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ORIGINAL ARTICLE

Insulin-like growth factor-related components and the risk of liver cancer in a nested case-control study

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Abstract Insulin-like growth factor-1 (IGF1) is a potent mitogen. IGF-binding protein-3 (IGFBP3) binds and inhibits IGF1. High circulating IGF1 levels and low IGFBP3 levels are associated with increased risk of several cancers. We examined relationships between serum levels of these factors and hepatoma risk in a case-control study nested in a prospective cohort study (the Japan Collaborative Cohort Study (JACC Study)). A baseline survey was conducted from 1988 to 1990, and 39,242 subjects donated blood samples. Participants diagnosed with hepatoma by 1997 were considered cases for nested case-control studies. Ninety-one cases and 263 sex- and age-matched controls were analyzed. A conditional logistic model was used to estimate odds ratios (ORs) for the incidence of hepatoma associated with serum IGF1 and IGFBP3 levels. Neither IGF1 nor the molar ratio of IGF1/IGFBP3 was correlated with hepatoma risk. After adjustment for hepatitis viral infection, body mass index, smoking, and alcohol intake, a higher molar difference of (IGFBP3 − IGF1) was associated with a decreased hepatoma risk more than IGFBP3 alone (p for trend <0.001 and = 0.003, respectively). People in the highest quartile had a lower risk (OR = 0.098; 95 % confidence interval = 0.026–0.368). In subgroup analyses of males and females, the molar difference was associated with a decreased hepatoma risk (p for trend <0.05). In non-elderly individuals, the difference was inversely correlated with the incidence of hepatoma (p for trend <0.01). The molar difference of (IGFBP3 − IGF1) may be inversely associated with the incidence of hepatoma.

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Keywords Hepatoma · Insulin-like growth factor (IGF) · IGF-binding protein (IGFBP) · Nested case-control study · Odds ratio

Abbreviations

BMI	Body mass index
CI	Confidence intervals
HCC	Hepatocellular carcinoma
IGF	Insulin-like growth factor
IGFBP	IGF-binding protein
IGF-1R	IGF-1 receptor
JACC	Japan Collaborative Cohort
OR	Odds ratio

Introduction

Signals from a variety of growth factors and their receptors are required for carcinogenesis and cancer development in

humans malignancies [1, 2]. The insulin-like growth factor (IGF) ligands, IGF1 and IGF2, and the type 1 insulin-like growth factor receptor (IGF-1R) compose a system that may be an important molecular target for cancer therapy [2–4]. Binding of ligands to IGF-1R causes receptor autophosphorylation and activates multiple downstream signaling pathways [5].

Expression of IGF-1R is induced during pathological and physiological conditions in hepatocytes as well as in liver cancer (hepatoma) cells [6]. Upregulation of IGF2 is an early event in hepatocarcinogenesis prior to the appearance of morphologically distinct dysplastic lesions. Elevated focal IGF2 transcript levels indicate an increased risk for hepatocellular and cholangiocellular carcinomas [7].

IGFs are produced by the liver and also by many extrahepatic sites including tumor cells and stromal fibroblasts [8]. In normal cells, the IGF/IGF-1R system is controlled by multiple steps [9]. Growth hormone, which is produced in the pituitary gland, stimulates the secretion of IGFs and IGF-binding proteins (IGFBPs) from hepatocytes. Activation of IGF-1R is tightly regulated by the amount of the free form of the ligands, which is controlled by the action of IGFBPs and the non-stimulatory receptor, type 2 IGF receptor (IGF-2R, also known as mannose 6-phosphate receptor) [5, 10]. IGFBP1–6 circulate and modulate IGF activity by reducing the bioavailability of IGFs for binding to IGF-1R. Approximately 98 % of IGF1 is in an inactive form in serum due to binding to one of the IGFBPs, which bind IGF in a 1:1 molar ratio. IGF-binding protein-3 (IGFBP3) is the most abundant IGFBP and accounts for almost 80 % of all IGF binding. The complex balance between IGFs and IGFBPs is modulated by specific IGFBP proteases, such as matrix metalloproteinase [11]. In addition, IGFBPs have IGF-independent actions, but their roles in cancer are not yet clear [10]. IGF-2R is also a negative regulator of IGF signaling and works as a decoy by binding IGFs.

