Research Article

Cancer Epidemiology, Biomarkers & Prevention

Associations of Plasma C-Peptide and IGFBP-1 Levels with Risk of Colorectal Adenoma in a Multiethnic Population

Loïc Le Marchand[1], Hansong Wang[1], Sabina Rinaldi[4], Rudolf Kaaks[4], Thomas M. Vogt[2], Lance Yokochi[3], and Robert Decker[2]

Abstract

Background: Circulating levels of insulin and insulin-like growth factor (IGF) hormones have been associated with colorectal cancer risk, but few studies have examined their associations with colorectal adenoma.

Methods: We measured plasma C-peptide, a marker of insulin secretion, and IGF hormones in a case-control study of 554 pathologically confirmed, first-time adenoma cases and 786 controls with normal endoscopy among Caucasians, Japanese, and Native Hawaiians in Hawaii.

Results: High plasma levels of C-peptide were statistically significantly associated with risk of colorectal adenoma [multivariate odds ratio (95% confidence interval) for increasing quartiles: 1.0, 0.91 (0.65-1.27), 1.21 (0.86-1.71), and 1.79 (1.23-2.60); P_{trend} = 0.0002]. We also observed a statistically significant inverse association between levels of plasma IGF binding protein-1 (IGFBP-1) and adenoma risk [1.0, 0.97 (0.70-1.34), 0.82 (0.58-1.15), and 0.47 (0.32-0.70); P_{trend} <0.0001]. These associations remain significant after adjusting for each other and were not confounded by known risk factors. IGF-I, IGFBP-3, body mass index, and waist or hip circumference were not independently associated with adenoma risk.

Conclusion: These results provide evidence for an association of insulin and IGFBP-1 levels with colorectal adenoma.

Impact: This study suggests that hyperinsulinemia and IGF hormones may act as etiologic factors in colorectal carcinogenesis, as early as during adenoma formation. *Cancer Epidemiol Biomarkers Prev; 19(6); 1471–7.* ©2010 AACR.

Introduction

High-caloric diets, lack of physical activity, and excess body weight have consistently been associated with colorectal cancer risk. These associations have been proposed to result from the proliferative and anti-apoptotic effects of the increased circulating insulin levels that are observed among overweight and obese individuals (1). Indeed, current epidemiologic evidence suggests that high prediagnostic insulin levels are associated with a 35% elevated risk of colorectal cancer (2, 3). In contrast, the evidence linking hyperinsulinemia to the risk of colorectal adenoma, a known colorectal cancer precursor, is more limited and has remained inconsistent (4-6). Insulin-like growth factor (IGF) hormones are also suspected to play a role in colon carcinogenesis through mechanisms similar to insulin, but their associations with colorectal cancer have been more inconsistent (7).

We report here on the largest study to date examining the association of plasma C-peptide (a marker of insulin secretion) and IGF hormones with colorectal adenoma risk.

Materials and Methods

Subjects

The study design and data collection for this colorectal adenoma study have been described in detail elsewhere (8, 9). Briefly, two flexible-sigmoidoscopy screening clinics were first used to recruit participants in Oahu, Hawaii. Adenoma cases were identified either as part of the baseline screening exam at the Hawaii site of the Prostate Lung Colorectal and Ovarian (PLCO) screening trial from July 1996 to February 2000 or at the Gastroenterology Screening Clinic of Kaiser Permanente Hawaii (KPH) from January 1995 to June 2006. In addition, starting in June 2002, we also attempted to recruit all eligible patients who underwent a colonoscopy at the KPH Gastroenterology Department. Cases were

Authors' Affiliations: [1]Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, [2]Kaiser Permanente Hawaii, and [3]Pacific Health Research Institute, Honolulu, Hawaii; and [4]International Agency for Research on Cancer, Lyon, France

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Current address for R. Kaaks: Division of Cancer Epidemiology, Deutsches Krebsforshungszentrum (DKFZ), Heildelberg, Germany.

