Insulin-like Growth Factor (IGF)-I, IGF-binding Protein-3 and Colorectal Adenomas in Japanese Men

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Several epidemiological studies have found that high levels of plasma insulin-like growth factor (IGF)-I and low levels of IGF-binding protein (IGFBP)-3 are related to an increased risk of colorectal cancer or late-stage adenomas. We examined the relation of body mass index, fasting and 2-h postload plasma glucose levels and plasma concentrations of IGF-I and IGFBP-3 to colorectal adenomas in middle-aged Japanese men. The study subjects comprised 157 cases of histologically diagnosed colorectal adenomas and 311 controls with normal colonoscopy or non-polyp benign lesions in a consecutive series of 803 men receiving a preretirement health examination at two hospitals of the Self Defense Forces (SDF). After adjustment for rank in the SDF, hospital, smoking and IGFBP-3, a statistically nonsignificant modest increase in the prevalence odds of colorectal adenomas was observed for the highest versus the lowest quartile level of IGF-I. The increase was slightly greater with further adjustment for 2-h glucose concentrations (adjusted odds ratio 1.8, 95% confidence interval 1.0–4.5, trend $P=0.06$). Men with high levels of IGFBP-3 showed only a minimal decrease in risk after adjustment for IGF-I. The association with IGF-I was less evident for advanced adenomas (≥ 5 mm in size or tubulovillous/villous). Fasting and 2-h glucose and body mass index were more strongly positively associated with colorectal adenomas than IGF-I, especially with advanced adenomas, independently of IGF-I and IGFBP-3. The findings suggest that plasma IGF-I and IGFBP-3 may be involved in colorectal tumorigenesis regardless of the stage in growth of adenoma, but not as a mediator for the effects of being overweight or of hyperglycemia.

Key words: IGF-I — IGFBP-3 — Obesity — Plasma glucose — Colorectal adenomas

There has been much interest recently in the role of insulin-like growth factor (IGF)-I in the etiology of colorectal cancer as well as of some other common cancers.[1, 2] IGF-I is a growth hormone-dependent peptide with a structural homology to insulin, and has mitogenic and anti-apoptotic properties.[2, 3] The IGF receptors are expressed in normal colorectal epithelia and colorectal cancer cells, and stimulate mitogenesis *in vitro* through activation by IGF-I. Acromegaly, characterized by chronic elevation of plasma IGF-I, is associated with increased proliferation of colonic epithelial cells and elevated risk of colorectal adenomas and cancer.[4, 5] IGF-binding protein-3 (IGFBP-3) is a major binding protein of circulating IGF-I, and thus can oppose the actions of IGF-I. IGFBP-3 also has an IGF-independent inhibitory effect on cell growth.[2, 3]

A limited number of epidemiological studies have reported that high circulating levels of IGF-I and low IGFBP-3 levels are associated with an increased risk of colorectal cancer[6–8] although the findings have not been reproduced in other studies.[9–11] Hyperinsulinemia has also been implicated in colorectal carcinogenesis on the basis of both experimental and epidemiological evidence.[12, 13] Insulin at supraphysiological levels can bind to IGF-I receptors and trigger a cascade of reactions in the signal transduction pathway.[2, 3] In addition, insulin not only enhances the growth hormone-dependent production of IGF-I and IGFBP-3, but also increases the bioactivity of IGF-I by inhibiting the synthesis of IGFBP-1 and IGFBP-2.[9]

Colorectal adenomas are well-established precancerous lesions.[14] Two studies showed that elevated levels of serum IGF-I and low levels of IGFBP-3 were associated independently with an increased risk of late-stage or high-risk colorectal adenomas, but not of adenomas at an early stage.[8, 15] In the study reported here, we examined the relation of plasma levels of IGF-I and IGFBP-3 to colorectal adenomas in middle-aged Japanese men. We also addressed the role of IGF-I and IGFBP-3 in the relation of overweight and hyperglycemia to colorectal adenomas. Overweight status and hyperglycemia are strong correlates of insulin resistance or hyperinsulinemia,[16] and have consistently been associated with increased risk of colorectal cancer and adenomas.[12, 13]

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MATERIALS AND METHODS

Subjects Study subjects were male self-defense officials who had received a preretirement health examination at the Self Defense Forces (SDF) Fukuoka and Kumamoto Hospitals during the period from 1995 to 1996. The preretirement health examination is a nationwide program offering a comprehensive medical examination, including screening colonoscopy and a 75-g oral glucose tolerance test, to those retiring from the SDF. Details of the health examination have been described elsewhere.[17, 18] Following the provision of written informed consent, a sample of 7 ml of venous blood was taken for research purposes after an overnight fast, and aliquots of plasma were stored in a deep freezer until analysis.

