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Insulin, Glucose, Insulin Resistance and Incident Colorectal Cancer in Male Smokers

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Abstract

Background & Aims—Hyperinsulinemia is a putative colorectal cancer (CRC) risk factor. Insulin resistance (IR) commonly precedes hyperinsulinemia and can be quantitatively measured using the homeostasis model assessment-insulin resistance (HOMA-IR) index. To date, few studies have directly examined serum insulin as an indicator of CRC risk and none have reported associations based on HOMA-IR.

Methods—We performed a case-cohort study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (n=29,133). Baseline exposure and fasting serum biomarker data were available for 134 incident CRC case and 399 non-case subjects. HOMA-IR was derived as fasting insulin x fasting glucose/22.5. Hazard ratios and 95% confidence intervals (HR; 95% CIs) were estimated using age-adjusted and multivariable-adjusted Cox proportional hazards regression models.

Results—Median (IQR) values for serum insulin, glucose and HOMA-IR were 4.1 (2.9–7.2) mIU/L, 101 (94–108) mg/dL, and 0.99 (0.69–1.98) for case subjects and 4.1 (2.7–6.1) mIU/L, 99 (93–107) mg/dL, and 1.02 (0.69–1.53) for non-case subjects, respectively. Based on comparison of the highest versus lowest quartiles for each biomarker, insulin (HR=1.84; 95% CI=1.03–3.30) and HOMA-IR (HR=1.85; 95% CI=1.06–3.24) were significantly associated with incident CRC, while glucose was marginally associated with incident CRC (HR=1.70; 95% CI=0.92–3.13), in age-adjusted risk models. However, trends across biomarker quartiles were somewhat inconsistent (p trend= 0.12, 0.04 and 0.12, respectively) and multivariable adjustment generally attenuated the observed risk estimates.

Conclusions—Data from this prospective study of male smokers provide limited support for hyperinsulinemia, hyperglycemia and/or insulin resistance as CRC risk factors. To our knowledge, these data represent the first reported associations between HOMA-IR and incident CRC.

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Introduction

Data from a variety of sources suggest that insulin may play a functional role in colorectal carcinogenesis (1–3). Insulin administration stimulates proliferation and reduces apoptosis in colorectal cancer (CRC) cell lines (4–6) and also promotes colorectal tumor growth in animal model systems (7–9). In addition, multiple epidemiological studies have reported positive associations between type 2 diabetes mellitus (DM) and CRC risk, as recently reviewed (3, 10). Since type 2 DM is characterized by increased circulating insulin concentration during the early stages of disease (11), these reports indirectly support the "hyperinsulinemia hypothesis". However, to date, few studies have directly examined serum or plasma insulin level as a CRC risk factor (12–15).

Insulin resistance (IR), defined as a subnormal glycemic response to endogenous insulin, precedes hyperinsulinemia among type 2 DM patients (11) and has been proposed as the primary mediator of increased CRC risk among obese individuals (1,16). IR is most accurately measured using the hyperinsulinemic-euglycemic clamp technique (17), but this method is impractical for large scale epidemiological studies. Several IR indices can be derived from fasting serum insulin and glucose levels, such as the homeostasis model assessment (HOMA-IR) (18,19). HOMA-IR has been positively associated with cancer risk outside of the colorectum (20,21), but no data have been reported with respect to HOMA-IR as an indicator of CRC risk.

In this prospective case-cohort study, we evaluated associations between baseline serum insulin, glucose and HOMA-IR levels with incident CRC among a subset of Finnish male smokers enrolled in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Since cigarette smoking has been shown to induce IR (22) and is also a putative CRC risk factor (23), we anticipated that investigation of the proposed risk associations might be particularly informative in this subject population. Also, because proximal and distal CRCs exhibit distinct molecular, histologic and clinical features (24–26), we estimated CRC risks overall and by anatomic subsite for each of the measured serum biomarkers.

Materials and Methods

Details regarding design and conduct of the ATBC Study have been previously described (27). In brief, 29,133 men ages 50 to 69 years who lived in southwestern Finland and smoked at least 5 cigarettes per day were recruited between 1985 and 1988. Individuals with a previous cancer history (except non-melanoma skin cancer) were excluded. Enrolled trial participants provided a fasting blood sample prior to randomization, from which serum specimens were isolated, aliquotted, and stored deep-frozen at −70º C for future analyses. Intervention groups were randomly assigned based on a complete 2 x 2 factorial study design (alpha-tocopherol alone; beta-carotene alone; both; or placebo). Written informed consent was obtained from all trial participants before randomization and the study was approved by the institutional review boards of both the National Public Health Institute in Finland and the U.S. National Cancer Institute.

Incident cancers in the ATBC Study cohort have been identified through the Finnish Cancer Registry, which provides nearly 100% case ascertainment (28). To facilitate efficient serum biomarker studies, a subcohort (n=400) of randomly selected trial participants was assembled from among all subjects who were alive and without a cancer diagnosis during the first 5 years of cohort follow-up. Subjects who developed incident cancer in one of several target organs, including the colorectum, after their fifth year of cohort follow-up through 12/31/1997 were then selected for batch analyses of serum glucose and insulin levels. In the present study, we included CRC case subjects for whom complete insulin and glucose data were available

(n=134). One subject in the subcohort was diagnosed with incident CRC during the first five years of cohort follow-up and was dropped from the non-case subcohort. Therefore, our final analytic cohort included 134 CRC case subjects and 399 non-case subjects. CRC diagnoses were confirmed by independent review of all relevant medical records by two study physicians (ICD-9 codes 153.0–153.4, 153.6–153.9 and 154.0–154.1). The interval between serum collection and follow-up was up to 12 years (median follow-up time for incident CRC diagnosis was 9 years).

