Cholesterol Excretion and Colon Cancer

Selwyn A. Broitman
Department of Microbiology, Boston University School of Medicine, Boston, Massachusetts 02118

Abstract

Populations consuming diets high in fat and cholesterol exhibit a greater incidence of colon cancer than those consuming less fat and cholesterol. Lowering elevated serum cholesterol levels experimentally or clinically is associated with increased large-bowel tumorigenesis. Thus, cholesterol lost to the gut, either dietary or endogenously synthesized, appears to have a role in large-bowel cancer. Whether the effect(s) is mediated by increases in fecal bile acid excretion or some other mechanism is not clear.

Throughout the years, cholesterol has enjoyed intermittent popularity both as a causative factor in CHD and a key factor in tumorigenesis. Demographic studies show that those populations with a high incidence of CHD similarly have a high incidence of colorectal cancer. These populations additionally exhibit a relatively high incidence of cancer of the breast, pancreas, and prostate as well as leukemias. Nevertheless, attempts to demonstrate a relationship between dietary cholesterol and/or plasma cholesterol and cancer have been unrewarding. Much of the controversy stems from inconsistencies between serum cholesterol levels and the incidence of various types of cancers. This is not surprising, since (a) serum cholesterol levels do not accurately reflect dietary cholesterol consumption, (b) only cancers at certain specific organ sites exhibit an epidemiological relationship to diet, (c) serum cholesterol levels vary in individuals depending upon the progression of malignant disease, the palliative surgery, or therapeutic interventions, and (d) in certain instances, there may be an inverse relationship between serum cholesterol levels and the occurrence of certain site-specific neoplasms.

This latter point is best exemplified by the work of Rose et al. (15) who noted the close correlation (r = 0.775) between the death rates for CHD and colon cancer in various populations throughout the world. In spite of this association between both diseases in a given population, Wynder (18) pointed out that risk factors for CHD, e.g., cigarette smoking, hypertension, and hypercholesteremia, do not correlate with the incidence of colon cancer. This implies that, in a given population consuming diets high in fat and cholesterol, certain individuals may be destined to develop CHD while others may be destined to develop colon cancer. With few exceptions, these groups appear to be mutually exclusive. If diet is indeed a common etiological factor for both these disease entities, then the effects of diet or various components of the diet must be manifest differently in each of these groups.

Rose et al. (15) provides additional information that may have a bearing on this. In their 6-country prospective study, they found only 90 individuals who had CHD but who also ultimately developed colon cancer. Of the serum cholesterol levels obtained on these individuals initially, almost two-thirds were below an expected level. They speculated that dietary regimens instituted after the diagnosis of CHD could be responsible for lowering serum cholesterol levels and perhaps increasing fecal bile acid secretion and thereby contribute to the development of colon cancer.

In an experimental model designed to partially mimic these epidemiological findings, Broitman et al. (3) fed rats diets high in saturated fat and cholesterol to maintain elevated serum cholesterol levels. Others were fed diets high in polyunsaturated fat to prevent elevations of serum cholesterol levels and presumably to "shunt" cholesterol and its metabolites into the bowel. In the rat, it is necessary to add cholic acid to the diet to promote cholesterol absorption, and this was included in both groups. Effects of these diets on colon tumorigenesis induced by DMH were observed. Animals fed the polyunsaturated fat and cholesterol diet had (a) lower serum cholesterol levels, (b) less vascular lipidosis, but (c) increased numbers of large-bowel tumors over those fed the saturated fat and cholesterol diet. Thus, dietary and/or endogenous cholesterol (or its metabolites) lost to the gut appeared to augment carcinogen-induced bowel tumorigenesis. Consequences of these high-fat high-cholesterol diets on various immune parameters are considered in another segment of this workshop (Working Group IV).

Because certain bile acids are reported to have promotional or cocarcinogenic effects on colon tumorigenesis in this model, it was necessary to continue studies in the same tumor model system in which cholesterol alone, cholic acid alone, and both cholesterol and cholic acid were added to a 20% saturated fat diet. No effect on DMH-induced tumorigenesis was apparent after the addition of cholic acid alone to the diet, while the addition of cholesterol or cholester and cholic acid to the diet significantly augmented large-bowel tumorigenesis. It was concluded that dietary and/or endogenous cholesterol may play a significant role in colon tumorigenesis. The early observations were confirmed by Cruse et al. (6) who demonstrated that the addition of cholesterol to a liquid diet, Vivonex, was associated with more DMH-induced colon tumors in rats than those fed Vivonex alone.

