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Serum Insulin-like Growth Factor I and Subsequent Risk of Colorectal Cancer among Japanese-American Men

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Recent reports suggest that colorectal cancer is positively related to insulin-like growth factor I (IGF-I) and inversely related to insulin-like growth factor binding protein 3 (IGFBP-3). To evaluate these associations further and separately for colon and rectal cancer, the authors conducted a nested case-control study in a cohort of 9,345 Japanese-American men examined in Hawaii in 1971–1977. A total of 177 incident colon cancer cases and 105 incident rectal cancer cases were identified from 1972 to 1996. These patients' stored sera and those of 282 age-matched controls were measured for IGF-I and IGFBP-3. The adjusted mean level of IGF-I was higher in colon cancer cases than in controls (154.7 ng/ml vs. 144.4 ng/ml; $p = 0.01$). However, the multivariate odds ratio for the highest quartile compared with the lowest was just 1.8 (95% confidence interval: 0.8, 4.3). Adjusted mean IGF-I levels were similar between rectal cancer cases and their controls. For IGFBP-3, adjusted mean levels were lower for both colon and rectal cancer cases than for their matched controls, but the differences were not significant. The IGF-I results weakly support findings from other studies and suggest that there are differences in IGF-I findings between colon and rectal cancer cases. It is possible that IGF-related risk is confounded by other factors that may vary among different cohorts. Further research is needed to clarify these relations.

colonic neoplasms; colorectal neoplasms; insulin-like growth factor I; insulin-like growth factor binding protein 3; rectal neoplasms

Abbreviations: IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein.

Insulin-like growth factors (IGFs) are peptides with anabolic, antiapoptotic, and mitogenic properties that affect a wide variety of cell types. They play a major role in regulating growth and development prior to adulthood and in regulating cell renewal dynamics throughout life. IGF physiology is complex and has been summarized in recent reviews (1–3). In the bloodstream, IGFs are bound with high affinity to IGF binding proteins (IGFBPs), which serve as carrier molecules. At least six IGFBPs have been cloned; IGFBP-3 provides the vast majority of IGF carrying capacity in serum. Most circulating IGF-I and IGFBP-3 originates in the liver. Hepatic production of both molecules is upregulated by growth hormone. Circulating concentrations of IGF-I and IGFBP-3 are correlated to some extent, not only because of this shared regulatory influence but also because IGFBP-3 concentration represents the vast majority of the IGF carrying capacity of serum and thus is a determinant of total IGF concentration.

IGF-responsive cells exhibit a specific IGF receptor of the tyrosine kinase class (1). The IGF bioactivity in the microenvironment of target cells does not depend exclusively on ligands delivered from the liver via the bloodstream, because IGFs are also synthesized within IGF-responsive tissues and can act in autocrine and paracrine (as well as endocrine) fashion. Furthermore, IGFBPs and various IGFBP proteases are expressed in a highly regulated manner in most IGF-responsive tissues. IGFBPs can act as modulators of IGF activity in the extravascular space by competing with IGF receptors for ligands, as well as through other mechanisms (3).

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Circulating concentrations of IGF-I and IGFBP-3 (and presumably their levels of tissue expression) vary considerably between normal individuals. Both genetic and nongenetic (including nutritional) factors contribute to the interindividual variation in IGF-I and IGFBP-3 concentrations (4). Recent investigations have provided data that suggest that risk of various epithelial cancers (5–9), including colorectal cancer in men (10) and women (11), is positively related to IGF-I levels and negatively related to IGFBP-3 levels. These results are biologically plausible (5), since there is experimental evidence that colonic epithelial cells as well as colorectal cancer cells are responsive to IGFs (12–16). One specific hypothesis is that in persons with higher IGF bioactivity, colorectal carcinogenesis is facilitated because of enhanced survival of partially transformed cells, leading to a larger pool of targets for subsequent "hits" in the process of stepwise carcinogenesis and more rapid completion of the process of malignant transformation. A second hypothesis is that the time required for the progression of a fully transformed cell to a clinical cancer is inversely related to IGF bioactivity.

