SERUM COMPONENTS AND RISK OF CANCER - I

Insulin-like Growth Factor (IGF)-I, IGF-II, IGF Binding Protein-3, and Risk of Colorectal Cancer: a Nested Case-control Study in the JACC Study

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Abstract

Insulin-like growth factor (IGF)-I and IGF-II are important mitogen and IGF binding protein-3 (IGFBP-3) exerts opposite effects. However, the results of epidemiological studies on cancer influence are somewhat controversial, and mainly from Western countries. In the present study, we therefore examined associations of serum IGF-I, IGF-II and IGFBP-3 with colorectal cancer risk among participants in the JACC Study in Japan. After matching 3 controls to cases by sex, age, and study area, a total 101 risk sets were examined using a conditional logistic regression model adjusted for body mass index, smoking habit, alcohol consumption and family history of colorectal cancer. The odds ratios (and 95% CIs) for colorectal cancer mortality among the highest tertiles of IGF-I, IGF-II, and IGFBP-3, compared to the lowest tertiles were 1.01 (0.49-2.10), 1.02 (0.55-1.91), and 1.22 (0.63-2.38), respectively. No linear trends were observed. The lack of any association was not altered after additional adjustment for mutual markers of IGF-I/IGF-II or IGFBP-3, 0.76 (0.34–1.71) for IGF-I, 0.66 (0.30–1.45) for IGF-II, and 1.11 (0.47-2.66) for IGFBP-3. Our prospective data thus indicated that there is no association of IGF-I, IGF-II, and IGFBP-3 with colorectal cancer risk in the Japanese population. Although these markers might be etiologically significant in relation to colorectal cancer, we did not obtain evidence supporting this hypothesis.

Keywords: Japan Collaborative Cohort Study - nested case-control study - colorectal cancer - IGF-I/II - IGFBP-3

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Introduction

Insulin-like growth factors (IGFs) are multifunctional peptides that regulate cell proliferation, differentiation, and apoptosis, and they are important in both normal and tumor growth (Khandwala et al., 2000). More than 90% of circulating IGFs are complexed with IGF binding protein-3 (IGFBP-3). Most IGFs and IGFBP-3 found in the circulation are produced in the liver and are up-regulated by growth hormone (Jones and Clemmons, 1995). These peptides are thus dependent on growth hormone, but are also affected by age, sex, and nutritional status (Rajaram et al., 1997).

Results of early studies on colorectal cancer risk suggested that high circulating IGF-I concentrations are associated with an increasing risk of cancer, whereas high IGFBP-3 concentrations are associated with a decreased risk (Giovannucci, 1999; Ma et al., 1999b). This hypothesis is supported by laboratory evidence: IGF-I is mitogenic and antiapoptotic (Rajaram et al., 1997), whereas IGFBP-3 might also be antiproliferative and proapoptotic (Firth and Baxter, 2002).

In contrast, meta-analyses in 2004 (Renehan et al., 2004) and 2006 (Morris et al., 2006) reported only a modest positive association of IGF-I and IGF-II with colorectal cancer risk, and the newer one suggested no value for cancer screening. These studies also found a lack of association between IGFBP-3 and colorectal cancer. However, the results were almost all from Western countries, with relatively low soy intake and high serum IGF-I concentrations (Takata et al., 2006).

We here report results on measurements of IGF-I, IGF-II, and IGFBP-3 from the Japan Collaborating Cohort Study for Evaluation of Cancer Risk (the JACC Study),

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with a nested case-control staudy of 101 new death cases of colorectal cancer and 302 controls.

Materials and Methods

Study population and serum samples

We conducted a nested case-control study within the JACC study, a large prospective study. The details of the JACC study have been described elsewhere.(Ohno and Tamakoshi, 2001; Tamakoshi et al., 2005) Briefly, from 1988 to 1990, we enrolled 127,500 apparently healthy inhabitants who lived in 45 areas throughout Japan. Among this baseline cohort, we followed 46,465 men and 64,327 women (110,792 in total), 40–79 years of age. At baseline, we asked the participants to complete a questionnaire that included information on demographic characteristics, lifestyle factors such as habits of smoking and alcohol consumption, family history, and medical history. Additionally, we collected a peripheral blood sample from 39,242 persons (35.4% of the respondents in the questionnaire survey) in 37 study areas. Sera were separated from samples at laboratories in or near the surveyed municipalities as soon as possible after sampling. Serum derived from each subject was divided into three to five tubes and stored at -80˚C until analysis. We obtained written informed consent from each participant in 32 areas, though consent was given only by leaders of the community in five areas. The whole study design and use of serum was approved by the Ethical Board at Nagoya University School of Medicine, where the central office of JACC Study was located.

