MINIREVIEW

Insulin Resistance and Its Contribution to Colon Carcinogenesis

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The insulin resistance-colon cancer hypothesis, stating that insulin resistance may be associated with the development of colorectal cancer, represents a significant advance in colon cancer, as it emphasizes the potential for this cancer to become a modifiable disease. The fact that the incidence of insulin resistance has been increasing in the United States and much of the rest of the Western world where colon cancer remains the second leading cause of cancer death makes the exploration of the interrelationship of these conditions a subject of high priority. Here, we review the salient features of insulin resistance, defined as impaired biological response to the action of insulin. Recent epidemiological studies, evaluating potential associations between colon cancer risk and diabetes mellitus, dietary intake and metabolic factors, and IGF levels in several clinical settings, provide strong support of the insulin resistance-colon cancer hypothesis (without establishing causality). Mechanistically, insulin resistance has been associated with hyperinsulinemia, increased levels of growth factors including IGF-1, and alterations in NF-κB and peroxisome proliferator-activated receptor signaling, which may promote colon cancer through their effects on colonocyte kinetics. It is a reasonable expectation that in the not too distant future, critical interventions to the already mapped molecular sequence of events, which link two apparently disparate entities, combined with lifestyle changes could abrogate the development of colon cancer. Exp Biol Med 228:396–405, 2003

Key words: insulin resistance; colon cancer; carcinogenesis; IGF-1; aging

The association between insulin resistance and the development of colorectal cancer represents a significant conceptual advance in colon cancer during the last decade (1, 2). The astute observation that these two apparently disparate conditions, insulin resistance and colon cancer, have many contributing factors in common has provided the impetus for a detailed evaluation of this hypothesis and some of its corollary ideas. The incidence of overweight and obesity, conditions often associated with type-2 diabetes, is escalating, reaching alarming levels in the United States and much of the rest of the Western world (3, 4). On the other hand, colon cancer is the second most frequent fatal cancer in these segments of the world and markedly increased in elderly individuals (5). The magnitude of this major public health problem is likely to grow, particularly because elderly people become more resistant to insulin over time and the percentage of this aged population is expected to double by the year 2035 (6). Thus, a thorough exploration of the interrelationship between insulin resistance and colon cancer and a deeper understanding of the underlying pathogenetic events have assumed compelling urgency.

In this review, we briefly present pivotal concepts, summarize several key studies assessing this association, and discuss mechanistic work that provides insights to the complex molecular events culminating in so profound a derangement of the host organism.

Insulin Resistance: An Overview

Insulin resistance is defined as impaired biological response to the action of insulin (7). It is characterized by compensatory hyperinsulinemia and is associated with increased risk for Type-2 diabetes. The syndrome of insulin resistance, also referred to as syndrome X or metabolic syndrome, is a cluster of various abnormalities including

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impaired glucose tolerance, insulin resistance, central obesity, hypertension, and dyslipidemia with a propensity to cardiovascular disease (8). Other metabolic abnormalities of this syndrome are disorders of coagulation such as high levels of plasminogen activator inhibitor type-1 and fibrinogen, as well as hyperuricemia and microalbuminuria (9). The concept of insulin resistance is not restricted to changes in carbohydrate, lipid, or protein metabolism, but encompasses other biological actions of insulin affecting growth, differentiation, DNA synthesis, and regulation of gene expression (10). Altogether, these metabolic and cellular changes seem to create an environment in which a number of risk factors accumulate and interact synergistically toward the development of cancer, and cardiovascular and renal disease.

Resistance to insulin usually develops long before any disease signs appear. It is present in 25% of nonobese persons with normal glucose tolerance and in the majority of individuals with impaired glucose tolerance (11). Hyperinsulinemia remains undiagnosed for many years, increasing the risk for the development of other components of the syndrome and subsequent diseases. Therefore, it is important to identify and treat individuals with insulin resistance as early as possible because prompt recognition and management of this metabolic syndrome has potentially a great preventive value (12).

Unfortunately, there is no simple, clinically applicable diagnostic test for insulin resistance. To complicate matters, the normal values in the measurement of insulin resistance vary widely and because of extensive overlap, they do not discriminate adequately between nondiabetics and diabetics (7).

