencies among different populations, and small sample sizes have limited the interpretation of these studies. New directions currently being undertaken in the molecular epidemiology of cancer, such as haplotype analyses and targeted pathway approaches, may yield more information to be used in elucidating the complex biologic mechanisms underlying cancer.

METHODOLOGICAL COMPLEXITY

Although hundreds of studies have evaluated the association between red and/or processed meat and cancer, a universal definition of red meat or of processed meat is not readily apparent as a “scientific variable.” Exacerbating this, or perhaps the genesis of this complication, is the fact that dietary patterns and food item availability vary from population to population and even with populations in demarcated regions. For example, in three different cohort studies:

- Red meat was defined as beef, pork, or lamb as a main dish in one study,
- Beef and pork were included with a variety of processed red meat items in another study, and
- Red meat was not defined at all in yet another study.

How meat is defined, quantified, and/or analyzed may have a greater impact on the results of epidemiologic studies of meat than for most dietary factors. This is because red and/or processed meat includes several individual meats originating from differing types of animals, cooking practices vary by choice within and across populations and by cut of meat, and preference for cooking doneness varies. As defined in many studies, red meat generally includes beef, pork, or lamb; however, patterns of consumption within these specific red meat items is variable.

Epidemiologically, evaluating processed meat is even more complex, as there is greater variability in the types of individual food items that are comprised within the broad category of “processed meat” such as bacon, sausage, lunch meats, and other types of meat (including non-red meats) that undergo preservation. In their report on diet and cancer, WCRF/AICR (2007) acknowledges the lack of clarity regarding the definition

of processed meat, as shown in their Box 4.3.1 (pg. 117). Specifically, they state “There is no generally agreed definition of ‘processed meat.’ The term is used inconsistently in epidemiologic studies. Judgements and recommendations are therefore less clear than they could be.” In addition to the ambiguity in the definition of processed meat, “some studies may have included processed meats in their classification of red meat intake,” thus, further confusing the relationship between red meat or processed meat and cancer.

In addition to the variability in meat definitions, the dietary instruments, (e.g., 33 item FFQ, 169 item FFQ), the analytical cut-points of intake groups (e.g., 203+ g/day vs. < 80 g/day; 56.6+ g/day vs. < 18.7 g/day), and the types of exposure metrics (e.g., servings per month, times per day, grams per day, unspecified quintiles of intake) are heterogeneous across studies. Regarding meat consumption and colorectal cancer, in a 2007 review (Baghurst 2007), it was concluded that the “evidence that eating red meat increases the risk for colorectal cancer remains weak and inconsistent.” This conclusion was based on variability in terms of meat definitions, dietary instruments, measurement and adjustment for potential confounding factors, outcomes measured (i.e., colon vs. rectal), range of meat consumption, and cultural and geographic differences.

Many of the salient factors that should be considered when evaluating and interpreting epidemiologic studies of red meat and processed meat and cancer are listed in Information Box 10.1.



INFORMATION BOX 10.1**COMPLEXITY IN EVALUATING AND INTERPRETING STUDIES OF DIETARY FACTORS AND CANCER****Food Measurement**

- Definitions of foods, such as red meat or processed meat, may vary considerably across studies
- Intake measurement error: dietary intake is usually based on self-reporting and individuals may not accurately recall their intake level, or they may not understand the specific dietary constituents they are consuming
- Dietary instruments, intake metrics, and comparison groups vary across studies
- Diet involves a complex set of intake components, many of which are highly correlated
- Many food groups, such as red meat, are composite foods, thus measuring and isolating independent effects is difficult
- Eating patterns may evolve and/or change over time, although some data suggest that this evolution may be gradual

Cancer

- Cancer progression may take as long as 40 years, thus, making the identification of risk factors that contribute to carcinogenesis difficult
- Cancer comprises a heterogeneous group of malignancies, many of which differ considerably with regards to etiologic factors
- Cancer is multifactorial; many cancer-causing agents can cause several types of cancer, and these agents can also have non-carcinogenic effects

Analytical Considerations

- Associations between diet and cancer may be confounded by a wide variety of factors, and residual confounding or incomplete control for possible confounding factors may impact results across studies
- Some biases are inherent to certain study designs, and associations may vary by design used
- Recall bias and information bias may affect study findings, particularly in case-control studies
- Units or metrics of intake vary across studies, which increases the difficulty of synthesizing the scientific evidence
- Unlike many other exposures, there is little range of variation when examining the effects of food (e.g., comparing the effects of consuming beef 4 times per week compared to twice per week)

Geographic Variability

- Dietary patterns and food item availability differs between populations
- Lifestyle and behavior characteristics vary across populations, as does quality of and access to health care; thus, these factors may confound associations between dietary factors and cancer
- Findings observed in a certain geographic region or among a specific type of population may not be generalizable to a broader population group