The Epidemiology of Large Bowel Cancer

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Summary

Results from epidemiological studies have provided clues as to etiological factors involved in the development of large bowel cancer. Overnutrition, especially in terms of dietary fat consumed, appears to be a key etiological variable affecting the rate of colon cancer. Epidemiologists can provide the leads for chemists and bacteriologists to pursue in population groups and for experimentalists to test in laboratory animals. Coordination of and cooperation between many disciplines is necessary in order to contribute to the prevention of this man-made disease.

Introduction

A primary thinking process of an epidemiologist when trying to elucidate the etiology of a given disease involves simple logic. When it comes to the large bowel, one would obviously consider factors present in the lumen of the large bowel, although one cannot exclude components that are carried to the wall of the large intestine by the blood. On the basis of such reasoning, we began to suspect, in our epidemiological study reported in 1967 (20), that colonic contents contained tumorigenic components. Additionally, because of the wide variation in the incidence of large bowel cancer throughout the world, we suspected that there had to be factors, probably dietary in nature and specifically related to dietary fat, that directly and indirectly affected the make-up of the feces and consequently tumorigenic components.

Demographic Leads

Significant leads may be derived from the markedly diverse distribution of large bowel cancer in various parts of the world and population groups within a given country. The major clues that, when viewed together, should be able to provide us with an idea of the etiological factors involved in the development of large bowel cancer, may be summarized as follows.

1. In general, the more economically developed a society is, the greater is its incidence of cancer of the colon, although not necessarily of the rectum (Chart 1). In reference to the rectum, it should be stressed that many vital statistics are misleading in that they have included rectal sigmoid lesions with rectal cancer. The etiology of rectal cancer, when defined in terms of the last 8 cm of the large bowel, appears to be different from cancer of the colon and cancer of the rectal sigmoid and, therefore, should be evaluated separately.

2. A world-wide correlation exists between colon cancer and fat consumption in various countries (Chart 2). Obviously, correlation does not necessarily mean causation, although it is apparent that, in the absence of correlation, causation is unlikely. One can establish a similar correlation with many other variables connected with increasing economic development, although, to be taken seriously, a correlation needs to have some logical basis.

3. There exists a negative correlation between gastric cancer and colon cancer (Chart 3). This finding suggests that factors enhancing the risk of colon cancer may at the same time protect against cancer of the stomach and vice versa.

4. A positive correlation exists between myocardial infarction and colon cancer (Chart 4). The main risk factors for myocardial infarction (hypercholesteremia, hypertension, and cigarette smoking) have been well established (7). The question that needs to be answered is whether any of these factors is related to colon cancer.

5. Incidence data from the United States, comparing data for 1947 and 1969, suggest a gradual increase in the incidence of cancer of the colon while showing a decrease in cancer of the rectum (Chart 5). Could this increased incidence in colon cancer, if real and not due to an increase in the discovery and reporting of Grade I cancers, be explained on the basis of environmental factors that have also increased?

6. The sex ratio of cancer of the colon is near unity, in contrast to cancer of the rectum, which is predominantly a male disease especially in later life (Chart 6). If one examines the sex ratio of colon cancer by age, one finds that before age 60 colon cancer tends to be slightly more common among females, while later in life it becomes more predominant among males. This finding is dissimilar to what is known for myocardial infarction, causing one to speculate whether female steroids that tend to lower serum cholesterol levels might in turn induce a greater excretion of cholesterol into the feces.

7. Among American blacks, there are different rates in certain rural parts of the South compared to blacks living in industrialized Northern cities (9). Could these differences be due to variation in diet?

8. Significant differences in colon cancer have been
shown between Puerto Rico and the United States (13) (Chart 7). The intake of fat and cholesterol is significantly lower on the island than on the United States mainland, but what additional environmental differences, especially in relation to diet between these 2 population groups, might account for the differences in the cancer rates?

9. In developing countries such as Colombia, the rate of polyps of the colon is considerably higher in cities than in rural areas, a finding consistent with differences in dietary habits (5).

10. Among economically developed countries such as Denmark and Finland, the rates of both colon cancer and rectal cancer are higher in the former country. What are the dietary differences between these 2 populations that could account for this?

11. The Seventh-Day Adventists, who consume less meat
than others, are reported to have a relatively low rate of colon cancer.3

12. Of particular interest have been the marked differences in a wide variety of cancers, including cancer of the colon but not cancer of the rectum, between Japanese and American populations (18). These differences are not only major but, since Japanese medical facilities and vital statistics records are equal to those prevalent in the U.S., we regard the differences to be real. There appear to be no genetic factors affecting this low rate of colon cancer in the Japanese, because the incidence of colon cancer increases among those Japanese moving to America in line with their adopting American dietary habits (10) (Chart 8). Of equal interest is the fact that colon cancer seems to be increasing in Japan itself, a finding consistent with the increasing Westernization of its diet (4).