Of the methods used to measure insulin resistance, three are most frequently used. The euglycemic insulin clamp technique (13, 14) is widely accepted as a research method, but is too cumbersome for clinical use. The minimal model method (15) is simpler, but the complexity of the sampling procedure, the sophisticated data analysis, and the cost make it also not suitable for clinical settings. The most practical approach is measurement of the fasting insulin level, which correlates well with insulin resistance (16). However, its use is limited by a rather high proportion of false-positive results and by lack of standardization. Addressing the latter issue, the ADA Task Force on standardization of insulin assay recommended to be certified by a central laboratory (17).

As often is the case in medicine, in the absence of a universally accepted simple, inexpensive, and reliable laboratory test, clinical suspicion should alert us to the diagnosis of insulin resistance. A strong family history of diabetes, history of gestational diabetes, polycystic ovarian syndrome, impaired glucose metabolism, and obesity (body mass index [BMI] $\geq$ 30 kg/m^2) should raise the possibility of insulin resistance (12). Indeed, the condition is common in individuals with fasting glucose level of 110–125 mg/dl or a 2-hr post-75 g glucose level of 140–199 mg/dl, and in those with abdominal obesity (waist-to-hip ratio greater than 1.0 in men and 0.8 in women). Several indices such as Fasting Insulin Resistance Index (FIRI) (18), Quantitative Insulin Sensitivity Check Index (QUICKI) (19), and Homeostasis Model Assessment (HOMA) method (20) have been devised to substitute for the laborious clamp technique, but their exact place as diagnostic methods is not firmly assessed.

The metabolic abnormalities of insulin resistance syndrome increase both morbidity and mortality (21). Whether treatment of insulin resistance can prevent the associated disorders is presently equivocal (7). Currently, the use of medications is indicated only when the individual has diabetes mellitus (DM). Effective interventions against insulin resistance include lifestyle modifications such as weight reduction, exercise, and a hypocaloric diet. It is also critical that susceptible individuals are encouraged to develop good habits at a young age because the metabolic changes in this syndrome are similar to those observed in early aging (Fig. 1).

Aging: A Link Between Insulin Resistance and Colon Cancer

Aging is a strong risk factor for both insulin resistance (22–24) and colon cancer (5). In fact, insulin resistance elicits many of the signs of early aging and is a common condition in older animals and humans (25, 26), suggesting that insulin-signaling pathways mediate aging processes. On the other hand, colon cancer is one of the most common age-related neoplasias with exponentially increased incidence rates during old age (27), leading to the hypothesis that older organisms are more susceptible to colon carcinogenesis due to aging-specific changes within the host (28).

In experimental animal systems, strategies that prolong life span prevent both insulin resistance and colon carcinogenesis. For example, in the F344 rat caloric restriction (CR), an aging-delay modality, retards or inhibits aging-

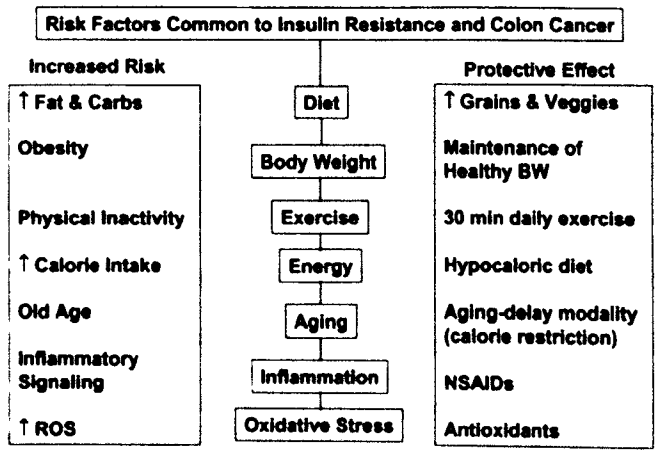

Figure 1. Risk factors for insulin resistance and colon cancer. These two clinical entities share seven factors that can modulate the risk of either one. On the left is shown how these factors can increase the risk for both insulin resistance and colon cancer, and on the right, how they can accomplish the opposite.

associated changes, including increased insulin sensitivity (29) body fat accumulation (30), and cholesterol and triglyceride levels (31). CR also inhibits the development of aberrant crypt foci (ACF) and colonic tumors in a rat model of colon carcinogenesis (32, 33). Animals on diets high in energy and fat had insulin resistance long before ACF formation, whereas diets with CR and n-3 fatty acids prevented both glucose intolerance and ACF growth (34, 35). In another study, the level of fat in the diet was modulated by CR and affected the development of advanced ACF and colonic tumors (36). When, in a noninsulin-dependent diabetes model, rats were subjected to 30% food restriction, their body weight, intraabdominal fat, plasma triglycerides, insulin and glucose, and tissue triglyceride accumulation were all decreased (37).

