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Insulin, Insulin-Like Growth Factors and Colon Cancer: A Review of the Evidence[1]

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ABSTRACT Insulin and insulin-like growth factor (IGF) axes are major determinants of proliferation and apoptosis and thus may influence carcinogenesis. In various animal models, modulation of insulin and IGF-1 levels through various means, including direct infusion, energy excess or restriction, genetically induced obesity, dietary quality including fatty acid and sucrose content, inhibition of normal insulin secretion and pharmacologic inhibition of IGF-1, influences colonic carcinogenesis. Human evidence also associates high levels of insulin and IGF-1 with increased risk of colon cancer. Clinical conditions associated with high levels of insulin (noninsulin-dependent diabetes mellitus and hypertriglyceridemia) and IGF-1 (acromegaly) are related to increased risk of colon cancer, and increased circulating concentrations of insulin and IGF-1 are related to a higher risk of colonic neoplasia. Determinants and markers of hyperinsulinemia (physical inactivity, high body mass index, central adiposity) and high IGF-1 levels (tall stature) are also related to higher risk. Many studies indicate that dietary patterns that stimulate insulin resistance or secretion, including high consumption of sucrose, various sources of starch, a high glycemic index and high saturated fatty acid intake, are associated with a higher risk of colon cancer. Although additional environmental and genetic factors affect colon cancer, the incidence of this malignancy was invariably low before the technological advances that rendered sedentary lifestyles and obesity common, and increased availability of highly processed carbohydrates and saturated fatty acids. Efforts to counter these patterns are likely to have the most potential to reduce colon cancer incidence, as well as cardiovascular disease and diabetes mellitus. J. Nutr. 131: 3109S–3120S, 2001.

KEY WORDS: • *insulin* • *insulin-like growth factors* • *colon cancer* • *adenomas*

The strong relationship between Westernization and colon cancer incidence has spawned a number of explanatory hypotheses, many focused on the influence of dietary fat and fiber on the colonic lumenal contents. Dietary fat induces secretion of bile acids (1), which are converted to secondary and tertiary bile acids by colonic bacteria (2). These bile acid products may promote tumors by increasing colonic cell proliferation or by mutagenesis (3,4). Fiber presumably dilutes fecal carcinogens and bile acids and reduces colonic transit time, further limiting exposure of the colonic mucosa to carcinogens (5). However, recent case-control, cohort and some randomized studies have cast doubt on the hypotheses that fat and fiber play the central role in colon carcinogenesis (6,7). In contrast, an increasing and diverse body of evidence indicates that variations in the levels of insulin and insulin-like growth factors (IGF)[3] could account for many of the nutritional and other risk factors of colon cancer and for its high incidence in Western countries. This hypothesis is consistent with a diverse body of data, including mechanistic, animal, clinical and epidemiologic studies, which will be reviewed here.

Mechanisms whereby insulin and IGF may be related to colon cancer

Insulin and the IGF axis each play important and complementary roles in metabolism and growth. Insulin influences metabolism on a short-term basis (e.g., after a meal), whereas the IGF axis exerts a longer-term integrating effect on growth. IGF-1 inhibits apoptosis and is required for cell cycle progression (8). More than 90% of circulating IGF-1 is complexed with insulin-like growth factor binding protein (IGFBP)-3. Most IGF-1 and IGFBP-3 found in the circulation are produced in the liver, and are up-regulated by growth hormone

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[3] Abbreviations used: BMI, body mass index; CI, confidence interval; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; OR, odds ratio; RR, relative risk; WHR, waist-to-hip ratio.

(9). The actions of IGFBP can oppose those of IGF-1 in part by binding IGF-1 and thus reducing free IGF-1 levels (10). In addition, IGFBP-3 may directly inhibit target cells (11). In tissues, IGFBP proteases enhance IGF-1 availability by cleaving IGFBP, thereby increasing free IGF-1 concentration (9). The biological activity of IGF is determined by the integrated actions of circulating IGF-1 and IGFBP and by local production of IGF, IGFBP and IGFBP proteases.

Both colorectal epithelia normal and cancer cells express IGF-1 receptors in vitro; when activated by IGF-1, the receptor-ligand complex inhibits apoptosis and allows progression through the cell cycle (12–16). Thus, IGF-1 can influence both premalignant and cancerous stages. Colorectal carcinogenesis results from an accumulation of specific molecular alterations (17), and increased cellular turnover may enhance the rate at which these alterations accumulate. The IGF axis could influence carcinogenesis by being one of the important determinants of cellular turnover. In the colon of acromegalic patients, who are characterized by growth hormone and IGF-1 hypersecretion, epithelial proliferation is increased, the proliferative zone is extended and growth hormone and IGF-1 levels correlate with cell proliferation (18). Moreover, in colon cancer cell lines, IGF-1 increases production of vascular endothelial growth factor, an angiogenic factor that supports tumor growth (19). Further support of a link between the IGF axis and cancer is that overexpression of IGF-1 receptors is critical for the survival of transformed cells (20).

Similar to IGF-1, insulin stimulates growth of normal colonic and carcinoma cells in vitro (14–16). Although colon cancer tissue has both insulin and IGF-1 receptors (13,21), the mitogenic properties of insulin, in contrast to its glycemic-control properties, may be mediated through IGF-1 receptors (22) or possibly hybrid IGF-1 and insulin receptors (23,24). However, mitogenicity occurs at supraphysiologic levels of insulin (25,26); thus other mediators of the mitogenic effects of insulin are likely to be operative. Insulin increases bioactive IGF-1 through various mechanisms. Growth hormone is the primary regulator for hepatic production of IGF-1, and hepatic growth hormone receptor number is partly regulated by insulin (9,27,28). Additionally, insulin reduces hepatic secretion of IGFBP-1 (29,30), a protein that binds IGF-1 with high affinity and inhibits IGF-1 action in vitro (31–33). Conditions associated with decreased insulin levels, including fasting, exercise and poorly controlled juvenile-onset diabetes mellitus, are associated with elevated IGFBP-1 (34–39). Long-term increases in insulin secretion also decrease another IGFBP, IGFBP-2 (40–43). By reducing levels of IGFBP-1 and IGFBP-2, high insulin levels increase free IGF-1 levels (**Fig. 1**).

The insulin and IGF-1 signal transduction pathway involved in the regulation of gene expression and mitogenicity is mediated by activation of the ras protein (44,45); *ras* mutations that increase activity of the ras protein occur in approximately half of colonic cancers (46) and may enhance growth of adenomas into cancers (17). In addition to a direct mitogenic effect, insulin may prime cells to the effects of specific growth factors by influencing farnesylation of ras, the modification of ras at its carboxyterminal with a C15-prenyl (farnesyl) group (47). Farnesylation of ras, catalyzed by a farnesyl transferase, determines localization of ras in the plasma membrane and is required for the function and transforming capabilities of *ras*. Insulin increases the pool of farnesylated ras protein in vitro (48) and in vivo (49), thereby priming the cellular response of growth factors that use this ras pathway, including IGF-1, epithelial growth factor and platelet-derived growth factor. Among various growth factors examined, only insulin appears capable of stimulating farnesyl transferase.

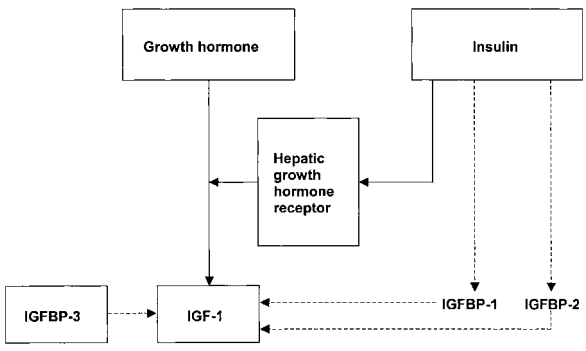

FIGURE 1 Mechanisms whereby insulin increases free insulin growth factor (IGF)-1. Solid lines indicate stimulating effect and broken lines indicate inhibition. IGFBP, insulin growth factor binding protein.

Animal models for IGF and insulin and colorectal tumors

Restriction of energy intake strongly inhibits carcinogenesis in numerous animal models. Many of the metabolic consequences of energy restriction result from the lowering of insulin and IGF-1 levels (50–52). Accumulating evidence indicates that lowering the level of insulin and IGF-1 is critical to the anticancer effects of energy restriction (53–55). For example, in one study, infusion of IGF-1 (via osmotic minipumps) to p53-deficient and energy-restricted mice treated with a bladder carcinogen entirely reversed the anticarcinogenic effects of energy restriction (56). Similarly, infusion of either growth hormone or IGF-1 countered the inhibitory effect of dietary restriction on mononuclear cell leukemia in Fischer rats (57). Also supporting a cancer-promoting role of IGF-1 is that octreotide, which reduces circulating IGF-1 levels, retards colonic tumor growth (58,59).

Strong evidence directly implicating a cancer-enhancing effect of insulin has come from models in which animals are treated with insulin injections. In one experiment, Fischer 344 rats were given a single azoxymethane injection and were later randomly assigned to groups receiving either insulin or saline injections. Insulin enhanced the growth of aberrant crypt foci, a colorectal cancer precursor (60), and increased the number and size of tumors (61). Similar findings were observed in more natural conditions when F344 rats were fed a high energy, high fat diet that led to impaired glucose tolerance, insulin resistance and elevated postprandial insulin (62). In contrast, energy restriction and increased (n-3) fatty acid intake improved insulin sensitivity and glucose tolerance and decreased promotion of aberrant crypt foci (63). The degree of insulin resistance induced by manipulating various dietary factors correlated strongly with the degree of tumor promotion, as assessed by aberrant crypt foci size ($r = 0.67$; $P < 0.001$). Dietary factors that enhance rat colon carcinogenesis show an influence on insulin resistance before an effect on colon carcinogenesis is observed (62). However, in one study (64), diets with a high glycemic index or low nutrient density or diets that increase some indirect markers of insulin resistance did not promote aberrant crypt foci growth in rat colons.

A recent study attempted to address hyperinsulinemia in breast cancer development (65). When lean or obese Zucker rats were treated with *N*-methyl-*N*-nitrosurea (intraperitoneal injections), mammary tumorigenesis was not enhanced. However, an unexpected finding was the development of colon carcinomas (13.3% incidence) in the obese rats. Typically, *N*-methyl-*N*-nitrosurea is able to induce colon tumors only when it is injected intrarectally.

Epidemiological evidence the IGF axis is associated with colorectal cancer risk

Clinical evidence (acromegaly). Acromegaly is a condition characterized by excessive production of growth hormone and IGF-1. Studies spanning the past two decades show that people with acromegaly are at elevated risk of developing both benign and malignant colorectal tumors (66–78). Although most of these studies are small, the consistent pattern strongly supports that high levels of IGF-1 enhance risk of colorectal neoplasia. In a recent study of acromegalic subjects ($n = 129$), the prevalence of colorectal neoplasia found during a colonoscopic examination was considerably higher than that expected from published rates for asymptomatic screened controls; specifically, the odds ratio (OR) was 13.5 [95% confidence interval (CI) = 3.1–75] for colorectal cancer and 4.2 (95% CI = 2.5–6.8) for adenoma (73). Extension of the previous report to 222 patients yielded the same results and also showed that at a repeat colonoscopy, serum IGF-1 levels were significantly higher in those with a recurrent adenoma than in those without [mean, 390 μg/L (51.1 nmol/L) vs. 244 μg/L (32.0 nmol/L); $P < 0.005$] (79). In the largest study, a multicenter retrospective cohort study (United Kingdom Acromegaly Study Group) of acromegalic patients ($n = 1362$) (78), the overall cancer mortality rate was not increased for acromegalic patients over the general population, but colon cancer mortality was increased (standardized mortality ratio, 2.47; 95% CI = 1.31–4.22). A higher risk in acromegalic patients is further supported by the increase in epithelial cell proliferation, the extension of the proliferative zone in the colonic mucosa and the presence of a correlation between growth hormone and IGF-1 levels with cell proliferation rate (18,79).

