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# A nested case-control study of stomach cancer and serum insulin-like growth factor (IGF)-1, IGF-2 and IGF-binding protein (IGFBP)-3

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ABSTRACT

We conducted this study to investigate the association between serum levels of insulin-like growth factor (IGF)-1, IGF-2, and IGF-binding protein (IGFBP)-3 and the incidence of stomach cancer. A nested case-control study of 161 stomach cancer incidences and 314 matched controls was established within the Japan Collaborative Cohort Study.

The adjusted ORs for IGF-1 quartile ranged from 0.84 and 1.13, but these were not statistically significant. Further, higher IGF-2 levels did not significantly correlate with the incidence of stomach cancer. A tendency for the risk of stomach cancer to decrease with increasing IGFBP-3 level was observed, but without statistical significance. A slight decrease in risk was seen with an increase in IGFBP-3 level, but neither change was statistically significant. To conclude, we found no association between IGF-1, IGF-2, or IGFBP-3 serum levels and the risk of stomach cancer. As this association has not been established, these findings need to be confirmed in future studies.



## 1. Introduction

Stomach cancer is the second most common cancer worldwide.[1] Japan is one of the countries with the highest incidence rate, while Western Europe and the United States of America generally have low incidences. Although the incidence of stomach cancer among Japanese has decreased over the past two decades, it remains the leading cause of cancer death.[2] Therefore, prevention for stomach cancer is important in Japan.

Insulin-like growth factors (IGFs) are polypeptides present in many tissue types that are bioactive in a number of ways,

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including cell proliferation, differentiation, apoptosis, and transformation.[3,4] The interaction between IGFs and their receptors is regulated by a group of binding proteins called IGF-binding proteins (IGFBPs). The most active of these is IGFBP-3, which binds the vast majority of circulating IGFs.

Review[5,6] and epidemiological studies assessing the relationship between serum IGF levels and the risk of lung,[7] breast,[8] colon,[9] and pancreatic cancer[10] have suggested that high circulating IGF concentrations are positively associated with an increased risk of cancer, except for high concentrations of IGFBP-3, which are associated with a decreased risk. Results have been inconsistent, however, possibly owing to differences in cancer site, study population, and design. In particular, few studies have attempted to assess the association between serum levels of IGFs and IGFBPs and stomach cancer.[11,12]

Here, we conducted a nested case-control design study within a large-scale cohort study in Japan to investigate the association between the IGF-1, IGF-2, and IGFBP-3 serum levels and the risk of stomach cancer incidence.

## 2. Materials and methods

### 2.1. Study population

The study was conducted as a nested case-control study within the Japan Collaborative Cohort Study (the JACC Study), a large-scale cohort study designed to evaluate the effects of various risks or protective factors on cancer mortality and incidence. Details of the JACC Study are described elsewhere.[13,14] Briefly, a baseline survey was conducted between 1988 and 1990. A total of 110,792 subjects aged 40 to 79 years from 45 areas throughout Japan were enrolled in the study and completed a self-administered questionnaire. We then followed these 110,792 subjects to identify cancer mortality. Vital statistics on the participants' population-register sheets from the Ministry of Home Affairs, Posts, and Telecommunications were reviewed annually, with permission, by each regional research centre. Cancer incidence could be determined in 64,820 subjects living in 24 of the 45 areas, in which cancer registries were available. Cancer incidence was collected through the local cancer registry and coded based on the International Classification of Diseases and Injuries (ICD), 10th Revision (ICD-10). Stomach cancer was defined as codes C16.0 to C16.9 of the ICD-10. During the baseline study, approximately one-third of the subjects (39,242 subjects) donated a peripheral serum sample, which was kept at −80 °C until analysed for the presence of biochemical substances.

The entire study design was approved by the Ethics Board of Nagoya University School of Medicine, which is where the central secretariat of the JACC study is located.

### 2.2. Case identification and control selection

Subjects were initially screened by limiting inclusion to those living in study areas where cancer incidence was available, followed by exclusion of those with a self-reported history of any type of cancer. A total of 804 new cases of stomach cancer were recorded through the end of 1997, for which sera were available for 161. Each of these patients had been matched with two controls for study area, gender and age using the baseline characteristics, from whom sera were also obtained. All controls were alive, had not migrated and were free of any cancer at the time of diagnosis of the case subject. Owing to a lack of eligible controls, eight of the cases were matched with a single control only. Thus, a total of 161 stomach cancer cases and 314 controls were involved in this nested case-control study.

