A Technical Summary of the Epidemiologic Evidence
Acknowledgements

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Partially funded by:
The Beef Checkoff through the National Cattlemen’s Beef Association (NCBA)
and the National Pork Board (NPB)
This technical report summarizes the currently available epidemiologic evidence surrounding red meat and processed meat consumption and cancer. Although discussed herein, this report is not intended to systematically address all of the components of causation, such as dose-response or biological plausibility, between red or processed meat and specific types of cancer. Rather, the purpose of this report is to synthesize scientific information pertaining to the cancer types for which intake of meat has been evaluated, and to recapitulate some of the observed statistical associations between red or processed meat intake and cancer. In addition, the methodological, analytical, and biological complexity is underscored so the reader can recognize and appreciate the challenges scientists are faced with when interpreting a large body of scientific and medical literature.

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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.
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DIET, MEAT, AND CANCER

A TECHNICAL SUMMARY OF THE EPIDEMIOLOGIC EVIDENCE
While there is scientific consensus that diet plays a significant role in cancer, the evidence regarding specific roles for food groups, individual foods, or food components remains unresolved. For persons who do not smoke, maintenance of a healthy weight may be the single most preventable factor for developing cancer.

CANCER

Approximately one in every three Americans will be diagnosed with cancer during their lifetime and one in four deaths in the United States is attributable to cancer (Jemal et al. 2008). Cancer is second to heart disease as the leading cause of death in the United States.

Cancer, which may originate from virtually every cell type in the body, is a diverse family of diseases consisting of more than 100 forms (Ecsedy and Hunter 2008). Despite the diversity, several features are common to all cancers, including: unrestricted cellular proliferation, circumvention of cell-cycle control, growth without appropriate signals, escape from programmed cell death, altered interactions between cells and the surrounding environment, evasion of immune-mediated eradication, and the hallmark of malignancy, which is invasiveness into normal tissue (Hanahan and Weinberg 2000). Although the specific etiology of the majority of cancer cases has yet to be identified, it is well-known that the cause of cancer is multifactorial, involving a complex interaction of genetic, lifestyle, infectious, and environmental factors. The progression of cancer commonly takes several years from cancer initiation to diagnosis of disease, thus, enhancing the difficulty in identifying the underlying factors involved in carcinogenesis.

In 2008, a total of 1,437,180 new cancer cases and 565,650 deaths from cancer were projected to occur in the United States (Jemal et al. 2008). Over the past decade cancer incidence rates in the United States have remained relatively stable while cancer death rates have declined (Jemal et al. 2008). Prostate cancer and breast cancer are the most commonly diagnosed cancers among American men and women, respectively, while lung cancer and colorectal cancer rank second and third. Lung cancer, however, is responsible for approximately one-third of all cancer deaths among men and one-fourth of all cancer deaths among women (Jemal et al. 2008), a statistic largely attributable to cigarette smoking.
DIET AND CANCER

The role that diet may play in human cancer has received a great deal of attention over the past few decades, leading some researchers to suggest that 35% to even 70% of all cancer deaths may be attributable to dietary factors (Doll and Peto 1981; Willett 2006). Although the exact proportion of cancers attributable to diet remains uncertain, there is scientific consensus that the relationship between diet and cancer is a significant public health issue.

Early evaluations of migrant populations revealed that adopting certain lifestyle and behavioral characteristics led to increased risks of some types of cancer, rather than the burden of cancer resting solely on the shoulders of genetic factors. For example, U.S. immigrants from Japan, a nation with higher rates of stomach cancer, were observed to have decreasing stomach cancer rates that began to reach U.S. rates after two generations of living in the United States (Haenszel and Kurihara 1968). Although genetic factors play a major, and possibly the most important, role in cancer development, observations of secular changes that result in modifying the rates of cancer suggested that diet may influence cancer risk. The hypothesis that diet may contribute to cancer causation began to take hold in the 1970s and was buttressed by experimental and epidemiologic evidence beginning in the early 1980s. Historically, nutrition studies in animals led to hypotheses that the same biological processes occur in humans, and preliminary animal models supported the theory that dietary variations affect cancer outcomes.

Among the first theories involving diet and cancer risk was that fat intake may be involved in carcinogenesis. For example, Tannenbaum and Silverstone (1953) demonstrated that increased intake of dietary fat in rodents increased the rate of mammary tumors. Subsequently, ecologic epidemiology studies of human populations were conducted to evaluate the correlation between the per capita consumption of certain food groups and cancer rates by country. As a result, it was found that countries with higher levels of dietary fat consumption also tended to have higher rates of some common types of cancer, such as breast and colorectal (Carroll 1975; Armstrong and Doll 1978). It wasn’t until the 1980s that the majority of more rigorously designed
### FIGURE 1.3
#### TEN LEADING CANCER TYPES IN THE UNITED STATES, 2008

<table>
<thead>
<tr>
<th></th>
<th>MALES</th>
<th>FEMALES</th>
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<tbody>
<tr>
<td><strong>ESTIMATED NEW CASES</strong>*</td>
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<tr>
<td>Prostate</td>
<td>186,320 (25%)</td>
<td>Breast</td>
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<tr>
<td>Lung and Bronchus</td>
<td>114,690 (15%)</td>
<td>Lung and Bronchus</td>
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<tr>
<td>Colon and Rectum</td>
<td>77,250 (10%)</td>
<td>Colon and Rectum</td>
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<tr>
<td>Urinary Bladder</td>
<td>51,230 (7%)</td>
<td>Uterine Corpus</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>35,450 (5%)</td>
<td>Non-Hodgkin Lymphoma</td>
</tr>
<tr>
<td>Melanoma of the Skin</td>
<td>34,950 (5%)</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Kidney and Renal Pelvis</td>
<td>33,130 (4%)</td>
<td>Melanoma of the Skin</td>
</tr>
<tr>
<td>Oral Cavity and Pharynx</td>
<td>25,310 (3%)</td>
<td>Ovary</td>
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<tr>
<td>Leukemia</td>
<td>25,180 (3%)</td>
<td>Kidney and Renal Pelvis</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,770 (3%)</td>
<td>Leukemia</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>745,180 (100%)</td>
<td><strong>All Sites</strong></td>
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<tr>
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<th><strong>ESTIMATED DEATHS</strong></th>
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<tr>
<td>Lung and Bronchus</td>
<td>90,810 (31%)</td>
<td>Lung and Bronchus</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,660 (10%)</td>
<td>Breast</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>24,260 (8%)</td>
<td>Colon and Rectum</td>
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<tr>
<td>Pancreas</td>
<td>17,500 (6%)</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Liver and Intrahepatic Bile Duct</td>
<td>12,570 (4%)</td>
<td>Ovary</td>
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<tr>
<td>Leukemia</td>
<td>12,460 (4%)</td>
<td>Non-Hodgkin Lymphoma</td>
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<tr>
<td>Esophagus</td>
<td>11,250 (4%)</td>
<td>Leukemia</td>
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<tr>
<td>Urinary Bladder</td>
<td>9,950 (3%)</td>
<td>Uterine Corpus</td>
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<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>9,790 (3%)</td>
<td>Liver and Intrahepatic Bile Duct</td>
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<td>Kidney and Renal Pelvis</td>
<td>8,100 (3%)</td>
<td>Brain and Other Nervous Systems</td>
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<tr>
<td><strong>All Sites</strong></td>
<td>294,120 (100%)</td>
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analytical epidemiologic studies, such as cohort and case-control studies, were initiated to examine potential causal relationships between diet and cancer, and the discipline of nutritional epidemiology began to burgeon. Fat consumption continued to be incriminated as a cancer-causing culprit, as well as being implicated as contributing to cardiovascular disease. Other emerging hypotheses included the possible role that fruit and vegetable consumption may play in cancer prevention. Despite the numerous scientific advancements, there is no conclusive evidence regarding specific roles for food groups and individual foods in cancer causation. In fact, what was thought

Over the past two decades, improvements in study designs, research methodologies, and analytical techniques have allowed researchers to investigate specific nutrients, foods, food groups, and dietary patterns while better measuring intake and nutritional components of diets. Despite the numerous scientific advancements, there is no conclusive evidence regarding specific roles for food groups and individual foods in cancer causation. In fact, what was thought

Despite the numerous scientific advancements, there is no conclusive evidence regarding specific roles for food groups and individual foods in cancer causation.

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*The spike in cancer incidence rates among men around 1990 was largely due to the introduction of PSA testing for prostate cancer.
to be a strong and “convincing” association between fruit and vegetable intake and cancer reduction, particularly colorectal cancer, has been weakened somewhat by more recent, large, well-conducted prospective studies, and the scientific evidence has been diluted (Boyle et al. 2008). This is not to say that intake of fruit and vegetables may not reduce the risk of some types of cancer, among other health outcomes, but the available scientific evidence is not as clear today as was thought 10 to 20 years ago. The same can be said for fat intake; large-scale epidemiologic investigations of prospective studies, such as meta- and pooled-analyses, have not supported positive associations between fat consumption and some of the more common types of cancer (Smith-Warner et al. 2001; Alexander et al. 2009; Alexander et al. 2009[submitted]).

Perhaps, researchers need better tools and dietary assessment methods, such as dietary biomarkers, to identify specific sub-groups of the population for which dietary factors may modify the risk of cancer. On the other hand, certain dietary factors once hypothesized to increase or decrease the risk of cancer, may not be directly involved in carcinogenesis. Further confounding the modern thinking on diet and cancer is the uncertainty in the stage of carcinogenesis on which dietary factors may act, and whether such possible risk is dose-dependent (Miller and Linseisen 2009).

It is noteworthy that juxtaposed with examinations of diet and nutrition, there have been epidemiologic evaluations of body mass index, body fatness, exercise and cancer risk. Although findings from epidemiologic investigations of these factors and cancer have not always been consistent, it is becoming increasingly clear that obesity and physical activity are modifiable factors that are essential in decreasing the risk of many types of cancer. Indeed, this is recognized on a global scale, as an increased emphasis has been placed upon the public health infrastructure to make body weight and physical activity a fundamental priority in the prevention of cancer (World Health Organization 2004; WCRF/AICR Policy Report 2009). Thus, findings and epidemiologic summaries presented in this report should be interpreted with the understanding that assessing cancer risk involves a multi-faceted approach whereby several risk factors may be intertwined.

**RED AND PROCESSED MEAT CONSUMPTION AND CANCER**

To date, the relation between diet and disease has been the subject of thousands of epidemiologic studies, and while these studies have led to the discovery of several important associations between diet and health outcomes, the scientific evidence between dietary factors and cancer prevention have been somewhat underwhelming considering the extent of the research. As such, many questions remain regarding the role of food and nutrition in the prevention and cause of cancer in humans. One such question: “Is there scientific evidence that dietary intake of red meat or processed meat has an effect on developing cancer?” is complex and not only involves factors related to the composition of meat or methods of meat processing and preparation, but also involves accounting for other dietary and lifestyle patterns and choices that may impact the risk of cancer, such as obesity, physical activity, alcohol consumption, smoking, family history of cancer, and adherence to cancer screening recommendations. Addressing this question is one of utmost significance because red meat is a nutrient-rich food that plays an important function in American diets by contributing a unique nutrient package.

… it is becoming increasingly clear that obesity and physical activity are modifiable factors that are essential in decreasing the risk of many types of cancer.
A 3-ounce serving of beef (179 calories) contributes less than 10 percent of calories to a 2,000-calorie diet, yet it supplies more than 10 percent of the Daily Value for:

**BEEF IS AN EXCELLENT SOURCE OF THESE NUTRIENTS**

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<tr>
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<th>Daily Value</th>
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<tr>
<td>Protein</td>
<td>51%</td>
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<tr>
<td>Zinc</td>
<td>38%</td>
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<tr>
<td>Vitamin B₁₂</td>
<td>37%</td>
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<tr>
<td>Selenium</td>
<td>26%</td>
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<td>Phosphorus</td>
<td>20%</td>
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**BEEF IS A GOOD SOURCE OF THESE NUTRIENTS**

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<tr>
<th>NUTRIENT</th>
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<tr>
<td>Choline*</td>
<td>18%</td>
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<tr>
<td>Niacin</td>
<td>17%</td>
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<tr>
<td>Vitamin B₆</td>
<td>15%</td>
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<tr>
<td>Riboflavin</td>
<td>12%</td>
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NDB 13364, composite of trimmed retail cuts, 0” trim, all grades, 3 ounces cooked, visible fat trimmed.


*Dietary Reference Intakes, Institute of Medicine of the National Academies Press, Washington, DC, 2006. (Highest adequate intake for choline (550mg).)

**BEEF’S NUTRIENT PROFILE**

Beef is an important dietary source of several key nutrients, as one 3-ounce serving of beef contributes less than 10% of the daily value of calories in a 2,000-calorie diet, while providing an excellent source (more than 20% of the daily value) of protein, zinc, vitamin B₁₂, selenium, and phosphorus and a good source (more than 10% of the daily value) of choline, niacin, vitamin B₆, iron, and riboflavin (USDA, ARS 2009). In a ranking of nutrient sources in the diet, beef was found to be the number one source of protein, vitamin B₁₂, zinc and monounsaturated fats; number two source of selenium; number three source of iron (behind fortified cereal and yeast bread), vitamin B₆, niacin and phosphorus; and the number four source of potassium and riboflavin (Cotton 2004). In addition, the fat profile of lean beef is comparable to that of skinless chicken.

Beef lipids encompass numerous fatty acids, and although animal fats are often considered synonymous with saturated fats, less than half of all fatty acids in beef fat are saturated (USDA, ARS 2009). In fact, beef typically contains a greater proportion of monounsaturated fat than saturated fat.

Beef is an important source of conjugated linoleic acid (CLA). Experimental animal models and in vitro studies have supported an anti-carcinogenic effect of CLA at a variety of anatomic sites, such as the colon, prostate, and mammary gland (Wahle et al. 2004; Bhattacharya et al. 2006). In experimental animal studies, CLA has been shown to inhibit the initiation, progression, and
metastasis of chemically-induced cancer (Wahle et al. 2004; Bhattacharya et al. 2006). However, data for CLA and cancer in human studies are limited, and additional research is necessary to fully understand the potential anti-carcinogenic effects of this fatty acid. Emerging research continues to provide further foundational support for beef’s position in a balanced and healthy diet.

As with beef, pork is a nutrient-dense food that can play an important role in helping achieve the recommendations of the Dietary Guidelines for Americans. In fact, a 3-ounce serving of roasted, trimmed pork contributes less than 10% of calories to a 2,000-calorie diet, although it is an excellent source of selenium, protein, thiamin, niacin, vitamin B\textsubscript{6}, and phosphorus and a good source of riboflavin, zinc,
Although beef and pork, as specific sources of food, may provide several key nutrients to an individual’s daily dietary intake, persons do not consume isolated foods or only specific nutrients; rather, the human diet comprises a wide variety of foods and patterns of foods that people typically consume on a day-to-day basis. Thus, analyses of dietary intake patterns have emerged as a complementary method to evaluate the relationship of overall diet and health outcomes. Dietary pattern analysis examines the broad spectrum of dietary habits among individuals, and scientists can estimate the risk of certain disease outcomes based on adherence to a particular dietary pattern. It has been argued that dietary patterns may be more relevant to understanding the relation between diet and chronic diseases, such as colorectal cancer, because they offer a broader representation of the diet than individual nutrients or foods. Numerous studies have examined dietary patterns characterized by higher intakes of red and processed meat and cancer outcomes, and while collectively, associations have been inconsistent, the majority of studies observed increased risks of cancer. Despite the nutritional value of beef and pork, meat consumption is typically classified under a “Western” dietary pattern, characterized largely by intake of refined sugars, sugary drinks, and high-fat dairy products. Moreover, persons classified in this rubric generally are more sedentary, have a higher body mass index, consume greater amounts of alcohol, and are more likely to smoke. In comparison a “prudent” dietary pattern is characterized by higher intakes of fruits, vegetables, legumes, fish, and whole grains.

Interpretation of dietary patterns studies is limited by a lack of specificity because “meat” is not analytically isolated, rather, it is included with numerous dietary factors (and associated with several possible confounding factors) that may be indicative of an overall unhealthy lifestyle. The purpose of this technical report is to provide a comprehensive summary of epidemiologic studies that specifically evaluate the relationship between red meat and processed meat consumption and cancer.
EPIDEMIOLOGY: DESIGN, METHODOLOGY, AND APPLICATIONS
EPIDEMIOLOGY: DESIGN, METHODOLOGY, AND APPLICATIONS

Epidemiology is the study of the occurrence of disease in human populations.

Nutritional epidemiology is the study of the dietary factors that influence disease frequency and distribution in human populations.

The Dictionary of Epidemiology defines epidemiology as the study of the distribution and determinants of health-related states and events (e.g., death or disease) in specified populations and the application of this study to the control of health problems (Last 2001). Epidemiologic studies provide data on associations between an exposure (e.g., red/processed meat) and a disease (e.g., cancer) among humans, while considering important factors that may influence results, such as bias and confounding. It is important to note that there is a distinction between an association (a statistical correlation between two variables) and causation. Associations may be observed in a single study or several studies; however, these associations may not be indicative of a relationship that is causal. Although a single epidemiologic study (or even a group of studies) is generally not sufficient to make a conclusion of causality, a number of guidelines have been developed that provide a basis to evaluate data from an entire collection of epidemiologic studies in order to determine whether a causal relationship is inferred.