Corresponding Author: Loïc Le Marchand, Epidemiology Program, Research Cancer Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Suite 407, Honolulu, HI 96813. Phone: 808-586-2988; Fax: 808-586-2082. E-mail: Loic@crch.hawaii.edu

doi: 10.1158/1055-9965.EPI-10-0128

Table 1. Main characteristics of study participants

	Cases (*n* = 554)	Controls (*n* = 786)	*P**
Male (%)	64.1	64.9	0.76
Race (%)			0.77
Japanese	34.8	34.5	
Caucasian	45.1	46.8	
Hawaiians	20.1	18.7	
Site and type of examination (%)			<0.0001
Kaiser (colonoscopy)	30.9	22.0	
Kaiser (flexible sigmoidoscopy)	51.8	51.2	
PLCO (flexible sigmoidoscopy)	17.3	26.8	
Age at blood draw, years	63 (57-69)	63 (58-69)	0.23
Previous history of colorectal endoscopy (%)	32.7	39.2	0.01
Ever use of aspirin† (%)	32.1	30.1	0.42
Past history of diabetes (%)	13.2	10.2	0.09
Education, years	14 (12-17)	16 (12-17)	0.01
Smoking status (%)			0.0003
Never smoker	40.7	48.0	
Past smoker	45.2	44.2	
Current smoker	14.1	7.8	
Pack-years‡	24 (10-43)	19 (5-37)	0.06
BMI, kg/m^2	26.6 (24.0-30.2)	25.9 (23.4-29.2)	0.002
Waist circumference, cm	95.0 (87.1-104.2)	93.0 (84.5-102.0)	0.005
Hip circumference, cm	104.0 (98.5-112.9)	103.1 (97.0-110.3)	0.01
Waist to hip ratio	0.91 (0.84-0.96)	0.91 (0.84-0.95)	0.11
Total calories, kcal/d	2,061 (1,587-2,821)	2,071 (1,620-2,779)	0.89
Alcohol consumption, g/d	2.0 (0.3-17.2)	1.3 (0.2-11.1)	0.02
Daily energy expenditure, MET	57 (49-66)	57 (50-66)	0.67
Dietary fiber from vegetables, g/d	15.9 (12.5-19.5)	16.5 (13.2-20.7)	0.004
Total calcium, mg/d§	828 (622-1,257)	918 (679-1,320)	0.01
Total folate, DFE/d§	769 (499-1,194)	933 (567-1,291)	<0.0001
Total processed meat, g/d	22.2 (10.9-42.0)	20.1 (8.5-39.2)	0.02

NOTE: Data are medians (interquartile range), except as indicated.

Abbreviations: DFE, dietary folate equivalents; MET, metabolic equivalents.

*P values are from Pearson's χ^2 test for percentages and Wilcoxon rank sum test for continuous traits comparing cases and controls.

†Ever use: twice a week for ≥3 consecutive months.

‡Pack-years: pack-years of cigarette/cigar/pipe smoking among ever smokers.

§From foods and supplements (adjusted for total calories).

patients with histologically confirmed first-time adenoma(s) of the colorectum and were of Japanese, Caucasian, or Hawaiian race/ethnicity. Controls were selected among individuals found to have a normal colon and rectum at endoscopy, and were individually matched to the cases (with a one to one ratio) on age, sex, race/ethnicity, screening date (±3 months), clinic, and type of examination (colonoscopy or flexible sigmoidoscopy). The study participation rate was 68% for cases and 69% for controls. Blood was provided by 87.5% of cases and 86.3% of controls who were interviewed. The present analyses were based on 554 cases and 786 controls who were interviewed up to February 2007 and gave a blood sample.

Exposure information was collected via an interview-administered questionnaire designed to obtain demographic and lifestyle information, including lifetime histories of tobacco smoking and alcohol drinking, weight at time of examination, usual physical activity, personal medical history, family history of colorectal cancer, and for females, reproductive and hormone use histories. The interview also included a validated food frequency questionnaire with >200 food items (10, 11) and a meat module assessing frequency of consumption and degree of doneness for various meats cooked with high-temperature methods (broiling, grilling/barbecuing, pan-frying). Detailed information on vitamin and mineral supplement use was also

collected. Each subject was also asked to donate a blood sample that was drawn in the morning after a 10-hour fast. Waist and hip circumferences were measured by trained study personnel. Specimens were processed within two hours of collection and stored at -80°C until laboratory analysis. All participants with an available plasma sample were included in the study regardless of whether both members of a matched case-control set had given blood.

