

# Metabolic syndrome, hyperinsulinemia, and colon cancer: a review<sup>1-3</sup>

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## ABSTRACT

An impressive body of epidemiologic data collected over the past decade indicates that the risk of colon cancer is elevated in those with metabolic syndrome. This evidence includes studies that examined the risk of colon cancer or adenoma in relation to determinants of the metabolic syndrome (obesity, abdominal distribution of adiposity, and physical inactivity), clinical consequences of this syndrome (type 2 diabetes and hypertension), plasma or serum components of the definition of metabolic syndrome (hypertriglyceridemia, hyperglycemia, and low HDL cholesterol), and markers of hyperinsulinemia or insulin resistance (insulin and C-peptide), which is the underlying metabolic defect of the metabolic syndrome. The mechanism underlying these associations is unknown but may involve the influence of hyperinsulinemia in enhancing free or bioavailable concentrations of insulin-like growth factor-1. Future studies should also be based on better measurements of insulin resistance,  $\beta$ -cell depletion, and insulin responses to better assess which aspects of insulin resistance are most closely related to the risk of colon neoplasia. *Am J Clin Nutr* 2007;86(suppl):836S–42S.

**KEY WORDS** Obesity, exercise, epidemiology, insulin, metabolic syndrome, colon cancer

## INTRODUCTION

The metabolic syndrome, also called the insulin resistance syndrome, encompasses several metabolic and physiologic disturbances. These include dyslipidemia (low concentrations of HDL cholesterol and elevated concentrations of triacylglycerols, VLDL, and small dense LDL), hypertension, chronic inflammation, procoagulation, and impaired fibrinolysis (1). Because this syndrome constitutes a cluster of factors, definitions are usually based on the presence of several factors, although chronic inflammation, procoagulation, and impaired fibrinolysis have not typically been included in the criteria. In 1998, the World Health Organization developed a definition of metabolic syndrome based on individuals showing evidence of insulin resistance and at least 2 of 4 other factors, including hypertension, hyperlipidemia, obesity, and microalbuminuria. In 2001, the National Cholesterol Education Program developed an alternative definition, which required  $\geq 3$  of the following 5 factors to be present: increased waist circumference, hypertriglyceridemia, low HDL cholesterol, hypertension, and elevated fasting glucose.

The etiology of the insulin resistance syndrome is multifactorial, and the mechanism underlying the intercorrelations among these metabolic conditions is not entirely clear. Nonetheless,

obesity (particularly visceral adiposity), physical inactivity, and insulin resistance are underlying factors in the etiology of this syndrome. Not surprisingly, metabolic syndrome is common in developed countries and is increasing in incidence in populations experiencing rising rates of obesity and overweight. In the United States, this syndrome affects  $\approx 25\%$  of persons over the age of 20 y, and the estimate may be as high as 45% in persons aged  $>50$  y (2).

The metabolic syndrome is a major risk factor for cardiovascular disease and adult-onset or type 2 diabetes mellitus. The idea that this syndrome could also be related to some cancers, particularly colon cancer, has been hypothesized relatively recently (3–6). This hypothesis was based largely on the similarity of some risk factors, primarily central obesity and physical inactivity, for cardiovascular disease, type 2 diabetes, and colon cancer. However, the overlap in risk factors for colon cancer with those for cardiovascular disease and diabetes could be coincidental to common etiologic factors such as physical inactivity, which could be acting through entirely different mechanisms for colon cancer. For example, physical activity could be decreasing the transit time of fecal matter, including carcinogens, in the large bowel, and because physical inactivity is also associated with the metabolic syndrome, an association between the metabolic syndrome and colon cancer could be indirect. A direct association implies that one or more of the metabolic disturbances inherent in the metabolic syndrome causally increases the risk of colon cancer.