Specifically, epidemiologists commonly apply the guidelines that were proposed by Sir Bradford Hill (1965) to evaluate causality. These guidelines have been refined and expanded by other epidemiologists over the years, although the fundamental framework remains in place (e.g., Gordis 2000; Hennekens et al. 1987). This systematic approach (Sir Bradford Hill guidelines to evaluate causality) emphasizes the use of multiple factors when making interpretations of epidemiologic research, such as the strength of observed associations within and across studies;
### FIGURE 2.1
**EXAMPLES OF GENERAL RANGE OF ASSOCIATIONS OF ESTABLISHED CAUSES OF CANCER**

<table>
<thead>
<tr>
<th>RISK FACTOR AND CANCER</th>
<th>RELATIVE RISK (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Ultraviolet Radiation and Melanoma (estimates based on lifetime exposure days and skin sensitivity)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Occupational Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Vinyl Chloride and Angiosarcoma of the Liver</td>
<td>1.8</td>
</tr>
<tr>
<td>Nickel and Lung Cancer</td>
<td>2</td>
</tr>
<tr>
<td><strong>Genetic Factors</strong></td>
<td></td>
</tr>
<tr>
<td>1st Degree Family History of Breast Cancer</td>
<td>1.8</td>
</tr>
<tr>
<td>Lynch Syndrome/Hereditary Nonpolyposis Colorectal Cancer (HNPCC)</td>
<td>50</td>
</tr>
<tr>
<td><strong>Viral Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Human Papillomavirus (HPV) and Cervical Cancer</td>
<td>7</td>
</tr>
<tr>
<td><strong>Lifestyle and Dietary Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking and Lung Cancer</td>
<td>8</td>
</tr>
<tr>
<td>Smoking and Esophageal Cancer</td>
<td>4</td>
</tr>
<tr>
<td>Smoking and Pancreatic Cancer</td>
<td>1.5</td>
</tr>
<tr>
<td>Aflatoxin and Liver Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol and Esophageal Cancer</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Comparison to Most Studies of Red Meat and Cancer</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factor and Cancer</th>
<th>Relative Risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraviolet Radiation and Melanoma (estimates based on lifetime exposure days and skin sensitivity)</td>
<td>2</td>
</tr>
<tr>
<td>Vinyl Chloride and Angiosarcoma of the Liver</td>
<td>1.8</td>
</tr>
<tr>
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<td>2</td>
</tr>
<tr>
<td>1st Degree Family History of Breast Cancer</td>
<td>1.8</td>
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<td>Lynch Syndrome/Hereditary Nonpolyposis Colorectal Cancer (HNPCC)</td>
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<tr>
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<tr>
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<td>Aflatoxin and Liver Cancer</td>
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<td>1.5</td>
</tr>
<tr>
<td>Comparison to Most Studies of Red Meat and Cancer</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Most epidemiologic studies are observational in design, that is, the number of outcomes (or disease events) is observed among a clearly defined study population consisting of exposed and non-exposed individuals. For example, the rate of disease is compared among individuals who consume red meat daily (i.e., the exposed group) to that of individuals who consume red meat infrequently, such as once per week (i.e., the non-exposed group).

There are two general classes of observational studies, descriptive and analytical. The primary function of a descriptive epidemiologic study is to characterize the distribution and/or occurrence of disease in time (e.g., trends over time), place (e.g., clustering, geographic location), and person (e.g., age, gender, race). Descriptive epidemiologic studies are useful in generating hypotheses about potential exposure-disease relationships; however, descriptive studies do not test these hypotheses and generally do not provide information regarding disease causality. Analytical epidemiologic studies, on the other hand, are conducted to identify associations between factors (e.g., diet, lifestyle factors, etc.) and disease, and are useful for testing hypotheses regarding etiology (causation). The two most commonly conducted types of analytical epidemiologic studies are cohort studies and case-control studies. Indeed, these are the most frequently utilized study designs to examine the association between meat consumption and cancer.

Evidence for exposure-response patterns; whether the exposure preceded the disease; consistency of the associations reported across studies; coherence of the evidence; and biological plausibility of the observed associations. Other important considerations when evaluating nutritional epidemiology studies include the variability of food item or food group definitions, how intake is characterized across studies, and differing patterns of intake and/or disease associations by key factors (e.g., gender, tumor site, age, etc.).

The application of the aforementioned guidelines may have some limitations inherent to nutritional epidemiology. For example, most associations between dietary factors and cancer have associations that are not considered strong (i.e., RR < 2.0 for most associations between dietary factors and cancer), and a dose-response gradient may be difficult to achieve. In comparison, the majority of established exposure-disease causal associations are of strong magnitude (i.e., RR > 2.0) as shown in Figure 2.1.
Understand epidemiologic study designs

Cohort studies (follow-up studies)

In a cohort study, researchers clearly define a disease-free (participants do not have the disease that is the focus of the investigation) study population (e.g., U.S. women aged 50 to 70) and study participants are followed over time to compare the incidence of disease between those who are grouped together based on certain factors, such as quantiles (i.e., intake groups) of meat intake. For example, the rate of cancer is compared between participants who consume meat three times or more per week with the rate of cancer among participants who consume meat one time or less per week. Thus, a cohort study facilitates an estimation of disease occurrence (incidence) because exposure is ascertained prior to the diagnosis of disease. Most cohort studies of diet and cancer are prospective, that is, the study population is defined in the present and then followed into the future to determine disease occurrence. In a retrospective cohort study, the study population is defined in the past and the disease occurrence is determined up to the present time.

Prospective cohort studies are the most methodologically rigorous observational studies and offer the best evidence to evaluate possible cause and effect. As mentioned, dietary information is collected prior to disease diagnosis, thereby decreasing the likelihood that the disease caused a change in dietary intake, or that disease diagnosis influenced the recall or reporting of past dietary habits. Because cohort studies are conducted longitudinally, repeated measurements of diet can be obtained throughout study follow-up and multiple disease endpoints can be evaluated. Cohort studies are less susceptible to bias compared with other study designs,
such as case-control studies. However, prospective cohort studies are expensive to conduct as it is often necessary to enroll thousands of persons in the study.

**Case-Control Studies**

In a case-control study, dietary (and other) information is collected from individuals who have already been diagnosed with the disease of interest (i.e., cases) and the same type of information is collected among a comparison group who does not have the disease of interest (i.e., controls). Case-control studies are generally less expensive to conduct than cohort studies and may be performed more efficiently because fewer participants are analyzed and no follow-up is necessary. However, case-control studies of dietary factors may produce inconsistent results because of the inherent potential for methodological bias, such as differential recall of dietary intake between cases and controls (e.g., cases may tend to over-report consumption than controls) or the selection of an inappropriate control group (e.g., control participants have a tendency to be healthier than eligible controls who choose not to participate) (Willett 2006).

Prospective cohort studies may avoid some of the biases of case-control studies in that dietary information is collected prior to disease; thus, the diagnosis of cancer should not affect the recall of dietary factors (Willett 2006). Despite these limitations, case-control studies may provide some scientific evidence regarding diet and cancer, particularly in the absence of data from prospective cohort studies. The statistic produced in a case-control analysis is referred to as an odds ratio (i.e., OR). Analytically, the odds of the case having a certain exposure factor (e.g., 5 or more servings of red/processed meat per week) is compared with the odds of the control having that same factor.

**Other Study Designs**

Many early investigations of diet and cancer, including meat and fat intake, consisted of ecological or correlational studies. These types of studies compare aggregate, or national-level, data between dietary factors and disease. For example, the average level of fat intake in the United States is correlated with the rates of breast cancer in the United States. Although these studies may be useful in comparing rates between countries, or generating an assessment of trends over time,
<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trials</td>
<td>Randomized clinical trials are commonly considered the gold standard in establishing a cause-and-effect relationship. However, these types of study designs are difficult (and may not be practical) to achieve for broad food groups, such as meat.</td>
</tr>
<tr>
<td>Meta-Analysis* (synthesizes data from other study designs)</td>
<td>A meta-analysis involves systematically combining results data across published studies to produce a summary estimate of relative risk. As more studies of meat intake and cancer are published and as more data become available, meta-analyses offer a systematic methodological approach to synthesize data across studies. A pooled analysis is a type of meta-analysis that incorporates data at the individual level rather than combining results data. *Of note, results from a meta-analysis are only as valid as the data from the original studies that are included in the analysis. For example, a meta-analysis of 20 case-control studies may offer a lower level of scientific evidence than individually examining five prospective cohort studies. A meta-analysis of clinical trial data may offer the best scientific evidence for causation. Thus, a meta-analysis may be viewed as an analytical technique rather than a study design.</td>
</tr>
<tr>
<td>Cohort Studies</td>
<td>Prospective cohort studies are considered to offer the best evidence of the observational studies of diet and cancer. The exposure information is ascertained prior to the onset of disease, allowing for the calculation of incidence. These designs may overcome some of the bias (e.g., recall bias) inherent to case-control studies. Most commonly cited design when interpreting studies of meat intake and cancer.</td>
</tr>
<tr>
<td>Case-Control Studies</td>
<td>Persons already diagnosed with the outcome of interest are compared with persons without the outcome. Diet is ascertained retrospectively, lending this type of design to information bias (i.e., differential recall of past dietary history between those with and without disease). Although hundreds of case-control studies of meat intake and cancer have been published, the weight of the evidence is usually only considered in the absence of data from prospective cohort studies.</td>
</tr>
<tr>
<td>Cross-Sectional Study</td>
<td>Compares groups in terms of exposure and outcome at a single point in time. Exposure and disease are ascertained contemporaneously, referred to as a “snapshot” of exposure and health status. One-dimensional analysis not useful for examining a cause and effect relationship.</td>
</tr>
<tr>
<td>Ecologic Study</td>
<td>Compares data on the aggregate level, such as the correlation between per capita intake of meat with national rates of cancer. Does not evaluate information at the individual level. May be considered “hypothesis generating.” Sometimes referred to as community-based or correlational studies.</td>
</tr>
<tr>
<td>Case Series</td>
<td>A collection of information pertaining to the health status of a series of individuals. These are commonly considered “case-only” evaluations, and no comparison groups are evaluated.</td>
</tr>
</tbody>
</table>
ecologic studies do not evaluate data at the individual level. Therefore, these study designs do not provide valid evidence for making examinations of causality, although they may substantiate scientific evidence from other study designs.

Another study design, a cross-sectional study, ascertains exposure and disease or other health-related characteristics in a defined population at a given point in time. These studies provide a “snapshot” picture of the exposure-disease relationship in a population. Because cross-sectional studies usually do not involve a time component, the dynamic interaction between exposure and disease is difficult to determine. Cross-sectional studies, commonly referred to as cross-sectional surveys, are based on prevalent rather than incident cases. Generally, the results of such studies cannot be used to infer causation.

The study designs that offer the best evidence for evaluating causality are randomized double-blind clinical trials. In these study designs, confounding by extraneous factors is theoretically minimized because study participants are randomly assigned to receive the intervention or the control. Clinical trials are commonly conducted on certain correlates of food, such as vitamins or minerals; however, trials of food items or food groups are not always feasible and are conducted infrequently. Thus, the most abundant scientific evidence surrounding red meat and processed meat intake and cancer come from epidemiologic cohort and case-control studies, which is the focus of this technical summary.

**SYNTHESIZING THE DATA: META-ANALYSIS**

A meta-analysis is a systematic quantitative method for which ‘results data’ from individual studies are combined to produce an overall or weighted summary association (an average relative risk estimate of all studies), commonly referred to as a summary relative risk estimate (SRRE).

In general, there are two types of meta-analysis models, fixed effects and random effects. In a fixed-effects model, it is assumed that the underlying effect is the same across studies and that the overall variation is random within each study but does not incorporate variation between studies. Random-effects models account for both within- and between-study variation, and allow for non-homogeneity between the effects of the various studies. Therefore, random-effects models are typically used in observational epidemiologic studies to account for between-study variation resulting from different methodological techniques and study designs. Statistically, confidence intervals are typically wider when using random-effects models because the between-study component is included in the algorithm.

An important function of a meta-analysis is testing for heterogeneity. Heterogeneity reflects unexplained variation between study results in a meta-analysis model, and a model that has significant heterogeneity may not be a valid quantitative summarization of studies. Heterogeneity may be the result of differences in study design, measurement techniques, patterns of associations by gender or race, or a plethora of other
characteristics. A single meta-analysis model will not indicate the exact source of heterogeneity; rather, researchers conduct a variety of sub-group and sensitivity analyses in an effort to identify possible sources of between-study variation. When interpreting findings from a meta-analysis, it is important to consider the studies that were included in the analytical model.

A detailed methodological protocol should be followed when selecting the studies and the data to be included in a meta-analysis. The results of a meta-analysis are only as valid as the studies comprised within the model. For example, if a meta-analysis is conducted on a group of case-control studies for which selection bias may have been an issue, producing a summary association from these studies may not be informative. On the other hand, a meta-analysis of well-conducted prospective studies may produce an accurate and valid summary relative risk and allow for the evaluation of patterns of associations across population sub-groups.

With the increasing number of published studies, more data are available to analyze using a meta-analysis technique. In turn, advanced meta-analytical methods are continually being incorporated.

A pooled analysis is a type of meta-analysis for which the individual level data are pooled together across study groups rather than the results data across studies. Simply put, a pooled analysis is a way of combining individuals across study centers to produce a larger study sample. This type of analytical methodology is optimum for calculating relative risk estimates. However, this approach may not be practical. For example, researchers from the individual study centers must be willing to share their data and cooperate with the study protocol. In addition, since the data are at the individual level, confidentiality may be a concern. The most comprehensive pooled analysis pertaining to nutritional epidemiology is the Harvard University Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project) [http://www.hsph.harvard.edu/poolingproject/about.html], which is an “international consortium of cohort studies with the goal of analyzing diet and cancer associations using standardized criteria across studies.” Their pooled analyses incorporate “individual data as opposed to a meta-analysis of the published literature.” To date, few pooling project studies pertaining to red meat and cancer have been published, and these only include breast cancer and kidney cancer. Of note, a pooling project analysis of meat and fat intake and colorectal cancer (no significant associations were reported for red meat, processed meat, or fat intake) was published as an abstract and presented at the American Association for Cancer Research 2004 annual conference but this analysis inexplicably was not published as a full manuscript (Cho & Smith-Warner 2004).

When interpreting findings from a meta-analysis, it is important to consider the studies that were included in the analytical model.
Section 2 — Epidemiology: Design, Methodology, and Applications

Forest Plot of a Meta-Analysis

- Statistical data (RRs and CIs) that are entered into the meta-analysis from each study.
- Horizontal bars represent the range of the confidence interval (CI).
- Circles represent the point estimates (RRs and ORs from each study).
- The relative weights represent how much statistical weight or influence that each study has on the summary association. Large studies with low standard error contribute more weight than small studies with high variability.
- Summary associations (SRRE) for all studies included in the meta-analysis model.
- 1.0 is the null value.
- Diamonds represent the summary relative risk estimate (SRRE). The horizontal tips of the diamonds represent the lower and upper bounds of the confidence interval.

### Table: MODEL STUDY NAME Rate Ratio Lower Limit Upper Limit Relative Weight Fixed Relative Weight Random

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Relative Weight Fixed</th>
<th>Relative Weight Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.00</td>
<td>0.64</td>
<td>1.55</td>
<td>20.44</td>
<td>19.80</td>
</tr>
<tr>
<td>B</td>
<td>0.83</td>
<td>0.53</td>
<td>1.29</td>
<td>19.92</td>
<td>19.49</td>
</tr>
<tr>
<td>C</td>
<td>1.07</td>
<td>0.58</td>
<td>1.97</td>
<td>10.54</td>
<td>12.59</td>
</tr>
<tr>
<td>D</td>
<td>1.89</td>
<td>1.14</td>
<td>3.14</td>
<td>15.28</td>
<td>16.42</td>
</tr>
<tr>
<td>E</td>
<td>0.70</td>
<td>0.31</td>
<td>1.57</td>
<td>6.08</td>
<td>8.12</td>
</tr>
<tr>
<td>F</td>
<td>1.20</td>
<td>0.82</td>
<td>1.75</td>
<td>27.74</td>
<td>23.59</td>
</tr>
<tr>
<td>Fixed</td>
<td>1.10</td>
<td>0.90</td>
<td>1.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>1.10</td>
<td>0.85</td>
<td>1.41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INTERPRETING RESULTS FROM EPIDEMIOLOGIC DATA

In an epidemiologic study, the association between a particular disease and dietary factor is measured using a relative risk (or odds ratio).

- If a relative risk is less than 1.0, the rate of disease is lower among high consumers, and the general interpretation is that there is an **inverse association** (i.e., negative association) between the dietary factor and the disease. If, for example, we were studying the association between fruit and vegetable intake and lung cancer, an inverse association would occur if the rate of lung cancer was lower among persons with high fruit and vegetable intake, compared to persons with low intake of fruits and vegetables.

- If a relative risk is equal or close to 1.0, the rate of disease is the same between the high and low consumers, and the general interpretation is that there is **no association** between the dietary factor and the disease.

- If a relative risk is greater than 1.0, the rate of the disease is higher among persons with a greater level of exposure, and the general interpretation is that there is a **positive association** between the factor and the disease. For example, a positive association would occur if the rate of colon cancer was higher among persons with a higher body mass index, compared to persons with a lower body mass index.

A relative risk is simply an estimate of the association between two factors that is measured from one study. It does not necessarily represent the true association between the disease and dietary factor, nor does it mean that there is a causal relationship between the two. The true association can be affected by numerous methodological and analytical factors, such as chance, bias, and/or confounding. These factors need to be considered and adequately accounted for prior to formalizing conclusions.

An observed association may simply be the result of a chance occurrence. Statistical methods are employed to test for this possibility and, if chance is an unlikely explanation, the relative risk is called ‘statistically significant’.

Confidence intervals (CI) are typically reported alongside each relative risk estimate to evaluate its statistical significance. A CI is a range of values for a relative risk that has a specified probability (e.g., 95%) of including the “true” relative risk. If the 95% CI does not include 1.0 (i.e., the null value representing no association), the probability of the association being due to chance alone is 5% or lower and the result is considered statistically significant. If, however, the 95% CI includes 1.0, then the probability that the association is due to chance alone is greater than 5% and the association is not considered statistically significant. For example, if a RR for high meat intake and pancreatic cancer is 1.9 (95% CI = 1.2-3.9), this would indicate a statistically significant positive association. The “best

### INFORMATION BOX 2.1
INTERPRETING RELATIVE RISKS

<table>
<thead>
<tr>
<th>Direction of Association</th>
<th>Comparison of disease rates between dietary intake groups (i.e., high intake vs. low intake)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR &lt; 1.0</td>
<td>Rate of disease is <em>lower</em> among high consumers compared with low consumers</td>
<td><strong>Inverse Association</strong></td>
</tr>
<tr>
<td>RR = 1.0</td>
<td>Rate of disease is <em>the same</em> between intake groups</td>
<td><strong>Null Association</strong></td>
</tr>
<tr>
<td>RR &gt; 1.0</td>
<td>Rate of disease is <em>higher</em> among high consumers compared with low consumers</td>
<td><strong>Positive Association</strong></td>
</tr>
</tbody>
</table>
A technical summary of the epidemiologic evidence

Section 2 — Epidemiology: Design, Methodology, and Applications

The "estimate" of the data is that persons with high levels of meat intake have a 90% greater risk of pancreatic cancer compared to persons with a low meat intake, although the increase in risk could plausibly be as low as 20%, or as high as 290%, or anywhere in between, based on the 95% CI.

