REVIEW ARTICLE

Dietary fibre and colon cancer: epidemiologic and experimental evidence

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Epidemiologic studies have identified two dietary factors, a relatively high intake of fat and a relatively low intake of fibre, that are associated with colon cancer in humans. However, a recent study has shown a low risk of large bowel cancer in a rural Finnish population with a high dietary intake of fat, but also a high intake of fibre. Observations in humans and studies in animals have indicated that dietary fibre may protect against colon carcinogenesis by binding bile acids in the intestinal tract, by a direct effect on the colonic mucosa and by an indirect effect on the metabolism of carcinogens. The strength of protection varies with the type of fibre.

Des études épidémiologiques ont identifié deux facteurs de l'alimentation, un apport relativement élevé de lipides et un apport relativement faible de fibres, qui sont associés au cancer du côlon chez l'humain. Toutefois, une étude récente a démontré un faible risque de cancer du gros intestin au sein d'une population rurale finlandaise ayant un fort apport alimentaire de lipides, mais aussi un apport élevé de fibres. Des observations chez l'humain et des études chez l'animal ont indiqué que les fibres alimentaires peuvent protéger contre la carcinogenèse dans le côlon en liant les acides biliaires dans les voies digestives, par un effet direct sur la muqueuse colique et par une action indirecte sur le métabolisme des carcinogènes. Le degré de protection varie avec le type de fibre.

During the past two decades epidemiologic studies have investigated the influence of environmental factors on the occurrence of cancer of the large bowel. Researchers have compared patterns of occurrence between and within population groups, studying in particular the differences in rates of the disease between the sexes, over time, and between groups categorized demographically, socioeconomically and according to migratory and dietary habits. The consistency of their findings suggests that environmental factors in general, and dietary factors in particular, play a dominant role in the development of cancer of the large bowel in humans.

This article evaluates current research on the relation between dietary factors, dietary fibre in particular, and large bowel cancer in humans, including the use of animals to determine if the implicated factors can be modified experimentally.

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Epidemiologic considerations

Cancer of the large bowel has been the subject of several types of epidemiologic review.[1-6]

International variation

Recent publications have compared the distribution of cancer of the colon and rectum between and within populations of different nations.[4,7,8] The highest incidence rates are found in North America, New Zealand and western Europe, except for Finland, intermediate rates are found in eastern Europe and the Balkans, and the lowest rates are found in Africa, Asia and Latin America, except for Uruguay and Argentina, where the mortality rates are similar to those in North America. The mortality data for most of the countries appear to be consistent with the incidence data.

Although some geographic and ethnic differences may result from inaccurate diagnosis and incomplete reporting, these can account for only a small portion of the international variations. In Norway, Sweden and Denmark the methods of diagnosing colon cancer as the cause of death are similar to those used in Finland; thus, the observed differences in mortality due to colon cancer between these countries appear to be valid.[9] In Sweden there is a graduated increase in incidence from north to south. The differences between the colon cancer mortality and incidence rates in the United States and western Europe and those in Japan are also valid because the quality of medical facilities and the methods of obtaining vital statistics are parallel in these countries.[2]

Migration

Further evidence for the importance of environmental factors in the occurrence of large bowel cancer has come from studies of migrant populations. The incidence is higher in both the first and second generations of Japanese who migrated to Hawaii and California than in those who remained in Japan,[10,11] despite an increase in the incidence and mortality of colon cancer within Japan parallel with the increasing westernization of the Japanese diet.[12,13] An upward trend in colon cancer mortality has also been observed in Polish immigrants to Australia.[14]

Socioeconomic status

In general, large bowel cancer is a disease of economically developed countries, with the exception of Japan and Finland. Within the high-risk areas, such as North America and western Europe, socioeconomic factors do not seem to have an effect on incidence. However, the situation for the populations of less developed countries is quite different. Recent findings in Cali, Colombia, where the overall incidence of large bowel cancer is one fifth that reported by United States registries, indicate that the risk of this cancer is four times greater in the upper than in the lower socioeconomic classes for both sexes and in all age groups.[15] Collateral studies in Cali revealed that the prevalence of adenomatous polyps of the colon is minimal in the poorest socioeconomic class,[15,16] a finding consistent with differences in dietary habits — nutritional studies have shown a very large socioeconomic difference in amounts of meat consumed in Cali.[17] That socioeconomic factors do not influence the development of large bowel cancer in the United States may be due to minimal differences between classes in the dietary pattern.