Case ascertainment and control selection

Subjects were followed from the date of the baseline survey through 31 December 1997. Vital status was checked annually using the residential registers. The cause and date of deaths were annually or biannually identified among the study subjects by reviewing all death certificates in each area, with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications).

In this study, the cases were defined as persons who had provided a baseline blood sample and subsequently died of colorectal cancer (coded as C18 to C20 in the International Statistical Classification of Disease and Relative Health Problem, 10th revision) during the study period. Of 526 colorectal cancer death identified, 101 persons (19.6%), 66 colon cancer and 35 rectum cancer, had provided blood samples for IGF-I, IGF-II and IGFBP-3 assays and thus formed the case group. For each case, three controls randomly selected from among the cohort participants who did not have a diagnosis of cancer, and were matched for each case by sex, age (±3 year), and study area. A total 302 persons formed the control group. There was one case in which only two controls could be matched.

Biochemical assays of sera

Serum concentrations of IGF-I, IGF-II, and IGFBP-3 were measured by immuno-radiometric assay, using commercially available kits (Daiichi Radioisotope Laboratory, Tokyo). Assay methods described in detail elsewhere (Ito et al., 2005). All assays were performed and interpreted by individuals who were blinded to the case-control status of samples. The intra-assay precisions obtained using different reference sera for each determination method was 2.15%-3.53%, 2.74%-4.45%, and 3.16%-4.19% of the coefficients variation values for IGF-I, IGF-II, and IGFBP-3, respectively.

Statistical analysis

The statistical analysis of the JACC data was carried out as follows: Pearson correlation coefficients were used to examine the association between IGF-I, IGF-II, IGFBP-3, and age within the controls. Conditional logistic regression models were used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for colorectal cancer for tertile levels of the markers, which takes account of the matching (101 pairs). Tertile cut points were determined on the distribution of control subjects. To determine if there was a significant linear association with risk of colorectal cancer, the original markers as continuous values were entered into the conditional logistic models. Body mass index (BMI), smoking habit, alcohol consumption and family history of colorectal cancer of parents or siblings were investigated as potential confounders. BMI was analyzed as a continuous measure. There were four categories for smoking habit (non-smokers, former smokers, current smokers, and unknown) and alcohol consumption (non-drinkers, former drinkers, current drinkers, and unknown). We additionally adjusted for IGFBP-3 concentration in them model for IGF-I and IGF-II, and also adjusted for IGF-I and IGF-II concentration in them model for IGFBP-3. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. All analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC).

Results

Table 1 gives details of the study population including the means and standardized deviations of age, IGF-I, IGF-II, IGFBP-3, and number of smokers, drinkers and those who had a family history of colorectal cancer at the entry

Table 1. Characteristics of Cases and Controls

Characteristic		Cases	Controls
Gender	Males	56 (55.4%)	167 (55.3%)
	Females	47 (44.6%)	135 (44.7%)
	Total	101	302
Age*		64.7 ± 8.1	64.9 ± 8.3
IGF-I (ng/ml)*		130.8 ± 52.0	134.2 ± 8.3
IGF-II (ng/ml)*		612.2 ± 138.3	618.3 ± 59.4
IGFBP-3 (μg/ml) *		3.02 ± 0.75	3.12 ± 0.89
BMI (kg/m^2) *		22.7 ± 2.5	22.9 ± 3.2
Colorectal cancer family history			
		4 (4.0%)	4 (1.3%)
Current smokers		23 (25.0%)	82 (29.3%)
Current drinkers		46 (48.9%)	146 (50.9%)

*Mean ± standard deviation

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Colorectal Cancer According to Tertiles of Serum Concentrations of IGF-I, IGF-II, and IGFBP-3, in the JACC Study

IGFs	1 (lowest)	2 (middle)	3 (highest)	P for trend
IGF-I (range, ng/ml)	4.1 - 104	105 - 144	145 - 350	
Number of cases/controls	30/92	36/103	35/107	
OR[1] (95% CI)	1.00 Reference	1.07 (0.55 - 2.07)	1.01 (0.49 - 2.10)	0.35
OR[2a] (95% CI)	1.00 Reference	0.92 (0.47 -1.84)	0.76 (0.34 - 1.71)	0.71
IGF-II (range, ng/ml)	280 - 554	555 - 654	655 - 1300	
Number of cases/controls	35/101	31/102	35/99	
OR[1] (95% CI)	1.00 Reference	0.91 (0.51 - 1.63)	1.02 (0.55 - 1.91)	0.65
OR[2a] (95% CI)	1.00 Reference	0.71 (0.37 - 1.36)	0.66 (0.30 - 1.45)	0.32
IGFBP-3 (range, μg/ml)	1.40 - 2.65	2.66 - 3.32	3.33 - 5.33	
Number of cases/controls	31/103	36/100	34/99	
OR[1] (95% CI)	1.00 Reference	1.26 (0.68 -2.35)	1.22 (0.63 -2.38)	0.16
OR[2b] (95% CI)	1.00 Reference	1.22 (0.63 -2.39)	1.11 (0.47 -2.66)	0.14

OR[1], adjusted for age, sex and area by matching and was also adjusted for smoking, alcohol consumption, body mass index, and family history of colorectal cancer; OR[2a], additionally adjusted for IGFBP-3 to the model for OR[1]; OR[2b], additionally adjusted for IGF-I and IGF-II to the model for OR[1]

into the JACC Study according to case-control status. No significant difference between cases and controls were observed.