Elevated serum IGF1 levels or free IGF1 levels, which are estimated by the molar ratio of IGF1 to IGFBP3, increase the risk of developing several cancers, including colon, prostate, and breast cancers [12–14]. In addition, low serum concentrations of IGFBP3 increase the risk of cancer [14]. However, limited information is available about IGF in liver cancer, and no information about the relationship between the incidence of hepatoma and the serum concentration of IGF and IGFBP has been published. Although the relationships between IGF/IGFBP and the risk of several cancer death from the Japan Collaborative Cohort Study (JACC Study) were reported [15, 16], the risk of hepatoma has not published. Thus, we want to reveal relationships between serum levels of these factors and liver cancer risk in a case-control study nested in a prospective cohort study (JACC Study).

Materials and methods

Study population and serum samples

We analyzed data from the JACC Study, which evaluated cancer risk associated with lifestyle factors in a Japanese population. The study has been described in detail previously [17–19]. A baseline survey was conducted in 45 areas between 1988 and 1990. Thirty-five percent of the cohort participants (39,242 subjects aged 40 to 79 years at baseline) donated blood samples, and these were stored at −80 °C until analyses were performed.

Follow-up, identification of hepatoma, and control selection

The incidence of cancer was followed in 24 study areas. Subjects were followed from the baseline survey. Individuals who moved away from the study area were treated as study dropouts, because deaths after such moves could not be confirmed in our follow-up system. Participants with a cancer history at baseline were excluded. The occurrence of cancer was confirmed in population-based cancer registries or by reviewing the records of local major hospitals. We defined liver cancer (hepatoma) as malignant neoplasm of the liver and intrahepatic bile ducts (C22) according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (http://www.who.int/classifications/icd/en/). Participants diagnosed with hepatoma by 1997 were regarded as cases for nested case-control studies. For each case, we randomly selected three controls that were matched for gender, age, and residential area; however, less than three controls were selected for some cases depend on the selection criterion. A total of 91 cases and 263 control subjects were eligible for the present analysis.

Biochemical assays of sera

Serum levels of IGF1 and IGFBP3 were measured at a single laboratory in 1999 and 2000 with an immunoradiometric assay using commercially available kits (Daiichi Radioisotope Lab., Tokyo, Japan) by trained staff who were blinded to the status of each case and control (SRL, Tokyo, Japan). Details of the measurement of serum IGF1 and IGFBP3 levels were described previously [20]. Hepatitis C virus antibody (third generation) and hepatitis B virus surface antigen were assayed in the same laboratory (SRL) [21].

Statistical analysis

Proportions and mean values of baseline characteristics between cases and their matched controls were compared using Fisher's exact test or a *t* test. Serum values were divided into

quartiles based on the distribution of serum values in all control subjects, with the first quartile used as a reference. IGF1 quartile values for quartiles 1, 2, 3, and 4 were <75.6, 75.6–110.0, 110.1–140.0, and >140.0 ng/mL, respectively. IGFBP3 quartile values for quartiles 1, 2, 3, and 4 were <2.30, 2.30–2.76, 2.77–3.37, and >3.37 ng/mL, respectively.

Because the molar ratio of IGF1 to IGFBP3 is considered to represent free IGF1, we also assessed the molar ratio of IGF1 to IGFBP3 (for conversion, 1 ng/mL is 0.130 nM for IGFI and 0.036 nM for IGFBP3) [14]. In addition, we assessed the molar difference between IGFBP3 and IGF1.

The odds ratios (ORs) for the incidence of hepatoma associated with serum IGF-related product levels were estimated using conditional logistic regression, which was adjusted for hepatitis viral infection. ORs were also adjusted for body mass index (BMI, computed as weight in kg divided by the square of the height in m), tobacco smoking status, and alcohol consumption in addition to hepatitis viral infection. The statistical significance of trends across exposure quartiles was assessed by including ordinal terms for each serum level quartile and entering the variable as a continuous term in the model. All *p* values and 95 % confidence intervals (95 % CI) presented in the tables were based on two-sided tests.

Results

Baseline characteristics are shown in Table 1. Case subjects were heavier and tended to have a higher BMI than control subjects, but no statistically significant difference was observed for other possible risk factors. Smoking habits were not different between the two groups. The percentage of current alcoholic beverage drinkers was higher in the control group. However, the percentage of former drinkers was higher in the case group, and the percentage of never drinkers was not different between the two groups. The mean serum concentration of IGF1 tended to be lower in the hepatoma group, but the difference was not significant. The mean serum level of IGFBP3 was significantly lower in the case group than in the controls.

