Dietary, Environmental, and Hereditary Factors in the Development of Colorectal Cancer

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Recent studies have attempted to identify factors that are associated with the development of colorectal cancer both in population groups with genetic predisposition to neoplasia and in individuals in the general population who are at high risk. Environmental and dietary elements suspected of inducing or promoting colon carcinogenesis and abnormalities observed in colonic cell development are under investigation. Colorectal cancer poses a major health problem in the United States and many other countries, and is currently responsible for a high proportion of the malignant neoplasms found in the United States. Recent figures have indicated over 112,000 new cases annually in the United States, and high mortality. The proportion of individuals who survive the disease varies with the stage at which it is detected, success being higher with earlier detection.

Environmental and Dietary Factors

There is reasonably strong evidence to indicate that environment has a role in the development of colorectal cancer; however, the most important elements involved are not clear because of conflicting findings. Numerous studies have shown a correlation between colon cancer, economic status, and geographic and dietary exposure. In industrialized countries, including those of northwest Europe and North America, a great deal of animal fat, protein, and refined carbohydrate is consumed; in these geographic regions, the incidence of colon cancer is much higher than in the developing countries of Africa, South America (except Argentina and Uruguay, whose populations are meat-eaters), rural India, and Japan, where much less meat is consumed and the diet is higher in vegetable fiber. These variations in incidence are not believed to be related to genetic differences because certain migrant groups tend to assume the colon cancer incidence rates of their adopted countries. For example, in studies of Japanese Issei (first generation) and Nisei (subsequent generation) migrants to Hawaii, a higher incidence of large bowel cancer was observed in individuals who no longer continued the practice of eating at least one Japanese-style meal daily. A rise in the consumption of meat was the major difference in diet between residents of Japan and Hawaii, and the increase in beef consumption paralleled the higher risk of bowel cancer among Japanese migrants. A correlation between the daily consumption of meat and the incidence of colorectal cancer has been demonstrated.
of colon cancer also has been noted in individuals from many countries, suggesting an etiologic role.7,8

Observations of this type have led investigators to postulate that diets high in animal protein and fat, characteristic of high-risk populations, are responsible for colon cancer. In one study of 28 countries, positive correlations were found between the incidence of colon cancer and the amount of meat the various populations consumed.9 On the basis of epidemiologic findings of this type it has been postulated that colon cancer is associated with intestinal flora, which might possibly synthesize carcinogenic or promotor elements from both food and secretions in the intestine, such as bile acids. Diet might be expected to influence not only the composition of the intestinal flora but also the quantity of substrates available for the production of carcinogens. Further studies have led to the concept that low fiber content of the diet also may be associated with the development of colon cancer.10 Of recent interest are studies that have correlated the content of trace metals in the soil with the incidence of colon cancer; here, selenium has been emphasized.11-15

A problem with epidemiologic data is that other factors in the environment could contribute significantly to the incidence of colon cancer. For example, the prevalence of infectious diseases and other chronic illnesses varies greatly among those populations who are at high and low risk, and these variations can also be correlated with the incidence of colon cancer. Other factors not related to food also change simultaneously with dietary habits, as populations undergo industrial and economic development. Even in dietary habits discrepancies exist; for example, in certain countries, and in the Mormon population of Utah, high meat and beef intake is associated with relatively lower risk of colon cancer than among other groups.16 The epidemiologic evidence available on the role of diet has therefore suggested that further studies be carried out; however, it has not supplied definite proof that any given dietary factors are causally related to variations in the incidence of colon cancer.

In attempting to explore the leads noted above, studies have been conducted to examine the fecal flora and related metabolic constituents obtained from individuals in different parts of the world. In an early analysis, fecal samples were obtained from individuals residing in England, Scotland, and the United States, regions having a high incidence of colorectal cancer, and from Uganda, India, and Japan, where low incidences of colorectal cancer occur. Some differences in relative numbers of several bacterial groups were observed. The British and American subjects had more gram-negative anaerobes than did the Ugandans, Indians, and Japanese, while the latter groups had larger amounts of aerobic bacteria. As a result, the ratio of anaerobes to aerobes was higher in individuals consuming a Western-style diet than in those consuming largely vegetarian diets.17

