Review

Epidemiology of Colorectal Cancer Revisited: Are Serum Triglycerides and/or Plasma Glucose Associated with Risk?

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Abstract
Several aspects of Western diets, alcohol use, and exercise patterns which are related to the risk of colorectal cancer have systemic effects in common. Those which increase the risk of colorectal cancer are positively associated with serum triglycerides and plasma glucose; those which decrease risk are negatively associated with serum triglycerides and plasma glucose. The observations suggest the hypothesis that serum triglycerides and/or plasma glucose may themselves be associated with colorectal cancer risk. Evidence for associations between colorectal neoplasia and triglycerides and glucose comes from two recent studies of adenomatous polyps, presumed precursors for colorectal cancer, and from previous studies of diabetes and cancer. In addition, three randomized trials, one in humans and two in animal models, suggest that diets which would be expected to increase serum triglycerides and plasma glucose increase the levels of cellular indicators of colorectal cancer risk.

Biological mechanisms explaining associations between colorectal neoplasia and serum triglycerides and/or plasma glucose might involve luminal or circulatory effects: (a) triglycerides and/or glucose may be associated with fecal bile acids, acids which are positively associated with colorectal cancer risk in epidemiological studies and which promote colorectal cancer in animal models; (b) serum triglycerides and/or plasma glucose might influence circulating hormones, such as insulin, which might themselves be involved in cancer development; (c) serum triglycerides and/or plasma glucose might be indicators of energy available through the circulation for neoplastic cells. Future research should examine the associations between the risk of colorectal neoplasia and serum triglycerides and plasma glucose, explore possible biological mechanisms, and develop an understanding of whether biological processes involving triglycerides, glucose, and insulin may be common to a number of sites of cancer.

References
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Introduction
Evidence from epidemiological and animal studies has suggested that dietary factors and related aspects of lifestyle are involved in the etiology of colorectal cancer. Western diets, typically dense in energy and fat and low in fiber, have been associated with increased risk, and vegetarian diets, or increased intake in a mixed diet of vegetables, fruits or other plant foods, especially those high in fiber, have been associated with reduced risk (1–3). In addition, there is evidence (3) of positive associations between risk and consumption of alcohol, (especially beer) and body size, although associations are less well established than for Western eating patterns. In contrast, exercise is consistently associated with reduced risk (3), and there is some evidence that consumption of fish oil may reduce risk (1, 2). These dietary and lifestyle risk factors for colorectal cancer have two systemic effects in common. Those which increase the risk of colorectal cancer are positively associated with serum triglycerides and plasma glucose; those which decrease risk are negatively associated with serum triglycerides and plasma glucose. Is it possible, then, that serum triglycerides and/or plasma glucose may themselves be associated with the risk of colorectal cancer? This paper presents epidemiological evidence for such associations. It also considers possible biological mechanisms. Study of biological mechanisms for colorectal cancer (1, 2) has concentrated on luminal factors such as fecal bile acid concentrations, stool bulk, and transit time. This paper suggests that circulatory effects might also be important.

Risk Factors for Colorectal Cancer
The extensive data from epidemiologic studies and from animal models suggesting that factors in Western diets may be related to the risk of colorectal cancer have been reviewed by expert committees of the National Academy of Science (1, 2). Positive associations with total energy, and with each of the energy-containing nutrients, fat, protein, and carbohydrate, have been reported in case-control and cohort studies (1–5). Negative associations have been observed with consumption of vegetables, fruits, and cereals (1–5), with possible protective mechanisms involving fiber, vitamins, and other components of these plant foods (3, 6). The accumulated evidence is of sufficient strength that scientific bodies and governments in North America and elsewhere (1, 2, 7–10) have advocated reduced consumption of fat and increased consumption of fruits, vegetables, and cereals. Evidence for other risk factors for colorectal cancer is accumulating. A positive association with consumption of alcohol (especially beer) has been observed in geographic correlation studies, two of four population cohort studies, and seven of fourteen case-control studies (3). Associations with body size and colorectal cancer risk have also not been entirely consistent and appear to differ some-
what with the measure of body size examined. A positive association with body mass has been suggested by two prospective studies (11, 12) and by the findings of the majority, but not all, of the case-control studies reviewed by Potter et al. (3). In addition, height, weight, and Quetelet’s Index were reported to be positively associated with colorectal cancer recurrence (13). The single investigation which examined the distribution of body fat (11) reported a small but not statistically significant increase in risk only in the highest quintile of measured waist to hip ratio. Three studies have reported positive associations with increased stature, independent of weight (11, 14, 15). A protective effect of fish oil has been suggested by the observation that Eskimos with diets rich in fish oils have low rates of cancer, including colorectal cancer. This possibility is supported in animal models where administration of fish oil not only failed to stimulate tumour growth as would be expected with high fat diets, but might even have an inhibiting effect (2, 16). A negative association has been consistently observed between exercise and the risk of colon cancer (3), when activity has been assessed in association with both occupation and leisure, but findings have been less consistent for colorectal cancer or for rectal cancer alone (3).

