Meat consumption and malignancy development

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FINAL APPROVAL OF SCHOLARLY PROJECT
For the Degree of Master of Science in Biomedical Sciences
Concentration in Physician Assistant Studies

Student Name __________________________ Allyson Bowman

Title of Scholarly Project __________________________ Meat consumption and malignancy development: A review of the literature

APPROVED

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Chapter 1 – Introduction

“With the exception of butter, no other food has been subjected to such intense
demonization in recent years as red meat” (Butler, 2003).

Much of the research on the environmental agents that may be involved in the
development of malignancies in humans is focused on dietary patterns. Both
epidemiological and experimental studies have demonstrated that nutrition and food
intake effect the risks of certain types of cancer (Bingham, 1999; Mangels, 1998;
Welland, 1998). Among the eating habits under scrutiny, high meat consumption seems
to repeatedly come under the investigative spotlight as a potential candidate for
explaining any association between lifestyle choices and cancer acquisition.

Health professionals, patients, and families have been fighting the war on cancer
for many years. With soaring cancer rates, and unsuccessful attempts to find a cancer
cure, the need to promote cancer education and prevention has never been more urgent.
With more than 1.3 million new cancer cases, and 550,000 cancer related deaths annually
in the United States (Hope, 2003), preventive factors that can produce even a small
reduction in the development of cancer are beneficial.

Purpose

The primary purpose of this review is to provide the reader with a synopsis of
studies available to date which have evaluated the incidence and/or mortality of cancer as
a function of the consumption of animal products. In this project, the global
epidemiological evidence on the association between meat consumption and cancer risk
was reviewed, and the results were qualitatively summarized to evaluate the current
status of the debate regarding the relationship between meat consumption and cancer
development. The goal of this project was to assess how the sum of these studies can mold our understanding of whether the observed links between meat consumption and cancer are casual observations or factual associations. Also, based on the conclusions derived from the summary of the reviewed literature, recommendations will be made to the reader regarding dietary habits which may result in improved health. Together, this summation will allow us to draw further insight into the relationship between meat consumption and malignancy development.

**Relevance to the Physician Assistant Profession**

A qualitative summary of the published literature on the risk of cancer and meat consumption is relevant not only to us as individuals, but also as health care providers. It is our obligation to be informed of the most up-to-date knowledge and research in order to provide our patients with the proper information to make educated decisions regarding their healthcare and nutrition. The public deserves to be informed of the influence of the foods they eat, so they may be equipped to make knowledgeable decisions concerning their diet. Therefore, it is crucial for every individual to be aware of whether or not a correlation between the consumption of meat products and the development of malignancies exists. Also, with relevance to the recent trend towards low carbohydrate diets, it is likely that our patients may inquire as to the potential long-term health implications of a diet high in meat products. As current and future Physician’s Assistants, we must be armed with the most recent knowledge in order to answer these questions, and help our patients achieve their optimal health.
Background

History

Much of the research on the environmental agents involved with the development of human cancer has focused on dietary patterns and eating habits. The German Cancer Research Center, Division of Clinical Epidemiology, Heidelberg, Germany, states that in addition to tobacco use, dietary choices have the largest impact on the development of cancer in humans (Tadjalli-Mehr et al., 2003).

In 1989, a report by the National Academy of Sciences implicated red meat as a causative factor in the etiology of colorectal cancer (National Academy of Science, 1989). Following this report, two ensuing articles were published reviewing the epidemiological evidence on colorectal cancer development and meat consumption. In 1997, the World Cancer Research Fund (WCRF) reported that red meat probably increases risk of colorectal cancer development. It was also reported by the WCRF that processed meat possibly increases the risk of colorectal cancer in humans, and recommended limiting red meat to <80g/day (World Cancer Research Fund, 1997). In 1998, the United Kingdom’s Chief Medical Officer’s Committee on Medical Aspects of Food (COMA) reported a positive association between consumption of red or processed meat and colorectal cancer risk. COMA recommended not increasing red or processed meat consumption from the average person’s intake (approximately 90g/day) and proposed that those consuming greater than 140g/day consider decreasing their intake (Chief Medical Officer’s Committee on Medical Aspects of Food, 1998). In 1999, the World Health Organization (WHO) reported analogous claims, stating that red meat is probably associated with an increased risk of colorectal cancer. However, this consensus
statement further proclaimed that the epidemiological studies concerning colorectal cancer risk and meat consumption were not consistent (Scheppach et al., 1999).

Several other studies have been published within the last ten years which report a positive association (i.e. increased risk) between meat consumption and cancer (Bodetta, 2001; Mangels, 1998; Ronco, De Stegani, Mendilaharsu, & Seneo-Pellegrini, 1996; Welland, 1998). In 1998, the American Institute for Cancer Research and the World Cancer Research Fund commissioned a review of the literature on diet and cancer, and concluded that inappropriate diets are responsible for approximately one-third of all cancer deaths (Mangels, 1998). Welland (1998) cites that red meat promotes the development of cancer of the colon and rectum, as well as other types of cancer. Through a case-control study of diet and stomach cancer in Uruguay, Bodetta (2001) found that total meat is linked to an increased risk of gastric cancer, while another case control study conducted in Uruguay found an increased risk associated with total meat and red meat consumption and breast cancer development (Ronco et al., 1996).

Studies rebuking the link between diet and cancer have also been published (Flood et al., 2003; Norbat, Lukanova, Ferrari, & Riboli, 2002). In 1999, Truswell reported that meat consumption and colorectal cancer risk was now “clearly negative” for association (Truswell, 1998). Following a meta-analysis of articles published during 1973-1999, Norbat et al. (2002) also reported that total meat consumption was not significantly associated with colorectal cancer risk. The American Journal of Epidemiology has also reported that neither red meat nor white meat not saturated fat nor unsaturated fat show any association with colorectal cancer (Flood et al., 2003).
Colorectal cancer has not been the only type of cancer researched regarding an association between malignancy development and meat consumption. In a population-based case-control study of women in Missouri, performed to evaluate the relationship between dietary fats and lung cancer development, it was found that red meat and dietary fats were not associated with lung cancer (Swanson et al., 1997). A cohort study by Michaud et al. (2001) reported that the consumption of red meat and dairy products seem to be linked to the increased risk of metastatic prostate cancer. Knekt et al. also reported a positive association between fried meat intake and the risk of female-hormone-related cancers, such as cancer of the breast, endometrium and ovary (Knekt, Steinech, Jaervinen, Hakulinen, & Aromaa, 1994).

The theories and research to account for this relationship between meat consumption and malignancy development are also conflicting. Some research indicates that the consumption of heterocyclic amines found in cooked meat is related to the development of cancer and should be avoided (Bingham, 1999). Alternate studies have pointed to the fat content in meat as the causative agent for its association with cancer development, such as an Argentinean case-control study by Navarro et al., which showed that the intake of total meat, red meat, and other types of meat were not related to an increased risk of colorectal cancer development (Navarro, Diaz, Munoz, Lantieri, & Eynard, 2003). While still other studies point to the consumption of iron in red meat as a confounding agent (Terry, Vainio, Wolk, & Weiderpass, 2002), or the importance of eating fruits and vegetables to provide the body with protection against the development of cancer (Gerber et al., 2002).
Current Debate

Currently, the debate around the relationship between meat consumption and cancer risk remains inconclusive. The published reports, reviews, and discussion articles are limited, inconsistent and incomplete, and the studies pertaining to the association between meat consumption and malignancy development result in argumentative claims. It is for this reason that a critical evaluation of the literature assessing the correlation between meat consumption and malignancy development, as well as further investigation of the relevant theories on the subject, is warranted and of significant beneficence to the medical community and population as a whole.
Chapter 2 – Methods

Scope

Inclusion Criteria

In this review of the literature, the criteria for inclusion of epidemiological studies consisted of cohort or case-control studies evaluating the relationship between red meat, total meat, white meat, and/or processed meat and cancer risk. A broad definition of “meat” was used, including: red meat, lamb, beef, pork, and processed meat, however, a distinction was made when referring to white meat such as chicken. The evaluated articles were published in English between 1993 and 2004 in order to pool the most current information published in the last 10 years. Studies included females, males, or both genders, at any age. Eligible outcomes also showed incidence of cancer and/or mortality as the endpoint. Risk estimates of cancer associated with meat consumption, and risk ratios (RR) and 95% confidence intervals (95% CI) were noted when available.

Exclusion Criteria

The criteria for exclusion included those studies which did not address the amount of meat eaten, but only whether or not participants ate meat. These studies were excluded due to the inability to assess true level of exposure to meat if the actual amount of intake was not somehow specified. Studies that did not meet the inclusion criteria were also not evaluated in this literature review.

Budget

The budget required for this project was minimal. Any negligible monetary expense went towards the printing of articles and research. However the amount of time required to fully explore the relevant literature and research was great.
Search Strategy

Electronic searches using MEDLINE, PUBMED, EBSCO, OHIOLINK databases were used to pool articles for evaluation of their inclusion criteria. The following search terms were exhausted: “meat consumption and malignancy/cancer, meat and cancer/malignancies, red meat and cancer/malignancies, meat preparation and cancer/malignancies, cooking methods and cancer/malignancies, chicken and cancer/malignancies, processed meat and cancer/malignancies, organic meat and cancer/malignancies, free range meat and cancer/malignancies.”

Evaluation of the Literature

Throughout my research, the quality of each study was evaluated by considering: the number of cases (study size), the method of dietary assessment, the participation rates (controls and cases in case-control studies) and follow-up rates (cohort studies), and control of confounding variables.

Several problems were encountered during the evaluation of the literature. Immediately, the vast variation in study methods used by different researchers became a source of frustration. Definitions of food items were not consistent among studies. The dissimilarity in definitions used for terms “meat” and “red meat” and/or the categorization of consumption level made direct comparison between studies difficult. Definitions used for terms such as “meat,” or “red meat” did not always include the same subcategories such as beef, lamb, pork, steak, bacon, sausage, etc. Definitions of cuts of meat varied from country to country, making it difficult to compare international study results. The classification of the amount/portion of food used to evaluate the relationship between dietary items and cancer development was also not consistent. Full explanations
of cooking methods were not always given (for example, cooking temperature, length of cooking time, or level of doneness), and meat freshness was rarely addressed.

These inconsistencies more or less prohibited the combining of relative risks of different studies to come up with an overall risk estimate in a classic meta-analytical sense. However, there is still great value to evaluating studies based on their reported associations between meat consumption and malignancy development. Although relative risks of studies may not be combined, studies can be grouped based on their reported associations (positive, negative, or no association). These groups of studies can then be evaluated to yield relevant trends, confirm or discount information found in the lay press, and make recommendations for health improvement.

_Evaluation of Research Tools_

It is important to consider the value of the epidemiological research tools used to assess the relationship of meat and cancer development, and the strengths and weaknesses of these different types of studies

_Descriptive Ecological Studies_

International comparisons of incidence/mortality of site specific cancers and dietary habits are considered to fall under the classification of descriptive ecological studies. For example, although published some 25 years ago, a study by Armstrong (1975) showed a strong and impressive correlation between breast cancer and fat consumption by plotting national mortality rates for breast cancer as a function of fat consumption per head of population. However, analytical studies show the weakness of a study such as that of Armstrong, which plots incidence/mortality rates. In a follow-up
study by Hunter et al. (1996), seven cohort studies were pooled, which showed no
evidence of a correlation between breast cancer and fat consumption.