Serologic evidence (circulating IGF-1 and IGFBP-3). Five recent studies examined circulating IGF-1 and IGFBP-3 in relation to colorectal neoplasia. On the basis of archived samples in the Physicians' Health Study, baseline plasma levels of IGF-1, IGF-2 and IGFBP-3 among 193 men diagnosed with colorectal cancer over a 12-y follow-up period were compared with those from 318 age- and smoking-matched controls (80). After adjustment for age, cigarette smoking, body mass, alcohol intake and IGFBP-3 levels, men in the top quintile of circulating IGF-1 had a relative risk (RR) of 2.51 (95% CI = 1.15–5.46; $P = 0.02$) compared with those in the bottom quintile. For IGFBP-3, the RR for top vs. bottom quintile was 0.28 (95% CI = 0.12–0.66; $P = 0.005$). Circulating IGF-2 level was unrelated to risk of colorectal cancer. The associations were similar even after the first 6 y of follow-up were excluded, strong evidence against any effect of undiagnosed tumor on plasma IGF.

In the Nurses' Health Study, three empirical stages of colorectal carcinogenesis were examined in relation to baseline plasma IGF-1 and IGFBP-3, i.e., low risk—small, tubular adenomas that may indicate adenoma formation or initiation; high risk—adenomas ≥1 cm in diameter or those with a villous component (tubulovillous, villous, in situ cancers), indicating adenoma progression; and adenocarcinomas (81). Cancer-free controls were matched to cases by age, time of blood draw and indication for endoscopy (for adenoma controls); prediagnostic plasma IGF-1 and IGFBP-3 levels were then measured. Controlling for IGFBP-3 level relative to women in the low tertile of IGF-1, those in the high tertile were at elevated risk of colorectal cancer (RR = 2.18; 95% CI, 0.94–5.08) and high risk adenoma (RR = 2.78; 95% CI, 0.76–9.76). Controlling for IGF-1 level, women in the high tertile of IGFBP-3 were at lower risk of colorectal cancer (RR = 0.28; 95% CI, 0.10–0.83) and high risk adenoma (RR = 0.28; 95% CI, 0.09–0.85). Neither IGF-1 nor IGFBP-3 had any appreciable relation to small, tubular adenomas.

Results from the Flexi-Scope Trial also found that high IGF-1 and low IGFBP-3 levels increased risk of high risk adenomas, defined as at least one adenoma ≥1 cm in diameter, of tubulovillous or villous morphology or with severe dysplasia, or the presence of three or more adenomas (82). Serum levels of IGF-1 and IGFBP-3 were measured for 100 individuals who then underwent a colonoscopy. For high risk adenoma, there was a positive association after controlling for IGFBP-3 [RR for a 1 SD increment = 4.39 (95% CI = 1.31–14.7); $P = 0.02$]; a significant inverse association was observed for IGFBP-3 [RR for a 1 SD increment = 0.41 (95% CI = 0.20–0.82); $P = 0.01$].

In a cohort of 14,275 women in New York, baseline IGF-1 and IGFBP were assayed from the serum of 102 women who subsequently developed colorectal cancer and 200 matched control subjects (83). Colorectal cancer showed a modest but positively increased risk with higher levels of IGF-1 but also an increased risk with higher levels of IGFBP-3. However, higher levels of IGFBP-1 and IGFBP-2 were associated with a decreased risk of colorectal cancer, suggesting that a higher level of bioavailable IGF-1 increases risk of colorectal cancer. As discussed above, insulin lowers IGFBP-1 and IGFBP-2.

A relatively small case-control study conducted in Greece of 41 patients with colorectal cancer and 50 healthy controls supported the suggestion that high levels of circulating IGF-1 and IGF-2 and lower levels of IGFBP-3 were associated with an increased risk of colorectal cancer (84). Because the blood samples were drawn after the diagnosis of cancer in the Greek study, it cannot be excluded that the tumor increased IGF levels. In addition to colorectal cancer, individuals with higher circulating IGF-1 and low IGFBP-3 levels are at increased risk of prostate cancer (85), premenopausal breast cancer (86) and lung cancer (87).

Related risk factors of the IGF axis from epidemiologic studies

Unfortunately, relatively little is known about determinants of normal variation of IGF-1 and IGFBP-3 levels (88). Genetic factors may be dominant in well-fed populations. In cases of serious energy or protein restriction, circulating IGF-1 levels are lowered substantially (50–52). However, the variation in IGF-1 and IGFBP-3 due to nutritional and other nongenetic factors in populations that do not endure periods of energy or protein shortages is unclear. Overfeeding is much less potent in increasing IGF-1 levels than underfeeding is in reducing IGF-1 levels (89). A recent study reported a moderate correlation between IGF-1 levels and alcohol consumption, but this association was observed only for men and IGFBP were not considered (90). Effective exposure of free IGF-1 is even more complicated because factors such as IGFBP-1 and IGFBP-2, influenced largely by insulin, may be critical.

Childhood and adolescent levels of IGF-1 influence linear growth and correlate with height (91). Height, however, appears to be either weakly correlated or uncorrelated with adult IGF-1 level, suggesting that the determinants of preadult IGF-1 differ from adult IGF-1 levels. Thus, adult height may be an indirect marker of IGF-1 levels during the growth period. Tallness is an independent risk factor for colorectal cancer in a number of studies (92–97), although not all studies show this association. The relative importance of the factors that determine height may differ in diverse populations de-

pending on factors such as nutritional status. Gunnell (98) noted that IGF may be more closely related to leg length than trunk length (the two components of height), and some studies indicate that leg length is the constituent most strongly related to various cancers (94,99,100). The relationship with tallness is consistent with high levels of circulating IGF-1 and perhaps other growth factors during the growth period, predisposing to higher risk of colorectal cancer.

In postmenopausal women, estrogen replacement therapy substantially lowers IGF-1 levels (101). This effect is interesting given the consistent inverse association between postmenopausal estrogen use and risk of colorectal neoplasia (102–104).

Epidemiologic evidence that insulin is associated with colorectal cancer risk

Clinical evidence [glucose intolerance, noninsulin dependent diabetes mellitus (type 2 diabetes)]. The geographic patterns for colon cancer and type 2 diabetes are strikingly similar; both diseases were considered relatively rare before industrialization or Westernization and their incidence usually increases in regions undergoing economic development. The major environmental determinants of type 2 diabetes include high body mass index (BMI), increased central obesity, physical inactivity, excessive intake of energy and dietary patterns that stimulate secretion of insulin (105). These factors are remarkably similar to the constellation of risk factors emerging for colon cancer, as discussed below.

The similar patterns for type 2 diabetes and colon cancer at the population level are consistent with a common etiology, but may also be due to common risk factors acting through independent pathways. Thus, demonstration of a prospective relationship between type 2 diabetes and colon cancer at the individual level, after controlling for common risk factors, would more convincingly implicate hyperinsulinemia. The temporal relation between type 2 diabetes and colon cancer risk is likely to be complex because early in the development of type 2 diabetes, hyperinsulinemia exists, but in later stages, β cell depletion leads to a hypoinsulinemic response. The progression from normal to impaired glucose tolerance with mild fasting hyperglycemia [fasting glucose 120–140 mg/dL (6.7–7.8 mmol/L)] to type 2 diabetes [fasting glucose >140 mg/dL (7.8 mmol/L)] is generally characterized by progressive fasting hyperinsulinemia, but the postprandial insulin response begins waning after the level of plasma glucose reaches 120 mg/dL (6.7 mmol/L). At higher levels of fasting blood glucose (i.e., greater severity type 2 diabetes), the postprandial insulin decreases to a subnormal level (106).

Many earlier studies reported a slightly higher risk of colon cancer (but not rectal cancer) in individuals with type 2 diabetes, particularly in men, but these studies were limited by reliance on death certificates (107), autopsies (108), cross-sectional data (109–111) and comparisons with external controls (112,113). These studies were generally relatively small and did not control for important covariates besides age. A positive association between prevalent type 2 diabetes and risk of colon cancer was observed in a case-control study by La Vecchia et al. (114); the RR for colon cancer among those with type 2 diabetes was 1.7 after adjustment for age, sex, area of residence, education, BMI and selected indicators of diet. In a more recent case-control study by Le Marchand et al. (115), type 2 diabetes was slightly associated with an elevated risk for colorectal cancer in men (RR = 1.2; 95% CI = 0.8–1.7) and significantly associated in women (RR = 1.8; 95% CI = 1.2–2.8), after controlling for numerous covariates including exercise and BMI. The associations were particularly strong for cases of colon cancer diagnosed at least 9 y after the diagnosis of diabetes (RR = 1.4 for men and 2.1 for women) and for the left colon in men (RR = 1.9; 95% CI = 1.1–3.5) and women (RR = 3.0; 95% CI = 1.2–7.1). One study examined risk of adenomas of the sigmoid colon and found a modestly elevated risk associated with type 2 diabetes (multivariate RR = 1.4; 95% CI = 1.0–2.0 for new type 2 diabetes and RR = 1.4; 95% CI = 0.8–2.2 for type 2 diabetes under treatment, with adjustment for various covariates including BMI) (116).

Among prospective studies, the largest was the Cancer Prevention Study (117), which encompassed 13 y of follow-up among 15,487 subjects with diabetes and 850,946 subjects without diabetes. An increased risk of colorectal cancer was noted in men (RR = 1.30; 95% CI = 1.03–1.65) and a modest nonsignificant elevation was seen in women (RR = 1.16; 95% CI = 0.87–1.53), with some covariates including physical activity and BMI controlled for. Several characteristics would have tended to attenuate any association, i.e., diabetes was assessed by a self-report from a checklist of diseases, which included insulin-dependent diabetes, and the analysis did not account for years since diabetes and included rectal cancer cases. In the prospective Nurses' Health Study (118), type 2 diabetes was associated with an elevated risk of colon cancer (age-adjusted RR = 1.60; 95% CI = 1.17–2.18); when controlled for a variety of factors, including BMI and physical activity, the RR was only slightly attenuated (RR = 1.49; 95% CI = 1.09–2.06). The association did not differ by colonic subsite and was not observed for rectal cancer (RR = 1.11). The association was strongest 11–15 y after diagnosis (multivariate RR = 2.83; 95%CI = 1.67–4.58) but became attenuated at >15 y after diagnosis (RR = 1.13; 95% CI = 0.56–2.28). The attenuation after 15 y is consistent with the increasing hypoinsulinemic response with worsening of the diabetic condition. Another recent study found that women, although not men, with a history of type 2 diabetes were at increased risk of colorectal cancer (age-adjusted RR = 1.55; 95% CI = 1.04–2.31) (119).

Serologic studies (hyperinsulinemia and hypertriglyceridemia). Data relating prediagnostic circulating insulin to risk of colorectal cancer are limited. The Cardiovascular Health Study followed ~6000 men and women ≥65 y old who had provided a blood sample (120). Various anthropometric measures were taken, and fasting glucose, 2-h glucose, fasting insulin and 2-h plasma insulin were measured. Over 7 y, 102 cases of colorectal cancer were identified. Waist circumference (RR = 2.2; 95% CI = 1.2–4.1, between high and low quintiles) and waist-to-hip (WHR) ratio (RR = 2.6; 95% CI = 1.4–4.8) were risk factors, whereas BMI had a nonsignificant positive association (RR = 1.4; 95% CI = 0.8–2.5). Fasting and 2-h glucose were significantly and linearly related to higher risk (P, trend = 0.02 for each). Fasting insulin was not related to a higher risk RR = 1.2; 95% CI = 0.7–2.1, but 2-h insulin was linearly associated with increased risk (RR = 2.0; 95% CI = 1.0–3.8) (P, trend = 0.04). As predicted (121), postprandial insulin, which encompasses both insulin resistance and secretory capacity of the pancreas, was a stronger predictor than fasting insulin.

