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Increase in Circulating Levels of IGF-1 and IGF-1/IGFBP-3 Molar Ratio over a Decade is Associated with Colorectal Adenomatous Polyps

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Abstract

High levels of circulating insulin-like growth factor-1 (IGF-1) have been associated with increased risk of several cancers. Regarding colorectal cancer, these associations are generally weak. We hypothesized that an increase in IGF-1 over time would be a stronger risk factor for cancer-related outcomes than the actual levels. In this analysis we utilized existing data from the Insulin Resistance and Atherosclerosis Study (IRAS). Circulating IGF-1 levels and molar ratios of IGF-1 to IGF binding protein 3 (IGFBP-3) were measured at three time points, within a 10-year follow-up period. We examined the associations of increase of the two variables with the presence of colorectal adenoma at the end of follow-up among participants with normal glucose tolerance at baseline. This included 143 individuals, from which 24 were diagnosed with adenomatous polyps. Although the mean levels of IGF-1 and IGF-1/IGFBP-3 decline with age, approximately 30% of the participants showed an increase of at least fifteen percent ("ever increase") in one or both of these variables, compared to baseline. We found a positive association between "ever increase" in IGF-1 o r IGF-1/IGFBP-3 and the presence of colorectal adenoma: ORs were 3.81 (95% CI: 1.30-10.8) and 2.83 (95% CI: 1.00-8.22), respectively. No association was found when analyzing the actual levels of both variables at any time point. Our data suggest that an increase in circulating IGF-1 or IGF-1/IGFBP-3 may represent a disturbed GH/IGF1 homeostasis, which could favor the development of precancerous lesions, such as colorectal adenoma.

Keywords

IGF-1; colorectal adenoma; biomarkers

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INTRODUCTION

The insulin-like growth factor 1 (IGF-1) and members of the IGF-binding protein family (IGFBPs) are essential for cell cycle regulation. IGF-1 possesses mitogenic and anti-apoptotic functions that are modulated by binding to IGFBPs[1]. The majority of the circulating IGF-1 is bound to IGFBPs (mainly IGFBP-3), while a very small percentage of IGF-1 remains in an unbound and biologically active form[2]. IGF-1 and IGFBP-3 levels are controlled by pituitary growth hormone (GH) and affected by multiple factors, such as gender, race, nutrition, lifestyle, and age (with a decline after puberty)[2-5].

Many *in vitro* and *in vivo* studies provide evidence for a role of IGF-1 (or its binding partners) in neoplasia, including growth of colorectal cancer[1]. However, there are some inconsistencies among the studies related to colorectal cancer risk and IGF-1 levels. A recent meta-analysis reveals a weak association between circulating IGF-1 and colorectal cancer, with a relative risk estimate of only 1.07 (95% CI: 1.01-1.14) per one standard deviation[6]. Furthermore, high levels of IGF-1 are not always associated with increased signaling activity. It has been speculated that in some individuals a higher IGF-1 level might reflect a homeostatic mechanism to control for deficiencies in IGF-1 receptors[1]. This allowed us to hypothesize that intra-individual changes in IGF-1 levels over time would be a stronger risk factor for colorectal cancer-related outcomes than the actual levels themselves. To examine this hypothesis, we analyzed existing data from the Insulin Resistance and Atherosclerosis Study (IRAS) sub-cohort of generally healthy individuals at the baseline. Specifically, we considered intra-individual dynamics of circulating IGF-1 and the IGF-1/IGFBP-3 molar ratio over a 10-year period and assessed their associations with the occurrence of colorectal adenomatous polyps. Because there is an overall age-related decrease in IGF-1 and IGF-1/IGFBP-3, we assumed that even a temporary increase in these variables would represent an aberrant trend in the homeostatic control of the GH/IGF-1 signaling pathway. Therefore, we hypothesized that an increase in IGF-1 levels and/or the IGF-1/IGFBP-3 ratio at any time point after baseline would be associated with the presence of colorectal polyps at the end of the 10-year follow-up period.