*Analytical Studies*

*Cohort studies.* Cohort studies include recruiting a group of subjects, recording
their consumption of meat products, and monitoring their subsequent health status, with
special attention to malignancy development. The strengths of this type of study lies in
the fact that at the time the participants are recruited, most participants are disease-free,
and therefore the information recalled by each participant can be expected to be
reasonably unbiased. In other words, they are not looking to blame something for their
disease. The weaknesses of cohort studies primarily involve time and costs.

*Case-control studies.* The strengths of case-control studies include that they are
cost effective, and can be accomplished in a short amount of time. However, choice of
poorly matched controls due to time constraints can yield misleading results and biased
conclusions. It is conceivable that cases have a natural tendency to seek out factors to
blame for their illness. This is of particular concern with the topic under evaluation due to
the public awareness and media attention given to cancer and it’s potential causes. It is
important to consider this possibility because misrepresentation could lead to recall bias.

Another weakness of case-control studies concerns the willingness of subjects to
participate. Cases may see value in the study, however, controls must be very giving and
philanthropic individuals to want to participate and give their time to such a cause.
Therefore, it is reasonable to think that controls may be more interested in health matters
and hence lead a generally healthier lifestyle than those who refuse to act as controls.
Intervention Study

An ideal study to evaluate the relationship between meat consumption and malignancy development would be “intervention” study. This would include a study in which subjects are randomly allocated to treatment (i.e. meat intake) thought to influence cancer risk. Obviously, this type of study is not conceivable due to its inherent ethical constraints.
Chapter 3 – Literature Review

This in-depth summary of the published literature on the association between cancer risk and meat consumption will address the relationship from several different angles. Firstly, the theories developed by various researchers to explain the positive or negative association between meat consumption and malignancy development will be reviewed. These different theories include the manner in which meat is prepared, the fat content in meat, and also the anticarcinogenic properties incorporated into our diets through certain types of meat and other foods, such as fruits and vegetables. Finally, this review of the literature will conclude with an evaluation of the relationship between meat consumption and specific sites of malignancy, such as colon, gastric, pancreatic, breast, prostate, and lung.

Meat Preparation

Not all of the studies incorporated into this extensive review of the literature provided definitions for the various types of meat preparation under investigation. As previously stated, this lack of precise explanation for the various methods of meat preparation, as well as the lack of consistency among different studies, limits the degree to which cross-evaluation of the reviewed studies can take place. However, for the purposes of this paper, I will refer to the definitions provided by Thorson (1999), in order to allow for a general understanding of each type of meat preparation. “Pan frying,” “shallow frying,” or “stir-frying” entails cooking meat between 175-300 degrees Celsius, without exposure of the meat directly to the heat source. “Baking” or “roasting” consists of meat heated in oven from below. “Broiling” involves cooking with heat source above. “Charbroiling,” “barbecuing,” or “grilling” implies that meat is placed directly on a grill
rack with a direct heat source below. “Charbroling,” “barbecuing,” or “grilling” also allows the potential for meat to come into direct contact with flames. Finally, “boiling” refers to meat placed in water and heated to boiling.

*Heterocyclic Amines and Polycyclic Aromatic Hydrocarbons*

Much of the research pertaining to an association between meat consumption and malignancy development, is focused on the theory that malignancy promoting heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are formed as a result of the method by which the meat is prepared (Anderson et. al., 2002; Bingham, 1999; Boddetta, 2001; Ferguson, 2002; Probst-Hensch et al., 1997). HCAs and PAHs are formed through temperature and time-dependent conditions during the cooking of meat. Polycyclic aromatic hydrocarbons are generated by incomplete combustion of organic material, as in the process of barbecuing meat over open flames. Heterocyclic Amines are formed from amino acids, creatinine, and naturally occurring sugars in meats cooked at high temperatures (frying, grilling, broiling). HCAs can also be formed in white meats (chicken and fish) that are cooked by similar methods (Anderson et al., 2002; Bingham, 1999; Boddetta, 2001; Ferguson, 2002; Probst-Hensch et al., 1997).

HCA formation depends on both the source of meat and different aspects of meat preparation (Probst-Hensch et al., 1997). HCA formation is promoted by high cooking temperatures (>150 degrees Celsius) and prolonged cooking times (>2 minutes). Direct exposure to heat, such as grilling, frying, and barbecuing, is more likely to lead to HCA formation, whereas baking and steaming are less likely (Ferguson, 2002).
Throughout my research I discovered studies which found both a positive or a negative association between heterocyclic amines and polycyclic aromatic hydrocarbons, meat consumption, and malignancy development.

**Positive associations.** Several studies have reported positive associations between HCAs, PAHs and cancer development. In a sigmoidoscopy-based case-control study by Probst-Hensch et al. (1997), subjects likely to have a high intake of HCAs (based on meat intake and cooking methods) were identified and evaluated for their risk of distal adenomas and compared to subjects likely to have a low intake of HCAs. Subjects who ate beef, pork, or lamb as a main dish at most once per week and who reported eating fried red meat at most 10% of the time, and who preferred red meat that was not well done or darkly browned, were assumed to have low exposure to HCAs. Subjects on the other end of the spectrum (those who ate beef, pork, or lamb as a main dish more than once per week, fried red meat more than 10% of the time, and/or preferred red meat well done or darkly browned) were hypothesized to have high levels of HCA exposure. Probst-Hensch et al. found a trend for increased adenoma prevalence with increasing HCA exposure. The high exposure group had an OR of 1.7 (CI 0.9-3.3, P-value for trend 0.05) for polyps.

A weakness of this study (Probst-Hensch et al., 1997) was that it looked only at adenomas in the left side of the colon (therefore creating an inability to generalize the results of this study to right-sided colon polyps). Potential biases of this study could be reduced with a colonoscopy-based study, although it is important to recognize that a patient’s symptoms may have lead him or her to receive a colonoscopy. This may lead to a change in diet or possibly cause recall bias.
Research from Welland (1998) showed that charred foods have also been associated with cancer risk. The findings of this research stated that using very high heat or a direct flame (grilling), produced cancer-causing heterocyclic amines, especially in meat, fish and poultry. Similar to the claims made by previous researchers, Welland concluded that heterocyclic amines increased the risk of many cancers, especially cancers of the colon and rectum.

Research from Bingham (1999) conferred with the previous findings and reports that the consumption of heterocyclic amines found in cooked meat were related to the development of cancer and should be avoided. In this review, international comparisons from cohort studies were examined. There are no quantitative estimates of the amounts of meat consumed by meat eaters in the reviewed studies. Type, amount, and cooking method of meat or protein associated with increased risk were not specified.

Bingham (1999) reported that possible mechanisms underlying the association between meat and malignancy development include the formation of heterocyclic amines in meat when it is cooked. Heterocyclic amines require acetylation by P450 enzymes. Therefore, individuals with a fast-acetylating genotype who eat high amounts of meat may be at increased risk for large-bowel cancer.

Also, NH3 and N-nitroso compounds formed from residues by bacteria in the large bowel are important (Bingham, 1999). NH3 promotes large-bowel tumors which are chemically induced by N-nitroso compounds. Some of the chromosomal mutations found in human colorectal cancer are consistent with effects of N-nitroso compounds and heterocyclic amines (Bingham).
Anderson et al. (2002) suggested that heterocyclic amines (HCAs), and polycyclic aromatic hydrocarbons (PAHs) may increase the risks of some types of cancer, especially pancreatic cancer. Lang, Butler, and Massengill et al. (1994) found possible biological components causing HCA’s to be associated with an increased risk of cancer development. This small case study showed well-done meat was associated with a higher risk of colorectal cancer.

The metabolic activation of food-borne heterocyclic amines to colon carcinogens in humans is hypothesized to occur via N-oxidation followed by O-acetylation to form carcinogenic-DNA adducts (Lang et al., 1997). These steps are catalyzed by hepatic cytochrome P4501A2 (CYP1A2) and acetyltransferase-2 (NAT-2), respectively, which are known to be polymorphic in humans. On the basis of this proposed metabolic activation pathway, patients at greatest risk to develop colorectal cancer or nonfamilial polyps should be those who possess both the rapid NAT-2 and rapid CYP1A2 phenotypes and are exposed to high dietary levels of carcinogenic heterocyclic amines (Lang et al., 1997).

Using a method that involved caffeine administration and high pressure liquid chromatographic analysis of urinary metabolites, Lang et al. (1997) determined the CYP1A2 and NAT-2 phenotypes of 205 controls and 75 cancer/polyp cases. Exposure information was obtained using a dietary and health habits questionnaire.

The researchers also found that both the rapid CYP1A2 and rapid NAT2 phenotypes were each slightly more prevalent in cases versus controls (57% and 52% versus 41% and 45%, respectively). However, the combined rapid CYP1A2-rapid NAT-
2 phenotype was found in 35% of cases and only 16% of the controls, giving an odds ratio of 2.79 ($P = 0.002$) (Lang et al., 1997).

Univariate analysis of the questionnaire indicated that age, rapid-rapid phenotype, and consumption of well-done red meat were associated with increased risk of colorectal neoplasia. Furthermore, a logistic regression model that included age, consumption of well-done red meat, and rapid-rapid phenotype as independent covariates gave odds ratios of 1.08, 2.08, and 2.91, respectively (Lang et al., 1994).

**Negative associations.** Conversely, Boddetta (2001) found that heterocyclic amines and N-nitroso compounds were not associated with a risk of gastric cancer. The researcher supported these claims through a case-control study on diet and stomach cancer conducted in Uruguay between September 1997 and August 1999. In this study, a total of 123 patients with stomach cancer were interviewed face-to-face in hospitals (Boddetta, 2001).

Some previous studies have suggested that heterocyclic amines, resulting from fried and broiled meat, might be associated with an increased risk of gastric cancer (DeStefani, Boffetta, Mendilaharsu, Carzoglio, & Deneo-Pellegrini, 1998; Ward, Sinha, Hienemann, Rothman, & Markin, 1997). In the study by Boddetta (2001), neither fried nor barbecued meat was associated with a significant elevated risk of gastric cancer. While nitrosamines showed a small elevated risk, estimated intake of heterocyclic amines was not associated with gastric cancer risk in this study.

Data from New Zealand compared 317 prostate cancer cases with 480 controls matched for age, and similar median intake of energy and fat (Norrish et al., 1999). Levels of meat doneness and daily intake of heterocyclic amines were determined from
self-reported dietary data and experimentally measured heterocyclic amine levels in locally sourced meat samples cooked under controlled conditions to varying degrees of doneness. Well-done beefsteaks showed a relative risk of 1.8, while no association was observed for other meats or for meat doneness. Ultimately, this 1999 study concluded that there was no clear association between prostate cancer risk and either estimated total or other individual HCAs (Norrish et al.).

*Meat Preparation Methods*

*Positive associations.* Several studies have reported a positive relationship between meat consumption and cancer based on preparation methods of meat. An interesting study from New Zealand showed differences in cancer between population groups living next to one another (Maori and New Zealand Europeans, otherwise referred to as non-Maori) with what superficially seem to be the same dietary practices and in a seemingly unpolluted environment (Ferguson, 2002).

Overall, the New Zealand cancer data rank the third highest in the world. In 1995, with colon cancer ranked as the top, breast cancer second and prostate cancer third (Ferguson, 2002). Meat and poultry account for about 20% of total energy intake. On average, New Zealand (non-Maori) women eat 39 grams of beef or lamb per day, and men consume 74 grams. However, there is significant variation within the population, and it seems as though the average serving of a piece of lamb or beef is 82 grams for women, and 114 grams for men. In general, the consumption of total energy, protein and fat is lower in women than in men, and lower for non-Maori (Europeans living in New Zealand) than Maori. Maori eat more meat (lamb, hogget, mutton) either alone or as part of mixed dishes (Ferguson).
There is considerable debate as to whether it is meat, the high fat content in meat, carcinogens generated during cooking (heterocyclic amines and polycyclic aromatic hydrocarbons), or N-nitroso compounds found in processed meat that serve as potential risk factors for malignancy development (Ferguson, 2002). In this study, meat consumption and meat cooking methods were examined for their relationship with some of the high cancer death rates in New Zealand (Ferguson).