13. A rather unusual etiological lead is furnished by the observation that patients with ureterocolonic anastomosis have an increased risk of developing cancer of the colon (12). What is particularly striking about this finding is that patients who, early in life, have such anastomosis involving the colon, develop cancer at this site at a relatively young age. Since such a correlation has not been reported for other conditions, it has been suggested that urine itself in some way acts as a tumorigenic agent. This unusual finding certainly should be of interest to experimentalists working in colon carcinogenesis.

In summary, the numerous leads derived from the demographic distribution of cancer of the colon need to be examined by the epidemiologists, interpreted for each of the populations, and considered in line with the incidence of the disease by its anatomic location in the large bowel, available retrospective and prospective epidemiological data, and general environmental data including nutrition.

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Large Bowel Cancer

Anatomic Distribution

The differences in the anatomic distribution of large bowel cancer among high- and low-risk population groups are of considerable interest to the epidemiologists. In general, there is a relatively greater incidence of right-sided colon cancer in the low-risk population groups, a fact that is particularly evident when comparing the distribution of this disease in American and Japanese populations (Chart 9).

Correa and Haenszel (4) have documented this finding by calculating a sigmoid/cecum ascending site ratio obtained from different cancer registries (Table 1). A particularly striking aspect of the lower rate of colon cancer among Seventh-Day Adventists is that, among the 25 reported cases of colon cancer, 16 occurred in the right side of the colon (R. L. Phillips and E. L. Wynder. Cancer of the Breast and Colon among Seventh-Day Adventists, manuscript in preparation). Along this line, it is not accidental that among Japanese immigrants to Hawaii it is in particular their rate of sigmoid lesions that increases (20).

As we have stressed previously, the incidence of cancer of the rectum seems to differ significantly less between high- and low-risk population groups, especially when including only those lesions occurring in the last 8 cm of the large bowel. As we have also indicated, rectal cancer is more common than colon cancer in males; this sex ratio difference further supports our contention that its etiology is at least in part different from that of the colon. Could it be that the usual absence of feces in the lower rectum could

Table 1
Colon cancer incidence, in ascending order, as reported by cancer registries for 7 areas

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>S/C-A</td>
<td>S/R</td>
</tr>
<tr>
<td>India</td>
<td>0.20</td>
<td>0.04</td>
</tr>
<tr>
<td>Colombia</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>Japan</td>
<td>0.41</td>
<td>0.10</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>0.71</td>
<td>0.16</td>
</tr>
<tr>
<td>Finland</td>
<td>0.60</td>
<td>0.16</td>
</tr>
<tr>
<td>Norway</td>
<td>1.17</td>
<td>0.55</td>
</tr>
<tr>
<td>Connecticut</td>
<td>1.56</td>
<td>0.68</td>
</tr>
</tbody>
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* See Ref. 4, p. 389.
* S/C-A, sigmoid/cecum-ascending; S/R, sigmoid/rectum.


Chart 9. Colon cancer mortality by site in United States and Japan, 1968, ages 35 to 84.
contribute to this difference in incidence?

In this regard, we should note the observations by Finegold (6) that the ratio of anaerobic to aerobic bacteria increases as feces pass from the ileum to the rectum, with the highest ratio in the sigmoid area (Table 2). Reasoning would suggest that the anaerobic bacteria contribute in some way to large bowel carcinogenesis.

Retrospective Studies

In 1967, we conducted a large-scale retrospective study (20) on large bowel cancer based on interviews with 761 patients with this type of cancer and concluded that, except for the established high risk for patients with ulcerative colitis and familial polyposis, no environmental factors could be identified that differed significantly between the control and study populations (Table 3). Some of these nonassociated factors, i.e., constipation, use of laxatives, and frequency of bowel movements, were of considerable interest, however. The fact that constipation did not relate to large bowel cancer and that women were significantly more constipated than men without a correspondingly higher rate indicated that transit time might not be an important variable in cancer of the colon. We suggested that there was no basis for the contention that increased transit time resulted in a decreased bacterial action on the contents of the colon. We believe that, even with the fast transit time reported among Africans (2), there is sufficient time for the bacterial conversion of substrates in the content of the colon. On the basis of a review of total etiological data available at that time, we concluded that dietary factors, especially the high intake of fat, appear to be associated with the etiology of large bowel cancer. There are differences in the etiology of cancer of the colon and of the rectum. Etiologically, cancer of the rectosigmoid regions appears to fit more closely with cancer of the colon than with cancer of the rectum.