A study based on prospectively collected serum samples from 14,275 women in New York examined the insulin-colorectal cancer hypothesis (83). The analysis was based on 102 women with colorectal cancer and 200 control subjects. Colorectal cancer risk increased with increasing levels of C-peptide, a marker for insulin secretion. The OR was 2.92 (95% CI = 1.26–6.75) for the highest vs. the lowest quintile (P, trend < 0.001). For colon cancer alone (n = 75 subjects), the

OR was 3.96 (95% CI = 1.49–10.50). A decrease in colorectal cancer risk was observed for increasing IGFBP-1 (OR = 0.48; 95% CI = 0.23–1.00; *P*, trend = 0.02) and IGFBP-2 (OR = 0.38; 95% CI = 0.15–0.94; *P*, trend = 0.06). As noted above, insulin levels are inversely associated with these IGFBP.

Several studies have examined colorectal adenoma or cancer in relation to hypertriglyceridemia, which may be considered a marker of insulin resistance (122,123). A Japanese case-control study compared serum lipids in 129 men and women with colorectal carcinoma in situ with levels in 258 matched control subjects (124). Even after adjustment for age, sex, BMI, alcohol consumption and smoking status, there was a strong direct association between plasma triglycerides and risk of colorectal carcinoma in situ. Compared with individuals in the bottom quartile [≤70 mg/dL (0.79 mmol/L)], the RR was 3.0 (95% CI = 1.4–6.4) for those in the top quartile [>150 mg/dL (1.70 mmol/L)]; *P* = 0.0008. A weaker association was observed for serum glucose (RR = 2.0; 95% CI = 0.9–4.4; *P* = 0.11). A German study found that low levels of HDL and high levels of VLDL (the major lipoprotein carrier of triglycerides) were associated with a two- to threefold higher risk of colorectal adenoma (125). Two other studies of serum lipids and risk of colorectal adenoma reported a moderate association with serum triglycerides (126,127).

Related risk factors of circulating insulin levels and hyperinsulinemia from epidemiologic studies. Insulin levels are strongly influenced by a variety of factors (**Fig. 2**). Fasting serum insulin level is largely determined by the degree of insulin resistance. Factors that increase insulin resistance will produce a compensatory fasting and postprandial hyperinsulinemia provided that adequate function of pancreatic β cells exists (i.e., a nondiabetic state). Excess adiposity, particularly visceral adipose, is a major determinant of insulin resistance. Physical activity strongly increases insulin sensitivity. Beyond the critical influence of overall energy intake, specific dietary factors or patterns may affect insulin resistance as well as determine the amount and nature of the postprandial rise in insulin. The effect of each of these factors on hyperinsulinemia and on risk of colon cancer is discussed.

Body mass, distribution of adiposity and risk of colonic neoplasia. A major determinant of insulin resistance, perhaps the most important, is energy balance. Negative energy balance profoundly decreases insulin levels, whereas positive energy balance increases circulating insulin. For epidemiologic purposes, chronic energy balance is very difficult to assess and is best approximated by level of obesity. In addition to BMI, visceral adiposity is a particularly critical determinant of insulin resistance and hyperinsulinemia (128). The correlation coefficients between plasma insulin levels and estimated measures of visceral adiposity, such as waist circumference or WHR are relatively high, ranging from 0.50 to 0.70 (129–131).

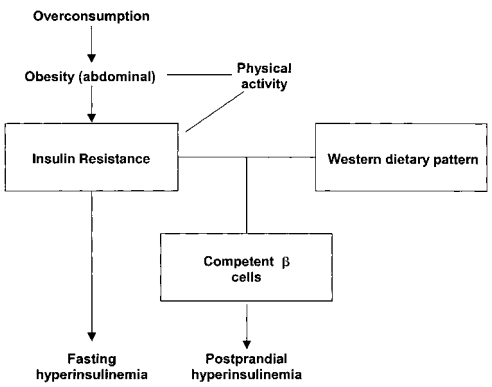

FIGURE 2 Determinants of hyperinsulinemia.

An association between obesity and risk of colon cancer is compelling, particularly in men, with evidence derived from prospective (92,132–141) and retrospective (142–146) studies. In a prospective study by Lee and Paffenbarger (133), men who were in the heaviest quintile of BMI during both college years and middle age had a RR of 2.40 (95% CI = 1.40–4.13) compared with men consistently in the lowest quintile. In another prospective study of colorectal cancer, men in the upper tertile of BMI had a RR of 2.40 (95% CI = 1.1–5.4) (132). Among U.S. male health professionals (92), the age-adjusted RR for BMI 29 or higher vs. < 22 was 1.82 (95% CI = 1.14–2.91; *P* < 0.001), but this association was somewhat attenuated in a multivariate model that included physical activity level among other covariates (RR = 1.48; 95% CI = 0.89–2.46; *P* = 0.02). In that study, when upper and lower quintiles were compared, the RR for colon cancer in relation to WHR was 3.41 (95% CI = 1.52–7.66) and for waist circumference it was 2.56 (95% CI = 1.33–4.96). These RR were only modestly attenuated when controlled for BMI. In one study of Japanese men (141), although a significant trend existed between BMI and colon cancer risk (*P* = 0.005), the association was relatively modest in size (RR = 1.38; 95% CI = 1.01–1.90). However, the cut-off points for the top vs. bottom category were ≥ 25.80 and < 21.70, which is much narrower than in most other studies. In the Cardiovascular Health Study (120), waist circumference (RR = 2.2; 95% CI = 1.2–4.1, between high and low quintiles) and WHR (RR = 2.6; 95% CI = 1.4–4.8) were risk factors, whereas BMI had a nonsignificant positive association (RR = 1.4; 95% CI = 0.8–2.5).

Of prospective studies that reported results separately for women, four reported direct associations between BMI and colon cancer risk (147–150), but some have not supported this association (132,134,136). In general, the association between BMI and colon cancer appears to be more consistently observed and stronger for men than for women. In the Nurses' Health Study, women who had a BMI > 29 had a RR of 1.45 (95% CI = 1.02–2.07) in comparison with women whose BMI was < 21. Data on body fat distribution and colon cancer risk are very limited. Two studies in women (147,149) reported suggestive but not significant positive associations between WHR and risk of colon cancer. Case-control studies have been somewhat less consistent with six supporting but nine not supporting an association, according to one summary (150). However, case-control data have been nearly as conflicting for men, for whom the prospective data are quite compelling. In part, the case-control literature may be less consistent because before 1990, most of the case-control studies relied on body weights that antedated the diagnosis of cancer by ≤3 y, and weight loss to undiagnosed cancers may have obscured associations.

In women, the association between BMI and colon cancer appears to exist at younger ages but is less evident at older ages (132,134,136,148–151), suggesting that the effect of obesity may differ by menopausal status. In postmenopausal women, in addition to being associated with high insulin, high BMI is also associated with higher estrogen levels, which, as suggested by the hormonal replacement studies, may confer some benefit against colorectal cancer (102–104). Thus, the apparently more complex relationship between BMI and colon cancer in women may stem from potentially complex interactions among insulin, IGF-1 and estrogen.

Obesity has also been examined in relation to risk of adenoma, either as a primary report or within the context of other findings. In all of these studies, the control group was free of adenomas as assessed by endoscopy. Five studies that assessed risk by adenoma size (92,125,152–154) found RR of two- to threefold for some measure of obesity and risk of large adenoma (≥1 cm) or high risk adenoma (≥2 cm, tubullovillous or villous, or multiple) but not for small adenoma. Neugut et al. (153) found a strong association between high BMI and risk of large adenoma in women (RR = 3.1) but a slight and not significant association in men (RR = 1.6). A case-control study by Sandler et al. (155) found that female cases had a higher mean BMI than controls (27.6 vs. 26.4), but the BMI was identical for male cases and controls (25.3).

Risk of adenoma seemed to be more strongly associated with central adiposity. In Japanese men (154), when modeled simultaneously, the RR of large adenoma for higher vs. low quartile for WHR was 3.4 (95% CI = 1.5–7.6), whereas that for BMI was 1.2 (95% CI = 0.5–2.5). For U.S. male health professionals, BMI had only a nonsignificant association with large adenomas (RR = 1.43; 95% CI = 0.78–1.62), whereas strong positive associations were found with waist circumference (RR = 2.48; 95% CI = 1.15–5.36; *P*, trend = 0.007) and WHR (RR = 3.42; 95% CI = 1.57–7.47; *P*, trend = 0.01). In women of the Nurses' Health Study (152), BMI was directly associated with risk of large distal colon adenoma (multivariate RR = 2.21; 95% CI = 1.18–4.16) for BMI ≥29 vs. <21). Waist circumference and WHR were not related to risk of large adenoma independently of BMI, but women with both a high BMI and high WHR were at greater risk (RR = 1.99; 95% CI = 0.98–4.05) than women with high BMI and relatively lower WHR (RR = 1.35, 95% CI = 0.61–2.97). Weight gain also is associated with increased risk of colon adenoma (156–158).

In summary, the overwhelming majority of studies indicate that higher BMI is associated with an elevated risk of colon cancer, although this association is less convincing for older women. This association is also observed for adenomas, particularly large adenomas, suggesting that some aspect of obesity is associated with promotion of adenomas. In a number of studies, particularly strong associations were observed for measures of visceral or central adiposity, consistent with a role of hyperinsulinemia.

Physical activity and risk of colonic neoplasia. Physical activity level contributes to insulin sensitivity in two ways. First, the level of physical activity is one of the determinants of obesity, which increases insulin resistance. Moreover, physical activity appears to result in a preferential loss of visceral adipose relative to subcutaneous adipose (159). Second, independent of its influence on adiposity, physical activity directly increases insulin sensitivity (160) and reduces plasma insulin levels (161–164). The increase in insulin sensitivity induced by an episode of exercise lasts for several days (165,166), and improvements in insulin sensitivity are enhanced with higher levels of physical activity (167,168). Skeletal muscle is the principal site of insulin-mediated glucose disposal (169). In normal subjects, variability in insulin-stimulated glycogen synthesis in muscle tissue accounts for most of the variance in insulin sensitivity (170), and in type 2 diabetes patients, impairment of this pathway is the major contributor to insulin resistance (171). Chronic physical inactivity contributes to insulin resistance, hyperinsulinemia, depletion of pancreatic β cells and ultimately to type 2 diabetes (106,172–175).

Results of prospective (119,132,133,149,176–183) and retrospective (142,143,184–194) studies support an association between physical inactivity and risk of colon cancer. In the Nurses' Health Study (195), women who were in the upper quintile of leisure-time physical activity were at almost half the risk of developing colon cancer compared with relatively inactive women (RR = 0.54; 95% CI = 0.33–0.90). When physical activity and BMI are assessed jointly, the highest risk of colon cancer occurs among those both physically inactive and with high BMI levels (92,151). In composite, the studies suggest a dose-response relationship with risk reduction across a wide range of activity levels and intensities. On the basis of an extensive review of the literature, Colditz et al. (196) reported an ~50% reduction in incidence of colon cancer among the most active individuals. Increased physical activity has also been associated with a reduced risk of colon adenoma, particularly large adenomas (92,152,197–199).

Many characteristics of the inverse association between physical activity level and risk of colon cancer indicate that it is causal. This association is consistent in numerous studies conducted in diverse populations for large adenomas and cancer in men and women and using retrospective and prospective assessments of activity. When assessed, dietary factors did not confound the inverse association between physical activity and colon cancer (92,149,151,176). Perhaps the most compelling evidence against an unmeasured confounding factor is that this relationship has been observed independently for occupational activity and for recreational activity (196). It is highly unlikely that a confounding factor would generate a similarly spurious relationship for both recreational and occupational activities in diverse populations.

Dietary determinants of hyperinsulinemia and risk of colon cancer. Energy balance is likely to be quantitatively the most important determinant of insulin resistance, but dietary patterns may also influence insulin resistance or the size of the postprandial spikes in insulin. The nature of carbohydrates and the specific fatty acids are particularly important. Dietary glucose, in the form of either simple sugars or starch, is eventually absorbed into the blood from the intestines, producing a compensatory increase of blood insulin. The effect of diet on the rapidity of the rise in blood glucose is complex—simple sugars tend to be absorbed quickly and starch that is easily digestible can also lead to a rapid rise in blood glucose.