### Common Risk Factors for Serum Triglycerides, Plasma Glucose, and Colorectal Cancer

The relationship between lifestyle risk factors and serum triglycerides and plasma glucose has been studied in the context of research into heart disease and diabetes, rather than in studies of cancer. However, the findings suggest that a number of factors which are positively related to the risk of colorectal cancer are also positively related to serum triglycerides and plasma glucose; other factors negatively related to colorectal cancer risk are negatively related to these physiological characteristics.

Comparison of persons on mixed Western diets with those on vegetarian diets has shown that those on Western diets have increased serum triglycerides and plasma glucose. Higher levels of serum triglycerides and blood glucose have been observed in populations that consume diets high in fat and low in complex carbohydrates (such as those in the United Kingdom and among African whites) than are found in populations which habitually consume diets which are low in fat and high in complex carbohydrates (such as those in Southern Africa and in Japan) (17-20). Diets high in fat and energy density have been shown in feeding trials to increase triglycerides when compared with low fat, low energy dense diets (21-23). High simple carbohydrate diets have long been recognized as associated with hypertriglyceridaemia but diets which are high in fiber-rich carbohydrates do not induce hypertriglyceridaemia when fed over prolonged periods (17, 24, 25). Indeed, feeding trials have shown that the more complex the carbohydrate source, the less the rise in triglycerides associated with the inclusion of high levels of simple carbohydrates, and that fiber is often, though not always, associated with reduced serum triglycerides (26-35). The effects of individual foods on plasma glucose have also been examined in feeding studies. A glycemic index has been developed which describes the postprandial glycemic response of individual foods compared to that of a standard glucose stimulus (17, 26). Plant foods, especially legumes, tend to produce low glycemic responses (26, 29, 33, 36, 37).

Alcohol, like carbohydrate, has long been recognized as increasing serum triglycerides (38), and beer is a source of both alcohol and carbohydrates (about 30 g/liter) (38). Alcohol intake has also been positively associated with hyperglycaemia (39), although the mechanism is unclear (38). Alcohol after meals, but not in a fasting state, results in hyperglycaemia in humans and animals (38). Thus, alcohol increases serum triglycerides and plasma glucose, especially when consumed in a nonfasting state.

Positive associations between obesity, serum triglycerides, and blood glucose are well established (40-42). Clinical studies have shown that the degree of obesity is associated with production of VLDL, triglyceride and elevated levels of blood glucose, and that increases in weight are associated with increases in triglycerides and glucose (42). Further, the regional distribution of body fat can influence both serum triglycerides and blood glucose (40-46).

In normal subjects, dietary supplementation with fish oil reduces serum triglycerides (47-49) without adverse effects on glucose, and in patients with hypertriglyceridaemia it may also reduce glucose (50). However, in patients with noninsulin-dependent diabetes, fish oil supplementation does not always reduce triglycerides (51) and may increase blood glucose levels (52-56). In nondiabetics, dietary enrichment with ω-3 fatty acids may increase their incorporation into pancreatic β cell phospholipid membranes, enhancing insulin secretion and reducing carbohydrate intolerance (52).