Plasma IGF hormones (IGF-I, IGFBP-1, IGFBP-3) and C-peptide were analyzed at the International Agency for Research on Cancer blinded to the subject's case-control status. Samples of cases and controls were assayed together in the same analytical batch giving priority to matched sets and, in situations in which plasma was not available for all members of a matched set (due to refusal to give blood), to cases and controls of the same sex, same ethnicity, and similar age. C-peptide concentrations were measured with RIA, IGF-I and IGFBP-3 concentrations by enzyme-linked immunoabsorbent assays, and IGFBP-1 by immunoradiometric assay (Diagnostic System Laboratories). The IGF-I assay included an initial acid-ethanol precipitation step to separate IGF-I from its binding proteins. Based on 52 blind duplicate sample pairs analyzed with the study samples, the mean coefficients of variation for these assays were 4.6%, 5.3%, 6.4%, and 6.5% for C-peptide, IGFBP-1, IGF-I, and IGFBP-3, respectively.

Statistical analysis

Pearson's χ^2 and Wilcoxon's rank sum test were used to compare the distribution of demographic characteristics between cases and controls. General linear model was used to compare body mass index (BMI), waist circumference, and plasma biomarker levels (C-peptide, IGF-I, IGFBP-1, IGFBP-3, and the molar IGF1/IGFBP3 ratio) across ethnic groups by gender, with or without adjustment for age at blood draw and months of postmenopausal estrogen use (men were assigned zero values). Kruskal-Wallis test was also applied in comparing the biomarkers among ethnic groups because not all biomarkers were normally distributed. Partial Spearman's correlation coefficients were computed to examine correlations among the blood biomarkers, BMI, waist and hip circumferences, waist to hip ratio, and energy in Metabolic Equivalents (METs) expended during an average day.

To estimate the risk of colorectal adenoma conferred by BMI and the various blood biomarkers, we used unconditional logistic regression to obtain odds ratios (OR) and 95% confidence intervals (95% CI). Because all subjects who gave blood (86.8% of interviewed subjects) were used in this analysis and because they differed across the three recruitment sources (PLCO, KPH screening clinic, KPH Gastroenterology Department) with respect to sex, age at blood draw, race/ethnicity, and BMI, our analysis was unmatched and adjusted for age at blood draw, race/ethnicity, sex, recruitment site, type of examination, and BMI. The regression models were further adjusted for other variables associated with adenoma risk, namely, average daily energy expenditure, pack-years of smoking, duration of postmenopausal estrogen use, daily intake of alcohol (quartiles), daily intake of total folate (from foods and supplements; ≤400, 400-1,000, ≥1,000 dietary folate equivalents/day), and the logarithm of daily caloric intake, where alcohol and folate intake were expressed as nutrient density. Some variables, such as lifetime use of aspirin, years of schooling, dietary fiber, waist and hip circumferences, waist to hip ratio, and total calcium and processed meat, were not included in the final model because they did not materially change the OR estimates or increase model-fit. BMI and the biomarker measurements were categorized into four levels according to the quartiles based on all study subjects. Linear trends in ORs were tested using the median values for each quartile.

Interactions between plasma biomarkers and sex, race, BMI (≤25, 25-≤30, >30 kg/m^2), history of diabetes, and

Table 2. Median BMI, waist circumference, and biomarker levels in control subjects

	Men (*n* = 510)				Women (*n* = 276)			
	JPN	CAU	NH	*P**	JPN	CAU	NH	*P**
BMI (kg/m^2)	25.8	26.5	28.5	$<10^{-4}$	23.8	24.9	28.1	$<10^{-4}$
Waist circumference (cm)	92	99	101	$<10^{-4}$	80	86	93	$<10^{-4}$
C-peptide (ng/mL)	3.0	3.4	3.5	0.008	2.8	3.0	4.2	0.002
IGF-I (ng/mL)	190	201	189	0.23	147	162	164	0.54
IGFBP-1 (ng/mL)	28.4	20.7	22.5	0.53	37.9	43.7	25.5	0.01†
IGFBP-3 (ng/mL)	3616	4031	3603	0.01†	4213	4420	4281	0.73
IGF-I/IGFBP-3	0.19	0.18	0.20	0.15	0.14	0.14	0.15	0.13

Abbreviations: JPN, Japanese; CAU, Caucasian; NH, Native Hawaiian.