Another dietary intervention that enhances longevity in rats is methionine restriction (MR), which shares many of the effects of CR while maintaining a reduced body weight apparently without a restriction in energy intake (38, 39). MR results in significantly decreased colonic cell proliferation and ACF formation (28), lifelong reduction in serum lipids and IGF-1 levels (R. Krajcik, personal communication), and remarkably increased blood glutathione and prevention of its depletion during aging (39). Interestingly, decreased blood levels of glutathione, a major regulator of oxidative stress, are often found in the elderly (40–42) and have been associated with the pathogenesis of diabetes (43) and cancer (44).

Although the main phenotypic change in CR and MR is a substantial decrease in fat mass, the role of visceral adipose tissue in obesity, diabetes, and aging, and its function as an endocrine tissue are now beginning to be appreciated (45). Increased accumulation of this metabolically active abdominal fat mass is a common and typical change in body composition during aging and is associated with increased plasma insulin levels and impaired glucose tolerance (46, 47). A cause-and-effect relationship between abdominal fat and insulin action, which explains the basal hyperinsulinemia in aging, was determined by surgical removal of selective abdominal fat depots from moderately obese Sprague-Dawley rats, resulting in dramatic improvement in insulin sensitivity (48). Furthermore, fat tissue produces various active peptides, cytokines, and complement factors, such as TNF-α (49), leptin (50), angiotensinogen (51), and plasminogen activator inhibitor-1 (52), which are implicated in the pathogenesis of chronic diseases including diabetes and cancer. The protective effects of CR and MR can be attributed to modulation of key fat-derived molecules that are involved in processes of insulin signaling, inflammation, oxidative stress, aging, and carcinogenesis (Fig. 2).

The importance of energy intake and balance toward a healthy body weight is reinforced by numerous epidemiological studies that examine the associations of diet, energy, BMI, physical activity, and diabetes with the risk of colon cancer (Table I).

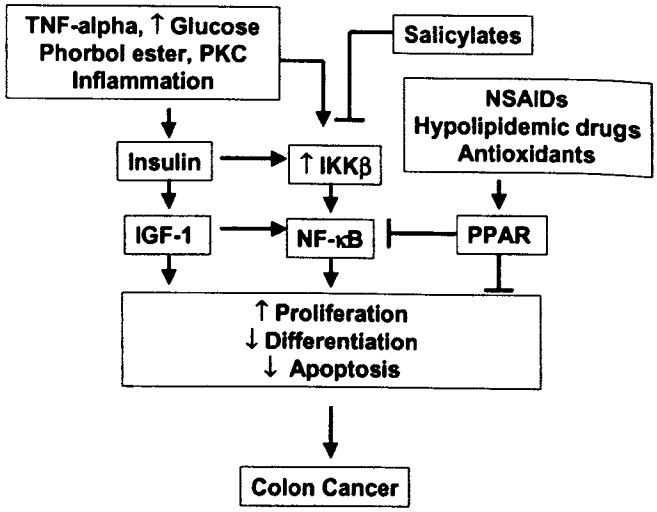

Figure 2. Mechanistic association between insulin resistance and colon cancer. The interplay of several factors participating in the pathogenesis of both entities that can ultimately affect colon cell kinetics leading to colon cancer is shown. Points of intervention by pharmacological agents are also depicted.

From Insulin Resistance to Colon Carcinogenesis: A Mechanistic Outline

To better appreciate the rationale behind some of the parameters assessed in epidemiological or clinical studies, we provide below an overview of the interplay between biochemical parameters of insulin action and colon cancer cell growth.

Insulin resistance exposes colonocytes over prolonged periods to hyperinsulinemia, hyperglycemia, elevated levels of triglycerides, nonesterified fatty acids, and insulin-like growth factor-1 (IGF-1). Such exposure could affect the growth, development, and homeostasis of the colonic cells (10, 53). In this context, it is of interest that in animals, insulin promotes the growth of ACF (34, 54).