A p-value is another way (and less preferred method) of considering the role of chance. A p-value tests the probability that the observed association is due to a chance finding, i.e., that there truly is no association between the two variables under consideration. Typically, the threshold for reporting a finding as statistically significant is a p-value of 0.05 or less.

BIAS AND CONFOUNDING

A confounder is an extraneous variable that may distort the association between a factor under study and the outcome of interest. By definition, a confounder (e.g., total energy intake) is independently associated with both the factor (e.g., red/processed meat) and the outcome (e.g., cancer). Therefore, it is of importance that the potential for confounding be eliminated or mitigated at either the design phase (through restriction, randomization, or matching) or the analytical phase (by statistical adjustment or stratification) of the study.

In epidemiologic parlance, bias is a systematic error that may result in an incorrect estimate of the association between an exposure and risk of disease. Although there are numerous types of biases, two of the most common types inherent to epidemiologic studies are selection bias and information bias. In addition, publication bias may affect quantitative reviews of the literature.

Selection bias arises when the exposure-disease association differs between those who participate in the study and those who are eligible to participate but do not. Selection bias can occur in either cohort or case-control studies, and can affect both the internal validity (are the measures of association unbiased?) and external validity (is the study population representative such that results can be generalized?) of a study. The probability of selection bias is theoretically reduced when participation levels are maximized. Furthermore, in case-control studies, it is particularly important that the control group is selected from the same study base as the case group. In this regard, data from hospital-based case-control studies should be interpreted carefully because the control group consists of other hospital patients, typically admitted for a select group of conditions, who may not be representative of the population which gave rise to the cases. Methods to minimize the potential impact of selection bias include clearly defining the study population, maximizing participation rates, identifying study participants without knowing their disease status, and including cases and controls who arise from the same population.

FIGURE 2.5
CONFOUNDING EXAMPLE

Obesity is independently associated with increasing the risk of colorectal cancer. If the highest consumers of red/processed meat are also obese, the association between red/processed meat and colorectal cancer may be distorted by the confounding effects of obesity if not fully controlled for in the analysis.
**Information Box 2.2**
**Common Types of Bias in Epidemiologic Studies**

<table>
<thead>
<tr>
<th>Selection Bias</th>
<th>Occurs when study participants are not representative of the target population upon which the conclusions are to be made</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias introduced by the differential selection of participants into the study</td>
<td></td>
</tr>
<tr>
<td>Differential drop-out of study participants during study follow-up (i.e., loss to follow-up)</td>
<td></td>
</tr>
<tr>
<td>Non-responders</td>
<td></td>
</tr>
<tr>
<td>Controls who choose to participate tend to be healthier than controls who are eligible but choose not to participate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Information Bias</th>
<th>Systematic error in the measurement of information on exposure or outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall bias: Occurs retrospectively when the ability to recall an exposure is not equal between the groups being compared</td>
<td></td>
</tr>
<tr>
<td>Interviewer bias: Investigator queries study respondents differently, such as probing</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publication Bias</th>
<th>Study findings are reported and published differentially, depending on the type and nature of the result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive associations have a tendency to be published in greater frequency than null associations, which may provide an artificial sense of consistency of direction across studies</td>
<td></td>
</tr>
</tbody>
</table>

*Information bias* is a systematic error in the measurement or ascertainment of exposure and/or outcome information. In case-control studies, dietary (and other) information is collected after the diagnosis of disease; thus, differential reporting of dietary intake between cases and controls may occur, and ultimately produce spurious associations. This is referred to as recall bias, which is a type of information bias. Because dietary data are collected before the onset of disease in prospective cohort studies, this particular type of information bias is considered to be negligible. Another type of bias to be cognizant of when interpreting a body of scientific literature is publication bias.

*Publication bias* occurs when findings from individual studies are differentially published. For example, studies that observe increased risks are more likely to be published (or the authors are more likely to report these data in their article) than studies that do not observe such associations.

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In epidemiologic parlance, bias is a systematic error that may result in an incorrect estimate of the association between an exposure and risk of disease.
ASSESSING FOOD INTAKE

Accurate measurement of food intake is paramount in studies of diet and cancer; thus, the interpretation of nutritional epidemiology studies is dependent upon the methods used to estimate dietary intake.

The food frequency questionnaire (FFQ) is a method for which participants are asked about the frequency of their food intake over a specified period of time. Some questionnaires may inquire about the amount of food consumed in addition to frequency of consumption. There are a few different variations of FFQs, but they are generally comparable at assessing diet and disease associations (Subar et al. 2001). The FFQ is the most commonly utilized dietary instrument to ascertain red/processed meat consumption across the epidemiologic literature.

Another method is dietary recall, in which an interviewer queries participants about the food they have consumed, often within a 24-hour period. The dietary recall method is used to describe actual intake; however, this method typically assesses a single day of intake, which is not representative of long-term intake and less frequently consumed foods are often missed (Willett 1998).

Participants can also keep track of the items that they consume for a period of time; this is known as the food diary or food record method. Weights and volumes of actual food consumed are recorded using measuring tools or cups. Diary data are commonly used as validation for food frequency questionnaires and have correlations that range from 0.25 to 0.75 indicating considerable variation in accuracy. As a result of these limitations in dietary assessment accuracy, researchers have suggested that relative risks lower than 1.8 may be beyond the statistical power of the study to validly detect a significant effect (Thompson et al. 2008).

A final method is the use of biochemical indicators to assess levels of nutrients in the body at a given point in time. Information Box 2.3 summarizes the different methods used to assess food intake.

The FFQ is the most commonly utilized dietary instrument to ascertain red/processed meat consumption across the epidemiologic literature.
# INFORMATION BOX 2.3
## ASSESSING FOOD INTAKE

<table>
<thead>
<tr>
<th>METHOD</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Food Frequency Questionnaire (FFQ)</strong></td>
<td>- Identifies usual food intake patterns</td>
<td>- Possible inaccuracies in:</td>
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<td></td>
<td>- Low respondent burden, self-administered</td>
<td>- Respondent memory of food consumption (differential recall)</td>
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<td></td>
<td>- Relatively inexpensive</td>
<td>- Estimation of portion size</td>
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<td></td>
<td>- May not be as sensitive to recent dietary changes</td>
<td>- Estimation of specific food constituents within a mixture</td>
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<td>- Relatively efficient in ascertaining information from a large study population</td>
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<td>- Generally effective at ranking individuals by frequency of intake</td>
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<tr>
<td><strong>Dietary Recall</strong></td>
<td>- Generally more accurate weights and volumes of food consumed</td>
<td>- Assesses a single day of intake which may not be representative of long-term intake</td>
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<td></td>
<td>- Can be administered at various intervals over time</td>
<td>- Less frequently consumed foods often missed</td>
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<td></td>
<td>- Can be administered to illiterate persons, thereby increasing eligible participants</td>
<td>- Typically requires a trained interviewer</td>
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<tr>
<td></td>
<td>- Typically efficient</td>
<td>- Can be expensive</td>
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<tr>
<td><strong>Food Diary/ Food Record</strong></td>
<td>- Measures intake and portion size over a period of time, usually three days to one week</td>
<td>- Respondents may inaccurately report intake</td>
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<td>- Accurate weights and volumes of food consumed; less reliance upon memory</td>
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<td>- High level of specificity (e.g., exact food names, brands, cooking methods)</td>
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<tr>
<td><strong>Biochemical Indicators</strong></td>
<td>- May be a more accurate and reliable indicator of actual intake</td>
<td>- Subject to within-participant variability</td>
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<td>- May have less error than other methods</td>
<td>- May only indicate short-term dietary intakes</td>
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<td>- May be used to more accurately assess micronutrient intake</td>
<td>- Biomarker may not be specific to a certain food or food group</td>
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<td>- May be used to validate self-reporting of food intake</td>
<td>- May be expensive</td>
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DIGESTIVE AND GASTROINTESTINAL CANCERS
A Technical Summary of the Epidemiologic Evidence

Colorectal Cancer
Stomach Cancer
Esophageal Cancer
Liver Cancer
Pancreatic Cancer
DIGESTIVE AND GASTROINTESTINAL CANCERS

A summary of epidemiologic studies of red meat or processed meat intake and colorectal cancer, stomach cancer, esophageal cancer, liver cancer, and pancreatic cancer.

COLORECTAL CANCER

The large intestine, or colon, is a muscular tube that is approximately five feet long. The colon absorbs water and nutrients from food and stores waste matter, which moves from the colon into the rectum. Cancer that forms in the tissues of the colon or rectum is referred to as colorectal cancer, although tumors in these locations may be viewed as distinct disease entities. The majority of colorectal cancers develop in a stepwise progression from normal epithelium (cellular tissue that covers organs) to adenomatous polyps (growths arising from the epithelial lining of the colon) to adenocarcinoma (cancer of glandular tissue) (Willett 2001). Although colorectal cancer carcinogenesis (process by which normal cells are transformed into cancer cells) is fairly well understood, relatively few factors have been established as causing colorectal cancer.

Colorectal cancer is the third most common cause of cancer among men and women in the United States, accounting for approximately 10% of all new cancer cases for each gender (Jemal et al. 2008). Internationally, age-standardized incidence rates of colorectal cancer are highest in industrialized nations and the disparity of rates between modernized countries and less developed countries is large (Parkin et al. 2002). The geographic variation in rates is thought to be partly attributable to lifestyle and environmental factors (Jacobs et al. 2007).

The specific causes of most colorectal cases are unknown; however some key clinical, genetic, and lifestyle characteristics have been associated with disease risk. Colorectal cancer is usually diagnosed among persons over age 50, and men are more likely to develop this malignancy than women. Individuals with a personal history of adenomatous polyps, a family history of colorectal cancer in a first-degree relative, and certain clinical conditions, such as inflammatory bowel disease, have an increased risk of colorectal cancer. Low physical activity, obesity, and high alcohol consumption (particularly among men) may increase the risk of colorectal cancer (WCRF/AICR 2007).

Because the colon and rectum are involved physiologically and anatomically in food digestion, absorption, and elimination, the role of diet as a contributing factor to colorectal cancer development has been examined in hundreds of scientific studies. However, there is controversy regarding the specific nutrients, individual foods, or food combinations
thought to contribute to colorectal cancer. Although results across most epidemiologic studies have been variable, high intake of garlic, milk, calcium, and dietary fiber may decrease the risk of colorectal cancer (Schottenfeld and Fraumeni 2006). Collectively, inverse associations between diets rich in vegetables and colorectal cancer have been observed in most epidemiologic studies; however, results are somewhat variable by study design (La Vecchia et al. 2001; Norat and Riboli 2002).

Results from epidemiologic studies of total meat or all meat types categorized together have been inconsistent, with inverse and positive associations observed. In a recent publication of the European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford) study, the authors reported that vegetarians had a statistically significant 39% increased rate of colorectal cancer compared with meat eaters (Key et al. 2009). The potential role that red meat and processed meat intake may play in colorectal carcinogenesis is equivocal. Although many researchers suggest that high intake of red/processed meat causes colorectal cancer, there is a lack of a clear scientific consensus.

In 2007, the World Cancer Research Fund (WCRF), in collaboration with the American Institute for Cancer Research (AICR), released a summary report entitled, “Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective.” This second report (the first was issued in 1997), evaluated the scientific evidence pertaining to numerous dietary factors and their relation with 17 different types of cancer. Twenty-two panelists formalized conclusions and recommendations based on the scientific literature that was assembled, synthesized, and disseminated by independent international working groups. Although the epidemiologic evidence across the consortium of peer-reviewed literature varies in terms of how red or processed meat is defined and analyzed, the WCRF/AICR panel concluded that consumption of red meat and/or processed meat is a convincing cause of colorectal cancer.

It was recommended that red meat consumption should be limited and processed meat be avoided. Specifically, WCRF/AICR recommends that persons who eat red meat should consume less than 500g (18 oz cooked) (700-750g raw) per week and very little (if any at all) should be processed. In this context, red meat is defined as beef, pork, lamb, and goat from domesticated animals, including that contained in processed food. Processed meat is defined as meat preserved by smoking, curing, or salting, or addition of chemical preservatives, including that contained in processed foods.

Despite their conclusions, it is unclear how WCRF/AICR arrived at their suggested quantitative intake recommendations based on the heterogeneity of the available data. Furthermore, the rationale for the designation of "convincing" has been questioned on several scientific and methodological grounds, including the inability to demonstrate associations between dietary factors and cancer with consistency over time (Boyle et al. 2008).
<table>
<thead>
<tr>
<th>AUTHOR AND YEAR</th>
<th>COHORT</th>
<th>RR AND 95% CI</th>
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<tr>
<td>Bostick 1994 (C) (W)</td>
<td>Iowa Women’s Health Study</td>
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<td>Brink 2005 (C)</td>
<td>Netherlands Cohort Study</td>
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<td>Brink 2005 (R)</td>
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<td>Chao 2005 (C)</td>
<td>Cancer Prevention Study II</td>
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<td>Chao 2005 (R)</td>
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<td>Chen 1998 (CRC) (M)</td>
<td>Physicians Health Study</td>
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<td>Chen 2003 (C)</td>
<td>China Cohort Study</td>
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<td>Cross 2007 (C)</td>
<td>NIH-AARP Diet and Health Study</td>
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<td>Cross 2007 (R)</td>
<td>NIH-AARP Diet and Health Study</td>
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<td>English 2004 (C)</td>
<td>Melbourne Collaborative Cohort Study</td>
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<td>English 2004 (R)</td>
<td>Melbourne Collaborative Cohort Study</td>
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<td>Flood 2003 (CRC) (W)</td>
<td>Breast Cancer Detection Demonstration Project</td>
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<td>Hsing 1998 (CRC) (M)</td>
<td>Lutheran Brotherhood Cohort Study</td>
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<td>Jarvinen 2001 (C)</td>
<td>Mobile Clinic Health Examination Survey</td>
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<td>Jarvinen 2001 (R)</td>
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<td>Kabat 2007 (C) (W)</td>
<td>Canadian National Breast Screening Survey</td>
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<td>Kabat 2007 (R) (W)</td>
<td>Canadian National Breast Screening Survey</td>
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<td>Kato 1997 (CRC) (W)</td>
<td>New York, Florida Cohort Study</td>
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<td>Khan 2004 (CRC) (M)</td>
<td>Japan Cohort Study</td>
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<td>Kojima 2004 (C) (M)</td>
<td>Japan Collaborative Cohort Study</td>
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<td>Japan Collaborative Cohort Study</td>
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<td>Kojima 2004 (R) (M)</td>
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<td>Kojima 2004 (R) (W)</td>
<td>Japan Collaborative Cohort Study</td>
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<tr>
<td>Larsson 2005 (CRC) (W)</td>
<td>Swedish Mammography Cohort Study</td>
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CRC: colorectal; C: colon; R: rectal; M: men; W: women
Most relative risks for the highest consumers of red meat or processed meat are in the positive direction, although few are statistically significant. Furthermore, most associations are relatively weak in magnitude (e.g., RRs < 1.40), most studies do not indicate a clear intake-response relationship, associations by anatomic tumor site (i.e., colon vs. rectum) are variable, and patterns of associations show a moderate discrepancy by gender. As with most epidemiologic studies of red/processed meat and cancer, intake metrics (i.e., units) vary across studies (e.g., grams per day, servings per week) as do the analytical cut-points used for comparison (e.g., 100g/day vs. 0g/day, 12 times/week vs. 3 times/week), thus, complicating the interpretation of results across studies.

Approximately 30 to 35 prospective studies have evaluated red or processed meat intake and colorectal cancer, of which, approximately 20 to 25 represent analyses of independent (non-overlapping) study populations. The majority of these studies have been conducted in the United States, Europe, and Japan. As mentioned, the units of dietary intake vary across studies, and the definitions and type(s) of red/processed meat groups or items vary as well. Several studies evaluated red meat with processed meat items included within the diet variable, while...
other studies reported single red meat items, such as beef or pork. Additionally, most studies of processed meat vary in terms of the definition of this variable, and the specific items comprised within this grouping. Postulated mechanisms implicating red meat as increasing the risk of colorectal cancer have not been consistently supported by the evidence. Furthermore, no meat-related factors, such as consumption of animal fat, cooking methods, exposure to heterocyclic amines, or heme iron intake have been established as being associated causally with the development of colorectal cancer. In a 2009 meta-analysis of animal fat intake and colorectal cancer, published in the *American Journal of Clinical Nutrition*, no statistically significant association was observed when data from cohort studies were analyzed (summary relative risk estimate = 1.04, 95% CI: 0.83-1.31) (Alexander et al. 2009).

Understanding possible relationships between meat consumption and colorectal cancer (or any cancer type for that matter) is complicated by methodological and analytical challenges. For example, a dietary pattern characterized by high consumption of red/processed meat and low fruit and vegetable intake has been associated positively with high body mass index, smoking, and alcohol intake, and has been associated inversely with physical activity, and socioeconomic status; in turn, these factors may confound or modify the association between red/processed meat intake and colorectal cancer. In addition, tumors arising in the proximal colon, distal colon, and rectum may have
variable pathologies, and consequently, dietary factors may influence cancer development differently according to anatomic site (Jacobs et al. 2007). Also, the location of colorectal tumor development may vary by gender and/or race (Alexander et al. 2007A; Jacobs et al. 2007), and whether there is a differential effect of red/processed meat intake and colorectal cancer among and between genders or ethnic groups remains uncertain.

In summary, associations from the majority of epidemiologic studies that examined the relation between red and processed meat consumption and colorectal cancer have been in the positive direction when men and women have been analyzed together, but overall, associations have been relatively weak in magnitude and not statistically significant. There are some apparent differences in the patterns of associations by gender; in fact, associations from some of the largest and most well-conducted cohort studies have been null or inverse among women. Therefore, consumption of red or processed meat does not appear to play a role in the development of colorectal cancer among women. Patterns of associations have been modestly stronger in magnitude among men; however, the variability in associations by gender has not been explained by biological or hormonal mechanisms.

Associations also vary by anatomic tumor site, with associations being stronger for rectal cancer than colon cancer. Variation of methodological and analytical characteristics, such as heterogeneity in meat definitions, dietary measurements used, analytical comparisons in terms of variability in intake cut-points, and the likelihood for residual confounding or bias complicates the interpretation of results across studies. Because of this methodological and analytical variability, the currently available epidemiologic evidence is not sufficient to support an independent association between red meat consumption or processed meat consumption and colorectal cancer. Additional research is necessary to further explore any potential associations among certain sub-groups, such as analyses for men and women stratified by tumor location.