*P values for crude differences in biomarker distribution across ethnic/racial groups within each sex.

†These P values became nonsignificant (>0.05) after adjustment for age at blood draw, and for postmenopausal estrogen use (men were assigned zero). The significance of other P values remained unchanged after adjustment.

Table 3. Partial Spearman rank correlation coefficients (n = 1,318)

	BMI (*P*)	Waist circumference (*P*)	C-peptide (*P*)	IGF-I (*P*)	IGFBP-1 (*P*)
Waist circumference.	0.85 (<0.0001)				
C-peptide	0.50 (<0.0001)	0.53 (<0.0001)			
IGF-I	–0.02 (0.45)	–0.02 (0.59)	0.06 (0.03)		
IGFBP-1	–0.44 (<.0001)	–0.44 (<0.0001)	–0.58 (<0.0001)	–0.20 (<0.0001)	
IGFBP-3	0.01 (0.78)	0.04 (0.14)	0.12 (<0.0001)	0.58 (<0.0001)	–0.19 (<0.0001)

NOTE: Values adjusted for age at blood draw, sex, ethnicity, case-control status, and duration of postmenopausal estrogen use (men were assigned 0).

age at blood draw (≤53, 53 to 65, >65 years) were assessed with the likelihood ratio test, comparing the likelihood of a main effect model with a model including both main effect and interaction terms. Possible interactions (up to the third order) among important biomarkers were also examined separately among subjects with and without a history of diabetes. All statistical tests were done with a significance level of 0.05 (two-sided) using SAS (version 9.1).

Results

Table 1 displays the main characteristics of the participants by case-control status. Compared with cases, controls were more educated, smoked less, had lower BMI and smaller waist and hip circumferences, were more likely to have had a previous colorectal endoscopy, and consumed less alcohol and processed meat, and more fiber from vegetables, total folate, and total calcium. The distribution of other variables, including aspirin use and daily energy expenditure, was similar between cases and controls.

Table 2 presents the median values of the anthropometric measurements and the blood biomarkers in control subjects only, by sex and race. BMI, waist circumference, and plasma C-peptide levels were significantly different across ethnic groups for both men and women ($P < 0.01$ with or without adjustment for age at blood draw, and for postmenopausal estrogen use in women). Unadjusted tests also suggested that the distributions of IGFBP-3 levels in men and IGFBP-1 levels in women were different across ethnic groups (both $P = 0.01$). However, these associations were weakened after controlling for age at blood draw in both sexes and further for menopausal estrogen use in women (both $P = 0.06$). The Kruskal-Wallis test gave similar P values to the general linear model test in the unadjusted analysis.

Table 3 shows the partial Spearman's correlation coefficients for the same variables, after adjustment for age at blood draw, sex, ethnicity, case-control status, and duration of postmenopausal estrogen use. Plasma C-peptide levels were highly negatively correlated with IGFBP-1 levels (r = -0.58; $P < 0.0001$). BMI was also correlated positively with C-peptide levels (r = 0.50; $P < 0.0001$) and negatively with IGFBP-1 levels (r = -0.44; $P < 0.0001$). Plasma IGF-I was also correlated with levels of its binding proteins [IGFBP-3 (r = 0.58; $P < 0.0001$) and IGFBP-1 (r = -0.20; $P < 0.0001$)]. The correlation between BMI and IGF-I or IGFBP-3 was not statistically significant. BMI was related positively to waist and hip circumferences, and to waist to hip ratio, and negatively to daily energy expenditure (correlation coefficients of 0.85, 0.84, 0.45, and -0.14, respectively; all $P < 0.0001$).