Hyperinsulinemia resulting from insulin resistance leads to increased levels of IGF-1, which promotes intestinal epithelial cell proliferation (55). IGF receptors are probably overexpressed in colon cancer cells (56–60). Prolonged hyperinsulinemia increases the levels of free IGF-1, partly by reducing the production of IGF-binding proteins (IGFBPs), which bind IGF-1 and inhibit its action (61). IGFBPs are thought to prevent IGF-1 or IGF-2 from binding to IGF-1 receptors and activating the signal pathways for cell proliferation. IGFBP-3, the most abundant of them, induces apoptosis and mediates the growth inhibitory effects of transforming growth factor-β (TGF-β). IGFBP proteases increase IGF-1 levels by degradation of IGFBPs. The interactions between IGF, IGFBPs, and IGFBP proteases determine the effects of the insulin-IGF axis on colon carcinogenesis. Indeed, studies have shown that subjects with high IGF-1 and low IGFBP-3 levels have an increased risk for colon cancer (61–63).

Conditions that promote insulin resistance include inflammation and cytokine production such as TNF-α, phor-

Table I. Epidemiological Studies of Insulin Resistance-Associated Factors and Colon Cancer Risk

Author, year (ref.)	Study	Subjects case/control (gender)	Risk factors	Cancer risk positively associated with:
Diabetes Mellitus (DM)				
Hu, 1999 (72)	Prospective	121,700 (F)	DM	History of DM for less than 15 years
Will, 1998 (73)	Prospective	866,433	DM	DM in men; nonsignificant association in women
Nilsen, 2001 (74)	Prospective	75,219	DM, PA, BW, Blood glucose	DM and blood glucose in women only; inverse association w/PA in men and no association with BMI
Kono, 1998 (75)	Prospective	7,637 (M)	DM, glucose tolerance	History of DM
La Vecchia, 1997 (76)	Case control	1,225/4,154	DM, Energy, PA, BW	History of DM for ≥10 years, diagnosed at age ≥40; no association with the other covariates
Dietary Intake/Anthropometric/ Metabolic Factors				
Slattery, 1997 (78)	Case control	1,993/2,410	Diet, Energy, PA, BW	Sucrose intake, glycemic index, energy, and BMI; inverse association with PA
Bostick, 1994 (84)	Prospective	35,215 (F)	Diet, Energy, PA, BW	Sucrose intake and BMI; no association with the other covariates
Schoen, 1999 (85)	Prospective	5,849	BW, fasting glucose	HWR and fasting glucose; no association with BMI
Giovannucci, 1996 (86)	Prospective	13,057 (F)	PA, BW	BMI and WHR; inverse association with PA
Franceschi, 2001 (87)	Case control	1,953/4,154	Diet, BW	Glycemic index; overweight and low fiber amplified the effect
Trevisan, 2001 (88)	Prospective	37,302	TGs, Cholesterol, Glucose, and BP	TGs, Cholesterol, glucose, and blood pressure
Terry, 2001 (103)	Prospective	61,463 (F)	Diet	Inverse association with fruit and vegetable intake
Levi, 1999 (104)	Case Control	223/491	Diet	Refined grain and red meat intake; inverse association with whole grain and fruit and vegetable intake
Giacosa, 1999 (105)	Meta-Analysis		PA and BW	BMI in men and HWR in women; inverse association with PA
Kono, 1999 (106)	Prospective	803 (M)	PA and BW	BMI and WHR (weight gain over the past 10 years); inverse association with PA
Marchand, 1997 (107)	Case Control	1,190/1,192	Energy, PA, and BW	Energy and BMI; inverse association with PA
Clinical Correlations (IGF Levels)				
Manousos, 1999 (89)	Case Control	41/50	IGF-1, IGF-2, and IGFBP	IGF-1 and IGF-2; inverse association with IGFBP
Giovannucci, 2000 (90)	Prospective	32,826 (F)	IGF-1 and IGFBP-3	IGF-1; inverse association with IGFBP-3
Ma, 1999 (63)	Prospective	22,071 (M)	IGF-1, IGF-2, and IGFBP-3	IGF-1; no association with IGF-2 and inverse association with IGFBP-3
Orme, 1998 (98)	Retrospective	1,382	Increased growth hormone	Acromegaly

