

Plasma Insulin, Glucose, IGF-I, IGF-II, and IGFBP-3 and Risk of Recurrent Colorectal Adenomas

Melissa Kang, Anne F Peery, Cameron Locklear, Joseph A Galanko, Robert S Sandler, Temitope O Keku

Melissa Kang, Anne F Peery, Joseph A Galanko, Robert S Sandler, Temitope O Keku, Center for Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill, NC, the United States

Cameron Locklear, School of Medicine, University of North Carolina, Chapel Hill, NC, the United States

Correspondence to: Temitope O Keku, University of North Carolina, 103 Mason Farm Road, 7340 Medical Biomolecular Research Building, CB # 7032, Chapel Hill, NC, the United States. tokeku@med.unc.edu

Telephone: +039-06-33775289 Fax: +039-06-4455292

Received: December 11, 2012 Revised: January 15, 2013

Accepted: January 28, 2013

Published online: April 21, 2013

ABSTRACT

AIM: Insulin and insulin-like growth factors (IGF's) are associated with an increased risk of colorectal adenomas. The association with recurrent adenomas is inadequately studied. We prospectively examined the relationship between insulin biomarkers and the risk of recurrent adenomas.

METHODS: Our analysis included 167 subjects with one or more adenomas detected on a baseline colonoscopy who had a surveillance colonoscopy within three to five years. We measured serum biomarkers in all subjects at baseline. ELISA was used to measure fasting plasma insulin, IGF-I, IGF-II, and IGF binding protein-3 (IGFBP-3). The hexokinase assay was used to measure fasting plasma glucose and immuno-turbidimetric assay to measure hemoglobin A1C.

RESULTS: Subjects with recurrent adenomas were more likely to be male, overweight and have ≥ 3 adenomas at baseline. We found no significant associations between insulin (OR=1.6, 95% CI 0.7-3.5), glucose (OR=1.4, 95% CI 0.7-3.1), IGF-I (OR=0.7, 95% CI 0.3-1.5), IGF-II (OR=1.0, 95% CI 0.5-2.3), IGFBP-3 (OR=0.1, 95% CI 0.5-2.1), or anthropometric measures and recurrent adenomas.

CONCLUSIONS: Our results do not support a role for insulin biomarkers and recurrent colorectal adenomas.

© 2013 ACT. All rights reserved.

Key words: Insulin; Colorectal Adenoma; Insulin-Like Growth Factor

Kang M, Peery AF, Locklear C, Galanko JA, Sandler RS, Keku TO.

Plasma Insulin, Glucose, IGF-I, IGF-II, and IGFBP-3 and Risk of Recurrent Colorectal Adenomas. *Journal of Gastroenterology and Hepatology Research* 2013; 2(4): 531-535 Available from: URL: <http://www.ghrnet.org/index./joghr/>

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer death in men and women in the United States^[1]. Obesity and type II diabetes are risk factors for development of CRC. Each condition is associated with increased serum glucose levels, hyperinsulinemia and insulin resistance^[2-7]. Patients who use prescription insulins have a 3-fold increased risk of developing colorectal adenomas and CRC^[8]. Insulin's role in carcinogenesis is proposed to be due to the hormone's positive effect on the growth and proliferation of cells^[9-11]. Insulin has structurally related peptides, insulin-like growth factor (IGF) I and II, that have been shown to regulate cell proliferation and suppress apoptosis when bound to their receptors^[12]. IGF binding proteins (IGFBPs), especially IGFBP-3, sequester and inhibit the actions of IGFs^[12].

While a number of cross-sectional and prospective studies have shown a positive relationship between plasma insulin, IGFs and the risk of colorectal adenomas, and an inverse relationship with IGFBP-3, the results are inconsistent^[13-23]. Some studies have reported no change in the risk of CRC or adenomas with insulin or IGFBP-3, while two papers reported that increased IGF-I was associated with decreased adenoma recurrence^[11,15,20,24-31]. Others observed that the association was dependent on the histologic grade of adenoma, with high levels of IGFBP-3 associated with decreased risk only for high grade adenomas^[13,19]. Most of these studies examined only one or two markers each, and no study prospectively investigated the effect of IGF-II on colorectal adenoma recurrence.