MATERIALS AND METHODS

Study Population

This colon study was nested in the IRAS multi-ethnic cohort study of which a full description has been published previously[7]. Between 1992 and 1994, the IRAS recruited 600 men and women with normal glucose tolerance (NGT) from four clinical centers; the age range was 40 to 69. Colonoscopies were conducted between 2002 and 2004 and details are described elsewhere[8]. All participants provided signed informed consent and the study was approved by the Institutional Review Boards of all collaborating organizations. All surviving IRAS cohort participants who were ≥49 years of age and mentally eligible were invited to undergo a screening colonoscopy. Participants with prior adenomatous polyps were included if their next colonoscopy exam was due within the study period. Patients with serious concurrent illnesses were excluded (e.g. recent heart attack, oxygen dependent pulmonary disease, renal failure, prosthetic heart valve, and colon cancer). After these exclusions, 335 IRAS participants who had normal glucose tolerance at baseline received colonoscopy. The histology reports were missing from 2 of the participants. Of the remaining 333 participants, 174 of them had baseline measurements of circulating IGF-1 and IGFBP-3 (1992-1994) and thus were eligible for the prospective cohort analysis. The final analytical cohort of 143 (82% of the eligible cohort) had all 3 sets of measurements available, including the IRAS follow-up (1997-1999) and colonoscopy (2002-2004) visits.

Colonoscopy

Experienced physicians performed the colonoscopies, reaching the cecum in 96% of participants. Size and location of all visible polyps were recorded and the polyps were removed. A standard histologic assessment was done by the local clinical laboratory. Within the analytical cohort, 118 participants (83%) had no adenomatous polyps or had hyperplastic polyps (further referred as “no adenoma”). No carcinomas were diagnosed, but 24 participants (17%) had adenomatous polyps (referred as “adenoma”).

Blood Collection

At the IRAS baseline and first follow-up, blood specimen collections were processed and plasma was stored at the University of South California Diabetes Research Center in Los Angeles, CA (at -80°C). At the colonoscopy visit, blood samples were processed and serum was sent to MECORE Laboratory in Bangor, ME (at -80°C).

IGF-1 and IGFBP-3 Measurements

The IGF-1 levels were measured using a radioimmunoassay (RIA) kit (American Laboratory Products Company, Salem, NH); the analytical sensitivity was 0.02 ng/ml. The cross-reactivity with IGF-2 in the assay was 0.05%. IGFBP-3 levels were determined using the “Active” IGFBP-3 IRMA kit (Diagnostic Systems Laboratories, Inc., Webster, TX); the calculated sensitivity was 0.5 ng/ml. For both IGF-1 and IGFBP-3, each participant’s baseline, follow-up and colonoscopy samples were grouped together and analyzed on the same assay. All samples were analyzed in duplicate. Assay performance was monitored using internal QC samples derived from project participants, assay controls provided by the kit manufacturers, and an in-house control provided by the laboratory performing the analyses. The in-house laboratory control, which was analyzed simultaneously with each batch of samples loaded onto an assay, was used to calculate assay variability. The interassay coefficient of variation for IGF-I was 5.69%, and 6.61% for IGFBP-3. To distinguish the bound from unbound components of IGF-1, the molar ratio of IGF-1/IGFBP-3 was calculated based on the fact that 1 ng/ml IGF-1 = 0.130 nMol IGF-1, and 1 ng/ml IGFBP-3 = 0.036 nMol IGFBP-3.

Statistical Analysis

Our analysis focused on intra-individual changes in the levels of IGF-1 and IGF-1/IGFBP-3 during a 10-year follow-up. Correlations between the three measurements were assessed using the Pearson correlation coefficient. The contribution of intra-individual variation to the total variance of both variables was estimated by partitioning the total variance into within- and between-subject variations, using one-way ANOVA models. Crude association between study participant characteristics and colorectal adenomatous polyps was assessed using the χ^2-test (and the Fisher exact test, when necessary). The Wilcoxon/Kruskal-Wallis test was used to assess whether the distribution of IGF-1 and IGF-1/IGFBP-3 differed by study participant characteristics, and compared means of the two main effect variables using t-tests.