The recent suggestion made by Breslow and Enstrom (1) on the basis of positive correlations between beer drinking and rectal cancer in different countries could not be confirmed on the basis of retrospective studies. In a similar retrospective study on large bowel cancer patients in Japan in 1969 (18), the data suggested a correlation between the Westernization of the Japanese diet and colon cancer. We did not find a similar correlation for cancer of the lower rectum. It is reasonable to assume that differences and changes in dietary intake, especially when involving Westernization of the diet, could be determined by retrospective techniques in a study in Japan. Such data-gathering techniques do not, however, appear applicable to United States populations. In the United States the total intake of fats, carbohydrates, and proteins is quite similar throughout the country and between various groups, although the sources from which these constituents come may be quite diversified. Therefore, we have discontinued taking dietary histories on American populations for some time, believing that such information is relatively useless, both quantitatively and qualitatively. This is particularly true when we are interested in what was eaten over the last 20 years, rather than what was eaten yesterday or during the previous year. The “shoe leather” epidemiologist should be the first to recognize that, in his inability to take meaningful dietary histories, he is faced with limitations that are unlikely to be overcome by an improvement in interview techniques alone.

We also reported data on serum cholesterol in our 1967 study conducted in the United States (20) and again in our Japanese study in 1969 (18). In neither study did we find a correlation between serum cholesterol and an increased risk of developing colon cancer, data that have been confirmed in a prospective study by Rose et al. (16).

Thus, the correlation noted for myocardial infarction and colon cancer cannot be explained on the basis of serum cholesterol levels as was also apparent from the finding that no correlation between myocardial infarction and colon cancer has been observed in individual patients. This does not deny, however, the possibility that diet, including cholesterol, could be a common denominator. It could be theorized that in one case the diet might contribute to an increase in serum cholesterol leading to arteriosclerosis, while in the other it might lead to an increased excretion of cholesterol into the feces and/or an increase in the formation of bile acids that, upon excretion into the feces and upon being metabolized, may contribute to an increased risk for colon cancer.

Selikoff et al. (17) have presented evidence that asbestos workers have an increased risk of developing colon cancer. If this increased risk should prove to be real, it will be of interest to consider the mechanism whereby asbestos fibers increase the chances of developing cancer of the large bowel. Could such an increased rate relate to the carcinogenicity of such asbestos fibers or could it be that asbestos fibers localize within the mucosa of the large bowel and act as a point around which various carcinogens in the contents of lumen could crystallize? This lead should be further explored both epidemiologically and experimentally.

Table 2

<table>
<thead>
<tr>
<th>Bacterial counts at various positions of the gastrointestinal tract*</th>
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<tbody>
<tr>
<td>All counts log_{10}/g sample.</td>
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<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
</tr>
<tr>
<td>Aerobes</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Anaerobes:aerobes</td>
</tr>
</tbody>
</table>

* Ref. 6, p. 376.

Table 3

<table>
<thead>
<tr>
<th>Epidemiological findings of large bowel cancer patients</th>
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<tbody>
<tr>
<td>Positive association</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Familial polyposis</td>
</tr>
<tr>
<td>Crohn's disease (?)</td>
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Nutrition

We have proposed that nutritional intake is the key etiological variable affecting the rate of colon cancer (19, 20). Burkitt et al. (3), reaching a similar conclusion, have emphasized that the fiber content of the diet may act as a protective factor. They have stressed changes in the dietary fiber, such as consumption time and consistency of stool bulk. There is, however, no correlation between the fiber content of foods and the incidence of colon cancer when judged on a worldwide basis. Also arguing against refined etiological variable affecting the rate of colon cancer (19, Nutrition emphasized that the fiber content of the diet may act as a protective factor. They have stressed changes in the dietary fiber, such as consumption time and consistency of stool bulk. There is, however, no correlation between the fiber content of foods and the incidence of colon cancer when judged on a worldwide basis. Also arguing against refined sugar as a factor is the fact that in Argentina, where the incidence of colon cancer is high, the consumption of refined carbohydrates is low (14). Furthermore, Haenszel et al. (8) have shown in the Hawaiian studies a positive correlation between colon cancer and the consumption of legumes that are high in fiber content.