IGF-I and IGFBP-3 were moderately correlated (r=0.57) and both declined with age (r=–0.39 for IGF-I and age and r=–0.28 for IGFBP-3 and age). IGF-II was more highly correlated with IGFBP-3 (r=0.75) and also declined with age (r=–0.21)

Table 2 shows the ORs of colorectal cancer according to tertile of IGF-I, IGF-II, and IGFBP-3. There were no statistically significant associations between colorectal cancer and any of serum markers after adjusting for BMI, smoking habit, alcohol consumption and family history of colorectal cancer. The ORs (and 95% CIs) among the highest tertile of IGF-I, IGF-II, IGFBP-3 compared to the lowest was 1.01 (0.49-2.10), 1.02 (0.55-1.91), and 1.22 (0.63–2.38), respectively. No linear trend was observed. The lack of association was not altered after additional adjustment for markers of IGF-I/IGF-II or IGFBP-3. The ORs (and 95% CIs) of IGF-I, IGFBP-3, IGF-I was 0.76 (0.34-1.71), 0.66 (0.30-1.45), and 1.11 (0.47-2.66), respectively. Again, no linear trend was observed. These results were not essentially changed using quartiles of IGF markers instead of the tertiles.

Discussion

Our results showed that none of IGF-I, IGF-II, nor IGFBP-3 associated significantly on colorectal cancer risk. Linear trend was also not observed. The lack of the associations was observed regardless of adjustment for mutual growth factor markers. Modest ORs and wide CIs were consistent to other studies.

The ORs from the previous studies varied between 1.10 and 2.51 in the highest quartile (or tertile) of IGF-I compared to the lowest, (Ma et al., 1999b; Giovannucci et al., 2000; Kaaks et al., 2000; Probst-Hensch et al., 2001; Palmqvist et al., 2002; Nomura et al., 2003; Morris et al., 2006) among which only one study found significance (Ma et al., 1999b). The significant OR was observed only when the model was adjusted for IGFBP-3. From two meta-analyses, the study adjusted for IGFBP-3 (Renehan et al., 2004) reported slightly stronger association (summary OR: 1.58, 95% CI: 1.11-2.27) than the other one without adjustment for IGFBP-3 (summary OR: 1.37, 95% CI: 1.05-1.78) (Morris et al., 2006). Both studies reported significant but modest results and the summary ORs of the meta-analyses were included within the 95% CI of the present study.

Results from a meta-analysis of IGF-II and colorectal cancer risk (Morris et al., 2006) showed a stronger association (summary OR: 1.95, 95% CI: 1.26-3.00) than that between IGF-I and colorectal cancer. Our 95% CI (0.55-1.91) did not include the summary OR. The reason of this inconsistency is not clear.

The association between IGFBP-3 and colorectal cancer risk has been found to be heterogeneous (Morris et al., 2006; Renehan et al., 2004), approximately half studies observed ORs larger than one, and the rest half observed values smaller than one. Both meta-analyses reported insignificant ORs. As a whole, although IGF-I, IGF-II and IGFBP-3 might be of etiological significance in relation to colorectal cancer, the association was not significant in this population

The strength of this study is the prospective design with stored blood samples. Retrospective case-control studies of growth factors and cancer tend to overestimate associations (Renehan et al., 2004). In addition, since the presence of malignant disease might affect the markers circulating concentrations, measurements from retrospective studies might reflect tumor marker status rather than true risk assessment.

Several limitations should be noted. First, we did not have follow-up information on IGF-I, IGF-II, and IGFBP-3. Due to rapid change of dietary habits of Japanese (Suzuki et al., 2005), serum concentration at the baseline might not reflect the status in several years later, which would generate random misclassification. Second, relatively small number of the cases prevented us subgroup analysis or analysis with an interaction term. Effect modification by sex, age, or location of the tumor (colon or rectum), or that between IGF-I and IGFPB-3 (Ma et al., 1999a) was not examined in the present study because of the small number of cases.

In conclusion, we did not find any association of IGF-I, IGF-II, and IGFBP-3 with colorectal cancer risk in our Japanese population. Although these markers might be etiologically significant in relation to colorectal cancer, the association was not significant in this population.

Member list of the JACC Study Group

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