Demographic, anthropometric, and exposure data were obtained from the ATBC Study baseline questionnaire and physical examination. Variables of interest for the present analyses included age at randomization, height, weight, body mass index (BMI; kg/m^2), systolic and diastolic blood pressure, occupational and recreational physical activity levels, history of DM, cigarette pack-years, education level, urban residence, dietary intake (total energy, carbohydrates, protein, fat, fiber, folate, and calcium), alcohol consumption and trial intervention group. Baseline serum total and HDL cholesterol levels had been previously measured (27) and were included in the current analyses as well.

Serum glucose and insulin concentrations were analyzed at Mayo Clinic Rochester by experienced laboratory personnel without prior knowledge of case status. Glucose was measured on the Hitachi 912 Chemistry Analyzer using the hexokinase reagent from Boehringer Mannheim (Indianapolis, IN 46256). Insulin was determined using a specific two-site immunoenzymatic assay performed on the Access automated immunoassay system (Beckman Instruments, Chaska, MN 55318) that has a molar cross-reactivity of 0.10% with proinsulin. Serum sets included case, control, and quality control samples. Based on results obtained with the quality control samples, within batch coefficients of variation were 1.1% for the serum glucose assay and 3.5% for the serum insulin assay. Between batch coefficients of variation for the serum glucose and serum insulin assays were 2.2% and 3.6%, respectively. HOMA-IR was derived as follows: fasting insulin x fasting glucose/22.5.

Distributions of demographic and clinical attributes were compared by case status using chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. For these analyses, data were descriptively displayed using frequencies and percents for categorical variables, and medians and inter-quartile ranges for continuous variables. The same set of covariates were compared across quartiles of the serum biomarkers using analyses of covariance for continuous variables, ordinary logistic regression analyses for binary variables, and multi-categorical nominal logistic regression analyses for all other categorical variables. Analyses were subset to participants in the original subcohort and were adjusted for age. Data were descriptively displayed using age-adjusted means and percents, as appropriate, with corresponding 95% confidence limits. P-values were calculated using tests for trend, assuming an inherent ordering of quartiles from lowest to highest. Pairwise associations of serum biomarkers were assessed using Spearman correlation coefficients. Cox proportional hazards regression models were fit to evaluate associations between the serum biomarkers and case status, using methods outlined by Prentice to account for the case-cohort study design (29). We used a robust variance estimate based on the infinitesimal jackknife approach to account for the oversampling of cases (30,31). For all Cox analyses, we modeled survival as a function of age, since age is a better predictor of CRC risk in this study than follow-up time (32).

Separate analyses were carried out for insulin, glucose, and HOMA-IR. The serum biomarker data were categorized into approximate quartiles based on the distribution of each variable within the nested subcohort, with the lowest quartile assigned as the reference group. P-values were again calculated using a one degree-of-freedom test for trend. Age-adjusted and multivariable-adjusted risk associations were assessed for incident CRC overall, as well as for proximal (ICD-9 codes 153.0, 153.1, 153.4, 153.6, 153.7) and distal (ICD-9 codes 153.2, 153.3,

1540, 154.1) tumors. Multivariable models were developed by adding potential confounders individually into the base model. Age at randomization and cigarette pack-years were included in all multivariable models, since all subjects were smokers and smoking is a putative CRC risk factor (23). Other variables listed in Table 1 were included in the final model if any of the following criteria were met for serum insulin, glucose or HOMA-IR: univariately associated with both the exposure and the outcome ($p<0.05$); inclusion changed the serum biomarker hazard ratio by at least 10%; associated with a p-value of less than or equal to 0.20 in the age- and smoking-adjusted risk model; or inclusion decreased the standard error for any of the serum biomarker risk estimates.

Effect modification of the insulin, glucose and HOMA-IR risk associations by total energy intake and factors associated with the insulin resistance syndrome (BMI, occupational physical activity, recreational physical activity, hypertension, total cholesterol, and HDL cholesterol) was investigated using cross-product terms in multivariable-adjusted Cox regression models. The serum biomarker trend variables were included in all such models to assess differences in the dose-response relationship across levels of the potential effect modifiers. All statistical tests were performed two-sided, with analyses carried out using the SAS (SAS Institute, Inc., Cary, NC) and S-Plus (Insightful, Inc., Seattle, WA) software systems.