On the other hand, data from another prospective cohort study (17) showed no statistically significant relation between IGF-I or IGFBP-3 level and colorectal cancer risk. In that study, however, an association between markers of insulin resistance and risk was seen, and the authors speculated that the risk associated with insulin resistance might be mediated by elevated tissue IGF bioactivity.

The colon cancer incidence rates of US White men and women are among the highest in the world (18). We decided to conduct a study among US men of Japanese ancestry, because they also have a high incidence of colon cancer. Furthermore, in contrast to past studies (11, 17), we separated rectal cancer from colon cancer because of differences in their epidemiologic patterns (19–21). Average annual colon cancer incidence rates are 34.4 per 100,000 among Hawaii Japanese men, 32.7 per 100,000 among Hawaii Caucasian men, and 30.7 per 100,000 among Caucasian men in Iowa (18). For rectal cancer, the average annual incidence rates are 19.0, 14.0, and 14.3 per 100,000, respectively, in the same three groups.

MATERIALS AND METHODS

Study population

From 1965 to 1968, 8,006 Japanese-American men on the Hawaiian island of Oahu were examined in the Honolulu Heart Program. They were born between 1900 and 1919 and were approximately 45–68 years of age at the time of examination (22). Approximately 6 years later (1971–1975), 6,860 of these men returned for another round of examination. At that time, a nonfasting venous blood sample was obtained. The serum samples were stored at –75°C. Serum samples were available for 6,811 (99 percent) of the 6,860 men who returned for the second examination.

The 6,860 men were asked to name their brothers at the time of their reexamination. As a result, 3,843 brothers born between 1889 and 1938 were identified. Of these, 2,553 (66 percent of the total) were subsequently recruited and examined between 1975 and 1977. A nonfasting venous blood sample was obtained from 2,534 of the examined brothers, and serum samples were stored at –75°C.

The data collected on these men included birthplace, religion, education, history of alcohol use, history of cigarette smoking, blood pressure, and body mass index (weight (kg)/height $(m)^2$). Serum cholesterol values were determined by the AutoAnalyzer N-24A method (23). Eighty of the 9,345 men had been diagnosed with colorectal cancer prior to their examination and thus were excluded from the study.

For identification of colorectal cancer cases occurring among the men during the study period, discharge records of all general hospitals on Oahu were monitored. Tumors that arose within 12 cm of the anal verge were classified as rectal cancers, while tumors that arose 12 cm beyond the anal verge were classified as colon cancers (24). Sources of information on tumor location included the operative record, the gross description of the specimen as furnished by the pathology report, and the proctosigmoidoscopy or colonoscopy report. In the absence of site measurements, tumors proximal to the line of peritoneal reflection in the surgical specimen were arbitrarily assigned to the colon, while those distal to the reflection were coded as rectal. To reduce the possibility that diagnosed cases would be missed, a computer linkage file was established with the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. The data should have been nearly complete, since only 2.5 percent of the 6,860 reexamined men could not be located on Oahu during a survey completed in 1993.

There were 354 colon adenocarcinoma cases and 105 rectal adenocarcinoma cases diagnosed from 1972 to 1996. These cases were confirmed by examination of tissue obtained surgically or by biopsy. An additional 22 colorectal cases were diagnosed clinically but were not confirmed histologically and were excluded from the study. Because resources were not sufficient to measure serum levels of IGF-I and IGFBP-3 in all 459 cases and potential controls, only 177 of the 354 colon cancer cases were included in the study (alternating cases were included on the basis of the date of diagnosis), along with all 105 rectal cancer cases.

Each case patient was matched with one control subject from the study. The controls were selected so that the members of each case-control pair were born within 1 year of each other, except for one pair (difference of 1 year and 4 months), and were examined within 1 month of each other, except for four pairs (median difference of 2 months). They were also matched according to whether they were among the 6,811 original cohort members or among the 2,534 brothers. Each control subject was alive and did not have any cancer diagnosis at the time of the diagnosis of his matched case. Therefore, death was not a competing risk in this study.

The frozen serum samples were sent in dry ice to McGill University in Montreal, Canada, for analysis. The laboratory technician could not distinguish the sera of cases from those of controls and treated them identically in the analysis.