Religion

Comparative studies of religious groups have allowed researchers to look for differences in lifestyle and site-specific cancer risks between groups in a small geographic area. For example, Seventh-Day Adventists traditionally consume less meat and adhere to a lacto-ovovegetarian diet; studies have indicated that the mortality from all forms of cancer in Adventists living in California is about 60% of that of a comparable sample of the general population.[18-20]

Similarly, the incidence of large bowel cancer is lower in Mormons (members of the Church of Jesus Christ of the Latter-Day Saints), who eat more whole-grain breads and cereals, than in other white population groups in the United States.[21,22]

Results of etiologic investigation

Correlation analysis

Since the risk of large bowel cancer closely parallels a country's level of economic development, cross-national correlations between the incidence of colon cancer and dietary habits have been used to select hypotheses for testing in case–control and cohort studies. These studies have shown that certain food preferences appear to be associated with either a high or a low risk of colon cancer. Such correlations may be spurious, but when they are supported by experimental evidence from animal studies, and underlying mechanisms can be described, further study seems worth while.[23]

It has been proposed that the occurrence of colon cancer is associated with the total dietary fat intake. Ingested fat is thought to influence the metabolic activity of the fecal microflora and thus to be involved in the pathogenesis of this type of cancer.[2,24] A worldwide correlation between the incidence of colon cancer and total fat consumption has been established.[6]

Gregor, Toman and Prusová[25] correlated data on cancer mortality and food consumption in 28 countries and found a high correlation ($r = 0.81$) between death from intestinal cancer and the consumption of animal protein. The dietary intake of fat and fibre was not analysed. They concluded that their data supported a promoter role for diet during development of the disease rather than a role in its initiation. Drasar and Irving,[26] comparing dietary data from the Food and Agriculture Organization (FAO) and colon cancer incidence data from 37 countries, showed that the incidence of colon cancer was highly correlated with the intake of animal protein and bound fat. (These two dietary items are themselves highly associated since most bound fat is of animal origin.) Enig, Munn and Keeney[27] found in the United States a significant positive correlation of colon cancer incidence with the intake of total fat and vegetable fat; no correlation was found between the intake of animal fat and either the incidence or the mortality of colon cancer. These results support the concept that it is the total dietary intake of fat that is a determinant of the incidence of colon cancer.

Several investigators have systematically examined correlations between per capita consumption of specific food items, based on FAO data, and the incidence and mortality of colon cancer. Armstrong and Doll[28] showed that the dietary variables chiefly associated with large bowel cancer rates are meat and animal protein; total fat, meat and animal protein are highly correlated. Howell[29] pointed out that colon cancer rates were related to the consumption of beef more than that of pork, poultry or fish.

Burkitt[30,31] observed the rarity of large bowel cancer in most African populations and suggested that populations consuming a diet rich in fibre have a lower incidence of this type of cancer, while those eating refined carbohydrates and little fibre have a higher incidence. He argued that large bowel tumours are related to factors characteristic of modern Western society whereby intestinal transit time is slowed, small firm stools are produced and the fecal bacterial flora is altered. Slower transit would allow more time for gut bacteria to degrade intraluminal components, produce carcinogens, and enable such carcinogens to act. There is, however, no support for the suggestion that faster transit results in increased degradation of substrates by gut bacteria.[32] A recent study comparing low-risk populations in Kuopio, Finland with those at high risk in

Copenhagen[33] indicated that transit time and stool weight had few significant correlations with diet and defecation habits, but that stool weights were higher in the Kuopio population. Our data also suggest that one of the factors contributing to the low risk of large bowel cancer in Kuopio appears to be that a high intake of dietary fibre (mainly cereal fibre) leads to increased stool bulk, in effect diluting tumourigenic compounds in the colon.[34] The results are consistent with a possible role for dietary fibre in the prevention of large bowel cancer in humans.

Case–control studies

Wynder and colleagues[2] conducted a large-scale retrospective study of patients with large bowel cancer in Japan that suggested a correlation between the westernization of the Japanese diet (including a higher content of fat and a lower content of fibre) and colon cancer. Recently, Dales and associates[35] found that among American blacks significantly more colon cancer patients than controls reported that their diet was high in saturated fat and low in fibre. Investigating many dietary constituents Modan and collaborators[36] discovered that those contributing less to the diets of patients with colon cancer than to the diets of controls were those containing fibre. Bjelke,[3] who interviewed hospitalized patients and controls in Minnesota and in Norway, learned that colorectal cancer patients less frequently ate vegetables; in particular the Minnesota patients ate less cabbage. Similarly, Graham and colleagues,[37] at Roswell Park Memorial Institute, Buffalo, New York, found that individuals who ate vegetables such as cabbage, broccoli and Brussels sprouts had a lower risk of colon cancer.