Patients with a history of colorectal adenomas are at increased risk for CRC. Guidelines recommend surveillance endoscopy to reduce the risk of CRC. Surveillance endoscopy is expensive and not without harm. Insulin biomarkers might help guide surveillance by helping to stratify risk. We prospectively evaluated a panel of markers in the insulin-IGF axis to test the hypothesis that insulin and IGFs concentrations would be associated with an increased risk of recurrent adenomas. We also hypothesized that concentration of IGFBP-3 would be inversely related to adenoma recurrence. Finally, we explored the relationship between diet, lifestyle and anthropometric measures to assess the risk of adenoma recurrence.

METHODS

Study population

Our subjects were participants in the Diet and Health Study (DHS) III and IV. The DHS were cross-sectional studies to assess environmental and lifestyle factors associated with colorectal adenoma. The DHS methods have been published in detail elsewhere^[15,32]. Study subjects had a baseline outpatient colonoscopy in Diet and Health Study (DHS) III or IV between August 1998 and March 2000 and November 2001 and December 2002, respectively, at the University of North Carolina Hospitals (UNC). The DHS collected data on age, sex, educational background, BMI, race, smoking history, nonsteroidal anti-inflammatory drug (NSAID) use, and physical activity. Detailed information was obtained in a phone interview using a validated instrument^[15,32]. The DHS excluded: age < 30 years, previous colon cancer, colon resection, polyposis or colitis.

We limited our analysis to subjects with one or more adenomas detected during the baseline colonoscopy who returned for a surveillance colonoscopy. We only included subjects with insulin and insulin related biomarkers measured at the baseline colonoscopy. Recurrence was defined as a colorectal adenoma detected at the time of the repeat colonoscopy in subjects with an adenoma at baseline. A pathologist classified all polyps using standard pathologic criteria. Advanced adenomas were defined as villous histology, one or more adenomas larger than 1 cm or ≥ 3 adenomas. The study was approved by the institutional review board at UNC School of Medicine.

Data collection

Study participants underwent colonoscopies after an overnight fast. At the time of the initial colonoscopy, the research assistant measured weight, height, waist-to-hip ratio and took blood samples. A telephone interview conducted within 12 weeks from the initial colonoscopy obtained information on diet and lifestyle factors. Dietary information was obtained using the Block food frequency questionnaire or NCI quantitative Diet History Questionnaire version 1.0^[15,32].

Laboratory analysis

Blood samples were obtained at the time of the initial colonoscopy and processed to separate the plasma. Plasma was stored at -80°C in multiple aliquots until assayed to prevent repeated freezing and thawing. Fasting plasma insulin, IGF-I, IGF-II, IGFBP-3, were measured by ELISA as previously described using Diagnostic Systems Laboratory kits (Webster, TX)^[15,32]. Fasting plasma glucose was measured by hexokinase assay (Sigma, St. Louis, MO) (DHS III), and hemoglobin A1c (HbA1c) (DHS IV) by immunoturbidimetric assay (Ortho Clinical Diagnostics, Rochester, NY). As some subjects only had fasting glucose measured while others had HbA1c measured, we combined the glucose and HbA1c into one dataset for the baseline characteristics. To achieve this, we used a linear regression model as described by Rohlfing *et al* to convert HbA1c values into glucose equivalents using the following equation: mean plasma glucose (mg/dL) = $(35.6 \times \text{HbA1c}) - 77.3$ ^[33].

Statistical analysis

Baseline characteristics for recurrent and non-recurrent groups were compared using Fishers exact test for categorical variables and *t*-test (for means) and the Mann-Whitney test (for medians) for continuous variables. Insulin and related markers were log-transformed because those measures were not normally distributed. Then mean logs were compared via a *t*-test. Odds ratios and 95% confidence intervals were

calculated to compare baseline tertiles of biomarkers to adenoma recurrence using logistic regression. Logistic regression models were run with follow-up adenoma as the response and baseline characteristic of interest as the predictor. Unadjusted models were run as well as models adjusting for age, race and sex. *P*-values < 0.05 were considered statistically significant. All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC).

RESULTS

We identified 403 subjects with one or more colorectal adenomas on baseline colonoscopy. Of these, 253 returned for a repeat colonoscopy. A total of 167 subjects had baseline plasma insulin, IGF-I, IGF-II and IGFBP-3 and glucose levels measured. Compared to those without recurrent adenomas, a higher proportion of subjects with recurrent adenomas were male, overweight and had ≥ 3 adenomas at baseline (Table 1). Although plasma levels of insulin were higher in those with recurrent adenomas compared to no recurrent adenomas, this was not statistically significant ($p=0.16$) (Table 1). IGF-I, IGF-II, IGFBP-3 and glucose at baseline were not significantly different between those with and without recurrent adenomas (Table 1).