Table 4 presents the ORs of adenoma risk associated with quartiles of BMI and the biomarkers, after adjustment for the matching variables and important risk factors (see Materials and Methods). Increased plasma levels of C-peptide were associated with a higher risk of adenoma (P_{trend} = 0.0002), after controlling for BMI and other risk factors. The OR for the highest compared with the lowest quartile was 1.79 (95% CI, 1.23-2.60) and 1.61 (95% CI, 1.07-2.45), before and after adjusting for plasma IGF-I, IGFBP-1, and IGFBP-3 levels, respectively. Higher plasma IGFBP-1 levels were associated with a decreased risk ($P_{trend} < 0.0001$). The ORs for the 4th compared with the 1st quartile were 0.47 (95% CI, 0.32-0.70) and 0.55 (95% CI, 0.36-0.85), before and after adjustment for C-peptide, IGF-I, and IGFBP-3 levels, respectively. BMI, IGF-I, IGFBP-3, or the ratio IGF-I/IGFBP-3 did not show any significant association with adenoma. No association was observed for waist and hip circumferences and waist to hip ratio after adjustment for BMI and other factors.

Race-specific ORs for plasma biomarkers are shown in Supplementary Table S1. Similar inverse associations were observed for plasma IGFBP-1 with adenoma risk in the three ethnic groups. The direct association with C-peptide and adenoma risk was observed for Japanese and whites but not for Native Hawaiians, possibly due to the relatively smaller sample size in this group. However, the test for interaction with race for C-peptide did not reach statistical significance (P = 0.12).

We also examined interactions between C-peptide and the IGF hormones with sex, race, age at blood draw, and history of diabetes on the association with adenoma. No notable interaction was observed in all

subjects or after stratification on history of diabetes. Supplementary Table S2 shows the adenoma ORs for the biomarkers after exclusion of subjects with a history of diabetes. The direct association with C-peptide and inverse association with IGFBP-1 remained statistically significant.

Discussion

In this case-control study, we observed a direct association of plasma levels of C-peptide, a marker of insulin secretion, and an inverse association of plasma IGFBP-1 with risk of colorectal adenoma. These associations were independent of each other and seemingly not explained by known risk factors. IGF-I, IGFBP-3, BMI, and waist or hip circumferences were not associated with adenoma risk in our data.

Although lifestyle factors associated with elevated insulin secretion have been linked to risks of adenoma and colorectal cancer, and although direct measures of circulating insulin have been associated with colorectal cancer risk (1, 3), few studies have assessed the association of hyperinsulinemia and colorectal adenoma. Schoen et al. (4) found a direct association between serum insulin and IGF-I levels and the presence of adenoma detected by flexible sigmoidoscopy at the Pittsburgh site of the PLCO trial (202 cases, 256 controls). An association was also observed between C-peptide, but not IGFBP-1, and colorectal adenoma in a case-control study nested in the Nurses' Health Study (380 case-control pairs; ref. 5). In

Table 4. Odds ratios (95% CI) for adenoma risk according to quartiles of the biomarkers and BMI