...the currently available epidemiologic evidence is not sufficient to support an independent association between red meat consumption or processed meat consumption and colorectal cancer.
The incidence of stomach (or gastric) cancer has declined dramatically in western countries over the past 40 years. In the United States, stomach cancer accounts for only about 1.5% of all new cancer cases (Jemal et al. 2008). In contrast, stomach cancer is the fourth most common cancer diagnosed worldwide, accounting for over 10% of all cancer deaths (Nyren and Adami 2008). Internationally, incidence rates vary more than 10-fold, with lower rates occurring in North America, Western Europe, Australia and New Zealand, and the highest rates occurring in Japan and Korea (Parkin et al. 2002). Variability in rates of stomach cancer may be attributable to differences in diagnostic methods and disease reporting, socioeconomic conditions, infection with Helicobacter pylori (H. pylori), and availability of fruits and vegetables.

Considerable epidemiologic research has contributed to the identification of several risk factors for stomach cancer. A variety of demographic factors, such as age, gender, race, and socioeconomic status are established as strong risk factors for stomach cancer. Infection with H. pylori is associated with risk of gastric non-cardia cancers, but may not be associated with cardia tumors (Helicobacter and Cancer Collaborative Group 2001). Other factors that may be associated with developing stomach cancer include having a personal history of chronic gastritis or gastric reflux, prior gastric surgery, high intake of salt, salty foods, or sodium, cigarette smoking, and certain genetic/heritable syndromes. High intake of non-starchy vegetables, allium vegetables, and/or fruits may decrease the risk of stomach cancer.

The relation between consumption of red meat, or specific types of red meat, and stomach cancer has been analyzed in more than 40 analytic cohort and case-control studies, although cohort data are limited to fewer than 10 studies. Compared with other cancer sites, studies of red/processed meat and stomach cancer have been conducted on a wider variety of geographic regions, which further complicates interpretation of epidemiologic data. Approximately four cohort studies evaluated red meat as a dietary group (Gonzalez et al. 2006; Larsson et al. 2006A; Cross et al. 2007; Sauvaget et al. 2005), while a similar number of studies evaluated individual red meat items, such as liver, beef, or pork (Larsson et al. 2007; Tokui et al. 2005; Ngoan et al. 2002; McCullough et al. 2001).
In an analysis of the European Prospective Investigation into Cancer and Nutrition cohort (EPIC), a statistically significant 50% increased risk of stomach cancer was observed among persons in the high red meat intake category (Gonzalez et al. 2006). Associations for red meat consumption were stronger for non-cardia tumors (RR = 1.65) than cardia tumors (RR = 1.17). Non-significant associations of 1.05, 1.07, and 1.06 were reported among the highest consumers of red meat in analyses of the NIH-AARP cohort (Cross et al. 2007), the Swedish Mammography cohort (Larsson et al. 2006A), and the Japanese Life Span Study cohort (Sauvaget et al. 2005), respectively. Positive associations between red meat and stomach cancer have been reported across most of the case-control studies, but relatively few associations have been statistically significant.

Associations across cohort and case-control studies for individual red meat items (i.e., beef, pork, and liver) have been highly variable. Approximately 20 studies have evaluated beef intake in relation to stomach cancer; however, results are inconsistent as positive, null, and inverse associations are observed with similar frequency. Results for the examination of pork or liver consumption and stomach cancer have been reported in approximately 12 studies, but associations have been reported in both the positive and inverse directions.

The association between processed meat consumption and stomach cancer has been examined in several epidemiologic studies, although the definition and types of processed meats that were evaluated vary frequently from study to study. Processed meats comprise a heterogeneous array of meat categories, and typically contain nitrates or nitrates, and may contain N-nitroso compounds. In addition to N-nitroso compounds, processed meats may also contain high amounts of salt, which can act as an irritant to the gastric mucosa, leading to gastritis, a precursor lesion to stomach cancer. In the 2007 WCRF/AICR report on diet and cancer, it was concluded that the evidence for processed meat intake and stomach cancer was inconsistent and that heterogeneity of associations across studies was likely caused by the diversity of processed meat definitions.

Collectively, most studies that examined the relation between processed meat intake and stomach cancer have reported increased risks. In a meta-analysis of seven cohort studies, consumption of processed meats was associated non-significantly with a 24% increased risk of stomach cancer, and a statistically significant 63% increased risk was observed in the analysis of 12 case-control studies (Larsson et al. 2006B). This disparity in risk by study design suggests that differential recall of dietary factors between cases and controls may have contributed to the higher associations observed in the case-control studies. In addition, the case-control studies have greater variation in terms of processed meat definitions, analytical metrics, and geographic study location.

Meta-analysis of three to nine cohort and/or case-control studies of individual processed meat items indicated statistically increased risks of 37%, 39%, and 64% for bacon, sausage, and ham, respectively (Larsson et al. 2006B). In an analysis of data from the EPIC cohort, a statistically significant 62% increased risk of stomach cancer was reported among persons in the high processed meat intake category (Gonzalez et al. 2006). Based on findings from additional analyses, the authors reported that increased risks were limited to persons who were positive for H. pylori infection (Gonzalez et al. 2006). In contrast to findings from several other studies, no association (RR = 1.0, 95% CI: 0.78-1.30) for stomach cancer was found among persons with the highest intake levels of processed meat in an analysis of the NIH-AARP cohort (Cross et al. 2007). Moreover, inverse associations were observed in the 2nd, 3rd, and 4th quintiles of processed meat intake.

Although several positive associations between red meat intake and stomach cancer have been reported in case-control studies, associations across three of four cohort studies were close to the null value and not statistically significant. Furthermore, no consistent patterns of associations are evident across the epidemiologic literature for individual red meat items, such as beef, pork, or liver.

When interpreting findings for processed meat intake and stomach cancer, several important caveats should be considered when assessing risk, such as: the variability of processed meat exposure definitions, the potential for confounding or effect modification including the potential influence of H. pylori infection on the reported associations, the fact that most associations have been modest in magnitude and findings across studies have been relatively inconsistent, the differences in patterns of associations by study design, and the potential for recall and/or selection bias. Because of these potential limitations, the available epidemiologic evidence is insufficient to support an independent positive association between processed meat intake and stomach cancer.
ESOPHAGEAL CANCER

The esophagus is a muscular tube that is responsible for moving food from the mouth and pharynx down to the stomach through peristalsis. Cancer that arises in the esophagus is called esophageal cancer. Esophageal cancer is diagnosed mainly in two histological types, squamous cell carcinoma and adenocarcinoma. More men are diagnosed with esophageal cancer than women (ACS 2008), and this malignancy is the 13th most commonly diagnosed cancer among men (Jemal et al. 2008). The incidence of esophageal cancer is three times higher among African-Americans than Caucasians (Adami et al. 2002). The diagnosis of esophageal cancer usually occurs later in life with a median age at diagnosis of 69 years (SEER 2009).

Risk factors for esophageal cancer may vary by histologic type. Smoking and heavy alcohol use are associated with increased risk of squamous cell esophageal cancer, and low fruit and vegetable intake are associated with increased risk of both squamous cell carcinoma of the esophagus and esophageal adenocarcinoma (Adami et al. 2002; Engel et al. 2003). Risk factors associated with esophageal adenocarcinoma include obesity, gastroesophageal reflux disease (GERD), and Barrett’s esophagus (Adami et al. 2002; Engel et al. 2003). Approximately 89% of squamous cell carcinoma may be attributed to smoking, alcohol use, and low fruit and vegetable consumption, and approximately 79% of esophageal adenocarcinoma cases can be attributed to ever smoking, obesity, reflux disease, and low fruit and vegetable consumption (Engel et al. 2003).

In their 2007 report on diet and cancer, the WCRF/AICR concluded there was limited evidence to suggest red or processed meat causes esophageal cancer. Few cohort studies specifically evaluated the influence of red meat on this cancer outcome; however, all reported positive associations. In a large cohort study of persons aged 50-71 years, Cross et al. (2007) reported weak to modest elevated risks of unspecified esophageal cancer across all quintiles of intake, although they reported the greatest risk in the second quintile of intake (RR = 1.56, 95% CI: 1.14-2.14). As described by Gonzalez et al. (2006) in an analysis of the European Prospective Investigation into Cancer and Nutrition cohort (EPIC), an elevated but non-significant risk of esophageal adenocarcinoma among persons in the second and third tertiles of red meat consumption was observed (RRs = 1.73 and 1.67, respectively). A prospective study of more than 10,000 Norwegian men evaluated unspecified esophageal cancer across beef and pork consumption categories and found there was a marginally significant increase in risk among people who consumed beef six or more times per month (RR = 2.8, 95% CI: 1.0-7.6), but the association among pork consumers was not significant (RR = 1.5, 95% 0.5-4.2) (Kjaerheim et al. 1998).

The association between red meat consumption and esophageal cancer has been evaluated in approximately 12 case-control studies. The majority of these studies reported positive but non-significant associations between red meat consumption and esophageal adenocarcinoma, esophageal squamous cell carcinoma, or unspecified esophageal cancer. Results from the case-control studies that specifically evaluated beef consumption were highly variable, with one study...
reporting a statistically significant 56% decrease in risk among persons in the highest tertile of consumption (De Stefani et al. 1999) and another study reporting more than a four-fold increase in risk (OR = 4.6, 95% CI: 2.1-10.3) among people in the highest beef consumption category (Rolon et al. 1995). These disparate results may be attributed to the inherent weaknesses of the case-control design, differences in the histological type of esophageal cancer, or variation in the confounders that were accounted for across the studies, such as smoking and/or alcohol intake. The majority of the case-control studies that specifically evaluated pork consumption found no association with esophageal cancer.

The association between processed meat and esophageal cancer has not been studied as extensively as red meat. To date, only a few cohort studies (Chyou et al. 1995; Gonzalez et al. 2006; Kjaerheim et al. 1998) have been conducted on this topic. Chyou et al. (1995) combined oropharyngeal, laryngeal and esophageal cancer into one endpoint and found a non-significant positive association with intake of ham, bacon and sausage (RR = 1.24, 95% CI: 0.73-2.1). A strong association between unspecific processed meat consumption and esophageal adenocarcinoma among people in the highest exposure category (RR = 3.54, 95% CI: 1.57-7.99) was reported in the EPIC cohort (Gonzalez et al. 2006). In a sample of more than 10,000 Norwegian men, Kjaerheim et al. (1998) reported positive associations among consumers of processed meat and bacon; however the association was only significant (marginally) among people who consumed bacon six or more times per month (RR = 2.2, 95% CI: 1.0-5.0).

Fewer than 10 case-control studies have evaluated the association between processed meat and esophageal cancer. Of these, only one study in Switzerland found a statistically significant increase in risk in the highest intake category of processed meat (OR = 4.68, 95% CI: 2.54-8.62), although the association was imprecise (Levi et al. 2004).

Collectively, most studies of red meat or processed meat and esophageal cancer have reported positive associations, although the evidence is limited to relatively few cohort studies. Additional well-conducted cohort studies are necessary to clarify any potential associations. Because esophageal carcinogenesis is influenced by some common factors (e.g., smoking, alcohol), results from epidemiologic studies should be viewed with consideration of control for potential confounders.
Since the liver is a key organ of the digestive system, there has been interest in assessing the influence of diet on liver cancer; however, very few studies have assessed the potential role of meat intake. In fact, most studies that addressed liver cancer reported on individual meat items (e.g., pork) rather than red meat or processed meat food categories. In the only U.S. prospective cohort study of red/processed meat and liver cancer, Cross et al. (2007) reported a statistically significant 61% increased risk among the highest consumers of red meat, but observed only a 9% non-significant risk among the highest consumers of processed meat.

Conflicting results for red meat were reported in a previous case-control study conducted in Italy, as a non-significant 20% decreased risk of liver cancer was observed in the high intake category (Tavani et al. 2000). No significant associations have been reported for either pork intake or beef intake in case-control studies or in a Japanese cohort study for which univariate (i.e., un-adjusted) analyses were conducted (Kurozawa et al. 2004; Lam et al. 1982).

Despite the positive association reported for red meat in a single cohort study, other studies have not observed consistent evidence of an increased risk of liver cancer among high consumers of beef, pork, or processed meat. In summary, the available epidemiologic evidence does not appear to support an independent association between red meat or processed meat consumption and liver cancer. Additional prospective studies may facilitate a clearer understanding of any potential associations.
PANCREATIC CANCER

The pancreas is an organ in the digestive and endocrine systems that aids in digestion by secreting digestive enzymes, and produces several important hormones, including insulin. Cancer that forms in the tissues of the pancreas is referred to as pancreatic cancer. Pancreatic cancer is a rare disease relative to other cancers, being the 11th most commonly diagnosed cancer in the United States (Jemal et al. 2008; Ries et al. 2007). Due to the high case-fatality rates, however, pancreatic cancer is the 4th leading cause of cancer death among men and women in the United States (Jemal et al. 2008). For all stages combined, the 5-year relative survival rate for pancreatic cancer is only 5%, making it one of the most lethal human cancers (Li et al. 2004). Approximately 90% of all new pancreatic cases are diagnosed among persons over the age of 50 and rates are slightly higher among men than women (Anderson et al. 1996). Rates in the United States are highest among African-American men and lowest among Asian/Pacific Islander females (Ries et al. 2007).

The causes of most pancreatic cancer cases are unknown; however, some lifestyle, medical, and genetic factors have been identified as being associated with increasing the risk of this disease. Among the most consistent risk factors reported across the epidemiologic literature is cigarette smoking, which may account for 25-29% of incident pancreatic cancer cases (Anderson et al. 1996). Other factors associated with pancreatic cancer risk include chronic pancreatitis, family history of pancreatic cancer in a first-degree relative, certain genetic/heritable syndromes, obesity, and having a personal history of diabetes.

Since the pancreas is involved in digestion and absorption, several studies have examined the role that dietary factors may play in pancreatic carcinogenesis. The association between consumption of red/processed meat and risk of pancreatic cancer has not been examined as extensively as other organ sites involved in food digestion and absorption, such as the stomach and colon, because of the rarity of the outcome. Pancreatic cancer is a relatively uncommon outcome with a high case-fatality rate, making it difficult to accurately and precisely assess its relation with dietary factors, such as meat intake.

To date, fewer than 10 cohort studies have analyzed either red meat or processed meat intake and pancreatic cancer. Overall, no patterns or trends between red meat intake and pancreatic cancer are evident across the epidemiologic literature, and most associations from cohort studies generally range between 0.9 and 1.4. In the two largest cohort studies published to date, associations between red meat and pancreatic cancer were modestly variable, both between studies and by gender. Coughlin et al. (2000) reported a non-significant 10% increased risk of pancreatic cancer among men, and a marginally significant 10% decreased risk among women. In an analysis of approximately 500,000 persons, Cross et al. (2007) reported a statistically significant 43% increased risk of pancreatic cancer among men, but a non-significant decreased risk of 8% was observed among women. Similarly variable results were seen in other cohort studies, such as an evaluation of the Nurses’ Health Study, which observed a 13% non-significant decreased risk of pancreatic cancer among women in the highest red meat intake category (Michaud et al. 2003). In contrast, Larsson et al. (2006C) reported non-significant 33% increased risk of pancreatic cancer among Swedish women in the highest red meat intake category. In a cohort study conducted in Hawaii and Los Angeles, Nothlings et al. (2005) reported a significant 45% increased risk of pancreatic cancer among the highest red meat consumers. In a cohort study of Finnish men, a non-significant 5% decreased risk of pancreatic cancer was reported among men in the highest category of red meat intake (Stolzenberg-Solomon et al. 2002).
A greater variation in exposure definitions are evident for processed meat than red meat, as approximately five cohort studies evaluated “processed meat” as an intake variable while approximately three cohort studies evaluated ham and/or sausage. Relatively similar to the associations for red meat, Cross et al. (2007) reported a statistically significant 31% increased risk among men in the highest processed meat intake category, and a non-significant 14% reduced risk among women in the same category. Nothlings et al. (2005) reported a significant positive association between processed meat and pancreatic cancer (RR = 1.68, 95% CI: 1.35-2.07), although processed poultry was included in their definition of processed meat. A non-significant RR of 1.28 was observed in an analysis of the Nurses’ Health Study (Michaud et al. 2003), while no associations between processed meat and pancreatic cancer were reported in Finnish (Stolzenberg-Solomon et al. 2002) or Swedish studies (Larsson et al. 2006C). Most associations for cohort analyses of ham, sausage, and/or bacon have been null or inverse (Isaksson et al. 2002; Khan et al. 2004; Michaud et al. 2003).

Associations between red meat and processed meat intake and pancreatic cancer have been inconsistent across studies. While increased risks have been reported in some cohort studies, other cohort studies have observed no risks or decreased risks, particularly among women and for specific meat items. Findings from case-control studies have been mixed, and while most odds ratios have been in the positive direction, intake definitions have been variable and recall and/or selection bias may be an issue due to the high case-fatality rate. Because pancreatic cancer is a rare disease with low survival, cohort studies must be very large in order to accrue a sufficient number of cases for analysis. Thus, only a modest number of cohort studies have been published to date, and the consortium of epidemiologic evidence for pancreatic cancer is somewhat limited. Collectively, the available epidemiologic evidence is not supportive of an independent association between red meat or processed meat intake and pancreatic cancer.

Pancreatic cancer is a relatively uncommon outcome with a high case-fatality rate, making it difficult to accurately and precisely assess its relation with dietary factors, such as meat intake.
BREAST CANCER
**Section 4 — Breast Cancer**

*Diet and breast cancer has been investigated extensively, although the overall evidence surrounding the potential relation between dietary factors and breast cancer carcinogenesis has resulted in the identification of very few risk factors.*

Breast cancer is a malignancy that forms in the tissues of the breast. Both women and men may develop breast cancer; however, this malignancy is rare among men. Thus, this section focuses on female breast cancer.

