Is the Changing Pattern of Colorectal Cancer Caused by Selenium Deficiency?

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An hypothesis is presented to explain the changing pattern of colorectal cancer seen within the United States and other western countries in the last 30 years, the simultaneous increase of right-sided colonic cancer and disappearance of rectal cancer. Review of experimental and epidemiologic data suggests that this change may be due to a new systemic deficiency of the trace element, selenium. This deficiency has arisen not just from decreased consumption of selenium in the last 30 years, but also from increased consumption of zinc and fluoride, which may antagonize the effect of selenium. [Key words: Colorectal cancer; Selenium; Zinc; Fluoride; Epidemiology of colorectal cancer]

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COLORECTAL CANCER WAS, until 1983, the most common visceral tumor in the United States. The lifetime risk of colorectal cancer developing is about 4 per cent. This incidence has been increasing slowly in societies in which the disease is endemic in both sexes and all age groups, with the exception of women in the fourth to sixth decades of life. The decreasing incidence in women is thought to be the result of the widespread use of oral contraceptives.[1] Yet, though the incidence and distribution of this disease within Western populations has been fairly stable, there has been, in the last 30 years, a remarkable change in the location of tumors within the colon.

Many of us were taught in medical school that 50 per cent of all colorectal tumors were detectable during digital examination of the rectum. Currently, the 60-cm flexible sigmoidoscope is considered to be a tool with roughly equivalent diagnostic accuracy. There is now extensive documentation of the simultaneous precipitous decline in the incidence of rectal cancer with an increase in right-sided colonic cancers.[2-4] This changing pattern may be caused by a new deficiency in the trace element, selenium; this deficiency is caused by a decreased dietary intake of selenium and an increased ingestion of substances that antagonize the anti-cancer effect of selenium.

There has been some speculation that cancer of the colon and cancer of the rectum might have different etiologies. This has arisen exclusively out of varying demographic patterns. There is no pathologic or experimental evidence to support this hypothesis. The same drugs that can induce colonic cancer experimentally also induce rectal cancer and the biologic behavior of these tumors in humans is quite similar.[5]

Epidemiologic studies have implied that there is a major environmental factor involved in the onset of colonic cancer. Specifically, low-fiber diet and high consumption of animal protein, beef fat, and beer have been associated with a high risk of colonic cancer. Populations eating a more primitive or more atypical diet that is lower in overall fat and higher in crude fiber have a much lower risk of acquiring colonic cancer. Also, individuals who move from low-risk environments to high-risk environments, such as Japan to Hawaii, change their risk of getting colonic cancer to that of their new home.

Though it has been proved that regular proctosigmoidoscopy and polypectomy can decrease the incidence of rectal cancer in isolated and well-studied populations,[6] annual proctosigmoidoscopy of individuals without symptoms is not performed in a large enough number of patients to account for the changing incidence of rectal cancer. In any case, this does not account for the simultaneous increase of right-sided colonic cancers.

The only dietary factor connected specifically with rectal cancer and not colonic cancer has been beer. The evidence for this comes primarily from the United Kingdom, where per capita beer consumption has declined in parallel to the declining incidence of rectal carcinoma.[2] This observation has not been reproduced experimentally.

Experimental Colonic Cancer

The injection of dimethyl-hydrazine (DMH) into rats or mice results in the formation of polyps and cancers identical to those found in humans. This model has been used to test the effect of a number of dietary constituents

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in experimental colonic carcinogenesis.[5] Among the substances tested in this model have been beer and ethanol. No increase in the number of tumors or change in the distribution of tumors was noted as a result of the addition of beer or ethanol to the diet of rats treated with DMH.

Of all the dietary constituents that have been tested in conjunction with the DMH-rat colon cancer model, only two have been found to alter the distribution of tumors within the colon. The first is DMH itself and relates to the dose administered to the rat. With increasing doses of DMH, more tumors were noted and they were clustered in the left side of the colon. As doses were decreased, a greater percentage of tumors were noted on the right, but the total number of tumors also dropped precipitously.[7] This result is not compatible with the epidemiology of colonic cancer, as the overall incidence has not been seen to decline.

The second substance noted to alter distribution of colonic cancers is selenium. In animals not receiving selenium supplementation, right colon tumors were noted to predominate over left colon tumors at a ratio of approximately 2:1. With supplementation of selenium to eight parts per million, there was over a 90 per cent reduction specifically of right colon tumors. There was no significant change in the number of left colon tumors.[8]

Selenium

Selenium was one of the first agents to be used in the chemotherapy of cancer. Its deficiency has been shown to cause muscular dystrophy in ruminants, pancreatic degeneration in poultry, and liver degeneration in rats.[9]

In humans, selenium is required for the function of glutathione peroxidase (E.C.1.11.1.9.). This enzyme catalyzes the intracellular removal of hydrogen peroxide and a number of organic peroxides in the following reaction:

$$2GSH + H_2O_2 \xrightarrow{G.P.} GSSG + 2H_2O$$

which prevents this reaction:

$$H_2O_2 + O_2 \longrightarrow 2\,OH^{\cdot} + {}^1O_2.$$

Decreased selenium intake and blood selenium levels have been directly correlated with lower activity of glutathione peroxidase. Failure to remove peroxides from the cell results in formation of oxygen radicals and oxidative damage to a number of macromolecules, including DNA. Normal function of the enzyme is therefore required in order to prevent cellular aging and possibly oncogenesis.