This study established its own database for levels of HCAs based upon analysis of meat samples from local sources, cooked under controlled conditions to certain levels of doneness which were considered to be typical in the New Zealand population. The meat was found to range from undetectable levels of HCAs to 28.6ng/g for a well-done chicken sample (Ferguson, 2002).

What is so significant about this study is the recognizable differences in cancer between population groups living in close proximity, with what seem to be the same dietary preferences. Most hypotheses do not explain the differences in the incidence of colorectal cancer between Maoris and Europeans within New Zealand. This study shows that there are meaningful differences between the different populations in meat preferences and meet cooking methods, which could very well play a role in the cause of the differing incidence of cancer among the populations under consideration. However, it is important to note that these differences have not yet been linked to risk of cancer in an epidemiological study (Ferguson, 2002).

Further Research concerning cooking methods, and cancer risk assessment through the selection of specific types of foods and plants may provide additional beneficial information. It is also important to recognize that data on meat from one
country cannot simply be extrapolated to another country. For example, New Zealand experiences fewer temperature extremes than the United States, and the animals are pasture-fed as opposed to grain-fed, which could lead to differences in nutrient composition (Ferguson, 2002).

Norbat et al. (2002) found that the consumption of red meat and processed meat increases the risk of colorectal cancer. Through a meta-analysis of articles published during 1973-1999, Norbat et al. calculated the mean relative risk for the highest quintile of meat intake vs. the lowest meat intake, and the relative risk per gram of meat intake.

The researchers found that high levels of red meat and processed meat consumption were associated with a moderate but statistically significant increase in colorectal cancer risk (Norbat et al., 2002). The average relative risks and 95% confidence intervals for the highest quintile of red meat consumption were 1.35 (95% CI 1.21-1.51) and processed meat, 1.31 (95% CI 1.13-1.51). The relative risks per gram intake were 1.23 (95% CI 1.08-1.41) for an increase of 120g/day of red meat and 1.36 (95% CI 1.15-1.61) for 30g/day of processed meat. Based on their findings, the researchers concluded that total meat consumption was not significantly associated with colorectal cancer risk (Norbat et al.).

The study conducted by Boddetta (2001) found that heterocyclic amines were not associated with gastric cancer, but total meat was linked to an increased risk of gastric cancer with calorie intake as a strong confounder. It was also concluded that cured meat has a positive association with gastric cancer, while salted meats associated with N-nitroso compounds are not associated with a risk of gastric cancer (Boddetta).
This study was conducted in Uruguay, which is traditionally involved in cattle farming, and characterized by a high meat consumption and high rates of gastric cancer (Boddetta, 2001). Conducted between September 1997 and August 1999, this case control study was focused on estimating meat and related nutrients (and bioactive substances) after adjusting for total energy intake (Boddetta).

All newly diagnosed and histologically verified cases of gastric cancer were considered eligible for the study (Boddetta, 2001). A total of 123 patients with stomach cancer were included in the study. Both cases and controls were interviewed face-to-face in the hospitals. Food items were recorded with estimated frequency of consumption per year. Patients were also questioned on the way that they cooked the meat, leading to a classification of fried, barbecued, or boiled. No information of the degree of doneness was recorded. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by unconditional logistic regression, after age, gender, residence, and urban/rural status were included (Boddetta).

Boddetta (2001) found that red meat intake showed a steep increase in risk of gastric cancer (OR 2.4, 95% CI 1.3-4.4, P 0.003). White meat intake was not associated with risk of gastric cancer (OR 1.0, 95% CI 0.6-1.8). A strongly positive association was also observed between total meat intake and gastric cancer (OR for the highest meat intake 4.6, 95% CI 2.3-9.0, P for linear trend <0.001). In the analysis of 13 different meat items (based on regression models that included adjustment terms for total energy), intake of beef, salami, sausage and ham showed positive associations with gastric cancer, which were not significant. Also, lamb, poultry, fish, bacon, sausage, mortadella, hot
dog, and salted meat were not associated with gastric cancer risk, while cured meat did reveal a positive association (Boddetta).

The strengths of this study include the high response rate for cases and controls, and the possibility to control for total energy intake, however it also has several limitations. For example, recall bias might have played a role, as in all case-control studies. It should also be noted that the study population came primarily from low socioeconomic households, with access to minimal information on the role of diet and stomach cancer. Errors in the measurements of dietary intake are also possible, and the possibility of differential reporting bias is not without reason. The cooking method was also recorded without information on the temperature used and without estimation of doneness (Boddetta, 2001).

Although Boddetta (2001) found a positive association between cured meat and gastric cancer, other studies prove to have opposing findings. A study by Blot, Henderson, and Boice (1999) reviewed a series of epidemiological studies over the past two decades that examined the relationship between the consumption of cured meats during pregnancy and the subsequent risk of brain tumors. In this study, computerized searches of biomedical literature were preformed to locate articles which mentioned N-nitroso compound exposure or meat intake in relation to any type of childhood cancer. A total of fourteen epidemiological studies were examined, thirteen of which used the case-control approach. The statistical methods used involved the calculation of odds ratios as measures of the association between cured meat intake and risk of childhood cancer. The odds ratios and confidence intervals were estimated by logistic regression analyses in order to take into consideration the potential confounding factors (Blot et al., 1999).
Of the fourteen studies evaluated, transplacental exposure to certain N-nitroso compounds were shown in experimental investigations to produce brain tumors in laboratory animals (Blot et al., 1999). However, most of the studies showed no significant association between total cured meat intake and childhood cancer risk, although, it is worth mentioning that more positive than negative relationships were found (Blot et al.).

The same study reported that it cannot be concluded that eating cured meat causes an increased risk of childhood brain cancer or any other cancers (Blot et al., 1999). Although N-nitroso compounds are sometimes found in cured meats, the investigators concluded that there is no empirical evidence that eating cured meats results in human neural nitrosourea exposure (Blot et al.).

Unlike the previous study, a study by Sinha et al. (1998) was able to account for meat doneness. They found an increase in the risk of lung cancer to be associated with the intake of red meat, especially well-done red meat and/or fried red meat, which was assumed by the researchers to possibly be associated to the cooking practices which produce carcinogens (Sinha et al.).

Another study by Anderson et al. (2002) concluded that cooking methods such as baking, broiling, stewing, and avoiding excess charring or brownness can minimize levels of HCAs and PAHs, which lead to a decreased risk of pancreatic cancer. In this study, meat intake, meat preparation methods, and doneness of meat were examined as risk factors for pancreatic cancer. In-person interviews were conducted with each of the subjects. Using 193 cases and 674 controls, a case-control study was performed in which individuals provided information on meat consumption and preparation. Cases included
patients with pancreatic cancer, which was confirmed by histology or cytology, or clinically symptomatic patients between April 1994 and September 1998. The target population was the Upper Midwest of the United States. All hospitals in the Twin Cities seven-country metropolitan area of Minneapolis and St, Paul, MN, and the Mayo Clinic were recruited for this study. The sample population was 97% Caucasian. The mean age of the cases was 65.4, and controls was 66.0. Males comprised 61% of the cases and 56.4% of the controls. Of the cases which were actually spoken to, approximately 75% participated in the study (Anderson et al.).

The assessment tool used by Anderson et al. (2002) was a food frequency questionnaire of meat intake. Subjects were queried about their frequency of meat consumption, portion size, and meat preparation methods. Red meat was classified into two categories: “red meat,” which included hamburger patties, beef-steak, bacon, sausage, and pork, and “other red meat,” which included meat in sauces and stews. Nutrient values were also utilized to estimate total calories and total fat consumption. Preferences for meat doneness were assessed by providing subjects with pictures of internal meat doneness and external brownness, which correlated to a numerical scale. The data was then analyzed using unconditional logistic regression (Anderson et al.).

After adjusting for age, sex, smoking, education, race, and diabetes, it was found that odds ratios increased with increased intake of grilled/barbequed red meat (Anderson et al., 2002). Cases reported a higher level of consumption of total meat, total red meat, and processed meat, as well as higher levels of fried and grilled/barbequed meat intake. The odds ratio and 95% confidence interval for barbequed meat consumption was found to be statistically significant (P<0.001). Other meat variables, including total meat,
processed meat, total red meat, total white meat, total broiled meat, total fried meat, or total meat cooked by methods other than grilling, did not show a statistically significant risk for pancreatic cancer (Anderson et al.).

This study concluded that grilled red meat is a risk factor for the development of cancer of the pancreas (Anderson et al., 2002). Increased risk was associated with fried meat intake, but these findings were not statistically significant (Anderson et al.).

Potential biases in epidemiological studies such as that by Anderson et al. (2002) are difficult to rule out. Although difficult to imagine in this study, selection bias could result in over-reporting by cases of specific meat preparation methods, particularly grilling and frying (Anderson et al.).

Well-done meat has been associated with increased risks of colorectal, breast, and lung cancers in humans (Probst-Hensch et al., 1997; Sinha et al., 1998; Lang et al., 1994). A case-control study performed in Uruguay by Ronco et al. (1996) reported an increased risk of breast cancer associated with the consumption of total meat and red meat intake. In this study, dietary patterns were assessed in detail (for cases, before diagnosis or symptoms occurred) using a food frequency questionnaire involving 64 food items, which allowed total energy intake to be calculated. After adjustment for potential confounders (which included family history of breast cancer, menopausal status, body-mass index, total energy and total alcohol intake), an increased risk associated with consumption of total meat intake, red meat intake, total fat and saturated fat intake was observed. The strongest effect was observed for red meat consumption in the upper quartile (OR: 4.2, 95% CI: 2.3-7.7), after controlling for protein and fat intake. When meat-cooking methods were analyzed, fried and broiled meat showed positive and
statistically significant trends, with risks of 5.3 (95% CI: 2.8-10.2) for fried meat and 2.2 (95% CI: 1.2-4.1) for broiled meat in the upper quartile (Ronco et al.).

In a case-control study by Probst-Hensch et al. (1997) a twofold increase of adenoma prevalence was observed in subjects with hypothesized high HCA consumption. The sigmoidoscopy-based study also concluded that frequent frying of meat was linked with an increased risk of adenoma prevalence. Eligible subjects were English-speaking, between 50-74 years of age, and residents of Los Angeles and Orange counties in California. All cases had a diagnosis of histologically confirmed adenoma. Controls had no past or current history of a colon polyp, and were matched by gender, age (within five years), and date of sigmoidoscopy (within three months) (Probst-Hensch et al.).

The response rate was 84% among cases, and 82% for controls (Probst-Hensch et al., 1997). During a 45-minute in-person interview, subjects provided information on smoking, drug use, physical activity, height, weight, and family history of cancer. A total of 519 cases and 556 controls completed a semiquantitative food frequency questionnaire. The average age of subjects was 62. The subject population was 55% White, 17% Black, 18% Hispanic, and 11% Asian. The questionnaire included information pertaining to diet in the year before the sigmoidoscopy, and allowed for one of nine responses corresponding to servings of food eaten, ranging from “never or less than once pre month” to “six or more per day.” Information pertaining to preparation of red meat in the year prior to the sigmoidoscopy was also obtained (ranging from rare to well done) and percent of time that red meat was barbecued on an outdoor grill, baked, broiled, friend, or prepared by another method was noted. Covariates considered were race, BMI, vigorous leisure time activity, smoking, intake of NSAIDS, family history of colon cancer, intake
of total energy, intake of fruits/vegetables, saturated fat and alcohol consumption (Probst-Hensch et al.).