A woman’s breast is composed of lobules (glands that produce milk), ducts, fatty and connective tissue, blood vessels, and lymph vessels. Most breast tumors begin in the ducts, although some tumors begin in the lobules and other breast tissues. Breast cancer is the most common malignancy among U.S. women, accounting for approximately 180,000 cases, or one-quarter of all female cancers, in 2008 (Jemal et al. 2008). This malignancy is the second leading cause of cancer mortality among women (ACS 2008). Internationally, age-standardized incidence rates of breast cancer are generally higher in North America, Europe, Australia and New Zealand, as compared to Africa, South America, and Asia (Parkin et al. 2005), with rates varying five-fold among different populations worldwide (Key et al. 2001; Lacey et al. 2002). Migrant studies, which evaluate changes in rates of breast cancer in women who move from countries with low breast cancer rates to those with high rates (or vice versa), have shown that rates become similar to those of the population in the new country, suggesting that environmental and lifestyle factors may partially explain some of this observed variation (Tominaga 1985; Ziegler et al. 1993).

Several important factors associated with increasing the risk of breast cancer have been identified, including having a first-degree family history of breast cancer, inherited genetic mutations, such as those in tumor suppressor genes BRCA1 and BRCA2, endogenous and exogenous hormone exposures, and clinico-pathological traits (Key et al. 2001; Collaborative Group 1997). High body mass index (BMI) has been associated with decreasing the risk of premenopausal breast cancer; conversely, high BMI has been associated with increased risks of postmenopausal breast cancer (Hankinson and Hunter 2002). Physical inactivity has been associated with increased risk of breast cancer, with more consistent results in studies of postmenopausal women than premenopausal women (van den Brandt et al. 2000).
Diet and breast cancer has been investigated extensively, although the overall evidence surrounding the potential relation between dietary factors and breast cancer carcinogenesis has resulted in the identification of very few risk factors. The most consistent dietary factor associated with increasing the risk of breast cancer is alcohol consumption (Key et al. 2001; Hankinson and Hunter 2002). Vitamin D intake may be associated with reducing the risk of breast cancer but more research is needed (Shin et al. 2002). No remarkable findings have been observed among the more well-studied foods and nutrients, such as fruits and vegetables, carbohydrates, fiber, or dietary fat.

In an analysis of the Pooling Project of Prospective Studies of Diet and Cancer, in which a standardized exposure and analytical methodology was implemented and primary data from eight large prospective cohort studies were analyzed, no significant associations between total fat or specific types of dietary fat were observed (Smith-Warner et al. 2001). In the recent Women’s Health Initiative Randomized Controlled Dietary Modification Trial in which the effects of a low-fat diet intervention among postmenopausal aged women were evaluated, a non-significant reduction of breast cancer risk (HR = 0.91, 95% CI: 0.83-1.01) among women in the intervention group was observed (Prentice et al. 2006). There is no consistent epidemiologic evidence indicating that consumption of fat from animal sources, a dietary correlate of red and processed meat intake, is associated with an increased risk of breast cancer (Lowe et al. 2009).

There is no consistent epidemiologic evidence indicating that consumption of fat from animal sources, a dietary correlate of red and processed meat intake, is associated with an increased risk of breast cancer.
As with most dietary factors, the association between meat consumption and breast cancer has been equivocal (Morimoto et al. 2009). The relationship between red meat or processed meat consumption and female breast cancer has been evaluated in numerous studies. Some U.S. and international ecologic studies have reported positive correlations between rates of breast cancer and per capita intake of meat (Armstrong and Doll 1975; Gray et al. 1979; Hems 1970); however, data at the individual level were not analyzed in these studies. Indeed, analytical epidemiologic studies that assessed individual dietary intake have not corroborated these findings, as associations across cohort and case-control studies have been variable.

In a 1993 meta-analysis of case-control and cohort studies, Boyd et al. reported a statistically significant positive association (summary estimate = 1.54, 95% CI: 1.31-1.82) between red meat intake and breast cancer. However, most recent cohort studies have not consistently observed positive associations between red meat or processed meat consumption and breast cancer. In fact, slight inverse associations for consumption of red meat (summary RR for each 100g/day increment = 0.98, 95% CI: 0.93-1.04) or processed meat (summary RR for each 10g/day increment = 0.98, 95% CI: 0.96-1.00) were reported in the comprehensive analysis of the Pooling Project of Prospective Studies of Diet and Cancer (Missmer et al. 2002). The Pooling Project analysis included data from eight cohorts in North America and Western Europe, and more than 7,000 women diagnosed with invasive breast cancer were analyzed.

### FIGURE 4.2
**PROSPECTIVE STUDIES OF RED MEAT INTAKE AND BREAST CANCER**

<table>
<thead>
<tr>
<th>AUTHOR AND YEAR</th>
<th>COHORT</th>
<th>RR AND 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Byrne 1996</td>
<td>NHANES / NHEFS</td>
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<td>Cho 2006</td>
<td>Nurses’ Health Study II</td>
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<tr>
<td>Cross 2007</td>
<td>NIH-AARP Diet and Health Study</td>
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<tr>
<td>Egeberg 2008</td>
<td>Diet, Cancer and Health Cohort Study</td>
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<td>Ferrucci 2009</td>
<td>PLCO Screening Trial</td>
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<td>Larsson 2009</td>
<td>Swedish Mammography Cohort Study</td>
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<tr>
<td>Missmer 2002</td>
<td>Pooling Project of Prospective Studies*</td>
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<tr>
<td>Pala 2009</td>
<td>EPIC Cohort Study</td>
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<tr>
<td>Shannon 2005</td>
<td>Shanghai Breast Self-Exam Trial</td>
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<tr>
<td>Taylor 2007</td>
<td>UK Women’s Cohort Study</td>
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<tr>
<td>van der Hel 2004</td>
<td>Monitoring Project on CVD Risk Factors</td>
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*Includes data pooled from eight cohorts
Since the Pooling Project publication, numerous analyses between meat intake and breast cancer have been conducted across large-scale prospective cohorts. In a 2007 publication of the National Institutes of Health (NIH)-AARP (formerly the American Association for Retired Persons) Diet and Health Study, in which approximately 200,000 women (and almost 6,000 breast cancer cases) were analyzed, no association between the highest intake quintiles for red meat (RR = 1.02, 95% CI: 0.93-1.12) or processed meat (RR = 1.03, 95% CI: 0.94-1.12) were found (Cross et al. 2007). Furthermore, no intake-response patterns for red or processed meat were observed. In a sub-group analysis of postmenopausal women from the NIH-AARP cohort, no associations were reported for red meat (RR = 1.05, 95% CI: 0.93-1.18) or processed meat (RR = 1.00, 95% CI: 0.90-1.12) and breast cancer (Kabat et al. 2009). Furthermore, cooking methods, meat doneness, or dietary mutagens were not associated with increasing the risk of breast cancer among postmenopausal women in this study.

In an analysis of the EPIC cohort, non-significant relative risks close to the null value were reported for red meat intake, and marginally significant, albeit weakly elevated relative risks were observed for processed meat consumption (Pala et al. 2009). No association between red or processed meat and breast cancer was observed in an analysis of the Swedish Mammography Cohort (Larsson et al. 2009). Non-significant weak-to-modest positive associations for red meat and processed meat were reported in Dutch (van der Hel et al. 2004) and Chinese (Shannon et al. 2005) cohort studies. In an analysis of the UK Women’s Cohort Study, Taylor et al. (2007) observed statistically significant positive associations among the highest consumers of red meat (RR = 1.41, 95% CI: 1.11-1.81) and processed meat (RR = 1.39, 95% CI: 1.09-1.78). Twelve percent and 59% statistically significant increased risks of breast cancer were reported for each increment of 50g/day for red meat and processed meat, respectively. In the Diet, Cancer and Health Cohort Study, significant positive associations between red meat (RR = 1.65, 95% CI: 1.09-2.50) and processed meat (RR = 1.59, 95% CI: 1.02-2.47) and breast cancer were reported (Egeberg et al. 2008).
Overall, more positive associations are observed among the case-control studies than are inverse associations, but no clear or consistent evidence regarding patterns of increased risks of breast cancer are apparent. Collectively, the case-control studies are more variable than the more rigorous cohort studies in regards to the geographic location of the study, collection of dietary information, type of red/processed meat variables that are analyzed, analytical comparisons, reporting of results data, range of associations, and degree of statistical adjustment.

Because female breast tissue may have increased mammary susceptibility to potential carcinogens during adolescence and early life (Linos and Willett 2007), there is increased interest in how and/or whether diet early in life may contribute to the development of adult cancer. In a case-control study nested within the Nurses’ Health Study I and II cohorts, the mothers of study participants were asked about their daughters’ perinatal and early childhood dietary habits (Michels et al. 2006). Pre-school intake of ground beef was associated with a non-significant 44% increased risk of adult breast cancer, while consumption of meat (as a main dish or as a sandwich or mixed dish) or hot dogs was associated inversely, albeit non-significantly, with subsequent breast cancer risk. In another study (Frazier et al. 2004), participants were asked to complete a questionnaire regarding diet during high school, a life period that may be affected by micronutrient intake during adolescent growth, and a non-significant positive association between the highest intake of red meat and subsequent risk of breast cancer was reported (RR = 1.22, 95% CI: 0.82-1.82), but no trend based on incremental intake was observed (p-value for trend = 0.17). Results from these studies may be subject to poor recall because study participants (or mothers of cases) reported dietary habits that likely occurred 30 to 40 or more years prior to information ascertainment and breast cancer diagnosis.

Another area of increasing scientific interest is the potential relation between dietary factors and breast cancer risk according to tumor hormone receptor status. Although breast tumors differ clinically and biologically by hormone receptor status (Cho et al. 2006), there is little evidence regarding the potential association between red/processed meat and hormone-receptor-status cancer. In an analysis of the Nurses’ Health Study II, a non-significant positive association between the highest intake quintile of red meat and total breast cancer was found (RR = 1.27, 95% CI: 0.96-1.67) (Cho et al. 2006). However, the positive association observed in this study was restricted to women with hormone receptor-positive cancer (ER+: estrogen receptor/PR+: progesterone receptor) (RR = 1.97, 95% CI: 1.35-2.88).
A non-significant inverse association was reported among women with hormone receptor-negative cancer (ER-/PR-) (RR = 0.89, 95% CI: 0.43-1.84). Positive associations were also reported for pork (as a main dish), hamburger, bacon, hot dogs, and other processed meats (e.g., sausage, salami, bologna) among women with ER+/PR+ cancer, while inverse associations for these same meat groups were observed among women with ER-/PR- cancer. The authors suggest that mutagenic by-products from cooked meat (e.g., heterocyclic amines), exogenous hormone residues, heme iron, or fat intake may affect breast cancer through hormone receptors, although additional prospective cohort studies are necessary to confirm or refute these hypotheses. Ferrucci et al. (2009) reported a significant positive association between red meat intake and breast cancer (RR = 1.59, 95% CI: 1.03-2.48) among women with ER+/PR+ cancer. Larsson et al. (2009), however, did not observe a significant positive association among women with ER+/PR+ cancer (RR = 1.10, 95% CI: 0.90-1.34).

The relationship between red meat and processed meat consumption and breast cancer has been the focus of several epidemiologic investigations, although the consortium of scientific evidence is not supportive of an independent association. Of note, breast cancer is a heterogeneous disease with differing etiologies; thus, the potential role that diet may play in the development of breast cancer among subgroups is of great public health importance. Menopausal status does not appear to appreciably modify the risk between red or processed meat intake and breast cancer. Recent studies have suggested that meat consumption may affect breast cancer risk through hormone receptor status, and that diet early in life may influence adult breast cancer; however, epidemiologic data for these hypotheses are limited and additional prospective studies are needed before conclusions can be drawn. In summary, on the basis of the available scientific evidence, primarily from prospective cohort studies and nested case-control studies, red meat or processed meat intake does not appear to be associated with breast cancer risk.
GENITOURINARY SYSTEM CANCERS
Epidemiologic studies of red meat or processed meat intake and cancer

- Prostate cancer
- Kidney cancer
- Bladder cancer
- Testicular and penile cancers
GENITOURINARY SYSTEM CANCERS

A summary of epidemiologic studies of red meat or processed meat intake and prostate cancer, kidney cancer, bladder cancer, and testicular and penile cancers.

SECTION 5 — GENITOURINARY SYSTEM CANCERS

PROSTATE CANCER

Cancer that forms in the tissues of the prostate, which is a walnut-sized reproductive gland in men located below the bladder, is referred to as prostate cancer. This gland contains cells that produce seminal fluid, which helps transport semen. Prostate cancer is the most commonly diagnosed malignancy in U.S. men, accounting for approximately one-quarter of all male cancers. This malignancy is responsible for approximately 10% of all cancer deaths among U.S. men. Worldwide, this disease is the second most common cancer in men, with only lung cancer accounting for more cancer diagnoses per year (Parkin et al. 2005).

Epidemiologic studies have identified some important risk factors for prostate cancer; however, the etiology is largely unknown. The risk of prostate cancer increases with increasing age, particularly after age 65. African-American men are more likely to be diagnosed than Caucasian men (Ries et al. 2007; ACS 2008). Persons with a positive family history of prostate cancer in a first-degree relative may be more likely to develop this malignancy.

The relationships between behavioral and dietary factors and prostate cancer have been examined in numerous epidemiologic studies; however, the role of these factors in potentially increasing or decreasing the risk of prostate cancer has not been clearly defined. In the 2007 WCRF/AICR report on diet and cancer, it was concluded that foods containing lycopene or selenium, and supplementation with selenium probably decrease the risk of prostate cancer, and that diets high in calcium probably increase the risk. In the same report, the association between processed meat intake and prostate cancer was judged to be suggestive, although it was acknowledged that data were limited.

More than a dozen cohort studies evaluated red meat consumption and prostate cancer, and results from these studies are not indicative of an increased risk of this malignancy (Alexander et al. 2009). In a 2007 analysis of approximately 300,000 men, Cross et al. (2007) reported no association (RR = 1.01, 95% CI: 0.96-1.07) with prostate cancer among men in the...
FIGURE 5.1
PROSPECTIVE STUDIES OF RED MEAT INTAKE AND PROSTATE CANCER

<table>
<thead>
<tr>
<th>AUTHOR AND YEAR</th>
<th>COHORT</th>
<th>RR AND 95% CI</th>
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<tr>
<td>Allen 2004</td>
<td>Hiroshima, Nagasaki-Japan Cohort Study</td>
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<td>Chan 2000</td>
<td>Alpha-Tocopherol Beta-Carotene Cancer Prevention Study</td>
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<td>Cross 2005</td>
<td>PLCO Cancer Screening Trial</td>
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<td>Cross 2007</td>
<td>NIH-AARP Diet and Health Study</td>
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<td>Gann 1994</td>
<td>Physicians Health Study</td>
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<td>Hsing 1990</td>
<td>Lutheran Brotherhood Cohort Study</td>
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<td>Koutros 2008</td>
<td>Agricultural Health Study</td>
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<td>Le Marchand 1994</td>
<td>Hawaii Cohort Study</td>
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<td>Michaud 2001</td>
<td>Health Professionals Follow-Up Study</td>
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<tr>
<td>Mills 1989</td>
<td>Seventh Day Adventist Cohort Study</td>
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<td>Park 2007</td>
<td>Multiethnic Cohort Study</td>
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<tr>
<td>Rodriguez 2006 (African-Americans)</td>
<td>Cancer Prevention Study II</td>
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<tr>
<td>Rodriguez 2006 (Caucasians)</td>
<td>Cancer Prevention Study II</td>
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<td>Rohrmann 2007</td>
<td>CLUE II</td>
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<td>Schuurman 1999</td>
<td>Netherlands Cohort Study</td>
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Rodriguez et al. (2006) evaluated meat intake and prostate cancer in the American Cancer Society’s (ACS) Cancer Prevention Study II (CPS II) Nutrition Cohort. A total of 5,028 and 85 incident prostate cancer cases were identified among 64,897 Caucasian men and 693 African-American men in the cohort, respectively. No association for the highest intake of red meat was found among Caucasian men (RR = 1.0, 95% CI: 0.9-1.1) and a non-significant positive association was observed among African-American men (RR = 1.7, 95% CI: 0.8-3.9), although data were considerably more sparse among African-American men.

In an analysis of data from the Agricultural Health Study, Koutros et al. (2008) reported no significant associations between consumption of red meat, beef steaks, hamburgers, pork chops/ham steaks, or bacon/sausages and total or advanced prostate cancer.
Results from case-control studies of red meat consumption and prostate cancer are variable; while some associations have been positive, some have been null and inverse. No association for red meat was found in a recently published Canadian case-control study of 1,800 prostate cancer cases (OR for highest intake category = 1.0, 95% CI: 0.8-1.3) (Hu et al. 2008).

Results for processed meat from the cohort studies are more heterogeneous than for red meat, and relatively more positive associations have been reported. However, null associations have been observed in the three largest cohort investigations (Cross et al. 2007; Park et al. 2007; Rodriquez et al. 2006). As with red meat intake, case-control studies of processed meat intake and prostate cancer have produced highly variable results. In the aforementioned Canadian case-control study (Hu et al. 2008), a statistically significant positive association between the highest intake category of processed meat and prostate cancer was reported (OR = 1.6, 95% CI: 1.2-2.2).

In a 2008 publication of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Crowe et al. (2008) evaluated the relationship between dietary fat intake, including fat from red and processed meat sources, and prostate cancer among approximately 150,000 men. The authors reported decreased risks of total (RR = 0.95, 95% CI: 0.83-1.07), low-grade (RR = 0.97, 95% CI: 0.79-1.18), and high-grade (RR = 0.84, 95% CI: 0.64-1.10) prostate cancer for each per-unit increase in fat from red and processed meat sources.

The available epidemiologic evidence is not supportive of an independent association between consumption of red meat and prostate cancer, as findings from the largest and most well conducted prospective cohort studies have been null. Regarding processed meat, the majority of studies have indicated an increased risk of prostate cancer. However, findings across studies have been variable and associations in some of the largest cohort studies have not been supportive of an independent relation between processed meat intake and prostate cancer (Alexander et al. 2009).
KIDNEY CANCER

The kidneys are the organs responsible for filtering waste products from the blood. Cancer that forms in the tissues of the kidney is referred to as kidney cancer or renal cancer. Cancers of the kidney and renal pelvis (referred to as kidney cancer henceforth) are the seventh most common cancers among U.S. men and the ninth most common cancers among U.S. women (Jemal et al. 2008). Kidney cancer accounts for approximately 3.8% of all new cancer cases and 2.3% of all cancer deaths among U.S. men and women (Jemal et al. 2008). In the United States and Europe, this malignancy is almost twice as common in men as women and the average age at the time of diagnosis is in the early 60s (McLaughlin et al. 2006; Parkin et al. 2002). An increasing trend in incidence and mortality rates have been observed for kidney cancer over the past 30 years, with the largest increases found among African-American men and African-American women (Ries et al. 2008).

