SECTION 3

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.

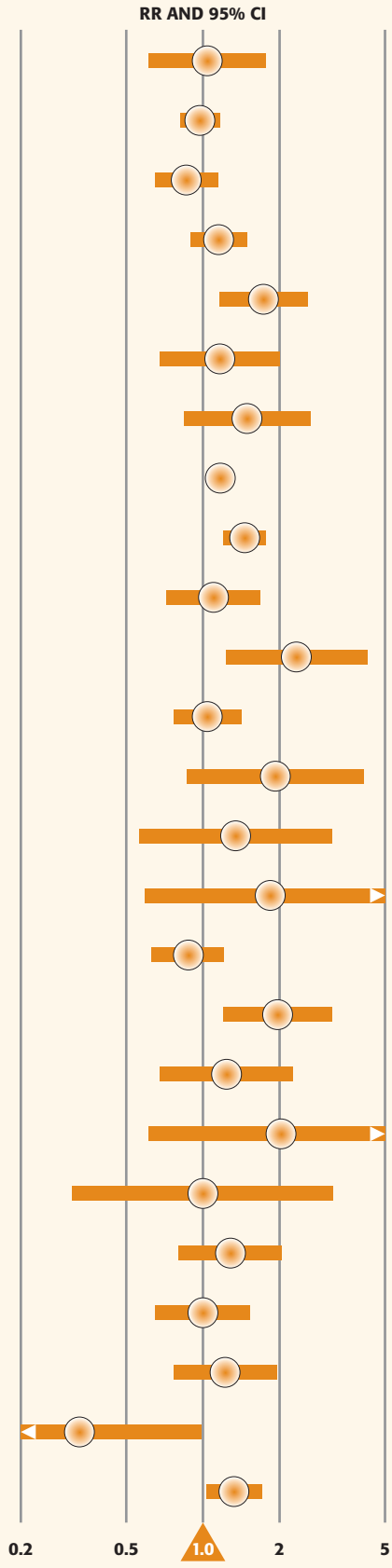
In 2007, the World Cancer Research Fund (WCRF), in collaboration with the American Institute for Cancer Research (AICR), released a summary report entitled, "Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective." This second report (the first was issued in 1997), evaluated 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 500 g (18 oz cooked) (700-750 g 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).