This article will review the evidence from the human studies that have examined factors related to the metabolic syndrome in relation to the risk of colon cancer. Because colon adenomas (especially large or advanced adenomas) are well-established precursor lesions for colon cancer, studies of adenomas will also be considered. Considered will be the following: 1) underlying determinants of the metabolic syndrome (physical inactivity, obesity, and visceral obesity), 2) clinical manifestations (type 2 diabetes mellitus, hypertension), 3) laboratory determinants of

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the metabolic syndrome (hypertriglyceridemia, low HDL cholesterol, and hyperglycemia), 4) clinically defined metabolic syndrome based on standard or modified criteria, and 5) hyperinsulinemia. For cancers, only studies that measured serologic factors prospectively, that is, before cancer diagnosis, are considered to avoid reverse causation bias.

### UNDERLYING RISK FACTORS, OBESITY, AND PHYSICAL INACTIVITY

Underlying risk factors for metabolic syndrome include physical inactivity and obesity, especially visceral or abdominal obesity. These factors are among the most consistent risk factors identified for colon cancer. The evidence that physical activity is a protective factor for colon cancer is strong and remarkably consistent (7). Generally, this association has been observed in prospective and case-control studies, for adenomas and cancer, for men and women, for occupational and leisure-time activities, and in a wide spectrum of populations. It is unlikely that all these relations are due to uncontrolled confounding; thus, physical inactivity is becoming widely accepted as a risk factor for colon cancer.

A higher body mass index (BMI) has been consistently associated with the risk of colon cancer (8). The strength of the association between obesity and colon cancer is generally stronger for men than for women. For example, in the recent European Prospective Investigation into Cancer and Nutrition (EPIC) study, which was based on 984 cases of colon cancer, a 55% increased risk of colon cancer was observed between the high and low quintiles of BMI in men, but no significant association was observed in women (9). One possible reason is that in postmenopausal women, higher BMI is correlated with higher estrogen concentrations, which may have a competing beneficial effect on colon cancer risk (8), although other explanations are possible.

Some studies have now considered anthropometric measures of adipose distribution in addition to BMI in relation to the risk of colon cancer or adenoma. In most of these studies, the association between waist circumference or waist-to-hip ratio and colon cancer risk was stronger than that between BMI and cancer risk (10–14). Interestingly, clearer associations with waist circumferences than with BMI were observed for women (9, 12–15), which suggests that measures of adipose distribution could yield stronger and more consistent associations than measures of BMI for women. For example, in the EPIC study mentioned above, higher waist circumference or waist-to-hip ratio was associated with an increased risk of colon cancer for women, whereas higher BMI was not (9). Similar results for circumference measures have been noted for large or advanced adenoma (11, 15, 16). In one study, a direct measure of visceral fat accumulation by computerized tomography scanning yielded a strong association with colorectal adenoma (17), although no association was observed with recurrent adenomas in another study (18). The lack of an association with recurrent adenomas may reflect that body fatness appears to increase adenoma growth rather than occurrence (19), which suggests that it is a promoting factor.

### CLINICAL CONDITIONS ASSOCIATED WITH METABOLIC SYNDROME AND COLON CANCER RISK

#### Diabetes mellitus

Adult-onset diabetes mellitus has generally been associated with a higher risk of colon cancer (20–25). Diabetes mellitus is

one of the clinical consequences of long-standing insulin resistance and the metabolic syndrome. A recent meta-analysis quantified the results of studies published through July 31, 2005 (26). The summary relative risk for diabetes as a risk factor for colon cancer was 1.43. This result was highly statistically significant and was observed for men and women; no heterogeneity among studies was noted. Also, the results were consistent between case-control and cohort studies and between studies conducted in the United States and in Europe. A subsequent study confirmed this association in a non-white population, specifically, in Singapore Chinese (27). The association between type 2 diabetes and risk of colon adenoma has not been as well studied, but a recent study reported that persons with diabetes (especially obese persons) have an increased risk of prevalent colon adenoma, especially advanced adenoma (28).

