DIET AND COLON CANCER

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SYNOPSIS

Colon cancer is the second most common internal malignancy in most Western countries. Epidemiological studies have emphasised environmental factors, in particular diet, as the cause of this disease. However, the role of specific factors in colonic cancer has not been defined but changes in the luminal environment of the large bowel secondary to dietary manipulation appear to be important. Food intake can modify bacterial fermentation products and proliferative activity of the colonic mucosa, factors which may affect the susceptibility of the colon to carcinogenesis. Micronutrients including several vitamins and the trace element selenium have been implicated as protective agents against colonic cancer.

To establish better preventative strategies and early diagnostic tests future research should study the effects of diet on luminal factors and host cell susceptibility. At present only broad dietary guidelines can be recommended: eat less, increase relative intake of fibre, fruit and vegetables and reduce dietary fat.

Colorectal cancer is the second most common cancer behind lung cancer in men and breast cancer in women. The disease will affect 1 in every 25 Australians and now as in 1960 only 40% of patients presenting with this cancer will survive 5 years (1, 2).

To reduce the number of deaths we need to understand the aetiology and achieve a higher cure rate for established disease.

THEORIES OF COLON CANCER AETIOLOGY

(A) GENETIC INFLUENCES

There appears to be some genetic tendency as first degree relatives have a higher incidence of colorectal cancer than the normal population (3). In addition, the high risk conditions, familial polyposis, Gardner's syndrome and the female genital cancer syndrome are autosomal dominant traits (4). However, the majority of colorectal cancer cannot be linked to genetics.

(B) DIET

Most epidemiological evidence points to diet as the major factor in colorectal cancer. In particular, migrants from areas of high cancer incidence to low incidence generally attain rates of colon cancer similar to those of their new environment (5).

(i) Fibre and colorectal cancer

Possible protective mechanisms of fibre include faecal bulking with dilution of carcinogens, shortened transit time, lower colonic pH, bile acid binding, reduced faecal ammonia levels and induction of protective enzymes by certain vegetables. Fibre intake is generally higher in lower incidence countries (6). However, reports from various centres are conflicting. For example, in New York (7) higher ingestion of fruits and vegetables has been associated with a lower cancer risk but Puerto Ricans with colon cancer actually reported greater fibre intake than did controls (8).

Earlier animal studies showed protective effects of fibre against experimentally-induced colon cancer. More recently work from Jacobs and coworkers have shown that many types of purified dietary fibre which stimulate colonic epithelial cell proliferation also enhance tumour formation (9).

Some of the inconsistencies of associations between fibre intake and colon cancer may relate to the heterogeneous nature of the fibre studied. All dietary fibre is not inert but varies in its digestibility, lignins (the main component of wheat bran) being the most resistant. The digestibility of fibre may relate to its metabolic and antineoplastic effects in the large bowel. Bacterial fermentation of digestible fibre, such as pectins, gives rise to the short chain fatty acid butyrate which has powerful antineoplastic properties in several tumour cell lines (10, 11). Our results in colostomy patients have shown high concentrations of butyrate in the right colon and relatively low concentrations in the left colon where most neoplasms occur (12).

(ii) Dietary fat and colon cancer

The association between per capita consumption of total fat, saturated fat and national incidence rates of colon cancer are strong (13). However, as for fibre intake, studies of fat intake and colon cancer in individual subjects have been quite inconsistent (7, 14). It is believed that high fat diets can lead to colon cancer through several mechanisms including DNA damage by electrophile-producing lipid peroxidation (15), mutagen production through deep frying (16), induction of enzymic activity of intestinal flora to regenerate potentially carcinogenic compounds (17) and increased production of co-carcinogenic secondary bile acids (18). Some studies of patients with colorectal carcinoma and adenomatous polyps have shown higher levels of faecal secondary bile acids compared with controls (19, 20). Increased numbers of anaerobes or increased fat intake may explain this observation.

Fat acts as a co-carcinogen which can be inhibited by simultaneous administration of purified fibres in animals with experimentally-induced colon cancer (21). In addition the tumour-enhancing effect of fat can be produced some time after the carcinogenic insult is applied proving that fat can act as a tumour promoter.

Omega 3 fatty acids found in fish oil have received interest recently because of their apparent ability to prevent coronary artery disease and improve rheumatoid arthritis (22, 23). These effects relate to their ability to inhibit platelet aggregation and to competitively inhibit arachidonic acid. This competitive inhibition leads to the production of relatively greater amounts of leukotriene B5 which is much less chemotactic to neutrophils than the normally produced leukotriene B4 (24). Eskimos have a high intake of these omega 3 fatty acids and exhibit less chronic diseases including rheumatoid arthritis, ulcerative colitis and colon cancer (25). Possible mechanisms of cancer protection by omega 3 fatty acids require further study.