TABLE 1. Characteristics of colon and rectal cancer cases and their matched controls, Oahu, Hawaii

Characteristic	Colon cancer (177 pairs)*			Rectal cancer (105 pairs)*		
	Cases	Controls	*p* value†	Cases	Controls	*p* value†
Born in the United States (%)	90.4	86.4	0.38	91.4	91.4	~1.00
Buddhist/Shinto religion (%)	66.7	65.0	0.92	74.3	61.9	0.16
High school education (%)	53.7	50.3	0.39	50.5	51.4	~1.00
Alcohol use (%)	79.7	77.4	0.65	78.1	71.4	0.26
Ever smoked cigarettes (%)	63.8	64.4	0.67	73.3	66.7	0.29
Mean systolic blood pressure (mm/Hg)	137.6	136.5	0.58	139.8	134.7	0.10
Mean body mass index‡	24.2	23.9	0.57	23.5	23.8	0.36
Mean serum cholesterol level (mg/dl)	216.1	215.5	0.86	214.7	214.9	0.98

* Number of matched case-control pairs.
† The exact binomial probability test for matched samples was used for comparing proportions; the paired *t* test was used for comparing means.
‡ Weight (kg)/height (m)^2.

Laboratory analysis

IGF-I and IGFBP-3 levels were determined using the enzyme-linked immunosorbent assay method as previously described (10). Reagents were purchased from Diagnostic Systems Laboratories (Webster, Texas). Intraassay and interassay coefficients of variation were less than 5 percent and less than 11 percent, respectively, for IGF-I and less than 7 percent and less than 12 percent, respectively, for IGFBP-3.

Statistical analysis

We used the binomial probability test, which is the exact test counterpart of the McNemar test (24), and the paired *t* test to compare proportions and mean values between cases and their matched controls (table 1). We then examined the frequency distributions of serum IGF-I and IGFBP-3 values in order to decide whether appropriate data transformation was needed for statistical analysis. Because both variables were reasonably symmetrically distributed, no data transformation was carried out. Analysis of covariance (25) was used to compare the mean serum IGF-I and IGFBP-3 levels between cases and matched controls, with adjustment for age (via matching), smoking history, body mass index, alcohol intake, and IGF-I or IGFBP-3 level (table 2).

Risks of colorectal cancer associated with serum IGF-I and IGFBP-3 levels were assessed through odds ratios estimated in generalized linear models, of which the response variable (colorectal cancer) was binomial and the link function was the logit (26). Since some of the men in our study sample were brothers whose risks of colorectal cancer were likely to be correlated, we used the generalized estimating equations approach, specifying an exchangeable "working" correlation matrix, to correct for possible intracluster correlation (27, 28).

We categorized values for each exposure variable (IGF-I and IGFBP-3) into quartiles or at the median according to the frequency distribution of the matched controls in order to create a set of binary indicator variables with the lowest category designated the reference group. These indicator vari-

TABLE 2. Crude and adjusted mean serum levels (ng/ml) of insulin-like growth factor I and insulin-like growth factor binding protein 3 in cancer cases and controls, Oahu, Hawaii

	Crude			Adjusted*		
	Cases	Controls	*p* value†	Cases	Controls	*p* value
Insulin-like growth factor I						
Colorectal cancer (282 pairs)‡	152.2	148.0	0.36	153.2	147.9	0.10
Colon cancer (177 pairs)	157.8	144.4	0.02	154.7	144.4	0.01
Rectal cancer (105 pairs)	142.9	154.1	0.13	150.6	152.9	0.67
Insulin-like growth factor binding protein 3						
Colorectal cancer (282 pairs)	3,418.7	3,418.0	0.99	3,376.3	3,438.0	0.21
Colon cancer (177 pairs)	3,505.8	3,423.1	0.35	3,420.2	3,491.6	0.27
Rectal cancer (105 pairs)	3,273.6	3,409.6	0.20	3,300.5	3,358.4	0.44

* Adjusted for age (via matching), smoking history, body mass index, alcohol intake, and level of insulin-like growth factor I or insulin-like growth factor binding protein 3 by analysis of covariance.
† Age-matched paired *t* test.
‡ Number of matched case-control pairs.