In a consecutive series of 803 men, 778 underwent total or partial colonoscopy. After exclusion of the 41 men with a history of colectomy, colorectal polypectomy, or a malignant neoplasm, and of the 2 men who were discovered at the preretirement colonoscopy to have colorectal cancer (*n*=2), there were 325 men with at least one colorectal polyp and 410 with normal colonoscopy (*n*=368) or non-polyp benign lesions such as colitis and diverticula (*n*=42). Of the 325 men with colorectal polyps, the 209 men with histologically confirmed adenomas without carcinoma were used as adenoma cases. The 410 men with normal colonoscopy or non-polyp benign lesions were used as controls. Plasma samples were not available for 52 adenoma cases and 99 controls, and thus 157 cases and 311 controls remained in the analysis. Of the 311 controls, 201 underwent total colonoscopy, and colonoscopy for the others was partial. Of the 157 adenoma cases, 136 had colon adenomas only; 17 had rectal adenomas only; and 4 had both colon and rectal adenomas. Numbers of cases having an adenoma of <5, 5–9 and ≥10 mm in diameter (size of the largest adenoma in the case of multiple adenomas) were 98, 53 and 5, respectively; adenoma size was not recorded for one case. Only 2 cases had tubulovillous or villous adenomas. We defined cases of advanced adenomas as those having an adenoma of ≥5 mm in diameter or a tubulovillous or villous adenoma; by this definition, there were 59 advanced adenoma cases.

Clinical and lifestyle factors Height and body weight were measured, and body mass index (kg/m^2) was calculated as an index of obesity. Medical history and current medication were ascertained by physicians or nurses by interview. Information on lifestyle factors was obtained using a self-administered questionnaire, as described in detail elsewhere.[18]

Laboratory assays Plasma IGF-I and IGFBP-3 levels were determined by an immunoradiometric assay at an external laboratory (CRC, Fukuoka) using commercial kits (Dai-ichi Radioisotope Laboratories, Tokyo). Details of the assay methods were described previously.[19] The intra-assay coefficients of variation in the measurement of standard samples with low and high concentrations were 3.9% and 1.2%, respectively, for IGF-I and 5.0% and 5.8%, respectively, for IGFBP-3. A 75-g oral glucose tolerance test was done after subjects had fasted overnight. Plasma glucose concentrations were determined by the glucose oxidase method using commercial reagents (Shinotest Co., Ltd., Tokyo) at each hospital laboratory.

Statistical analysis The means of variables under study were compared between adenoma cases and controls by using Student's *t* test. Logistic regression analysis was used to examine the association of fasting and 2-h postload plasma glucose concentrations, body mass index, IGF-I and IGFBP-3 with colorectal adenomas after controlling for hospital, SDF rank and cigarette smoking. Cigarette smoking was related to an increased risk of colorectal adenomas,[20] and was also a strong correlate of IGF-I and IGFBP-3 in the study population.[19] Neither alcohol use nor physical activity seemed to be an important confounding factor; alcohol use was a correlate of plasma IGF-I and IGFBP-3,[19] but was unrelated to colorectal adenomas,[21] and physical activity was virtually unrelated to IGF-I and IGFBP-3.[19] Plasma concentrations of fasting glucose, 2-h glucose, IGF-I and IGFBP-3 were classified into 3 levels using the 25th and 75th percentiles of the distribution of each among the controls. Likewise, body mass index was categorized into 3 classes at the lower and upper quartile points. Age was not taken into account in the analyses because of the limited age range (47–55 years) of the study population, of which 99% was between the ages of 50 and 54 years. Cigarette smoking was categorized into 0, 1–399, 400–799 or ≥800 cigarette-years (numbers of cigarettes smoked per day multiplied by years of smoking), and rank in the SDF was categorized into low, middle or high. Indicator variables were created for these covariates and fitted in the regression models. Odds ratio (OR) and 95% confidence interval (CI) were estimated from the logistic regression coefficient and standard error for an indicator variable corresponding to a category of a factor. Trends in the associations with the variables of interest were tested with ordinal scores (0, 1 and 2) assigned to the three levels for the variables under study. Two-sided *P*<0.05 was regarded as statistically significant. All statistical analyses were done by using SAS version 6.12 (SAS Institute, Cary, NC).