Sucrose and fructose. Sucrose and fructose are the major sweeteners in most populations. In animals, diets very high in sucrose or fructose induce hypertriglyceridemia and hyperinsulinemia (200). The decreased insulin sensitivity caused by high sucrose diets is likely related to the fructose component of sucrose (201). In humans, the effect of sucrose or fructose on insulin sensitivity is less clear, possibly resulting from less variation in diet, heterogeneity in study populations and complexities of study design. Nonetheless, some evidence suggests that at least for carbohydrate-sensitive individuals (those with hypertriglyceridemia and hyperinsulinemia), high sucrose or high fructose diets may further decrease insulin sensitivity (202–205). Of note, sucrose intake is significantly correlated with fasting insulin even after adjustment for other predictors of insulin levels (including BMI, WHR and other dietary variables) (206), suggesting that sucrose influences insulin sensitivity. However, although the effect of sucrose on insulin sensitivity in humans is controversial, high sucrose diets do induce high peaks and lower troughs for serum insulin (204).

Animals studies have found with relative consistency that dietary sucrose is a colon tumor promotor (207–211). Because sucrose is absorbed in the small intestine well before it reaches the large intestine, any influence on the large bowel is likely to be through circulatory factors. Sucrose intake definitely increases insulin resistance in animals (200) and, as discussed

above, hyperinsulinemia enhances colon carcinogenesis in animal studies.

Human studies of colon cancer also suggest an adverse effect of sucrose. In 1994, Bostick et al. (147) summarized the literature and reported that high sucrose intakes were associated with an increased risk of colon cancer in 12 of 14 epidemiologic studies that presented relevant data. An additional study found that frequency of eating snacks, which tend to consist of refined, high sucrose foods, was associated with a higher risk of colon cancer (212). Subsequently, a case-control study conducted in Uruguay found that sucrose intake was associated with an increased risk of colorectal cancer, and the RR for the upper vs. lower quartile was 2.18 (95% CI = 1.35–3.51). A large case-control study in Italy found a significant trend of increasing risk of colon cancer with increasing intake of cakes, desserts and refined sugar (213,214). In a recent large case-control study conducted in the United States (215), the dietary sucrose-to-fiber ratio was associated with an increased risk of colon cancer, particularly in men and women who were sedentary and thus relatively insulin resistant. For men and women, relative to those who were active and lean and had a low sucrose-to-fiber ratio, the RR was 4.58 (95% CI = 2.33–8.98) for those who were sedentary and consumed a high dietary sucrose-to-fiber ratio, but among sedentary people with a low dietary sucrose-to-fiber ratio, the RR was only 2.40 (95% CI = 1.17–4.89).

One study examined dietary, lifestyle and demographic factors in relation to colorectal epithelial cell proliferation kinetics. Sucrose was associated with higher proliferation rates (labeling index) and with the shift of the proliferation zone from one confined to the lower 60% of the colonic crypt to one that includes the entire crypt (216). Both these kinetic indicators are similarly altered in individuals at increased risk for colon cancer. Among many dietary factors assessed, sucrose had the strongest effect in the upward shift of the proliferation zone. However, in a study in which 107 patients were randomly assigned to a low sucrose diet or were instructed to continue their usual diet for 1 mo, overall proliferation or the distribution of proliferation along the crypt was not affected (217).

Starch. In typical diets of most populations, starch is the greatest source of glucose. Of note, the major sources of starch in various populations have been related to a higher risk of colon cancer, including rice in Japan (218), pasta, rice, bread, polenta, potatoes and cereals in Southern Europe (213,214), potatoes in Australia (219) and total starch in Russia (220). A meal high in refined sugars and carbohydrates produces a sharp glycemic response due to readily absorbable glucose, but the absolute starch or sugar content of a food alone will be a poor determinant of the blood glucose response. The assessment of starchy foods has revealed large differences in the rates of digestion, based primarily on the form of starch (amylose vs. amylopectin), complementary dietary factors such as fiber content, phytates, lectins, tannins, saponins and enzyme inhibitors, how food is processed and possibly host factors (221). A large case-control study in Italy found a significant trend of increasing risk of colon cancer with increasing intake of bread and cereal dishes, potatoes, cakes and desserts and refined sugar but a slight inverse association with whole-meal bread (213,214), suggesting that more refined sources of sugars and starch tend to increase risk. In an ecological study conducted in 65 rural counties in China, county per capita intakes of rice, processed starch and sugar were correlated with colon cancer incidence rates (222).

Glycemic index. A more direct way to account for the effect on blood glucose and insulin levels by various foods is through the glycemic index (223). Low glycemic index foods are digested more slowly, thus reducing the immediate postprandial glycemic response; that is, the slower the rate of digestion, the flatter the blood glucose response will be. In a recent large case-control study conducted in the United States (215), a dietary glycemic index was developed on the basis of responses to a dietary questionnaire. Men and women who consumed a diet with a high glycemic index were at elevated risk of colon cancer, and those at highest risk from a high dietary glycemic index were those who were sedentary (for men, relative to those who were sedentary and had a low-glycemic index diet, RR = 3.46; 95% CI = 1.78–6.70, and for women RR = 2.00; 95% CI = 0.98–4.07). For those who were physically active, the glycemic index was not an important risk factor. Similar patterns were observed with a high dietary sucrose-to-fiber ratio in this study, as described above. An insulinemic index may be a more optimal way to test the hyperinsulinemia hypothesis, but currently data are not sufficient for constructing such an index.

Dietary patterns. Although individual dietary factors have been studied in relation to outcomes such as insulin sensitivity and colon cancer risk, the whole dietary pattern, involving all of the interactions and synergisms, has recently become of interest. Of note, some recent studies using factor analysis have related risk of cancer to specific dietary patterns. For example, a dietary pattern termed the Western diet has been associated with increased risk of colon cancer (224). A Western dietary pattern includes a diverse array of factors, including red and processed meats, high saturated and *trans* fats, and highly processed carbohydrates and sugars. Interestingly, in the Nurses' Health Study, such a dietary pattern was also been shown to be related to higher circulating insulin levels (225).

Summary

In summary, insulin and the IGF axis mediate many of the physiologic consequences of nutritional status. In this review, a diverse body of evidence that related high levels of insulin and IGF-1 to colon cancer risk was summarized. Mechanistically, as major determinants of proliferation and apoptosis, there is a strong rationale to suspect that these factors influence carcinogenesis. In various animal models, modulation of insulin and IGF-1 levels through various means, including direct infusion, energy excess or restriction, dietary quality, including sucrose content, genetically induced obesity, inhibition of normal insulin secretion and pharmacologic inhibition of IGF-1 influences colonic carcinogenesis. Human studies consistently show that high levels of insulin and IGF-1 increase risk of colon cancer. People with type 2 diabetes and people with acromegaly, who have high levels of insulin and IGF-1, respectively, are at elevated risk of colon cancer in most studies. Recently, studies that have directly assessed circulating concentrations of C-peptide, 2-h insulin and IGF-1 (and IGFBP-3, IGFBP-1 and IGFBP-2) found that these predict risk of colon cancer and adenoma. Determinants (physical inactivity, high BMI, central adiposity) and markers (hypertriglyceridemia) of insulin resistance and of high IGF-1 levels (tall stature) are consistently related to higher risk of colon neoplasia. The relation between diet quality and insulin is complex and has not been studied systematically in relation to colon cancer. Nonetheless, many studies indicate that high consumption of sucrose, various starches and diets with a high glycemic index and general dietary patterns that stimulate insulin secretion are associated with a higher risk of colon cancer. These dietary patterns may be particularly deleterious

in those with a sedentary lifestyle and who thus are relatively insulin resistant.

In aggregate, evidence strongly implicates insulin and the IGF axis as critical determinants of colon cancer. Although additional environmental and genetic factors are likely to affect colon cancer, the incidence of this malignancy was invariably low before the technological advances that rendered sedentary lifestyles and obesity common and that made highly processed carbohydrates widely available. These factors affect cardiovascular disease, diabetes mellitus, colon cancer and perhaps other cancers. Public health efforts to counter these patterns are likely to have the most potential to improve general health status as well as reduce colon cancer incidence.

LITERATURE CITED

1. Hill, M. J. (1977) The role of unsaturated bile acids in the etiology of large bowel cancer. In: Origins of Human Cancer (Hiatt, H. H., Watson, J. D.& Winsten, J. A., eds.), pp. 1627–1640. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

2. Reddy, B. S. (1981) Diet and excretion of bile acids. Cancer Res. 41: 3766–3768.

3. Chomchai, C., Bhadrachari, N. & Nigro, N. D. (1974) The effect of bile on the induction of experimental intestinal tumors in rats. Dis. Colon Rectum 17: 310–312.

4. Narisawa, T., Magadia, N. E., Weisburger, J. H. & Wynder, E. L. (1974) Promoting effect of bile acids on colon carcinogenesis after intrarectal instillation of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine in rats. J. Natl. Cancer Inst. 53: 1093–1097.

5. Liu, K., Stamler, J., Moss, D., Garside, D., Persky, V. & Soltero, I. (1979) Dietary cholesterol, fat, and fibre, and colon-cancer mortality. An analysis of international data. Lancet 2: 782–785.

6. Fuchs, C. S., Colditz, G. A., Stampfer, M. J., Speizer, F. E., Giovannucci, E., Hunter, D. J., Rosner, B. & Willett, W. C. (1999) Dietary fiber and the risk of colorectal cancer and adenoma in women. N. Engl. J. Med. 340: 169–176.

7. Alberts, D. S., Martinez, M. E., Roe, D. J., Guillen-Rodriguez, J. M., Marshall, J. R., van Leeuwen, J. B., Reid, M. E., Ritenbaugh, C., Vargas, P. A., Bhattacharyya, A. B., Earnest, D. L. & Sampliner, R. E. (2000) Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. N. Engl. J. Med. 342: 1156–1162.

8. Aaronson, S. (1991) Growth factors and cancer. Science (Washington, DC) 254: 1146–1153.

9. Jones, J. & Clemmons, D. (1995) Insulin-like growth factors and their binding proteins: biological actions. Endocr. Rev. 16: 3–34.

10. Rechler, M. (1997) Growth inhibition by insulin-like growth factor (IGF) binding protein-3–what's IGF got to do with it? Endocrinology 138: 2645–2647.

11. Rajah, R., Valentinis, B. & Cohen, P. (1997) Insulin-like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor-β1 on programmed cell death through a p53 and IGF-independent mechanism. J. Biol. Chem. 272: 12181–12188.

12. Pollak, M. N., Perdue, J. F., Margolese, R. G., Baer, K. & Richard, M. (1987) Presence of somatomedin receptors on primary human breast and colon carcinomas. Cancer Lett. 38: 223–230.

13. Guo, Y. S., Narayan, S., Yallampalli, C. & Singh, P. (1992) Characterization of insulin-like growth factor I receptors in human colon cancer. Gastroenterology 102: 1101–1108.

14. Watkins, L., Lewis, L. & Levine, A. (1990) Characterization of the synergistic effect of insulin and transferrin and the regulation of their receptors on a human colon carcinoma cell line. Int. J. Cancer 45: 372–375.

15. Koenuma, M., Yamori, T. & Tsuruo, T. (1989) Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Jpn. J. Cancer Res. 80: 51–58.

16. Bjork, J., Nilsson, J., Hultcrantz, R. & Johansson, C. (1993) Growth-regulatory effects of sensory neuropeptides, epidermal growth factor, insulin, and somatostatin on the non-transformed intestinal epithelial cell line IEC-6 and the colon cancer cell line HT 29. Scand. J. Gastroenterol. 28: 879–884.

17. Vogelstein, B., Fearon, E. R., Hamilton, S. R., Kern, S. E., Preisinger, A. C., Leppert, M., Nakamura, Y., White, R., Smits, A. M. M. & Bos, J. L. (1988) Genetic alterations during colorectal-tumor development. N. Engl. J. Med. 319: 525–532.

18. Cats, A., Dullaart, R., Kleibeuker, J., Kuipers, F., Sluiter, W., Hardonk, M. & de Vries, E. (1996) Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res. 56: 523–526.