Selenium deficiency has been linked to cancer in a number of ways. Populations living in selenium-deficient areas have an increase in the incidence of cancer in general and increased incidences of both breast and colonic cancer in particular. Cancer patients also tend to have low blood selenium levels. Experiments have demonstrated that induction of tumors is decreased in animals that have received selenium supplementation, as well as a decreased incidence of mutation in the Ames salmonella microsomal assay test and decreased induction of sister chromatid exchange in cells exposed to mutagen after selenium supplementation.[10]

Causes of Selenium Deficiency

If selenium deficiency is related to the changing distribution of colorectal cancer, how might this deficiency have come about? There are certainly large geographic areas that have a deficiency in the bioavailability of selenium — all of New Zealand is the best example — but major shifts in the sources of food to these areas have not occurred. Since the late 1940s, annual per capita meat consumption has increased at least 50 per cent in the United States and more than 100 per cent in the United Kingdom.[2] Increased meat consumption is accompanied by an increase in dietary fat and, most importantly, a concomitant decrease in dietary grain and vegetables. The amount of selenium in meat is relatively low, when compared with the amount of selenium in seafood and whole grain cereals (about 25 per cent).

Another means of becoming selenium deficient is the increased ingestion of trace elements that antagonize the anti-cancer effect of selenium. One possible antagonist is zinc. Zinc, which is known to prevent the dietary uptake of selenium, abolishes the protective effect of selenium in experimental carcinogenesis in laboratory animals. Blood levels of zinc also have been directly related to cancer mortality, particularly of carcinoma of the breast and colon. One of the most prominent sources of dietary zinc is meat.[11] Zinc from plant sources is bound to phytate and excreted in the feces. Phytate in vegetable diets also binds zinc in salivary and digestive secretions, and this may result in net zinc excretion in vegans. Zinc from meat sources is, on the other hand, present in higher concentrations and is entirely available for absorption.[12] This may be the most plausible explanation for the association of colonic cancer with beef consumption, since efforts to demonstrate the specific carcinogenic effect of meat protein or fat in experimental colonic carcinogenesis have been unsuccessful.[5]

Another potential selenium antagonist is fluoride. Initial fears about the relationship of fluoride supplementation to overall cancer mortality have been largely ameliorated.[13] Yet in the studies of cancer incidence and mortality that were undertaken in fluoridated areas, the following data have emerged. Mortality from rectal

cancer was found to be 33 per cent lower in areas with high natural fluoride levels than in areas with very low naturally occurring fluoride. No difference was seen in mortality from proximal colonic cancer. In areas with artificial fluoride supplementation, mortality from rectal cancer was also found to decrease by 9 per cent when compared with presupplementation mortalities. The most important finding of all is that in comparing cancer incidence in two major U.S. cities, one with early artificial fluoride supplementation (Denver, Colorado) and one with late artificial fluoridation (Birmingham, Alabama), it was found between 1948 and 1971 that in women there was a relative decrease in rectal cancer and an increase in proximal colonic cancer in Denver, the city with early artificial fluoridation of the water supply.[14]

Is the association of fluoride with changing patterns of colorectal cancer related to selenium deficiency? In the last 30 years most water supplies have been fluoridated in order to prevent dental caries. In areas of abundant naturally occurring selenium, such as South Dakota, the protective effect of fluoride supplementation in dental caries has been noted to be decreased.[15] A reciprocal antagonism might occur, that is, abundant fluoride might similarly abolish the protective effect of selenium.

Summary

Trace element nutrition is a new and complex field. It has been possible to determine how much of each element can be ingested in order to prevent gross symptoms of deficiency or toxicity. However, the interaction of various trace elements in the incidence and distribution of chronic or insidious diseases such as colorectal cancer has not been investigated. In experimental studies, deficiency of selenium has been shown to increase the incidence of right-sided colon tumors. Increased ingestion of zinc may have precipitated this effect in humans. Increased dietary fluoride has been associated in epidemiologic studies with a decreased mortality from rectal cancer and an increased incidence of proximal colonic cancers. Experimental studies using the rat-DMH colon cancer model might demonstrate a causal relationship in these observations and determine the degree to which zinc, selenium, and fluoride are related to the changing pattern of colorectal cancer in humans.

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