RESULTS

Body mass index was statistically significantly greater in men with colorectal adenomas (*P*=0.004) and those with advanced adenomas (*P*=0.01) than in control subjects (Table I). Fasting and 2-h glucose concentrations were slightly higher in adenoma cases, particularly those with advanced adenomas, than in controls, but none of the dif-

Table I. Means of Fasting and Post-load Plasma Glucose Concentrations, Body Mass Index and Plasma IGF-I and IGFBP-3 Concentrations in Controls and Colorectal Adenoma Cases

Variable (unit)	Control (n=311)	All adenomas (n=157)	Advanced adenomas[a] (n=59)
Fasting glucose (mg/dl)	95 (12)	98 (19)	100 (27)
2-h glucose (mg/dl)[b]	120 (41)	124 (39)	128 (41)
Body mass index (kg/m²)	23.2 (2.4)	23.8 (2.5)[c]	24.0 (2.4)[c]
IGF-I (ng/ml)	177 (51)	179 (44)	181 (43)
IGFBP-3 (μg/ml)	2.92 (0.53)	2.96 (0.56)	3.08 (0.53)[d]
IGF-I/IGFBP-3[e]	0.219 (0.048)	0.220 (0.041)	0.214 (0.041)

Values in parentheses are standard deviations.
a) Adenoma of ≥5 mm in diameter, tubulovillous/villous adenomas or multiple adenomas.
b) Measurements of 2-h plasma glucose were missing for 6 controls, 3 cases of adenomas, and 2 cases of advanced adenomas.
c) $P<0.01$ as compared with controls.
d) $P<0.05$ as compared with controls.
e) Molar ratio.

Table II. Relation of Fasting and Post-load Plasma Glucose, Body Mass Index, IGF-I and IGFBP-3 to Colorectal Adenomas

Variable (unit)	Low	Middle	High	Trend[a]
Fasting glucose (mg/dl)				
Range	74–87	88–100	101–292	
No.[b]	28/82	79/150	50/79	
OR (95% CI)[c]	1.0	1.4 (0.8–2.4)	1.8 (1.0–3.2)	$P=0.05$
2-h glucose (mg/dl)[d]				
Range	44–94	95–137	138–366	
No.[b]	26/77	81/151	47/77	
OR (95% CI)[c]	1.0 (referent)	1.6 (0.9–2.7)	1.7 (1.0–3.1)	$P=0.08$
Body mass index (kg/m²)				
Range	17.2–21.5	21.6–24.7	24.8–32.8	
No.[b]	23/80	86/155	48/76	
OR (95% CI)[c]	1.0 (referent)	2.3 (1.3–3.9)	2.3 (1.2–4.2)	$P=0.01$
IGF-I (ng/ml)				
Range	60–143	144–202	203–561	
No.[b]	34/79	75/155	48/77	
OR (95% CI)[c]	1.0 (referent)	1.1 (0.7–1.9)	1.5 (0.9–2.7)	$P=0.15$
IGFBP-3 (μg/ml)				
Range	1.14–2.60	2.61–3.27	3.28–4.61	
No.[b]	38/80	80/153	39/78	
OR (95% CI)[c]	1.0 (referent)	1.3 (0.8–2.1)	1.0 (0.6–1.8)	$P=0.99$
IGF-I/IGFBP-3[e]				
Range	0.106–0.188	0.189–0.246	0.247–0.479	
No.[b]	39/77	78/157	40/77	
OR (95% CI)[c]	1.0 (referent)	0.9 (0.6–1.5)	1.1 (0.6–1.9)	$P=0.76$

OR, odds ratio; CI, confidence interval.
a) Ordinal scores (0, 1 and 2) were assigned to the low, intermediate and high levels.
b) Numbers of cases/controls.
c) Adjusted for hospital, rank in the Self Defense Forces and smoking.
d) Measurements of 2-h plasma glucose were missing for 6 controls and 3 cases of adenomas.
e) Molar ratio.