### 2.3. Laboratory assays

Serum samples were assayed in 1999 and 2000 by trained staff blinded to case/control status. The measurements of each batch of case and its matched controls were performed on the same day, with the same reagents. Serum levels of IGF-1, IGF-2, and IGFBP-3 were measured by immunoradiometric assay using commercially available kits (Daiichi Radioisotope Lab, Tokyo, Japan). The mean intra-assay coefficient of variation for the quality control serum samples was 2.1–3.5% for IGF-1; 2.74–4.45% for IGF-2; and 3.16–4.19% for IGFBP-3. The stability of the standard curves as well as the sensibility and reproducibility of the assays were examined in a pilot analysis. The ranges of reliable measurement were 40–2050 ng/mL for IGF-1; 10–1640 ng/mL for IGF-2; and 0.06–10.10μg/mL for IGFBP-3.

Serological testing was also done to detect infection with *Helicobacter pylori* (*H. pylori* using HM-CAPTM (Enteric Products, Westbury, NY, USA) using a Japanese (J-HM-CAP) antigen. Immunoglobulin G antibody serum titers of 2.3 or greater were considered positive for infection.

### 2.4. Statistical analysis

Proportions and mean values of baseline characteristics between the cases and their matched controls were compared using the Mantel–Haenszel chi-square test and analysis of variance. Correlations between serum IGF levels and age were determined at baseline using the generalised linear model. Serum values were then divided into quartiles, based on the distribution of serum value in the cases and controls combined. The 1st quartile was used as the reference category.

The risk of stomach cancer associated with IGF serum levels were assessed using odds ratios (ORs) estimated by the conditional logistic model. The following variables were considered potential confounders and included in the model: body mass index (computed as weight in kilograms divided by the square of the height in metres), tobacco smoking status, *H. pylori* infection, history of diabetes, history of gastric ulcer, preference for salty foods, and educational level.

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. All statistical analyses were performed using Stata version 9.0 software.[15]

## 3. Results

Among 161 stomach cancer cases, there were 27 cases diagnosed before age 60 years, 75 from age 60 to 69, and 59 from age 70 or over. Lag time between blood sampling and diagno-

sis time varied from 12 to 113 months, with a median of 50 months. Pathologic examination was performed for all cases, of which 130 (81%) were adenocarcinoma. In terms of location, there were five cases located in the cardia of the stomach (C16.0), four in the fundus (C16.1), 30 in the body (C16.2), 27 in the pyloric antrum (C16.3), and five in the pylorus (C16.4), while 90 cases were reported as unspecified stomach cancer (C16.9). Table 1 shows the baseline characteristics of 161 stomach cancer cases and 314 matched controls. Mean age was 62.3 and 62.0 years, respectively. There was no difference in body mass index (BMI) between the case and control groups. The proportion of current smokers was higher in the case group than in the control ($p = 0.02$), but no difference was seen for a history of diabetes or gastric ulcer ($p = 0.45$ and 0.46, respectively). For the cases, serum IGF-1, IGF-2, and IGFBP-3 showed an inverse correlation with age at baseline, coefficient slopes were −1.47, −4.46, and −0.02, respectively. The same pattern was seen for the controls, with coefficient slopes of −1.08, −5.22, and −0.03, respectively. Mean levels of IGF-1, IGF-2, and IGFBP-3 for the cases versus the controls were 129.3 ng/mL versus 128.0 ng/mL, 588.7 versus 592.0 ng/mL, and 3.0μg/mL versus 3.1 μg/mL, respectively, showing no significant difference for any ($p = 0.80$; 0.78 and 0.39, respectively).

IGF-1 quartile values were ⩽90, 91–120, 121–150, and ⩾151 ng/mL for the quartiles 1, 2, 3, and 4, respectively. Respective values were ⩽510, 511–590, 591–670, and ⩾671 ng/mL for IGF-2; and ⩽2.42, 2.43–2.99, 3.00–3.64, and ⩾3.65 μg/mL for IGFBP-3. Table 2 shows adjusted ORs for stomach cancer incidence according to serum IGF-1, IGF-2, and IGFBP-3 level quar-