Table 1 Selected baseline characteristics of case and control group

	Cases	Controls	*p* value
Number of subjects	91	263	
Age	64.5 ± 7.4	64.1 ± 6.6	0.624
Male (%)	51 (56.0 %)	157 (59.5 %)	0.622[a]
Height	156.3 ± 9.0	156.2 ± 8.0	0.905
Weight	55.4 ± 9.0	54.5 ± 7.9	0.339
BMI (kg/m^2)	22.7 ± 2.9	22.3 ± 2.6	0.323
Cigarette smoking (*n*)	86	247	0.296[a]
Never (%)	37 (43.0)	116 (47.0)	
Past (%)	17 (19.8)	61 (24.7)	
Current (%)	32 (38.2)	70 (28.3)	
Alcohol intake (*n*)	88	254	0.0012[a]
Never (%)	38 (43.2)	106 (41.7)	
Past (%)	15 (17.0)	12 (4.7)	
Current (%)	35 (39.8)	136 (53.6)	
Hepatitis virus infection	59 (64.8 %)	44 (16.7 %)	<0.001[a]
IGF1 (ng/mL)	97.9 ± 51.9	109.9 ± 53.0	0.061
IGFBP3 (ng/mL)	2.25 ± 0.80	2.84 ± 0.82	<0.001

[a] Fisher's exact test

The concentration of IGF1 tended to be inversely correlated with the risk of hepatoma after adjustment for hepatitis viral infection (*p* for trend = 0.096, Table 2). The highest quartile of IGF1 tended to show the lowest risk of hepatoma (OR = 0.448; 95 % CI = 0.143–1.405). The serum level of IGFBP3 was significantly and inversely correlated with the risk of hepatoma (*p* for trend = 0.001). The highest quartile of IGFBP3 showed the lowest risk of hepatoma (OR = 0.203; 95 % CI = 0.069–0.595).

A higher molar ratio of IGF1 to IGFBP3, which represents free IGF1, tended to be associated with an increased risk of hepatoma after adjustment for hepatitis viral infection (*p* for trend = 0.086, Table 3). A higher molar difference of (IGFBP3 − IGF1), which represents free IGFBP3, was associated with a decreased risk of hepatoma after adjustment for hepatitis viral infection (*p* for trend <0.001, Table 3). The highest quartile of the molar difference of (IGFBP3 − IGF1) showed the lowest risk of hepatoma (OR = 0.125; 95 % CI = 0.041–0.386).

We then analyzed ORs after adjustment for hepatitis viral infection, BMI, tobacco smoking status, and alcohol consumption for the incidence of hepatoma associated with serum IGF-related product levels. A higher concentration of IGF1 tended to decrease the risk of hepatoma (*p* for trend = 0.106, Table 2). The concentration of IGFBP3 was inversely correlated with the risk of hepatoma (*p* for trend = 0.003). The highest quartile of IGFBP3 showed the lowest risk of hepatoma (OR = 0.202; 95 % CI = 0.059–0.692). The molar ratio of IGF1 to IGFBP3 was not correlated with the risk of hepatoma after adjustment for hepatitis virus, BMI, tobacco, and alcohol (*p* for trend = 0.224, Table 3). A higher molar difference of (IGFBP3 − IGF1) was associated with a decreased risk of hepatoma after adjustment for hepatitis virus, BMI, tobacco, and alcohol (*p* for trend <0.001). The highest quartile of the molar difference of (IGFBP3 − IGF1) showed the lowest risk of hepatoma (OR = 0.098; 95 % CI = 0.026–0.368). Thus, the molecular difference between IGFBP3 and IGF1 may most accurately represent the risk of hepatoma in this study.

To analyze the interaction with gender and age, ORs were calculated in subgroups. A high serum level of IGFBP3 was also related to a decreased risk of hepatoma after adjustment for hepatitis viral infection, BMI, tobacco, and alcohol in both subgroups of males and non-elderly

Table 2 Odds ratios and 95 % confidence intervals for hepatic cancer with reference to serum concentrations of IGF1 and IGFBP3