	Quartiles				
	1st	2nd	3rd	4th	P_{trend}
C-peptide					
Ca/Co	117/218	112/224	144/191	181/153	
Median (ng/mL)	1.9	2.8	4.1	6.7	
OR (95% CI)*	1.0	0.91 (0.65-1.27)	1.21 (0.86-1.71)	1.79 (1.23-2.60)	0.0002
OR (95% CI)†	1.0	0.89 (0.62-1.26)	1.09 (0.75-1.58)	1.61 (1.07-2.45)	0.004
IGF-I					
Ca/Co	134/201	151/185	149/186	120/214	
Median (ng/mL)	110	162	200	263	
OR (95% CI)	1.0	1.22 (0.88-1.69)	1.23 (0.88-1.72)	0.85 (0.60-1.20)	0.29
OR (95% CI)†	1.0	1.21 (0.85-1.72)	1.15 (0.79-1.69)	0.83 (0.54-1.27)	0.26
IGFBP-1					
Ca/Co	167/168	152/182	141/193	92/242	
Median (ng/mL)	6.6	16.3	31.7	62.6	
OR (95% CI)	1.0	0.97 (0.70-1.34)	0.82 (0.58-1.15)	0.47 (0.32-0.70)	<0.0001
OR (95% CI)†	1.0	1.08 (0.77-1.51)	0.96 (0.66-1.38)	0.55 (0.36-0.85)	0.001
IGFBP-3					
Ca/Co	142/193	128/205	146/189	136/197	
Median (ng/mL)	2,637	3,641	4,419	5,309	
OR (95% CI)	1.0	0.87 (0.63-1.21)	1.00 (0.71-1.39)	0.79 (0.56-1.12)	0.29
OR (95% CI)†	1.0	0.83 (0.58-1.19)	0.94 (0.65-1.37)	0.78 (0.51-1.19)	0.37
IGF-I/IGFBP-3					
Ca/Co	139/194	137/197	147/189	129/204	
Median	0.12	0.15	0.19	0.24	
OR (95% CI)	1.0	1.11 (0.79-1.54)	1.28 (0.91-1.81)	1.16 (0.81-1.68)	0.39
OR (95% CI)†	1.0	1.09 (0.78-1.54)	1.19 (0.83-1.69)	1.09 (0.75-1.59)	0.65
BMI					
Ca/Co	120/217	139/195	137/196	158/178	
Median (kg/m^2)	22.1	25.0	27.7	32.6	
OR (95% CI)	1.0	1.23 (0.86-1.76)	1.11 (0.72-1.71)	1.18 (0.61-2.27)	0.74
OR (95% CI)†	1.0	1.13 (0.78-1.65)	1.03 (0.65-1.63)	1.07 (0.54-2.11)	0.93

Abbreviation: Ca/Co, cases/controls.

*Adjusted for sex, race, age at blood draw, recruitment clinic, examination type, daily energy expenditure, BMI (where appropriate), pack-years of smoking, duration of post-menopausal estrogen use, and alcohol and total folate intakes, and log of energy intake.

†Further adjusted for the other biomarkers (IGF-I, IGFBP-1, IGFBP-3, or C-peptide).

contrast, no association was found for C-peptide or IGFBP-1 concentrations with adenoma in a case-control study nested in the CLUE II cohort (132 cases, 260 controls; ref. 6).

The associations that we observed with plasma C-peptide and IGFBP-1 were stronger and independent from those with body size and physical activity, suggesting that these biomarkers are not solely surrogate markers for lifestyle and anthropometric characteristics. C-peptide is considered a better marker of insulin secretion than insulin itself because it has a longer half-life and its levels do not fluctuate as much. IGFBP-1 is known to be modulated by insulin levels and can regulate the bioactivity of IGF-I (7). IGF-I circulating levels are mainly dependent on growth hormone secretion and are weakly affected by insulin in well-nourished populations. Thus, this study suggests that insulin secretion and increased biologically available IGF-I may be etiologic factors in the formation of adenoma, as it has been proposed for colorectal cancer. Possible mechanisms include the proliferative and mitogenic/antiapoptotic effects of insulin and IGF-I (1, 7).

Of note in our data is the suggestion of a lack of association between plasma C-peptide and adenoma risk among Native Hawaiians. The native Polynesian populations of Hawaii and New Zealand are known to experience high rates of obesity and type 2 diabetes but only low to moderate rates of colorectal cancer. This is consistent with the recent observation of a lack of association between diabetes history and colorectal cancer risk among Native Hawaiian participants in the Multiethnic Cohort Study.[5] In contrast, diabetes was associated with an increased colorectal cancer risk among the other racial/ethnic groups (whites, Japanese Americans, Latinos, and African Americans) in this prospective study. Native Hawaiians tended to have higher C-peptide levels in our study (Table 2). Whether our results are explained by a ceiling effect, above which insulin would not affect colorectal neoplasia, and/or by a more rapid progression to insulin deficiency in Native Hawaiians, or by other mechanisms, will require further study.

