Fat and colon cancer: how firm is the epidemiologic evidence?1–3

Laurence N Kolonel, MD, PhD

Introduction

Because of inherent limitations in the methodologies of epidemiologic and experimental research for elucidating causal relationships in humans, scientists need to evaluate both bodies of literature jointly to reach meaningful conclusions. Others in this symposium have reviewed animal studies on fat and cancer. This paper focuses on the epidemiologic evidence pertaining to fat as a risk factor for colon cancer in man. Other hypotheses, especially that caloric intake per se is a risk factor, will also be considered.

Correlational studies

A number of investigators (1–15) have correlated the per capita consumption of fats in various countries with corresponding rates of incidence and mortality for colon cancer (Table 1). Positive associations were found in several instances. Drasar and Irving (1) used incidence data, Armstrong and Doll (3) used both incidence and mortality data, and Knox (4) used mortality data. All three groups found significant positive correlations between total fat intake and risk of colon cancer. In a similar analysis by McKeown-Eyssen and Bright-See (6), animal fat in particular was found to be most strongly associated. Because of the substantial overlap in the data sources for these analyses, it is not surprising that the findings agree.

On the other hand, when other population data have been examined in correlational analyses, the findings have been different. Enstrom (7) found no association between per capita fat consumption by state in the United States and colorectal cancer mortality, and Bingham et al (8) reported a negative result from a similar analysis by region in Great Britain. Both Enstrom (7) and McMichael et al (9) also noted inconsistencies between national and international trends in the consumption of dietary fat and corresponding colorectal-cancer mortality rates.

The examination of special population groups has also produced little support for the fat–colon-cancer hypothesis. Lyon and Sorenson (10) observed that incidence of colon cancer is substantially lower in both Mormon and non-Mormon residents of Utah than in the United States as a whole, despite very little difference in per capita consumption of fat between Utah and the country overall. Similar discrepancies have been noted for Polynesians in New Zealand and Hawaii relative to corresponding Caucasian populations (12–14). In both locations, the Polynesians and Caucasians have similar average levels of fat consumption, yet incidence of colon cancer and mortality rates among Polynesians are substantially lower.

Kolonel et al (15) have noted additional inconsistencies among the ethnic groups in Hawaii. For example, first- and second-generation Japanese migrants have similar incidence rates of colon cancer, although fat intake is higher in the second-generation group.

Some of these correlational studies, and others, also examined the association between consumption of meat and risk of colon cancer. In Western populations with relatively high meat intakes, this food may serve as a surrogate for fat consumption, especially animal fat. The findings have again been inconsistent, however. Some investigators reported positive
associations (2–6), while others reported a lack of association (7–11).

Overall, the results of these correlational analyses do not offer a clear picture with regard to fat intake and colon cancer. Some of the inconsistencies may reflect limitations of correlational analyses, which cannot adequately control for confounding factors and which do not necessarily include the same subjects in the sources for the exposure and disease data. Nevertheless, because dietary variability with regard to a major nutrient like fat may not be sufficiently great within homogeneous population groups, intergroup correlations may actually be more likely than case-control or cohort studies to reveal true associations.

Analytic studies

The assessment of nutrient consumption in individuals is difficult and most analytic epidemiologic studies of diet and colon cancer have only partially quantified intakes, by determining the frequency of consumption of selected foods. Investigations of dietary fat and colon cancer are summarized in Table 2 (16–31). One case-control study in Canada (16, 17) did investigate quantitative diet history. In that study, colon-cancer cases were matched on age, sex, and residence with neighborhood controls, and on age and sex with hospital controls. In a multivariate analysis, the investigators found the strongest association between colon cancer and fat, especially saturated fat (including a dose-response gradient), although positive associations were also seen for total protein and total caloric intake.

Garland et al (29) reported the results of an analysis in a male prospective cohort, based on nutrient assessments from 28-day diet histories, though the actual methodology was not well described. They found no association between fat intake (as percentage of calories) and risk of colon cancer nor for animal protein or mean caloric intake. In a similar analysis on a cohort of Japanese men in Hawaii based on 24-h diet recall data, Stemmermann et al (27) reported an inverse association between dietary fat and colon cancer, though no dose-response gradient was included.