To characterize intra-individual changes in IGF-1 and IGF-1/IGFBP-3 over time, we calculated for each individual the percent difference between baseline levels (1992-1994) and levels at each of the two later measurements (1997-1999 and 2002-2004). T h e random error of circulating IGF-1 measurements was estimated to range between 12% and 17.6% for lower and higher values respectively[3]. Based on these estimates, we reasoned that a difference between IGF-1 measurements within 15% would be within the margin of error. Therefore, we categorized change patterns as “no increase” (±15% and/or < 15% from baseline) and “ever increase” (at least one increase > 15%).

To assess associations between the two main effect variables (IGF-1 and IGF-1/IGFBP-3) and colorectal adenomatous polyps, ORs and their 95% confidence intervals (CIs) were calculated from logistic regression models. Table 3 shows the means of both variables for controls and cases, as well as the estimated ORs for colorectal adenomas by levels of IGF-1 and IGF-1/IGFBP-3 at each time point. Both IGF-1 and IGF-1/IGFBP-3 were specified as continuous variables. The ORs were scaled to the difference between the 75th and the 25th percentile of the baseline distribution (51 units for IGF-1 and 0.052 units for IGF-1/IGFBP-3). The following variables were included as covariates: concurrent measurement of IGFBP-3, age (baseline), gender, center, race/ethnicity, concurrent BMI, and report of previous polyps (yes/no). Additionally, ORs for "ever increase" *vs* "no increase" in IGF-1 and IGF-1/IGFBP-3 were calculated; the following covariates included age (baseline), gender, center, race/ethnicity, BMI (baseline), and report of previous polyps (yes/no). Because the categories "ever increase" and "no increase" were based on relative changes in percentage, the respective models also included baseline levels of IGF-1 and took into account the influence of the actual levels. In the case of IGF-1, the model also included baseline IGFBP-3 levels.

RESULTS

Our analytical cohort included 143 participants from whom the IGF-1 and IGFBP-3 measurements were available for all three time points within the 10-year period of the IRAStudy. This group of subjects had similar distributions for gender, age, race/ethnicity, diabetic status, and baseline levels of IGF-1 and IGFBP-3, compared to the entire cohort of participants screened for colon lesions (n=335). Among the baseline characteristics, only BMI, and the presence of prior polyps displayed an association with the presence of adenomatous polyps at the colonoscopy visit (p-value for χ^2 test ≤ 0.1, Table 1).

Overall, circulating levels of IGF-1 and the ratio IGF-1/IGFBP-3 were tightly correlated over the 10-year follow-up period; the Pearson correlation coefficients ranged between 0.7 and 0.8 (p-values < 0.0001). The within-person variations of IGF-1 and IGF-1/IGFBP-3, compared to their total variation in the 10-year period, is 24% and 29%, respectively. This indicates that the majority of variability is due to differences in the levels between individuals.

With respect to baseline characteristics, both IGF-1 and IGF-1/IGFBP-3 decreases with age. Similarly, IGF-1 and IGF-1/IGFBP-3 levels decline with BMI. Women tend to have lower levels than men. The IGF-1/IGFBP-3 ratio is significantly lower in Caucasians and Hispanics compared to African Americans; and participants reporting previous polyps have a lower IGF-1/IGFBP-3 ratio (Table 2).

