Colorectal Cancer and Meat Consumption: Recent Views from Epidemiology

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COLORECTAL CANCER AND MEAT CONSUMPTION:
RECENT VIEWS FROM EPIDEMIOLOGY
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Colorectal cancer is the second leading cause of cancer death in the United States and the third most commonly diagnosed form of cancer in men and women (CDC 2003). The risk for developing colorectal cancer increases with age (90 percent of cases occur in individuals over 50) and with personal or familial predisposition to cancer. Numerous studies over the years also show connections between lifestyle factors—such as eating a diet high in saturated fat and low in fruits and vegetables, smoking and not exercising regularly—and the incidence of this cancer. However, the links between certain dietary factors and the risk of colorectal cancer remain contentious. Meat consumption, in particular, emerges as an arena of debate among epidemiologists. It is difficult to separate meat consumption from other confounding factors that strongly affect colorectal cancer risk, such as obesity and physical inactivity, and studies report disparate findings on the statistical relationship between meat eating and cancer. Furthermore, researchers
are unsure what specifically about meat, and particularly red meat, may increase cancer risk. Studies have been conducted on iron and fat content, the presence of carcinogenic nitrates in processed meats, methods of cooking meat and genetic susceptibility in an attempt to locate a direct connection. Finally, it is difficult to ascertain accurate information related to meat consumption in retrospective studies, and the wide variety of potential exposures addressed in cohort studies on cancer may make it difficult to isolate meat consumption as a risk factor.

Despite these difficulties, research on food-related cancer risk is vitally important. Meat consumption in the United States is at a record high—In 2000, Americans consumed 195 pounds of meat per person, 57 pounds above the average annual consumption 50 years earlier (USDA 2002). The increased availability and convenience of processed meat products, rising consumer incomes and lower overall meat prices have led to this growth (ibid). Furthermore, low-carbohydrate/high-protein diet trends strongly encourage the consumption of meat and dairy products, which may lead to inadequate intake of dietary fiber, fruits and vegetables. Although some epidemiological reports have not supported a strong protective influence of the latter foods in relationship to colorectal cancer, they provide other micronutrients and health benefits that should not be overlooked (Giovannucci 2003). “Low-carb” diets are not necessarily problematic in and of themselves, particularly in light of the fact that obesity—largely a result of increased carbohydrate and fat intake along with reduced physical activity—is itself a risk factor for several types of cancer (Abu-Abid et al. 2002). Nevertheless, long-term adherence to a meat-heavy diet may increase colorectal cancer risks if the connection between meat consumption and cancer is proven. If the majority of colorectal cancers can be prevented through lifestyle alterations concerning food intake these factors need to be clearly delineated for clinical and preventive purposes. This paper will provide a broad overview of the current epidemiological data regarding colorectal cancer and meat consumption. A comparison of the results of several studies will provide a path on which to follow the most recent debates over meat consumption and colorectal cancer.

LITERATURE REVIEW:

Numerous detailed investigations—including mechanistic studies, animal experiments, clinical trials and epidemiological investigations—have explored the relationship between diet and colorectal cancer risk and meat consumption has emerged as the strongest correlation factor in many studies (Willett 2005). Although the associations seen in case-control studies have been largely positive, the relationship appears to be less consistent in cohort studies. For example, in a 1990 prospective study of 88,752 women, Willett et al. showed evidence that a high intake of animal fat increases the risk of colon cancer. Those who consumed beef, pork or lamb every day had a relative risk of 2.49 (95 percent CI), as compared to those who ate meat less than once a month. A parallel cohort study of 47,949 male health professionals by Giovannucci et al. also supported the hypothesis that intake of red meat is related to an elevated risk of colon cancer, although intake of animal fat was not positively correlated (1994). Another prospective cohort study in the Netherlands did not support the role of fresh meats and dietary fats in the etiology of colon cancer; however, researchers found that some processed meats may increase risk
Goldbohm et al. 1994). Finally, a cohort study of a low-risk Seventh Day Adventist population in California (n=32,051) found a positive association with total meat intake, but argued that the risks associated with red meat intake were potentially masking a more complex etiology (Singh and Fraser 1998). A meta-analysis of cohort studies on meat consumption and colorectal cancer by Sandhu et al. reported a pooled summary odds ratio of 1.21 (95 percent CI: 1.10, 1.33) for a 100 gram/day increase in total meat consumption, and a slightly higher ratio for increased daily red meat consumption (2001). A meta-analysis of case-control and cohort studies by Norat et al. showed similar results, albeit with a slightly higher odds ratio (1.35) for high levels of meat consumption compared to lower levels (2000). This abbreviated sample of studies reflects some of the larger debates in this area of epidemiologic inquiry. A more in-depth examination of two recent cohort studies with disparate findings will bring the debate into greater detail.