19. Warren, R., Yuan, H., Matli, M., Ferrara, N. & Donner, D. (1996) Induction of vascular endothelial growth factor by insulin-like growth factor 1 in colorectal carcinoma. J. Biol. Chem. 271: 29483–29488.

20. Baserga, R. (1995) The insulin-like growth factor I receptor: a key to tumor growth? Cancer Res. 55: 249–252.

21. MacDonald, R. S., Thornton, W. H., Jr. & Bean, T. L. (1993) Insulin and IGF-I receptors in a human intestinal adenocarcinoma cell line (Caco-2) regulation of Na+ glucose transport across the brush border. J. Recept. Res. 13: 1093–1113.

22. Macaulay, V. M. (1992) Insulin-like growth factors and cancer. Br. J. Cancer 65: 311–320.

23. Soos, M. A., Whittaker, J., Lammers, R., Ullrich, A. & Siddle, K. (1990) Receptors for insulin and insulin-like growth factor-I can form hybrid dimers. Characterisation of hybrid receptors in transfected cells. Biochem. J. 270: 383–390.

24. Bach, L. A. & Rechler, M. M. (1992) Insulin-like growth factors and diabetes. Diabetes Metab. Rev. 8: 229–257.

25. Flier, J. S., Usher, P. & Moses, A. C. (1986) Monoclonal antibody to the type I insulin-like growth factor (IGF-I) receptor blocks IGF-I receptor-mediated DNA synthesis: clarification of the mitogenic mechanisms of IGF-I and insulin in human skin fibroblasts. Proc. Natl. Acad. Sci. U.S.A. 83: 664–668.

26. Moller, D. E. & Flier, J. S. (1991) Insulin resistance—mechanisms, syndromes, and implications. N. Engl. J. Med. 325: 938–948.

27. Underwood, L. E., Thissen, J. P., Lemozy, S., Ketelslegers, J. M. & Clemmons, D. R. (1994) Hormonal and nutritional regulation of IGF-I and its binding proteins. Horm. Res. 42: 145–151.

28. Smith, W. J., Underwood, L. E. & Clemmons, D. R. (1995) Effects of caloric or protein restriction on insulin-like growth factor-1 (IGF-1) and IGF-binding proteins in children and adults. J. Clin. Endocrinol. Metab. 80: 443–449.

29. Ooi, G. T., Tseng, L. Y., Tran, M. Q. & Rechler, M. M. (1992) Insulin rapidly decreases insulin-like growth factor binding protein-1 gene transcription in streptozotocin-diabetic rats. Mol. Endocrinol. 6: 2219–2228.

30. Powell, D. R., Suwanichkul, A., Cubbage, M. L., DePaolis, L. A., Snuggs, M. B. & Lee, P. D. (1991) Insulin inhibits transcription of the human gene for insulin-like growth factor-binding protein-1. J. Biol. Chem. 266: 18868–18876.

31. Katz, L.E.L., Cohen, P. & Rosenfeld, R. (1995) Clinical significance of IGF binding proteins. Endocrinologist 5: 36–43.

32. Cohen, P., Fielder, P. J., Hasegawa, Y., Frisch, H., Giudice, L. C. & Rosenfeld, R. G. (1991) Clinical aspects of insulin-like growth factor binding proteins. Acta Endocrinol. 124 (suppl. 2): 74–85.

33. Lee, P. D., Conover, C. A. & Powell, D. R. (1993) Regulation and function of insulin-like growth factor-binding protein-1. Proc. Soc. Exp. Biol. Med. 204: 4–29.

34. Cotterill, A. M., Holly, J. M. & Wass, J. A. (1993) The regulation of insulin-like growth factor binding protein (IGFBP)-1 during prolonged fasting. Clin. Endocrinol. 39: 357–362.

35. Busby, W. H., Snyder, D. K. & Clemmons, D. R. (1988) Radioimmunoassay of a 26,000-dalton plasma insulin-like growth factor-binding protein: control by nutritional variables. J. Clin. Endocrinol. Metab. 67: 1225–1230.

36. Suikkari, A. M., Sane, T., Seppala, M., Yki-Jarvinen, H., Karonen, S. L. & Koivisto, V. A. (1989) Prolonged exercise increases serum insulin-like growth factor-binding protein concentrations. J. Clin. Endocrinol. Metab. 68: 141–144.

37. Batch, J. A., Baxter, R. C. & Werther, G. (1991) Abnormal regulation of insulin-like growth factor binding proteins in adolescents with insulin-dependent diabetes. J. Clin. Endocrinol. Metab. 73: 964–968.

38. Brismar, K., Gutniak, M., Povoa, G., Werner, S. & Hall, K. (1988) Insulin regulates the 35 kDa IGF binding protein in patients with diabetes mellitus. J. Endocrinol. Investig. 11: 599–602.

39. Suikkari, A. M., Koivisto, V. A., Rutamen, E. M., Yki-Jarvinen, H., Karonen, S. L. & Seppala, M. (1988) Insulin regulates the serum levels of low-molecular weight insulin-like growth factor-binding protein. J. Clin. Endocrinol. Metab. 66: 266–272.

40. Argente, J., Caballo, N., Barrios, V., Munoz, M. T., Pozo, J., Chowen, J. A. & Hernandez, M. (1997) Disturbances in the growth hormone-insulin-like growth factor axis in children and adolescents with different eating disorders. Horm. Res. 48: 16–18.

41. Counts, D. R., Gwirtsman, H., Carlsson, L. M., Lesem, M. & Cutler, G. B. J. (1992) The effect of anorexia nervosa and refeeding on growth hormone-binding protein, the insulin-like growth factors (IGFs) and the IGF-binding proteins. J. Clin. Endocrinol. Metab. 75: 762–767.

42. Strasser-Vogel, B., Blum, W. F., Past, R., Kessler, U., Hoeflich, A., Meiler, B. & Kiess, W. (1995) Insulin-like growth factor (IGF)-I and -II and IGF-binding proteins-1, -2, and -3 in children and adolescents with diabetes mellitus: correlation with metabolic control and height attainment. J. Clin. Endocrinol. Metab. 80: 1207–1213.

43. Nam, S. Y., Lee, E. J., Kim, K. R., Cha, B. S., Song, Y. D., Lim, S. K., Lee, H. C. & Huh, K. B. (1997) Effect of obesity on total and free insulin-like growth factor (IGF)-I and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. Int. J. Obes. Relat. Metab. Disord. 21: 355–359.

44. Burgering, B. M., Medema, R. H., Maassen, J. A., van de Wetering, M. L., van der Eb, A. J., McCormick, F. & Bos, J. L. (1991) Insulin stimulation of gene expression mediated by p21ras activation. EMBO J. 10: 1103–1109.

45. Jhun, B. H., Meinkoth, J. L., Leitner, J. W., Draznin, B. & Olefsky, J. M. (1994) Insulin and insulin-like growth factor-I signal transduction requires p21ras. J. Biol. Chem. 269: 5699–5704.

46. Bos, J. L. (1988) The ras gene family and human carcinogenesis. Mutat. Res. 195: 255–271.

47. Gutierrez, L., Magee, A. I., Marshall, C. J. & Hancock, J. F. (1989) Post-translational processing of p21ras is two-step and involves carboxyl-methylation and carboxy-terminal proteolysis. EMBO J. 8: 1093–1098.

48. Leitner, J. W., Kline, T., Carel, K., Goalstone, M. & Draznin, B. (1997)

Hyperinsulinemia potentiates activation of p21Ras by growth factors. Endocrinology 138: 2211–2214.

49. Goalstone, M. L., Wall, K., Leitner, J. W., Kurowski, T., Ruderman, N., Pan, S. J., Ivy, J. L., Moller, D. E. & Draznin, B. (1999) Increased amounts of farnesylated p21Ras in tissues of hyperinsulinaemic animals. Diabetologia 42: 310–316.

50. Isley, W. L., Underwood, L. E. & Clemmons, D. R. (1983) Dietary components that regulate serum somatomedin-C concentrations in humans. J. Clin. Investig. 71: 175–182.

51. Clemmons, D. R., Underwood, L. E., Dickerson, R. N., Brown, R. O., Hak, L. J., MacPhee, R. D. & Heizer, W. D. (1985) Use of plasma somatomedin-C/insulin-like growth factor I measurements to monitor the response to nutritional repletion in malnourished patients. Am. J. Clin. Nutr. 41: 191–198.

52. Unterman, T. G., Vazquez, R. M., Slas, A. J., Martyn, P. A. & Phillips, L. S. (1985) Nutrition and somatomedin. XIII. Usefulness of somatomedin-C in nutritional assessment. Am. J. Med. 78: 228–234.

53. Ruggeri, B. A., Klurfeld, D. M., Kritchevsky, D. & Furlanetto, R. W. (1989) Caloric restriction and 7,12-dimethylbenz(a)anthracene-induced mammary tumor growth in rats: alterations in circulating insulin, insulin-like growth factors I and II, and epidermal growth factor. Cancer Res. 49: 4130–4134.

54. Klurfeld, D. M., Lloyd, L. M., Welch, C. B., Davis, M. J., Tulp, O. L. & Kritchevsky, D. (1991) Reduction of enhanced mammary carcinogenesis in LA/N-cp (corpulent) rats by energy restriction. Proc. Soc. Exp. Biol. Med. 196: 381–384.

55. Mukherjee, P., Sotnikov, A. V., Mangian, H. J., Zhou, J. R., Visek, W. J. & Clinton, S. K. (1999) Energy intake and prostate tumor growth, angiogenesis, and vascular endothelial growth factor expression. J. Natl. Cancer. Inst. 91: 512–523.

56. Dunn, S. E., Kari, F. W., French, J., Leininger, J. R., Travlos, G., Wilson, R. & Barrett, J. C. (1997) Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. Cancer Res. 57: 4667–4672.

57. Hursting, S. D., Switzer, B. R., French, J. E. & Kari, F. W. (1993) The growth hormone: insulin-like growth factor 1 axis is a mediator of diet restriction-induced inhibition of mononuclear cell leukemia in Fischer rats. Cancer Res. 53: 2750–2757.

58. Dy, D., Whitehead, R. & Morris, D. (1992) SMS 201.995 inhibits in vitro and in vivo growth of human colon cancer. Cancer Res. 52: 917–923.

59. Pollak, M. N., Polychronakos, C. & Guyda, H. (1989) Somatostatin analogue SMS 201–995 reduces serum IGF-I levels in patients with neoplasms potentially dependent on IGF-I. Anticancer Res. 9: 889–891.

60. Corpet, D., Jacquinet, C., Peiffer, G. & Taché, S. (1997) Insulin injections promote the growth of aberrant crypt foci in the colon of rats. Nutr. Cancer 27: 316–320.

61. Tran, T. T., Medline, A. & Bruce, R. (1996) Insulin promotion of colon tumors in rats. Cancer Epidemiol. Biomark. Prev. 5: 1013–1015.

62. Koohestani, N., Tran, T. T., Lee, W., Wolever, T. M. & Bruce, W. R. (1997) Insulin resistance and promotion of aberrant crypt foci in the colons of rats on a high-fat diet. Nutr. Cancer 29: 69–76.

63. Koohestani, N., Chia, M. C., Pham, N. A., Tran, T. T., Minkin, S., Wolever, T. M. & Bruce, W. R. (1998) Aberrant crypt focus promotion and glucose intolerance: correlation in the rat across diets differing in fat, n-3 fatty acids and energy. Carcinogenesis 19: 1679–1684.

64. Corpet, D. E., Peiffer, G. & Taché, S. (1998) Glycemic index, nutrient density, and promotion of aberrant crypt foci in rat colon. Nutr. Cancer 32: 29–36.

65. Lee, W. M., Lu, S., Medline, A. & Archer, M. C. (2001) Susceptibility of lean and obese Zucker rats to tumorigenesis induced by *N*-methyl-*N*-nitrosurea. Cancer Lett. 162: 155–160.

66. Klein, I., Parveen, G., Gavaler, J. & Vanthiel, D. (1982) Colonic polyps in patients with acromegaly. Ann. Intern. Med. 97: 27–30.