The analysis of the relationship between actual levels of IGF-1 and IGF-1/IGFBP-3 at three time points and occurrence of colorectal adenoma at the end of follow-up showed no association, with odds ratios varying around null (Table 3, Part A). Over the 10-year time period, 43 (30.1%) individuals showed a significant increase in IGF-1, and 44 (32.1%) showed an increase in IGF-1/IGFBP-3, both categorized as "ever increase." "Ever increase" *vs* "no increase" was associated with adenomatous polyps; the ORs were 3.81 for changes in IGF-1 levels (95% CI: 1.35-11.30), and 2.83 for changes in IGF-1/IGFBP-3 (95% CI: 1.00-8.22) (Table 3, Part B). Approximately half of the participants with adenoma at the end of the study showed "ever increase" in IGF-1 or IGF-1/IGFBP-3, while only about a quarter of the controls showed an increase in one of the variables. To further explore whether the observed associations with "ever increase" depended on the analytical approach, we conducted a series of sensitivity analyses. First, we excluded participants with hyperplasia from the "no adenoma" group to provide further contrast for the case/non-case comparison:

the ORs were 3.08 for IGF-1 (95% CI: 1.09-2.75), and 2.62 for IGF-1/IGFBP-3 (95% CI: 0.88-7.82). Second, we expanded the analytical cohort by including an additional 32 participants for whom only two out of three measurements were available; among these participants, those with an increase above 15% (at either time point compared to baseline) were added to the "ever increase" category: the ORs were 4.41 for IGF-1 (95% CI: 1.78-11.4), and 3.41 for IGF-1/IGFBP-3 (95% CI: 1.35-8.87). Finally, based on the fact that the estimated random error of measurement of circulating IGF-1 levels varies between 12.0 and 17.6%[3], we changed the cut-off point for categorization of "ever increase" to ≥ 18%. As a consequence our newly calculated ORs were 3.13 for IGF-1 (95% CI: 1.08-9.32), and 3.33 for IGF-1/IGFBP-3 (95% CI: 1.17-9.75). In conclusion, these three sensitivity analyses confirm the stability of our observed associations between "ever increase" of IGF-1 or IGF-1/IGFBP-3 and colorectal adenomas, irrespective of the analytical approach used.

DISCUSSION

To our knowledge, this study is the first to focus on temporal patterns of IGF-1 in relation to a cancer-related outcome. Our main objective was to examine whether intra-individual dynamics of circulating IGF-1 and IGF-1/IGFBP-3 can explain the relationship between IGF-1 and adenomatous polyps to a greater extent than IGF-1 levels measured at a single point in time.

Our findings clearly indicate there is a relationship between IGF-1 patterns and colorectal adenomatous polyps (Table 3). This suggests a relatively greater importance of IGF-1 stability (i.e. GH/IGF-1 homeostatic control) as compared with actual IGF-1 values. In our study, the actual values of IGF-1 and IGF-1/IGFBP-3 showed no association with colorectal adenoma (Table 3, Part A). In the literature, the association between components of the GH/IGF-1 pathway and colorectal cancer risk is highly disputed. Meta-analyses suggest a modest association between circulating IGF-1 and colorectal cancer risk[6, 9]. Studies focused specifically on adenoma polyps include two nested case-control studies conducted in the US[10, 11] and a cross-sectional study conducted in Japan[12]. The results of the nested case-control studies showed that mainly advanced adenomatous polyps are associated with IGF-1 levels and IGF-1/IGFBP-3 ratio (or IGFBP-3 levels)[10, 11]. The cross-sectional study in men showed no significant association between IGF-1 or IGFBP-3 and colorectal adenoma, regardless of stage[12].

Our results indicate that at an increase (>15%) in either of the main effect variables during the 10 years prior to colonoscopy is positively associated with occurrence of colorectal adenomatous polyps (Table 3, Part B). After adjusting for baseline IGF-1, the association with IGF-1 "ever increase" was independent of actual IGF-1 values. Furthermore, inclusion of the baseline IGF-1 and the "ever increase" pattern into the same model revealed a striking contrast between these variables' associations with colorectal adenomatous polyps. For baseline IGF-1 levels, the OR comparing the 75th with the 25th percentiles was 0.81 (95% CI: 0.39-1.57), whereas the OR comparing "ever increase" to "no increase" was 3.65 (95% CI: 1.30-10.8).