FIGURE 3.1
PROSPECTIVE STUDIES OF RED MEAT INTAKE AND COLORECTAL CANCER

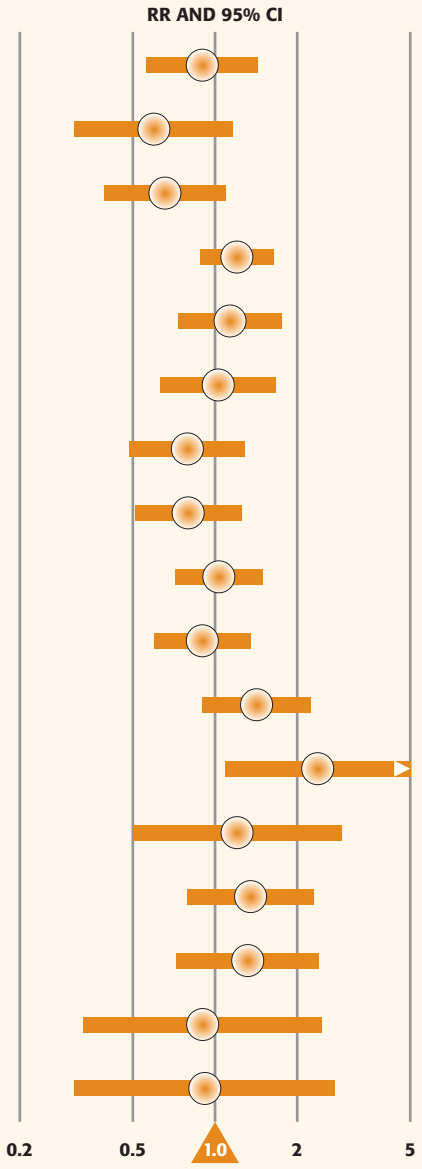
AUTHOR AND YEAR	COHORT
Bostick 1994 (C) (W)	Iowa Women's Health Study
Brink 2005 (C)	Netherlands Cohort Study
Brink 2005 (R)	Netherlands Cohort Study
Chao 2005 (C)	Cancer Prevention Study II
Chao 2005 (R)	Cancer Prevention Study II
Chen 1998 (CRC) (M)	Physicians Health Study
Chen 2003 (C)	China Cohort Study
Cross 2007 (C)	NIH-AARP Diet and Health Study
Cross 2007 (R)	NIH-AARP Diet and Health Study
English 2004 (C)	Melbourne Collaborative Cohort Study
English 2004 (R)	Melbourne Collaborative Cohort Study
Flood 2003 (CRC) (W)	Breast Cancer Detection Demonstration Project
Hsing 1998 (CRC) (M)	Lutheran Brotherhood Cohort Study
Jarvinen 2001 (C)	Mobile Clinic Health Examination Survey
Jarvinen 2001 (R)	Mobile Clinic Health Examination Survey
Kabat 2007 (C) (W)	Canadian National Breast Screening Survey
Kabat 2007 (R) (W)	Canadian National Breast Screening Survey
Kato 1997 (CRC) (W)	New York, Florida Cohort Study
Khan 2004 (CRC) (M)	Japan Cohort Study
Khan 2004 (CRC) (W)	Japan Cohort Study
Kojima 2004 (C) (M)	Japan Collaborative Cohort Study
Kojima 2004 (C) (W)	Japan Collaborative Cohort Study
Kojima 2004 (R) (M)	Japan Collaborative Cohort Study
Kojima 2004 (R) (W)	Japan Collaborative Cohort Study
Larsson 2005 (CRC) (W)	Swedish Mammography Cohort Study



CRC: colorectal; C: colon; R: rectal; M: men; W: women

FIGURE 3.1 CONTINUED
PROSPECTIVE STUDIES OF RED MEAT INTAKE AND COLORECTAL CANCER

AUTHOR AND YEAR	COHORT
Lee 2009 (C) (W)	Shanghai Women's Health Study
Lee 2009 (R) (W)	Shanghai Women's Health Study
Lin 2004 (CRC) (W)	Women's Health Study
Norat 2005 (C)	EPIC Cohort Study
Norat 2005 (R)	EPIC Cohort Study
Oba 2006 (C) (M)	Japan Cohort Study
Oba 2006 (C) (W)	Japan Cohort Study
Pietinen 1999 (CRC) (M)	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study
Sato 2006 (C)	Miyagi Cohort Study
Sato 2006 (R)	Miyagi Cohort Study
Singh 1998 (C)	Adventist Health Study
Tiemersma 2002 (CRC) (M)	Monitoring Project on Cardiovascular Disease Risk Factors
Tiemersma 2002 (CRC) (W)	Monitoring Project on Cardiovascular Disease Risk Factors
Wei 2004 (C) (M)	Health Professionals Follow-Up Study
Wei 2004 (C) (W)	Nurses' Health Study
Wei 2004 (R) (M)	Health Professionals Follow-Up Study
Wei 2004 (R) (W)	Nurses' Health Study