67. Ituarte, E., Petrini, J. & Hershman, J. (1984) Acromegaly and colon cancer. Ann. Intern. Med. 101: 627–628.

68. Pines, A., Rozen, P., Ron, E. & Gilat, T. (1985) Gastrointestinal tumors in acromegalic patients. Am. J. Gastroenterol. 80: 266–269.

69. Ritter, M., Richter, W. & Schwandt, P. (1987) Acromegaly and colon cancer. Ann. Intern. Med. 106: 636–637.

70. Ziel, F. & Peters, A. (1988) Acromegaly and gastrointestinal adenocarcinomas. Ann. Intern. Med. 109: 514–515.

71. Brunner, J., Johnson, C., Zafar, S., Peterson, E., Brunner, J. & Mellinger, R. (1990) Colon cancer and polyps in acromegaly: increased risk associated with family history of colon cancer. Clin. Endocrinol. 32: 65–71.

72. Terzolo, M., Tappero, G., Borretta, G., Asnaghi, G., Pia, A., Reimondo, G., Boccuzzi, A., Cesario, F., Rovero, E., Paccotti, P. & Angeli, A. (1994) High prevalence of colonic polyps in patients with acromegaly. Influence of sex and age. Arch. Intern. Med. 154: 1272–1276.

73. Jenkins, P., Fairclough, P., Richards, T., Lowe, D., Monson, J., Grossman, A., Wass, J. & Besser, M. (1997) Acromegaly, colonic polyps and carcinoma. Clin. Endocrinol. 47: 17–22.

74. Ron, E., Gridley, G., Hrubec, Z., Page, W., Arora, S. & Fraumeni, J., Jr. (1991) Acromegaly and gastrointestinal cancer. Cancer 68: 1673–1677.

75. Barzilay, J., Heatley, G. & Cushing, G. (1991) Benign and malignant tumors in patients with acromegaly. Arch. Intern. Med. 151: 1629–1632.

76. Cheung, N. W. & Boyages, S. C. (1997) Increased incidence of neoplasia in females with acromegaly. Clin. Endocrinol. 47: 323–327.

77. Vasen, H. F., van Erpecum, K. J., Roelfsema, F., Raue, F., Koppeschaar, H., Griffioen, G. & van Berge Henegouwen, G. P. (1994) Increased prevalence of colonic adenomas in patients with acromegaly. Eur. J. Endocrinol. 131: 235–237.

78. Orme, S. M., McNally, R. J., Cartwrigh, R. A. & Belchetz, P. E. (1998) Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J. Clin. Endocrinol. Metab. 83: 2730–2734.

79. Jenkins, P. J. (2000) Acromegaly and colon cancer. Growth Horm. IGF Res. 10 (suppl. A): S35–S36.

80. Ma, J., Pollak, M. N., Giovannucci, E., Chan, J. M., Tao, T., Hennekens, C. H. & Stampfer, M. J. (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3. J. Natl. Cancer Inst. 91: 620–625.

81. Giovannucci, E., Pollak, M. N., Platz, E. A., Willett, W. C., Stampfer, M. J., Majeed, N., Colditz, G. A., Speizer, F. E. & Hankinson, S. E. (2000) A prospective study of plasma insulin-like growth factor-I and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol. Biomark. Prev. 9: 345–349.

82. Renehan, A. G., Painter, J. E., Atkin, W. S., Potten, C. S., Shalet, S. M. & O'Dwyer, S. T. (2001) High-risk colorectal adenomas and serum insulin-like growth factors. Br. J. Surg. 88: 107–113.

83. Kaaks, R., Toniolo, P., Akhmedkhanov, A., Lukanova, A., Biessy, C., Dechaud, H., Rinaldi, S., Zeleniuch-Jacquotte, A., Shore, R. E. & Riboli, E. (2000) Serum C-peptide, insulin-like growth factor (IGF)-1, IGF-binding proteins, and colorectal cancer risk in women. J. Natl. Cancer Inst. 92: 1592–1600.

84. Manousos, O., Souglakos, J., Bosetti, C., Tzonou, A., Chatzidakis, V., Trichopoulos, D., Adami, H. O. & Mantzoros, C. (1999) IGF-I and IGF-II in relation to colorectal cancer. Int. J. Cancer 83: 15–17.

85. Chan, J. M., Stampfer, M. J., Giovannucci, E., Gann, P. H., Ma, J., Wilkinson, P., Hennekens, C. H. & Pollak, M. (1998) Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science (Washington, DC) 279: 563–566.

86. Hankinson, S. E., Willett, W. C., Colditz, G. A., Hunter, D. J., Michaud, D. S., Deroo, B., Rosner, B., Speizer, F. E. & Pollak, M. (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351: 1393–1396.

87. Yu, H., Spitz, M. R., Mistry, J., Gu, J., Hong, W. K. & Wu, X. (1999) Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. J. Natl. Cancer Inst. 91: 151–156.

88. Harrela, M., Koistinen, H., Kaprio, J., Lehtovirta, M., Tuomilehto, J., Eriksson, J., Toivanen, L., Koskenvuo, M., Leinonen, P., Koistinen, R. & Seppälä, M. (1996) Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. J. Clin. Investig. 98: 2612–2615.

89. Thissen, J. P., Ketelslegers, J. M. & Underwood, L. E. (1994) Nutritional regulation of the insulin-like growth factors. Endocr. Rev. 15: 80–101.

90. Goodman-Gruen, D. & Barrett-Connor, E. (1997) Epidemiology of insulin-like growth factor-I in elderly men and women: The Rancho Bernardo Study. Am. J. Epidemiol. 145: 970–976.

91. Juul, A., Bang, P., Hertel, N. T., Main, K., Dalgaard, P., Jorgensen, K., Muller, J., Hall, K. & Skakkebaek, N. E. (1994) Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J. Clin. Endocrinol. Metab. 78: 744–752.

92. Giovannucci, E., Ascherio, A., Rimm, E. B., Colditz, G. A., Stampfer, M. J. & Willett, W. C. (1995) Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann. Intern. Med. 122: 327–334.

93. Chute, C. G., Willett, W. C., Colditz, G. A., Stampfer, M. J., Baron, J. A., Rosner, B. & Speizer, F. E. (1991) A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women. Cancer Causes Control 2: 117–124.

94. Albanes, D., Jones, D. Y., Schatzkin, A., Micozzi, M. S. & Taylor, P. R. (1988) Adult stature and risk of cancer. Cancer Res. 48: 1658–1662.

95. Hebert, P. R., Ajani, U., Cook, N. R., Lee, I.-M., Chan, K. S. & Hennekens, C. H. (1997) Adult height and incidence of cancer in male physicians (United States). Cancer Causes Control 8: 591–597.

96. Ghadirian, P., Maisonneuve, P., Perret, C., Lacroix, A. & Boyle, P. (1998) Epidemiology of sociodemographic characteristics, lifestyle, medical history, and colon cancer: a case-control study among French Canadians in Montreal. Cancer Detect. Prev. 22: 396–404.

97. Robsahm, T. E. & Tretli, S. (1999) Height, weight and gastrointestinal cancer: a follow-up study in Norway. Eur. J. Cancer Prev. 8: 105–113.

98. Gunnell, D. (2000) Height, insulin-like growth factors and cancer risk. Growth Horm. IGF Res. 10: S39–S40.

99. Gunnell, D. J., Smith, G. D., Holly, J. M. & Frankel, S. (1998) Leg length and risk of cancer in the Boyd Orr cohort. Br. Med. J. 317: 1350–1351.

100. Swanson, C. A., Coates, R. J., Schoenberg, J. B., Malone, K. E., Gammon, M. D., Stanford, J. L., Shorr, I. J., Potischman, N. A. & Brinton, L. A. (1996) Body size and breast cancer risk among women under age 45 years. Am. J. Epidemiol. 143: 698–706.

101. Campagnoli, C., Ambroggio, S., Biglia, N. & Sismondi, P. (1999) Conjugated estrogens and breast cancer risk. Gynecol. Endocrinol. 13: 13–19.

102. Calle, E. E., Miracle-McMahill, H. L., Thun, M. J. & Heath, C. W., Jr. (1995) Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. J. Natl. Cancer Inst. 87: 517–523.

103. Newcomb, P. A. & Storer, B. E. (1995) Postmenopausal hormone use and risk of large-bowel cancer. J. Natl. Cancer Inst. 87: 1067–1071.

104. Grodstein, F., Martinez, M. E., Platz, E. A., Giovannucci, E., Colditz, G. A., Kautzky, M., Fuchs, C. & Stampfer, M. J. (1998) Postmenopausal hormone use and risk for colorectal cancer and adenoma. Ann. Intern. Med. 128: 705–712.

105. Tuomilehto, J., Knowler, W. C. & Zimmet, P. (1992) Primary prevention of non-insulin-dependent diabetes mellitus. Diabetes Metab. Rev. 8: 339–353.

106. DeFronzo, R. A., Bonadonna, R. C. & Ferrannini, E. (1992) Pathogenesis of NIDDM. A balanced overview. Diabetes Care 15: 318–368.

107. Wilson, E. B. & Maher, H. C. (1932) Cancer and tuberculosis with some comments on cancer and other diseases. Am. J. Cancer 16: 227–250.

108. Bell, E. T. (1957) Carcinoma of the pancreas. Am. J. Pathol. 33: 499–523.

109. Ragozzino, M., Melton, J. M., III, Chu, C. P. & Palumbo, P. J. (1982) Subsequent cancer risk in the incidence cohort of Rochester, Minnesota, residents with diabetes mellitus. J. Chronic Dis. 35: 13–19.

110. O'Mara, B. A., Byers, T. & Schoenfeld, E. (1985) Diabetes mellitus and cancer risk: a multisite case-control study. J. Chronic Dis. 38: 435–441.

111. Williams, J. C., Walsh, D. A. & Jackson, J. F. (1984) Colon carcinoma and diabetes mellitus. Cancer 54: 3070–3071.

112. Kessler, I. I. (1970) Cancer mortality among diabetics. J. Natl. Cancer Inst. 44: 673–686.

113. Adami, H.-O., McLaughlin, J., Ekbom, A., Berne, C., Silverman, D., Hacker, D. & Persson, I. (1991) Cancer risk in patients with diabetes mellitus. Cancer Causes Control 2: 307–314.

114. La Vecchia, C., D'Avanzo, B., Negri, E. & Franceschi, S. (1991) History of selected diseases and the risk of colorectal cancer. Eur. J. Cancer 27: 582–586.

115. Le Marchand, L., Wilkens, L. R., Kolonel, L. N., Hankin, J. H. & Lyu, L.-C. (1997) Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. Cancer Res. 57: 4787–4794.

116. Kono, S., Honjo, S., Todoroki, I., Nishiwaki, M., Hamada, H., Nishikawa, H., Koga, H., Ogawa, S. & Nakagawa, K. (1998) Glucose intolerance and adenomas of the sigmoid colon in Japanese men (Japan). Cancer Causes Control 9: 441–446.

117. Will, J. C., Galuska, D. A., Vinicor, F. & Calle, E. E. (1998) Colorectal cancer: another complication of diabetes mellitus? Am. J. Epidemiol 147: 816–825.

118. Hu, F. B., Manson, J. E., Liu, S., Hunter, D., Colditz, G. A., Michels, K. B., Speizer, F. E. & Giovannucci, E. (1999) Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. J. Natl. Cancer Inst. 91: 542–547.

119. Nilsen, T. I. & Vatten, L. J. (2001) Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. Br. J. Cancer 84: 417–422.

120. Schoen, R. E., Tangen, C. M., Kuller, L. H., Burke, G. L., Cushman, M., Tracy, R. P., Dobs, A. & Savage, P. J. (1999) Increased blood glucose and insulin, body size, and incident colorectal cancer. J. Natl. Cancer Inst. 91: 1147–1154.

121. Giovannucci, E. (1995) Insulin and colon cancer. Cancer Causes Control 6: 164–179.

122. Topping, D. L. & Mayes, P. A. (1972) The immediate effects of insulin and fructose on the metabolism of the perfused liver. Changes in lipoprotein secretion, fatty acid oxidation and esterification, lipogenesis and carbohydrate metabolism. Biochem. J. 126: 295–311.