We cannot compare directly our results on IGF-1 change patterns with previously published reports. Previous literature shows considerable inter-individual variation of IGF-1[4, 13, 14] and a relatively low intra-individual variation[15, 16] indicating that IGF-1 levels represent a relatively stable individual physiological characteristic. Therefore, sharp increases in IGF-1 in the aging population (against age-related decrease) may surface as a reflection of more complex underlying disturbances in GH/IGF-1 homeostasis. Such disturbances may signify a greater risk for pre-cancerous transformation or other chronic diseases outcomes[13, 15, 16]. Similarly, variation patterns in other biological variables are stronger predictors of mortality

and chronic disease outcomes than their actual values[17]. For example, in analyses of weight change in the entire IRAS colon study cohort (n=600), investigators found a stronger association between weight gain and colorectal adenomatous polyps than with BMI at baseline[8].

Finally, several of our findings agree with previously published reports, confirming comparability of our results to those obtained from other populations. Consistent with these reports, we found that IGF-1 decreases with age[2], that males have higher levels of IGF-1 (or IGF-1/IGFBP-3) than females[18], and that BMI is negatively associated with IGF-1 levels[5].

Our analysis has possible limitations. One possible limitation is the vague temporal sequence of the examined exposure and outcome. In this instance, however, “reverse causality” (i.e., colorectal adenoma influencing the circulating levels of IGF-1) is unlikely. Although transformed cells may produce IGF-1 as an autocrine growth promoter, such autocrine production of IGF-1 is unlikely to be reflected at the systemic level of circulating IGF-1. A relatively small sample size represents another possible limitation. To avoid any interference with other (metabolic) pathways that might influence the levels of IGF-1 or IGFBPs [2], our study cohort was limited to patients without diabetes or impaired glucose tolerance. Further, the small number of cases (n=24) did not allow for a comparison of associations with advanced adenomatous polyps. Such comparisons would contribute significantly to the assessment of the biological plausibility of our findings.

Our findings have important implications for future studies. Although overall circulating levels of IGF-1 present a stable characteristic, approximately 30% (43/143) of individuals may experience a temporary increase in circulating IGF-1 and supposedly suffer instability in the GH/IGF-1 axis. Therefore, we believe that measurements of this biomarker should include several time points over a relatively long lifespan.

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Novelty

This study suggests that participants with higher levels of IGF-1 or IGF-1/IGFBP-3 do not have a higher risk of developing colorectal adenomatous polyps, precursors of colorectal cancer. However, an increase in these variables over time show a consistent association with the presence of adenomatous polyps suggesting the importance of the stability of the GH/IGF-1 signaling pathway. To the best of our knowledge, all previous studies with cancer-related outcomes have involved a one-time measurement of IGF-1, IGFBP-3 and/or their ratio. Our analysis is the first to indicate the possible importance of the IGF-1 homeostasis in carcinogenesis.

Impact

Because temporal alteration in IGF-1 levels may contribute more significantly to the process of carcinogenesis than the actual IGF-1 levels themselves, several measurements of this biomarker at different time points over a relatively long lifespan should be taken into consideration in future studies. This is important considering the burden of colorectal cancer in the Western world.

Table 1

Prevalence of colorectal adenoma by demographic characteristics and risk factors among 143 participants in the IRAS cohort study (1992-1994 to 2002-2004).

Characteristics		Adenoma/All (% of all)	*P* for χ^2 test
Study population		24/119 (16.8)	*N/A*
Gender	Males	11/66 (16.7)	1.0
	Females	13/77 (16.9)	
Age at 1992-1994 (y)	50-59	8/53 (15.1)	0.5
	60-69	8/55 (14.6)	
	70-80	8/25 (22.9)	
Center	Los Angeles, CA	4/26 (15.4)	0.7
	Oakland, CA	7/30 (23.3)	
	San Antonio, TX	5/38 (13.2)	
	San Luis Valley, CO	8/49 (16.3)	
Race/Ethnicity	Non-Hispanic White	7/59 (11.9)	0.4
	Black	7/34 (20.6)	
	Hispanic	10/50 (20.0)	
BMI at 1992-1994	Normal (<25)	5/56 (8.9)	0.1
	Overweight (25-30)	13/53 (24.5)	
	Obese (>30)	6/33 (18.2)	
	Missing	1	
Smoking status at 1992-1994	Never	9/62 (14.5)	0.5
	Former	13/63 (20.6)	
	Current	2 /18 (11.1)	
Previous polyps	No	19/130 (14.6)	0.04 (Fisher exact test)
	Yes	5 /13 (38.5)	

Table 2

Baseline levels of IGF-1 and IGF-1/IGFBP-3 in subgroups with different characteristics.