Table III. Relation of Fasting and Post-load Plasma Glucose, Body Mass Index, IGF-I and IGFBP-3 to Advanced Colorectal Adenomas[a]

Variable (unit)	Category			Trend[b]
	Low	Intermediate	High	
Fasting glucose (mg/dl)				
Range	74–87	88–100	101–292	
No.[c]	7/82	31/150	21/79	
OR (95% CI)[d]	1.0	2.0 (0.8–5.0)	2.7 (1.0–6.9)[e]	$P=0.046$
2-h glucose (mg/dl)[f]				
Range	52–94	95–137	138–366	
No.[c]	8/77	30/151	19/77	
OR (95% CI)[d]	1.0 (referent)	1.8 (0.8–4.4)	2.7 (1.0–6.8)[e]	$P=0.04$
Body mass index (kg/m^2)				
Range	17.2–21.5	21.6–24.7	24.8–32.8	
No.[c]	5/80	34/155	20/76	
OR (95% CI)[d]	1.0 (referent)	4.5 (1.6–12.5)	4.5 (1.5–13.2)	$P=0.01$
IGF-I (ng/ml)				
Range	60–143	144–202	203–561	
No.[c]	9/79	35/155	15/77	
OR (95% CI)[d]	1.0 (referent)	1.8 (0.8–4.0)	1.4 (0.5–3.6)	$P=0.57$
IGFBP-3 (μg/ml)				
Range	1.14–2.60	2.61–3.27	3.28–4.61	
No.[c]	12/80	32/153	15/78	
OR (95% CI)[d]	1.0 (referent)	1.5 (0.7–3.2)	1.0 (0.4–2.5)	$P=0.97$
IGF-I/IGFBP-3[g]				
Range	0.106–0.188	0.189–0.246	0.247–0.479	
No.[c]	16/77	32/157	11/77	
OR (95% CI)[d]	1.0 (referent)	0.9 (0.4–1.8)	0.7 (0.3–1.6)	$P=0.39$

OR, odds ratio; CI, confidence interval.

a) Adenoma of ≥5 mm in diameter or tubulovillous/villous adenoma.

b) Ordinal scores (0, 1 and 2) were assigned to the low, intermediate and high levels.

c) Numbers of cases/controls.

d) Adjusted for hospital, rank in the Self Defense Forces and smoking.

e) $P<0.05$.

f) Measurements of 2-h plasma glucose were missing for 6 controls and 2 cases of advanced adenomas.

g) Molar ratio.

ferences was statistically significant. While there was no measurable difference in IGF-I between adenoma cases and controls, cases of advanced adenomas had higher concentrations of IGFBP-3 than controls ($P=0.03$).

In the control subjects, both IGF-I and IGFBP-3 showed weak or moderate positive correlations with glucose concentrations and body mass index. Pearson's correlation coefficients of IGF-I with fasting glucose, 2-h glucose and body mass index were 0.09, 0.08 and 0.21, respectively; the corresponding values for IGFBP-3 were 0.25, 0.10 and 0.30, respectively. The correlation coefficient between IGF-I and IGFBP-3 was 0.60.