Certain interesting possibilities regarding colon tumorigenesis may be entertained by these studies. It was necessary to use saturated or polyunsaturated fats to channel cholesterol in different directions in the animal model to illustrate the dichotomous effects. However, in human populations, extremes in diet are not necessary for these effects since inherent individual differences in the disbursement of dietary and endogenous cholesterol occur. It is known, for example, that some individuals who consume high-fat high-cholesterol diets exhibit serum cholesterol levels in the hypercholesterolemic range and are at greater risk to CHD than are others who are...
normcholesterolemic. There are also many individuals who consume essentially the same diet but whose serum cholesterol levels remain "normal" or below normal (14). Presumably, in this latter group, a greater proportion of their intake of dietary and endogenously synthesized cholesterol is lost through the gut. If cholesterol or its neutral sterol metabolites in the bowel lumen increase the risk to colon cancer, is this latter group of individuals at higher risk to colon cancer relative to the first? The answer may be yes.

Table 1 lists representative studies concerned with quantitating bile acid and neutral sterol excretion in the feces of individuals with colon cancer or with various disease entities associated with an increased risk to colon cancer. With one exception, all studies illustrate that individuals with colon cancer or individuals who are at increased risk to colon cancer lose more cholesterol through their gut than control individuals. It might be possible to highlight individuals who disburse higher than "normal" quantities of cholesterol in their stool and who may be at increased risk to colon cancer by merely detecting lower than "normal" serum cholesterol levels. A negative association between serum cholesterol levels and colon cancer (2) has been suggested although the data is not yet convincing. It would seem worthwhile to explore this point.

Secondly, do attempts to lower serum cholesterol by drugs (and/or diet) which increase the quantity of cholesterol lost to the gut increase the risk for colon cancer? At present an affirmative answer can only be suggested by the recently completed clofibrate studies (16). Clofibrate, a presumed safe hypolipidemic agent, or a placebo was administered to over 10,000 male volunteers 30 to 54 years of age whose serum cholesterol levels were in the upper third of serum cholesterol distribution. Reduction in serum cholesterol levels was approximately 9% over a 5-year period (Table 2). The incidence of major ischemic heart disease and nonfatal myocardial infarction in the clofibrate group compared to controls was substantially reduced. Evidence for a shift in solubility of gall bladder bile was provided by the increase in the number of cholesterolecorticostereosyntheses for stones performed in the clofibrate group relative to the control group. In addition, the total mortality from causes other than ischemic heart disease was substantially increased in the clofibrate group. Within this group was a disproportionate increase in gastrointestinal tract and a few respiratory tract neoplasms. The numbers of cancer deaths in these studies were too small a sample for statistical evaluation. However, the data is suggestive enough to promote concern regarding the effects of lowering serum cholesterol with drugs to the development of gastrointestinal tract neoplasms.

It would thus seem reasonable to explore further the relationship of cholesterol, its intake, synthesis, and excretion, and its oxidation products in the gut lumen to colon tumorigenesis.

Addendum

Since this note was prepared, 2 additional articles have appeared which are germane to the topic. Liu et al. (1), using food disappearance data from 20 industrialized countries and simple correlation analysis, showed that, when cholesterol is controlled, the partial correlations of dietary fat and fiber with the mortality rate of colon cancer were no longer significant. Cross-classification showed a highly significant main effect for cholesterol but not for fat or fiber. They suggested that the data support a causal relationship between dietary cholesterol and colon cancer. Williams et al. (2), using data from the Framingham Heart Study, showed that serum cholesterol levels were inversely associated with colon cancer and cancer at other sites only in men.

References to Addendum


References

9. Moskovitz, M., White, C., and Flock, M. H. Acid and neutral sterol excretion


Cholesterol Excretion and Colon Cancer

Selwyn A. Broitman


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/41/9_Part_2/3738

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.