At the conclusion of this study, cases were found to more likely be obese, current smokers, consume alcoholic beverages frequently, be physically less active, less likely to use NSAIDS, had a higher mean daily intake of calories, fat, protein, carbohydrates, and cholesterol, and had a lower mean intake of fiber (Probst-Hensch, et al., 1997). Cases more frequently consumed bacon, processed meat, hamburger, beef/pork/lamb as a sandwich/mixed dish, and beef/pork/lamb as a main dish. Cases were also more likely to prepare red meat by frying to a well-done degree, with a darkly browned meat surface (Probst-Hensch, et al.).

**Negative associations.** Several studies have reported a negative relationship or decreased risk of cancer associated with various cooking methods of meat. Although as previously discussed, Probst-Hensch et al. (1997) reported some positive correlations, the researchers also came to conclusions which did not support the association between meat consumption and malignancy development. Through their research, Probst-Hensch et al. found that neither the degree of doneness nor the degree to which the surface of the meat was darkened was statistically significant with adenoma prevalence. Comparing well done to rare/medium rare meat gave an OR of 1.1 (95% CI 0.7-1.7, P-value for trend 0.6), and comparing darkly browned to lightly browned meat gave an OR of 1.3 (95% CI 0.8-2.2, P-value for trend 0.3). Likewise, frequent barbecuing of meat was not associated with adenoma prevalence (Probst-Hensch, et al.).

Cooking preference was also examined in relation to the incidence of non-Hodgkin’s lymphoma in the Iowa Women’s Health Study (Chiu et al., 1996). Although
the authors of the study reported an increase in the risk of Hodgkin’s lymphoma in association with red meat consumption (relative risk for the top third versus the bottom third of 1.73, 95% CI 1.01-2.97), they also pointed out another interesting finding. When they examined the participants preferred method of cooking, they found a statistically significant decrease in risk of lymphoma development associated with meat which was prepared medium to well done. In this particular study, the researchers proposed the explanation that there could possible be some sort of transmissible agent, or oncogenic virus in the meat, which was not satisfactorily eliminated in meats which were consumed rare (Chiu et al.).

In a Finnish cohort study, it was concluded that, overall, there was no cancer association with fried meat (Knekt, et al., 1994). In this study by Knekt et al., relationships between intake of fried meat and subsequent risk of cancers at different sites were studied among 9,990 Finnish men and women, ranging from 15-99 years of age and initially cancer free. The baseline study was carried out in 1966-1972, and cases of cancer were identified through data linkage with the Finnish Cancer Registry. During 24-years of follow-up, 853 cancer cases were diagnosed. The intake of fried meat was estimated from a dietary history interview covering the total diet of the participants during the previous year. At the conclusion of the study, the researchers found a positive association between fried meat intake and the risk of female-hormone-related cancers (cancer of the breast, endometrium and ovary). The relative risks of these cancers combined between persons in the highest and lowest tertiles of daily intake of fried meat adjusted for age, personal characteristics and intake of other main food groups was 1.77 (95% CI 1.11-2.84). However, the researchers concluded that no associations were
observed with respect to other single cancer sites or to all sites of cancer combined (Knekt, et al.).

Male specific cancers have also been studied. Epidemiologic studies have described positive associations between prostate cancer risk and meat consumption, but underlying mechanisms have not been identified (Norrish et al., 1999). The study by Norrish et al. examines the associations between prostate cancer risk and both estimated daily intake of heterocyclic amines from cooked meat and the level of meat doneness. In this study, data from New Zealand compared 317 prostate cancer cases with 480 controls, which were matched for age, and similar median intake of energy and fat. Self-reported dietary data and experimentally measured heterocyclic amine levels were used to determine levels of meat doneness and daily intake of heterocyclic amines (Norrish et al.).

Norrish et al. (1999) concluded that meat doneness was weakly and inconsistently associated with prostate cancer risk for individual types of meat, but increased risk was observed for well-done beefsteak (relative risk = 1.68; 95% confidence interval = 1.02-2.77; two-sided P for trend = .03). Age-adjusted and multivariate analyses did not confirm a statistically significant increase in prostate cancer risk with increasing either total meat intake or red meat consumption. Doneness of beefsteak was positively associated with prostate cancer risk (relative risk of 1.8), but there were no associations observed for other meats or meat doneness. Overall, there was no clear association between prostate cancer risk and either estimated total or other individual HCA levels (Norrish et al.).
Colorectal cancer and its association with different types of meat preparation has also recently been evaluated by several studies (Nowell et al., 2002; Flood et al., 2003). In a study by Nowell et al., the associations between environmental exposures, metabolic polymorphisms and cancer risk were preformed though a case-control study of colorectal cancer.

In this study, a total of 157 cases and 380 controls matched by sex, decade of age, ethnicity, and country of residence participated in an in-person interview that evaluated meat consumption, cooking methods, and degree of doneness (Nowell et al., 2002). A color atlas of foods was provided to demonstrate degrees of doneness and estimate food preparation techniques. Food models were used to estimate serving portion sizes. Five meats were included in this model (burgers, steaks, pork chops, bacon and sausage), cooked well or very well done. Univariate analyses for association with colorectal cancer case status was used to evaluate data regarding individual food items cooked to different levels of doneness. At the conclusion of the study, only a non-significant trend in risk with meat doneness was observed (Nowell et al.).

Flood et al. (2003) conducted an investigation of the association between consumption of meat and fat with colorectal cancer. The sample group included a cohort of women in the US. A total of 45,496 women completed a 62-item National Cancer Institute food frequency questionnaire between 1987 and 1989. The sample was obtained from the Breast Cancer Detection Demonstration Project (BCDDP), a breast cancer screening project conducted under the sponsorship of the National Cancer Institute and the American Cancer Society. This project ran from 1973-1980 and enrolled 283,222 women in 27 cites across the US. In 1979, the National Cancer Institute developed a
follow-up cohort, which included a total of 64,182 women, 96% of which completed the baseline questionnaire. Participants were then subsequently mailed questionnaires during three separate follow-up periods: 1987-1989, 1992-1995, and 1995-1998. Colorectal cancer cases were then identified from self-reports on these questionnaires, and when possible, pathology reports were obtained (Flood et al.).

Cox proportional hazards regression was used to estimate relative risks and 95% confidence intervals for total meat, red meat, white meat, processed meat, and well-done meat intakes, in addition to total fat, saturated fat, and unsaturated fat (Flood et al., 2003). Additional confounding variables were also considered in the study, such as smoking, education, body mass index, height, weekday physical activity index, alcohol, folate, vitamin D, calcium, fiber, fruits, vegetables, grains and NSAID use. It was determined that none of these variables generated any material changes in either the meat or fat model (Flood et al.).

In this study, there was no evidence to support that eating processed meat added any additional cancer risk (Flood et al., 2003). This study suggests that within the range of consumption typically observed in the US, processed meat is not associated with colorectal cancer risk. However, the authors of the study cannot rule out the possibility of a modest association. Explanation for the null results of this study could be due to the method of dietary assessment used for this cohort, or complications could have arisen from measurement error in food frequency questionnaire-based dietary assessment. Another explanation for the null results may be due to the inability of this study to classify subjects according to their heterocyclic amine exposure. It is also important to
note that in this study, there were no direct measurements of cooking methods, therefore the heterocyclic amine exposure of each subject to unknown (Flood et al.).

The findings of Flood et al. (2003) are confirmed by the 2001 research conducted by Boddetta. In this case-control study, Boddetta (2001) found that salted meats associated with N-nitroso compounds were not correlated with a risk of gastric cancer, therefore coming to the conclusion that heterocyclic amines are not associated with cancer of the stomach.

Meat and Fat

There is substantial interest in the potential association between meat, fat and cancer risk. This interest possibly stems from the general observations of the substantial variations in cancer incidences and mortality of one country to another and the variations in dietary fat intakes within individual subpopulations. With most affluent Western societies deriving between 30 to 40% of their dietary calories from fat (Steinbach, Heymsfeld, Olansen, Tighe, & Holt, 1994), the possibility for an effect of total energy intake (i.e. total calorie intake) on cancer risk, in addition to the apparent effect of fat on cancer risk, exists.

Mechanisms

Several researchers have proposed potential mechanisms to explain the possible association (positive and/or negative) between the consumption of fat found in meat, and cancer development.

Prostaglandin synthesis. Zhao, Kushi, Klien, and Prentice (1991) have proposed that fat causes an unwanted effect on prostaglandins, cell-to-cell communication, and steroid hormone synthesis. These conclusions were made through the review of Fourteen
studies which found n-3 fatty acids to be negatively associated (i.e. protective) with colon cancer in lab rats (Zhao et al., 1991).

Free radicals. Another potential mechanism to explain the relationship between fat consumption and cancer development deals with the generation of free radicals. Oxidation of fats (especially unsaturated fats) cause an increase in free radicals which can promote a change in cell composition and therefore lead to carcinogenesis (Zhao et al., 1991).

Bile acids. Also, it has been reported that the consumption of meat fat causes increased bile acid production, which then converts to mutagenic secondary bile acids (Weisch, 1987). Harris (1999) suggested that meat increases the speed of bile acid formation, which is carcinogenic, and lacks fiber, which lengthens its intestinal transit time, allowing dietary carcinogens to be in contact with the intestinal mucosa for an extended amount of time.

Estrogens. Currently, there is little doubt that a woman’s cumulative exposure to estrogen is closely involved in determining her lifetime risk of breast cancer development. Adlercreutz (1990) performed an exhaustive review of the literature looking at the effects of dietary manipulation on the secretion of estradiol and the effect of various dietary components on these hormones. The conclusions of this review provided the recommendation that a reduction in fat intake to between 15-35% of total energy is necessary in order to observe significant reductions in plasma estrogen, estradiol and testosterone, and hence reduce cancer risk (Adlercreutz).

Terry et al. (2002) found that there was no clear association between the consumption of foods or food groups and endometrial cancer risk. This was determined
through data from a large, case-control study of Swedish-born postmenopausal women and using unconditional logistic regression to estimate odds ratios and 95% confidence intervals. The participants included 709 cases and 2,887 controls, ranging in age from 50-74, and residing in Sweden between 1994-1995. The case patients were identified through six regional cancer registries in Sweden. Control women were randomly selected from a population register including all residents in Sweden. Data was obtained through mailed questionnaires. The women were asked about their usual consumption of foods one year before the diagnosis of their cancer, and controls were asked about their usual consumption of foods one year before completing the questionnaire. It is important to note that recall bias is possible in this data, since food recall was asked retrospectively. Selection bias also may have existed due to the fact 25% of potential cases and 32% of controls declined to participate in the study (Terry et al.).

*Total Energy Intake*

Obvious ethical difficulties prevent the study of the effects of energy deprivation in humans. Nevertheless, Steinbach et al. (1994) has been able to demonstrate favorable effects of energy deprivation on the proliferation of the colonic epithelium in obese patients. This proliferation can be viewed as a potential marker for the risk of colon cancer. The researchers concluded that colon cancer is a disease whose incidence appears to be related to energy expenditure and storage (Steinbach et al.).