All other case-control and cohort studies have been based on the frequency of consumption of high-fat foods rather than on determination of fat intake itself. Some of these studies found positive associations between consumption of high-fat foods and risk of colon cancer. Wynder et al (18) reported that cases consumed more milk, fat, and calories than did controls; Dales et al (20) reported that cases consumed more high-fat foods than did controls, based on a study among blacks in northern California; and Pickle et al (21) reported that cases, particularly those of Bo-
TABLE 2
Analytic studies of dietary fat and colon cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample size</th>
<th>Association with dietary fat</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(16, 17)</td>
<td>348 cases</td>
<td>Positive</td>
<td>Quantitative diet history method; also positive for total protein, total calories</td>
</tr>
<tr>
<td></td>
<td>542 neighborhood controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>535 hospital controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(18)</td>
<td>69 cases</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>307 hospital controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(19)</td>
<td>179 colorectal cases</td>
<td>Positive</td>
<td>Based on data for meat</td>
</tr>
<tr>
<td></td>
<td>357 hospital controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(20)</td>
<td>77 cases</td>
<td>Positive</td>
<td>Weak and in males only; no association for meat; synergistic interaction with fiber in sexes combined</td>
</tr>
<tr>
<td></td>
<td>215 hospital and multiphasic controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(21)</td>
<td>58 cases</td>
<td>Positive</td>
<td>Also positive for meat</td>
</tr>
<tr>
<td></td>
<td>115 hospital controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(22)</td>
<td>65 cases</td>
<td>Positive</td>
<td>Based on data for meat; also interaction with fiber</td>
</tr>
<tr>
<td></td>
<td>100 hospital controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(23)</td>
<td>207 cases</td>
<td>None</td>
<td>Also no association for meat</td>
</tr>
<tr>
<td></td>
<td>1020 hospital controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(24)</td>
<td>198 cases</td>
<td>None</td>
<td>Also no association for meat</td>
</tr>
<tr>
<td></td>
<td>396 surgical and neighborhood controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(25)</td>
<td>256 cases</td>
<td>None</td>
<td>Based on data for meat</td>
</tr>
<tr>
<td></td>
<td>783 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(26)</td>
<td>588 colorectal cases</td>
<td>None</td>
<td>Based on data for meat</td>
</tr>
<tr>
<td></td>
<td>1176 hospital controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(27)</td>
<td>7074 male subjects</td>
<td>Inverse</td>
<td>24-h diet recall method</td>
</tr>
<tr>
<td>(28)</td>
<td>265 118 subjects</td>
<td>Inverse</td>
<td>Inverse findings in males only</td>
</tr>
<tr>
<td>(29)</td>
<td>1954 male subjects</td>
<td>None</td>
<td>Based on percent of calories; also no association for animal protein and mean calories</td>
</tr>
<tr>
<td>(30)</td>
<td>25 493 subjects</td>
<td>None</td>
<td>Positive association with obesity</td>
</tr>
<tr>
<td>(31)</td>
<td>1142 subjects</td>
<td>None</td>
<td>Based on colon cancer risk in spouses</td>
</tr>
</tbody>
</table>

Hemian ancestry, consumed more of certain high-fat foods than did controls, based on a study in Nebraska. None of these independent associations was very strong.

When Dales et al (20) stratified their subjects into high and low groups with respect to consumption of foods containing both fat and fiber, however, they found a significantly increased relative risk of 2.7 for subjects with a high-fat, low-fiber intake relative to those with a low-fat, high-fiber intake. On the other hand, several other reports have been negative, including case-control studies by Higginson (23) in Kansas and Modan et al (24) in Israel, a cohort study by Phillips and Snowdon (30) among Seventh Day Adventists in California, and an examination of colon-cancer risks in spouses by Jensen et al (31) in Sweden.

Like the literature on correlational studies, the literature on analytical studies includes reports on consumption of meat in relation to risk of colon cancer (Table 2). Haenszel et al (19) reported a positive association with intake of meat, especially beef, in a case-control study among the Japanese in Hawaii. Pickle et al (21) and Manousos et al (22) found similar associations with intake of meat in case-control studies conducted in Nebraska and Greece, respectively.

In contrast, the previously cited case-control studies by Dales et al (20), Higginson (23), and Modan et al (24), as well as studies by Graham et al (25) and Haenszel et al (26) found no association between intake of meat and this cancer site. Similar to the previously mentioned inverse association with fat reported by Stemmermann et al (27) among male Japanese in Hawaii, Hirayama (5, 28) found a protective
effect of meat against colon cancer in men in a very large cohort of Japanese subjects in Japan. Thus, the analytic epidemiologic studies on fat and colon cancer are no more consistent than the correlational ones. As mentioned earlier, this situation may reflect methodological difficulties in obtaining adequate dietary information from subjects with and without colon cancer. It may also reflect a failure to account for other risk or protective factors in the same analysis.