The ORs of colorectal adenomas for the high and intermediate levels of body mass index were of the same magnitude and significantly greater than unity. Despite the absence of a monotonic increase in the OR with body mass index, the associated test for trend was statistically significant. Borderline significant, moderate increases in the OR of adenomas were observed for the highest levels of fasting glucose and 2-h glucose (Table II). There was a weak, positive association between IGF-I and colorectal adenomas, while IGFBP-3 showed no clear association with colorectal adenomas. In the analysis of advanced adenomas (Table III), positive associations with fasting glucose, 2-h glucose, and body mass index were more pronounced, and all of these associations showed statistically significant, positive trends. The OR for the intermediate level of IGF-I was greater than that observed at the corresponding level of IGF-I for all adenomas combined, but the positive trend was less marked. As with the associ-

Table IV. Adjusted Odds Ratios of Colorectal Adenomas in Relation to IGF-I, IGFBP-3, Fasting and Post-load Plasma Glucose and Body Mass Index with Mutual Adjustment[a]

Variable	Category			Trend[b]
	Low	Intermediate	High	
All adenomas				
Model 1				
IGF-I	1.0 (referent)	1.1 (0.7–1.9)	1.7 (0.9–3.2)	P=0.10
IGFBP-3	1.0 (referent)	1.2 (0.7–2.0)	0.8 (0.4–1.5)	P=0.44
Model 2				
IGF-I	1.0 (referent)	1.1 (0.6–1.8)	1.6 (0.9–3.1)	P=0.13
IGFBP-3	1.0 (referent)	1.1 (0.7–1.9)	0.7 (0.3–1.3)	P=0.23
Fasting glucose	1.0 (referent)	1.4 (0.8–2.3)	1.9 (1.0–3.5)[c]	P=0.04
Model 3				
IGF-I	1.0 (referent)	1.1 (0.7–2.0)	1.8 (1.0–3.5)	P=0.06
IGFBP-3	1.0 (referent)	1.2 (0.7–2.0)	0.7 (0.4–1.4)	P=0.32
2-h glucose	1.0 (referent)	1.6 (0.9–2.8)	1.8 (1.0–3.4)[c]	P=0.05
Model 4				
IGF-I	1.0 (referent)	1.0 (0.6–1.7)	1.5 (0.8–2.8)	P=0.22
IGFBP-3	1.0 (referent)	1.1 (0.7–1.9)	0.7 (0.4–1.4)	P=0.29
Body mass index	1.0 (referent)	2.3 (1.3–4.0)	2.3 (1.2–4.4)	P=0.02
Advanced adenomas[d]				
Model 1				
IGF-I	1.0 (referent)	1.7 (0.7–4.1)	1.5 (0.5–4.1)	P=0.52
IGFBP-3	1.0 (referent)	1.3 (0.6–2.9)	0.9 (0.3–2.3)	P=0.73
Model 2				
IGF-I	1.0 (referent)	1.7 (0.7–3.9)	1.4 (0.5–4.0)	P=0.56
IGFBP-3	1.0 (referent)	1.2 (0.5–2.6)	0.7 (0.3–1.9)	P=0.44
Fasting glucose	1.0 (referent)	2.0 (0.8–4.9)	2.8 (1.1–7.5)	P=0.04
Model 3				
IGF-I	1.0 (referent)	1.7 (0.7–4.0)	1.7 (0.6–4.6)	P=0.37
IGFBP-3	1.0 (referent)	1.3 (0.6–3.0)	0.7 (0.3–1.9)	P=0.43
2-h glucose	1.0 (referent)	1.9 (0.8–4.5)	3.0 (1.1–7.7)	P=0.02
Model 4				
IGF-I	1.0 (referent)	1.4 (0.6–3.3)	1.1 (0.4–3.2)	P=0.92
IGFBP-3	1.0 (referent)	1.2 (0.5–2.7)	0.8 (0.3–2.1)	P=0.53
Body mass index	1.0 (referent)	4.5 (1.6–12.8)	4.6 (1.5–14.1)	P=0.01

Values in parentheses are 95% confidence intervals.
a) Adjusted for hospital, rank in the Self Defense Forces, smoking and the rest of the variables listed for each model.
b) Ordinal scores (0, 1 and 2) were assigned to the low, intermediate and high levels.
c) $P<0.05$.
d) Adenoma of ≥5 mm in diameter or tubulovillous/villous adenoma.

ation for all adenomas combined, there was little variation in risk of advanced adenomas with increasing IGFBP-3 levels. The molar ratio of IGF-I to IGFBP-3 was not measurably associated either with all adenomas combined or with advanced adenomas (Tables II and III).