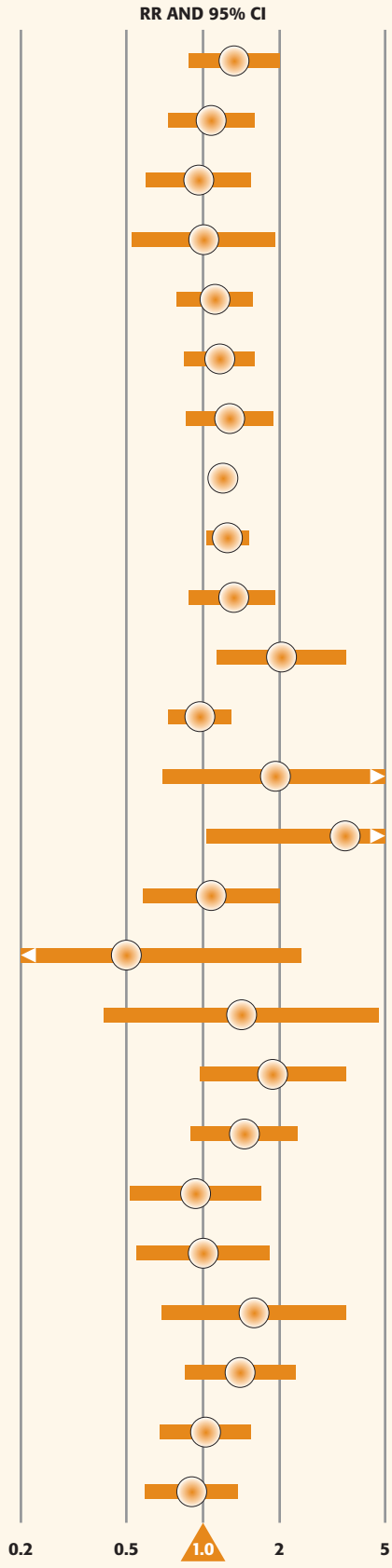
CRC: colorectal; C: colon; R: rectal; M: men; W: women

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., 100 g/day vs. 0 g/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

FIGURE 3.2
PROSPECTIVE STUDIES OF PROCESSED MEAT INTAKE AND COLORECTAL CANCER

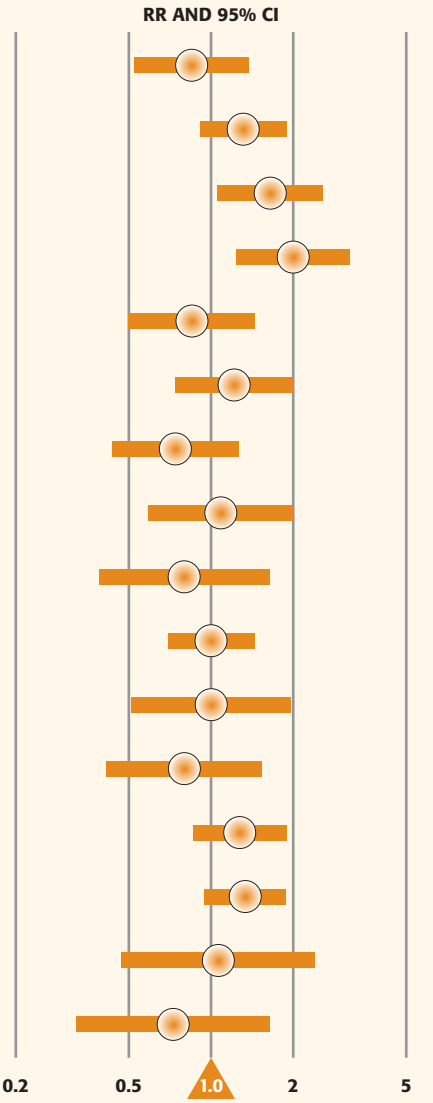
AUTHOR AND YEAR	COHORT
Balder 2006 (C) (M)	Netherlands Cohort Study
Balder 2006 (C) (W)	Netherlands Cohort Study
Balder 2006 (R) (M)	Netherlands Cohort Study
Balder 2006 (R) (W)	Netherlands Cohort Study
Chao 2005 (C) (M)	Cancer Prevention Study II
Chao 2005 (C) (W)	Cancer Prevention Study II
Chao 2005 (R)	Cancer Prevention Study II
Cross 2007 (C)	NIH-AARP Diet and Health Study
Cross 2007 (R)	NIH-AARP Diet and Health Study
English 2004 (C)	Melbourne Collaborative Cohort Study
English 2004 (R)	Melbourne Collaborative Cohort Study
Flood 2003 (CRC) (W)	Breast Cancer Detection Demonstration Project
Gaard 1996 (C) (M)	Norway Cohort Study
Gaard 1996 (C) (W)	Norway Cohort Study
Kato 1997 (CRC) (W)	New York, Florida Cohort Study
Khan 2004 (CRC) (M)	Japan Cohort Study
Khan 2004 (CRC) (W)	Japan Cohort Study
Knekt 1999 (CRC)	Mobile Clinic Health Examination Survey
Kojima 2004 (C) (M)	Japan Collaborative Cohort Study
Kojima 2004 (C) (W)	Japan Collaborative Cohort Study
Kojima 2004 (R) (M)	Japan Collaborative Cohort Study
Kojima 2004 (R) (W)	Japan Collaborative Cohort Study
Larsson 2005 (C-dist) (W)	Swedish Mammography Cohort Study
Larsson 2005 (C-prox) (W)	Swedish Mammography Cohort Study
Larsson 2005 (R) (W)	Swedish Mammography Cohort Study