Concentrations of acid and neutral steroids in the feces also differed when individuals on high and low meat diets were compared. Fecal specimens from British and Americans on high meat diets contained higher amounts of steroids than feces of Ugandans, Indians, and Japanese, whose diets contained little or no animal fat and protein. The amounts of neutral steroids were low in the feces of Ugandans and Indians, intermediate in the feces of Japanese, and high in the feces of British and Americans. Microbial conversion products of cholesterol, coprostanol, and coprostanone also contributed a smaller amount to the total neutral steroid content of the feces of the Ugandans, Indians, and Japanese than to the feces of the Western group. Acid steroid concentrations were greater in the feces of British and Americans than in the Ugandans, Indians, and Japanese; the extent of conversion of acid steroids also appeared to be higher in the British and Americans than in other groups. The daily fecal excretion of cholesterol metabolites also was believed
to be greater in Americans who consume a diet containing meat than in Americans on a meatless diet.\textsuperscript{17,18}

In further attempts to elucidate mechanisms of colon carcinogenesis, other studies have suggested no significant differences in bacterial counts or species isolated from the feces of volunteers on high meat or meatless diets. Although minor quantitative variations were present, unique organisms in high- or low-risk groups were not observed; organisms present in individuals on high-risk diets were also found in individuals on low-risk diets. It was thus suggested that taxonomic grouping of bacteria is not important in analyzing the effects of diet on intestinal flora; rather, the effect of altered diet on bacterial metabolic activity might be of greater interest, and in fact more useful, in trying to understand the real factors contributing to colon cancer development.\textsuperscript{19,20} It was also of interest that alterations in flora were believed to be affected by situations producing anger or stress in the host. Some individuals in the general population, and also those with the high-risk disease familial polyposis, excreted significantly higher amounts of cholesterol than the others.\textsuperscript{21-23}

In related studies, secondary bile acids in the feces were found to be higher during fatty meat ingestion when concentrations of total bile acids were high, leading to the concept that secondary bile acids were products of the dehydroxylation of primary fecal bile acids by intestinal bacteria.\textsuperscript{18,24} In further support of the above, high-fat, high-meat mixed Western diet and non-meat diet, for which protein contents were similar, were compared in human volunteers for steroid content of feces.\textsuperscript{25} The findings indicated that total anaerobic microflora count and fecal excretion of secondary bile acids and cholesterol metabolites were greater during consumption of the mixed Western diet than of the non-meat diet, supporting a role of dietary fat in the composition of intestinal flora and level of steroid conversion products in feces.

Individuals with colon cancer thus have been reported to have higher amounts of steroids and steroid conversion products such as deoxycholic acids, lithocholic acid, and cholesterol metabolites in their feces than controls without cancer. It has also been reported that the activity of fecal 7α-dehydroxylase is higher in patients with colon cancer compared to controls, in association with the conversion of cholic and chenodeoxycholic acids to deoxycholic and lithocholic acids. A high frequency of individuals with cancer of the large bowel were reported to have greater concentrations of bile acids in their feces than did patients with other diseases.\textsuperscript{25,26} The colon cancer patients also had greater amounts of acid steroids in the form of secondary bile acids than did the other patients.

These findings continue to support the view that there may be an association between fecal steroids and the production of cancer. However, since normal North Americans appear to show two patterns of neutral sterol conversion as measured by fecal analysis,\textsuperscript{22} important genetic factors may be operative in this area: "high converters" have a stable pattern of extensive conversion of cholesterol, sitosterol, and campesterol by the intestinal flora to degradation products, while "low converters" produce little or no such conversion.

Animal studies have been quite useful in attempting to elucidate the role of genetic, dietary, and environmental elements in the etiology of colon cancer. For example, an experiment has indicated a greater susceptibility to colon tumor induction by 1,2-dimethylhydrazine in rats fed high-fat diets, compared to animals fed a diet containing a normal amount of fat.\textsuperscript{27} Fecal excretion of acid and neutral steroids was also greater in animals fed high-fat diets than in animals on low-fat diets.

Among concepts believed to be relevant to cancer development, the multi-stage evolution of neoplasms and the presence of "promoting" agents in addition to direct or indirect acting carcinogens have been important. In the experimental work just cited, bile acids appear to have a potentiating effect in inducing
colon carcinoma in laboratory animals and are believed to be promoting agents. The development of colonic tumors in rats exposed to the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine was increased by instilling lithocholic or taurodeoxycholic acids intrarectally.28 The carcinogenic effect of azoxymethane in rats was enhanced by increasing the concentration of bile reaching the colon, by feeding cholestyramine, and by diverting the bile flow to the lower section of the small intestine.29,30 Cholestyramine has been reported to increase the frequency of intestinal neoplasms induced by 1,2-dimethylhydrazine in germ-free rats.31 Of interest is the report that vitamin A-deficient rats had increased susceptibility to dimethylhydrazine-induced colon cancer.32,33