Of particular interest is the role of fiber, which may act by influencing the concentration or metabolism of bile acids, the presence of which in the stool is influenced by dietary fat (32). Although both analytic and correlational studies that examined the fiber hypothesis independently have led to mixed results (eg, 2, 16, 20, 26, 33–35), few investigators have looked for interactive effects between fat and fiber. For example, the report by Dales et al (20) found only a weak positive association for dietary fat alone and colon cancer but a much stronger association when fat and fiber were considered together. In fact, fat and fiber showed an apparent synergistic effect in their data.

In a similar approach, Manousos et al (22) combined data on consumption of meats and certain vegetables into a risk score for each subject in their case-control study in Greece. Risk of colon cancer was significantly increased in those subjects with scores in the highest and next-to-highest quintiles, ie, those with high meat and low vegetable intakes (relative risks of 8.0 and 3.1, respectively). Another dietary factor that may modify the effect of fat is calcium, which has recently been associated with risk of colon cancer (29, 36).

Related studies on fecal steroids

A substantial number of studies have attempted to demonstrate differences in bile acid or neutral steroid composition of the stool between high- and low-risk populations for colon cancer or between cancer cases and controls. Because intake of dietary fat influences the distribution and concentration in the stool of these metabolites, some of which may be carcinogenic in man, such studies represent an effort to support the dietary fat hypothesis by establishing a possible mechanism of action. With few exceptions (37–41), these metabolic studies have not been designed epidemiologically. The findings have been inconsistent, no doubt partly because of methodologic limitations but also because of the complexity of metabolic interactions in the gastrointestinal tract. Overall, these studies have not yet added much to substantiate the fat hypothesis (42).

Possible role of calories

The results of the epidemiologic studies of colon cancer in relation to dietary fat do not conclusively support the hypothesis. A number of limitations of these studies have been noted, including both methodologic considerations and failure to deal with other potential risk or protective factors in the diet. In particular, the possible interaction between dietary fat and fiber has been mentioned. Indeed, those case-control studies that did look for this interaction and the one that most fully assessed fat intake (16, 20, 22) all found support for a possible role of dietary fat in the etiology of this cancer.

Another possibility that was not considered is that fat itself is not a risk factor but serves as a surrogate measure because of its high correlation with the true causal factor. In epidemiologic studies, it is difficult to separate the effects of highly intercorrelated factors, such as dietary fat, animal protein, and total calories. Several correlation studies (eg, 1–3) reported significant associations of protein, particularly animal, with colon cancer as did the case-control study of Jain et al (16). Except for the study by Armstrong and Doll (3), however, the association with fat tended to be stronger than with protein in these studies. The findings with respect to intake of meat can also be interpreted to reflect dietary protein, as meat is a major source of protein in Western diets. Thus, one can reasonably suggest that the findings for both fat and protein could be a reflection of a true association with total calories.

Some of the epidemiologic studies reviewed in this paper did assess caloric intake, although it was not possible in most of the case-control studies that used only a limited food list to determine intakes. Of the correlational studies,
Armstrong and Doll (3) found a somewhat weaker correlation between calories than between fat and colon cancer whereas Knox (4) found similar correlations for fat and total calories with colon-cancer mortality.

The case-control study by Jain et al (16) found a positive association between total caloric intake and risk of colon cancer, but the effect was weaker than for fat. Garland et al (29), on the other hand, found no association between colon cancer and mean caloric intake in their cohort. Interestingly, but not unexpectedly, studies that found an association with fat (eg, Jain et al) also found an association with calories, while those that did not find an association with fat (eg, Garland et al) did not find an association with calories.

Any relationship to caloric intake is itself likely to be complex. Exercise has been suggested to have a protective effect against colon cancer, despite the usually increased caloric intake among highly active people (43, 44). On the other hand, obesity, especially that occurring later in life, has also been associated with risk of colon cancer (30, 45, 46), suggesting that net energy balance may be an important factor in risk of colon cancer and may account for the variable associations with fat and calories in various studies.

In summary, because of the inconsistencies in the epidemiologic data on dietary fat, one cannot yet conclude that this nutrient is a causal factor for colon cancer, though most of the more completely analyzed studies suggest a positive relationship. Given the present inconclusiveness of the epidemiologic evidence and the very high intercorrelation between fat and total calories in most Western diets, a role for total calories as an independent risk factor deserves consideration.

References
22. Manousos O, Day NE, Trichopoulos D, Gerovassilis...