Flood et al. conducted a follow-up cohort study of women originally enrolled in the Breast Cancer Detection Demonstration Program. From 1987-89, 45,496 women completed a 62-item food frequency questionnaire, and participants subsequently completed three separate follow-up questionnaires over the next decade. The final analytic cohort of 41,073 individuals included in the analysis had complete follow-up from 1995-1998. Women in this cohort lived across the United States, average age at entry into the study was 62 years, and roughly 89 percent of the participants were White. Four hundred and eighty-seven of these women developed colorectal cancer during the study, and were identified through self-reports, cancer registries and the National Death index. Although the authors hypothesized that total meat intake would have an association with colorectal cancer, the results of this study did not provide evidence to support an association between total meat intake, total fat or any of their subtypes (e.g., red meat, animal fats) and colorectal cancer.

The authors presented several explanations for the null results. First, the method of dietary assessment used in this study may be imperfect. Aside from the potential measurement errors in any food frequency questionnaire, there was some debate over the small number of items in this particular survey. The authors argued that food frequency questionnaires used by other researchers (e.g., with 127, 150, and 276 items) yielded similar results, and the survey utilized here adequately assessed meat consumption patterns. However, the authors admitted that this instrument did not incorporate questions related to food preparation methods, some of which may be related to increased cancer risk. A potential issue in this study was the exclusion of 65 women with “unusually high intakes of meat.” Flood et al. argued that inclusion of these women did not materially alter the results of this analysis; nonetheless, it could be debated that although statistical data may not have been affected, this group could provide particularly revealing qualitative data. Although the authors conducted a lengthy defense of their methodology and accounted for several types of bias, the data may still show a modest association between colorectal cancer and meat consumption.

A similar dietary assessment based on a self-administered 68-item Block food frequency questionnaire was utilized by Chao et al. in their study of a cohort of 148,610 Americans (2005). Participants were enrolled in the Cancer Prevention Study II Nutrition Cohort and resided in 21 states with population-based cancer registries.
Information on meat consumption was provided in 1992/3, and the cohort was re-contacted at two-year intervals for updated information. Follow-up through 2001 found 1,667 cases of colorectal cancer among the group. Eighty percent of these cases were self-reported and confirmed via medical records and cancer registries, 289 (17 percent) were identified as interval deaths, and the other 3 percent were identified while verifying a different reported cancer. The long study period meant that the authors were able to assess long-term meat consumption levels in relationship to cancer etiology and risk. A major finding in this study was gender variation—the median meat intake among men was roughly two-thirds greater than that of women. No strong general association was observed between red meat consumption or reported levels of meat doneness and colorectal cancer. However, prolonged high consumption of red meat and processed meat were associated with a statistically significant increase in the risk of distal colon cancer.

The strength of this study is that it assessed the risks associated with meat consumption over a period of time in a large cohort. A possible limitation is the reliance on self-reported data, particularly in relationship to the reported “doneness” of meat. Potential confounders were taken into account, although men and women who reported higher meat consumption levels were also more likely to report lower educational attainment, no recreational physical activity, higher BMI, smoking, regular consumption of alcohol, and higher caloric intake and lower fruit/vegetable intake. This massive confounding of potentially carcinogenic factors with higher levels of meat intake draws attention to the difficulty in identifying single etiologic factors. Although Chao et al. were able to control for several factors known to influence colorectal cancer risk, the degree to which multiple lifestyle variables systematically interact to prevent or lead to cancer is difficult to ascertain.