#### Hypertension

Only relatively few studies have considered hypertension as a risk factor for colon cancer or adenoma. Although hypertension is correlated with the metabolic syndrome and is part of the criteria for its diagnosis, some studies suggest that it may constitute a factor distinct from insulin resistance and hyperinsulinemia (29, 30). Hypertension may be influenced by factors related to abdominal adiposity but that are etiologically independent of insulin resistance (31). A recent study found a 35% increased risk of colorectal cancer associated with high blood pressure (32). This finding was confirmed in another prospective study (33), but a study of Finnish male smokers did not support this association (34). In a Chinese population, patients with rectosigmoid adenomas had higher systolic and diastolic blood pressure than did polyp-free control subjects (35).

### LABORATORY DETERMINANTS OF THE METABOLIC SYNDROME

#### Blood triacylglycerols

Hypertriglyceridemia is a component of the definition of metabolic syndrome (36, 37). In fact, it may be a particularly important component of this syndrome; for example, a recent alternative definition of the metabolic syndrome (“the hypertriglyceridemic waist”) has been proposed for men that is solely based on waist circumference >90 cm and triacylglycerol concentrations >2.0 nmol/L (38). Several studies have examined hypertriglyceridemia in relation to risk of colorectal or colon cancer. In a large prospective study, high circulating triacylglycerol concentrations were associated with a nonsignificant two-fold elevation in risk in men, but no clear association was observed in women (39). In another prospective study, men and women in the top quartile of triacylglycerols had a 40% increased risk of colorectal cancer, although this association was not significant (10). In other prospective studies in the United States, elevated triacylglycerol concentrations were not a risk factor for colon cancer (25, 28, 32), although the number of cases was relatively small and colon cancer was not distinguished from colorectal cancer. One study did not find an association between baseline triacylglycerol concentration and risk of colorectal cancer in Hawaiian Japanese men, but there was 30 y of follow-up after the blood measure and any secular changes in triacylglycerol concentrations were not taken into account (40). A Japanese case-control study compared serum

triacylglycerol concentrations in 129 men and women with colorectal carcinoma in situ with concentrations in 258 age- and sex-matched individuals and found a strong 3-fold higher (multivariate) risk associated with hypertriglyceridemia (41).

Hypertriglyceridemia has also been examined in relation to colorectal adenoma risk. In a study conducted in Germany, a high circulating concentration of VLDL (the major lipoprotein carrier of triacylglycerols) was associated with a statistically significant 2- to 3-fold higher risk of colorectal adenomas (42). In a case-control study of colorectal adenomas in Korea, an increasing trend with serum triacylglycerols was noted (43). One study found an increased risk in Japanese men but not women (44). In a Chinese population, patients with rectosigmoid adenomas had higher triacylglycerol concentrations than did polyp-free control subjects (35). Three other studies reported that persons with higher concentrations of serum triacylglycerols had a moderate, although not statistically significant, increase in risk of colorectal adenoma (45–47). Thus, although the association with triacylglycerols appears less consistent for cancers, it is more striking for adenomas and more consistent in Asian populations (41, 43–45).

### HDL cholesterol

A low concentration of HDL cholesterol is a criterion for the metabolic syndrome, and this factor has received some study in relation to colon adenoma or cancer risk. A study conducted in Italy found no association between HDL-cholesterol concentrations and colorectal cancer risk (39). In a US cohort study, men and women in the top quartile of HDL cholesterol had an  $\approx 40\%$  nonsignificant reduction in risk of colorectal cancer relative to those in the bottom quartile (10). One study found a borderline increased risk of colorectal cancer associated with low HDL cholesterol (32), whereas another study found no association in male smokers (34). In a German study, low concentrations of HDL were associated with a 2- to 3-fold significantly higher risk of colorectal adenomas (42). In a Chinese population, patients with rectosigmoid adenomas had lower HDL-cholesterol concentrations than did polyp-free control subjects (35). A potential complicating factor for HDL cholesterol is that alcohol, which likely increases the risk of colon cancer, is associated with higher HDL concentrations; this pattern would tend to cause negative confounding of the association between HDL cholesterol and risk of colon neoplasia (that is, alcohol could obscure an association between low HDL cholesterol and higher risk of colonic neoplasia because those with low HDL-cholesterol concentrations would tend to be nondrinkers of alcohol).