Table 1 Baseline characteristics of study participants who returned for follow up.

Characteristic	Recurrent adenomas (n=96)	No recurrent adenomas (n=157)	<i>p</i> value
Age [mean (SE)]	60.4 (1.0)	58.6 (0.8)	0.17
Race [n (%)]			
Caucasian	71 (82)	109 (76)	0.41
African American	16 (18)	34 (24)	
Gender [n (%)]			
Male	63 (66)	80 (52)	0.03
Female	32 (34)	75 (48)	
Smoking [n (%)]			
Never	39 (43)	68 (47)	0.47
Former	40 (44)	54 (37)	
Current	11 (12)	24 (16)	
Family history of CRC [n (%)]	19 (21)	27 (19)	0.74
BMI [n (%)]			
Normal	26 (28)	56 (38)	0.003
Overweight	42 (45)	35 (24)	
Obese	25 (27)	55 (38)	
Waist-hip Ratio [mean (SE)]	0.97 (0.01)	0.94 (0.01)	0.08
Calories kcal/day [mean (SE)]	1.74 (77)	1.78 (62)	0.76
Time to repeat colonoscopy, day [mean (SE)]	1.23 (80)	1.28 (50)	0.64
Adenoma grade [n (%)]			
Tubular	83 (86)	140 (89)	0.55
Villous	13 (14)	17 (11)	
# adenomas [n (%)]			
1-2	62 (75)	132 (91)	0.002
≥ 3	21 (25)	13 (9)	
Adenoma size [mean (SE)]			
<1cm	64 (67)	116 (75)	0.19
>1cm	32 (33)	39 (25)	
Diagnosis of diabetes [n (%)]	16 (18)	22 (15)	0.59
Alcohol grams per day [median (min, max)]	1.5 (0, 63.3)	2.5 (0, 81.2)	0.88
Calcium mg per day [mean (SE)]	901 (50)	984 (46)	0.23
NSAID use # per month [median (min, max)]	0 (0, 122)	0 (0, 184)	0.69
Insulin, microunits/mL [mean (SE)] ¹	2.10 (0.12)	1.90 (0.09)	0.16
IGF-I, ng/mL [mean (SE)] ¹	4.88 (0.06)	4.90 (0.05)	0.85
IGF-II, ng/mL [mean (SE)] ¹	6.29 (0.05)	6.32 (0.03)	0.57
IGFBP-3, ng/mL [mean (SE)] ¹	7.81 (0.05)	7.78 (0.04)	0.64
Glucose, mg/dL [mean (SE)] ¹	4.82 (0.03)	4.81 (0.03)	0.80

¹ Recurrent adenomas (n=67) and No recurrent adenomas (n=100) for insulin and other markers in the insulin-IGF axis. These were log transformed due to skewness of data.

While the risk of adenoma recurrence increased with increasing insulin and decreased with IGFBP-3, especially for those with baseline advanced adenomas, the trend was not statistically significant (Table 2). Similarly, IGF-I, IGF-II and glucose did not reveal any appreciable trends (Table 2).

When baseline anthropometric measures and adenoma characteristics were analyzed for adenoma recurrence, having 3 or more adenomas at baseline was significantly related to adenoma recurrence (OR=4.7, CI 95% 1.9-11.5) (Table 3). Adenoma size >1cm, BMI >25, villous histology, NSAIDs use, smoking, or calcium intake did not reveal significant associations (Table 3).

Table 2 Odds ratios (OR) (95% CI) for adenoma recurrence risk according to tertiles of biomarkers.

Measure	Reference	OR (95% CI) for all baseline adenomas		OR (95% CI) for only baseline advanced adenomas ¹	
	Tertile1	Tertile2	Tertile3	Tertile2	Tertile3
Insulin	1.0	0.9 (0.4, 2.0)	1.6 (0.7, 3.5)	1.5 (0.3, 8.5)	2.9 (0.4, 21.8)
IGF-I	1.0	0.6 (0.3, 1.3)	0.7 (0.3, 1.5)	1.4 (0.3, 6.1)	0.5 (0.09, 3.0)
IGF-II	1.0	1.0 (0.4, 2.1)	1.0 (0.5, 2.3)	0.6 (0.1, 2.8)	1.1 (0.2, 6.1)
IGFBP-3	1.0	0.5 (0.2, 1.1)	1.0 (0.5, 2.1)	0.2 (0.03, 1.1)	0.6 (0.1, 3.2)
Glucose	1.0	0.8 (0.3, 1.8)	1.4 (0.7, 3.1)	0.4 (0.08, 2.3)	0.9 (0.2, 4.2)

Adjusted for age, race and gender. ¹Advanced adenomas included villous histology, size >1cm or ≥ 3 adenomas.