These studies indicate that diets with a high intake of total fat and beef and a low intake of certain fibres and certain vegetables are generally associated with an increased incidence of large bowel cancer in humans.

Suggested hypothesis

A current hypothesis is that colon cancer may stem from the combined action of as-yet-unidentified initiating carcinogens and promoting agents.[38-40] The level of the constituents within the lumen of the large bowel that have cocarcinogenic or promoting properties dependent on a high dietary intake of fat, namely bile acids, would relate to the development of large bowel cancer.[38-42] The amount of dietary fat and meat also determines the activity of the gut microflora that metabolize bile acids and other intraluminal compounds into promoters or carcinogens in the large bowel.[38-40,42-44] The most likely reason for the protective effect of certain dietary fibres is that they not only increase stool bulk, thus diluting promoters and carcinogens, but also modify the metabolism of tumourigenic compounds in the gut.

Protective effect of dietary fibre against colon cancer

Possible mechanism

Dietary fibre has been defined as that part of ingested plant material that is resistant to digestion by the secretions of the gastrointestinal tract. It comprises a heterogeneous group of carbohydrates, including cellulose, hemicellulose and pectin, and a noncarbohydrate substance, lignin.[45] Digestion of plant fibres by bacteria depends on the chemical and physical structure of the fibre.[46-48] According to Van Soest,[49] fibres can be classified into three groups: vegetable fibres, which are highly fermentable and have little indigestible residue; brans, which are less fermentable; and chemically purified fibres, such as cellulose, which are relatively nonfermentable. Pectins and gums, soluble substances that are not true fibres, are considered part of the dietary fibre complex because of the similar effects they can elicit in the diet. Wheat bran is mainly hemicellulose, with smaller amounts of lignin and cellulose, whereas vegetable and fruit fibres have different percentages of cellulose, hemicellulose and lignin.

The protective effect of dietary fibre may be due to adsorption, dilution or metabolism of cocarcinogens, promoters and yet-to-be-identified carcinogens by the components of the fibre.[5,34,50,51] There is evidence that alfalfa, wheat straw and some other fibres can bind considerable amounts of bile acids in vitro.[52] This indicates that the different types of non-nutritive fibres possess specific binding properties. Dietary fibre could also affect the enterohepatic circulation of bile salts.[53] Fibre not only influences bile acid metabolism,[34,54] thereby reducing the formation of potential tumour promoters in the colon, but also exerts a solvent-like effect in that it dilutes potential carcinogens and cocarcinogens by its bulking effect[34] and is able to bind bile acids[52] and certain carcinogenic compounds.[55]

Although the concept of fibre involvement in colon carcinogenesis is simple and attractive, and appears to be firmly based on logic, the data often appear contradictory and confusing. Discrepancies may have arisen from the general misuse of fibre terminology. As well, experimental design has failed to account for the possible subtle effect of inhibitors, especially in relation to the promoting process. Evaluations of the biologic function of dietary fibre have often lacked complete information on the nature of the fibre.

Metabolic factors

Investigations have been carried out in several laboratories to determine whether there are differences in fecal constituents between populations at high and low risk of colon cancer, and whether changes in the fibre content of the diet would alter the concentration of fecal bile acids and the activity of fecal microflora.

Recently, we studied healthy individuals in Kuopio, Finland, an area of low risk for the development of colon cancer.[34] Dietary histories indicated that the total fat consumption is similar to that in the United States but that the main source of fat is milk and other dairy products, while in the United States the main source is meat. The Finnish intake of cereal fibre is higher and the daily output of feces three times higher than that of healthy individuals in the United States. The concentration of fecal

secondary bile acids, mainly deoxycholic acid and lithocholic acid, and the extent of fecal bacterial β-glucuronidase activity are less in Kuopio than in the United States, but the total daily output is the same in the two populations because of the threefold greater daily output of feces in Kuopio. This suggests that increased fecal bulk dilutes suspected carcinogens and promoters that may be in direct contact with the large bowel mucosa.