Ghadirin et al. (1997), however, found no association between the risk of colon cancer and total intake, or total protein intake. This was determined through a population based case-control study of colon cancer and diet conducted in Greater Montreal (Ghadirin et al.).
This Canadian study included a total of 402 cases (200 males and 202 females, ranging in age from 35-79 years), identified between 1989-1993 through 5 major teaching hospitals in Montreal (Ghadirin et al., 1997). All patients had a histological diagnosis of colon cancer. A total of 669 controls (239 males and 429 females) were selected by a random digital dialing method, and were matched by age, residence, and language. Both cases and controls were interviewed in the respondent’s home or in the hospital. The questionnaire used was developed by the National Cancer Institute of Canada and underwent both validity and repeatability testing. The questionnaire asked for data such as “demographics, body measurements, physical activity, family history, history of rectal examination, occupation, smoking history, and history of vitamin consumption.” The frequency of food consumption and the amounts of >200 different types of food were evaluated. The questionnaire spanned 12 months, 2 years prior to diagnosis for cases and a similar amount of time for controls. Data from the study was scanned using standard descriptive statistics. Odds ratios and 95% confidence intervals were estimated using unconditional logistic regression. Adjustments were made for age, gender, marital status, history of colon cancer in primary relatives, and total energy intake. The findings of this study found no association between the risk of colon cancer and total intake (OR 1.17, P 0.3039) and total protein intake (OR 1.11, P 0.4870) (Ghadirin et al.).

Total Fat Intake.

Negative publicity over trans-fatty acids has grown abundant through many media outlets. However, two recent studies have concluded that trans-fatty acids do not, in fact,
seem to have any carcinogenic effects (Stender, Dyerberg, Holmer, Overseen, & Sanstrom, 1995; Ip & Marshall, 1996).

A 1997 Hawaiian based case-control study by Marchand, Wilkens, Hankin, Kolonel, and Lyu, (1997) also found that the consumption of total fat, saturated fat, and polyunsaturated fat were not related to the risk of colorectal cancer (Marchand, et al., 1997). These claims were confirmed in a 2003 cohort study by Flood et al., which reported that neither red meat nor white meat nor saturated fat nor unsaturated fat showed any association with colorectal cancer (Flood et. al., 2003).

An Argentinean case-control study by Navarro et al. (2003) showed that the intake of total meat, red meat, and other types of meat were not related to an increased risk of colorectal cancer development. According to this study, red meat did, however, produce a different pattern of risk of colorectal cancer according to its fat content. Navarro et al. found that cases consumed more cholesterol and total lipids from meat sources than controls. Also, lean cuts of beef were associated with a decreased risk of colorectal cancer development, while an increased risk of colorectal cancer development was found for patients consuming large amounts of processed meats, specifically cold cuts and sausages and bovine viscera (Navarro et al.).

A study by Giovannucci, Stampfer, Colditz, Rimm, and Willett (1992) found that rates of colorectal cancer in various countries are strongly correlated with per-capita consumption of red meat and animal fat and inversely associated with fiber consumption. The purpose the study, conducted by Giovannucci et al. (2002), was to determine the relationship between dietary factors and risk of colorectal adenomas. Using data from the Health Professionals Follow-up Study, 170 cases were reviewed. Cases included 7284
male health professionals with adenomas of the left colon or rectum who completed a food-frequency questionnaire in 1986 and who had a colonoscopy or sigmoidoscopy between 1986 and 1988 (Giovannucci et al.).

After adjustment for total energy intake, saturated fat was found to be positively associated with risk of colorectal adenoma (P for trend <0.006); RR for the highest versus the lowest quintile of intake was 2.0 (95% CI 1.2-3.2) (Giovannucci et al., 1992). For subjects on a high-saturated fat, low-fiber diet, the RR was 3.7 (95% CI 1.5-8.8) compared with those on a low-saturated fat, high-fiber diet. The researchers also found that the ratio of the intake of red meat to the intake of chicken and fish was positively associated with risk of adenoma (P for trend <0.02) (Giovannucci et al.).

Giovannucci et al. (1992) proposed that the seemingly protective effect of chicken may represent the outcome of other factors (e.g. low fat intake) correlated with frequent chicken intake. They also recommended substituting chicken and fish for red meat and to increase intake of vegetables, fruits, and grains to reduce risk of colorectal cancer (Giovannucci et al.).

Butler (2003) presented the argument that the problems associated with beef are not due to beef itself, nor the fat found in beef, but rather due to the populations increased total fat and sugar consumption over the past 40 years. The majority of the meat industry in North America is based on grain-fed beef, as opposed to grass-fed and organic beef. Countries which predominately carry organic and grass-fed beef have a decreased association between beef consumption and cancer (Butler).

Another important point made by Butler (2003) reveals that the way North America and Europe raise and process their cattle differ from that of other countries. In
Australia and New Zealand grass-fed and organic beef are the rule, and in these countries the association between beef consumption and disease is much less. Grain-based feedlots are used in much of North America where cancer rates are higher (Butler).

**Micronutrients**

Some researchers have proposed that neither meat, nor the fat content found in meat, are to blame for the development of malignancies. In fact, it has been reported by some researchers that meat possesses its own anticarcinogenic properties (Butler, 2003; Christman, Sheikhnejad, Dizik, Abileah, & Wainfan, 1993; Harris, 1999), while others have theorized that it is not meat that we should be focused on in regards to cancer risk, but rather to nutrition as a whole (Butler; Ghadirin et al., 1997; Giovannucci et al., 1992).

It has also been proposed that different micronutrients, found in meat, provide an anticarcinogenic effect. These micronutrients include anti-oxidants, linoleic acid and methionone (Christman et al., 1993).

**Anti-oxidants.** Antioxidants help to decrease the free radical chain reaction. Free radicals have the ability to covalently bond with DNA, which damages its structure and function. DNA damage is critical to cancer. Therefore, there is a negative impact of consuming free radicals and a benefit of consuming anti-oxidants (Harris, 1999). In 1993, Christman et al. reported that anti-oxidants such as zinc, camosin, and anserine dipeptides have anticarcinogenic properties.

Similarly, in 1999, Harris concluded that a diet high in plant source food would be high in anti-oxidants and thus provide a protective effect against cancer. Harris pulled data from the USDA database to compare the nutrient/calorie ratio of the highest plant sources and highest animal sources for vitamins C, E, and beta-carotene. Animal source
food does not have near the amount of protective anti-oxidants as plant source food. The varieties of phytochemicals present in plant source foods have demonstrated a protective effect against DNA damage from free radicals that leads to cancer (Harris).

*Linoleic Acid.* Conjugated linoleic acid (CLA) supports proper fat metabolism and may prevent certain types of cancer (Butler, 2003). Linoleic Acid has been found to inhibit cancer development in animals (Christman et al., 1993), and is up to five times higher in grass-fed beef than in grain-fed beef (Butler).

*Methionine.* Christman et al. (1993) also reported that methionine, which is found in some meat products, maintains the level of methylation of cells, which controls cell proliferation (Christman et al.).

*Fruits & Vegetables*

It has been proposed that any association between large amounts of meat consumption and colorectal cancer development may be due to the result of deficiencies of other protective dietary factors such as fruits and vegetables (Bingham, 1999; Harris, 1999; Hill, 1997; Hill, 1999, Mangels, 1998; Gerber et al., 2002; Tadjalli-Mehr et al., 2003). Some researchers have even proposed that up to 80% of breast, bowel and prostate cancers are attributed to dietary practices (Bingham).

In 1998, The American Institute for Cancer Research and the World Cancer Research Fund commissioned a review of the literature on diet and cancer. Although specifics of the review, methods, and limitations were not cited, nor was an explanation of the development of the expert panel used to conduct the study, the conclusions made were strong. The panel concluded that inappropriate diets are responsible for approximately one-third of all cancer deaths. They also concluded that vegetarians have
decreased incidence of several kinds of cancer. They attributed this reduction in cancer
to the exclusion of meat from the diet and increased intake of plant source foods
(Mangels, 1998). Similarly, through a critical analysis of epidemiological and
experimental studies over the last 20 years, Gerber et al. (2002) found that there was an
inverse relationship between the intake of fruits and vegetables and the risk of cancer.

In 1999, Harris found that the intake of animal source food correlated with
country-by-country incidence of various types of cancer. The less animal source food per
capita, the lower the cancer rate. The conclusions drawn by Harris were derived from
multiple regression analysis on cancer incidence country-by-country using Food and
Agriculture Organization food consumption data. Sample information concerning the
number of people or gender was not included. Harris found that the rates for several
types of cancer (breast, colon, lung, and ovarian) correlated with the consumption of
animal source food. A moderate negative (protective) correlation with these cancers and
plant source was also reported (Harris).

Giovannucci et al. (1992) found that all sources of fiber (vegetables, fruits, and
grains) were associated with decreased risk of adenoma. In this cohort study, dietary
fiber was inversely associated with risk of adenoma (P for trend less than .0001). All
sources of fiber (vegetables, fruits, and grains) were found to be associated with
decreased risk of adenoma (Giovannucci et al.).

A population based case-control study by Ghadirin et al. (1997) came to similar
conclusions. Conducted in Greater Montreal to assess the food habits of French
Canadians, this study revealed that the consumption of vegetable source fiber had a
strong inverse association to colon cancer risk (OR 0.57, 95% CI 0.39-0.84), while
dietary fiber consumed from cereals showed no association (OR 0.78, 95% CI 0.53-1.13, P 0.1046). It was also found that total fiber decreased colon cancer risk by 38% (Ghadirin et al.).

As previously stated, “diet” is difficult to measure and allows for a great deal of recall error. Case-control studies, such as that by Ghadirin et al. (1997) above, also present difficulties due to potential biases in the sense that cases may report eating more food overall and particularly more fat rich foods than normal healthy individuals. Nevertheless, there is considerable promise for colorectal carcinoma control through primary prevention and diet modification. The findings by Ghadirin et al. reinforce the importance of eating an increased amount of vegetables and fiber in the prevention of colon cancer (Ghadirin et al.).

Terry et al. (2002) reinforced the findings by Ghadirin et al. (1997) through a large population-based case-control study. In this study, Terry et al. found that high consumption of some foods, such as legumes, Brassica vegetables, and coffee, might be linked with a minimal to moderate decreased risk of the development of endometrial cancer.

In 1998, the AICR panel of international experts reviewed the findings of over 4500 studies to develop practical recommendations to minimize cancer risk and maximize health. They confirmed that a predominantly plant-based diet with a wide variety of fruits and vegetables contains many vitamins, minerals, fiber and phytochemicals which can protect us from cancer. The panel also suggested that diets high in plant-sources could also prevent cancer due to the fact that they contain little red
meat. Overall, the panel proclaims that a diet high in plant-based foods will help lower cancer risk (Welland, 1998).

*Evaluation by Cancer Site*

**Colorectal Cancer**

Colon cancer is one of the leading cancers in both incidence and mortality in most developed countries. It affects men and women equally, yet the variability in its international incidence is marked. The highest rates of colorectal cancer are primarily found in industrialized Western countries (Australia, New Zealand, North America, and most Western European countries) where the incidence of colorectal cancer lies between 25 to 35 per 100,000 (Potter, Slattery, Bostick, & Gapstur, 1993). These numbers are even more profound when compared to that of Asia, India, Africa, and South America, where the colorectal cancer incidence is reported to be one to three per 100,000 (Potter et al., 1993). There is considerable support that this international variability may be attributable to lifestyle and environmental factors. This claim is particularly supported by the observation that the incidences of colon cancer in developing countries in Asian and African regions are found to consistently rise with their degree of westernization (Potter et al.).

Colon cancer is the second most common cancer (incidence and mortality) for both men and women (Ghadirin et al., 1997). The highest incidence of colon malignancies occurs in the United States, Canada, and New Zealand (Ghadirin et al.). The lowest incidence occurs in Asia, Africa, and Latin America (Ghadirin et al.).