Epidemiologic investigations have identified some important risk factors for kidney cancer. Cigarette smoking and obesity have been established as causal factors for increasing the risk of kidney cancer; each of these factors may be responsible for 20% to 30% of all new cases (McLaughlin et al. 2006; Lindblad et al. 2002; Calle and Kaaks 2004).

In 1997, WCRF/AICR concluded that red meat consumption is a possible cause of kidney cancer; however, in their 2007 report they judged that the available epidemiologic evidence was limited-suggestive and no conclusions were drawn. Faramawi et al. published a meta-analysis in the same year (2007), and the authors concluded that red meat and processed meat were positively associated with kidney cancer risk. Their analysis, however, was based on data from only six case-control studies of red meat and four case-control studies of processed meat.

In a recent publication of red meat and processed meat based on an evaluation of the Pooling Project of Prospective Studies of Diet and Cancer, Lee et al. (2008) analyzed primary data for 530,469 women and 244,483 men from 13 international cohorts for which 1,478 kidney cancer cases were observed. Lee and colleagues found no association between the highest level of red meat consumption and kidney cancer, and they observed a weakly elevated non-significant association for processed meat intake. Moreover, no trend (p = 0.93) of kidney cancer risk based on increasing red meat intake categories was reported, and no association for each increase of two

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FIGURE 5.3
PROSPECTIVE AND CASE-CONTROL STUDIES OF RED MEAT INTAKE AND KIDNEY CANCER

<table>
<thead>
<tr>
<th>AUTHOR AND YEAR</th>
<th>COHORT</th>
<th>RR AND 95% CI</th>
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<tr>
<td>Bravi 2007</td>
<td>Case-Control Study</td>
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<tr>
<td>Cross 2007</td>
<td>NIH-AARP Diet and Health Study</td>
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<tr>
<td>De Stefani 1998</td>
<td>Case-Control Study</td>
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<td>Fraser 1990</td>
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<td>Hsu 2007</td>
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<td>Hu 2003</td>
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<tr>
<td>Lee 2008</td>
<td>Pooling Project of Prospective Studies*</td>
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<tr>
<td>MaClure and Willett 1990</td>
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<td>Washio 2005</td>
<td>Japan Collaborative Cohort Study</td>
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<td>Walk 1996</td>
<td>Multi-Center Case-Control Study</td>
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*Includes data pooled from 13 cohorts
servings of red meat per week (RR = 1.00, 95% CI: 0.95-1.06) was observed. The authors reported a 1% increased risk of kidney cancer for every two-serving increase of processed meat consumption per week, but this association was not statistically significant. Alexander and Cushing (2009) conducted a comprehensive quantitative assessment evaluating the association between red meat and processed meat intake and kidney cancer, based on all available epidemiologic data. Specifically, data reported in the Pooling Project publication were combined with data from independent cohort and case-control studies using a meta-analysis design. The summary association for all studies that reported results for red meat was 1.12 (95% CI: 0.98-1.29; p-value for heterogeneity = 0.015), and the summary association based on data from prospective cohorts was 1.02 (95% CI: 0.91-1.15).

Five studies were identified that simultaneously adjusted for smoking, body mass index, and total energy intake. The summary association based on the analysis of these studies was 1.02 (95% CI: 0.91-1.15). No significant association was observed in the meta-analysis of processed meat consumption (summary relative risk = 1.07, 95% CI: 0.94-1.23), although a significant association was observed when only data from cohort studies were analyzed (summary relative risk = 1.19, 95% CI: 1.03-1.37). As with red meat, the summary association was attenuated among the five studies that controlled for the potential confounding influence of smoking, body mass index, and total energy intake (summary relative risk = 1.05, 95% CI: 0.86-1.29).

Epidemiologic studies have elucidated some key factors responsible for increasing the risk of kidney carcinogenesis; however, consumption of meat is not one of the accountable factors. Collectively, results from epidemiologic cohort and case-control studies of red meat and processed meat are inconsistent, while many associations are in the positive direction, several studies observed decreased risks of kidney cancer. Although the summary associations based on the meta-analysis were positive, all were weak in magnitude, most were not statistically significant, and associations were close to the null value among studies that adjusted for smoking, body mass index, and total energy intake (Alexander and Cushing 2009). Furthermore, no consistent patterns or trends of increased risks with increasing levels of red or processed meat intake are reported in the individual studies. In summary, the epidemiologic evidence, based on a substantial number of studies, is not supportive of an independent relationship between red meat or processed meat consumption and kidney cancer.

**FIGURE 5.4**
PROSPECTIVE AND CASE-CONTROL STUDIES OF PROCESSED MEAT INTAKE AND KIDNEY CANCER

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<td>Hsu 2007</td>
<td>Case-Control Study</td>
<td></td>
</tr>
<tr>
<td>Hu 2003</td>
<td>Case-Control Study</td>
<td></td>
</tr>
<tr>
<td>Lee 2008</td>
<td>Pooling Project of Prospective Studies*</td>
<td></td>
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<tr>
<td>MaClure and Willett 1990</td>
<td>Case-Control Study</td>
<td></td>
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<tr>
<td>Washio 2005</td>
<td>Japan Collaborative Cohort Study</td>
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<tr>
<td>Wolk 1996</td>
<td>Multi-Center Case-Control Study</td>
<td></td>
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<tr>
<td>Yuan 1998</td>
<td>Case-Control Study</td>
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</tbody>
</table>

*Includes data pooled from 13 cohorts
Some key cohort studies have evaluated the relationship between meat consumption and bladder cancer. In a 2009 publication of a Swedish cohort study of women, Larsson et al. observed no associations between red meat or processed meat intake and bladder cancer. The authors concluded that their results do not support the hypothesis that red/processed meat is associated with developing bladder cancer. In a U.S. cohort, Cross et al. (2007) reported weakly elevated but non-significant associations between red and processed meat intake and cancer of the bladder. In addition, the authors observed no significant trends of increased risk with increased levels of consumption. In a combined analysis of the Health Professionals Follow-Up Study (HPFS) and the Nurses’ Health Study (NHS), non-significant inverse associations were reported for red meat, hamburger, and hot dogs, no association was reported for processed meat, and a statistically significant positive association was observed for the highest intake level of bacon (Michaud et al. 2006).

**FIGURE 5.5**
**RECENT PROSPECTIVE STUDIES OF RED AND PROCESSED MEAT INTAKE AND BLADDER CANCER**

<table>
<thead>
<tr>
<th>AUTHOR AND YEAR</th>
<th>COHORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross 2007 (Processed Meat)</td>
<td>NIH-AARP Diet and Health Study</td>
</tr>
<tr>
<td>Cross 2007 (Red Meat)</td>
<td>NIH-AARP Diet and Health Study</td>
</tr>
<tr>
<td>Larsson 2008 (Processed Meat)</td>
<td>Swedish Mammography Cohort Study</td>
</tr>
<tr>
<td>Larsson 2008 (Red Meat)</td>
<td>Swedish Mammography Cohort Study</td>
</tr>
<tr>
<td>Michaud 2006 (Processed Meat) (M)</td>
<td>Health Professionals Follow-Up Study</td>
</tr>
<tr>
<td>Michaud 2006 (Red Meat) (M)</td>
<td>Health Professionals Follow-Up Study</td>
</tr>
<tr>
<td>Michaud 2006 (Processed Meat) (W)</td>
<td>Nurses’ Health Study</td>
</tr>
<tr>
<td>Michaud 2006 (Red Meat) (W)</td>
<td>Nurses’ Health Study</td>
</tr>
</tbody>
</table>

M: men; W: women
Associations from case-control studies have been somewhat inconsistent. A marginally significant 30% increased risk was reported for red meat and a significant 60% increased risk was reported for processed meat in a Canadian case-control study (Hu et al. 2008). Tavani et al. (2000) observed a significant 60% increased risk among the highest consumers of red meat in a study conducted in Italy. In contrast, Wakai et al. (2004) observed non-significant decreased risks for beef, pork, ham and sausage, and Castelao et al. (2004) reported non-significant inverse associations for the highest intake levels of processed meat and preformed nitrosamine. In a recently published case-control study conducted in Spain, a non-significant odds ratio of 0.8 was reported for red meat intake and a non-significant odds ratio of 1.2 was reported for processed meat intake (Garcia-Closas et al. 2007).

Some large prospective cohort studies and several case-control studies of red meat and processed meat intake and bladder cancer have been published, facilitating a comprehensive assessment of the epidemiologic literature. Results from cohort studies have been generally null, with non-significant associations at or near 1.0, and some relative risks in the positive and inverse directions. Findings from case-control studies have been more variable, with positive as well as inverse associations being reported. In summary, the available epidemiologic evidence does not support an independent association between intake of red meat or processed meat and the development of bladder cancer.

Results from cohort studies have been generally null, with non-significant associations at or near 1.0, and some relative risks in the positive and inverse directions.
Section 5 — Genitourinary System Cancers

Testicular and Penile Cancers

The testicles (i.e., testes), are male reproductive glands that produce sperm and the hormone testosterone. Young and middle-aged men are at greatest risk for developing testicular cancer, although this malignancy is rare. The primary risk factor for testicular cancer is a condition called cryptorchidism, or undescended testes. Penile cancer, although very rare in the United States and Europe, is more common in certain locations of South America and Africa (ACS 2008). Circumcision shortly after birth can decrease the risk of developing penile cancer, while HIV infection or infection with the human papillomavirus (HPV) may increase risk.

No dietary factors have been established as contributing to the risk of testicular or penile cancer. In a recent case-control study conducted in Canada, Hu et al. (2008) reported that the highest consumers of processed meat had a statistically significant 50% increased risk of testicular cancer. Red meat was not associated with cancer of the testes in this study. In summary, the available epidemiologic data are limited regarding testicular and penile cancer, and the scientific community has not implicated meat consumption as being involved in the development of these malignancies.
GYNECOLOGIC CANCERS
EPIDEMIOLOGIC STUDIES OF RED MEAT OR PROCESSED MEAT INTAKE AND CANCER

- OVARIAN CANCER
- ENDOMETRIAL CANCER
- CERVICAL AND VAGINAL CANCERS
GYNECOLOGIC CANCERS

A summary of epidemiologic studies of red meat or processed meat intake and ovarian cancer, endometrial cancer, and cervical and vaginal cancers.

OVARIAN CANCER

The ovaries are female reproductive organs that store and release the egg that is needed for conception. Ovaries also regulate the menstruation cycle through the production of estrogen and progesterone. Ovarian cancer has the highest fatality-to-case ratio of any gynecological malignancy.

Since this malignancy has nonspecific symptoms, the majority of women are diagnosed when the disease has already become metastatic, resulting in a poor prognosis. The consequence of a late diagnosis enhances the need for prevention; however, the causes of ovarian cancer are largely unknown. It has been suggested that meat consumption increases the risk of ovarian cancer as a result of exposure to endogenous hormones (Thomas et al. 1999), but there is limited epidemiological evidence related to diet due to the low incidence of this disease. In fact, in the WCRF/AICR report on diet and cancer, it was concluded that there is limited information to confirm an association between any dietary factors and ovarian cancer (WCRF/AICR 2007).

Since ovarian cancer has nonspecific symptoms, the majority of women are diagnosed when the disease has already become metastatic, resulting in a poor prognosis.
To date, there are approximately eight cohort studies that evaluated the association between meat consumption and ovarian cancer. Of these, three studies specifically reported results for red meat, three studies included both red and processed meats, one study focused solely on fried meat, and one study did not specify the type of meat that was included in their analysis. All of these studies showed a slight increase in risk of ovarian cancer; however, with the exception of fried meats, the results were not statistically significant (Schulz et al. 2007).

On the contrary, significant associations between red meat consumption and ovarian cancer have been found in some case-control studies. In general, most case-control studies that evaluated red or processed meat consumption and ovarian cancer outcomes, reported associations ranging from 1.2 to 1.6 for red meat and 1.0 to 1.2 for processed meats.

Collectively, the available epidemiologic evidence surrounding red meat and processed meat consumption does not appear to support an independent association with ovarian cancer. This conclusion is based largely on findings from prospective cohort studies for which non-significant associations were observed.
ENDOMETRIAL CANCER

The endometrium is the lining on the inside of the uterus. During pregnancy, the endometrium forms the placenta that nourishes the fetus. When a woman is not pregnant, the endometrium sheds during menstruation. Endometrial cancer is the most common gynecological malignancy in the United States (Bandera et al. 2007). There is substantial evidence to suggest a strong association between hormone levels and the risk of endometrial cancer. Therefore, factors that increase circulating hormone levels, such as obesity and exposure to unopposed estrogens, are known to be associated with endometrial cancer (Ganmaa et al. 2005).

It has been postulated that a diet high in meat may increase the risk of endometrial cancer; however, few nutritional epidemiologic studies have evaluated endometrial cancer as an endpoint (Bandera et al. 2007). In their 2007 report, the WCRF/AICR concluded there was limited evidence to suggest that red or processed meat consumption causes endometrial cancer. Only three cohort studies have evaluated the association between red meat intake and endometrial cancer, with no evidence of increased risk. In the NIH-AARP cohort study, Cross et al. (2007) reported a statistically significant inverse trend across all red meat consumption groups, with the strongest protective effect observed in the highest quintile of consumption (RR = 0.75, 95% CI: 0.62-0.91). In the Canadian National Breast Screening Study, which includes more than 31,000 women aged 40-59 years, a non-significant 14% decrease in risk among women in the highest meat consumption category was reported (Kabat et al. 2008). In the Women’s Health Study, which included 23,000 postmenopausal women, a non-significant 10% increase in risk of endometrial cancer among women in the highest tertile of red meat consumption was observed (Zheng et al. 1995).

Several case-control studies have evaluated red meat and endometrial cancer, and results from these studies have been summarized in a meta-analysis (Bandera et al. 2007). The results of the meta-analysis, based on data from seven studies, indicated a significant 51% increased risk of endometrial cancer per 100g/day of red meat consumption (Meta OR = 1.51, 95% CI: 1.19-1.93).

Data on processed meat and endometrial cancer are limited. Two cohort studies have evaluated the association between processed meat consumption and endometrial cancer. Cross et al. (2007) found no association between consumption of processed meat and risk of endometrial cancer. In the Canadian National Breast Screening Study, processed meat was analyzed together with fish intake, and a significant 50% increased risk was observed among women in the highest tertile of consumption compared with women in the lowest tertile of consumption (Zheng et al. 1995). Only three case-control studies have evaluated processed meat intake and endometrial cancer risk, with inconsistent results.

Although some case-control studies have indicated positive associations between red meat consumption and endometrial cancer, data from prospective cohort studies have been conflicting. Additional large-scale cohort studies are required to clarify any potential associations between meat consumption and endometrial cancer. As it stands, the available epidemiologic evidence does not support an independent association between red meat or processed meat intake and endometrial carcinogenesis.
CERVICAL AND VAGINAL CANCER

Cancers arising in the cervix and vagina are known to be strongly associated with human papillomavirus (HPV) and exposure to diethylstilbestrol (DES), respectively. As a result, nutritional epidemiology studies of these cancer outcomes are conducted infrequently. In the aforementioned cohort study by Cross et al. (2007), no association was found for red meat intake and cervical cancer, although a non-significant 72% increased risk was observed among the highest consumers of processed meat and there was a statistically significant trend across exposure categories. Interpretation of the potential association between red meat or processed meat intake and cervical or vaginal cancer is limited by sparse data. The available epidemiologic evidence does not indicate a statistically significant positive effect.
LUNG CANCER
Cancer of the lung is the most commonly diagnosed cancer in the United States, accounting for an estimated 15% of all cancer diagnoses in 2008, which is second only to prostate and breast cancer for men and women, respectively (ACS 2008). In addition, lung cancer is the most common cause of cancer death with a five year survival rate of approximately 15% for all stages combined (ACS 2008).

Lung cancer is cancer that forms in the tissue of the lung. The lungs are responsible for the exchange of gases in the air with the circulatory system.

The rate of lung cancer increases with increasing age; however, a recent decline in the incidence among older age groups appears to correspond with the declining rates of tobacco use (Adami et al. 2002; Schottenfeld and Fraumeni 1996). Worldwide, this malignancy is at least two times more common among men than women, although the incidence among women in the United States has increased due to a higher prevalence of tobacco use (Jemal et al. 2008; Schottenfeld and Fraumeni 1996). Tobacco smoking is the strongest and most established risk factor for lung cancer, contributing to approximately 87% of lung cancer deaths in the United States (ACS 2008). Risk of lung cancer increases with duration and quantity of tobacco smoking, and cessation of smoking results in a decrease in cancer risk over time (Adami et al. 2002; Jemal et al. 2008).

Some occupational and environmental factors, such as radon, secondhand smoke, certain metals, and air pollution, have been associated with increasing the risk of lung cancer (Adami et al. 2002). A variety of food groups, individual food items, and specific micronutrients have been evaluated with respect to lung cancer risk in numerous epidemiologic studies and experimental trials. Collectively, associations for most factors have been equivocal, although high-dose supplementation with beta-carotene likely increases the risk of lung cancer and high intake of fruits or foods containing carotenoids may decrease risk (WCRF/AICR 2007).
Although lung cancer is the most commonly diagnosed cancer in the United States, the epidemiologic cohort data for meat intake is relatively sparse. Indeed, in the 2007 WCRF/AICR report on diet and cancer, it was stated that the evidence surrounding red/processed meat intake and lung cancer was limited and inconsistent. In a large prospective cohort study, Cross et al. (2007) reported a statistically significant 20% increased risk of lung cancer among the highest consumers of red meat (RR = 1.20, 95% CI: 1.10-1.31). In an analysis of lung cancer mortality using data from the 1987 National Health Interview Survey, a marginally significant positive association was reported for a broad category of red meats (RR = 1.6, 95% CI: 1.0-2.6), and positive associations of 1.6, 1.3, and 2.0 were observed for pork, beef (e.g., roasts and steak), and ground beef (e.g., hamburgers, meatloaf), respectively (Breslow et al. 2000). Non-significant associations of 1.1 and 1.3 for a variable labeled “meat (except chicken)” were reported among men and women, respectively, in a Japanese cohort study (Khan et al. 2004).