Recent studies also indicate that the dietary intake of fibre is significantly higher in Kuopio than in Copenhagen, a high-risk area for the development of colon cancer.[33] Transit times were not different, but stool weight was significantly higher in Kuopio, particularly in the autumn. This suggests that certain foods may have effects on transit time independent of their effects on stool weight. Cummings and associates[56] demonstrated that fibre from carrot, cabbage, apple, bran and guar gum produces different responses in fecal weight in humans related to the intake of pentose-containing polysaccharides in the fibre. The fecal weight increased by 127% when bran was added to the diet and 20% when guar gum was added; carrot, cabbage and apple produced intermediate changes. Adding fibre to the diet shortened the mean transit time through the gut and significantly diluted an inert marker in the feces. In another study, Cummings and collaborators[57] reported that an increase in cereal fibre intake from 17 to 45 g/d increased the fecal weight from 79 to 228 g/d and diluted the fecal bile acids. Kay and Truswell[58] showed that adding wheat fibre to the diet decreased the concentration of fecal bile acids and neutral steroids because of the bulking effect of fibre, whereas the addition of pectin to the diet increased the fecal steroid and bile acid output. These results suggest that the effect on fecal bile acid excretion may depend on the type of fibre consumed.

The relation between dietary fibre consumption and fecal mutagenic activity has been studied. This activity was more frequent in South African whites living in urban areas, who have a high risk of colon cancer, than in South African blacks living in urban or rural areas, who consume a low-fat and high-fibre diet and have a low risk of colon cancer.[59] Similarly, fecal mutagenic activity was more frequent in persons from New York consuming a high-fat, low-fibre diet than in a rural Finnish population consuming a high-fat, high-fibre diet.[60] Bruce and associates[61] have reported the presence of mutagenic substances in the stools of some individuals consuming a mixed Western diet. They identified these substances as N-nitroso compounds and believed they were produced in the body rather than ingested. The fecal mutagenic activity was reduced when the diet was supplemented with ascorbic acid, α-tocopherol or fibre.[62]

If fecal mutagens are involved in the genesis of colon cancer, it would be of interest to extend these studies to populations at varied levels of risk for colon cancer development. It is possible that the fecal samples may contain comutagens and antimutagens that contribute to the overall mutagenic potential of the feces. Isolation and identification of these compounds could lead to a better understanding of the mutagenic load in the colon.

Experimental evidence

The relation between dietary fibre consumption and colon cancer has been studied in experiments with animals. Wilson, Hutcheson and Wideman[63] found that Sprague-Dawley rats fed a diet containing 20% corn oil or beef fat and 20% wheat bran had fewer colon tumours induced by 1,2-dimethylhydrazine than rats fed a control diet containing 20% fat and no bran. There was no difference in the incidence of colon cancer between the rats fed corn oil and those fed beef fat. Recently, Freeman, Spiller and Kim[64] compared the incidence of colon tumours induced by 1,2-dimethylhydrazine in Sprague-Dawley rats fed either a fibre-free diet or a diet containing 4.5% purified cellulose. Among the animals ingesting cellulose fewer had colonic neoplasms, and the total number of colon tumours in this group was lower. This protective effect appeared to be associated with a shift in tumour distribution from the proximal colon to a more distal site.[64] Although the mechanism for this apparent redistribution of tumours within the colon remains obscure, some change in the luminal physiochemical environment or some inherent difference in the mucosa of the two areas may be responsible.

A recent study by Fleiszer and colleagues[65] indicated that the incidence of colon tumours induced by 1,2-dimethylhydrazine in rats decreases as the dietary intake of fibre increases. The diets in that study differed not only in consistency (that is, solid or liquid) but also in the proportions of protein and fats, which have been shown to have an independent effect on colon carcinogenesis induced by 1,2-dimethylhydrazine. Some reduction in tumour incidence in the rats ingesting a high-fibre diet might be expected on the basis of reduced energy intake. However, the study's findings suggest that reduced intake alone cannot account for the significant protective effect of dietary bran.