TABLE 3. Adjusted odds ratios* for colon, rectal, and colorectal cancer by quartiles of serum levels of insulin-like growth factor I and insulin-like growth factor binding protein 3, Oahu, Hawaii

	Quartile†						*p* for trend
	2		3		4		
	OR‡	95% CI‡	OR	95% CI	OR	95% CI	
Insulin-like growth factor I							
Colorectal cancer (282 pairs)§	1.2	0.7, 2.0	1.8	1.0, 3.2	1.5	0.8, 2.8	0.13
Colon cancer (177 pairs)	1.0	0.5, 2.1	2.2	1.1, 4.4	1.8	0.8, 4.3	0.12
Rectal cancer (105 pairs)	0.8	0.4, 1.9	0.8	0.4, 1.9	0.6	0.2, 1.6	0.32
Insulin-like growth factor binding protein 3							
Colorectal cancer (282 pairs)	1.3	0.8, 2.1	0.9	0.5, 1.6	0.8	0.4, 1.6	0.45
Colon cancer (177 pairs)	1.3	0.6, 2.8	1.0	0.6, 1.6	0.9	0.5, 1.5	0.60
Rectal cancer (105 pairs)	1.4	0.8, 2.7	0.9	0.5, 1.8	0.9	0.4, 2.0	0.34

* Adjusted odds ratios and 95% confidence intervals were estimated by the generalized estimating equations approach to correct for intracluster correlation. The odds ratios were statistically adjusted for smoking history, body mass index, alcohol intake, and insulin-like growth factor I or insulin-like growth factor binding protein 3, in addition to age (by matching).

† Quartiles were based on the frequency distribution in the controls. Quartile 1 was the reference category.

‡ OR, odds ratio; CI, confidence interval.

§ Number of matched case-control pairs.

ables and other confounding covariates (age, smoking history, body mass index, alcohol intake, and IGF-I or IGFBP-3 level) were used as explanatory variables in the generalized linear model for the estimation of odds ratios. Tests for trend were performed using the four class midpoints as explanatory variables, and the score statistic was used to determine statistical significance. All *p* values and confidence intervals presented in the tables were based on two-sided tests.

RESULTS

The mean age of the 177 colon cancer cases and their matched controls at the time of their examination was 60.1 years, and their ages ranged from 47.6 to 76.5 years and from 47.5 to 76.6 years, respectively. The mean age was 60.3 years for the 105 rectal cancer cases and 60.4 years for their matched controls. Their ages ranged from 48.3 to 76.0 years and from 48.0 to 75.8 years, respectively. The average interval from examination to diagnosis was 12.0 years for colon cancer patients and 10.3 years for rectal cancer patients. This resulted in an average age at the time of diagnosis of 72.1 years for colon cancer cases and 70.6 years for rectal cancer cases.

Comparisons of colon and rectal cancer cases with their respective controls according to baseline characteristics are presented in table 1. Colon cancer patients and their controls did not differ in terms of birthplace, religion, education, alcohol use, cigarette smoking history, blood pressure, body mass index, or serum cholesterol level. The same pattern was present for rectal cancer cases and their matched controls.

Among all of the controls, IGF-I and IGFBP-3 were both inversely correlated with age at examination ($r = -0.26$ and $r = -0.28$, respectively). As expected, IGF-I was positively correlated with IGFBP-3 ($r = 0.69$).

The colon, rectal, and colorectal cancer cases were compared with their respective matched controls according to their mean levels of IGF-I and IGFBP-3, with and without adjustment for cigarette smoking history, body mass index, alcohol intake history, and IGF-I or IGFBP-3 level. As table 2 shows, the unadjusted mean IGF-I level was higher in colon cancer cases than in controls (157.8 ng/ml – 144.4 ng/ml = 13.4 ng/ml; $p = 0.02$), but none of the other unadjusted mean comparisons showed significant differences. After adjustment, the mean level of IGF-I remained higher in colon cancer cases than in controls (154.7 ng/ml – 144.4 ng/ml = 10.3 ng/ml; $p = 0.01$), while there was no difference in adjusted mean IGF-I levels between rectal cancer cases and their matched controls. For IGFBP-3, the adjusted mean levels were lower for both colon and rectal cancer cases than for their matched controls, but the differences were not statistically significant.