The connection between genes and meat consumption, in addition to other lifestyle factors, has emerged as a recent area of focus in the epidemiology of colorectal cancer. Carcinogenic mutations that contribute to hereditary colorectal cancer have been identified in several genes, and determining the heritability and causes of these mutations is central to the management and prevention of cancer (de la Chappelle 2004). There are several approaches to examining the ways in which genetic and environmental factors interact in the case of colorectal cancer. One tactic is to look at family studies. For instance, Keku et al. used data from a case-control study of colon cancer among African Americans and Whites in North Carolina to examine the relationship between family history and genetic polymorphisms (2003). This study found that participants with one or more first-degree relatives with colon cancer showed a slightly higher prevalence of at-risk genotypes, but the aggregation of environmental risk factors and polymorphisms inherent to close relatives proved difficult to tease apart (ibid). Another approach to characterizing genetic and environmental risk factors is to utilize migrant studies. Kolonel et al. are currently investigating a large multiethnic cohort study in order to differentiate the genetic and environmental contributions to certain kinds of cancer among diverse ethnic groups (2004). Although their results remain preliminary, large population-based studies like this one are crucial to identifying genetic variations in cancer. In terms of understanding the links between genetics, meat consumption and colorectal cancer, much of the extant body of epidemiological literature focuses on how risk is modified by
genetic variants in individuals, rather than groups.

Initially, meat was studied in connection to colorectal cancer because of its high fat content, but other attributes are being examined for carcinogenic effects in connection to genetic mutations. In other words, it is no longer clear if the association between meat eating and colorectal cancer is due to meat consumption and overall diet patterns, or if cancer results from the by-products related to meat preparation methods. In particular, certain high-temperature cooking practices (particularly pan frying and grilling) result in the production of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). These compounds are known to be potent mutagens and have proven carcinogenic in animal studies, but the impact of these compounds in humans remains unclear. It has been hypothesized that individuals with certain genetically determined rapid metabolizers of carcinogenic compounds may be more susceptible to colorectal cancer. This speculation is elaborated upon in the following studies.

Kampman et al. hypothesized that varying results in studies examining the link between diet and colorectal cancer risk may actually be due to different meat preparation methods typically used in various populations (1999). They further pointed out that the genetic heterogeneity of study populations could play a role, and conducted a case-control study to evaluate whether or not meat consumption and genetic variation are associated with risk of colon cancer. In this study, 1,542 colon cancer cases from Utah, northern California and Minnesota were matched with 1,860 population-based controls. Interviewer-administered questionnaires took place between February 1992 and April 1995 and surveyed participants on their eating habits two years prior. The frequency of consumption was recorded for over 800 separate food items, and three-dimensional food models and utensils were used to aid participants in assessing serving sizes. Questions related to the “doneness” of meat and various cooking methods of meat were recorded in order to estimate potential exposure to mutagens. Interviewees were also asked about other health related activities, demographics and family histories and DNA samples were taken from each individual. Results of this study showed that caloric intake, the percentage of energy consumed as fat, and total fat and cholesterol intake were markedly higher for colon cancer cases. However, there were no significant differences in colon cancer risk across specific genotypes, and little association was found between meat consumption and colon cancer. There was a slight increase in risk associated with the doneness of meat, but overall there was little support for the general hypothesis that high levels of meat consumption are related to high colorectal cancer risk, even when modified by genetic factors.

It is troubling that the authors make only passing reference to biases associated with a retrospective design, an area that surely deserves more attention in a study that asks participants to recall the frequencies of what they ate two years earlier. Moreover, although Kampman et al. designed this study to include a large number of participants in several areas of the U.S., a prerequisite for participation was the ability to speak English, and 91 percent of the group was White. While 4.5 percent were Hispanic and 4.5 percent were African American, these are not particularly representative samples and this study did not include information from other ethnic minorities within the country. The statistics in this study were not “adjusted” or extrapolated for race, so it remains unclear as to whether
or not the findings apply to all groups or primarily to whites. This analysis is particularly troublesome due to the fact that the highest incidence rates for colorectal cancer occur among African Americans.