On the other hand, we have shown a correlation between the intake of dietary fat and colon cancer. The studies by Haenszel et al. (8) in Hawaii have also shown a correlation between beef and colon cancer. We are suggesting that there may be nothing "carcinogenic" about beef itself, but rather, since meat contributes about 42% of the total fat calories in our population (Chart 10), it is the fat and/or cholesterol content of our diet that is principally related to cancer of the large bowel. We are suggesting that the fat content of the diet, which normally parallels cholesterol consumption, has a significant effect on bacterial flora, especially on the concentration of anaerobic bacteria. The large-scale metabolic epidemiological studies by Hill et al. (11) and similar studies by Reddy and Wynder (15) have reached similar conclusions. The fat content of the diet also increases the substrates, in terms of bile acids and cholesterol, leading to a greater production of bile acid metabolites and cholesterol metabolites among which, we suggest, there are components that possess tumorigenic activity. The questions that need to be answered are: whether carcinogens are present in the colonic lumen or whether they are synthesized by the colonic mucosa, and how the bacterial metabolites act and/or interact.

The epidemiologist in this regard can provide only the leads. It has been up to the metabolic epidemiologist, working together with chemists and bacteriologists, as exemplified by Williams and Hill in England and Reddy and Mastromarino of our group, to: (a) establish the differences in the makeup of the fecal constituents between high- and low-risk population groups and between patients with colon cancer, ulcerative colitis, familial polyposis, and polyps and patients with no known large bowel disorders; (b) determine how bacterial flora taken from patients with large bowel disease and from high- and low-risk populations differ in their ability to degrade bile acids and cholesterol; and (c) give suggestions to the laboratory investigators as to certain fecal components such as bile acids or cholesterol metabolites that should be tested in experimental animals. Further data resulting from such an interdisciplinary effort will be presented later at this conference. Another approach could deal with a reduction of anaerobic bacteria by other than dietary means, such as reducing the pH of the stool, an approach that deserves greater attention.

Preventive Measures

A major epidemiological implication is that colon cancer could be prevented by dietary modification. While we are undertaking various programs in metabolic epidemiology and experimental studies, the question that should be answered is what dietary recommendation should be presented to the public today. The history of preventive medicine has repeatedly shown that waiting for all the facts to be studied before making appropriate recommendations frequently causes valuable years to be lost, years during which preventive measures could have produced beneficial effect. History has amply shown that preventive measures have been successful long before the pathogenesis of a disease was fully understood. In making recommendations or suggestions, the risk/benefit issue must be considered. No risks appear to be involved in suggesting that the present American diet be modified to be consonant with the Prudent Diet (Chart 11). The benefits may already be considerable in terms of the effect this diet may have on cardiovascular diseases. Such a diet has been recommended by many experts concerned with cardiovascular disease prevention. What we are suggesting is that we join our colleagues in the cardiovascular disease area by recommending the establishment of the Prudent Diet (both in terms of individual practice and the modification of food at its source) so that we can in fact have a national American Prudent Diet, a diet especially essential for a largely sedentary population.

Epilog

It is apparent from this discussion and other presentations at this conference that cancer etiology, perhaps more than any other aspect of cancer research, requires an
interdisciplinary approach. The epidemiologist can provide basic leads; the chemist and bacteriologist can explore these leads by using human material; and the experimentalist, working in a laboratory situation with laboratory animals, can test a variety of suspected large bowel carcinogens in a number of combinations. The public health oriented scientist can make appropriate preventive suggestions. The epidemiologist will finally have to establish whether the preventive measures have been successful in reducing the incidence of disease. It needs to be recognized that each of these specialists has limitations, but fortunately only his own limitations. The animal experimentalist needs to be aware of the fact that small laboratory animals cannot develop a bacterial flora similar to humans, and thus produce many of the cholesterol and bile acid metabolites that humans are able to produce. What has taken evolution millions of years to accomplish cannot be modified within a few generations. There are parts of the human anatomy and metabolism that cannot be duplicated in smaller animals. On the other hand, it appears reasonable to assume that the colonic wall, as a bioassay system, may be quite adequate to test potential large bowel carcinogens and that the results may then be applicable to the human condition.

The solution to the etiology of colon cancer requires a coordinated effort, which we are attempting to carry out in our institute and which is now being well organized within the Division of Cancer Cause and Prevention of the National Cancer Institute and the Task Force on Large Bowel Cancer at M. D. Anderson Tumor Institute. As we have reported, epidemiological evidence indicates that large bowel cancer is largely man-made and thus is also largely preventable. The interdisciplinary approach to this problem can contribute to making such prevention a realistic goal.

Chart 11. Prudent Diet (D) and present American diet (B).

References

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