**Table 1 – Selected baseline characteristics of the case and control groups**

| | Cases | Controls | *p* value[a] |
|---|---|---|---|
| Number of subjects | 161 | 314 | |
| Age (SD)[b] | 62.3 (7.85) | 62.0 (7.84) | Matching factor |
| Male (%) | 74 (46.00) | 146 (46.50) | Matching factor |
| Mean of body mass index (SD)[b] | 22.6 (2.81) | 22.5 (2.58) | 0.78 |
| Tobacco smoking status | | | |
| Never smoker (%) | 76 (47.2) | 155 (49.4) | 0.02 |
| Former smoker (%) | 26 (16.2) | 59 (18.8) | |
| Current smoker (%) | 52 (32.3) | 71 (22.6) | |
| Missing (%) | 7 (4.3) | 29 (9.2) | |
| Helicobacter pylori infection (%) | 140 (86.9) | 246 (78.3) | 0.02 |
| History of diabetes (%) | 7 (4.4) | 19 (6.0) | 0.45 |
| History of gastric ulcer (%) | 28 (17.4) | 47 (14.9) | 0.46 |
| Preference for salty food (%) | 57 (35.4) | 86 (27.4) | 0.06 |
| Education level | | | |
| Less than 15 years (%) | 45 (27.9) | 84 (26.7) | 0.61 |
| From 15 to 18 years (%) | 69 (42.9) | 139 (44.3) | |
| More than 18 years (%) | 21 (13.1) | 47 (15.0) | |
| Missing (%) | 26 (16.1) | 44 (14.0) | |
| Mean (ng/mL) of IGF-1 (SD)[b] | 129.3 (52.30) | 128.0 (51.33) | 0.80 |
| Mean (ng/mL) of IGF-2 (SD)[b] | 588.7 (139.65) | 592.0 (135.49) | 0.78 |
| Mean (μg/mL) of IGFBP-3 (SD)[b] | 3.0 (0.88) | 3.1 (0.91) | 0.39 |

a *p* value: based on the analysis of variance for continuous variables and Mantel–Haenszel chi-square test for categorical variables.
b SD: denotes standard deviation.

**Table 2 – Crude and adjusted odds ratios (ORs) of serum levels of insulin-like growth factor (IGF)-1, IGF-2 and IGFBP-3 with the risk of stomach cancer**

| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | *p* for trend |
|---|---|---|---|---|---|
| Insulin-like growth factor 1 | | | | | |
| Crude OR (95%CI) | 1.0 (reference) | 0.91 (0.51–1.63) | 1.01 (0.59–1.94) | 0.90 (0.50–1.65) | 0.89 |
| Adjusted OR[a] (95%CI) | 1.0 (reference) | 0.84 (0.46–1.55) | 1.13 (0.60–2.13) | 0.91 (0.49–1.68) | 0.98 |
| Insulin-like growth factor 2 | | | | | |
| Crude OR (95%CI) | 1.0 (reference) | 0.86 (0.51–1.43) | 0.69 (0.37–1.20) | 1.01 (0.61–1.84) | 0.98 |
| Adjusted OR[a] (95%CI) | 1.0 (reference) | 0.79 (0.46–1.35) | 0.70 (0.38–1.29) | 1.13 (0.63–2.00) | 0.72 |
| Insulin-like growth factor binding protein 3 | | | | | |
| Crude OR (95%CI) | 1.0 (reference) | 0.65 (0.38–1.11) | 0.69 (0.40–1.18) | 0.84 (0.49–1.46) | 0.58 |
| Adjusted OR[a] (95%CI) | 1.0 (reference) | 0.66 (0.38–1.15) | 0.70 (0.40–1.23) | 0.85 (0.51–1.52) | 0.63 |

a OR adjusted for body mass index, tobacco smoking status, Helicobacter pylori infection, history of diabetes, history of gastric ulcer, preference for salty food, and educational level in the model.

**Table 3 – Crude and adjusted odds ratios (ORs) between the risk of stomach cancer and quartiles of ratio of IGF-1/IGFBP-3 and IGF-2/IGFBP-3**

| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | *p* for trend |
|---|---|---|---|---|---|
| Ratio between IGF-1/IGFBP-3 | | | | | |
| Crude OR (95%CI) | 1.0 (reference) | 0.64 (0.35–1.16) | 0.98 (0.54–1.79) | 1.30 (0.71–2.38) | 0.16 |
| Adjusted OR[a] (95%CI) | 1.0 (reference) | 0.65 (0.35–1.20) | 0.97 (0.52–1.83) | 1.38 (0.74–2.59) | 0.12 |
| Ratio between IGF-2/IGFBP-3 | | | | | |
| Crude OR (95%CI) | 1.0 (reference) | 0.95 (0.54–1.67) | 0.97 (0.55–1.71) | 1.33 (0.75–2.37) | 0.22 |
| Adjusted OR[a] (95%CI) | 1.0 (reference) | 0.90 (0.50–1.61) | 0.98 (0.55–1.75) | 1.49 (0.83–2.67) | 0.17 |

a OR adjusted for body mass index, tobacco smoking status, Helicobacter pylori infection, history of diabetes, history of gastric ulcer, preference for salty food, and educational level in the model.

tile after adjustment for potential confounding factors. The adjusted ORs for IGF-1 quartile ranged from 0.84 and 1.13, but these were not significant. Further, increasing IGF-2 levels did not significantly correlate with the incidence of stomach cancer. A slight decrease in risk was seen with an increase in IGFBP-3 level, but neither change was statistically significant.