	Quartile				
	1 (referent)	2	3	4	*p* for trend
IGF1					
ng/mL (range)	<75.6	75.6–110.0	110.1–140.0	>140.0	
No. of case/control	31/65	35/84	13/54	12/60	
OR adjusted 1 (95 % CI)	1	0.846 (0.358–1.999)	0.504 (0.176–1.446)	0.448 (0.143–1.405)	0.096
No. of case/control	29/56	32/73	11/51	12/59	
OR adjusted 2 (95 % CI)	1	1.007 (0.381–2.665)	0.585 (0.182–1.879)	0.422 (0.119–1.503)	0.106
IGFBP3					
ng/mL (range)	<2.30	2.30–2.76	2.77–3.37	>3.37	
No. of case/control	55/66	13/66	14/66	9/65	
OR adjusted 1 (95 % CI)	1	0.347 (0.146–0.823)	0.253 (0.100–0.645)	0.203 (0.069–0.595)	0.001
No. of case/control	51/57	11/63	14/63	8/58	
OR adjusted 2 (95 % CI)	1	0.447 (0.169–1.181)	0.261 (0.096–0.713)	0.202 (0.059–0.692)	0.003

adjusted 1 adjusted for hepatitis viral infection, *adjusted 2* adjusted for hepatitis viral infection, cigarette smoking, BMI, and alcohol intake

participants (population ≤65 years old) (p for trend = 0.018 and 0.004, respectively, Table 4). However, this correlation was not observed in other subgroups of females and elderly individuals (population >65 years old) (p for trend = 0.117 and 0.505, respectively, Table 4).

In both the male and female population, a high molar difference of (IGFBP3 − IGF1) was associated with a decreased risk of hepatoma after adjustment for hepatitis viral infection (p for trend <0.001 for both, Table 5). The highest quartile of the molar difference between IGFBP3 and IGF1 showed the lowest risk of hepatoma (males, OR = 0.085; females, OR = 0.164). After adjustment for hepatitis viral infection, BMI, tobacco, and alcohol, a high molar difference of (IGFBP3 − IGF1) was still related to the incidence of hepatoma in both groups (p for trend = 0.004 in males and 0.026 in females). The highest quartile of the molar difference showed the lowest risk of hepatoma (males, OR = 0.064; females, OR = 0.121).

In both the elderly and non-elderly populations, the molar difference between IGFBP3 and IGF1 was inversely correlated with the risk of hepatoma after adjustment for hepatitis viral infection (p for trend = 0.001 and <0.001, respectively, Table 5). The highest quartile of the molar difference showed the lowest risk of hepatoma (non-elderly, OR = 0.032; elderly, OR = 0.209). After adjustment for hepatitis viral infection, BMI, tobacco, and alcohol, a high molar difference of

Table 3 Odds ratios and 95 % confidence intervals for hepatic cancer according to molar ratio and difference of IGF1 and IGFBP3

	Quartile				
	1 (referent)	2	3	4	*p* for trend
IGF1/IGFBP3					
Molar ratio	<0.11	0.11–0.14	0.15–0.18	>0.18	
No. of case/control	30/65	27/65	23/66	11/67	
OR adjusted 1 (95 % CI)	1	1.531 (0.569–4.121)	1.772 (0.642–4.891)	2.518 (0.872–7.273)	0.086
No. of case/control	28/64	25/64	20/58	11/53	
OR adjusted 2 (95 % CI)	1	1.830 (0.621–5.394)	1.836 (0.637–5.290)	2.250 (0.698–7.251)	0.224
IGFBP3 − IGF1					
Molar difference	<70.51	70.51–85.57	85.58–104.10	>104.10	
No. of case/control	58/66	15/66	10/66	8/65	
OR adjusted 1 (95 % CI)	1	0.280 (0.116–0.676)	0.160 (0.058–0.446)	0.125 (0.041–0.386)	<0.001
No. of case/control	53/59	14/62	10/62	7/58	
OR adjusted 2 (95 % CI)	1	0.267 (0.096–0.743)	0.170 (0.056–0.517)	0.098 (0.026–0.368)	<0.001

adjusted 1 adjusted for hepatitis viral infection, *adjusted 2* adjusted for hepatitis viral infection, cigarette smoking, BMI, and alcohol intake

Table 4 Odds ratios and 95 % CIs for hepatic cancer with reference to serum concentration of IGFBP3 among subgroups