### Blood glucose

Blood glucose concentrations have been studied in relation to colorectal cancer and adenoma. For cancer, in a large study of Norwegian men and women, women with elevated blood glucose concentrations had a significantly elevated relative risk (RR = 1.98) of colorectal cancer, but no significant association was seen in men (48). In a prospective study in Italy, elevated glucose was associated with a significantly elevated risk for both men and women (combined RR = 1.80) (39). In another study (49), compared with individuals with normal glucose tolerance, those with impaired glucose tolerance (but not type 2 diabetes) had a two-fold increased rate of total mortality; almost one-half of the excess risk resulted from cancer deaths, particularly from

colon cancer. In contrast, persons with diabetes had a 3- to 4-fold higher rate of total mortality, mostly because of cardiovascular consequences, but their cancer mortality was not appreciably increased. In the Chicago Heart Association Detection Project in Industry, elevated postload glucose concentrations ( $\geq 200$  mg/dL) were associated with an increased risk of colorectal cancer mortality in men (RR = 1.51) and in women (RR = 1.86) (33). In the Cardiovascular Health Study, individuals in the top quartile of fasting glucose (RR = 1.8) or 2-h glucose (RR = 2.4) had elevated risks of colorectal cancer relative to those in the bottom quartiles (10).

Glycosylated hemoglobin is a marker of the average glycemia over the previous 2 mo, and elevated glycosylated hemoglobin is used as an indicator of chronic hyperglycemia. Higher glycosylated hemoglobin was associated with an elevated risk of colorectal cancer in the CLUE II cohort (25). However, in a smaller study, no relation was observed between glycosylated hemoglobin and colorectal cancer incidence, although an association was found for colorectal cancer mortality (50).

For colorectal adenoma, a borderline two-fold higher risk was observed for those with higher serum glucose in a Japanese study (41). In another study of colon adenoma in Japanese men, fasting glucose (RR = 1.8) and 2-h glucose (RR = 1.8) were related to elevated risk when the high and low quartiles were compared (51). In a third study of colon adenoma in Japanese men, impaired glucose tolerance was not related to risk, although diabetic subjects were at elevated risk in that study (52). In a Chinese population, patients with rectosigmoid adenomas had significantly higher blood glucose concentrations than did polyp-free control subjects (35). One study in Italy used fructosamine, equivalent to total serum glycated proteins, as a marker of blood glucose concentrations in the previous 3 wk; individuals with higher concentrations of fructosamine had a 2.3-fold elevated risk of adenomas compared with those with lower concentrations (47). In the Nurses' Health Study, glycosylated hemoglobin was associated with a not statistically significant increased risk (RR = 1.47 for the top versus the bottom quartile) of colorectal adenoma (53). In a study of patients undergoing colonoscopy at the University of Carolina hospitals, those in the highest quartile of blood glucose had a 1.8-fold not significantly higher risk of adenoma (54). In a case-control study of colorectal adenomas in Korea, a significant inverse trend with increasing serum glucose was found (43). Overall, the association with hyperglycemia seems particularly consistent for adenomas.