Evidence suggests that exercise reduces serum triglycerides and improves glucose tolerance (57, 58). Studies comparing lipids in persons with different levels of physical activity have found higher serum triglycerides in inactive people (59-64). Studies of physical training have found reductions in triglycerides (65-67), together with increases in glucose tolerance (58).

Thus, factors which may be positively associated with colorectal cancer, Western eating patterns, alcohol use, and obesity are also positively associated with serum triglycerides and plasma glucose, and factors which may be negatively associated with colorectal cancer, diets which emphasize fruits and vegetables, fish oil consumption, and exercise, are associated both with reduced colorectal cancer risk and with reduced serum triglycerides and plasma glucose. Such associations suggest the possibility of direct associations between colorectal cancer and serum triglycerides and/or plasma glucose.

### Associations of Serum Triglycerides and Glucose Metabolism with Colorectal Cancer

The relationship between colorectal cancer and serum triglycerides or plasma glucose has not been studied directly. Rates of colorectal cancer and coronary heart disease are correlated internationally (r = 0.77) (68), so one might expect to find international correlations between colorectal cancer and serum lipids and/or glucose as they are risk factors for heart disease (69-72). However, no studies have examined these relationships, perhaps because reliable fasting blood data are not available at the national level (73). Information bearing on the relationship between colorectal neoplasia and triglyceride and glucose metabolism comes from prospective and case-control studies (1-5). Of these investigations, several are population-based and include controls from a general population (6, 7). Two prospective studies (6, 7) compared persons on mixed Western diets with persons on vegetarian, or mixed diets (8). The single investigation (9) that examined the distribution of body fat (11) reported a majority, but not all, of the case-control studies reviewed by Potter et al. (3).
Diets high in simple carbohydrates and low in fiber increase serum triglycerides and plasma glucose, so it might be expected that such diets would be associated with increased risk of colorectal neoplasia. Associations between colorectal cancer and sucrose have been in the direction of increased risk, although not always statistically significant. Two cohort studies (11, 74) reported close to a 2-fold increase in risk comparing groups with highest to lowest intake of all nondairy sucrose-containing foods (RR = 2.0, \( P \) for trend = 0.03) (11), or with pie and cake (RR = 1.7, \( P \) for trend > 0.05) (74). Nine of 10 case-control studies reviewed by Bostick et al. (11) reported relative risks between 1.0 and 2.3 with intake of sucrose or sucrose-containing foods, although only 3 reached statistical significance at the 5% level; a single study reported a nonsignificant reduction in risk (RR = 0.7, \( P \) for trend > 0.05) (75). Three randomized trials of diets high in sucrose and low in dietary fiber, one in human volunteers (76) and two in animal models (77, 78), have supported a positive association by observing associations with colonic cell proliferation and/or rates of growth of dysplastic crypt foci, indicators of risk of neoplasia (79–87). Slavin et al. (76) found that consumption of a liquid diet high in simple carbohydrate was associated with higher rates of rectal cell proliferation in each of 5 crypt compartments than were seen when healthy volunteers consumed their normal diets, or when the liquid diet was supplemented with breads containing cereal or vegetable fiber. The finding that total cell proliferation was highest on the fiber-free diet (\( P < 0.03 \)) is compatible with the ability, discussed above, of dietary fiber to counteract the increase in serum triglycerides produced by intake of simple carbohydrates (27, 28). Using the azoxymethane (AOM) rat model, Stamp et al. (77) observed increased colorectal cell proliferation and aberrant crypt foci after gastric gavage with sucrose and fructose compared to controls who received a water gavage (4.1 mitotic cells/crypt with sucrose compared to 0.4 with water, \( P < 0.001 \); 3.1 aberrant crypt foci/colon with sucrose compared to 7.2 with water, \( P < 0.001 \)). Finally, Caderni et al. (78) have compared rats fed for 105 days with a simple carbohydrate (sucrose) with rats fed a complex carbohydrate (starch). Colonic cell proliferation and size of dysplastic crypt foci were greatest in the sucrose fed rats (mean labeling index: 10.4 with sucrose compared to 4.4 with starch, \( P < 0.001 \); size of dysplastic crypt foci: 2.9 dysplastic crypts/focus with sucrose compared to 2.6 with starch, \( P < 0.05 \)). These studies demonstrate that diets expected to increase serum triglycerides and plasma glucose are associated with indicators of risk of neoplasia in the colon but, because serum triglycerides and glucose were not assessed in the investigations, direct associations have still to be demonstrated. Further investigations would be needed to determine whether the diets affected the colon through systemic effects involving the circulation and/or through luminal effects.