In a further attempt to understand the possible role of biliary metabolites in the development of colon cancer, the question of significant conversion of bile acids and cholesterol by bacteria is being assessed. In one area of investigation, fecal bacteria containing the enzymes 7-hydroxycholanoyl dehydroxylase and 3-oxocholanoyl44 dehydrogenase are being studied. These enzymes can convert primary bile acids to secondary ones and produce double bond formation on the bile acid nucleus. Thus, the possibility has been considered that both unsaturated and saturated bile acids contribute to the etiology of colon cancer, fulfilling roles of co-carcinogen and carcinogen.34

In a further area of investigation, it has been postulated that cholesterol metabolites may be important compounds in the pathogenesis of colon cancer, since fecal microbial 7-hydroxycholanoyl dehydroxylase and cholesterol dehydrogenase activities were noted to be higher in cancer patients compared to controls. Anaerobic intestinal bacteria produce double bond formation on the production of secondary bile acids and cholesterol metabolites.

Thus, it is believed by some investigators that metabolic products of biliary metabolism, low dietary fiber content, and bacterial and intestinal cellular enzymes are key factors increasing colon cancer risk. However, lack of a clear understanding of environmental relationships to colon cancer, highlighted by discrepancies in current data, remains. For example, Mormon and Seventh-Day Adventist populations have similar colorectal cancer standardized mortality rates despite greatly different rates of consumption of meat and beef. In Finland, the correlations also are poor. In animal and human studies, no specific bowel carcinogens have so far been detected. Work on additional factors that may be operative but have not been studied is needed.

Here, genotypic variability among individuals and population groups may be important, with the possibility that these may be greater than heretofore suspected; variability also may occur in the interaction of dietary elements with cells having different genotypic predispositions to neoplasia.

Increased Susceptibility With Genetic Predisposition

The development of colorectal cancer has been shown to be influenced by genotypic predisposition. This is known to occur in a small percentage of total cases; it also has been postulated that genotypic predisposition may be responsible for a larger fraction of total colon cancer incidence than previously shown. The degree to which interactions among dietary elements and colonic cells may be enhanced by genotypic factors is unknown. Recent findings have indicated that familial associations in colon cancer in the general population are higher than in control groups, suggesting that inherited factors may well have a greater role in the genesis of colorectal cancer than has been generally believed. In addition to earlier ones, recent studies have shown a significant increase in the number of deaths due to colorectal cancer among first-degree relatives of index cases compared with the expected incidence. Factors associated with the in-
creased risk were early age of onset, the presence of adenomas or other carcinomas in the operative specimen, and a history of previous carcinoma.35

The genetic origin of several varieties of precancerous colorectal disease involving polyp formation has been well described. Inherited adenomatosis of the colon and rectum (familial polyposis, ACR) is associated with innumerable colonic adenomas. For this disease, it has been possible to estimate population frequency, relative fitness, and mutation rate. In inherited adenomatosis, carcinomas and the largest adenomas most often occur in the distal colon; this is similar to the occurrence of adenomas and carcinomas in the general population. Recent studies have shown that early abnormalities can be detected in colonic cells,36,37 in cutaneous cells,38 and in stool contents21,22,39,40 of affected individuals and of some of their asymptomatic progeny.

Gardner's syndrome has been identified as a variant of familial polyposis, an autosomal dominant disorder showing a high degree of penetrance.42 Adenomatous polyps of the colon, and occasionally of the small intestine, are formed, and
there is a propensity for adenocarcinomas to develop within the polyps. Other characteristic features include sebaceous cysts, desmoid tumors, fibromas, facial bone osteomas, and abnormal dentition. These conditions may appear singly or in combination. An increased susceptibility to other carcinomas, including lesions of the thyroid, ampulla of Vater, duodenum, and adrenal gland, has been reported to be associated with Gardner's syndrome and with familial polyposis. It has been estimated that one in seven cases of inherited familial polyposis is identifiable as Gardner's syndrome. Frequency in the population is estimated as approximately one in 8,000 for familial polyposis and one in 14,000 for Gardner's syndrome.

Variants of familial polyposis and Gardner's syndrome include Turcot syndrome, i.e., polyposis coli associated with tumors of the central nervous system. In addition, the Oldfield syndrome has been described, with extensive familial sebaceous cysts, polyposis coli, and adenocarcinoma. An additional autosomal dominant inherited disease with variable expression is the Peutz-Jeghers syndrome, characterized by melanin pigmentation of the buccal mucosa, lips, face, fingers, toes, vagina, and anus. Polyps of the gastrointestinal tract, specifically in the small intestine, are found, with additional polyps appearing in the colon and rectum. However, these polyps are usually hamartomas rather than adenomas. The disorder appears to have very little malignant potential compared to familial polyposis or Gardner's syndrome, but some associated stomach and duodenal carcinomas have been reported.