The association between red meat and lung cancer has been evaluated in approximately 12 case-control studies, and although the results have been variable, most associations are positive. In the most recent case-control study, Lam et al. (2009) analyzed approximately 2,000 lung cancer cases who were recruited from 13 hospitals in Italy. A statistically significant positive association was observed among the highest consumers of red meat (OR = 1.8, 95% CI: 1.5-2.2). When analyzed by histologic subtype, significant positive associations were restricted to adenocarcinomas and squamous cell carcinomas, but not small cell lung cancer.

Associations between processed meat intake and lung cancer have been more heterogeneous than results for red meat consumption. Cross et al. (2007) reported a statistically significant 16% increased risk of lung cancer among persons in the highest processed meat intake category (RR = 1.16, 95% CI: 1.06-1.26). In contrast, Breslow et al. (2000) observed an inverse association between the highest quartile of processed meat intake and lung cancer mortality (OR = 0.8, 95% CI: 0.5-1.4). The authors also reported non-significant relative risks of 0.8, 0.9, 1.0, and 1.2 for the highest intake categories of hot dogs, ham/lunch meats, sausage, and bacon respectively. Conflicting associations for ham/sausage intake were reported in two Japanese cohort studies: Ozasa et al. (2001) observed a statistically significant inverse association among men (RR = 0.72, 95% CI: 0.52-0.99) and a significant positive association among women (RR = 1.79, 95% CI: 1.07-3.01), and Khan et al. (2004) reported a non-significant positive association among men (RR = 1.1, 95% CI: 0.5-2.3) and a non-significant inverse association among women (RR = 0.4, 95% CI: 0.1-3.1). In a cohort of Norwegian men and women, five or more “main meals with meat” were associated with a non-significant 10% decreased risk of lung cancer, but specific meat categories (i.e., red or processed) were not analyzed (Veierod et al. 1997). In the same study, intake of five or more frankfurters per month was associated with a marginally significant two-fold risk of lung cancer.
## FIGURE 7.1

**PROSPECTIVE STUDIES OF RED AND PROCESSED MEAT INTAKE AND LUNG CANCER**

<table>
<thead>
<tr>
<th>AUTHOR AND YEAR</th>
<th>COHORT</th>
<th>COMPARISON*</th>
<th>RR AND 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross 2007</td>
<td>NIH-AARP Diet and Health Study</td>
<td>Red Meat</td>
<td></td>
</tr>
<tr>
<td>Breslow 2000</td>
<td>National Health Interview Survey</td>
<td>Red Meat</td>
<td></td>
</tr>
<tr>
<td>Khan 2004 (M)</td>
<td>Japan Cohort Study</td>
<td>Meat (except chicken)</td>
<td></td>
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<tr>
<td>Khan 2004 (W)</td>
<td>Japan Cohort Study</td>
<td>Meat (except chicken)</td>
<td></td>
</tr>
<tr>
<td>Cross 2007</td>
<td>NIH-AARP Diet and Health Study</td>
<td>Processed Meat</td>
<td></td>
</tr>
<tr>
<td>Breslow 2000</td>
<td>National Health Interview Survey</td>
<td>Processed Meat</td>
<td></td>
</tr>
<tr>
<td>Ozasa 2001 (M)</td>
<td>Japan Collaborative Cohort Study</td>
<td>Ham/Sausage</td>
<td></td>
</tr>
<tr>
<td>Ozasa 2001 (W)</td>
<td>Japan Collaborative Cohort Study</td>
<td>Ham/Sausage</td>
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</tr>
<tr>
<td>Khan 2004 (M)</td>
<td>Japan Cohort Study</td>
<td>Ham/Sausage</td>
<td></td>
</tr>
<tr>
<td>Khan 2004 (W)</td>
<td>Japan Cohort Study</td>
<td>Ham/Sausage</td>
<td></td>
</tr>
</tbody>
</table>

*Comparisons based on high vs. low intake
M: men; W: women

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### COMPARISON

- **Study Details:**
  - **Cohort:** NIH-AARP Diet and Health Study, National Health Interview Survey, Japan Cohort Study.
  - **Meat Types:** Red Meat, Processed Meat.
  - **Comparisons:** Beef (steaks and roasts), Ground Beef (burgers/meatloaf), Pork (chops and roasts), Meat (except chicken), Bacon, Sausage, Hot Dogs, Ham/Lunch Meat, Ham/Sausage.

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**Note:**

- Figure 7.1 illustrates the prospective studies of red and processed meat intake and lung cancer. The data is sourced from various cohort studies, focusing on the intake of different meat types and their associations with lung cancer risk. The RR and 95% CI values are depicted graphically, indicating varying levels of risk across different studies.

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**Legend:**

- RR: Relative Risk
- CI: Confidence Interval

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**Source:**

Similar to the cohort studies, findings for processed meat and individual processed meat items have been inconsistent across the case-control studies. For example, Lam et al. (2009) reported a statistically significant positive association among persons in the highest processed meat intake category (OR = 1.7, 95% CI: 1.4-2.1) in a case-control study conducted in Italy, while De Stefani et al. (2002) reported an inverse association (OR = 0.83, 95% CI: 0.55-1.26) for processed meat in a study conducted in Uruguay.

When interpreting results between dietary factors and lung cancer, a central focus should be on the adequacy of adjustment and/or control for smoking history. Indeed, in the aforementioned evaluation by Cross et al. (2007), detailed control for smoking history did not attenuate their results but the authors indicated that residual confounding remains a potential issue because smoking is such a strong risk factor. Smokers generally have less healthy diets, are more sedentary, and may be leaner than non-smokers; thus, interpretation of the nutritional epidemiology literature with respect to lung cancer (and other smoking-related malignancies for that matter) should consider the potential confounding influence of smoking status.

Postulated mechanisms for which meat intake may be associated with lung carcinogenesis include exposure to meat mutagens, such as heterocyclic amines and polycyclic aromatic hydrocarbons produced by high temperature cooking, intake of dietary heme iron, and endogenous formation of N-nitroso compounds (Lam et al. 2009). However, none of these factors have been established as contributing to an increased risk of lung cancer among consumers of red or processed meat. Lam et al. (2009) reported positive associations with intakes of the meat mutagens PhIP, MelIQx, and Bap derived from high cooking temperatures. Sinha et al. (2000) reported a positive association for MelIQx but not for DiMeIQx or PhIP. Findings for meat mutagens should be interpreted with some reservation as these chemicals are commonly quantified based on indirect estimates.

It remains unclear whether confounding and/or residual confounding by smoking status, or low fruit and vegetable (to a lesser extent) consumption may have contributed to the observed positive associations across the epidemiologic literature. In addition, cooking practices, particularly for red meat, that result in the production of heterocyclic amines or polycyclic aromatic hydrocarbons may contribute to the pattern of positive associations. More prospective cohort studies are needed to clarify any potential associations between red meat or processed meat consumption and lung cancer, independent of the effects of smoking, low intake of fruits and vegetables, and cooking practices.
LYMPHOHEMATOPOIETIC CANCERS
EPIDEMIOLOGIC STUDIES OF RED MEAT OR PROCESSED MEAT INTAKE AND CANCER

NON-HODGKIN LYMPHOMA
HODGKIN LYMPHOMA
MULTIPLE MYELOMA
LEUKEMIA
Cancers of the lymphohematopoietic system include the heterogeneous group of lymphomas, leukemias, and multiple myelomas. Collectively, it is estimated that this group of cancers is the sixth most common type worldwide (Jemal et al. 2008).

**NON-HODGKIN LYMPHOMA**

The non-Hodgkin lymphomas (NHL) are a heterogeneous group of malignancies arising from lymphoid tissue, with varied clinical and biological features (Alexander et al. 2007B). Because of this heterogeneity, NHL is divided into B-cell and T-cell neoplasms based on histologic characteristics, especially lymphocyte developmental stage, and are classified further according to clinical features. Incidence rates of NHL increased during the 1970s and 1980s, but generally stabilized during the 1990s. NHL is currently the fifth most commonly diagnosed cancer among men and women in the United States (Jemal et al. 2008). To date, little is known about the etiology of NHL, as either a general class of malignancies or specific histologic types. Family history of NHL or other hematolymphoproliferative cancers and personal history of any one of several autoimmune disorders are associated with increased risk of NHL, but are not likely to account for a large proportion of cases (Alexander et al. 2007B). Infectious diseases, such as HIV/AIDS, human herpesvirus 8, and Epstein-Barr appear to be associated with differing types of NHL, such as some B-cell lymphomas (Alexander et al. 2007B).

In an analysis of more than 1,500 NHL cases, Cross et al. (2007) observed no effect of red or processed meat intake on risk of NHL. Similarly, Ward et al. (1994) found no significant difference in risk between the highest and lowest categories of processed meat intake (OR for processed meats among women = 1.2, 95% CI: 0.7–2.1; among men = 0.6, 95% CI: 0.4–1.1).
In a Japanese case-control study, no association between beef consumption and NHL was reported (OR = 0.99, 95% CI: 0.69–1.43) (Matsuo et al. 2001), while in Italian (Tavani et al. 2000) and Canadian (Hu et al. 2008) case-control studies, non-significant positive associations of 1.1 and 1.2 were reported for intake of red meat and processed meat. Zhang et al. (1999) reported a significant positive association between intake of beef, pork, or lamb as a main dish and NHL risk (at least once per day vs. < 1 per week) (RR = 2.2, 95% CI: 1.1–4.4), although the excess risk appeared confined to red meat that was broiled or barbecued rather than cooked by other methods (e.g., roasting, pan-frying, boiling, stewing). In contrast, Cross et al. (2006) reported a non-significant 33% decreased risk of NHL among the highest consumers of barbequed red meat.

Although somewhat limited, the available epidemiologic evidence is not supportive of an independent association between red or processed meat intake and NHL. Additional research is necessary to explore any potential associations among specific histologic types of this malignancy.

**HODGKIN LYMPHOMA**

Hodgkin lymphoma is a rare malignancy, accounting for less than 10,000 cases in the United States per annum (Jemal et al. 2008). Although relatively little is known about the specific causes of Hodgkin lymphoma, diet does not appear to influence risk of disease. Epidemiologic data for Hodgkin lymphoma and red or processed meat consumption are limited. Tavani et al. (2000) reported a non-significant positive association between high red meat intake and Hodgkin lymphoma in a case-control study conducted in Italy (OR = 1.6, 95% CI: 0.9–2.9). Prospective cohort studies are needed to evaluate red/processed meat intake and Hodgkin lymphoma.
LYMPHOHEMATOPOIETIC CANCERS

In a U.S. case-control study, inverse associations for red and processed meat were observed among Caucasians (OR for red meat = 0.8, OR for processed meat = 0.7), while positive (OR = 1.3) and null (OR = 1.0) associations were reported for red meat and processed meat, respectively, among African-Americans (Brown et al. 2001). Tavani et al. (2000) reported a non-significant association between the highest category of red meat intake and multiple myeloma in an Italian case-control study (OR = 1.4, 95% CI: 0.9-2.2).

The scientific evidence for red/processed meat and multiple myeloma is limited to few studies, and collectively, the epidemiologic data do not appear to support an independent association between red meat or processed meat consumption and this malignancy.

MULTIPLE MYELOMA

Multiple myeloma is a malignancy of plasma cells, resulting in an overproduction of light and heavy chain monoclonal immunoglobulins (Alexander et al. 2007C). Multiple myeloma is a relatively uncommon cancer, accounting for fewer than 20,000 cases annually (Jemal et al. 2008). The specific causes of this malignancy are largely unknown, with no established lifestyle, occupational, or environmental factors. African-Americans are twice as likely to be diagnosed with multiple myeloma than Caucasians, and men are more likely to develop this cancer than women. Persons with a positive family history of lymphohematopoietic cancer and those with a pre-cursor condition called monoclonal gammopathy of undetermined significance are at an increased risk of multiple myeloma (Alexander et al. 2007C).

Dietary risk factors for multiple myeloma have been studied infrequently, and no consistent associations have emerged from the literature. In the largest cohort evaluation of meat intake and multiple myeloma, no association was reported for the highest intake category of red meat (RR = 1.03, 95% CI: 0.77-1.39), but a modest association was observed for processed meat (RR = 1.30, 95% CI: 0.98-1.71) (Cross et al. 2007). In a U.S. case-control study, inverse associations for red and processed meat were observed among Caucasians (OR for red meat = 0.8, OR for processed meat = 0.7), while positive (OR = 1.3) and null (OR = 1.0) associations were reported for red meat and processed meat, respectively, among African-Americans (Brown et al. 2001). Tavani et al. (2000) reported a non-significant association between the highest category of red meat intake and multiple myeloma in an Italian case-control study (OR = 1.4, 95% CI: 0.9-2.2).

The scientific evidence for red/processed meat and multiple myeloma is limited to few studies, and collectively, the epidemiologic data do not appear to support an independent association between red meat or processed meat consumption and this malignancy.

Dietary risk factors for multiple myeloma have been studied infrequently, and no consistent associations have emerged from the literature.
LEUKEMIA

The leukemias comprise a diverse group of acute, chronic myelogeneous, and lymphocytic malignancies that originate in various cells of the hematopoietic system (Petridou et al. 2008). The incidence rates of leukemia by age groups vary according to malignancy type. Leukemia, primarily acute lymphoid leukemia, is the most common form of malignancy among children (Petridou et al. 2008). Other types of leukemia, such as chronic lymphocytic leukemia, commonly occur among the elderly. Although a few risk factors have been identified as contributing to certain types of leukemia, no dietary factors have been identified as playing a significant role in leukemogenesis.

In a large prospective cohort study, red meat intake and processed meat intake were associated with non-significant decreased risks (range 9%-20%) of leukemia in all non-referent quintiles of consumption (Cross et al. 2007). In a Canadian case-control study, all non-referent quartiles were 1.0 for red meat and 1.6 for processed meat (Hu et al. 2008). Consumption of cured meat/fish was associated positively with childhood leukemia (OR = 1.74, 95% CI: 1.15-2.64), but this result was modified markedly by vegetable and bean-curd intake (Liu et al. 2009).

The epidemiologic evidence for red/processed meat consumption and leukemia is limited, and the available data do not indicate an increased risk. Additional studies are necessary to adequately evaluate meat intake and specific types of adult and child leukemia.
OTHER CANCERS
HEAD AND NECK CANCERS

ENDOCRINE CANCERS
THYROID CANCER

SKIN CANCER

BRAIN AND CENTRAL NERVOUS SYSTEM CANCERS
OTHER CANCERS

A summary of epidemiologic studies of red meat or processed meat intake and head and neck cancers, endocrine cancers, thyroid cancer, skin cancer, brain and central nervous system cancer.

HEAD AND NECK CANCERS

Head and neck cancers include malignancies located in the nasal cavity, sinuses, lips/mouth, salivary gland, throat, and larynx. Collectively, cancers of the mouth, pharynx, and larynx are the seventh most commonly diagnosed cancers worldwide, while nasopharyngeal cancer is very rare, ranking as the 23rd most common malignancy worldwide (WCRF/AICR 2007). Malignancies from this group are more likely to be diagnosed among men than women. Tobacco, including smokeless tobacco, and alcohol intake are important risk factors for several types of head and neck cancers. The highest rates of nasopharyngeal cancer are found in Southeast Asia, and intake of Cantonese-style salted fish may increase the risk of this malignancy.

Few epidemiologic studies have evaluated the potential role of meat intake on risk of this group of malignancies. Indeed, in the WCRF/AICR report on diet and cancer, no conclusions for red or processed meat intake were made because of limited data (WCRF/AICR 2007). In an analysis of the NIH-AARP cohort, non-significant associations for oral cavity/pharyngeal cancer were reported among persons in the highest intake categories for red meat (RR = 1.03) and processed meat (RR = 1.17) (Cross et al. 2007). Associations were slightly stronger in magnitude, albeit not statistically significant, between red meat (RR = 1.43) and processed meat (RR = 1.33) and laryngeal cancer (Cross et al. 2007).

Tavani et al. (2000), in a case-control study conducted in Italy, reported a non-significant 10% decreased risk of oral cavity, pharyngeal, and esophageal cancer (grouped as one outcome), and a marginally significant 30% decreased risk of laryngeal cancer among persons in the high red meat intake category. Overall, the epidemiologic data between red meat or processed meat intake and the head and neck malignancies are insufficient to evaluate an independent association.
Thyroid Cancer
The thyroid gland, an organ located at the base of the throat, produces hormones that assist in controlling some important physiological functions, such as heart rate, blood pressure, body temperature, and weight. Cancer of the thyroid is relatively uncommon, accounting for approximately 37,000 incident cases in the United States in 2008, with most cases diagnosed among women (Jemal et al. 2008). Ionizing radiation is the most well-established risk factor for thyroid cancer, while most causes of this malignancy remain relatively obscure (Ron and Schneider 2006). Iodine is a possible risk factor for thyroid cancer; however, more studies are needed to determine whether too much or too little iodine in the diet increases or decreases certain thyroid cancer sub-types. Indeed, several studies have evaluated fish consumption as a surrogate measure for iodine intake, although results have not been consistent.

There is little epidemiologic data pertaining to red/processed meat and thyroid cancer. In a cohort analysis of more than 275 thyroid cancer cases, non-significant decreased risks of 21%, 21%, and 8% were observed in the third, fourth, and fifth red meat intake quintiles (Cross et al. 2007). Similar associations were observed for processed meat consumption; decreased risks ranging between 7% and 29% were reported in the non-referent quintiles of intake. In a case-control study conducted in Italy, a marginally significant increased risk of thyroid cancer was reported among high consumers of red meat (OR = 1.5, 95% CI: 1.0-2.1) (Tavani et al. 2000).

The available epidemiologic evidence between red meat or processed meat intake and thyroid cancer is limited. On the basis of the inverse associations from the large prospective cohort study, red or processed meat consumption does not appear to increase the risk of thyroid cancer.
SKIN CANCER

The skin is the largest organ in the human body, and is a fundamental component of the defense mechanisms to keep infections and microorganisms from entering internal organ systems. The skin also serves to regulate body temperature, retain water, excrete wastes, and synthesize vitamin D from the sun. The three primary types of skin cancer are melanoma, basal cell carcinoma, and squamous cell carcinoma. From a clinical and epidemiologic perspective, basal cell and squamous cell carcinomas are considered to be ‘non-melanoma’ skin cancers. They are the most common types of skin cancer, with more than one million cases diagnosed annually in the United States (Miller and Weistock 1994). However, since non-melanoma skin cancers are generally slow-growing cancers that can be easily located on the epidermis layer, they are usually very treatable. On the contrary, melanoma is diagnosed less frequently and has a considerably higher case-fatality rate. For the year 2008, it was estimated that more than 62,000 people in the United States would be diagnosed with melanoma skin cancer and that more than 8,000 people would die from the disease (Jemal et al. 2008).