Note. DM, diabetes mellitus; PA, physical activity; BW, body weight; TGs, triglycerides; BP, blood pressure; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; WHR, waist-to-hip ratio.

bol ester treatment, and PKC activation (10, 53). One mechanism through which these factors may elicit their effects is activation of IκB kinase β (IKKβ), an upstream activator of NF-κB. Therefore, mitogenic and antiapoptotic effects of insulin are apparently mediated through both IGF-1 and NF-κB signaling (Fig. 2). The notion that IKKβ is a key mediator in insulin resistance was strongly supported by recent work demonstrating that high doses of salicylates, which inhibit IKKβ activation, reversed hyperglycemia, hyperinsulinemia, and dyslipidemia in obese rodents by sensitizing insulin signaling (64). Notably, this effect of salicylates was independent of COX inhibition by salicylates.

A recent study in humans provides additional credence to these pathways. Hundal *et al.* (65) studied nine type 2 diabetics before and after 2 weeks of treatment with aspirin (approximately 7 g/day). High-dose aspirin treatment reduced fasting plasma glucose by approximately 25% and was associated with approximately 15% reduction in total cholesterol and C-reactive protein, 50% reduction in triglycerides, and 30% reduction in insulin clearance, despite no change in body weight. Aspirin treatment also reduced basal rates of hepatic glucose production by about 20% and improved insulin-stimulated peripheral glucose uptake by 20% under matched plasma insulin concentrations during the clamp technique. These data are the first to provide direct support for the hypothesis that IKKβ represents a new target for treating type 2 DM. Interestingly, aspirin and other nonsteroidal anti-inflammatory agents (NSAIDs) that reduce the risk of colon cancer by about one-half are also found to mediate their chemopreventive action through similar signaling pathways (66).

Another potential target for interventions in insulin resistance and colon cancer is the PPAR signaling. PPARs are nuclear receptors that dimerize with retinoid receptors to act as transcription factors and have been implicated in lipid, glucose, and energy homeostasis, providing a molecular link between nutrition and gene expression (67). They also seem to exert antiproliferative, proapoptotic, and anti-inflammatory effects that may be mediated, in part, by antagonizing the activities of NF-κB (68). Specifically, PPAR-γ loss-of-function mutations are associated with human colon cancer (69), and ligands of PPAR-γ induce growth arrest and differentiation markers in human colon cancer cells (70). Furthermore, compounds such as hypolipidemic drugs, certain NSAIDs, and antioxidants, which are found to activate PPARs, can also correct the abnormal NF-κB activity associated with age-related inflammatory dysregulations (71).

The Epidemiological Evidence

The potential relationship between insulin resistance and colon cancer has been examined by several studies. Here, we summarize the findings of 20 such studies (Table I), grouped into three categories, which represent the most interesting areas of inquiry on this topic. They have addressed associations between colon cancer risk and DM, dietary intake and metabolic factors, and IGF levels in several clinical settings.

DM and Colon Cancer. Several large prospective studies have provided convincing evidence for an association between DM and colon cancer. The five studies summarized here showed a positive association between colon cancer and DM, although the types and degrees of this association varied or even conflicted among them. The most notable variation concerned the gender effect on this association.

Hu *et al.* (72) showed a significant positive association between history of diabetes and the risk of colorectal cancer in female registered nurses of The Nurses Health Study, which followed them for 18 years. The relative risk (RR) for colorectal cancer was 1.43 (95% confidence interval [CI] = 1.10–1.87; P = .009) becoming 2.39 (1.46–3.92; P = .0005) for fatal colorectal cancer. Of note, the RR was diminished for women with diabetes diagnosed for over 15 years. This could reflect progression of type 2 DM resulting in relative hypoinsulinemia, in which case, it could support the notion that hyperinsulinemia, a compensatory response to insulin resistance, contributes to the development of colon cancer. Will *et al.* (73) compared the likelihood of developing colorectal cancer in diabetic with nondiabetic subjects of the Cancer Prevention Study of the American Cancer Society over a 13-year follow-up. After adjusting for BMI, family history, physical activity, race, smoking, dietary intake, and alcohol and aspirin use, the risk of colorectal cancer in diabetics was significantly increased in men (RR = 1.30; 1.03–1.65) and had a nonsignificant increase in women (RR = 1.16; 0.87–1.53). Nilsen *et al.* (74) investigated the association between colorectal cancer risk and factors related to hyperinsulinemia and insulin resistance, including diabetes, blood glucose, physical activity, and BMI in subjects followed up for 12 years. The risk of colorectal cancer was significantly increased in women (age adjusted RR = 1.55; 1.04–2.31), but not in men with a history of type 2 DM. Kono *et al.* (75) compared 821 cases of sigmoid colon adenomas a precursor of colon cancer with 4372 controls. Based on data from a 75-g oral glucose tolerance test and medical history, individuals were classified into normal, impaired glucose tolerance, newly diagnosed noninsulin-dependent DM, or DM under treatment. Adenomas in the sigmoid colon were positively associated with noninsulin-dependent DM.