Table 3 shows the odds ratios for colon, rectal, and colorectal cancer by quartiles of serum IGF-I and IGFBP-3 levels, after adjustment for age (by matching), cigarette smoking history, body mass index, alcohol intake, and either IGF-I or IGFBP-3. Although the odds ratios for colon cancer were elevated in the third (odds ratio = 2.2) and fourth (odds ratio = 1.8) quartiles for IGF-I, the trend was not significant ($p = 0.12$). The *p* value for trend also was not remarkable for any of the other comparisons in table 3. We repeated the analysis with further adjustment for age via the generalized estimating equations approach in table 3 and found that the results were nearly identical.

Table 4 shows the joint-effect odds ratios by serum levels of IGF-I and IGFBP-3 for colon, rectal, and colorectal cancer. The odds ratio for colorectal cancer was 0.5 (95 percent confidence interval: 0.3, 0.9) for persons who had an IGF-I value equal to or below the median and an IGFBP-3 value above the median. However, the odds ratios for

TABLE 4. Joint-effect odds ratios* for colon, rectal, and colorectal cancer by serum levels of insulin-like growth factor I and insulin-like growth factor binding protein 3, Oahu, Hawaii

	Joint-effect variable†					
	Low IGF-I‡ High IGFBP-3‡		High IGF-I Low IGFBP-3		High IGF-I High IGFBP-3	
	OR‡	95% CI‡	OR	95% CI	OR	95% CI
Colorectal cancer (282 pairs)§	0.5	0.3, 0.9	1.1	0.7, 1.9	1.2	0.8, 1.7
Colon cancer (177 pairs)	0.4	0.2, 1.0	1.5	0.8, 3.0	1.5	0.9, 2.4
Rectal cancer (105 pairs)	0.7	0.3, 1.6	0.6	0.3, 1.5	0.6	0.3, 1.1

* Adjusted odds ratios and 95 confidence intervals were estimated by the generalized estimating equations approach to correct for intracluster correlation. The odds ratios were statistically adjusted for smoking history, body mass index, alcohol intake, and insulin-like growth factor I or insulin-like growth factor binding protein 3, in addition to age (by matching).

† "Low" was a level less than or equal to the median value; "high" was a level greater than the median value. The median value was based on the frequency distribution in the controls. Quartile 1 was the reference category (low levels of both insulin-like growth factor I and insulin-like growth factor binding protein 3).

‡ IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein 3; OR, odds ratio; CI, confidence interval.

§ Number of matched case-control pairs.

colorectal cancer when IGF-I levels were above the median were not affected by IGFBP-3 values below or above the median. None of the other odds ratios in the table were statistically significant.

The colon and rectal cancer cases were stratified by time interval from examination to diagnosis for assessment of the possible effects of preclinical disease on IGF-I and IGFBP-3 levels (table 5). There were 67 colon and 55 rectal cancer cases diagnosed within 10 years of the examination and 110 colon and 50 rectal cancer cases diagnosed more than 10 years after examination. For colon cancer, the odds ratio for the fourth quartile of IGF-I versus the first was 1.5 for cases diagnosed within 10 years of examination and 1.9 for cases diagnosed more than 10 years after examination, but none of the two-sided p values for trend were statistically significant. There also was no significant trend for the IGFBP-3 values and colon cancer. For rectal cancer, a similar lack of association was present for both IGF-I and IGFBP-3 with regard to time interval from examination to diagnosis.

The cases were additionally separated into two groups by age at examination: those who were aged 60 years or less at the time of examination and those who were more than 60 years of age at examination (table 5). For colon cancer cases who were younger at the time of examination, the highest quartile group of IGF-I values had an odds ratio of 2.4, but the linear trend was not significant. There also was no significant trend in the colon cancer odds ratios for IGF-I among the older subjects or for IGFBP-3 in both age groups. There was a similar lack of trend in the odds ratios for rectal cancer by IGF-I or IGFBP-3 values.