In another study, Cruse, Lewin and Clark[66] found that a diet containing 20% wheat bran had no effect on colon carcinogenesis induced by 1,2-dimethylhydrazine in rats. However, the doses of the chemical in their experiment were so high that any protective effect of bran might have been unobservable. In a study of the effect of diet on chemical carcinogenesis it is important to avoid exposing the animal to an excessive level of carcinogen for a long period, as this may obscure more subtle changes induced by certain dietary modifications. In fact, the data presented by Cruse and associates[66] suggest that a high-fibre diet reduces the frequency of death due to 1,2-dimethylhydrazine in rats.[67]

The effect of a diet containing 15% alfalfa, pectin or wheat bran on colon carcinogenesis by methylnitrosourea or azoxymethane was studied in F344 rats by Watanabe and colleagues.[68] The animals fed the alfalfa diet and treated with methylnitrosourea had a higher in-

cidence of colon tumours than those fed a control diet containing only 5% cellulose or containing pectin or wheat bran; there was no difference in the frequency of colon carcinogenesis between the rats fed a diet containing pectin and those fed a diet containing wheat bran. The frequency of colon carcinogenesis induced by azoxymethane in rats fed a diet containing pectin or wheat bran was lower than that in rats fed a control diet or the alfalfa diet. The concentration of fecal bile acids, particularly hyodeoxycholic acid, deoxycholic acid and lithocholic acid, was lower in rats fed wheat bran than in those fed a control diet, but the daily output of these constituents was the same in the two groups.[69] Alfalfa had no effect on this concentration but did cause an increase in the daily excretion of deoxycholic acid and lithocholic acid. In contrast, pectin caused a marked increase in both the concentration and the daily output of bile acids. Thus, the concentration of fecal secondary bile acids in rats fed wheat bran and alfalfa diets correlated well with the incidence of colon cancer in these animals. On the other hand, the low incidence of azoxymethane-induced colon tumours in rats fed the pectin diet might not be explicable on the basis of bile acid excretion, but might be explained in part by the presence of natural inhibitors that modify the metabolism of the carcinogen.[70,71]

The effect of alfalfa, wheat bran and cellulose on the incidence of intestinal tumours induced by azoxymethane was further studied in Sprague-Dawley rats fed diets containing 10% fibre and 30% beef fat, 20% fibre and 6% beef fat or 30% fibre and 6% beef fat.[50] The presence of 10% fibre in the high-fat diet did not reduce the frequency of intestinal tumours. Apparently the effect of azoxymethane plus the high dietary intake of fat was too great to be affected by the dietary fibre. The presence of 20% bran or cellulose or 30% of any fibre in a diet containing 6% fat significantly reduced the frequency of intestinal tumours. All the groups except that with a diet containing 20% alfalfa had a lower frequency of tumours in the proximal half of the large bowel than the groups not ingesting fibre. The concentration but not the total daily excretion of fecal steroids was significantly lower in the groups with a lower tumour frequency.

Bauer and associates[72] have demonstrated that the protective effect of dietary fibre against colon carcinogenesis probably occurs at the promotional stage rather than in the initiating period. Rats were fed a fibre-free diet or diets containing 20% wheat bran, 20% carrot fibre or 6.5% citrus pectin from 3 days before the first injection of 1,2-dimethylhydrazine until 14 days after the last injection. They were then transferred to a standard rat pellet diet for 10 to 12 weeks. There was no difference in the incidence of colorectal tumours between the groups fed a fibre-free diet and those fed a diet containing wheat bran or carrot fibre. However, it is possible that the high tumour yield resulting from large doses of the carcinogen in this study masked any protective effect of dietary fibre. In addition, these results and those of others[50,63-65,68] have suggested that the continual feeding of a high-fibre diet protects against colon carcinogenesis, while a switch from a high-fibre to a low-fibre diet after administration of the carcinogen has no observable effect. These observations imply that dietary fibre protects against tumourigenesis during the promotional phase.

Discussion

All these findings indicate that there is a need to standardize experimental protocols in animal studies of the effect of fibre on chemically induced colon carcinogenesis. Variables such as animal strain, previous diet, type, dose and route of administration of carcinogen, and duration of the experiment should be considered when comparing data from different laboratories. There should be a systematic study of the effects of various standardized dietary fibres and fibre components on chemically induced colon carcinogenesis. Interrelations between dietary fat and fibre should also be investigated.

These limited results suggest that the protection against colon carcinogenesis afforded by dietary fibre depends on the source of fibre and the type of carcinogen. The inhibition of tumour formation by dietary fibre may be due to the dilution of promoters in the lumen of the large intestine by the additional bulk.[34,50,69] But it may also depend on the capacity of various fibres to bind bile acids in the intestinal tract[52] as well as the direct effect of the fibre on colonic mucosa[73] and the indirect effect on the metabolism of carcinogens.[70,71] Although additional studies are warranted to elucidate how various fibres protect against colon carcinogenesis, the data from humans and animals suggest that increased intake of cereal fibre should reduce the risk of large bowel cancer.

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This list is an acknowledgement of books received. It does not preclude review at a later date.

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