### THE METABOLIC SYNDROME AND RISK OF COLON CANCER

Thus far, studies of determinants, clinical correlates, and biochemical components of the metabolic syndrome have been summarized. Some studies have now examined standard definitions (obesity, high blood pressure, high serum triacylglycerols, high blood glucose, and low serum HDL cholesterol) of the metabolic syndrome in relation to colorectal cancer risk. In one such study (39), both men and women who were defined as having the metabolic syndrome were at significantly elevated risk of fatal colon cancer (RR = 2.99), but this was based on only 6 cases in the metabolic syndrome group. In another study, which used less traditional criteria (3 of 4 of highest quartile of sex-specific distribution of postload glucose, high BMI, high systolic blood pressure, or resting heart rate), men and women classified with



the metabolic syndrome had a significantly elevated RR (RR = 1.50) relative to those without this syndrome (33). In another study, baseline metabolic syndrome components ( $\geq 3$  components versus 0 components) had a positive association (RR = 1.49) that was stronger in men (RR = 1.78) than in women (RR = 1.16) (32). Furthermore, a dose-response relation with colon cancer was noted with the number of metabolic syndrome components. In Finnish male smokers, subjects with a cluster of 3 components of the metabolic syndrome [hypertension, BMI (in  $\text{kg}/\text{m}^2$ )  $> 25$ , and low HDL cholesterol] had a significantly increased risk of colorectal cancer (RR = 1.40) and colon cancer (RR = 1.58) (34).

The metabolic syndrome has also been examined in relation to colorectal adenoma risk. In a Chinese study of rectosigmoid adenoma, risk increased with increasing number of metabolic syndrome criteria present (1 versus 0: RR = 1.22; 2 versus 0: RR = 1.47; 3 versus 0: RR = 1.78) (35). A study in Taiwan assessed patients for metabolic syndrome by using the criteria of the National Cholesterol Education Program Adult Treatment Panel III and modified Asian criteria. The metabolic syndrome was associated with odds ratios (ORs) of 1.35 for colorectal neoplasia, 1.62 for proximal lesions, 2.15 for synchronous lesions, and 2.30 for synchronous lesions located at both sides of the colon (55). In a study of Japanese men, the metabolic syndrome defined by abdominal obesity in combination with any 2 of the following conditions (elevated triacylglycerols, lowered HDL cholesterol, elevated blood pressure, and raised fasting glucose) was associated with a significant 40–50% increase in risk of adenoma (56). Increased risk was more evident for proximal than distal colon or rectal adenomas and was almost exclusively observed for large lesions ( $> 5$  mm in diameter).

#### HYPERINSULINEMIA AND COLORECTAL CANCER AND ADENOMA

Insulin resistance is believed to be one of the underlying mechanisms of the metabolic syndrome, but measures of insulin resistance or concentrations are not generally part of the definition of this syndrome for clinical purposes. Insulin resistance and hyperinsulinemia can be measured in several ways (eg, fasting, nonfasting, post-glucose load, proinsulin, C-peptide, etc). Schoen et al (10) found on the basis of 102 cases of colorectal cancer that fasting insulin was not related to an increased risk (RR = 1.2), whereas 2-h insulin was related to a significantly increased risk (RR = 2.0). In a prospective study of women in New York state, a 3-fold higher risk of colorectal cancer was observed in those in the top quartile of C-peptide, an indicator of insulin secretion (57), and a 4-fold higher risk was observed for colon cancer (58). A study in northern Sweden, which was based on 110 cases of colorectal cancer, did not find an appreciably elevated risk associated with total insulin (included fasting and nonfasting; RR = 1.2), although a suggestive association was observed in analyses based on fasting ( $> 4$  h) cases alone (RR = 1.68) (59). In the CLUE II cohort, baseline insulin concentrations (a mixture of fasting and nonfasting) were not related to risk of colorectal cancer (25). In the Physicians' Health Study, men with C-peptide in the top versus the bottom quintile had a 2.7-fold significantly higher risk of colorectal cancer after control for BMI and exercise; this RR increased to 3.4 after the analysis was controlled for indicators of the metabolic syndrome (based on the following 4 criteria: plasma HDL cholesterol  $< 40$

mg/mL, triacylglycerols in the upper 20th percentile, BMI  $> 25$ , and blood pressure  $> 130/85$  mm Hg or use of antihypertensive drugs; 60). In the Nurses' Health Study, women in the highest quartile of C-peptide had a borderline increased risk of colon cancer (RR = 1.76) compared with those in the bottom quartile (61).