Results

Selected baseline characteristics of the CRC case and subcohort non-case subjects are shown in Table 1. CRC case subjects were slightly older ($p<0.001$) and less physically active at work ($p=0.006$) than the non-case subjects. Median (IQR) values for serum insulin, glucose and HOMA-IR were 4.1 (2.9–7.2) mIU/L, 101 (94–108) mg/dL, and 0.99 (0.69–1.98) for case subjects and 4.1 (2.7–6.1) mIU/L, 99 (93–107) mg/dL, and 1.02 (0.69–1.53) for non-case subjects, respectively. Age-adjusted baseline characteristics of the nested subcohort are provided by quartile of HOMA-IR in Table 2. BMI, history of DM, hypertension at baseline, protein intake, fat intake, and calcium intake were positively associated with HOMA-IR, while alcohol intake, recreational physical activity and HDL cholesterol were inversely associated with this insulin resistance biomarker ($p < 0.05$ for each variable). Serum insulin and glucose levels also increased progressively across HOMA-IR quartiles (p trend < 0.001 for each biomarker) and correlations between the serum biomarkers were strong: insulin:glucose ($r=0.44$), insulin:HOMA-IR ($r=0.98$) and glucose:HOMA-IR ($r=0.58$).

In age-adjusted risk models (Table 3), serum biomarker levels in the highest versus lowest quartiles were associated with increased CRC risk for insulin (HR=1.84; 95% CI=1.03–3.30), glucose (HR=1.70; 95% CI=0.92–3.13) and HOMA-IR (HR=1.85; 95% CI=1.06–3.24). The trends across quartiles were somewhat inconsistent, however (p trend= 0.12, 0.04 and 0.12, respectively). Multivariable adjustment generally attenuated the observed risk associations, with slightly lower risk estimates for each extreme quartile comparison and absence of statistically significant trends across quartiles: insulin (HR=1.74; 95% CI=0.74–4.07; p trend=0.40), glucose (HR=1.65; 95% CI=0.78–3.49; p trend=0.16) and HOMA-IR (HR=1.71; 95% CI=0.77–3.78; p trend=0.38). Further analyses based on proximal and distal CRC subsites did not reveal any material differences in the associations with insulin, glucose, or HOMA-IR (Table 3). Consideration of rectal cancers separately from distal colon cancers also did not appreciably alter the subsite-specific risk estimates (data not shown). No statistically significant effect modification on the serum biomarker risk associations was detected from total energy intake, BMI, hypertension, occupational physical activity, recreational physical activity, total cholesterol, or HDL cholesterol level ($p > 0.05$ for each comparison).

Discussion

In this prospective study of Finnish male smokers, baseline fasting insulin and HOMA-IR were positively associated with incident CRC in age-adjusted risk models. Glucose was also associated with increased CRC risk, but the age-adjusted risk estimate did not achieve statistical significance. These data add to the limited number of published reports wherein circulating insulin and/or glucose concentrations have been directly examined in relation to incident CRC. To our knowledge, we also provide the first report of HOMA-IR as an indicator of CRC risk. These data support the hypothesis that hyperinsulinemia, hyperglycemia and/or insulin resistance may be functionally involved in colorectal carcinogenesis. However, given the somewhat inconsistent CRC risk estimates observed across biomarker quartiles, we speculate that serial analyses of fasting and non-fasting serum samples may permit more accurate characterization of chronic insulin and glucose exposures.

Previous studies of circulating insulin concentration (either fasting or non-fasting) and CRC risk have yielded inconsistent results. In the Cardiovascular Health Study, fasting insulin levels did not show a linear relationship with incident CRC (statistical test not provided)(12); however, insulin levels above the cohort median were associated with increased CRC risk in secondary analyses (RR=1.6; 95% CI=1.1–2.4). Further, insulin levels obtained two hours after a 75 gram oral glucose load were associated with a two-fold CRC risk elevation (RR=2.0; 95% CI=1.0–3.8 for comparison of extreme quartiles; p trend = 0.04). Conversely, in a nested case-control study from Northern Sweden (13), non-fasting insulin levels were actually higher among controls than cases, with mean values of 81.6 and 64.2 pmol/L, respectively ($p<0.05$). Adjusting for smoking status in logistic regression models reversed the directionality of the observed association, but the risk estimate remained statistically non-significant (OR=1.22; 95% CI=0.64–2.31 for comparison of highest to lowest quartiles; p trend=0.41). Similarly, a nested case-control study of Washington County, Maryland residents found no significant association between non-fasting insulin levels and incident CRC (OR=0.78; 95% CI=0.45–1.35 for comparison of highest to lowest quartiles; p trend = 0.24) (14). More recently, two case-control studies reported positive associations between fasting insulin levels and prevalent colorectal adenomas (15,35).

C-peptide, which is cleaved from proinsulin, has a relatively long half-life in the peripheral circulation (36) and may provide a more accurate assessment of overall insulin exposure (i.e., basal plus stimulated levels). In the New York University Women's Health Study (37), CRC risk was increased by approximately three-fold among subjects with C-peptide levels in the highest versus lowest quintiles (OR=2.92; 95% CI=1.26–6.75; p trend = 0.001). Further adjustment for BMI modestly strengthened the observed risk association (OR=3.28; 95% CI=1.30–8.26). A nested case-control study of Physicians' Health Study participants (38) also found that C-peptide levels were positively associated with incident CRC (RR=2.7; 95% CI=1.2–6.2; p trend = 0.05). Subgroup analyses restricted to subjects whose blood samples were collected after fasting for at least 4 hours revealed a slightly lower, statistically non-significant risk estimate. In contrast, C-peptide levels were not associated with CRC risk (RR=1.17; 95% CI=0.63–2.20) in a nested case-control study of Nurses' Health Study participants (39).