A large case-control study conducted in Italy on 1225 cases of colon cancer and 4154 controls who were in the hospital for non-neoplastic diseases (76). Subjects diagnosed with diabetes at age of 40 years or older had a slightly increased risk of colon cancer (OR = 1.4; 1.1–1.7). This association became stronger (OR = 1.6; 1.1–2.3) for subjects with a history of diabetes for 10 or more years and were 60 years or older at the time of colon cancer diagnosis. There was no association with BMI, physical activity, alcohol drinking, energy, and fiber intake.

Taken together, these findings support the notion that hyperinsulinemia predisposes one to an increased risk of colon malignancy.

Dietary Intake/Metabolic Factors and Colon Cancer. The 12 studies tabulated under this subgroup have assessed the relationship between four parameters that contribute to, or are markers of, obesity, which is closely linked to the syndrome of insulin resistance (Table I). They include energy intake, physical activity, BMI (a reliable marker of obesity), and waist-to-hip ratio that mirrors the distribution of fat in the body.

High-energy intake and diminished physical activity, each alone or more often in combination, are critical and frequent contributors to obesity. Increased visceral adipose tissue, a predominant feature in about one-third of obese in the United States, leads to increased waist-to-hip ratio, an anthropometric parameter, which should raise the clinical suspicion of insulin resistance. Indeed, visceral adipose tissue is considered an active endocrine tissue (45, 48, 77) and its expansion is associated with increased plasma insulin levels and impaired glucose tolerance (46, 47). Here, we present the salient points of some of the studies belonging to this group.

Slattery *et al.* (78), using a validated history questionnaire, examined the association between dietary sugars, glycemic index, and colon cancer. The glycemic index describes the rate of glucose appearance in blood after the ingestion of a carbohydrate-rich meal and determines the relative glycemic responses of different foods (79, 80). A higher sucrose:dietary fiber ratio was associated with increased risk of proximal colon cancer in both men and women. As the level of physical activity decreased, the sucrose:dietary fiber ratio and BMI increased, and the risk of colon cancer increased. These associations were stronger for men (OR = 5.9; 2.23–15.6) than for women (OR = 3.45; 1.29–9.23). Of note, animal studies showing that sucrose increases ACF formation and colonocyte proliferation suggest a potential mechanism for the role of sucrose in colon cancer (81–83).

Bostick *et al.* (84) (The Iowa Women's Health Study) evaluated the incidence of colon cancer in relation to the dietary intake of sugar, meat, fat intake, and nondietary risk factors. Subjects, aged 55 to 69 years, completed mailed questionnaires in 1986 through 1992, whereas 212 incidental colon cancers were documented. Sucrose-containing foods, height, and BMI were associated significantly with colon cancer.

Schoen *et al.* (85) analyzed the medical records from hospitalizations for incidental colorectal cancer in subjects from the Cardiovascular Health Study. This study involved

subjects over the age of 64 years; 102 colorectal cancers were identified over a median follow-up of 77 months. There was approximately a 2-fold increased risk of colorectal cancer in those with the highest fasting glucose. Although both waist circumference and waist-to-hip ratio were significantly associated with increased risk, the association for BMI was only weakly positive, suggesting that central obesity plays a role in colon cancer.

Giovannucci *et al.* (86) evaluated females participating in the Nurses Health Cohort Study for BMI, pattern of adipose distribution, and physical activity in relation to colon cancer risk. Obesity was associated with an increased risk of large colonic adenomas and physical activity was inversely associated with occurrence or progression of adenomas in the distal colon.