Table 3 Baseline characteristics and OR (95% CI) for recurrence of adenomas.

	Unadjusted OR (95% CI)	Adjusted ¹ OR (95% CI)
Villous histology		
No	1.0	1.0
Yes	1.3 (0.6, 2.8)	1.3 (0.5, 3.1)
# of adenomas		
1-2	1.0	1.0
≥ 3	3.5 (1.6, 7.3)	4.7 (1.9, 11.5)
Size of adenomas		
<1cm	1.0	1.0
>1cm	1.5 (0.9, 2.6)	1.5 (0.8, 2.8)
NSAIDs >15 times/month		
No	1.0	1.0
Yes	1.0 (0.5, 1.7)	0.7 (0.4, 1.5)
Smoking		
Never	1.0	1.0
Former	0.8 (0.4, 1.8)	1.2 (0.6, 2.1)
Current	1.3 (0.7, 2.3)	0.9 (0.4, 2.0)
BMI		
Normal	1.0	1.0
Overweight, Obese	1.6 (0.9, 2.8)	1.6 (0.9, 3.0)
Calcium		
<1000mg/day	1.0	1.0
>1000mg/day	0.9 (0.5, 1.6)	0.9 (0.5, 1.7)

¹ Adjusted for age, race and gender

DISCUSSION

Our study prospectively evaluated the contribution of insulin, glucose, IGF-I, IGF-II and IGFBP-3 to the risk of recurrent adenomas. We assayed these biomarkers as well as other factors known to affect adenoma risk at the time of initial colonoscopy. We then determined whether baseline characteristics would predict future adenomas. Specifically, we tested the hypothesis that a single measure of circulating levels of plasma insulin and insulin related peptides would be positively correlated with risk of colorectal adenoma recurrence. Our results revealed that there was no significant association of insulin with adenoma recurrence. Likewise, there were no associations between IGF-I, IGF-II, IGFBP-3 and recurrence. The only risk factor that predicted recurrence was ≥ 3 adenomas during the initial colonoscopy. We observed a trend toward

recurrent adenoma risk with higher BMI which is consistent with the published literature^[34,35]. Likely because of small numbers, significant correlations were not found between smoking, calcium and NSAID use with recurrent adenomas even though smoking is reported to increase the risk while calcium and NSAID use decrease the risk of adenomas^[36-42].

Given the conflicting results of prior literature on effects of insulin, glucose, IGF-I, IGF-II, and IGFBP-3 on adenoma risk as well as inherent biases and limitations of cross-sectional studies, we evaluated these biomarkers in a prospective fashion. In our sample increasing insulin did not significantly increase the risk for adenoma recurrence. Biologically it is plausible that higher insulin levels increase the risk for adenoma formation. We previously demonstrated that increasing insulin was associated with decreased apoptosis, and these were associated with adenoma incidence^[15]. Because all of the subjects in this study had adenomas, they were at the higher end of the risk spectrum and it may not have been possible to detect associations in this small study.

We did not observe any significant relationships between IGF-I and adenoma recurrence. This contradicts the result of two prospective studies that observed an inverse association of increasing tertiles of IGF-I with decreased risk of adenoma recurrence^[22,23]. A potential explanation could be the different patient populations in these studies. Hoyo *et al* demonstrated that serum IGF-I and IGFBP-3 differ by race and smoking status, and our study included higher proportion of African Americans than that of Jacobs *et al*^[23,43].

We decided to evaluate the role of IGF-II because the risk for CRC has been shown to increase with higher quartiles of IGF-II^[27,44]. To the best of our knowledge, this is the first study prospectively evaluating the relationship between IGF-II and colorectal adenoma recurrence. We did not observe an association between IGF-II and adenoma recurrence in this study. As proliferating CRC cells are associated with overexpression of IGF-II and its receptors^[45,46], it is possible that the effects of IGF-II are more prominent late in the process of carcinogenesis rather than in the earlier stages of neoplasia, such as in colorectal adenomas.