When both IGF-I and IGFBP-3 were simultaneously included as explanatory variables in the model, the positive association with IGF-I became slightly stronger, although neither the increased OR nor the trend was statistically significant (Table IV). Again, the association with

IGF-I was less marked for advanced adenomas rather than for all adenomas combined. To examine the effect of fasting glucose, 2-h post-load glucose and body mass index on the relation of IGF-I and IGFBP-3 with colorectal adenomas, each of the three covariates was separately included in models with IGF-I and IGFBP-3. Further adjustment for 2-h glucose concentrations resulted in a nearly significant positive trend for all adenomas in association with IGF-I. On the other hand, with adjustment for body mass index, the association between IGF-I and all

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adenomas were rather weakened, and that for advanced adenomas was almost nullified. The OR for the highest level of IGFBP-3 was slightly lower than unity, whichever of the covariates was included in the model.

As shown in Table IV, the results shown in Tables II and III for the associations of adenomas with fasting glucose, 2-h glucose and body mass index were not affected by adjustment for IGF-I and IGFBP-3, and these associations were generally more substantial than the association with IGF-I, especially for advanced adenomas.

DISCUSSION

The present study showed a suggestive increase in the risk of colorectal adenomas associated with high levels of plasma IGF-I. There was only a minimal decrease in the risk of colorectal adenomas associated with high levels of IGFBP-3 after adjustment for IGF-I. In studies of colorectal adenomas in the United States[8] and England,[15] an increased risk associated with IGF-I and a decreased risk associated with IGFBP-3 were observed after mutual adjustment for IGF-I and IGFBP-3, and these associations were confined to late-stage adenomas or high-risk adenomas. Adenomas of 10 mm or greater in diameter or of tubulovillous or villous morphology were defined as late-stage adenomas in one of these studies,[8] and the presence of 3 or more adenomas was additionally included in the definition of high-risk adenomas in the other study.[15] In the present study, the majority of colorectal adenomas were tubular adenomas less than 10 mm in diameter, and there were only 6 cases who had either an adenoma that was at least 10 mm in diameter or an adenoma with tubulovillous or villous morphology. When the analysis was repeated after excluding these 6 cases, the results were essentially the same as those reported above (data not shown). The association of IGF-I with advanced adenomas was less evident than that observed with all adenomas combined in the present study. However, the associations for advanced adenomas were somewhat unstable due to the small number of such cases. The present study suggests that IGF-I and IGFBP-3 may be involved in the development of colorectal adenomas regardless of the stage in growth of adenomas.

It is conceivable that differences between studies in their background levels of IGF-I and IGFBP-3 might account for the somewhat different findings. Although direct comparison is compromised to some extent by between-study differences in assay methods, the mean levels of IGF-I and IGFBP-3 in the present study population did not differ much from those reported in the previous studies of colorectal adenomas, in which the findings were more pronounced for advanced adenomas.[8, 15] The means of serum IGF-I and IGFBP-3 in control subjects in the study reported by Renehan *et al.*[15] were 168 (standard

deviation [SD] 56) ng/ml and 3.46 (SD 0.62) μg/ml, respectively, and those in the Nurses' Health Study[8] were 167 ng/ml and 3.84 μg/ml, respectively. The corresponding values in the present study were 178 (SD 54) ng/ml and 2.94 (SD 0.51) μg/ml, respectively.

The positive association between IGF-I and colorectal adenomas was slightly more pronounced when adjustment was made for 2-h postload plasma glucose concentrations. Elevated levels of postload plasma glucose are an indirect measure of insulin resistance or hyperinsulinemia.[16] As mentioned earlier, insulin increases bioavailability of IGF-I by inhibiting the synthesis of IGFBP-1 and IGFBP-2.[9] It has also been shown that insulin increases IGFBP-3 proteolysis, thereby leading to an increase in the bioavailability of IGF-I.[22, 23] Given that IGFBP-3 is the main binding protein of IGF-I in blood, the latter may be more relevant to the present findings. The slightly more evident association between IGF-I and adenoma risk observed after adjustment for postload glucose may have reflected the effect of bioactive circulating IGF-I levels.