Direct evidence of an association between serum triglycerides and presumed precursors of colorectal cancer, adenomatous colorectal polyps (88, 89), has been observed in studies conducted in Toronto (90–92). As part of a randomized trial designed to examine the effects of manipulating colonic fermentation on markers of colorectal cancer risk, Kashtan et al. (90) measured pretrial blood lipids in 45 patients with a history of colorectal adenomatous polyps and in 49 controls who were free of polyps on colonoscopy. Average serum triglyceride levels were 17% higher (\( P = 0.06 \)) in polyp patients than in controls. In patients with adenomatous polyps who participated in a randomized trial examining the effect on polyp recurrence of a low fat, high, fiber diet (91), associations were observed between serum triglycerides assessed after 1 year of diet counseling and the rate of polyp recurrence (92, 93). Associations were J-shaped, with polyp recurrence increasing steadily from the second to the fourth quartiles of serum triglycerides (recurrence rates in quartiles 1 to 4 were 31.6, 15.0, 20.0, and 25.0%, \( P > 0.2 \) for men; and 8.3, 7.1, 14.3, and 30.8%, \( P = 0.15 \) for women). These findings suggest associations but lack power because of small sample sizes (\( n = 79 \) for men; \( n = 58 \) for women); larger studies would therefore be needed to confirm them and to examine the possibility of nonlinear associations. Clues to the biology of associations are provided by the observation in the same trial (91) of positive correlations (\( r = 0.42, P < 0.001 \) in men; \( r = 0.21, P > 0.05 \) in women) between serum triglycerides measured after 12 months on study and fecal bile acids, acids which are related to the risk of colorectal cancer in human studies and which promote colorectal neoplasia in animal models (94–100). In addition, it is of interest that fecal bile acids after one year of diet counselling exhibited J-shaped patterns of association with the rate of recurrence of adenomatous polyps similar to those observed for triglycerides (recurrence rates in quartiles 1 to 4 were 16.7, 11.1, 22.2, and 33.3%, \( P > 0.2 \) for men; and 7.7, 7.7, 21.4, and 30.8%, \( P = 0.06 \) for women). These findings suggest that factors in the circulation and in the lumen may both be associated with polyp recurrence but the biological mechanisms for these associations have still to be determined. That serum triglycerides and fecal bile acids may themselves be biologically associated has recently been postulated by Angelin and Einaron (101) as described below.