Our current analysis had several strengths. This was a prospective study focusing on the temporal effect of insulin-IGF axis on colorectal adenoma recurrence. Further, we attempted to incorporate many relevant CRC and adenoma risk factors and investigated plasma insulin, glucose, IGF-I, IGF-II and IGFBP-3. However, as participants were volunteers and selected for initial colonoscopy, the conclusions may not be exactly generalizable to the entire population. Also, we only had one time point for biomarker collection and thus, were unable to assess the effect of change in the levels of these markers over time on the recurrent adenoma risk. Future studies could address the possible differential influence of insulin and IGF's on advanced adenomas at baseline and at follow up.

In conclusion, these data do not suggest a role of circulating insulin in the development of recurrent adenomas. The current study also does not support the use of a single measurement of IGF-I, IGF-II or IGFBP-3 in surveillance of recurrent colorectal adenomas. As such, these biomarkers are not likely to be useful to predict risk for recurrent adenomas.

ACKNOWLEDGMENTS

This research was supported, in part, by grants from the National Institutes of Health (P30 DK 034987, T35 DK007386, R01 CA44684, T32 DK007737, T32 DK07634).

REFERENCES

- 1 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA: a cancer journal for clinicians* 2012; **62**: 10-29
- 2 Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: A review. *The American journal of clinical nutrition* 2007; **86**: s836-842
- 3 Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nature reviews. Cancer* 2004; **4**: 579-591
- 4 Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: A meta-analysis of prospective studies. *The American journal of clinical nutrition* 2007; **86**: 556-565
- 5 Kabat GC, Kim MY, Strickler HD, Shikany JM, Lane D, Luo J, Ning Y, Gunter MJ, Rohan TE. A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women. *British journal of cancer* 2012; **106**: 227-232
- 6 Yamamoto S, Nakagawa T, Matsushita Y, Kusano S, Hayashi T, Irokawa M, Aoki T, Korogi Y, Mizoue T. Visceral fat area and markers of insulin resistance in relation to colorectal neoplasia. *Diabetes care* 2010; **33**: 184-189
- 7 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. *Journal of the National Cancer Institute* 1999; **91**: 1147-1154
- 8 Call R, Grimsley M, Cadwallader L, Cialone L, Hill M, Hreish V, King ST, Riche DM. Insulin--carcinogen or mitogen? Preclinical and clinical evidence from prostate, breast, pancreatic, and colorectal cancer research. *Postgraduate medicine* 2010; **122**: 158-165
- 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; **147**: 1830-1837
- 10 Nagel JM, Staffa J, Renner-Muller I, Horst D, Vogeser M, Langkamp M, Hoeflich A, Goke B, Kolligs FT, Mantzoros CS. Insulin glargine and nph insulin increase to a similar degree epithelial cell proliferation and aberrant crypt foci formation in colons of diabetic mice. *Hormones & cancer* 2010; **1**: 320-330
- 11 Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H. Insulin analogues display igf-i-like mitogenic and anti-apoptotic activities in cultured cancer cells. *Diabetes/ metabolism research and reviews* 2009; **25**: 41-49
- 12 Durai R, Yang W, Gupta S, Seifalian AM, Winslet MC. The role of the insulin-like growth factor system in colorectal cancer: Review of current knowledge. *International journal of colorectal disease* 2005; **20**: 203-220
- 13 Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, Majeed N, Colditz GA, Speizer FE, Hankinson SE. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 345-349