A 2003 case-control study by Butler et al. utilized a random recruitment approach in North Carolina where race, sex and age-specific incidence rates for colon cancer were incorporated into the selection process in order to attain approximately equal numbers of white and African American participants. A total of 701 African-American (274 cases, 427 controls) and 957 white (346 cases, 611 controls) participants completed 150-item food frequency questionnaires that were administered by specially trained nurses in the individuals' homes. The mean age of participants was 65. Data was also collected on frequency of meat consumption, cooking method, and level of doneness. Rather than asking about the preferred level of doneness, this study used color photographs of various kinds of meat cooked in different ways to more accurately ascertain classifications of doneness. This method of determining cooking levels was a particular strength of this study, as it significantly reduces informant subjectivity in reporting dietary patterns. Data collected on meat consumption was used to estimate levels of HCAs, benzopyrene and mutagenicity. Results showed that African Americans consumed more pan-fried red meat, well-/very well done red meat, white meat and pan-fried chicken, and were exposed to higher levels of mutagens overall. Dose-dependent associations between colon cancer and meat intake did not differ by race, however. Sixteen percent more cases than controls volunteers to be included in the study, potentially creating a degree of selection bias, and there were more white participants overall. On the whole, this study found a modest, positive association between colon cancer and red meat intake, particularly for pan-fried or well/very-well done red meat.

Subsequent research has attempted to more carefully delineate the precise interplay of genetics and meat preparation, despite some conflicting evidence that there may not be a direct association. Murtaugh et al. hypothesized that two genetic characteristics related to the metabolism of HCAs and PAHs (the NAT2-imputed phenotype and the GSTM1 genotype) may interact with meat consumption or meat preparation to alter rectal cancer risk (2004). Nine hundred and fifty two rectal cancer cases and 1,205 controls were recruited from a population-based study in Utah and Northern California between September 1997 and February 2002. Data was collected during in-person interviews that lasted approximately two hours. Participants, who were between the ages of 30 and 79 years and 82 percent white, were asked to recall the foods eaten during the calendar year occurring two years before their diagnosis (cases) or recruitment into the study (controls). Information was gathered on the frequency that foods were eaten, serving size, preparation methods and doneness of meat (e.g., rare, medium, well). Statistical analysis determined risk across medians, thirds or quartiles of dietary intake, and accounted for BMI, age, physical activity, energy intake, dietary fiber, calcium intake and smoking status. Additionally, blood was drawn from study participants in order to assess the GSTM1 and NAT2 status of each individual.

The results of this study did not support a strong direct association between meat consumption and the risk of rectal cancer. Murtaugh et al. did find a modest, non-significant increase in the risk of rectal cancer related to consumption of well-done meat and
white meat cooked at high temperatures—but only among men. Gender specific differences in association were not reconciled in this article. Furthermore, there was little evidence to support a direct association of the GSTM1 genotype to risk for rectal cancer, and findings related to NAT2 status and cancer were inconsistent. The authors concluded that since there was no correlation between meat consumption and rectal cancer per se, the mutagens such as HCA—and not the meat itself—are the likely cause of the disease. This conclusion, however, was not based on a direct measurement of mutagens, but on an inferred estimate computed from participants’ responses about preferred doneness of meat. Although the authors mentioned that recall bias may skew the information provided by cases, this may have further skewed the conclusions of the study. Also mentioned is the fact that residual confounding of other healthy habits could occur because PAH is sometimes found in grains, fruits and vegetables. Overall, the direct connection between mutagens and rectal cancer seems undefined here.

Murtaugh et al. conducted another study analyzing the case-control group described above alongside a group of 1,346 cases of colon cancer and 1,544 matched controls (2005). This time, the authors hypothesized that a different genotype, the CYP1A1, would be associated with the risk of colorectal cancers and meat cooked at high temperatures. Similar to the 2004 report, nearly all of the participants were white, but the colon cancer informants were between 64-65 years of age, making this a much narrower age range when compared to the rectal cancer study participants. This age difference was not accounted for in the article. This study had several unexpected results—white meat prepared at high temperatures and white meat drippings were associated with an increased risk of colorectal cancer in individuals with a particular CYP1A1 variant, and risk increased among women with a high red meat mutagen index and particular genotypes. In other words, the findings of this study and the 2004 results are in some ways contradictory, which essentially reflects the conflicts in the realm of nutrient-gene interactions studies related to colorectal cancer. Even within similar groups, examined using identical methods and analyzed by the same researchers, there are often disparate findings.