As expected, given the importance of *H. pylori* infection as a risk factor for stomach cancer development, a large number of both cases and controls tested positive for infection (86.9% and 78.3%, respectively). Adjusted OR in the study was 2.05 (1.16–3.61) to reflect the risk of *H. pylori* infection (data not shown).

Risk was also evaluated for its association with the ratios of IGF-1 to IGFBP-3 and of IGF-2 to IGFBP-3 (Table 3). Results showed no significant association in the highest quartile for either.

## 4. Discussion

This study identified no association between the level of IGF-1, IGF-2, or IGFBP-3 and the incidence of stomach cancer.

The molecular and biochemical roles of the IGF family in cancer development have been well investigated.[16–19] Briefly, IGF-1 and IGF-2 are single-chain polypeptides whose molecular structures resemble those of pro-insulin. They exert their effect by interacting with a specific receptor on the cell membrane, and this interaction is regulated by a group of specific binding proteins (IGFBP). At least six IGFBPs have been cloned; among these IGFBP-3 takes up the vast majority of the IGF carrying capacity in the serum. IGF-1 and IGF-2 have several bioactive functions,[4,17] including roles in mitosis, antiapoptosis, induction of vascular growth, and increased cell migration, which might aid tumour growth. It is thought, however, that IGF-2 plays a less important role than IGF-1.[20,21] Conventional thinking would suggest that IGFBP-3 acts to diminish the risk of cancer, inhibit growth through ligand sequestration, and perhaps also be antiproliferative and proapoptotic.[22]

Several review studies have addressed the relationship between the insulin-like growth factor family and cancer development.[5,6] Higher concentrations of IGF-1 were associated with prostate, colorectal, and pre-menopausal breast cancer, whereas higher concentrations of IGFBP-3 were inversely associated with cancer at these sites.[5,6] However, to date, few studies have examined the association between IGFs and IGFBP and stomach cancer, and no evidence of a relationship has been established. A clinical study[11] in Korea examined the change in serum IGF-1 and IGF-2 levels in 20 stomach cancer cases after surgery using blood samples obtained within 10 days before and once after surgery. Results showed that the serum concentrations of IGF-1 and IGF-2 were significantly lower after surgery, but that both pre- and postoperative serum concentrations were still higher than those obtained from 20 age- and sex-matched controls. A clinical study in Italy[23] reported that IGF-1 levels were higher in 26 stomach cancer patients than in a healthy control group. Moreover, it is known that radical surgery with complete tumour ablation induces a significant decrease in IGF-1 levels. A study in Japan[12] reported that there were no differences between IGF-1, IGF-2, and IGFBP-3 levels in stomach cancer cases and matched controls. However, these two latter studies simply compared the average serum IGF levels between the stomach cancer group and controls, and did not include any adjustment for potential confounding factors. The present study, in contrast, was conducted as a nested case-control study within a large-scale cohort with adjustment for confounders. Nevertheless, the results revealed no increase or decrease in risk associated with IGF-1, IGF-2, or IGFBP-3.

Although our study is based on a relatively small sample size, its strength lies in the fact that it is a large-scale cohort study, scattered throughout Japan. However, to reduce the cost of the cohort study, a nested case-control study design was used to estimate the association with stomach cancer incidence. Nested investigations are able to establish the temporal nature of an association, in contrast with standard case-controls studies, which are not. In addition, serum samples were obtained from about one-third of the total study population.[13] These samples were collected at the time the baseline study was conducted, and all controls were alive and free of any cancer at the time of matching with the cases, thus avoiding the possible effects of the disease process on levels.

Several limitations of the study warrant mention. First, the serum biomarkers were analysed using a single sample collected at the study baseline, and the concentrations of IGFs may have changed over time. Second, serum samples were available for only 161 of 804 cases, which may have led to potential selection bias. However, there was no difference in mean age between the 161 patients and stomach cancer cases without a blood sample (data not shown).