123. Tobey, T. A., Greenfield, M., Kraemer, F. & Reaven, G. M. (1981) Relationship between insulin resistance, insulin secretion, very low density lipoprotein kinetics, and plasma triglyceride levels in normotriglyceridemic man. Metabolism 30: 165–171.

124. Yamada, K., Araki, S., Tamura, M., Saka, I. I., Takahashi, Y., Kashihara, H. & Kono, S. (1998) Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. Int. J. Epidemiol. 27: 794–798.

125. Bayerdorffer, E., Mannes, G. A., Richter, W. O., Ochsenkuhn, T., Seeholzer, G., Kopke, W., Wiebecke, B. & Paumgartner, G. (1993) Decreased high-density lipoprotein cholesterol and increased low-density cholesterol levels in patients with colorectal adenomas. Ann. Intern. Med. 118: 481–487.

126. Bird, C. L., Ingles, S. A., Frankl, H. D., Lee, E. R., Longnecker, M. P. & Haile, R. W. (1996) Serum lipids and adenomas of the left colon and rectum. Cancer Epidemiol. Biomark. Prev. 5: 607–612.

127. Manus, B., Adang, R. P., Ambergen, A. W., Bragelmann, R., Armbrecht, U. & Stockbrugger, R. W. (1997) The risk factor profile of recto-sigmoid adenomas: a prospective screening study of 665 patients in a clinical rehabilitation centre. Eur. J. Cancer Prev. 6: 38–43.

128. Bjorntorp, P. (1991) Metabolic implications of body fat distribution. Diabetes Care 14: 1132–1143.

129. Kissebah, A. H., Vydelingum, N., Murray, R., Evans, D. J., Hartz, A. J., Kalkhoff, R. K. & Adams, P. W. (1982) Relation of body fat distribution to metabolic complications of obesity. J. Clin. Endocrinol. Metab 54: 254–260.

130. Krotkiewski, M., Bjorntorp, P., Sjostrom, L. & Smith, U. (1983) Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. J. Clin. Investig. 72: 1150–1162.

131. Donahue, R. P., Abbott, R. D., Bloom, E., Reed, D. M. & Yano, K. (1987) Central obesity and coronary heart disease in men. Lancet 1: 821–824.

132. Wu, A. H., Paganini-Hill, A., Ross, R. K. & Henderson, B. E. (1987) Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. Br. J. Cancer 55: 687–694.

133. Lee, I. M., Paffenbarger, R. S., Jr. & Hsieh, C. C. (1991) Physical activity and risk of developing colorectal cancer among college alumni. J. Natl. Cancer Inst. 83: 1324–1329.

134. Lew, E. A. & Garfinkel, L. (1979) Variations in mortality by weight among 750,000 men and women. J. Chronic Dis. 32: 563–576.

135. Waaler, H. T. (1984) Height, weight and mortality. The Norwegian experience. Acta Med. Scand. Suppl. 679: 1–56.

136. Phillips, R. L. & Snowdon, D. A. (1985) Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists. J. Natl. Cancer Inst. 74: 307–317.

137. Garland, C., Shekelle, R. B., Barrett-Conner, E., Criqui, M. H., Rossof, A. H. & Paul, O. (1985) Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet 1: 307–309.

138. Klatsky, A. L., Armstrong, M. A., Friedman, G. D. & Hiatt, R. A. (1988) The relations of alcoholic beverage use to colon and rectal cancer. Am. J. Epidemiol. 128: 1007–1015.

139. Must, A., Jacques, P. F., Dallal, G. E., Bajema, C. J. & Dietz, W. H. (1992) Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N. Engl. J. Med. 327: 1350–1355.

140. Le Marchand, L., Wilkins, L. R. & Mi, M. P. (1992) Obesity in youth and middle age and risk of colorectal cancer in men. Cancer Causes Control 3: 349–354.

141. Chyou, P.-H., Nomura, A. M. Y. & Stemmermann, G. N. (1996) A prospective study of colon and rectal cancer among Hawaii Japanese men. Ann. Epidemiol. 6: 276–282.

142. Whittemore, A. S., Wu-Williams, A. H., Lee, M., Zheng, S., Gallagher, R. P., Jiao, D. A., Zhou, L., Wang, X. H., Chen, K., & Jung, D. (1990) Diet, physical activity and colorectal cancer among Chinese in North America and China. J. Natl. Cancer Inst. 82: 915–926.

143. Kune, G., Kune, S. & Wason, L. (1990) Body weight and physical activity as predictors of colorectal cancer risk. Nutr. Cancer 13: 9–17.

144. Graham, S., Marshall, J., Haughey, B., Mittelman, A., Swanson, M., Zielezny, M., Byers, T., Wilkinson, G. & West, D. (1988) Dietary epidemiology of cancer of the colon in western New York. Am. J. Epidemiol. 128: 490–503.

145. West, D. W., Slattery, M. L., Robison, L. M., Schuman, K. L., Ford, M. H., Mahoney, A. W., Lyon, J. L. & Sorensen, A. W. (1989) Dietary intake and colon cancer: sex- and anatomic site-specific associations. Am. J. Epidemiol. 130: 883–894.

146. Dietz, A. T., Newcomb, P. A., Marcus, P. M. & Strer, B. E. (1995) The association of body size and large bowel cancer risk in Wisconsin (United States) women. Cancer Causes Control 6: 30–36.

147. Bostick, R. M., Potter, J. D., Kushi, L. H., Sellers, T. A., Steinmetz, K. A., McKenzie, D. R., Gapstur, S. M. & Folsom, A. R. (1994) Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control 5: 38–52.

148. Chute, C. G., Willett, W. C., Colditz, G. A., Stampfer, M. J., Rosner, B. & Speizer, F. E. (1991) A prospective study of reproductive history and exogenous estrogens on the risk of colorectal cancer in women. Epidemiology 2: 201–207.

149. Martinez, M. E., Giovannucci, E., Spiegelman, D., Stampfer, M. J., Hunter, D. J., Speizer, F. E., Willett, W. C. & Colditz, G. A. (1996) Physical activity, body size, and colorectal cancer in women. Am. J. Epidemiol. 143: S73 (abs.).

150. Ford, E. S. (1999) Body mass index and colon cancer in a national sample of adult US men and women. Am. J. Epidemiol. 150:390–339.

151. Slattery, M. L., Potter, J., Caan, B., Edwards, S., Coates, A., Ma, K.-N. & Berry, T. D. (1997) Energy balance and colon cancer—beyond physical activity. Cancer Res. 57: 75–80.

152. Giovannucci, E., Colditz, G. A., Stampfer, M. J. & Willett, W. C. (1996) Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 7: 253–263.

153. Neugut, A. I., Lee, W. C., Garbowski, G. C., Waye, J. D., Forde, K. A., Treat, M. R. & Fenoglio-Preiser, C. (1991) Obesity and colorectal adenomatous polyps. J. Natl. Cancer Inst. 83: 359–361.

154. Shinchi, K., Kono, S., Honjo, S., Todoroki, I., Sakurai, Y., Imanishi, K., Nishikawa, H., Ogawa, S., Katsurada, M. & Hirohata, T. (1994) Obesity and adenomatous polyps of the sigmoid colon. Jpn. J. Cancer Res. 85: 479–484.

155. Sandler, R. S., Lyles, C. M., Peipins, L. A., McAuliffe, C. A., Woosley, J. T. & Kupper, L. L. (1993) Diet and risk of colorectal adenomas: macronutrients, cholesterol and fiber. J. Natl. Cancer Inst. 85: 884–891.

156. Lubin, F., Rozen, P., Arieli, B., Farbstein, M., Knaani, Y., Bat, L. & Farbstein, H. (1997) Nutritional and lifestyle habits and water-fiber interaction in colorectal adenoma etiology. Cancer Epidemiol. Biomark. Prev. 6: 79–85.

157. Kono, S., Handa, K., Hayabuchi, H., Kiyohara, C., Inoue, H., Marugame, T., Shinomiya, S., Hamada, H., Onuma, K. & Koga, H. (1999) Obesity, weight gain and risk of colon adenomas in Japanese men. Jpn. J. Cancer Res. 90: 805–811.

158. Bird, C. L., Frankl, H. D., Lee, E. R. & Haile, R. W. (1998) Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. Am. J. Epidemiol. 147: 670–680.

159. Ross, R. (1997) Effects of diet- and exercise-induced weight loss on visceral adipose tissue in men and women. Sports Med. 24: 55–64.

160. Koivisto, V. A., Yki-Jarvinen, H. & DeFronzo, R. A. (1986) Physical training and insulin sensitivity. Diabetes Metab. Rev. 1: 445–481.

161. Regensteiner, J. G., Mayer, E. J., Shetterly, S. M., Eckel, R. H., Haskell, W. L., Marshall, J. A., Baxter, J. & Hamman, R. F. (1991) Relationship between habitual physical activity and insulin levels among nondiabetic men and women. San Luis Valley Diabetes Study. Diabetes Care 14: 1066–1074.

162. Dowse, G. K., Zimmet, P. Z., Gareeboo, H., George, K., Alberti, M. M., Tuomilehto, J., Finch, C. F., Chitson, P. & Tulsidas, H. (1991) Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. Diabetes Care 14: 271–282.

163. Lindgarde, F. & Saltin, B. (1981) Daily physical activity, work capacity and glucose tolerance in lean and obese normoglycaemic middle-aged men. Diabetologia 20: 134–138.

164. Wang, J. T., Ho, L. T., Tang, K. T., Wang, L. M., Chen, Y. D. & Reaven, G. M. (1989) Effect of habitual physical activity on age-related glucose intolerance. J. Am. Geriatr. Soc. 37: 203–209.

165. Schneider, S. H., Amorosa, L. F., Khachadurian, A. K. & Ruderman, N. B. (1984) Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. Diabetologia 26: 355–360.

166. Burstein, R., Polychronakos, C., Toews, C. J., MacDougall, J. D., Guyda, H. J. & Posner, B. I. (1985) Acute reversal of the enhanced insulin action in trained athletes. Association with insulin receptor changes. Diabetes 34: 756–760.

167. Blair, S. N., Kohl, H. W., Gordon, N. F. & Paffenbarger, R. S., Jr. (1992) How much physical activity is good for health? Annu. Rev. Public Health 13: 99–126.

168. Kriska, A. M. & Bennett, P. H. (1992) An epidemiological perspective of the relationship between physical activity and NIDDM: from activity assessment to intervention. Diabetes Metab. Rev. 8: 355–372.

169. DeFronzo, R. A., Jacot, E., Jequier, E., Maeder, E., Wahren, J. & Felber, J. P. (1981) The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes 30: 1000–1007.

170. Lillioja, S., Mott, D. M., Zawadzki, J. K., Young, A. A., Abbott, W. G. & Bogardus, C. (1986) Glucose storage is a major determinant of in vivo "insulin resistance" in subjects with normal glucose tolerance. J. Clin. Endocrinol. Metab. 62: 922–927.

171. Shulman, G. I., Rothman, D. L., Jue, T., Stein, P., DeFronzo, R. A. & Shulman, R. G. (1990) Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by ^{13}C nuclear magnetic resonance spectroscopy. N. Engl. J. Med. 322: 223–228.

172. Hamman, R. F. (1992) Genetic and environmental determinants of non-insulin-dependent diabetes mellitus (NIDDM). Diabetes Metab. Rev. 8: 287–338.

173. Helmrich, S. P., Ragland, D. R., Leung, R. W. & Paffenbarger, R. S., Jr. (1991) Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N. Engl. J. Med. 325: 147–152.

174. Manson, J. E., Rimm, E. B., Stampfer, M. J., Colditz, G. A., Willett, W. C., Krolewski, A. S., Rosner, B., Hennekens, C. H. & Speizer, F. E. (1991) Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 338: 774–778.

175. Manson, J. E., Nathan, D. M., Krolewski, A. S., Stampfer, M. J., Willett, W. C. & Hennekens, C. H. (1992) A prospective study of exercise and incidence of diabetes among US male physicians. J. Am. Med. Assoc. 268: 63–67.