*Case control studies.* A small case control study by Lang et al. (1994) showed well-done meat was associated with a higher risk of colorectal cancer. Participant’s
exposure information for this study was obtained using a dietary and health habits questionnaire. Through univariate analysis of the questionnaire, the researchers concluded that age and consumption of well done red meat were associated with increased risk of colorectal neoplasia. Furthermore, a logistic regression model that included age and consumption of well done red meat as independent covariates gave odds ratios of 1.08 and 2.08 respectively (Lang et al.).

The study by Probst-Hensch et al. (1997), which has previously been mentioned in this review, also found a linear trend of increasing adenoma prevalence with increasing consumption only for beef, pork, or lamb as a main dish without adjustment for saturated fat (OR 1.7, CI 1.1-2.5, P-value for trend 0.04). Overall intake of red meat was also associated with an increased risk of adenomas (P-value for trend 0.02) in this population-based, case-control study (Probst-Hensch et al.).

Probst-Hensch et al. (1997) was unable to consistently detect an increased adenoma prevalence among participants who either consumed meat items with presumably high HCA levels, or who reported to prepare red meat in methods potentially leading to high HCA concentrations (Probst-Hensch et al.).

Also conducted in 1997, and previously mentioned in this review was the case-control study by Ghadirin et al. At the conclusion of this study, the researchers found that there was no association between the risk of colon cancer and total intake (OR 1.17, P 0.3039). Likewise, there was no significant difference between cases and controls for source of energy intake (Ghadirin et al.).

A population-based case-control study in Hawaii was performed by Marchand et al. (1997) to look at different population groups, their diet, and the development of
colorectal cancer. Conducted in 1997, this study interviewed 698 male and 494 female Caucasian, Japanese, Filipino, Hawaiian, and Chinese patients diagnosed between 1987-1991 with pathologically identified adenocarcinoma of the colon or rectum. A total of 1,192 population controls were matched for age, gender and ethnicity. Odds ration, adjusted for caloric intake and other dietary and non-dietary risk factors were estimated using conditional logistic regression (Marchand et al.).

In this 1997 study, Marchand’s group found that the ratio of consumed polyunsaturated fat to saturated fat was found to have an inverse relationship with the development of colorectal cancer with odds ratios of 0.6 in both males and females (95% CI 0.4-1.0 for males, 0.3-0.9 for females) for the highest compared to the lowest quartile (P < 0.05 for trend). In men only, intakes of red meat were associated with the risk of cancer development in the right side of the colon, and processed meat was associated with the risk of cancer in the rectum. Fish and fat-trimmed red meat were not related to an increased risk of colorectal cancer development. In both males and females, chicken eaten without the skin was associated with an inverse risk of colorectal cancer. The strongest correlation to colorectal cancer development was found for eggs, with an odds ratio of 2.7 for men (95% CI 1.7-4.0) and 2.3 for women (95% CI 1.4-3.7) for the highest compared with the lowest quartile of intake (P < 0.001 for trend). This association was dose-dependent, not accounted for by known confounders or other dietary explanations, and was very consistent between both males and females, ethnic groups, and involving all areas of the large colon (Marchand et al.).

It is possible that the associations with animal products gathered in this study may be due to over-representation of health conscious individuals in the control group,
although this is unlikely due to the high participation rate of 71% (Marchand et al., 1997). A difference between cases and controls and their ability to recall past dietary intake is also of concern in this type of study. Therefore, the uses of detailed questionnaires were administered to carefully trained interviewers to try and limit any measurement error that might result (Marchand et al.).

Welland (1998) proclaimed that using very high heat or direct flame (grilling), produced cancer-causing heterocyclic amines, especially in meat, fish and poultry. As stated previously in this review, heterocyclic amines increase the risk of many cancers, especially cancers of the colon and rectum (Welland).

Through a large case-control study of colon cancer and dietary risk factors, Nowell et al. (2002) found only a non-significant trend in risk with meat doneness. However, the researchers did find that higher exposure to heterocyclic amines was strongly associated with colorectal cancer risk.

Navarro et al. (2003) conducted a case-control study with 287 patients diagnosed with colorectal adenocarcinoma and 566 controls. Both cases and controls were interviewed concerning their dietary habits and consumption of different meat types. Cases were patients admitted to the nine largest hospitals in greater Cordoba, ranging in age from 24 to 80 years old, with a primary diagnosis of colorectal adenocarcinoma. Overall, 163 men and 124 women, with a mean age 60.74 were interviewed as cases. Controls were patients in the same geographic area and admitted to the same hospitals for reasons other than malignancies or conditions related to the digestive tract. Overall, 309 men and 255 women, ranging in age from 23-80, with a mean age of 58.2, were interviewed as controls. In most cases, interviewers were unaware of subject status as
case or control. The investigators also considered different types of meat in this study. These types of meat included fatty and lean beef, bovine viscera (large and small bowels, salivary and mammary glands, pancreas, kidney, and liver), pork, cold cuts (ham, bologna, salami, and cured meat of pork), sausages, chicken, and fish (Navarro et al.).

Multiple logistic regression was used to determine odds ratios and their related 95% confidence intervals (Navarro et al., 2003). The median intake of all meats, especially bovine, reached 287g/day in men and 205g/day in women. Meats were found to provide about 50% of total energy intake and approximately 64-67% of total protein consumption. Only 25% of men, and 20% of women’s total meat intake came from white meat (Navarro et al.).

At the conclusion of this study, Navarro et al. (2003) found that there was an increased risk of colorectal cancer development for patients consuming large amounts of processed meats, specifically cold cuts and sausages (OR 1.47, CI 1.02-2.15) and bovine viscera (OR 1.73, CI 1.18-2.54). They also reported that lean cuts of beef were associated with a decreased risk of colorectal cancer development (OR 0.64, CI 0.43-0.94) (Navarro et al.).

*Cohort studies.* Tiemersma et al. (2002) evaluated meat consumption and cigarette smoking. In this study, a total of 102 incident cases of colorectal cancer and a random sample of 537 controls matched for age and gender were analyzed in 8.5 years of follow-up from a Dutch prospective study. Information regarding smoking and dietary habits were also collected (Tiemersma et al.).

The researchers of this study found that the consumption of red meat elevated the risk for colorectal cancer among men. Smoking cigarettes for at least 16 years also
increased the risk of colorectal cancer. The intake of poultry and fish, however, decreased the risk in women. Overall, Timersma et al. (2002) concluded that former long-term smoking and meat consumption were associated with colorectal cancer in this study.

Flood et al. (2003) found that during 386,716 person-years of follow-up, there were 487 incident cases of colorectal cancer. Of these, 96% were adenocarcinomas. The average age of the participants was 61.9 years. Relative risks for increasing quintiles of total meat and red meat consumption indicated no association with colorectal cancer for red meat (relative risk for high compared with low quintile 1.10, 95% CI 0.83, 1.45). For total fat, there was also no association with increasing quintiles of consumption (relative risk for high compared with low quintile 1.14, 95% CI 0.86, 1.53) (Flood et al.).

The study by Flood et al. (2003) provided no evidence of an association between either meat or fat (or any of their subtypes) and colorectal cancer incidence. Neither red meat nor white meat nor saturated fat nor unsaturated fat showed any association with colorectal cancer in this cohort (Flood et al.).

*Descriptive ecological studies.* Conclusions from several descriptive ecological studies examining the relationship between meat consumption and cancer risk are also worth mentioning.

Bingham (1999) examined international comparisons from cohort studies and found that vegetarians do not have reduced risk of bowel cancer. Also, through a meta-analysis Norbat et al. (2002) found that total meat consumption was not significantly associated with colorectal cancer risk, but the consumption of red meat and processed meat increased the risk of colorectal cancer.
Gastric Cancer

Throughout my research, I came across two studies evaluating the relationship between meat consumption and gastric cancer risk (Boddetta, 2001; Mangels, 1998). In 1998, the American Institute for Cancer Research and the World Cancer Research Fund commissioned a review of the literature on diet and cancer and concluded that a higher intake of fruits and vegetables decreased the risk of stomach cancer (Mangels).

As detailed previously in this literature review, Bodetta (2001) conducted a case-control study in Uruguay including 123 patients with stomach cancer. All cases were questioned on the way that they cooked their meat, leading to a classification of fried, barbecued, or boiled. It is important to note, that no information of the degree of doneness was recorded in this study (Bodetta).

In the analysis of 13 different meat items, Bodetta (2001) found that red meat intake showed a steep increase in risk of gastric cancer (OR 2.4, 95% CI 1.3-4.4, P 0.003). A strongly positive association was also observed between total meat intake and gastric cancer. White meat intake was not found to be associated with risk of gastric cancer (Bodetta).

According to this study, high intake of total meat was associated with a strong increase in risk of gastric cancer (Boddetta, 2001). The researcher also concluded that calorie intake is a strong confounder of the relationship between meat and gastric cancer (Boddetta).
Pancreatic Cancer

Several studies evaluating the relationship between pancreatic cancer and meat consumption were eligible for inclusion into this literature review. Of these studies, several reported significant findings which are worth discussion.

Knekt et al. (1994) reported that the association with fried meat was not found in a large Finnish cohort. The researchers also reported an increased risk ratio (i.e. greater than 1) associated with the top 1/3 of fried meat consumers for cancer of the pancreas and nervous system (Knekt et al.). Similarly, Mangles (1998) concluded that increased meat consumption probably increases the risk of cancer of pancreas.

Anderson et al. (2002) conducted in-person interviews using 193 cases and 674 controls in order to formulate a case-control study in which individuals provided information on their meat consumption and preparation. Of the cases that were actually spoken to, approximately 75% participated in the study (Anderson et al.).

Anderson et al. (2002) found that although total meat intake and red meat intake were increased in cases as opposed to controls, they were not significant predictors of cancer risk. However, a positive and strong association was observed for barbequed red meat consumption. The odds ratio and 95% confidence interval for barbequed meat consumption was 1.03, and the test for trend was statistically significant (P<0.001) (Anderson et al.).

The researchers concluded that the risk of cancer development increased with reported increases in meat intake (Anderson et al., 2002). Consumption of broiled meat (which does not contain a high level of HCAs or PAHs) did not show an increased risk of pancreatic carcinoma. Also, increased risk was associated with fried meat intake, but
these findings were not statistically significant. Likewise, findings were not significantly changed by additional adjustments for calories, total fat, fruit and vegetables, or alcohol intake (Anderson et al.).

**Breast Cancer**

A total of 6 studies evaluating the relationship between meat consumption and breast cancer were eligible for inclusion. Knekt et al. (1994) evaluated the intake of fried meat and found a positive association between fried meat intake and the risk of female-hormone-related cancers (cancer of the breast, endometrium and ovary). This was concluded from the results of a 24-year follow-up, in which 853 cancer cases were diagnosed. The intake of fried meat was estimated from a dietary history interview covering the total diet of the participants during the previous year. The relative risk of these cancers combined between persons in the highest and lowest tertiles of daily intake of fried meat adjusted for age, personal characteristics and intake of other main food groups was 1.77 (95% CI 1.11-2.84) (Knekt et al.).

Ronco et al. (1996) conducted a case-control study on breast cancer in Uruguay using a food frequency questionnaire involving 64 food items in 1996. After adjustment for potential confounders (which included family history of breast cancer, menopausal status, body-mass index, total energy and total alcohol intake), an increased risk associated with consumption of total meat intake, red meat intake, total fat and saturated fat intake was observed. The strongest effect was observed for red meat intake (OR 4.2, 95% CI 2.3-7.7), after controlling for protein and fat intake. At the conclusion of the study, the researchers reported that an increased risk on breast cancer was associated with consumption of total meat intake and red meat intake (Ronco et al.).
As detailed previously in this literature review, three other studies were evaluated for their findings on the relationship between meat consumption and malignancies of the breast. Mangles (1998) reported that increased meat consumption probably increases the risk of cancer breast. Also, Harris (1999) reported that breast cancer incidence was found to have the highest correlation (P < .001) with animal source calories, and a negative (protective) correlation (P .046) was found with plant protein consumption. However, based on international comparisons from cohort studies, Bingham (1999) reported that vegetarians do not have a reduced risk of breast cancer.