Characteristics		Number	Mean (SD)	
			IGF-1 (ng/ml)	IGF-1/IGFBP-3 (molar ratio)
Gender	Males	66	139 (45)	0.151 (0.038)
	Females	77	112 (36)	0.124 (0.039)
	p-value[a]		<0.0001	<0.0001
Age	50-59	53	141 (46)	0.150 (0.044)
	60-69	55	119 (36)	0.132 (0.037)
	70-80	35	108 (38)	0.122 (0.034)
	p-value		0.001	0.003
Center	Los Angeles, CA	26	137 (54)	0.148 (0.049)
	Oakland, CA	30	126 (38)	0.146 (0.043)
	San Antonio, TX	38	118 (40)	0.132 (0.040)
	San Luis Valley, CO	49	122 (40)	0.128 (0.032)
	p-value		0.3	0.1
Race/ethnicity	White	59	126 (41)	0.135 (0.039)
	Black	34	132 (49)	0.152 (0.047)
	Hispanic	50	117 (39)	0.127 (0.033)
	p-value		0.2	0.02
BMI	Normal (<25)	56	127 (37)	0.142 (0.037)
	Overweight (25-30)	53	133 (47)	0.143 (0.043)
	Obese (>30)	33	107 (40)	0.118 (0.038)
	p-value		0.02	0.01
Smoking	Never	62	131 (45)	0.140 (0.041)
	Former	63	118 (41)	0.132 (0.041)
	Current	18	120 (36)	0.137 (0.034)
	p-value		0.2	0.5
Previous polyps	No	130	126 (43)	0.139 (0.041)
	Yes	13	109 (30)	0.114 (0.027)
	p-value		0.08	0.04

[a] p-value for Wilcoxon/Kruskal-Wallis test

Table 3

Means of IGF-1 and IGF-1/IGFBP-3 at three time intervals and the odds ratios for colorectal adenomas by the levels of the serum hormone measurements at each time point and by their patterns of change over the period of ten years.

	MEAN (SD)				OR (95% CI)	
	IGF-1 (ng/ml)		IGF-1/IGFBP-3 (molar ratio)		IGF-1 (ng/ml)	IGF-1/IGFBP-3 (molar ratio)
	controls	cases	controls	cases		
A. Time points:						
1. 1992-1994[a]	126 (42)	118 (44)	0.14 (0.04)	0.13 (0.04)	0.76 (0.32,1.66)	0.74 (0.33,1.56)
2. 1997-1999[a]	118 (41)	118 (42)	0.14 (0.04)	0.13 (0.03)	1.13 (0.50, 2.44)	1.04 (0.50,2.06)
3. 2002-2004[a]	120 (50)	123 (52)	0.13 (0.04)	0.14 (0.04)	1.24 (0.64, 2.40)	1.44 (0.73,2.86)
B. Pattern of change in IGF-1 or IGF-1/IGFBP-3 in the 10-year follow-up period:						
Ever Increase *versus* No Increase[b]					3.81 (1.35,11.30)	2.83 (1.00, 8.22)

[a]ORs are adjusted for age (baseline), center, race/ethnicity, gender, and the following concurrent measurements: BMI and IGFBP-3; OR is scaled to the difference between 25% to 75% percentile in all subjects at baseline.

[b]ORs are adjusted for age (baseline), center, race/ethnicity, gender, and BMI (baseline), IGF-1 (baseline); additionally, ORs for IGF-1 are adjusted for baseline IGFBP-3.