Franceschi *et al.* (87) compared subjects hospitalized for acute conditions (controls) in relation to colorectal risk with dietary GI and glycemic load used as indicators of dietary insulin demand. After adjustment for sociodemographic factors, number of daily meals, physical activity, and intakes of fiber, alcohol, and energy, the OR was increased for colorectal cancer. Colorectal cancer risk had a positive correlation to glycemic index (OR = 1.7; 1.4–2.0) and glycemic load (OR = 1.8; 1.5–2.2).

Trevisan *et al.* (88) reported findings from The Risk Factors and Life Expectancy Project, composed of nine different large-scale epidemiological studies done in Italy between 1978 and 1987 that followed up subjects for an average of 7 years. The risk of colorectal cancer mortality was examined in subjects with the cluster of metabolic abnormalities associated with insulin resistance, such as abnormalities in serum triglycerides, cholesterol, blood glucose and blood pressure, and compared with controls without these abnormalities. The calculated hazard ratios and 95% CI in the presence of these cluster of metabolic abnormalities were 2.96 (1.05–8.31) for men, and 2.71 (0.59–12.50) for women, and 2.99 (1.27–7.01) for both genders combined. These associations were independent of age, smoking, and consumption of alcoholic beverages, which were potential cofounders. The study suggests that insulin resistance and the associated metabolic abnormalities have a causative effect in colorectal cancer.

IGF Levels and Colon Cancer. IGF currently appears to be a key player, or at least one of the best-understood players, in the signaling path that links insulin resistance to colon cancer. The basic tenet is that insulin resistance increases not only the levels of insulin, but also those of IGF, which, in turn, increases the risk of colon cancer (Fig. 2). It was only natural that several investigators, whose work is discussed in this last subgroup, have exploited several informative clinical settings to correlate IGF levels with either colon cancer risk or colon cancer itself.

Manousos *et al.* (89) determined serum levels of IGF-1, IGF-2, and IGFBP in 41 patients already diagnosed with colorectal cancer and 50 healthy controls. After adjustment for age, gender, education, height, and BMI, elevated levels of IGF-1 and IGF-2 and lower levels of IGFBP were positively associated with colorectal cancer. Giovannucci *et al.* (90) (The Nurses Health Study) examined baseline plasma levels of IGF-1 and IGFBP-3 and the risk of adenoma or colorectal. Blood samples were obtained from 32,826 women between 1989 and 1990. Cancer-free controls were matched to cases (2:1 for cancers and 1:1 for adenomas) and IGF-1 and IGFBP-3 levels were measured. During follow-up between 1989 and 1994, 90 cases of large (≥1 cm) adenomas of intermediate or late stage, 107 small tubular adenomas (<1 cm), and 79 new cases of colorectal cancer were documented. After controlling for IGFBP-3 level, relative to the women in the low tertile of IGF-1, those in the high tertile had an increased colorectal cancer risk (RR = 2.18; 0.94–5.08) and a high risk of adenoma (RR = 2.78; 0.76–9.76). Women in the high tertile of IGFBP-3, after controlling for IGF-1 level, were at lower risk of colorectal cancer (RR = 0.28; 0.10–0.83) and lower risk of intermediate/late-stage colorectal adenoma (RR = 0.28; 0.09–0.85). There was no association of IGF-1 or IGFBP-3 with early stage adenoma. The data from this study showed that high levels of IGF-1 and low levels of IGFBP-3 were associated with an increased risk of large or tubulovillous/villous colorectal adenoma and cancer.

The Physicians Health Study (PHS) (62) examined plasma levels of IGF-1 and IGFPB-3 and colorectal cancer in men. This was a prospective case-control study nested in the PHS, which was a randomized, double-blind, placebo-controlled trial of aspirin and β-carotene among 22,071 healthy male physicians 40–84 years of age in 1982. Blood samples of 14,916 men who were cancer free were collected. One hundred ninety-three men over 14 years of follow-up later diagnosed with colorectal cancer had IGF-1, IGF-2, and IGFBP-3 levels assayed and compared with 318 age- and smoking-matched control subjects. IGFBP-3, age, smoking, BMI, and alcohol intake were controlled for, and the results showed that men in the top quintile of circulating IGF-1 had an increased risk of colorectal cancer (RR = 2.51; 1.15–5.46; $P = 0.02$) compared with men in the bottom quintile. Men with higher IGFBP-3 had a lower risk (RR = 0.28; 0.12–0.66; $P = 0.005$) comparing the top with the bottom quintile. IGF-2 in this study was not associated with risk. The associations remained during the first and the second 7-year follow-up, excluding the possible effect of undiagnosed cancer on IGF levels. These findings again support that circulating IGF-1 and IGFBP-3 are associated with colorectal cancer risk.