176. Thun, M. J., Calle, E. E., Namboodiri, M. M., Flanders, W. D., Coates, R. J., Byers, T., Boffetta, P., Garfinkel, L. & Heath, C. W. Jr. (1992) Risk factors for fatal colon cancer in a large prospective study. J. Natl. Cancer Inst. 84: 1491–1500.

177. Ballard-Barbash, R., Schatzkin, A., Albanes, D., Schiffman, M. H., Kreger, B. E., Kannel, W. B., Anderson, K. M. & Elsel, W. E. (1990) Physical activity and risk of large bowel cancer in the Framingham Study. Cancer Res. 50: 3610–3613.

178. Albanes, D., Blair, A. & Taylor, P. R. (1989) Physical activity and risk of cancer in the NHANES I population. Am. J. Public Health 79: 744–750.

179. Severson, R. K., Nomura, A. M. Y., Grove, J. S. & Stemmermann, G. N. (1989) A prospective analysis of physical activity and cancer. Am. J. Epidemiol. 130: 522–529.

180. Lynge, E. & Thygesen, L. (1988) Use of surveillance systems for occupational cancer: data from the Danish national system. Int. J. Epidemiol. 17: 493–500.

181. Gerhardsson, M., Floderus, B. & Norell, S. E. (1988) Physical activity and colon cancer risk. Int. J. Epidemiol. 17: 743–746.

182. Paffenbarger, R.S.J., Hyde, R. T. & Wing, A. L. (1987) Physical activity and incidence of cancer in diverse populations: a preliminary report. Am. J. Clin. Nutr. 45 (suppl.): 312–317.

183. Gerhardsson, M., Norell, S. E., Kiviranta, H., Pedersen, N. L. & Ahlbom, A. (1986) Sedentary jobs and colon cancer. Am. J. Epidemiol. 123: 775–780.

184. Markowitz, S., Morabia, A., Garibaldi, K. & Wynder, E. (1992) Effect of occupational and recreational activity on the risk of colorectal cancer among males: a case-control study. Int. J. Epidemiol. 21: 1057–1062.

185. Slattery, M. L., Schumacher, M. C., Smith, K. R., West, D. W. & Abd-Elghany, N. (1988) Physical activity, diet, and risk of colon cancer in Utah. Am. J. Epidemiol. 128: 989–999.

186. Peters, R. K., Garabrant, D. H., Yu, M. C. & Mack, T. M. (1989) A case-control study of occupational and dietary factors in colorectal cancer in young men by subsite. Cancer Res. 49: 5459–5468.

187. Brownson, R. C., Zahm, S. H., Chang, J. C. & Blair, A. (1989) Occupational risk of colon cancer. An analysis of anatomic subsite. Am. J. Epidemiol. 130: 675–687.

188. Benito, E., Obrador, A., Stiggelbout, A., Bosch, F. X., Mulet, M., Muñoz, N. & Kaldor, J. (1990) A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. Int. J. Cancer 45: 69–76.

189. Kato, I., Tominaga, S., Matsuura, A., Yoshii, Y., Shirai, M. & Kobayashi, S. (1990) A comparative case-control study of colorectal cancer and adenoma. Jpn. J. Cancer Res. 81: 1101–1108.

190. Kato, I., Tominaga, S. & Ikari, A. (1990) A case-control study of male colorectal cancer in Aichi Prefecture, Japan: with special reference to occupational activity level, drinking habits and family history. Jpn. J. Cancer Res. 81: 115–121.

191. Gerhardsson de Verdier, M., Hagman, U., Steineck, G., Rieger, A. & Norell, S. E. (1990) Diet, body mass and colorectal cancer: a case-referent study in Stockholm. Int. J. Cancer 46: 832–838.

192. Fredriksson, M., Bengtsson, N. O., Hardell, L. & Axelson, O. (1989) Colon cancer, physical activity, and occupational exposures. A case-control study. Cancer 63: 1838–1842.

193. Fraser, G. & Pearce, N. (1993) Occupational physical activity and risk of cancer of the colon and rectum in New Zealand males. Cancer Causes Control 4: 45–50.

194. Longnecker, M. P., Gerhardsson de Verdier, M., Frumkin, H. & Carpenter, C. (1995) A case-control study of physical activity in relation to risk of cancer of the right colon and rectum in men. Int. J. Epidemiol. 24: 42–50.

195. Martinez, M. E., Giovannucci, E., Spiegelman, D., Hunter, D. J., Willett, W. C. & Colditz, G. A. (1997) Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J. Natl. Cancer Inst. 89: 948–955.

196. Colditz, G., Cannuscio, C. & Frazier, A. (1997) Physical activity and reduced risk of colon cancer: implications for prevention. Cancer Causes Control 8: 649–667.

197. Kono, S., Shinchi, K., Ikeda, N., Yanai, F. & Imanishi, K. (1991) Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defense officials in Japan. J. Clin. Epidemiol. 44: 1255–1261.

198. Little, J., Logan, R. F., Hawtin, P. G., Hardcastle, J. D. & Turner, I. D. (1993) Colorectal adenomas and energy intake, body size and physical activity: a case-control study of subjects participating in the Nottingham faecal occult blood screening programme. Br. J. Cancer 67: 172–176.

199. Neugut, A. I., Terry, M. B., Hocking, G., Mosca, L., Garbowski, G. C., Forde, K. A., Treat, M. R. & Waye, J. (1996) Leisure and occupational physical activity and risk of colorectal adenomatous polyps. Int. J. Cancer 68: 744–748.

200. Daly, M. E., Vale, C., Walker, M., Alberti, K. & Mathers, J. C. (1997) Dietary carbohydrates and insulin sensitivity—a review of the evidence and clinical implications. Am. J. Clin. Nutr. 66: 1072–1085.

201. Thresher, J. S., Podolin, D. A., Wei, Y., Mazzeo, R. S. & Pagliassotti, M. J. (2000) Comparison of the effects of sucrose and fructose on insulin action and glucose tolerance. Am. J. Physiol. 279: R1334–R1340.

202. Reiser, S., Bohn, E., Hallfrisch, J., Michaelis, O. E., IV, Keeney, M. & Prather, E. S. (1981) Serum insulin and glucose in hyperinsulinemic subjects fed three different levels of sucrose. Am. J. Clin. Nutr. 34: 2348–2358.

203. Reiser, S., Handler, H. B., Gardner, L. B., Hallfrisch, J. G., Michaelis, O. E. & Prather, E. S. (1979) Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and gluccose response to a sucrose load. Am. J. Clin. Nutr. 32: 2206–2216.

204. Daly, M. E., Vale, C., Walker, M., Littlefield, A., Alberti, K. G. & Mathers, J. C. (1998) Acute effects on insulin sensitivity and diurnal metabolic profiles of a high-sucrose compared with a high-starch diet. Am. J. Clin. Nutr. 67: 1186–1196.

205. Hallfrisch, J., Ellwood, K. C., Michaelis, O. E., Reiser, S., O'Dorisio, T. M. & Prather, E. S. (1983) Effects of dietary fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. J. Nutr. 113: 1819–1826.

206. Manolio, T. A., Savage, P. J., Burke, G. L., Hilner, J. E., Liu, K., Orchard, T. J., Sidney, S. & Oberman, A. (1991) Correlates of fasting insulin levels in young adults: the CARDIA study. J. Clin. Epidemiol. 44: 571–578.

207. Stamp, D., Zhang, X. M., Medline, A., Bruce, W. R. & Archer, M. C. (1993) Sucrose enhancement of the early steps of colon carcinogenesis in mice. Carcinogenesis 14: 777–779.

208. Luceri, C., Caderni, G., Lancioni, L., Aiolli, S., Dolara, P., Mastrandrea, V., Scardazza, F. & Morozzi, G. (1996) Effects of repeated boluses of sucrose on proliferation and on AOM-induced aberrant crypt foci in rat colon. Nutr. Cancer 25: 187–196.

209. Kristiansen, E., Meyer, O. & Thorup, I. (1996) Refined carbohydrate enhancement of aberrant crypt foci (ACF) in rat colon induced by the food-borne carcinogen 2-amino-3-methyl-imidazo[4,5-f]quinoline (IQ). Cancer Lett. 105: 147–151.

210. Caderni, G., Lancioni, L., Luceri, C., Giannini, A., Lodovici, M., Biggeri, A. & Dolara, P. (1997) Dietary sucrose and starch affect dysplastic characteristics in carcinogen-induced aberrant crypt foci in rat colon. Cancer Lett. 114: 39–41.

211. Caderni, G., Luceri, C., Lancioni, L. & Dolara, P. (1996) Dietary sucrose, glucose, fructose, and starches affect colonic functions in rats. Nutr. Cancer 25: 179–186.

212. Gerhardsson de Verdier, M. & Longnecker, M. P. (1992) Eating

frequency—a neglected risk factor for colon cancer? Cancer Causes Control 3: 77–81.

213. Franceschi, S., Favero, A., La Vecchia, C., Negri, E., Conti, E., Montella, M., Giacosa, A., Nanni, O. & Decarli, A. (1997) Food groups and risk of colorectal cancer in Italy. Int. J. Cancer 72: 56–61.

214. Franceschi, S., Favero, A., Parpinel, M., Giacosa, A. & La Vecchia, C. (1998) Italian study on colorectal cancer with emphasis on influence of cereals. Eur. J. Cancer Prev. 7: S19–S23.

215. Slattery, M. L., Benson, J., Berry, T. D., Duncan, D., Edwards, S. L., Caan, B. J. & Potter, J. D. (1997) Dietary sugar and colon cancer. Cancer Epidemiol. Biomark. Prev. 6: 677–685.

216. Bostick, R. M., Fosdick, L., Grandits, G. A., Lillemoe, T. J., Wood, J. R., Grambsch, P., Louis, T. A. & Potter, J. D. (1997) Colorectal epithelial cell proliferative kinetics and risk factors for colon cancer in sporadic adenoma patients. Cancer Epidemiol. Biomark. Prev. 6: 1011–1019.

217. Caderni, G., Lancioni, L., Palli, D., Saieva, C., Trallori, G., Manneschi, L., Renai, F., Marcoccia, M., Russo, A. & Dolara, P. (1998) A dietary trial with a short-term low-sucrose diet in an Italian population: effects on colorectal mucosal proliferation. Nutr. Cancer 32: 159–164.

218. Wynder, E. L., Kajitani, T., Ishikawa, S., Dodo, H. & Takano, A. (1969) Environmental factors of cancer of the colon and rectum. II. Japanese epidemiological data. Cancer 23: 1210–1220.

219. Steinmetz, K. A. & Potter, J. D. (1993) Food-group consumption and colon cancer in the Adelaide Case-Control Study. I. Vegetables and fruit. Int. J. Cancer 53: 711–719.

220. Zaridze, D., Filipchenko, V., Kustov, V., Serdyuk, V. & Duffy, S. (1993) Diet and colorectal cancer: results of two case-control studies in Russia. Eur. J. Cancer 29A: 112–115.

221. Trout, D. L., Behall, K. M. & Osilesi, O. (1993) Prediction of glycemic index for starchy foods. Am. J. Clin. Nutr. 58: 873–878.

222. Zhuo, X. G. & Watanabe, S. (1999) Factor analysis of digestive cancer mortality and food consumption in 65 Chinese counties. J. Epidemiol. 9: 275–284.

223. Wolever, T.M.S., Jenkins, D. J., Jenkins, A. L. & Josse, R. G. (1991) The glycemic index: methodology and clinical implications. Am. J. Clin. Nutr. 54: 846–854.

224. Slattery, M. L., Boucher, K. M., Caan, B. J., Potter, J. D. & Ma, K. N. (1998) Eating patterns and risk of colon cancer. Am. J. Epidemiol. 148: 4–16.

225. Fung, T. T., Rimm, E. B., Spiegelman, D., Rifai, N., Tofler, G. H., Willett, W. C. & Hu, F. B. (2001) The association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. Am. J. Clin. Nutr. 73: 61–67.