In summary, we found no association between IGF-1, IGF-2, or IGFBP-3 serum levels and the risk of stomach cancer. As this association has not been established, these findings need to be confirmed in future studies.

## Conflict of interest statement

None declared.

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## REFERENCES

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999;**80**:827–41.
2. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor and Welfare. *Vital statistics of Japan*. Tokyo: Health and Welfare Statistics Association; 2004.
3. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev* 1995;**16**: 3–34.
4. Khandwala HM, McCutcheon IE, Flyvbjerg A, Friend KE. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. *Endocr Rev* 2000;**21**:215–44.
5. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 2004;**363**: 1346–53.
6. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst* 2000;**92**:1472–89.
7. Yu H, Spitz MR, Mistry J, Gu J, Hong WK, Wu X. Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. *J Natl Cancer Inst* 1999;**91**:151–6.
8. Sugumar A, Liu YC, Xia Q, Koh YS, Matsuo K. Insulin-like growth factor (IGF)-I and IGF-binding protein 3 and the risk of premenopausal breast cancer: a meta-analysis of literature. *Int J Cancer* 2004;**111**:293–7.
9. Nomura AM, Stemmermann GN, Lee J, Pollak MN. Serum insulin-like growth factor I and subsequent risk of colorectal cancer among Japanese-American men. *Am J Epidemiol* 2003;**158**:424–31.
10. Lin Y, Tamakoshi A, Kikuchi S, et al. Serum insulin-like growth factor-I, insulin-like growth factor binding protein-3, and the risk of pancreatic cancer death. *Int J Cancer* 2004;**110**:584–8.
11. Lee DY, Yang DH, Kang CW, et al. Serum insulin-like growth factors (IGFs) and IGF binding protein (IGFBP)-3 in patients with gastric cancer: IGFBP-3 protease activity induced by surgery. *J Korean Med Sci* 1997;**12**:32–9.
12. Yatsuya H, Toyoshima H, Tamakoshi K, et al. Serum levels of insulin-like growth factor I, II, and binding protein 3, transforming growth factor beta-1, soluble fas ligand and superoxide dismutase activity in stomach cancer cases and their controls in the JACC Study. *J Epidemiol* 2005;**15**(Suppl 2):S120–5.
13. Tamakoshi A, Yoshimura T, Inaba Y, et al. Profile of the JACC study. *J Epidemiol* 2005;**15**(Suppl 1):S4–8.
14. Ohno Y, Tamakoshi A. Japan collaborative cohort study for evaluation of cancer risk sponsored by monbusho (JACC study). *J Epidemiol* 2001;**11**:144–50.
15. StataCorp. *Stata Statistical Sofware: Release* 9. College Station, Texas: StataCorp LP; 2005.

16. Oh Y, Muller HL, Neely EK, Lamson G, Rosenfeld RG. New concepts in insulin-like growth factor receptor physiology. *Growth Regul* 1993;**3**:113–23.
17. Sara VR, Hall K. Insulin-like growth factors and their binding proteins. *Physiol Rev* 1990;**70**:591–614.
18. LeRoith D, Baserga R, Helman L, Roberts CTJ. Insulin-like growth factors and cancer. *Ann Intern Med* 1995;**122**:54–9.
19. Pietrzkowski Z, Mulholland G, Gomella L, Jameson BA, Wernicke D, Baserga R. Inhibition of growth of prostatic cancer cell lines by peptide analogues of insulin-like growth factor 1. *Cancer Res* 1993;**53**:1102–6.
20. Frostad S, Bruserud O. In vitro effects of insulin-like growth factor-1 (IGF-1) on proliferation and constitutive cytokine secretion by acute myelogenous leukemia blasts. *Eur J Haematol* 1999;**62**:191–8.
21. Singh P, Dai B, Yallampalli U, Lu X, Schroy PC. Proliferation and differentiation of a human colon cancer cell line (CaCo2) is associated with significant changes in the expression and secretion of insulin-like growth factor (IGF) IGF-II and IGF binding protein-4: role of IGF-II. *Endocrinology* 1996;**137**:1764–74.
22. Firth SM, Baxter RC. Cellular actions of the insulin-like growth factor binding proteins. *Endocr Rev* 2002;**23**:824–54.
23. Franciosi CM, Piacentini MG, Conti M, et al. IGF-1 and IGF-1BP3 in gastric adenocarcinoma. Preliminary study. *Hepatogastroenterology* 2003;**50**:297–300.