Hyperglycemia has also been evaluated as a potential CRC risk factor, but existing data remain inconclusive. In the aforementioned Cardiovascular Health Study (12), subjects in the highest quartile for fasting glucose at baseline were nearly two times more likely to develop incident CRC, compared to subjects in the lowest quartile (RR=1.8; 95% CI=1.0–3.1; p trend = 0.02). CRC risk was similarly elevated among women (RR=1.98; 95% CI=1.31–2.98), but not men (RR=0.90; 95% CI=0.58–1.40) with elevated blood glucose levels in a prospective, community-based study from Norway (40). However, two other cohort studies from Korea

(41) and Japan (42) found no significant associations between fasting serum glucose level and incident CRC. Glycosylated hemoglobin, which provides an indication of average blood glucose levels over the preceding 3 months, was positively associated with CRC risk in the European Prospective Investigation into Cancer-Norfolk Study (RR=1.34; 95% CI=1.12–1.59 for every 1% absolute increase in HbA1c level)(43) and in the Washington County nested case-control study (OR, 1.57; 95% CI, 0.94–2.60 for comparison of extreme quartiles; p trend = 0.02)(14), but not in the Nurses' Health Study (39). Blood glucose levels following oral glucose challenge have also shown mixed results with respect to predicting CRC risk. Among subjects in the Cardiovascular Health Study (12), post-challenge glucose levels were associated with a higher CRC risk (RR=2.4; 95% CI=1.2–4.7; p trend = 0.02) than were fasting glucose levels (RR=1.8; 95% CI=1.0–3.1; p trend 0.02). Extended follow-up from another prospective study of cardiovascular disease screening program participants (44) demonstrated a 64% increase in CRC mortality among those with post-challenge glucose levels in the highest versus lowest quartiles (RR=1.64; 95% CI = 1.13–2.37; p trend = 0.05). In the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study, impaired glucose tolerance was associated with a strikingly elevated risk for colon cancer mortality (RR=4.24; 95% CI=1.25–14.41), although the point estimate was based on relatively few fatal events (n=15)(45). Further, a relatively small study from Japan reported that post-challenge glucose levels (OR=1.41; 95% CI=1.05–1.88) were positively associated with prevalent colorectal adenomas (46). In contrast, Smith, et al. found null associations for both colon (RR=1.03; 95% CI=0.88–1.24) and rectal (RR=0.94; 95% CI=0.70–1.27) cancer morality among subjects in the highest versus lowest quartiles for post-load glucose levels in a large study of male civil servants from the United Kingdom (47).

Insulin resistance has been observed to be a risk factor for several chronic conditions, including atherosclerosis, hypertension, dyslipidemia and non-alcoholic fatty liver disease, as well as extra-colonic cancers (20,21,34,48–53). Since HOMA-IR is derived from paired serum insulin and glucose values, this composite index may provide an earlier indication of evolving hyperinsulinemia and/or hyperglycemia. However, CRC risks associated with baseline insulin, glucose and HOMA-IR were not appreciably different in our study. Because consensus has not been achieved regarding the most appropriate IR index to use for epidemiologic research (17,54), we also analyzed CRC risks based on the Quantitative Insulin Sensitivity Check Index (QUICKI). The observed risk estimates were similar to HOMA-IR (data not shown).

The range of insulin values observed in our study was relatively narrow, possibly representing the degree of the overnight fast, but which limited the ability to detect small effect sizes. Because insulin assay techniques are not standardized, comparison of absolute insulin values across studies is largely uninformative (55). In the only other prospective study of fasting insulin levels and incident CRC reported to date (12), distribution of the predictor variable appears to have been more pronounced (range 4-400 IU/mL in men, 3-400 in women) than observed here, but the association with CRC risk also failed to achieve statistical significance. It is also possible that insulin-like growth factor proteins, such as IGF-1 and IGFBP3, might be more relevant to colorectal carcinogenesis than insulin, glucose or HOMA-IR. However, existing data remain inconsistent (56) and preliminary analyses of IGF-1 and IGFBP3 levels in our case-cohort study did not reveal any statistically significant associations with incident CRC (57).

The relatively restricted demographic characteristics of our subject population (i.e., all older male smokers) should be taken into account when interpreting the external validity of these observations. Nonetheless, several strengths of our study are worthy of consideration. First, analyses of serum samples obtained > 5 years prior to incident CRC diagnosis effectively removed the possibility that the serum biomarker levels were influenced by physiologic factors or lifestyle changes induced by subclinical colorectal neoplasia. Second, the identification of

CRC cases and controls from within the same source population minimized the chance of selection bias. Third, adjustment for multiple conditions associated with the insulin resistance syndrome (33,34), as well as other potential confounding variables, allowed us to define independent associations between serum insulin, glucose and HOMA-IR levels with incident CRC. In fact, we may have overadjusted for one or more factors within the causal pathway, since multivariable adjustment generally attenduated the observed risk estimates. As noted above, measurement of insulin and glucose levels from a single, fasting serum sample may not adequately characterize long-term exposure. Several prior observational studies have reported stronger CRC risk associations based on non-fasting or time-averaged indicators of hyperinsulinemia or hyperglycemia, suggesting that stimulated insulin and glucose levels may also be more relevant to colorectal carcinogenesis.