Prostate Cancer

A total of 3 studies located throughout my research examined the relationship between meat consumption and prostate cancer risk. Mangels (1998) reported that increased meat consumption probably increases risk of prostate carcinoma. However, Norrish et al. (1999) reported that meat doneness was weakly and inconsistently associated with prostate cancer risk for individual types of meat, but increased for well-done beefsteak (RR 1.68; 95% CI 1.02-2.77; two-sided P for trend .03). The conclusions by Norrish et al. were developed after evaluating 317 prostate cancer cases and 480 controls, using self-reported dietary data and experimentally measured heterocyclic amine levels for varying degrees of meat doneness. Age-adjusted and multivariate analyses did not confirm a statistically significant increase in prostate cancer risk with increasing either total meat intake or red meat consumption. Norrish et al. concluded that there was no clear association between prostate cancer risk and either estimated total or other individual heterocyclic amines.
A cohort study by Michaud et al. (2001) reported that the consumption of red meat and dairy products seem to be linked to an increased risk of metastatic prostate cancer (RR 1.6 for top vs. bottom quintile comparison, 95% CI 1.0-2.5). This information was retrieved through the detailed dietary information contributed by a group of 51,529 men between 1986 and 1996. During that time, 1897 total cases of prostate cancer and 249 cases of metastatic prostate cancers were identified. The researchers found that processed meats, bacon and beef, pork or lamb each contributed to an increased risk of metastatic prostate cancer. Michaud et al. concluded that a high intake of both red meat and dairy products was associated with a statistically significant two-fold increased risk of metastatic prostate cancer compared to low intake of both products.

Through logistic regression for analyses of diet and prostate cancer, the Michaud et al. (2001) study also found that the consumption of total meat, red meat, and dairy products were not linked with a risk of beginning or advanced prostate cancer.

**Lung Cancer**

Several studies have also been published evaluating the relationship between meat consumption and lung cancer acquisition. A 1997, population-based case-control study of women in Missouri, reported that red meat and dietary fats were not found to be associated with lung cancer. In this study, Swanson et al. (1997) invited all cases of newly diagnosed, primary lung cancer in women ranging in age from 35-84 years of age to participate in the study. Population-based controls were also invited to participate. Interviews were obtained from 624 controls and 587 cases of primary lung cancer. The researchers found that energy and age-adjusted relative risks suggested a direct relationship between dietary fats, frequency of meat consumption and risk of lung cancer.
Interestingly, after adjustment for confounding variables, dietary fats no longer showed an associated risk with lung cancer, but a link between frequent meat consumption and lung cancer remained. Specifically, risk of lung cancer was increased (95% CI 1.2-3.0) in those women in the highest quintile of red meat intake as compared to women in the lowest quintile (Swanson et al.).

It is important, however, to note that the effect reported by Swanson et al. (1997) were limited to those cases in which proxy elicited the dietary information. Therefore, after adjusting for possible confounders and eliminating data received from participants who responded by proxy, the consumption of red meat and dietary fats were not associated with lung cancer in this study (Swanson et al.).

Mangels (1998) reported that higher intakes of fruits and vegetables decrease the risk of lung cancer. Also, Sinha et al. (1998) preformed a study evaluating fried, well-done red meat and the risk of lung cancer in women living the United States. This was organized through a population-based, case-control study including both smoking and non-smoking women in Missouri (Sinha et al). A total of 593 cases and 623 controls were matched. Each participant completed a 100-item food frequency questionnaire, which included detailed questions regarding meat consumption. From these food-frequency questionnaires, the amount of meat eaten in grams/day was estimated according to the method of preparation, and level of doneness (Sinha et al.).

At the conclusion of their study, Sinha et al. (1998) reported that the risk of lung cancer was increased with total meat consumption (OR 1.6, 95% CI 1.1-2.4), red meat (OR 1.8, 95% CI 1.2-2.7), well-done red meat (OR 1.5, 95% CI 1.1-2.1), and fried red meat (OR 1.5, 95% CI 1.1-2.0). The odds ratios for a 10-gram increase in consumption
were 1.04 for total meat, 1.06 for red meat, 1.08 for well-done red meat, and 1.09 for fried red meat. Ultimately, the researchers concluded that an increase in the risk of lung cancer was associated to the intake of red meat, especially well-done red meat and/or fried red meat (Sinha et al.).

Through multiple regression analysis, Harris (1999) reported that lung cancer was correlated to the consumption of animal fat (P <.01), and that plant sources had a negative (protective) effect. Harris also noted that data on tobacco was not available, and concedes that tobacco abuse is the most important predictor of lung cancer mortality rates.
Chapter 4 – Discussion & Conclusions

The use of appropriate diets may prevent 3-4 million cases of cancer each year on a global scale (Mangels, 1998). However, the problem of deciding whether a diet high in meat products has adverse health consequences, or whether it is simply a marker of diets which are inadequate in some of the beneficial components of fruits, vegetables and cereal foods is still unresolved.

Conclusions

Meat Preparation

A total of 16 studies were critically reviewed regarding the relationship between different types of meat preparation and malignancy development. Of these studies, 5 found a positive association between grilled, barbequed or well-done meat and cancer risk (Anderson et al., 2002; Lang et al., 1994; Sinha et al., 1998; Welland, 1998; Chin et al., 1996), while 4 found a no association (Boddetta, 2001; Norrish et al., 1999; Nowell et al. 2002; Probst-Hensch et al., 1997). A total of 3 studies found a positive association between processed meat and cancer risk (Bingham, 1999; Marchaund et al., 1997; Michaud et al., 2001), while one found no association (Flood et al., 2003). A total of 3 studies found a positive association between fried meat consumption and cancer risk (Knekt et al., 1994; Probst-Hensch et al.; Sinha et al.), while one found a positive but non-significant association (Anderson et al.), and only one found no association (Bodetta). One study found a positive association between cured meat and cancer risk (Bodetta), while one found no association (Blot et al., 1999). Also, one study found a decreased but non-significant risk between broiled meat and cancer risk (Anderson et al.).
While the association between doneness of meat and cancer at a particular site has been examined in more than one study, the findings appear inconsistent, and do not allow for sweeping generalizations about meat consumption, the way meat is prepared, and its association with the production of cancer development as a whole.

**Meat and Fat**

A total of 13 studies were evaluated for their relevance to the association between fat intake and cancer risk. Of these studies, 7 found a positive association between fat and cancer risk (Adlercreutz, 1990; Butler, 2003; Giovannucci et al., 1993; Harris, 1999; Navarro et al., 2003; Weisch, 1987; & Zhao et al., 1991) while 6 found no association between these variables (Flood et al., 2003; Hunter et al., 1996; Ip et al., 1996; Marchand et al., 1997; Stender et al., 1995; Swanson et al., 1997).

**Fruits and Vegetables**

A total of 10 studies were evaluated for their reported association between fruit and vegetable consumption and cancer risk. All 10 studies found an inverse association between the two variables (Gerber et al., 2002; Ghadirin et al., 1997; Giovannucci et al., 1992; Harris, 1999; Hill, 1997; Hill, 1999; Mangels, 1998; Maneusos, Day, Trichopoulos, Gerovassilis, & Tzonou, 1983; Tadjalli-Mehr et al., 2003; & Terry et al., 2002). More research needs to be done to scientifically prove the protective benefits and mechanisms of a plant-based diet in the prevention of cancer (Tadjalli-Mehr et al.).

**Colorectal Cancer**

A total of 15 publications were evaluated for their reported findings on the association between meat consumption and colorectal cancer risk. Of those studies which used the term “red meat,” 7 found a significant positive association between
colorectal cancer and red meat (Bingham, 1999; Giovannucci et al., 1992; Lang et al., 1994; Maneusos et al., 1983; Marchand et al., 1997; Norbat et al., 2002; Tiemersma et al., 2002; & Welland, 1998), while 4 found no association between the 2 variables (Flood et al., 2003; Navarro et al., 2003; Nowell et al., 2002; Probst-Hensch et al., 1997). It is important to note that even with the seemingly implicit heading of “red meat,” there were still discrepancies in the definition of red meat among different studies, making direct comparison between the studies difficult.

Another explanation for the null results of the study by Flood et al. (2003) may be the inability of this study to classify subjects according to their heterocyclic amine exposure. There were no direct measurements of cooking methods in this study, therefore the HCA exposure of each subject is unknown. It is important, however, to recognize that food frequency questionnaire measurement error could also account for the failure of this study to recognize any association between meat and colorectal cancer risk. This statement is true, especially if the true effect of meat or fat is only modest (Flood et al.).

Several studies evaluated total intake of meat, which generally refers to all meat products, and colorectal cancer risk. Of those studies, 2 found a significant positive association between total meat intake and colorectal cancer risk (Harris, 1999 & Mangles, 1998), and 2 found no association (Navarro et al., 2003 & Norbat et al., 2002)

Other reported findings included in the reviewed literature included colorectal cancer risk in relation to processed meat, other meat, and total energy intake. A total of 4 studies found a positive association between processed meat and colon cancer risk (Bingham, 1999; Marchand et al., 1997; Navarro et al., 2003 & Norbat et al., 2002). A
total of 5 studies found no association between colon cancer risk and consumption of “other meat,” such as white meat, pork, or chicken (Bingham, 1999; Flood et al., 2003; Marchand et al.; Navarro et al., 2003, Tiemersma et al., 2002). In regards to total energy intake, one study found a positive association with colorectal cancer risk (Steinbach et al., 1994), while one found no associations (Ghadirin et al., 1997).

The qualities of these studies are variable in regards to aspects such as size of study, response rates and approach of dietary information gathering. Most of these studies adjusted for age and gender, however, not all of these studies matched the cases and controls for total energy intake and other dietary factors.

This critical review of the epidemiological data has produced little support for the conclusion reached in three earlier review papers that meat is “consistently, almost universally, positively associated” with the risk of colon cancer (Potter et al., 1993; Trichopoulos & Polychronopoulou, 1986; Sian, 1987).

As described previously, there are apparent inconsistencies between and within studies. Some studies demonstrate a positive association with some or all meat consumption categories, while others have reported a negative association with some or all of the categories under consideration.

Although published in 1983, a case-control study by Maneusos et al. still has significant conclusions that are worth mentioning at this point in the discussion concerning meat consumption and colorectal cancer development. In this case-control study of colorectal cancer in Greece, the consumption of beef and lamb was found to have an increased risk in colorectal cancer development, and three vegetables (spinach, cabbage or lettuce and beets) were found to have a decreased risk (Maneusos et al.,
The researchers were able to show that people who consumed a high meat, low vegetable diet (in the top 20%) were eight times as likely to be in the colon cancer group as compared to those who consumed a low meat, high vegetable diet (in the lowest 20%). However, what is striking is that the authors seemed to overlook that the relationship was not dose-related. This seems to imply that consuming both meat and vegetables either in moderation or in an optimal ratio could be more beneficial than diets which are either very low in meat or very high in vegetables (Maneusos et al.).

Overall the evidence incriminating meat as the risk factor in developing colon cancer is weak. Epidemiological data have yet to provide a clear answer to the question of whether high meat consumption increases the risk of colon cancer. To some degree, the inconsistency of findings might reflect the sameness of study design and methodology, and the similarity of tools used for assessment of dietary intake.