CRC: colorectal; C: colon; R: rectal; M: men; W: women

FIGURE 3.2 CONTINUED
PROSPECTIVE STUDIES OF PROCESSED MEAT INTAKE AND COLORECTAL CANCER

AUTHOR AND YEAR	COHORT
Lin 2004 (CRC) (W)	Women's Health Study
Norat 2005 (C)	EPIC Cohort Study
Norat 2005 (R)	EPIC Cohort Study
Oba 2006 (C) (M)	Japan Cohort Study
Oba 2006 (C) (W)	Japan Cohort Study
Pietinen 1999 (CRC) (M)	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study
Sato 2006 (C)	Miyagi Cohort Study
Sato 2006 (R)	Miyagi Cohort Study
Sellers 1998 (C) (W) fam hx	Iowa Women's Health Study
Sellers 1998 (C) (W) no fam hx	Iowa Women's Health Study
Tiemersma 2002 (CRC) (M)	Monitoring Project on Cardiovascular Disease Risk Factors
Tiemersma 2002 (CRC) (W)	Monitoring Project on Cardiovascular Disease Risk Factors
Wei 2004 (C) (M)	Health Professionals Follow-Up Study
Wei 2004 (C) (W)	Nurses' Health Study
Wei 2004 (R) (M)	Health Professionals Follow-Up Study
Wei 2004 (R) (W)	Nurses' Health Study



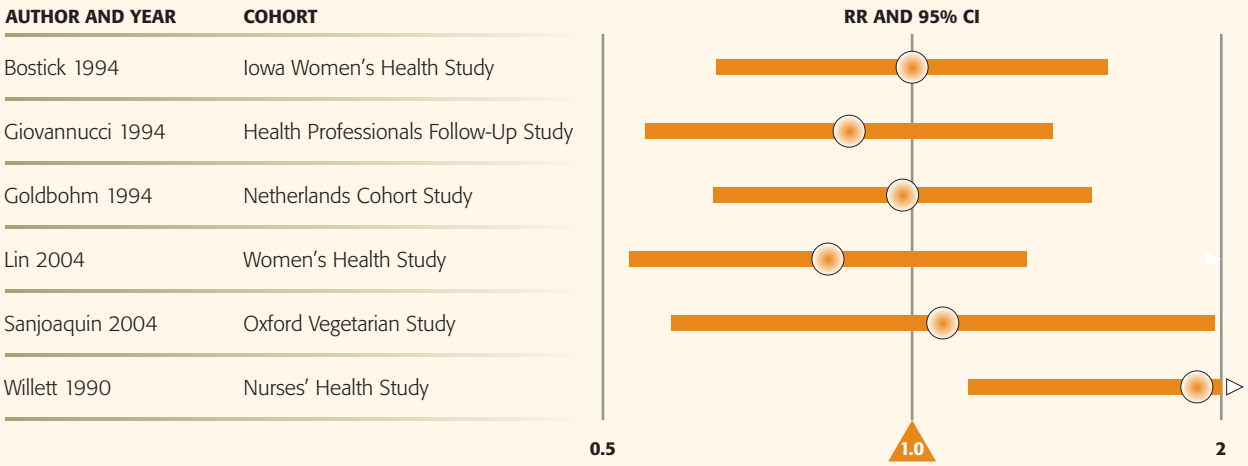
CRC: colorectal; C: colon; R: rectal; M: men; W: women

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

FIGURE 3.3
PROSPECTIVE STUDIES OF ANIMAL FAT INTAKE AND COLORECTAL CANCER



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.