A potential limitation of this study is that biomarker levels were measured after diagnosis of adenoma, and only once. Thus, it is not known whether the levels measured reflect the participants' past habitual levels. Adenoma patients are not typically asked to change their lifestyle as a result of their diagnosis, suggesting that postpolypectomy levels may reflect past levels. It is also unlikely that colorectal adenomas would affect production or circulating levels of C-peptide and IGF hormones. Two independent studies measured within-person variation in IGF-I by collecting two separate samples from the same individuals 6 and 8 weeks apart, with correlations of 0.94 and 0.65, respectively (12, 13). The coefficient of variation for C-peptide measured for 7 consecutive days and 2 weeks apart was reported to be 9.3% and 9.7%, respectively (14, 15). Thus, a single measurement should be reasonably representative of usual levels. Finally, our study was not adequately powered to allow for meaningful interaction or subgroup (e.g., by anatomical subsite or size of adenoma) analyses.

In summary, this study provides evidence for an association of insulin and IGFBP-1 with colorectal adenoma and suggests that hyperinsulinemia and IGF hormones may act as etiologic factors in colorectal carcinogenesis, as early as during adenoma formation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Barbara Saltzman and Jean Sato for coordinating the data collection, Maj Earle and Anne Tome for help with data management, and David Achaintre for carrying out the laboratory analyses.

Grant Support

National Cancer Institute grant R01 CA72520.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 02/02/2010; revised 03/18/2010; accepted 03/22/2010; published OnlineFirst 05/25/2010.

[5] J. He, D.O. Stram, L.N. Kolonel, B.E. Henderson, L. Le Marchand, C.A. Haiman. The association of diabetes with colorectal cancer risk: The Multiethnic Cohort. Submitted.

References

1. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J Nutr 2001;131:3109–20S.
2. Pisani P. Hyper-insulinaemia and cancer, meta-analysis of epidemiological studies. Arch Physiol Biochem 2008;114:63–70.
3. Jenab M, Riboli E, Cleveland RJ, et al. Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2007;121:368–76.
4. Schoen RE, Weissfeld JL, Kuller LH, et al. Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. Gastroenterology 2005;129:464–75.
5. Wei EK, Ma J, Pollak MN, et al. C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, and the risk of distal colorectal adenoma in women. Caner Epidemiol Biomarkers Prev 2006; 15:750–5.
6. Tsilidis KK, Brancati FL, Pollak MN, et al. Metabolic syndrome components and colorectal adenoma in the CLUE II cohort. Cancer Causes Control 2010;21:1–10.

7. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. Trends Endocrinol Metab 2006;17:328–36.
8. Le Marchand L, Donlon T, Seifried A, Kaaks R, Rinaldi S, Wilkens L. Association of a common polymorphism in the human GH1 gene and colorectal neoplasia. J Natl Cancer Inst 2002;94:454–60.
9. Saltzman BS, Yamamoto JF, Decker R, et al. Association of genetic variation in the transforming growth factor β-1 gene with serum levels and risk of colorectal neoplasia. Cancer Res 2008;68:1236–44.
10. Hankin JH, Yoshizawa CN, Kolonel LN. Reproducibility of a diet history in older men in Hawaii. Nutr Cancer 1990;13:12940.
11. Hankin JH, Wilkens LR, Kolonel LN, Yoshizawa CN. Validation of a quantitative diet history method in Hawaii. Am J Epidemiol 1991;133:616–28.
12. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor and prostate cancer risk: a prospective study. Science 1998;279:563–9.
13. Goodman-Gruen D, Barrett-Connor E. Epidemiology of insulin-like growth factor-I in elderly men and women. The Rancho Bernardo Study. Am J Epidemiol 1997;145:970–6.
14. Ricos C, Arbos MA. Quality goals for hormone testing. Ann Clin Biochem 1990;27:353–8.
15. Utzschneider KM, Prigeon RL, Tong J, et al. Within-subject variability of measures of β cell function derived from a 2 h OGTT: implications for research studies. Diabetologia 2007;50:2516–25.