Direct evidence of an association between plasma glucose and cancer comes from studies early this century when patients with various sites of cancer were observed to have higher plasma glucose than were healthy individuals (102–107). Indeed, in 1919 it was even proposed that blood sugar be used to screen for cancer (107). Recently, two cohort studies designed to study heart disease have reported associations between glucose assessed after glucose challenge and mortality from colorectal cancer 12–20 years later (108, 109), but both were able to observe only small numbers of colorectal cancer deaths. The Chicago Heart Association Detection Project in Industry (108) concluded that women who died of colon, but not rectal, cancers had higher mean plasma glucose than did survivors (mean plasma glucose, 156.1 in colon cancer decedents and 140.0 in survivors). They also reported that mean plasma glucose levels were higher among men who died of colon (plasma glucose, 145.9) and rectal cancers (plasma glucose, 146.9) than among survivors (plasma glucose, 144.5). However, no statistical tests were reported for individual cancer sites. In the Whitehall Study (109), nondiabetic men experienced a small but nonsignificant increase in risk associated with blood glucose (\( RR = 1.03 \) for an increase of 1 SD in glucose; 95% confidence interval, 0.88–1.24) but exhibited no increase in risk of rectal cancer (\( RR = 0.94 \) for...
Diabetics have high levels of plasma glucose and serum triglycerides so studies of the association of diabetes and colorectal cancer might provide relevant information. A study of death certificates in Massachusetts (110) reported that diabetes and colorectal cancer occurred together on death certificates more frequently than expected (SMR = 1.23 for men and 1.08 for women) but reported no tests of significance. Two case-control studies (111, 112) reported associations between colorectal cancer and diabetes. Clicksman and Rawson (111) observed an excess of abnormal glucose tolerance tests in colorectal cancer patients compared with controls with benign diseases (OR = 2.4) but provided no statistical evaluation. O’Mara et al. (112) observed elevated but nonsignificant (P > 0.05) odds ratios for history of diabetes among 27 cases with colon cancer (OR = 1.2 for men and 1.4 for women) but reported lower odds ratios for 26 cases of rectal cancer (OR = 1.1 for men and 1.0 for women). Cohort studies of diabetics which have attempted analysis of individual cancers have been able to observe only small numbers of colorectal cancers. Adami et al. (113) observed nonsignificant (P > 0.05) increases for male colon (RR = 1.2) and rectal cancers (RR = 1.3) based on 94 and 73 cases, respectively, but observed no excess for female bowel cancers. Ragozzino et al. (114) reported a relative risk of 1.3 (95% confidence interval, 0.8–1.9) for colorectal cancer based on 22 cases. Kessler (115) observed an SMR of 1.09 (P > 0.3) for colon cancer based on 147 cases but found no increase for rectal cancer (SMR = 0.81; P > 0.1) based on 45 cases. Smith et al. (109) found no excess of colon cancer (RR = 0.62; 95% confidence interval, 0.09–4.47) among diabetics based on 1 case of colon cancer and no excess among men with impaired glucose tolerance (RR = 0.81; 95% confidence interval, 0.35–1.83) based on 6 cases. Considering the high cardiovascular mortality and reduced expectation of life in diabetics (116), it is perhaps surprising that any excess of cancer mortality was reported in these studies. However, the small numbers of cases and other methodological problems associated with studies of individual cancer sites (102) suggest that further data will be needed before firm conclusions can be drawn.

In summary, data which have bearing on the relationship between colorectal neoplasia and serum triglycerides or plasma glucose are generally compatible with the hypothesis of a positive association. However, studies are needed to establish associations directly and to examine their biological basis.

Possible Biological Mechanisms

The risk of colorectal neoplasia has usually been thought to be associated with factors affecting the colonic lumen. In particular, fecal bile acids have been shown to promote colorectal neoplasia in animal models and have been positively related to the risk of colorectal cancer in a number of epidemiological studies (94–100). An association between serum triglycerides and colorectal neoplasia might therefore be observed if serum triglycerides were biologically associated with fecal bile acids. Such an association has recently been suggested by Angelin and Einarson (101), who have proposed a link between perturbations of bile acid enterohepatic circulation and VLDL triglyceride production. Because VLDL triglycerides constitute the majority of total fasting triglycerides, such an association could account for the positive correlations between total serum triglycerides and fecal bile acids, and between serum triglycerides and polyps, described above. Further, an observation of higher bile acid concentrations in healthy volunteers fed 165 g of refined sugar daily compared with volunteers who consumed 60 g of sugar (117) suggests that the possibility of an association between bile acids and plasma glucose should also be explored, since a high sugar diet should increase plasma glucose as well as triglycerides. The relationships of serum triglycerides and plasma glucose to bile acid metabolism therefore warrant further study.

However, it is also possible that the risk of colorectal neoplasia is directly related to factors in the circulation. Two biological mechanisms might explain associations between colorectal neoplasia and serum triglycerides and plasma glucose.