		Quartile				
		1 (referent)	2	3	4	*p* for trend
IGFBP3	ng/mL (range)	<2.30	2.30–2.76	2.77–3.37	>3.37	
Male	No. of case/control	37/41	6/41	5/42	3/32	
	OR adjusted 1 (95 % CI)	1	0.301 (0.081–1.119)	0.213 (0.052–0.880)	0.131 (0.023–0.767)	0.010
	No. of case/control	36/39	5/40	5/41	3/29	
	OR adjusted 2 (95 % CI)	1	0.482 (0.117–1.986)	0.180 (0.037–0.883)	0.123 (0.015–1.027)	0.018
Female	No. of case/control	18/25	7/25	9/24	6/33	
	OR adjusted 1 (95 % CI)	1	0.404 (0.120–1.355)	0.294 (0.076–1.137)	0.279 (0.068–1.148)	0.056
	No. of case/control	15/18	6/23	9/22	5/27	
	OR adjusted 2 (95 % CI)	1	0.365 (0.079–1.673)	0.444 (0.084–2.355)	0.246 (0.045–1.351)	0.117
≤65 years old	No. of case/control	29/33	6/33	8/40	4/43	
	OR adjusted 1 (95 % CI)	1	0.212 (0.042–1.068)	0.085 (0.015–0.466)	0.041 (0.004–0.388)	0.002
	No. of case/control	27/30	5/33	8/38	4/40	
	OR adjusted 2 (95 % CI)	1	0.213 (0.035–1.287)	0.063 (0.009–0.414)	0.065 (0.007–0.606)	0.004
>65 years old	No. of case/control	26/33	7/33	6/26	5/22	
	OR adjusted 1 (95 % CI)	1	0.382 (0.117–1.245)	0.515 (0.145–1.824)	0.425 (0.098–1.840)	0.205
	No. of case/control	24/27	6/30	6/25	4/16	
	OR adjusted 2 (95 % CI)	1	0.465 (0.106–2.039)	0.701 (0.168–2.942)	0.511 (0.071–3.684)	0.505

adjusted 1 adjusted for hepatitis viral infection, *adjusted 2* adjusted for hepatitis viral infection, cigarette smoking, BMI, and alcohol intake

(IGFBP3 − IGF1) was still related to the incidence of hepatoma (p for trend = 0.002) in the non-elderly group. The highest quartile of the molar difference showed the lowest risk of hepatoma (OR = 0.039). However, in the population >65 years

Table 5 Odds ratios and 95 % CIs for hepatic cancer according to molar difference (IGFBP3 − IGF1) among subgroups

		Quartile				
		1 (referent)	2	3	4	*p* for trend
IGFBP3 − IGF1	Molar difference	<70.51	70.51–85.57	85.58–104.10	>104.10	
Male	No. of case/control	40/45	5/43	3/38	3/30	
	OR adjusted 1 (95 % CI)	1	0.224 (0.060–0.830)	0.108 (0.020–0.584)	0.085 (0.012–0.576)	<0.001
	No. of case/control	38/43	5/43	3/36	3/27	
	OR adjusted 2 (95 % CI)	1	0.208 (0.049–0.886)	0.079 (0.012–0.539)	0.064 (0.006–0.661)	0.004
Female	No. of case/control	18/21	10/23	7/28	5/35	
	OR adjusted 1 (95 % CI)	1	0.354 (0.100–1.257)	0.213 (0.052–0.861)	0.164 (0.038–0.708)	<0.001
	No. of case/control	15/16	9/19	7/26	4/29	
	OR adjusted 2 (95 % CI)	1	0.374 (0.064–2.173)	0.360 (0.070–1.843)	0.121 (0.019–0.761)	0.026
≤65 years old	No. of case/control	30/35	9/31	4/41	4/42	
	OR adjusted 1 (95 % CI)	1	0.145 (0.024–0.887)	0.030 (0.003–0.262)	0.032 (0.003–0.334)	<0.001
	No. of case/control	28/32	8/31	4/39	4/39	
	OR adjusted 2 (95 % CI)	1	0.115 (0.012–1.080)	0.017 (0.001–0.201)	0.039 (0.003–0.493)	0.002
>65 years old	No. of case/control	28/31	6/35	6/25	4/23	
	OR adjusted 1 (95 % CI)	1	0.284 (0.088–0.920)	0.386 (0.107–1.395)	0.209 (0.046–0.945)	0.001
	No. of case/control	25/27	6/31	6/23	3/17	
	OR adjusted 2 (95 % CI)	1	0.286 (0.065–1.260)	0.722 (0.169–3.083)	0.125 (0.015–1.074)	0.134

adjusted 1 adjusted for hepatitis viral infection, *adjusted 2* adjusted for hepatitis viral infection, cigarette smoking, BMI, and alcohol intake

old, the molar difference of (IGFBP3 − IGF1) tended to be inversely correlated with the risk of hepatoma, but the difference was not statistically significantly (p for trend = 0.134). Thus, the molar difference of (IGFBP3 − IGF1) may be a candidate predictive marker of hepatoma in both genders in the non-elderly but not the elderly population.