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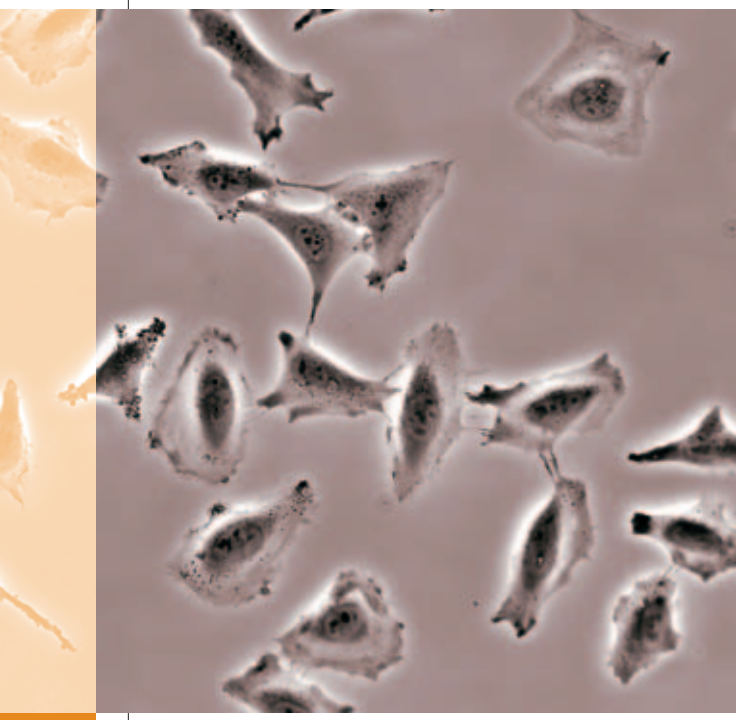
STOMACH CANCER

Following mastication, the second phase of food digestion occurs in the stomach. The stomach is a highly acidic environment, and this organ produces and secretes both gastric acid and digestive enzymes that break food down into small molecules that can then be absorbed within the small intestine. Cancer that forms in the tissues of the stomach lining is referred to as stomach or gastric cancer. Gastric cardia cancers (or proximal cancers) are those occurring in, or close to, the gastroesophageal junction, or the part of the stomach that connects the bottom of the esophagus to the stomach, while non-cardia tumors (or distal cancers) occur more distally from this junction.



Cancer cells in culture

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 nitrites 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 unspecific 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.

LIVER CANCER

The liver is the largest internal organ in the human body and it is the only internal organ capable of regeneration. Its primary functions are to remove toxicants, synthesize proteins, and produce chemicals that aid in digestion. In the United States, although liver and intrahepatic bile duct cancer accounts for only 1.3% of all cancer diagnoses, this malignancy is the fifth most common cause of cancer mortality among men and 9th most common cause among women (Jemal et al. 2008).

Internationally, there is marked geographic variability in liver cancer rates, both between and within countries, which, in large part, is thought to be a reflection of chronic hepatitis B and C virus infections (Bosch et al. 1999; 2004). These infections account for the majority of liver cancer cases worldwide (Bosch et al. 1999; 2004). Other risk factors for liver cancer include cirrhosis and exposure to aflatoxins, which are made by molds and fungi that contaminate peanuts, soybeans, wheat, corn, and rice (WCRF/AICR 2007). Smoking and alcohol consumption may increase the risk of liver cancer as well (WCRF/AICR 2007; Bosch et al. 2004).

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.

In summary, the available epidemiologic evidence does not appear to support an independent association between red meat or processed meat consumption and liver cancer.

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.