The strongest and most established risk factor for skin cancer is direct exposure to ultraviolet (UV) radiation from the sun. Risk for skin cancer increases with age, and persons with a family history of skin cancer, particularly melanoma, have an increased risk of developing this malignancy.

No dietary factors have been consistently associated with skin cancer, and few epidemiologic studies have investigated the relationship between red or processed meat intake and skin cancer. In a cohort study of approximately 500,000 people aged 50-71 years, Cross et al. (2007) evaluated the association between red meat and processed meat and melanoma among more than 1,500 cases. Reduced risks of melanoma were observed in all red meat and processed meat intake categories. In fact, a statistically significant 18% decreased risk was reported among the persons in the highest processed meat intake category (RR = 0.82, 95% CI: 0.71-0.96) and a statistically significant 19% decreased risk was reported among persons in the lowest processed meat category (RR = 0.81, 95% CI: 0.70-0.94).
BRAIN AND CENTRAL NERVOUS SYSTEM CANCERS

The human brain is the foundation of the central nervous system and it is responsible for controlling the physical, biological, and emotional functions of the body and mind. Malignancies of the nervous system are rare and account for only 2% of all cancers. Although it is largely known that diet is associated with mental function, very few epidemiologic studies have evaluated the influence of diet on the etiology of malignancies in the nervous system (Society for Neuroscience). In fact, in the WCRF/AICR report, it was stated that the narrative review did not produce any findings and that it is unlikely that any further investigation is warranted (WCRF/AICR 2007).

Recently, one cohort study and one case-control study were published that evaluated the relationship between meat consumption and brain cancer. In an analysis of the National Institutes of Health and the American Association for Retired Persons (NIH-AARP) cohort, non-significant inverse associations between consumption of red and processed meat were reported (Cross et al. 2007). No significant elevations in risk were found in a case-control study conducted in eight Canadian providences (Hu et al. 2008). Although limited by few studies, the available epidemiologic evidence does not support a causal association between red or processed meat intake and brain cancer.
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).
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 nitrates 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...
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
EXTRAPOLATING EPIDEMIOLOGIC EVIDENCE INTO PUBLIC HEALTH RECOMMENDATIONS
USE OF EPIDEMIOLOGY TO MAKE PUBLIC HEALTH DIETARY RECOMMENDATIONS

The role of epidemiology in the regulatory sector is widespread, as epidemiology is an amalgamated science, involving many disciplines, including biology, toxicology, statistics, exposure measurement, and risk assessment among others.

The U.S. Environmental Protection Agency (EPA) relies upon epidemiology to study environmental issues, educate the general public about the environment, set national standards, and develop and enforce environmental regulations. Similarly, the Occupational Safety and Health Administration (OSHA) utilizes data from epidemiologic investigations to assure safe and healthful working conditions pertaining to such areas as worker injury, disease transmission, and exposure assessment. Regarding diet and nutrition, the U.S. Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA) rely upon epidemiologic data (as well as other sources and types of data) to make public health dietary recommendations.

Findings from epidemiologic studies may facilitate a clear, accurate, and precise measure of public health risk (or benefit) between a particular exposure or set of exposures and a particular outcome or set of outcomes. On the other hand, a collection of epidemiologic studies may perplex the issue if findings across studies are inconsistent or unclear; thus, not providing relevant scientific guidance from a regulatory or policy viewpoint. Indeed, results from epidemiologic studies must be interpreted with respect to methodological and analytical considerations, such as strength of the association, consistency, biological plausibility as well as the possible influence of bias and confounding, in order to ensure a valid and systematic interpretation of the totality of scientific evidence. Epidemiologists utilize pragmatic definitions of causation to support the translation of research evidence into public health interventions or recommendations (Schottenfeld and Fraumeni 2006). The considerations of a causal assessment are discussed in this section.

In epidemiologic parlance, there are nine considerations (or criteria), referred to as “causal criteria,” in assessing a causal relationship between a risk factor and disease outcome. These considerations, originally developed...
Section 11 — Extrapolating Epidemiologic Evidence into Public Health Recommendations

by Sir Austin Bradford Hill in 1965 (Hill 1965), were intended to be applied to evidence related to an already established statistical association. The considerations have since been modified slightly or expounded upon over time by other researchers to account for the refinements in the science of epidemiology. The considerations are: temporality, strength of association, consistency, dose-response, biological plausibility, specificity, experimentation, coherence, and analogy. These considerations are typically applied to a body of epidemiologic literature, rather than a single study.

The application of these considerations is both extensive and variable. Hill’s criteria have been applied in hundreds of scientific settings over the past fifty years, involving numerous types of exposures.

### INFORMATION BOX 11.1
**SCIENTIFIC CONSIDERATIONS FOR ASSESSING CAUSATION**

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporality</td>
<td>The factor must precede the outcome; however, this does not guarantee causation because many alternative explanations remain to be considered. If the outcome precedes exposure, then causation can be ruled out.</td>
</tr>
<tr>
<td>Strength of Association</td>
<td>The magnitude of the relative risk estimate. Typically, the stronger the relative risk, the more likely the observed association is causal.</td>
</tr>
<tr>
<td>Consistency</td>
<td>Refers to the extent to which the study results are similar (e.g., direction and magnitude of associations) across the entire body of evidence.</td>
</tr>
<tr>
<td>Dose-response (biologic gradient)</td>
<td>Refers to the extent to which the relative risk estimates increase in magnitude as the dose of the exposure increases. Typically, it is believed that a regularly increasing relationship between exposure and risk estimate is more likely to represent a causal relationship than other patterns.</td>
</tr>
<tr>
<td>Biologic Plausibility</td>
<td>Refers to the extent to which a mechanism of action has been proposed and/or studied, typically in laboratory studies involving animals and/or human tissues.</td>
</tr>
<tr>
<td>Specificity</td>
<td>Refers to the idea that some diseases may have a single (specific) cause and it refers to the precision with which the exposure and/or the outcome can be defined and characterized.</td>
</tr>
<tr>
<td>Coherence</td>
<td>Refers to the extent to which the evidence and hypotheses for the results fit together into a reasonable and well-tested explanation.</td>
</tr>
<tr>
<td>Experimentation</td>
<td>Refers to the extent to which a randomized clinical trial (e.g., a prevention trial) has been undertaken (not in reference to animal experimentation). This is an uncommon condition to be satisfied, due to the high cost of prevention trials.</td>
</tr>
<tr>
<td>Analogy</td>
<td>The extent to which the purported exposure-disease relationship under consideration is similar (in types and characteristics of evidence) to other relationships, known to be causal or not.</td>
</tr>
</tbody>
</table>
and numerous types of health outcomes. Although generally considered the architectural framework upon which causation is assessed, the application of these considerations has not been met with uniform scientific agreement. Until a better alternative is proposed (with a demonstrated improvement in causal claim outcomes) however, these criteria remain a critically important approach to causal inference.

Extrapolating data from epidemiologic studies of red or processed meat intake and cancer to make public health recommendations is extremely difficult given the scientific uncertainty surrounding this complex topic. Although all of the causal criteria components of red/processed meat intake and specific types of cancer are not addressed systematically in this summary of epidemiologic findings, the nine causal considerations are applied generally to red/processed meat intake and cancer as follows:

**Temporality**
Of the observational studies, prospective cohort studies offer the best support of a temporal relationship. This, in addition to the potential for information bias, is one of the reasons why interpretation of the diet and cancer literature is commonly based solely upon prospective studies. For some cancer sites, such as colorectal and breast, there is a relatively large volume of prospective studies of meat consumption. However, for some cancers, such as liver cancer and gynecological cancers, there are relatively few prospective studies, which limit a causal assessment.

**Strength of Association**
The strength or weakness of an observed association in epidemiological studies is a key consideration in making claims of causation, and relative risk estimates less than 1.5 are generally considered “weak” in magnitude. A “weak” association is less likely to reflect a causal association than a “strong” association because other alternative explanations are more likely. Thus, reflecting scientific uncertainty as unknown (and/or other unmeasured) confounding factors (or residual confounding) and bias may be acting in ways such that the observed association is, in fact, not an association at all. For example, a weak association represented by an RR of 1.20 with a hypothetical 95% CI of 1.02 to 1.38 (i.e., statistically significant) may be due to confounding factors rather than the exposure of interest because appropriately measuring and controlling for the relevant confounding factors may result in an attenuated RR of 1.15 with a non-significant confidence interval of 0.95 to 1.35.

On the other hand, an RR of 8.0 with a hypothetically statistically significant 95% CI of 5.0 to 11.0 is much less likely to be explained by confounding or bias. For example, even if control for confounding attenuates the RR 25% to 6.0 (still a very strong magnitude) the confidence interval remains statistically significant with a similar 25% attenuation (95% CI: 3.75-8.25).

As can be seen in this hypothetical example, the larger the magnitude of the association (commonly resulting in a lower bound of the confidence interval that is further away from 1.0), the less likely it is that the association will fall to a level that is not statistically significant. Therefore, the stronger the association, the more likely it is that the relationship is causal. Of note, a strong association is neither necessary nor sufficient for causality, and a weak association is neither necessary nor sufficient for an absence of causality (Rothman et al. 2008).

The strength of association is merely one of many considerations, albeit a very important one, that must be taken into account before making a causal claim. In sum, the more uncertainty that exists in causal claims, the more uncertainty exists in the extent to which the dietary recommendations emerging from those claims will do what they are intended to do, that is, to prevent disease. Therefore, making a dietary recommendation from “weak” associations may mean that the interventions are less likely to be effective, if effective at all. Indeed, most associations between red/processed meat and cancer across the entire body of epidemiologic literature are considered “weak” associations, with relative risks below 1.50 and most being not statistically significant.
Consistency

Typically, it is believed that the more consistent the results, the more likely it is that the observed association is causal. Although for some cancer sites, the majority of epidemiologic associations for red meat and processed meat are in the positive direction, the results across studies are inconsistent in terms of the magnitude of effect. Furthermore, for some malignancies, associations are variable by certain characteristics, such as gender and tumor site for colorectal cancer. For many cancer sites, the epidemiologic evidence is limited to few studies, thereby precluding a formal assessment of quantitative consistency.

Dose-Response

The biological gradient, or dose-response relationship, is one of the most important considerations for making public health recommendations because in theory, this would quantify the recommended consumption level of a food or food group. However, there is no established dose-response relationship between red or processed meat intake and cancer risk. Furthermore, there is no threshold of intake for which risk of cancer begins to increase. Estimating a dose-response relationship using epidemiologic dietary data is complex, as intake data for meat are commonly measured in a variety of units (e.g., grams, servings) and analytical comparisons vary (e.g., 5+ servings per week vs. 1 or fewer servings per week; 80 or more grams per day vs. 20 or fewer grams per day).

Biological Plausibility and Coherence

These considerations are intertwined, and are commonly reviewed without distinction. That is, there should be a plausible biological mechanism(s), and the cause and effect relationship should not conflict with what is known about the natural history and biology of the disease. Several postulated mechanisms have been proposed for red/processed meat consumption and cancer, including dietary mutagens such as heterocyclic amines or polycyclic aromatic hydrocarbons derived from high temperature cooking, heme iron, nitrosamines, and dietary fat. However, epidemiologic investigations of these factors among human populations have not produced consistent (or coherent) results.

Specificity

This criterion refers to an outcome that has a specific cause or to an exposure that produces a specific outcome. For most diseases, cancer in particular, this criterion cannot be satisfied and it is rarely applied in epidemiology. It is well-accepted that carcinogenesis is multifactorial, that is, many cancer-causing agents can cause several types of cancer, and these agents can also have non-carcinogenic effects (Schottenfeld and Fraumeni 2006).

Experimentation

This criterion refers to reducing or eliminating the exposure of interest in an effort to see if there is an impact on disease incidence. This is not a practical application in the study of meat consumption and cancer.

Making a dietary recommendation from “weak” associations may mean that the interventions are less likely to be effective, if effective at all. Indeed, most associations between red/processed meat and cancer across the entire body of epidemiologic literature are considered “weak” associations, with relative risks below 1.50 and most being not statistically significant.
Analogy

This criterion refers to the extent to which the purported exposure-disease relationship under consideration is similar to that of another exposure-disease relationship. For example, if a specific dietary factor is thought to cause a specific type of cancer, then the same dietary factor may cause cancer at a neighboring organ site. This appears to contrast the specificity criterion if attempting to relate the exposure under investigation to a different cancer site. It is unclear whether or how analogy could be applied to the epidemiologic studies of red/processed meat intake and cancer.

Dietary recommendations (like all public health recommendations) are complex decisions that involve scientific, economic, policy, and ethical considerations. The underlying science surrounding the exposure and disease relationship should be the foundation upon which the recommendation process is built. If the underlying science is tenuous or unclear, then the subsequent public health recommendations may not achieve the effect they are intended to elicit.

Public health recommendations are also policy decisions in the sense that from these recommendations can emerge regulations, laws, and popular practices (e.g., food choices and preferences), all of which may impact commerce as well. Finally, public health recommendations are also ethical decisions; making a recommendation for an individual or a population to change or not to change their lifestyle involves balancing risks and benefits, inasmuch as a governing principle of the practice of public health is beneficence, defined as the balance of doing good and preventing harm.
The meat and beans group is composed of beef, pork, lamb, veal, game, poultry, fish, shellfish, frankfurters, sausages, bacon, luncheon meats, and organ meats, and meat alternates including eggs, soy-based products such as tofu and meat analogs, nuts, and seeds. Dry beans and peas may be considered as a vegetable or as a meat alternate. According to MyPyramid, it is recommended that two to three servings of foods from the meat and beans group (also called the meat, poultry, fish, dry beans, eggs, and nuts group) should be consumed daily, and that the total amount of these servings should be the equivalent of 5 to 7 ounces of cooked lean meat, poultry, or fish per day (Cook and Friday 2005). Contrary to the popular misperception that red meat is over-consumed, on average Americans over the age of 2 consume only 2.3 ounces of red meat per day, which is less than 1/2 of the total meat and meat equivalent recommended in MyPyramid and is well within the WCRF/AICR suggested 18 ounces or less of red meat per week (USDA, ARS 2005).
### Figure 11.1
**Comparison of Meat and Beans Group Intake to MyPyramid Recommendations**

#### Males

<table>
<thead>
<tr>
<th>AGE</th>
<th>MyPyramid Recommendation (ounces)</th>
<th>Total Meat and Beans Group Intake (ounces)</th>
<th>Total Red Meat Intake* (ounces)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5</td>
<td>2-5</td>
<td>3</td>
<td>1.15</td>
</tr>
<tr>
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#### Females

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<th>AGE</th>
<th>MyPyramid Recommendation (ounces)</th>
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<th>Total Red Meat Intake* (ounces)</th>
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**All 2 and Over** | 2-7 | 5.3 | 2.3

*Includes Total Red Meat + Organ Meat + 1/2 of Frankfurter and Lunch Meat.


### Summary Statement

A balanced diet builds upon the foundation of healthful foods from a variety of groups such as whole grains, legumes, fruits, vegetables, low-fat dairy products, and lean meats. Without question, the nutrients provided by lean meats, including beef and pork, offer a calorically efficient source of biologically available essential nutrients that make important contributions to a healthy diet. Scientific evidence has clearly shown that beef and pork provide an abundance of essential amino acids, are rich in certain vitamins, such as B vitamins, and contain several important minerals, such as iron and zinc. Nevertheless, lean red meat is often misperceived as an unhealthy food, largely due to the fact that red/processed meat is categorized as a fundamental component of a “Western” dietary pattern. A Western dietary pattern, however, is notably different than the currently recommended balanced diet in that it typically includes an excess of refined sugars, processed grains, and alcohol, and a deficit of fruits, vegetables, and fiber. As such, positive associations between Western dietary patterns and cancer are most likely due to factors other than intake of red or processed meats.

As a specific food group, red/processed meat has been implicated as increasing the risk of colorectal cancer, and has been suggested to be associated positively with other types of cancer; however, the currently available epidemiologic evidence is not sufficient to support a causal relationship with any type of cancer. This conclusion is supported by the facts that most associations between red/processed meat are weak in magnitude and not statistically significant, results are inconsistent across studies and within sub-groups of certain cancer types, associations are likely to be confounded by other dietary factors as well as lifestyle characteristics, evaluations of postulated mechanisms among human populations have not produced consistent results, and measurement error complicates interpretation of the literature.

Future directions of research should focus on measuring diet with increased accuracy, such as biochemical indicators of consumption, evaluating sub-groups who may be at higher or lower risk of developing certain types of cancer, improving methods for estimating and controlling potential confounding factors, adopting a more uniform strategy for characterizing and analyzing meat intake, and eliminating the influence of publication bias.
EPIEDEMIOLGY
Nutritional epidemiology is the study of the dietary factors that influence disease frequency and distribution in human populations. Epidemiologically, disentangling the potential effects of dietary factors, such as red meat or processed meat intake, and risk of cancer is a methodologically challenging endeavor. 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, collinearity of red meat intake with other food items, and many lifestyle and behavior characteristics.

CANCER
Cancer is multifactorial, involving a complex interaction of genetic, lifestyle, infectious, and environmental factors. The progression of cancer commonly takes several years from cancer initiation to diagnosis of disease, thus enhancing the difficulty in identifying the underlying factors involved in carcinogenesis.

RED/PROCESSED MEAT INTAKE AND CANCER
There are several postulated mechanisms (e.g., heterocyclic amines, heme iron) 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.

The relationship between red/processed meat intake and cancer has been evaluated in hundreds of epidemiologic studies. With critical consideration of the extensive 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 cancer.

CURRENT RECOMMENDATIONS
According to recent data, the U.S. general population is consuming meat within current recommendations. Lean beef and pork are excellent sources of protein and provide an abundance of essential nutrients. Thus, a balanced diet consisting of whole grains, fruits, vegetables, legumes, low-fat dairy products, and lean meats, including beef and pork, serve as the foundation of a healthy diet.

FUTURE DIRECTIONS
New scientific methods of determining genetic risks, as well as improved ways of measuring diet, such as biochemical indicators of food intake, will continue to add to the body of knowledge in this ever-expanding area of research.

THE BOTTOM LINE
REFERENCES
REFERENCES


A TECHNICAL SUMMARY OF THE EPIDEMIOLOGIC EVIDENCE


REFERENCES