To date, epidemiological findings regarding the relationship of IGF-I and IGFBP-3 with colorectal cancer are rather inconsistent. A small case-control in Greece[6] reported an increased risk of colorectal cancer associated with high levels of serum IGF-I and a decreased risk with high levels of IGFBP-3. In two prospective studies of male physicians and female nurses in the United States,[7, 8] a positive association with IGF-I and a protective association with IGFBP-3 were shown after mutual adjustment for IGF-I and IGFBP-3. In these studies, IGF-I showed only a weak, positive association with colorectal cancer risk when IGFBP-3 was not taken into account. Contrary to these studies, two prospective studies of women in the United States[9] and of men in China[10] demonstrated an increased risk of colorectal cancer associated with elevated levels of IGFBP-3, and the risk of colorectal cancer was modestly, statistically nonsignificantly, increased among those with the highest levels of IGF-I without adjustment for IGFBP-3. In a recent prospective study in Sweden,[11] both IGF-I and IGFBP-3 were associated positively with colon cancer, but inversely with rectal cancer, whether or not mutual adjustment was made for IGF-I and IGFBP-3. These inconsistent findings suggest that the role of IGF-I and IGFBP-3 in colorectal carcinogenesis may differ in different populations, possibly modified by other factors associated with colorectal cancer. Interestingly, in a prospective study of male physicians in the United States,[24] an increased risk of colorectal cancer associated with high levels of IGF-I relative to IGFBP-3 was noted only in those with a low intake of calcium.

The observed increases in the risk of colorectal adenomas associated with a high body mass index and elevated levels of plasma glucose are not novel findings. As reviewed elsewhere,[12, 13, 25] many studies have shown an

increased risk of colorectal cancer or adenomas associated with overweight status, hyperglycemia and diabetes mellitus. In previous studies of men in the SDF as well, overweight status[26, 27] and diabetes mellitus[28, 29] were each associated with an increased risk of colon adenomas. Of interest in the present study was that the increased risks of colorectal adenomas associated with high body mass index and hyperglycemia were totally independent of plasma IGF-I and IGFBP-3 levels. It is notable that body mass index and plasma glucose levels were more strongly associated with colorectal adenomas than IGF-I. The findings suggest that these factors exert effects on colorectal tumorigenesis through a mechanism or mechanisms other than the IGF system.

A strength of the present study is that the study subjects were relatively homogeneous with respect to age, ethnicity and occupation. In cross-sectional studies, the temporal relationship is generally uncertain regarding a biomarker and disease. However, the presence of colorectal adenomas does not seem to affect plasma IFG-I and IGFBP-3 levels. It has been shown that plasma IGF-I and IGFBP-3 in individuals with colorectal adenomas do not change after polypectomy[15] whereas elevated levels of serum IGF-II and IGFBP-2 in those with colorectal adenomas decrease after polypectomy.[30] Colonoscopy was partial in 35% of the controls, and some of the controls may have had adenomas at proximal sites. This type of misclassification necessarily would have attenuated the true association. In fact, when controls with partial colonoscopy were excluded, a slightly stronger association between IGF-I and all adenomas emerged; adjusted ORs for the intermediate and high levels of IGF-I were 1.4 (95% CI 0.8−2.4) and 2.0 (1.0−4.0), respectively (trend $P=0.048$), after adjustment for hospital, rank, smoking and IGFBP-3.

Another limitation of the study is that approximately a quarter of adenoma cases and controls each were not included in the present analysis because plasma samples were not available. It is, however, unlikely that the observed associations were ascribed to this exclusion, as indicated by the confirmatory findings regarding body mass index and hyperglycemia. Finally, men serving in the SDF until retirement are not representative of middle-aged Japanese men. Thus, it may be difficult to generalize the present findings.

In conclusion, high levels of plasma IGF-I were associated with a small, statistically nonsignificant increase in the risk of colorectal adenomas after adjustment for IGFBP-3 in a population of middle-aged Japanese men. The majority of adenomas were relatively small and of tubular type. In this regard, the findings are at variance with those reported in previous studies of Caucasians. However, increased risks associated with high body mass index and elevated plasma glucose levels were more substantial, and independent of IGF-I and IGFBP-3. Further studies are needed to clarify the roles of IGF-I and IGFBP-3 in the development of colorectal adenomas and cancer.

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