In summary, data from this prospective study support the possibility that aberrant insulin and/or glucose homeostasis, perhaps as a consequence of insulin resistance, may be functionally related to CRC risk. In light of the emerging obesity epidemic in most industrialized societies, additional investigation is needed to determine whether or not CRC represents another disease entity associated with, or resulting from, the insulin resistance syndrome (33,34). Further development of quantitative IR biomarkers that accurately reflect long-term insulin and glucose exposure may also be rewarding with respect to identifying population subsets that are at increased CRC risk.

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References

1. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? Cancer Epidemiol Biomarkers Prev 1994;3:687–95. [PubMed: 7881343]
2. Kim YI. Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link? Nutr Rev 1998;56:275–9. [PubMed: 9763878]
3. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:3109S–20S. [PubMed: 11694656]
4. Koenuma M, Yamori T, Tsuruo T. Insulin and insulin-like growth factor 1 stimulate proliferation of metastatic variants of colon carcinoma 26. Jpn J Cancer Res 1989;80:51–8. [PubMed: 2540132]
5. Wu X, Fan Z, Masui H, Rosen N, Mendelsohn J. Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. J Clin Invest 1995;95:1897–905. [PubMed: 7706497]
6. Bjork J, Nilsson J, Hultcrantz R, Johansson C. 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 1993;28:879–84. [PubMed: 7505479]
7. Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev 1996;5:1013–5. [PubMed: 8959325]
8. Corpet DE, Jacquinet C, Peiffer G, Tache S. Insulin injections promote the growth of aberrant crypt foci in the colon of rats. Nutr Cancer 1997;27:316–20. [PubMed: 9101563]
9. Tran TT, Naigamwalla D, Oprescu AI, Lam L, McKeown-Eyssen G, Bruce WR, Giacca A. Hyperinsulinemia, But Not Other Factors Associated with Insulin Resistance, Acutely Enhances Colorectal Epithelial Proliferation In Vivo. Endocrinology. 2006
10. Chang CK, Ulrich CM. Hyperinsulinaemia and hyperglycaemia: possible risk factors of colorectal cancer among diabetic patients. Diabetologia 2003;46:595–607. [PubMed: 12764580]

11. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004;88:787–835. [PubMed: 15308380]ix
12. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, Dobs A, Savage PJ. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999;91:1147–54. [PubMed: 10393723]
13. Palmqvist R, Stattin P, Rinaldi S, Biessy C, Stenling R, Riboli E, Hallmans G, Kaaks R. Plasma insulin, IGF-binding proteins-1 and -2 and risk of colorectal cancer: a prospective study in northern Sweden. Int J Cancer 2003;107:89–93. [PubMed: 12925961]
14. Saydah SH, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12:412–8. [PubMed: 12750235]
15. Schoen RE, Weissfeld JL, Kuller LH, Thaete FL, Evans RW, Hayes RB, Rosen CJ. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. Gastroenterology 2005;129:464–75. [PubMed: 16083703]
16. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164–79. [PubMed: 7749056]
17. Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med 2002;19:527–34. [PubMed: 12099954]
18. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000;23:57–63. [PubMed: 10857969]
19. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW. Diagnosing insulin resistance in the general population. Diabetes Care 2001;24:460–4. [PubMed: 11289468]
20. Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: findings from the British Women's Heart and Health Study. Cancer Causes Control 2004;15:267–75. [PubMed: 15090721]
21. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. Jama 2005;294:2872–8. [PubMed: 16352795]
22. Mallampalli A, Guntupalli KK. Smoking and systemic disease. Med Clin North Am 2004;88:1431–51. [PubMed: 15464106]x
23. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2001;10:725–31. [PubMed: 11440957]
24. Breivik J, Lothe RA, Meling GI, Rognum TO, Borresen-Dale AL, Gaudernack G. Different genetic pathways to proximal and distal colorectal cancer influenced by sex-related factors. Int J Cancer 1997;74:664–9. [PubMed: 9421366]
25. Ward R, Meagher A, Tomlinson I, O'Connor T, Norrie M, Wu R, Hawkins N. Microsatellite instability and the clinicopathological features of sporadic colorectal cancer. Gut 2001;48:821–9. [PubMed: 11358903]
26. Lindblom A. Different mechanisms in the tumorigenesis of proximal and distal colon cancers. Curr Opin Oncol 2001;13:63–9. [PubMed: 11148689]
27. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods participant characteristics, and compliance. The ATBC Cancer Prevention Study Group. Ann Epidemiol 1994;4:1–10. [PubMed: 8205268]
28. Korhonen P, Malila N, Pukkala E, Teppo L, Albanes D, Virtamo J. The Finnish Cancer Registry as follow-up source of a large trial cohort--accuracy and delay. Acta Oncol 2002;41:381–8. [PubMed: 12234031]
29. Prentice RL. A case-cohort design for epidemiologic studies and disease prevention trials. Biometrika 1986;73:1–11.
30. Lin DY, Ying Z. Cox regression with incomplete covariance measurements. J Am Statist Assoc 1993;88:1341–9.
31. Barlow WE. Robust variance estimation for the case-cohort design. Biometrics 1994;50:1064–72. [PubMed: 7786988]