Discussion

High serum IGF1 levels and low serum concentrations of IBFBP3 are risk factors for several cancers [12–14]. Moreover, IGF ligands play several roles in carcinogenesis and tumor progression of liver cancer, and IGFBPs could block those effects of IGFs [2, 3]. In this study, serum levels of IGF1 tended to be related to a low OR for hepatoma, and levels of IGFBP3 showed a low OR. As IGFBP3 has both IGF-dependent and IGF-independent antitumor effects [10], IGFBP3 was appropriately correlated with a low OR for hepatoma. However, we observed a discrepancy between the previous data of hepatocarcinogenic effects of IGF and our current result of an inverse relationship between the tumor marker and the ligands [22–24].

Because the molar ratio of IGF1 to IGFBP3 is considered to represent free and active IGF1 in previous reports [14], we analyzed this ratio in our study. A high molar ratio of IGF1/IGFBP3 tended to show a high OR for hepatoma, which may indicate that free IGF1 plays a part in hepatocarcinogenesis. However, IGFBP3 alone showed a stronger association with the OR of hepatoma than this molar ratio.

IGF ligands and IGFBP form a complex in serum in a 1:1 molar ratio, and the molar concentration of IGFBP3 in serum is usually higher than that of IGF1. Thus, a molar difference between IGFBP3 and IGF ligands may represent the serum concentration of free-form IGFBP3. The molar difference between IGFBP3 and IGF1 was significantly and inversely correlated with the incidence of hepatoma. Moreover, this parameter showed the tightest association with OR for hepatoma among all parameters. Thus, free IGFBP3 in serum may reflect a reduced risk of hepatoma.

In the analysis of the OR for hepatoma after adjustment for hepatitis viral infection, BMI, cigarette smoking, and alcohol intake, the molar difference of (IGFBP3 − IGF1) showed a more significant correlation with an inverse risk of hepatoma compared to IGFBP3 alone. Analyses of age or gender subgroups confirmed that a low molar difference of (IGFBP3 − IGF1) showed a high risk of hepatoma. This association was slightly strengthened with the additional adjustment for the history of diabetes, as diabetes mellitus is strongly associated with several cancer risks, including liver cancer [25, 26]. Therefore, this parameter may be a candidate predictive marker of hepatoma, although not in the elderly population.

Both IGF and IGFBP are produced mainly by hepatocytes in healthy adults. In patients with chronic hepatitis, the serum concentration of IGF1 varies compared to healthy controls [27–29]. In the chronic hepatitis group, IGFBP3 levels were lower compared with controls in one study but not in another [30, 31]. Thus, no consensus exists about the serum levels of IGF1 and IGFBP3 in patients with chronic hepatitis. The serum levels of IGF1 and IGFBP3 were significantly reduced in cirrhosis and hepatocellular carcinoma (HCC) patients compared to controls [28, 30, 32, 33]. In patients who developed HCC from cirrhosis, IGF1 levels significantly decrease during follow-up [31]. HCC is associated with a higher IGF1/IGFBP3 ratio than liver cirrhosis [32]. A low serum concentration of IGF1 may have tended to show a higher risk of hepatoma in this study perhaps due to an influence of preexisting hepatic hypofunction due to the presence of latent liver cirrhosis in this cohort. However, it is unlikely that a significant number of participants with cirrhosis were present in this cohort.

The level of IGF-1R is increased and that of the IGF-2R is decreased in cirrhotic hepatocytes [7, 34]. Moreover, in patients with chronic hepatitis, the hepatocyte IGF1/IGFBP3 ratio is higher than the serum IGF1/IGFBP3 ratio [29]. Thus, the local concentration of IGF ligands around hepatocytes may be high, even though the serum concentrations are low in patients with liver cirrhosis. This may be another reason why low serum concentrations of IGF1 tended to show a higher risk of hepatoma.

The advantages of this study are that samples were from a large-scale population-based study, and the data were adjusted for hepatitis viral infection. A limitation of this study is that some data about BMI, tobacco smoking status, and alcohol consumption were missing in this JACC Study due to the self-administered questionnaire [17]. Another limitation is that both the numbers of blood samples and hepatoma cases were not large.

Our result may suggest that high circulating IGFBP3 levels, especially free IGFBP3 detected as the molar difference of (IGFBP3 − IGF1), represent an important predictive marker of a low future risk of liver cancer.

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Compliance with ethical standards

Conflicts of interest None

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