Several studies have also considered insulin or C-peptide concentrations in relation to adenoma risk. In one study (52), fasting plasma insulin was not related to increased risk of adenomas (RR = 1.1). In contrast, in a study of patients undergoing colonoscopy at the University of Carolina hospitals, those in the highest quartile of insulin had a 2.2-fold significantly higher risk of adenoma (54). In the Nurses' Health Study, high concentrations of C-peptide were significantly associated with risk of distal colorectal adenoma (RR = 1.63), even after control for BMI and physical activity level (53).

#### DISCUSSION

Elevated BMI, physical inactivity, and visceral adiposity as assessed by circumference measures were found to be consistent risk factors for colon cancer and adenoma. These factors are the major modifiable determinants of insulin resistance and hyperinsulinemia and the metabolic syndrome. Patients with type 2 diabetes, one of the major consequences of long-standing insulin resistance, have a higher risk of colon cancer. The serologic manifestations of the metabolic syndrome, including hypertriglyceridemia, low HDL cholesterol, and an elevated fasting or 2-h glucose concentration, have also been examined in relation to colon cancer and adenoma risk. In most studies, an increased risk of colon cancer or adenoma is found, especially for elevated fasting or 2-h glucose, with overall relative risks ranging from  $\approx 1.5$  to 2. Fewer studies of hypertension have been done, which may or may not be etiologically part of this syndrome. Six studies examined the metabolic syndrome and risk of colorectal cancer or adenoma on the basis of standard or slightly modified criteria, and all found a suggestive or significantly increased risk. Most studies of 2-h insulin or C-peptide concentrations, which are markers of hyperinsulinemia, have found an association with colon cancer or adenoma risk. Thus, studies based on determinants, metabolic consequences, and disease consequences of the metabolic syndrome support the concept that persons with the metabolic syndrome are indeed at increased risk of colon cancer.

The general consistency of the findings is remarkable given the limitations of many of the studies. Various study designs were used, and risk was examined in both men and women, in various and diverse populations, and for adenomas and cancer. In the serologic studies, only one measurement was taken, to presumably estimate long-term exposure. Most studies were based on modest numbers of cases and thus had relatively low power to assess moderate-sized effects. Also, heterogeneity existed in the measurements in terms of fasting status and time of day that blood was collected, and inevitably some degree of measurement error occurs in laboratory assays. Finally, in studies that separated colon cancer and rectal cancers, the association with these factors was almost invariably present in colon cancer or adenoma and rarely for rectal lesions. However, many of the studies only assessed colorectal cancer or adenoma as a group. All of these limitations would tend to weaken any true effects of these factors and risk of colonic neoplasia. Because the data were collected before the outcome in these studies, the sources of error and



imprecision should have been nondifferential regarding case-control status.

On the basis of this review, it appears evident that colon neoplasia is associated with the metabolic syndrome in some way, but the studies do not clarify which component or components of the metabolic syndrome, if any, are causally related to colon cancer. Biologically plausible roles have been suggested for the effects of hypertriglyceridemia and hyperglycemia (5) or of hyperinsulinemia (3). These factors are closely interrelated, which makes it difficult to tease their role apart. However, the natural history of glucose intolerance and diabetes could be exploited to distinguish which of these effects are most critical. Type 2 diabetes typically develops after long-term insulin resistance, in which higher concentrations of insulin are required to achieve normal utilization of circulating glucose. Initially, equilibrium is achieved primarily through the increased production of insulin by the pancreas, which results in compensatory hyperinsulinemia. Over many years or decades, pancreatic  $\beta$ -cell failure in susceptible persons leads to the reduced secretion of insulin, which is ultimately inadequate to meet the enhanced insulin requirements;  $\beta$ -cell failure eventually leads to hypoinsulinemia, which is most evident in the postprandial phase (62). Thus, in the initial stages of impaired glucose tolerance and diabetes mellitus, hyperinsulinemia predominates, whereas in later stages, hypoinsulinemia occurs; hypertriglyceridemia and hyperglycemia tend to worsen progressively across all stages.