One or more adenomas occur in five to 10 percent of the general population; these, too, can be associated with the development of adenocarcinoma, particularly when villous structures develop. Kindreds have also been reported to show an association of single and multiple adenomas with adenocarcinomas, a link that appears to be genetically influenced. Studies by Woolf et al. showed that 45 percent of the adult members of one generation had solitary adenomas and demonstrated the occurrence of adenomas in multiple generations. That family also had a high incidence of colon carcinoma, and the disease appeared to have an autosomal dominant mode of inheritance. Another inherited disorder is juvenile polyposis of the colon, in which the polyps are hamartomas and are not viewed as potentially malignant. Relatives of these juveniles do, however, express an above-normal rate of adenomas and colorectal adenocarcinomas.

The disease hereditary adenocarcinomatosis also has been observed in familial aggregates. The disease is inherited as an autosomal dominant with 90 percent penetrance, with a striking incidence of primary cancers at multiple anatomic sites including the colon, and an early age of onset in families highly predisposed to cancer. The general concept of "cancer families" has now been broadened to include neoplasms of different types, in addition to those affecting a single organ such as the colon. The neoplasms in those families appear to be influenced by genetic predisposition and affect diverse organs, especially the colon and endometrium. They tend to develop earlier in life than usual and may occur separately or as multiple cancers in family members. Since adenocarcinomas of the colon and reproductive sites are known to coexist excessively in studies of multiple primary cancers, the familial syndrome may represent a scattering over the family tree of tumors that share etiologic influences.

Phenotypic Expressions of Inherited Disease

Specific abnormalities have been observed in the cells and in the intestinal contents of individuals with hereditary predisposition to colorectal cancer that are now serving as indices for experimental studies in two areas relevant to phenotypic expression of inherited disease. One is in the identification and definition of population groups at high risk for colorectal cancer; another is in studies at-
tempting to define interactions that may occur between cells genotypically predisposed to neoplasia and carcinogenic or promotor elements. These abnormalities are enumerated in Table 1. In individuals with familial polyposis and Gardner's syndrome, proliferative abnormalities in colonic epithelial cells have aided identification of early disease and affected individuals. Proliferating colonic epithelial cells that have inherited the germinal mutation fail to repress DNA synthesis, and they undergo abnormal maturation as they migrate through the colonic crypts. Morphologically identifiable adenomatous cells that fail to repress proliferative activity develop and accumulate in the mucosa, and malignant cells evolve as these accumulations of adenomatous cells enlarge. \[36,37,51\] The development of villous components in the polyoid lesions is associated with the development of cancer.\[52,53\]

Recent studies also have indicated that abnormal phenotypic expressions of inherited familial polyposis extend to cutaneous cells. A recent study reported increased heteroploidy in cutaneous epidermal cells derived from individuals with Gardner's syndrome.\[54\] In cutaneous fibroblasts, various abnormalities, including overgrowth and cytoskeletal structure defects have been detected.\[55\] Abnormal ploidy in cells of polyph also has been observed.

An immunologic abnormality associated with increased susceptibility to colon cancer in asymptomatic progeny of nonpolyposis familial aggregates has recently been observed. It manifested itself as an inappropriate suppression of a potentially normal lymphocyte ability to respond to an allogenic stimulus. This defect in re-cognitive immunity appeared to be the same defect that was demonstrated in individuals with established cancers.\[56\] Studies to extend these various findings to additional familial aggregates and to related disorders leading to colon cancer are now under way and offer the possibility of new means for the early detection of susceptible population groups.

Related studies also are in progress to identify abnormal constituents of feces and to examine their potential carcinogenic activity in colon cells. Specifically, in the high-risk group with familial polyposis, several recent reports compared fecal neutral steroids and bile acids in patients with familial polyposis with those in controls.\[21,22,39,40\] Individuals with familial polyposis excreted higher amounts of undegraded cholesterol than controls. Nondegraded cholesterol was also found in a small fraction of individuals in the general population. Further studies are in progress to assess the utility of these variations in cholesterol and its metabolites in screening high-risk population groups for disease, and to determine their possible role in the development of colon cancer. Similarly, a wide variety of analyses (including neutral steroids and bile acids, metabolic activity of fecal microflora, mutagens in feces, and nitroso-group exchange reactions in fecal bacteria) are presently under way to evaluate the fecal contents of high-risk groups and to attempt to determine significant parameters in these populations. The application of findings of this type to colon cancer prevention awaits more definite data on the effect of dietary and other modes of intervention on both fecal chemistry parameters and the neoplastic transformation of colonic cells.

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