CONCLUSIONS:

An enormous body of literature exists on the subject of colorectal cancer and diet, and it can be difficult to navigate the wide range of findings in a cohesive manner. The articles reviewed here are in large part a reflection of trends in colorectal cancer research and diet. These trends guide new research pursuits and steer publication patterns in ways that are not always immediately apparent. During the 1980s, high total fat consumption was believed to be the primary causal factor for high rates of many kinds of cancer, and dietary recommendations and policy were based around this presumed correlation (Willett 2005). When studies failed to find overwhelming support for the dietary fat hypothesis, attention moved to the role of fruit and vegetable consumption. Researchers in the 1990s worked to find evidence to support the national Five-A-Day program encouraging increased fruit and vegetable intake (ibid). Although case-control studies continue to provide evidence for decreased colorectal cancer risk in relationship to plant foods and fiber (cf. Slattery et al. 2004), large cohort studies have been less supportive of a benefit. Currently, meat consumption is viewed in light of obesity, the “newest” risk
factor for cancer. The genetic components of colorectal cancer etiology and meat consumption are also a new avenue of research. Meat intake has been examined throughout this period, often in opposition to the consumption of other foods. In other words, while the findings of various studies may appear to be mixed and inconclusive, this may in part be an artifact of trends in epidemiological research. It is likely that the single-risk factor approach is simply not useful in analyses of colorectal cancer-instead of looking to one food consumption pattern, such as meat intake, it is probable that multiple factors must be examined over time in order to fully grasp cancer etiology. Similarly, looking to the effects of a single genetic variation or mutagenic factor may not be the most germane approach for developing prevention methods or policy recommendations. Although the potential for clinical treatment could be improved through genetic research, the applications for information on the specific correlations between meat consumption, mutagens, and colorectal cancer remains nascent in public health. Again, the question is whether or not single-factor approaches are truly useful to epidemiologists examining colorectal cancer.

An issue at the heart of the "single-factor" debate is the role of confounding variables in cancer research. Healthy habits tend to be less examined in studies, and publication bias may further exacerbate this matter. For example, in the case of meat consumption, eating fish and skinless chicken are habits associated with a larger healthful diet, yet they are analyzed alongside other types of meat consumption. Does eating more fish, in and of itself, reduce the risk of cancer? Or is an overall adjustment in dietary patterns and other lifestyle habits associated with increased fish consumption the "real" factor? In situations such as this it would be helpful to include a qualitative component to research—individuals could then provide more detailed information about their overall dietary patterns in order to produce a more accurate picture of the risk factors associated with colorectal cancer.

Issues with case-control and cohort study methodology also cloud epidemiological assessments. Cohort studies may not reflect the behaviors of the highest risk groups, leading to partial assessments of disease causation and risk factors. Particularly damaging is the fact that many cohorts are primarily groups of white individuals with some degree of health insurance—not those who are most at risk. Furthermore, since the risk of colorectal cancer increases with age, cohort studies may not follow subjects for a significant length of time to assess this variable. In case-control studies, recall bias is often cited as problematic. However, it is also possible that the controls who volunteer to participate are inherently more health-conscious, or at least more interested in health issues, than the cases. For instance, cases will be more likely to remember their consumption of pan-fried red meat, and controls are more likely to report consuming more fruits and vegetables overall. Then, when cases and controls are compared, this may well lead to an apparent inverse association (Willett 2005).

In the circumstance of diet trends (e.g., the Atkins Diet) it is particularly difficult to interpret findings because many aspects of diet and lifestyle are often changed simultaneously. Moreover, the fact that meat consumption has increased so significantly over the past 50 years makes it difficult to ascertain whether or not recent assessments of diet are applicable to general patterns in cancer. Since data collection focuses on the years imme-
diately preceding diagnosis or recruitment into the study it is difficult to know if recent consumption or long-term consumption makes a greater difference. There is a major lack of data on childhood diets, which may also play a role in cancer etiology. It is also interesting that no major studies have been conducted on vegetarians, who currently number around 5.7 million in the United States. This seems to be a straightforward means of controlling for meat consumption, although other confounding healthy variables may be problematic.

Overall, based on the evidence presented here, it seems likely that there is at least some modest positive association between meat consumption and colorectal cancer. Unfortunately, it is impossible to discern what aspects of meat consumption present the greatest risks, and researchers have yet to provide sufficient evidence for any one causal factor. Genetic studies seem to be closest to identifying a singular risk factor for colorectal cancer, but the practical applications of these studies in community and behavioral health are questionable and carry the jeopardy of ignoring lifestyle factors. In general, public health practitioners and clinicians would be wise to encourage a balanced diet; lowered consumption of meat is should not be a goal in and of itself, but rather part of an overall lifestyle adjustment for better health.

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