- 14 Flood A, Mai V, Pfeiffer R, Kahle L, Remaley AT, Lanza E, Schatzkin A. Elevated serum concentrations of insulin and glucose increase risk of recurrent colorectal adenomas. *Gastroenterology* 2007; **133**: 1423-1429
- 15 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**: 2076-2081
- 16 Soubry A, Il'yasova D, Sedjo R, Wang F, Byers T, Rosen C, Yashin A, Ukraintseva S, Haffner S, D'Agostino R, Jr. Increase in circulating levels of igf-1 and igf-1/igfbp-3 molar ratio over a decade is associated with colorectal adenomatous polyps. *International journal of cancer. Journal international du cancer* 2012; **131**: 512-517
- 17 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**: 464-475
- 18 Gao Y, Katki H, Graubard B, Pollak M, Martin M, Tao Y, Schoen RE, Church T, Hayes RB, Greene MH, Berndt SI. Serum igf1, igf2 and igfbp3 and risk of advanced colorectal adenoma. *International journal of cancer. Journal international du cancer* 2012; **131**: E105-113
- 19 Renehan AG, Painter JE, Atkin WS, Potten CS, Shalet SM, O'Dwyer ST. High-risk colorectal adenomas and serum insulin-like growth factors. *The British journal of surgery* 2001; **88**: 107-113
- 20 Renehan AG, Painter JE, O'Halloran D, Atkin WS, Potten CS, O'Dwyer ST, Shalet SM. Circulating insulin-like growth factor ii and colorectal adenomas. *The Journal of clinical endocrinology and metabolism* 2000; **85**: 3402-3408
- 21 Sedjo RL, D'Agostino RB, Jr., Ahnen D, Levin TR, Haffner SM, Tooze JA, Byers T. Lack of association between insulin sensitivity and colorectal adenoma risk. *Nutrition and cancer* 2011; **63**: 6-11
- 22 Flood A, Mai V, Pfeiffer R, Kahle L, Rosen CJ, Lanza E, Schatzkin A. Serum concentrations of insulin-like growth factor and insulin-like growth factor binding protein 3 and recurrent colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 2008; **B**: 1493-1498
- 23 Jacobs ET, Martinez ME, Alberts DS, Ashbeck EL, Gapstur SM, Lance P, Thompson PA. Plasma insulin-like growth factor i is inversely associated with colorectal adenoma recurrence: A novel hypothesis. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 300-305
- 24 Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (igf)-i and igf-binding protein-3. *Journal of the National Cancer Institute* 1999; **91**: 620-625
- 25 Rinaldi S, Cleveland R, Norat T, Biessy C, Rohrmann S, Linseisen J, Boeing H, Pischon T, Panico S, Agnoli C, Palli D, Tumino R, Vineis P, Peeters PH, van Gils CH, Bueno-de-Mesquita BH, Vrieling A, Allen NE, Roddam A, Bingham S, Khaw KT, Manjer J, Borgquist S, Dumeaux V, Torhild Gram I, Lund E, Trichopoulou A, Makrygiannis G, Benetou V, Molina E, Donate Suarez I, Barricarte Gurrea A, Gonzalez CA, Tormo MJ, Altzibar JM, Olsen A, Tjonneland A, Gronbaek H, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Slimani N, Boffetta P, Jenab M, Riboli E, Kaaks R. Serum levels of igf-i, igfbp-3 and colorectal cancer risk: Results from the epic cohort, plus a meta-analysis of prospective studies. *International journal of cancer. Journal international du cancer* 2010; **126**: 1702-1715
- 26 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. *Journal of the National Cancer Institute* 2000; **92**: 1592-1600
- 27 Probst-Hensch NM, Yuan JM, Stanczyk FZ, Gao YT, Ross RK, Yu MC. Igf-1, igf-2 and igfbp-3 in prediagnostic serum: Association with colorectal cancer in a cohort of chinese men in shanghai. *British journal of cancer* 2001; **85**: 1695-1699
- 28 Chronis A, Thomopoulos K, Sapountzis A, Triantos C, Kalafateli M, Kalofonos C, Nikolopoulou V. Adiposity factors are not related to the presence of colorectal adenomas. *Clinical and experimental gastroenterology* 2011; **4**: 257-261
- 29 Le Marchand L, Wang H, Rinaldi S, Kaaks R, Vogt TM,