32. Korn EL, Graubard BI, Mitdthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol 1997;145:72–80. [PubMed: 8982025]
33. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 2003;9:237–52. [PubMed: 12924350]
34. Reaven GM. The insulin resistance syndrome. Curr Atheroscler Rep 2003;5:364–71. [PubMed: 12911846]
35. Keku TO, Lund PK, Galanko J, Simmons JG, Woosley JT, Sandler RS. Insulin resistance, apoptosis, and colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev 2005;14:2076–81. [PubMed: 16172212]
36. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 1992;41:368–77. [PubMed: 1551497]
37. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE, Riboli E. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 2000;92:1592–600. [PubMed: 11018095]
38. Ma J, Giovannucci E, Pollak M, Leavitt A, Tao Y, Gaziano JM, Stampfer MJ. A prospective study of plasma C-peptide and colorectal cancer risk in men. J Natl Cancer Inst 2004;96:546–53. [PubMed: 15069117]
39. Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, Giovannucci E. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2005;14:850–5. [PubMed: 15824155]
40. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. Br J Cancer 2001;84:417–22. [PubMed: 11161410]
41. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. Jama 2005;293:194–202. [PubMed: 15644546]
42. Tsushima M, Nomura AM, Lee J, Stemmermann GN. Prospective study of the association of serum triglyceride and glucose with colorectal cancer. Dig Dis Sci 2005;50:499–505. [PubMed: 15810632]
43. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study. Cancer Epidemiol Biomarkers Prev 2004;13:915–9. [PubMed: 15184246]
44. Colangelo LA, Gapstur SM, Gann PH, Dyer AR, Liu K. Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer Epidemiol Biomarkers Prev 2002;11:385–91. [PubMed: 11927499]
45. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and the risk of cancer death in the United States. Am J Epidemiol 2003;157:1092–100. [PubMed: 12796045]
46. Marugame T, Lee K, Eguchi H, Oda T, Shinchi K, Kono S. Relation of impaired glucose tolerance and diabetes mellitus to colorectal adenomas in Japan. Cancer Causes Control 2002;13:917–21. [PubMed: 12588087]
47. Smith GD, Egger M, Shipley MJ, Marmot MG. Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. Am J Epidemiol 1992;136:1110–4. [PubMed: 1462971]
48. Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model. The Mexico City Diabetes Study Diabetes Care 1996;19:1138–41.
49. Vanhala P, Vanhala M, Kumpusalo E, Keinanen-Kiukaanniemi S. The quantitative insulin sensitivity check index QUICKI predicts the onset of type 2 diabetes better than fasting plasma insulin in obese subjects: a 5-year follow-up study. J Clin Endocrinol Metab 2002;87:5834–7. [PubMed: 12466395]
50. Rajala U, Laakso M, Paivansalo M, Pelkonen O, Suramo I, Keinanen-Kiukaanniemi S. Low insulin sensitivity measured by both quantitative insulin sensitivity check index and homeostasis model

assessment method as a risk factor of increased intima-media thickness of the carotid artery. J Clin Endocrinol Metab 2002;87:5092–7. [PubMed: 12414877]

51. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002;25:1177–84. [PubMed: 12087016]
52. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Cacciatori V, Santi L, Targher G, Bonadonna R, Muggeo M. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care 2002;25:1135–41. [PubMed: 12087010]
53. Hedblad B, Nilsson P, Engstrom G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diabet Med 2002;19:470–5. [PubMed: 12060058]
54. Monzillo LU, Hamdy O. Evaluation of insulin sensitivity in clinical practice and in research settings. Nutr Rev 2003;61:397–412. [PubMed: 14968910]
55. Chevenne D, Trivin F, Porquet D. Insulin assays and reference values. Diabetes Metab 1999;25:459–76. [PubMed: 10633871]
56. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346–53. [PubMed: 15110491]
57. Limburg PJ, Vierkant R, Stolzenberg-Solomon R, Sellers T, Pollak M, Virtamo J, Albanes D. Insulin, insulin-like growth factor proteins, and colorectal cancer risk in the ATBC study. Gastroenterology 2003;124:A78.