DISCUSSION

A weakly positive association of IGF-I with colon cancer was found among these Hawaii Japanese men, who are known to have a high incidence of colon and rectal cancer. When the subjects were separated into quartile groups, the colon cancer cases in the third quartile (IGF-I values of 137–174 ng/ml) and the fourth quartile (IGF-I values greater than 174 ng/ml) had increased risks in comparison with controls (odds ratios of 2.2 and 1.8, respectively), but the trend was not statistically significant. There was no association of IGF-I with rectal cancer.

Our colon cancer results for IGF-I are reasonably consistent with the results of two previous cohort studies that also tested prediagnostic blood samples for IGF-I and IGFBP-3. The Physicians' Health Study recorded relative risks of 2.1 for colon cancer and 2.5 for colorectal cancer in the highest IGF-I quintile (10). The Nurses' Health Study reported a relative risk of 2.2 for colorectal cancer in the highest IGF-I tertile (11). In these studies, the association with IGF-I became more apparent after adjustment for IGFBP-3.

A third cohort study carried out among women in New York City also found positive associations for colon cancer and colorectal cancer (odds ratios of 1.4 and 1.2, respectively, in the highest quintile), but the results were not statistically significant (17). Two earlier case-control studies did not find any association with IGF-I, but these investigations each involved fewer than 30 cases and used blood samples that had been obtained after diagnosis of colorectal cancer (29, 30). Interpretation of results from studies in which samples were obtained after a cancer diagnosis is difficult, because malnutrition associated with cancer can suppress IGF-I levels so that they no longer reflect levels the subjects had at the time they were at risk.

In contrast to past studies that combined colon cancer cases with rectal cancer cases, usually because of limited numbers of cases, we separated rectal cancer from colon cancer. Studies have found differences in the epidemiology of colon cancer and rectal cancer (19–21). Time trend patterns in many European countries have shown that the incidence of colon cancer has risen, especially among men, while the incidence of rectal cancer has not increased appreciably (19).

Both the Physicians' Health Study (10) and the Nurses' Health Study (11) reported an inverse association between

TABLE 5. Adjusted odds ratios* for colon and rectal cancer by quartiles of serum levels of insulin-like growth factor I and insulin-like growth factor binding protein 3, according to age at examination and time interval between examination and diagnosis, Oahu, Hawaii

	Quartile†			*p* for trend
	2	3	4	
Colon cancer				
Interval since examination ≤ 10 years (67 cases)				
IGF-I‡	1.0	2.7	1.5	0.46
IGFBP-3‡	0.6	0.5	1.0	0.93
Interval since examination > 10 years (110 cases)				
IGF-I	1.0	1.8	1.9	0.15
IGFBP-3	2.3	1.2	0.8	0.52
Age at examination ≤ 60 years (108 cases)				
IGF-I	1.7	2.3	2.4	0.12
IGFBP-3	1.6	1.1	0.8	0.43
Age at examination > 60 years (69 cases)				
IGF-I	0.6	2.3	0.8	0.74
IGFBP-3	1.4	0.8	1.5	0.76
Rectal cancer				
Interval since examination ≤ 10 years (55 cases)				
IGF-I	0.9	1.0	0.8	0.84
IGFBP-3	0.9	1.0	0.7	0.72
Interval since examination > 10 years (50 cases)				
IGF-I	0.8	0.7	0.4	0.28
IGFBP-3	0.8	0.8	0.4	0.27
Age at examination ≤ 60 years (60 cases)				
IGF-I	1.0	0.8	0.8	0.63
IGFBP-3	0.9	1.2	0.6	0.50
Age at examination > 60 years (45 cases)				
IGF-I	0.5	0.8	0.3	0.27
IGFBP-3	0.9	0.5	0.6	0.35

* Adjusted odds ratios were estimated by the generalized estimating equations approach to correct for intracluster correlation. The odds ratios were statistically adjusted for smoking history, body mass index, alcohol intake, and insulin-like growth factor I or insulin-like growth factor binding protein 3, in addition to age (by matching).