- Yokochi L, Decker R. Associations of plasma c-peptide and igfbp-1 levels with risk of colorectal adenoma in a multiethnic population. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1471-1477
- 30 Suzuki S, Kojima M, Tokudome S, Suzuki K, Ozasa K, Ito Y, Inaba Y, Tajima K, Nakachi K, Watanabe Y, Tamakoshi A. Insulin-like growth factor (igf)-i, igf-ii, igf binding protein-3, and risk of colorectal cancer: A nested case-control study in the japan collaborative cohort study. *Asian Pacific journal of cancer prevention: APJCP* 2009; **10** Suppl: 45-49
- 31 Manousos O, Souglakos J, Bosetti C, Tzonou A, Chatzidakis V, Trichopoulos D, Adami HO, Mantzoros C. Igf-i and igf-ii in relation to colorectal cancer. *International journal of cancer. Journal internationale du cancer* 1999; **83**: 15-17
- 32 Keku TO, Sandler RS, Simmons JG, Galanko J, Woosley JT, Proffitt M, Omofoye O, McDoom M, Lund PK. Local igfbp-3 mRNA expression, apoptosis and risk of colorectal adenomas. *BMC cancer* 2008; **8**: 143
- 33 Rohlffing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and hba(1c): Analysis of glucose profiles and hba(1c) in the diabetes control and complications trial. *Diabetes care* 2002; **25**: 275-278
- 34 Stein B, Anderson JC, Rajapakse R, Alpern ZA, Messina CR, Walker G. Body mass index as a predictor of colorectal neoplasia in ethnically diverse screening population. *Digestive diseases and sciences* 2010; **55**: 2945-2952
- 35 Okabayashi K, Ashrafian H, Hasegawa H, Yoo JH, Patel VM, Harling L, Rowland SP, Ali M, Kitagawa Y, Darzi A, Athanasiou T. Body mass index category as a risk factor for colorectal adenomas: A systematic review and meta-analysis. *The American journal of gastroenterology* 2012; **107**: 1175-1185; quiz 1186
- 36 Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU. A randomized trial of aspirin to prevent colorectal adenomas. *The New England journal of medicine* 2003; **348**: 891-899
- 37 Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, Petrelli N, Pipas JM, Karp DD, Loprinzi CL, Steinbach G, Schilsky R. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *The New England journal of medicine* 2003; **348**: 883-890
- 38 Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. Cigarette smoking, alcohol use, and colorectal adenoma in Japanese men and women. *Diseases of the colon and rectum* 1999; **42**: 337-342
- 39 Anderson JC, Stein B, Kahi CJ, Rajapakse R, Walker G, Alpern Z. Association of smoking and flat adenomas: Results from an asymptomatic population screened with a high-definition colonoscope. *Gastrointestinal endoscopy* 2010; **71**: 1234-1240
- 40 Voutsinas J, Wilkens LR, Franke A, Vogt TM, Yokochi LA, Decker R, Le Marchand L. Heterocyclic amine intake, smoking, cytochrome p450 1a2 and n-acetylation phenotypes, and risk of colorectal adenoma in a multiethnic population. *Gut* 2012;
- 41 Grau MV, Baron JA, Sandler RS, Wallace K, Haile RW, Church TR, Beck GJ, Summers RW, Barry EL, Cole BF, Snover DC, Rothstein R, Mandel JS. Prolonged effect of calcium supplementation on risk of colorectal adenomas in a randomized trial. *Journal of the National Cancer Institute* 2007; **99**: 129-136
- 42 Kesse E, Boutron-Ruault MC, Norat T, Riboli E, Clavel-Chapelon F. Dietary calcium, phosphorus, vitamin d, dairy products and the risk of colorectal adenoma and cancer among french women of the e3n-epic prospective study. *International journal of cancer. Journal internationale du cancer* 2005; **117**: 137-144
- 43 Hoyo C, Grubber J, Demark-Wahnefried W, Lobaugh B, Jeffreys AS, Grambow SC, Marks JR, Keku TO, Walther PJ, Schildkraut JM. Predictors of variation in serum igf1 and igfbp3 levels in healthy african american and white men. *Journal of the National Medical Association* 2009; **101**: 711-716
- 44 Hunt KJ, Toniolo P, Akhmedkhanov A, Lukanova A, Dechaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE, Riboli E, Kaaks R. Insulin-like growth factor ii and colorectal cancer risk in women. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 901-905
- 45 Zarrilli R, Pignata S, Romano M, Gravina A, Casola S, Bruni CB, Acquaviva AM. Expression of insulin-like growth factor (igf)-ii and igf-i receptor during proliferation and differentiation of caco-2 human colon carcinoma cells. *Cell growth & differentiation: the molecular biology journal of the American Association for Cancer Research* 1994; **5**: 1085-1091
- 46 Weber MM, Fottner C, Liu SB, Jung MC, Engelhardt D, Baretton GB. Overexpression of the insulin-like growth factor i receptor in human colon carcinomas. *Cancer* 2002; **95**: 2086-2095

Peer reviewers: Isidoro DI CARLO, MD, PhD, FACS, Associate, Professor of Surgery, University of Catania, Department of Surgical Sciences, Organ Transplantation and Advanced Technologies, Cannizzaro Hospital, Via Messina 826, 95126 Catania, Italy; Sylvain Manfredi, MD, PhD, SMAD, CHU Pontchaillou, 2 rue H le Guilloux, 35000 Rennes, France.