First, hormones may play a key role. Increased blood glucose increases insulin secretion and increased triglycerides are secondary to hyperinsulinemia and insulin resistance (118). Thus, increased triglycerides and glucose could be indicators of increased insulin levels. The possible role of insulin in colorectal neoplasia is suggested by several lines of evidence. Insulin is considered to be a growth factor (119), and insulin receptors are observed in both normal and malignant colorectal cells (120). Insulin receptors can be bound by insulin-like growth factors, factors which are expressed by colorectal cancers (121). Insulin has been shown to increase insulin-like growth factor I in rats (122), and a binding protein for this growth factor inhibits the growth of colon cancer cells in vitro (123). In addition, a recent case-control study reported a strong direct association between insulin and breast cancer (124), a site which shares common epidemiological risk factors with colon cancer (1, 2). An effect of insulin in carcinogenesis is further suggested by the observation that exogenous insulin induces liver carcinogenesis in hypophysectomized rats fed an otherwise ineffective dose of carcinogen (125), as well as by the finding that insulin is capable of damaging DNA in endothelial cells (126). Further, insulin is negatively associated with somatostatin (127), a hormone with atrophic effects (128) which has been shown to inhibit mouse colon adenocarcinoma (129) and human pancreatic tumors (130). Because fiber reduces the insulin response (131, 132), and long-term ingestion of fructose can affect cellular insulin binding and sensitivity (133), it is possible that dietary associations with colorectal cancer could arise through effects on insulin. The interrelationships among insulin and related

![Figure 1](image_url) Fig. 1. A model illustrating factors in the colonic lumen, which may link environmental factors to colorectal cancer risk.
hormones, serum triglycerides, plasma glucose, foods, and colorectal neoplasia require further study.

Second, an association between colorectal neoplasia and circulating levels of serum triglycerides and/or plasma glucose could arise if triglycerides or glucose was an indicator of energy available for neoplastic cells.

Normal cells of the colonic epithelium are capable of both aerobic and anaerobic metabolism, using short chain fatty acids, amino acids, and glucose as fuel (134). However, short chain fatty acids are the predominant energy source (135, 136). Indeed, availability of the short chain fatty acid, butyrate, as a fuel suppresses glucose utilization, especially in the left side of the bowel (136). Butyrate may be an especially important source of energy because it has regulatory effects on nucleic acid metabolism (137, 138) and acts as a differentiating agent (139), so it may assist in maintaining the health of the large bowel epithelium (135).

In contrast to the normal colonic epithelium, neoplastic cells switch from aerobic to anaerobic metabolism (140, 141), and anaerobic metabolism uses glucose rather than fatty acids for fuel. Thus, plasma glucose might be associated with colorectal neoplasia by acting as direct source of energy for neoplastic cells. In contrast to plasma glucose, the fats transported by serum triglycerides could not provide energy for neoplastic colonic cells. However, fasting serum triglycerides may be a general marker of energy availability because VLDL triglycerides (the major component of serum triglycerides) represent the triglycerides which are being sent from the liver to the adipose tissues for long-term storage, as well as to peripheral tissues for energy.

Because diets which increase plasma glucose are those which tend to be low in plant food, the high levels of colorectal cancer in the Western world might arise from the low levels of plant food in the Western diet and from corresponding increases in availability of plasma glucose as an energy source for neoplastic cells. Further, there is a preponderance of left-sided colon cancer in Western populations. This might be explained by the increase of glucose availability to the area of the colon which is the most vascularized (the left side), and by depletion of butyrate formed from fermentation of fiber from plant foods, a fuel on which the left side of the colon is especially reliant (136).

Thus, several biological mechanisms involving either luminal or circulatory paths could account for associations between the risk of colorectal neoplasia and serum triglycerides and plasma glucose.

**Research Implications**

A first step in examining the hypothesis that serum triglycerides and/or plasma glucose may be associated with the risk of colorectal cancer is to establish directly that an association exists between these blood characteristics and colorectal neoplasia. Observational epidemiological investigations could establish such associations. However, to ensure that either triglycerides or glucose was not merely correlated with some ultimate biological causes of malignant disease which had not yet been recognized, human trials would need to demonstrate that reduction in levels of serum triglycerides or plasma glucose could reduce the risk of colorectal neoplasia, just as experimental studies were needed to examine the possibility of a direct association between serum cholesterol and coronary heart disease.