By considering the natural history of metabolic changes in impaired glucose intolerance, several lines of evidence seem to suggest that the hyperinsulinemia is the most critical factor. First, in the Nurses' Health Study, an increased risk of colon cancer was observed in women who had been recently diagnosed with diabetes, but the risk was attenuated 15 y after the diagnosis. This pattern appears consistent with an effect of hyperinsulinemia, which is more evident earlier in the natural course of the disease (24). Second, in one study (49), persons with impaired glucose tolerance (but not diabetes) experienced an excess of colon cancer deaths, but persons with diabetes had a 3- to 4-fold higher rate of total mortality that was mostly a result of cardiovascular disease, a pattern more consistent with an effect of hyperinsulinemia rather than hyperglycemia. Third, in the Physicians' Health Study (60), C-peptide concentrations, which are a measure of insulin secretion, were a stronger predictor of colorectal cancer risk than was the metabolic syndrome (based on low plasma HDL cholesterol, high triacylglycerols, high BMI, and hypertension), and C-peptide became an even stronger predictor after controlling for these. Fourth, postprandial insulin (10) and nonfasting C-peptide (58, 60), a measure of insulin secretion that accounts for  $\beta$ -cell function and for the hyperinsulinemic effect of diet, are stronger predictors of colon cancer risk than is the fasting insulin concentration (10, 59), which may be a more direct measure of insulin resistance. Finally, in one study, chronic insulin therapy was associated with a significantly increased risk of colorectal cancer among patients with type 2 diabetes, with a 21% increase in risk with each incremental year of insulin therapy (63). In persons with type 2 diabetes, exogenous insulin therapy is associated with hyperinsulinemia despite the waning endogenous production because exogenous insulin is inefficient in maintaining glucose efficiency in the persistence of insulin resistance (64).

These epidemiologic data tend to point to a primary influence of hyperinsulinemia, but this contention must be evaluated

through more mechanistically based studies. Of note, in a rat model, insulin, during a 10-h euglycemic clamp, increased colorectal epithelial proliferation in a dose-dependent manner, and the addition of hyperglycemia did not further increase proliferation (65). Further, intralipid infusion alone did not increase cell proliferation. At least on the basis of this study, hyperinsulinemia seems to be the key component in increasing the cell proliferation rate. The underlying mechanism for the association with hyperinsulinemia remains unknown; however, this may involve the influence of hyperinsulinemia in enhancing free or bioavailable IGF-1 concentrations, which have been related to cancer risk (8).

In conclusion, a large body of epidemiologic data strongly supports that persons with the metabolic syndrome are at increased risk of colon cancer and adenoma. This evidence is based on studies of determinants of the metabolic syndrome (obesity, abdominal distribution of adiposity, physical inactivity), clinical consequences (type 2 diabetes, hypertension) of this syndrome, plasma or serum components of the definition of metabolic syndrome (hypertriglyceridemia, hyperglycemia, low HDL cholesterol), and markers of hyperinsulinemia or insulin resistance (insulin, C-peptide) in relation to colon cancer or adenoma risk. Furthermore, although the evidence is not yet conclusive, epidemiologic and animal evidence tends to support more strongly a direct role of hyperinsulinemia than other aspects of the insulin resistance syndrome for colon cancer risk. Further study is needed in this area. For example, studies that simultaneously assess more direct measures of insulin resistance (eg, homeostasis model assessment of insulin resistance) and of insulin secretion capacity (eg, on the basis of C-peptide and proinsulin) would be informative by directly comparing simultaneously how indicators of insulin secretion and insulin resistance are related to cancer risk.

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