Table 1

Baseline Characteristics of Case-Cohort Study Participants, by Case Status

Characteristic[1]	Incident CRC Cases (N=134)	Subcohort Non-Cases (N=399)	p-value[2]
Demographics			
Age at randomization, years	59 (55–62)	56 (52–60)	<0.001
Body mass index, kg/m^2	26.6 (24.0–29.8)	26.2 (23.9–28.9)	0.39
Primary school education or less, N (%)	108 (81)	313 (78)	0.59
Urban residence, N (%)	89 (66)	269 (67)	0.83
Cigarette pack-years	32 (22–44)	35 (25–45)	0.27
History of diabetes mellitus, N (%)	3 (2)	18 (5)	0.24
Hypertension at baseline, N (%)[3]	96 (72)	257 (64)	0.13
Dietary intake			
Total energy, kcal/d	2704 (2222–3253)	2721 (2314–3256)	0.62
Carbohydrates, g/d	293 (229–346)	294 (240–360)	0.43
Protein, g/d	98 (81–118)	100 (83–121)	0.70
Fat, g/d	115 (93–150)	115 (95–148)	0.80
Fiber, g/d	23.1 (18.5–29.7)	24.3 (18.4–31.5)	0.44
Folate, mg/d[4]	327 (250–396)	327 (268–399)	0.52
Calcium, mg/d[4]	1311 (969–1696)	1370 (1028–1729)	0.28
Alcohol, g/day	10.7 (2.8–27.4)	11.4 (2.2–26.9)	0.55
Physical Activity			
Occupational, N (%)			0.006
Sedentary	22 (16)	54 (14)	
Light/Moderate	35 (26)	161 (40)	
Heavy	8 (6)	36 (9)	
Non-working	69 (52)	148 (37)	
Recreational, N (%)			0.70
Sedentary	52 (39)	171 (43)	
Light/Moderate	74 (55)	204 (51)	
Heavy	8 (6)	24 (6)	
Serum Cholesterol			
Total, mmol/L	6.1 (5.4–6.8)	6.3 (5.5–7.1)	0.17
HDL, mmol/L	1.11 (0.95–1.37)	1.16 (0.98–1.37)	0.28

[1] Median (interquartile range) unless otherwise indicated.

[2] Based on chi-square test (categorical variables) or Wilcoxon rank sum test (continuous variables).

[3] Defined as systolic blood pressure > 140 mm HG or diastolic blood pressure > 90 mm Hg.

[4] Including supplements.

Table 2

Age-Adjusted Baseline Characteristics of Subcohort Non-Case Subjects, by Quartile of Homeostasis Model Assessment-Insulin Resistance (HOMA-IR)

Characteristic	HOMA-IR Quartile 1	Quartile 2	Quartile 3	Quartile 4	p trend
Demographics					
Age at randomization, years[1]	56.5 (55.5–57.4)	56.3 (55.3–57.2)	56.0 (55.0–57.0)	56.7 (55.7–57.7)	0.81
Body mass index (kg/m^2)[2]	24.3 (23.6–24.9)	25.2 (24.5–25.8)	27.1 (26.5–27.8)	29.9 (29.2–30.5)	<0.001
Primary school education or less[3]	82.4 (75.0–89.8)	79.9 (72.0–87.8)	68.8 (59.6–78.0)	84.7 (77.7–91.7)	0.78
Urban residence[3]	73.0 (61.4–79.1)	63.3 (53.8–72.8)	72.2 (63.4–81.1)	62.2 (52.8–71.7)	0.47
Cigarette pack-years[2]	36 (33–39)	38 (34–41)	33 (30–36)	37 (34–41)	0.95
Self-reported diabetes mellitus[3]	0 (–)	0.8 (0–2.6)	2.4 (0–5.4)	15.0 (8.0–21.9)	<0.001
Hypertension at baseline[3]	50.3 (40.6–60.0)	65.6 (56.2–74.9)	66.7 (57.4–76.0)	76.6 (68.4–84.9)	<0.001
Dietary intake (per day)[2,4]					
Total energy, kcal	2853 (2689–3018)	2779 (2614–2944)	2816 (2648–2983)	2893 (2729–3057)	0.68
Carbohydrates, g	308 (299–317)	310 (301–319)	303 (294–312)	298 (289–307)	0.08
Protein, g	101 (98–103)	102 (100–105)	105 (102–108)	107 (104–110)	0.001
Fat, g	121 (117–125)	120 (117–124)	125 (121–128)	127 (124–131)	0.007
Fiber, g	26.2 (24.6–27.7)	25.8 (24.2–27.3)	25.3 (23.8–26.9)	25.0 (23.4–26.9)	0.24
Folate, mg	328 (316–340)	345 (334–357)	345 (333–357)	346 (334–357)	0.05
Calcium, mg	1380 (1289–1471)	1377 (1286–1469)	1443 (1351–1536)	1585 (1495–1677)	0.001
Alcohol, g	23.0 (18.4–27.7)	20.8 (16.2–25.5)	17.8 (13.1–22.5)	16.8 (12.2–21.4)	0.04
Physical Activity					
Occupational[3]					0.16
Sedentary	10.8 (4.8–16.9)	12.6 (6.0–19.1)	14.5 (7.6–21.5)	14.0 (7.2–20.8)	
Light/Moderate	39.7 (30.2–49.2)	39.7 (30.1–49.4)	42.0 (32.2–51.7)	33.4 (24.2–42.6)	
Heavy	11.5 (5.3–17.7)	11.2 (5.0–17.4)	6.6 (1.7–11.6)	5.4 (1.0–9.8)	
Non-working	38.0 (28.5–47.4)	36.5 (27.0–46.0)	36.9 (27.3–46.4)	47.2 (37.5–56.9)	
Recreational[3]					0.04
Sedentary	42.4 (32.8–52.0)	37.4 (27.9–47.0)	35.6 (26.1–45.0)	54.7 (45.0–64.4)	
Light/Moderate	46.2 (36.5–55.9)	57.4 (47.6–67.1)	59.1 (49.4–68.9)	42.2 (32.6–51.9)	
Heavy	11.9 (5.2–17.6)	5.2 (0.8–9.5)	5.3 (0.9–9.8)	3.1 (0–6.5)	
Serum Biomarkers					
Total cholesterol, mmol/L[2]	6.2 (6.0–6.4)	6.3 (6.1–6.5)	6.6 (6.4–6.8)	6.3 (6.1–6.5)	0.21
HDL cholesterol, mmol/L[2]	1.34 (1.28–1.40)	1.26 (1.20–1.32)	1.18 (1.12–1.24)	1.06 (1.00–1.12)	<0.001
Insulin, mIU/mL[2]	2.08 (1.54–2.63)	3.53 (2.97–4.08)	5.00 (4.44–5.55)	9.97 (9.42–10.52)	<0.001
Glucose, mg/dL[2]	92 (88–96)	99 (95–103)	102 (98–107)	121 (116–125)	<0.001

[1] Unadjusted analysis of variance.