† Quartiles were based on the frequency distribution in the controls. Quartile 1 was the reference category.

‡ IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein 3.

IGFBP-3 and colorectal cancer. Although colon and rectal cancer cases had lower IGFBP-3 levels than controls in our investigation, the differences were not statistically significant. The New York cohort study did not find an inverse association of IGFBP-3 with colon or colorectal cancer (17). The reasons for this disparity require further investigation. All four of the above studies had similar advantages, such as a large, homogeneous study population, a prospective study design, collection of blood prior to cancer diagnosis, a representative control population, a large number of tissue-confirmed cases, and almost complete follow-up of the study cohort.

The joint-effect data shown in table 4 suggest that IGF-I and IGFBP-3 may interact as determinants of risk. In particular, persons with low IGF-I levels and high IGFBP-3 levels were at reduced risk. The physiology underlying this observation deserves further study. While circulating levels of IGF-I and IGFBP-3 are generally highly correlated ($r = 0.69$ in the present study), the subset of persons who are outliers with a high IGFBP-3 level and a low IGF-I level may have less bioavailable IGF-I and/or less IGF-I receptor activation than other persons.

Serum samples for our study were collected at least 20 years prior to assay. There have been no formal studies of the stability of IGF-related serum proteins over a period of decades. We cannot rule out the possibility that random variations in degradation between samples over time could have resulted in underestimation of any associations.

Statistically, the generalized estimating equations approach was used to correct for intracluster correlation, because 2,534 men were brothers of the original group of 6,860 cohort members recruited into the study. In actuality, there were two pairs of brothers in which both men were cases, three pairs of brothers in which both men were controls, and 15 pairs of brothers in which one was a case and one was a control. There were no instances of three or more brothers in the study. As a result, odds ratios and confidence intervals estimated by conditional logistic regression (which does not correct for intracluster correlation) produced results virtually identical to those presented in table 2–5 (data not shown).

In a previous report based on all 8,006 Japanese men who were examined from 1965 to 1968, we found that risk of colon cancer increased with body mass index and that risks of both colon cancer and rectal cancer increased with alcohol intake (ounces per month) and pack-years of smoking in the whole cohort (31). These variables were not significantly different between cases and controls in the subsample in this study, as table 1 shows. Part of this variance could be attributed to the numbers of subjects for the respective studies. For instance, the body mass index was 24.3 in 330 colon cancer cases, 23.4 in 123 rectal cancer cases, and 23.8 in 7,487 noncases in the previous report (31), which resulted in a significant difference between colon cancer cases and noncases. These body mass indices compare favorably with the results shown in table 1. In analyzing the associations with IGF-I and IGFBP-3 in this investigation, we adjusted for cigarette smoking history, body mass index, and alcohol intake, as was done in other cohort studies (10, 11, 17).

Although the present report is consistent with three prior prospective studies in that all showed a trend towards higher colon cancer risk with a higher IGF-I level, the trend reached significance in only two of the four cohorts. Further research is needed to determine the basis for discrepancies among epidemiologic studies in this area. One possibility involves confounding of IGF-related risk by other factors that may vary among cohorts, such as obesity, ethnicity, and dietary habits. For example, when we separated the subjects in our study into tertile groups based on body mass index, the adjusted difference in IGF-I concentration between colon cancer cases and their controls was greatest in the highest tertile group (162.8 ng/ml – 144.0 ng/ml = 18.8 ng/ml; $p = 0.02$). This suggests that in populations with a higher body mass index, an association between IGF-I and colon cancer risk may be more noticeable.

There is a paucity of studies concerning ethnic or genetic influences on levels of IGF-related analytes. Early evidence suggests that some of these factors may affect circulating IGF-I or IGFBP-3 levels (32–35). These differences in circulating levels may reflect subtle differences in gene expression that have an impact on the strength of any relation between circulating levels and cancer risk. Furthermore, it is possible that in subjects who already have a relatively high risk because of genetic or dietary factors, high IGF-I levels contribute relatively little to the probability of colon or rectal cancer.

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