(iii) Energy intake and colon cancer

The incidence of colon cancer is higher in developed countries where caloric intake is high. Obesity is directly correlated with cancer in general (26) and in a study of women with colonic neoplasia their frequency of eating was significantly greater when compared with controls (27).

One of the mechanisms proposed for the role of overfeeding in cancer is the stimulation of mitotic activity. Increased proliferative activity of colonic epithelial cells is normally produced by feeding. However, abnormally increased proliferation is seen in certain high risk colon cancer groups, eg ulcerative colitis and familial polyposis. Increased caloric intake is associated with increased cell proliferation and increased experimentally-induced cancer incidence in the rat (28). Greater exposure to luminal contents followed by mucosal hyperplasia may explain the significant increase in large bowel tumours seen in carcinogen-treated rats after jejunoileal bypass surgery (29). In addition, the characteristic higher incidence of tumours in the left side in carcinogenic-treated rats is equalised by performing a double barrelled, defunctioned colostomy suggesting that left sided predominance is maintained by regional differences in luminal environment which are abolished by defunction (30).

We have found significantly greater proliferative activity in the distal compared with proximal colon in 72 h fasted rats. Refeeding abolishes this difference (unpublished observation). Inherent variation in proliferative activity in the large bowel could help explain the predeliction of the left colon for tumour formation. In addition, manipulation of cell proliferation by

caloric intake may be an important mechanism for colon cancer formation.

Ornithine decarboxylase is the rate limiting enzyme for the synthesis of polyamines which are necessary for cellular proliferation and differentiation (31). The concentration of this enzyme is increased in the mucosa of high risk patients with familial polyposis (32) and in rats treated with the carcinogens deoxycholate and azoxymethane (33, 34). In addition, this enzyme can be markedly induced by refeeding after a prolonged fast (33), and by certain dietary fats and amines (15, 35). Inhibition of ornithine decarboxylase protects against experimental intestinal carcinogenesis, probably by preventing normal cell proliferation (36). Further study of this enzyme is indicated to characterise its value as a preneoplastic marker and to improve understanding of the association between cellular proliferation and colon cancer.

(iv) Vitamins

(a) Vitamin A

Vitamin A plays a role in controlling cell differentiation and has oxygen radical quenching actions (37). Cancer rates have been reportedly higher in persons with lowest levels of the vitamin A precursor retinol in some (38, 39) but not all studies (40, 41).

(b) Vitamin E

This vitamin is an important intracellular antioxidant and in some experimental models acts as an anticarcinogen (42, 43). Evidence in man does not suggest a major role for vitamin E in colon cancer protection (40, 44).

(c) Vitamin D

Low serum calcium and dietary vitamin D intake have been positively correlated with colorectal cancer in men (45). The mechanism could relate to bile acid binding by calcium salts in the colonic lumen (46).

(d) Vitamin C

Intake of slow release vitamin C can favourably modify the characteristic neoplastic changes in individuals with genetically-initiated polyposis (47). However, there is minimal direct evidence to support a role for this antioxidant in cancer prevention.

(v) Trace Elements

Dietary fibre can reduce the bioavailability of several trace elements. Before recommending increased dietary fibre supplementation it is important to examine the possible roles of these micronutrients in cell proliferation and tumour protection.

(a) Selenium

Selenium has a key role in glutathione peroxidase activity, an enzyme which protects against oxidative damage at a cellular level. Inhibition of tumour cell induction in skin, liver, colon and breast tissue has been noted with selenium (15). Some studies show low serum selenium levels in cancer patients (44, 48).

(b) Zinc and Copper

Zinc metalloenzymes are essential to DNA synthesis and normal repair mechanisms (49). In the small bowel the rate of cellular proliferation in jejunal crypts is significantly lower in zinc-deficient rats (50). In addition, metallothionein an intestinal glycoprotein induced by parenteral or enteral zinc appears to play a role in host cellular defense mechanisms.

Superoxide dismutase is a copper dependent metalloenzyme which is abundant in the liver and other tissues (49). It catalyzes the quenching of superoxide, an anion which has been implicated in DNA damage. Therefore, copper deficiency could indirectly lead to cellular damage by oxygen radicals.

Zinc and copper deficiencies have not yet been causally linked to colon cancer but further studies are indicated to examine their roles in colonic cellular proliferation and DNA repair.

Most dietary customs implicated in increasing the risk of colon cancer include overnutrition, excess intake of fat and a deficiency of fibre. However, neither epidemiological nor laboratory studies have definitely linked any particular substance with cancer of the large bowel. As yet we do not know enough to confidently prescribe a risk-reducing diet other than in the most general terms: eat less, increase fibre, fruit and vegetables; and reduce fat. The changes are unlikely to be harmful and may be beneficial in preventing other diseases.

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