Understanding the biology of associations between triglycerides, glucose, and colorectal neoplasia would require studies to determine the relative importance of luminal and circulatory factors. If fecal bile acids or other luminal factors were the major determinant of colorectal neoplasia (Fig. 1), associations between colorectal neoplasia and circulatory factors would occur only because the circulatory and luminal factors shared common environmental risk factors or common biological pathways; no direct biological association would exist between colorectal neoplasia and serum triglycerides and/or plasma glucose. In contrast, serum triglycerides and/or plasma glucose could be the major determinant of colorectal neoplasia, acting directly on the metabolism of neoplastic cells or through insulin or other hormones. In this case, luminal factors would have no direct biological association with colorectal neoplasia; associations would occur only because fecal bile acids shared common environmental or biological determinants with serum triglycerides and/or plasma glucose (Fig. 2). Distinguishing the relative contributions of these models of colorectal neoplasia will be the next major challenge.

Understanding the development of colorectal cancer, and its relationship to polyps, will ultimately require understanding the relationship between physiological mechanisms and the genetics of neoplasia. Fearon and Vogelstein (142) have postulated a sequence of genetic changes which occur as polyps develop through the proposed adenoma-carcinoma sequence. It would be of considerable interest to determine whether these genetic changes are associated with the changes in enzyme profiles involved in the switch from aerobic to anaerobic metabolism described by Jass as associated with increasing dysplasia in polyps (140, 141). It would also be of interest to examine the relationship between the genetic changes and the ability of the cell to respond to insulin and related growth factors.

The possibility that factors in the circulation may be associated with the risk of colorectal cancer is appealing because it could lead to research which might explain the correlations between colorectal cancer and cancers of the
breast, endometrium, ovary, and prostate, sites which share some risk factors (1, 2) and which might be influenced by biological mechanisms affecting proliferation such as those described for colorectal cancer. Because serum triglycerides and plasma glucose have also been positively associated with cardiovascular disease (69–72), these factors might account for associations between colorectal cancer and heart disease (68). However, much remains to be understood about the relationship between colorectal cancer and cardiovascular disease. Because circulatory risk factors for cardiovascular disease, cholesterol, and other blood components share some dietary and lifestyle risk factors with serum triglycerides and plasma glucose, a positive association might be expected between serum cholesterol and the risk of colorectal cancer. In the 1980s, however, some studies reported increased colorectal cancer risk associated with low cholesterol levels (143–146). In 1990, a conference was held to evaluate the evidence on associations between cholesterol and a number of diseases, including large bowel cancer, from a meta-analysis of 19 of 20 cohort studies with relevant data (147). Because it was recognized that a negative association would be observed if malignancy caused a drop in cholesterol in the years before diagnosis, this analysis considered only deaths occurring at least 5 years after baseline cholesterol measurement. The analysis found that there was little evidence of a gradient of risk of colon cancer across cholesterol classes, although there was some evidence of variability among studies. The authors recognized that information was needed about the time course of cholesterol change in disease, and there is still a need for studies which can distinguish clearly between the biological effects of early disease and the effects of factors which influence tumor growth in the period before diagnosis. While the meta-analysis of the relationship between cholesterol and colon cancer took account of a number of demographic and lifestyle-confounding variables, it was not able to consider the effects of other blood lipids or measures of glucose metabolism. Reduction in the risk of colorectal and other cancers will require determination of optimal levels of blood lipids, glucose, and insulin, in combination as well as singly. In this context, the syndrome of insulin resistance is of interest because it is a multifaceted syndrome with a combination of dyslipidemia and hyperinsulinemia and it has been associated with atherosclerotic cardiovascular disease, noninsulin-dependent diabetes mellitus, hypertension, and obesity (148). Further research appears justified to explore the relationship of cancers to the abnormal lipids and increased levels of insulin in the insulin-resistance syndrome.

Epidemiological research has made great progress in identifying dietary and other lifestyle risk factors associated with colorectal cancer and other malignancies. Future research will require collaboration between basic scientists and epidemiologists in order to determine the relative importance of luminal and circulatory factors in colorectal neoplasia, to develop an understanding of the effects of dietary and lifestyle risk factors on the relevant biological and metabolic processes, to link these models with an understanding of the genetics of neoplastic cells, and to develop an understanding of biological processes which may be common to a number of sites of cancer.

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References


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