[2] Analyses of covariance, adjusting for age; mean (95% confidence interval).

[3] Binary and multi-categorical logistic regression analyses, adjusting for age; percent (95% confidence interval).

[4] In addition to age, dietary variables were also adjusted for energy, with the exception of alcohol; folate and calcium intake include supplements.

Table 3

Associations Between Fasting Insulin, Glucose, HOMA-IR and Incident Colorectal Cancer, Overall and by Anatomic Subsite

	Quartile 1 (< 2.8)	Quartile 2 (2.9–4.1)	Insulin, μIU/mL Quartile 3 (4.2–6.1)	Quartile 4 (> 6.1)	p trend[1]
All CRC Cases/Subcohort Non-Cases, N	31/104	37/97	25/103	41/95	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.40 (0.78–2.51)	0.94 (0.51–1.74)	1.84 (1.03–3.30)	0.12
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.43 (0.74–2.78)	0.77 (0.35–1.69)	1.74 (0.74–4.07)	0.40
Proximal CRC Cases/Subcohort Non-Cases, N	13/104	13/97	9/103	12/95	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.30 (0.56–3.04)	0.91 (0.36–2.33)	1.53 (0.62–3.76)	0.54
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.36 (0.53–3.52)	0.82 (0.26–2.65)	1.62 (0.45–5.86)	0.64
Distal CRC Cases/Subcohort Non-Cases, N	18/104	24/97	16/103	29/95	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.46 (0.72–2.97)	0.96 (0.46–1.99)	2.03 (1.04–3.97)	0.10
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.45 (0.65–3.27)	0.73 (0.28–1.87)	1.73 (0.63–4.77)	0.49
	Quartile 1 (< 92)	**Quartile 2 (93–98)**	**Glucose, mg/dL Quartile 3 (99–107)**	**Quartile 4 (> 107)**	**p trend[1]**
All CRC Cases/Subcohort Non-Cases, N	23/99	32/100	44/101	35/99	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.35 (0.72–2.50)	2.08 (1.14–3.79)	1.70 (0.92–3.13)	0.04
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.19 (0.58–2.43)	1.95 (0.97–3.91)	1.65 (0.78–3.49)	0.16
Proximal CRC Cases/Subcohort Non-Cases, N	8/99	14/100	15/101	10/99	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.57 (0.62–3.96)	2.15 (0.85–5.41)	1.45 (0.55–3.84)	0.33
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.67 (0.59–4.73)	1.92 (0.66–5.58)	1.38 (0.42–4.52)	0.52
Distal CRC Cases/Subcohort Non-Cases, N	15/99	18/100	29/101	25/99	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.22 (0.58–2.57)	2.04 (1.02–4.09)	1.81 (0.90–3.66)	0.04
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.03 (0.42–2.51)	2.09 (0.89–4.91)	1.85 (0.77–4.45)	0.08
	Quartile 1 (< 92)	**Quartile 2 (93–98)**	**HOMA-IR Quartile 3 (99–107)**	**Quartile 4 (> 107)**	**p trend[1]**
All CRC Cases/Subcohort Non-Cases, N	33/102	37/99	18/98	46/100	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.27 (0.71–2.26)	0.67 (0.35–1.30)	1.85 (1.06–3.24)	0.12
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.30 (0.68–2.47)	0.51 (0.23–1.16)	1.71 (0.77–3.78)	0.38
Proximal CRC Cases/Subcohort Non-Cases, N	14/102	12/99	6/98	15/100	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.11 (0.47–2.61)	0.63 (0.22–1.79)	1.70 (0.73–3.97)	0.40
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.33 (0.52–3.42)	0.47 (0.13–1.67)	1.96 (0.56–6.91)	0.54
Distal CRC Cases/Subcohort Non-Cases, N	19/102	25/99	12/98	31/100	
Age-Adjusted Hazard Ratio (95% CI)	1.00 (ref.)	1.36 (0.69–2.70)	0.70 (0.32–1.52)	1.94 (1.01–3.73)	0.15
Multivariable-Adjusted Hazard Ratio (95% CI)[2]	1.00 (ref.)	1.31 (0.60–2.87)	0.53 (0.20–1.38)	1.58 (0.63–3.93)	0.53

All risk estimates are based on Cox proportional hazards regression analyses, modeling risk as a function of age, and accounting for the case-cohort study design.

[1] Based on test for trend.

[2] Insulin analyses are adjusted for cigarette pack-years, body mass index, protein intake, fat intake, fiber intake, alcohol consumption, caloric intake, history of diabetes mellitus and occupational physical activity.