Nevertheless, given that 80% of all papers, which have studied the association between the consumption of fruit and vegetables and the risk of colorectal cancer, have reported statistically significant negative or inverse associations, it would be careless to dismiss the research tools as simply inadequate for the task of assessing the relationship between meat intake and colorectal cancer development (Steinmetz & Potter, 1993). A more reasonable conclusion seems to be that if meat contributes any increment to the risk of colorectal cancer than that increment is fairly small.

**Gastric Cancer**

Of the reviewed studies which were eligible for inclusion into this literature review, only one was found to have a positive association between gastric cancer and
meat consumption, red meat, total meat, and total energy intake (Boddetta, 2001), while white meat was found to have no association (Boddetta).

This study by Boddetta (2001) has several limitations. Recall bias might have played a role, as is possible in all case-control studies. Errors in the measurements of dietary intake are also likely, and the possibility of differential reporting bias is possible. Nevertheless, it is worthwhile to note that the strengths of this study include the high response rate for cases and controls, and the possibility to control for total energy intake.

Pancreatic Cancer

A total of 3 studies which evaluated the risk of pancreatic cancer development and its association to meat consumption were eligible for inclusion into this review. Of these studies, one found a positive association with red meat (Anderson et al., 2002), while another found a positive, but non-significant association with red meat and pancreatic cancer development (Knekt et al., 1994). Only one study reported a positive association between total meat consumption and cancer risk (Mangels, 1998), while another reported a positive, but non-significant association between the two variables (Anderson et al.).

Breast Cancer

Of the 6 studies evaluated in this review, only one found a positive association between red meat and breast cancer risk (Ronco et al., 1996). However, a total of 4 studies found a positive association between total meat intake and breast cancer risk (Bingham, 1999; Harris, 1999; Mangels, 1998 & Ronco et al.).
Prostate Cancer

Of the three studies evaluated for their reported findings concerning the association between meat consumption and prostate cancer risk, one reported a positive association between red meat and prostate cancer (Michaud et al., 2001). One study also reported a positive association between total meat consumption and cancer risk (Mangels, 1998), and only one reported no association (Michaud et al.).

Lung Cancer

A total of 3 studies evaluating the association between meat consumption and lung cancer development were eligible for inclusion into this literature review. Of these studies, only one found a positive association between red meat and lung cancer risk (Sinha et al., 1998). Likewise, only one study reported no association between the two variables (Swanson et al., 1997).

Although these results are compelling, further studies are warranted, especially with more detailed information dietary questionnaires on meat preparation and cooking practices. The findings of these studies also need to be viewed in accordance with other risk factors, such as smoking, which is by far the largest risk factor for lung cancer, and cannot be discounted even when other modest risk factors are found (Sinha et al., 1998).

Recommendations

Estimates from the American Cancer Society are that one of every two men and one in three women will get cancer over their lifetime (Welland, 1998). However, based on the conclusions drawn from this literature review, there seems to be a way to improve ones odds through making the right lifestyle choices such as eating properly, exercising, and not smoking.
Although definitive conclusions cannot be drawn from the evaluated studies, recommendations can be made based on their wealth of findings. Even though the relevance between meat consumption and cancer development remains unclear, it would seem prudent to instill several of these recommendations into one's dietary habits in order to maximize overall health.

Firstly, it would be wise to choose lean cuts of meat trimmed of fat (which are becoming increasingly available from producers and retailers), because a diet high in saturated fat and low in fiber increases the risk of colorectal adenoma (Giovannucci et al., 1992). Untrimmed red meat and processed meat may increase the risk of colorectal cancer development, while chicken eaten without the skin may decrease the risk of cancer development (Marchand et al., 1997).

Also, pay attention to the ratio of polyunsaturated to saturated fat, for it may be a better indicator of colorectal cancer risk than the absolute amount of specific fats consumed (Adlercreutz, 1990; Butler, 2003; Flood et al., 2003; Giovannucci et al., 1993; Harris, 1999; Hunter et al., 1996; Ip et al., 1996; Marchand et al., 1997; Navarro et al., 2003; Stender et al., 1995; Swanson et al., 1997; Weisch, 1987; & Zhao et al., 1991).

Limit intake of red meat to less than three ounces a day, if eaten at all (Welland, 1998). Also, limit fatty foods, such as foods of animal origin (Welland). Substitute chicken and fish for red meat and increase intake of vegetables, fruits, and grains to reduce risk of some types of cancer (Giovannucci et al., 1992).

As stated before, heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are formed through temperature and time-dependent conditions during the cooking of meat, and may increase the risk of some types of cancers
Cooking methods such as baking, broiling, and stewing, and avoiding excess charring or brownness can minimize levels of HCAs and PAHs in barbequed and fried meat (Anderson et. al.; Ferguson, 2002). Use of decreased temperature cooking methods such as stewing, roasting, broiling and microwaving could also prevent the formation of HCAs and PAHs (Anderson et al.; Bingham, 1999; Boddetta, 2001; Ferguson; Probst-Hensch et al, 1997). These findings suggest that individuals may decrease their risk of developing some types of cancer by changing their cooking methods.

There seems to be a role for increased consumption of fruits and vegetables in the primary prevention of malignancy development (Gerber et al., 2002; Ghadirin et al., 1997; Giovannucci et al., 1992; Harris, 1999; Hill, 1997; Hill, 1999; Mangels, 1998; Maneusos, Day, Trichopoulos et al., 1983; Tadjalli-Mehr et al., 2003; & Terry et al., 2002). A diet rich in fruits and vegetables, and low in red meat (if eaten at all), can significantly reduce the risk of cancer development (Mangels). Fruits and vegetables provide many phytochemicals, which may explain their protective effect against the development of some types of cancer (Gerber et al.). Green-leafy vegetables and citrus fruits were found to be especially potent cancer-fighters (Welland, 1998). Recommendations from some experts suggest a predominantly plant-based diet with a variety of fruits, vegetables and legumes (Mangels). Eating five or more servings or a variety of fruits and vegetables per day has been recommended by some researchers (Welland, 1998), while others have proclaimed a minimum of 400g of fruits and vegetables per day can lower an individual’s cancer risk (Gerber et al.).
The American Cancer Society estimates that these protective life choices can reduce your risk of cancer by 60 to 70% (Welland).

**Need for Further Research**

While significant conclusions and recommendations have been extrapolated from this extensive literature review, the need for further research has also been highlighted. The studies surrounding the meat consumption/malignancy connection are vast, however, the need for further research on the subject is readily apparent.

Firstly, there is a necessity to standardize the definitions under evaluation. The word “meat,” and its subcategories have no precise usage among studies. It is sometimes used to refer to all non-fish and non-poultry meat items, and sometimes it is used to include poultry. This ambiguity presents difficulties when trying to compare results from studies generated in different countries or regions.

The terminology used for different cooking methods also varies around the world. Sources of heat for grilling can also be different. For example, Argentina dry heat is obtained from coal, charcoal, firewood or gas, while in Uruguay, most of the heat is obtained from firewood and coal (Matos et al., 2002). Due to these ambiguities, interpretation of data can be confusing. This is further complicated by the fact that depending on direct flame use and different combustibles, more carcinogenic compounds may potentially be generated.

Information regarding global correlations between meat consumption and malignancy development would be valuable. It is important to recognize that data on meat from one country cannot simply be extrapolated to another country. For example, New Zealand experiences fewer temperature extremes than the United States, and the
animals are pasture-fed as opposed to grain-fed, which leads to differences in nutrient composition (Ferguson, 2002).

*Heterocyclic Amines and Polycyclic Aromatic Hydrocarbons*

While studies both confirming and discounting the carcinogenic effects of heterocyclic amines and polycyclic aromatic hydrocarbons have been published, the need for further research exists. The issue of HCAs and PAHs effect on the progression of adenomas to cancer deserves further investigation (Probst-Hensch, et al., 1997). The observed associations between HCAs, PAHs, and cancer also requires further research through an in-depth study with chemically validated questionnaires (Matos & Brnadani., 2002), consumption trends, and precise cooking methods.

While experimental studies have shown a strong effect of heterocyclic amines and cancer development in rats (Ronco et al., 1996), further studies should be performed in humans, using markers of heterocyclic amine exposure. Assessment of exposure to specific heterocyclic amines might be superior to analysis of meat intake and cooking methods in predicting risk of colorectal cancer (Nowell et al., 2002).

It is also important to note that the interaction between meat, N-nitroso compounds and vegetable intake on the risk of cancer has not been studied comprehensively (Bingham, 1999). Nitrosamines and other heterocyclic amines found in cooked meat (Nowell et al., 2002) were not evaluated by most of the studies in this literature review and should be assessed for their link to cancer risk.

*Meat Preparation*

The interpretation of epidemiological data on cooked meat is difficult due to the many confounders that can be encountered such as animal fat, other animal proteins, and
other types of ingested foods, such as vegetables and fruits, which may decrease the risk of certain cancers (Welland, 1998). Further epidemiological efforts are needed to ascertain the potential link between fried-food mutagens and cancer risk (Knekt et al., 1994).

Future studies should also include information about the cooking of individual meat items (Probst-Hensch et al., 1997), for example, how specific red meat items, chicken, and other types of meat are preferentially prepared. Further research should also be conducted with attention to details such as precise temperature of cooking and estimation of doneness, and other components of meat, such as meat freshness.

**Meat and Fat**

There is a need for the assessment of individual fatty acids and their correlation with cancer development. There are, of course, serious methodological constraints hindering a study of this kind, which would set out to evaluate the human health consequences of just one specific fatty acid in a diet containing many fatty acids (Stender et al., 1995; Ip et al., 1996).

Further research regarding the individual type of meat and its correlation to malignancy development is also warranted. However, considering that the fat content in meat can vary, it is hard to draw conclusions based on a type of meat, rather than fat content (Navarro, 2003).

**Fruits and Vegetables**

More investigation on the identification of the biologically active constituents of fruits and vegetables, and the mechanism by which they contribute to lowering the risk of cancer is also needed. This additional scientific support could increase public awareness
and update public health policy (Gerber et al., 2002). Tadjalli-Mehr et al. (2003) confirm that additional research needs to be done to scientifically support the protective benefits of a plant based diet in the prevention of cancer.

Significant conclusions, recommendations and areas for future research have been identified in this extensive review of the literature spanning the past 10 years. However, the larger question remains; Is red meat consumption associated with other unhealthy behaviors, such as smoking, or high caffeine consumption? Or, are fish and poultry consumption correlated with healthier habits, such as increased intake of fruits and vegetables and exercise? The absolute answers to these questions may be unattainable due to study constraints and ethical concerns. Nevertheless, by utilizing the information and recommendations presented in this review, we may be able to make choices to maximize our health, and minimize our risk of disease.
References


Abstract

Objective. The relationship between cancer risk and meat consumption remains controversial. The epidemiological evidence on the association between meat consumption and cancer risk was reviewed to assess the meat/cancer relationship.

Method. An extensive review of the past 10 years of literature on meat consumption and cancer risk was completed using MEDLINE, PUBMED, EBSCO, and OHIOLINK databases. Results. The associations between meat consumption and cancer risk were not consistent. A wide variation in the definitions used for the term “meat,” and in the categorization of meat consumption level, made direct comparison of studies difficult.

Conclusion. Any effect of meat consumption on cancer risk is likely to be small, or even a residual effect of a decreased consumption of fiber. Healthy diet recommendations include using decreased temperature cooking methods, choosing lean cuts of meat, limiting intake of red meat, and increasing intake of vegetables, fruits, and grains.