Several studies have shown increased colon cancer in acromegaly, a rather rare clinical entity (91–95). What led investigators to scrutinize its association with colon cancer is the fact that, in addition to increased growth hormone levels, acromegalics have elevated IGF levels, which were shown to increase the proliferation of their colonocytes (96, 97). Recently, a large multicenter retrospective cohort study (98), for the United Kingdom Acromegaly Study Group involving 1,362 subjects, colon cancer mortality was sig-

nificantly increased (standardized mortality ratio 2.47; 95% CI 1.31–4.22), although the overall mortality rate was similar to the general population. A nonsignificant increase in colon cancer incidence was reported (standardized incidence ratio 1.68; $P = 0.06$). This likely contributes to the elevated risk of developing colon cancer in acromegaly.

Conclusion

A plethora of epidemiological findings strongly supports the insulin resistance-colon cancer hypothesis, nearly a decade after it was articulated by McKeown-Eyssen and Giovannucci (1, 2). Although the data summarized above do not always agree in their details, the general theme that runs through them is indeed consistent. One should not be surprised by "deviations" of this type, which are almost inherent in epidemiological studies of multifactorial and complex processes. Existing data do not establish causality, but they have advanced this hypothesis to a level that justifies rigorous studies to provide proof of it.

Far less apparent is the underlying mechanism. In fact, several equally plausible interpretations can be entertained based on the available information, creating a classic case of a "science black box." For example, the hyperinsulinemia of insulin resistance could be the central player in the carcinogenic process. Alternatively, downstream factors such as IGF-1 could play that role. A third possibility is a mechanism altogether different from changes in insulin or growth factor levels, in which case the latter would be "derivative changes" not critical to the process. Obviously, the situation has reached the stage where direct, decisive studies will be required to determine which one of these (and perhaps additional) alternative interpretations is correct.

Mechanism aside, these findings raise practical issues with respect to colon cancer risk in patients with insulin resistance, like the following two: Does the presence of insulin resistance justify colonoscopic surveillance, and if yes, at what time it should commence? And, when should recommendations for lifestyle changes be made and how rigorous they should be? At the present time, these issues remain unresolved. Unanswered questions that would bear on formulating recommendations for colonoscopy concern the magnitude of risk imposed by insulin resistance and its timing. For example, current recommendations for colonoscopic surveillance (99) may have to be modified for individuals with insulin resistance starting at a young age.

It is not an unreasonable expectation that critical interventions to the molecular changes that have already been mapped will be devised; such interventions could abrogate the development of colon cancer. Recently, acarbose, a β-glycosidase inhibitor, was shown to favorably modify insulin resistance by reverting impaired glucose tolerance to normal (100). Evidence is also accumulating that salicylates (or NO-releasing aspirin, an apparently safer version of aspirin (101), may ameliorate insulin resistance. We speculate that aspirin prevents colon cancer by influencing these pathways as well, expanding the pleiotropic effects of aspirin. This speculation is in accordance with our model of redundancy in aspirin's mode of action on cancer (102).

The insulin resistance-colon cancer hypothesis brings together two entities that were hitherto considered unlikely to interact, thus challenging our intellectual comfort from textbook descriptions. What we tend to forget is that both occur in the same organism, and that interplay between entities or commonality of mechanisms may be more widespread than we suspect. Nonetheless, if this sequence of events were to be established conclusively, colon cancer would definitively be a modifiable disease either through lifestyle changes or via appropriate pharmacological interventions or both.

Insulin resistance impacts health in a significant way because it involves a significant segment of the population and encompasses a broad nosological spectrum. Given the current level of development of the concept of insulin resistance and colon cancer, we anticipate mechanism-driven interventions to prevent and/or manage insulin resistance in the future, which may reduce dramatically the incidence of colon cancer as well.

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