Serum Hepatocyte Growth Factor and Cancer Mortality in an Apparently Healthy Japanese Population

Maki Otsuka, Hisashi Adachi, David R. Jacobs Jr, Yuji Hirai, Mika Enomoto, Ako Fukami, Shun-ichi Kumagae, Yasuki Nanjo, Kuniko Yoshikawa, Eishi Esaki, Eita Kumagai, Kanako Yoko, Kinuka Ogata, Eri Tsukagawa, Akiko Kasahara, Kyoko Ohbu, and Tsutomu Imaizumi

Department of Internal Medicine, Division of Cardio-Vascular Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan
Department of Community Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan
University of Minnesota, School of Public Health, Division of Epidemiology, Minneapolis, Minnesota, USA

ABSTRACT

Background: In patients with cancer, hepatocyte growth factor (HGF) is elevated and is a predictor of prognosis. We investigated whether serum HGF was a predictive marker for cancer death in a population of community-dwelling Japanese.

Methods: We studied 1492 apparently healthy Japanese adults who underwent health examinations in 1999. Those who reported a history of liver disease or malignancy on a baseline questionnaire were excluded, and plasma HGF was measured in the remaining 1470 participants, who were followed periodically for 10 years. Multivariate proportional hazards regression was used to estimate cancer mortality.

Results: A total of 169 participants died during follow-up (61 from cancer, 32 from cerebrocardiovascular disease, and 76 from other diseases). Mean HGF at baseline was significantly higher among decedents than among survivors (0.26 ± 0.11 vs 0.23 ± 0.09 ng/ml, respectively; P < 0.01). The Cox proportional hazards model showed that age, systolic blood pressure, HGF (hazard ratio, 1.27; 95% CI, 1.06–1.52; P = 0.009), albumin level, smoking status, and creatinine were independent predictors of all-cause death. Age, HGF (hazard ratio, 1.31; 95% CI, 1.04–1.65; P = 0.02), and total cholesterol were independent predictive markers for cancer death.

Conclusions: Serum HGF was a predictor of cancer death in an apparently healthy population of community-dwelling Japanese.

Key words: cytokine; prospective study; Seven Countries Study; mortality; cancer

INTRODUCTION

Hepatocyte growth factor (HGF) was discovered in 1984, purified and isolated in 1986, and first characterized as a strong mitogen for hepatocytes. It is produced in a number of organs and is now known to be a multifunctional factor with various biological activities. HGF was found to be elevated in serum from patients with liver disease and cancer, including those with malignancies of the breast, stomach, colorectum, and lung. Furthermore, HGF was inversely correlated with survival time in cancer patients, which indicates that it might be a prognostic marker in such patients. However, existing reports are limited to patients with diagnosed cancer. Thus, we examined whether serum HGF was a predictor of cancer death among apparently healthy Japanese living in the general community.
and smoking were classified as current habitual use or not. Use of medication for hypertension, hyperlipidemia, and diabetes was coded as dummy variables. Body mass index (BMI) was calculated from measurements of height and body weight. Blood pressure was measured twice with participants in the supine position. A second blood pressure reading was taken after 5 deep breaths, and the fifth-phase diastolic pressure was recorded and used in the analysis. Blood samples obtained from the antecubital vein were centrifuged and frozen. Using these samples, we measured serum glycosylated hemoglobin A1c (Japan Diabetes Society; HbA1c [JDS]), lipids (total cholesterol, high-density lipoprotein [HDL]-cholesterol, and triglycerides), blood urea nitrogen (BUN), creatinine, uric acid, albumin, C-reactive protein (CRP), and liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and γ-glutamyl transpeptidase [γ-GTP]). Plasma HGF was measured by enzyme-linked immunosorbent assay (ELISA).

Intra- and inter-assay coefficients of variation of HGF, as determined by a commercially available laboratory (Kyodo Igaku Laboratory, Fukuoka, Japan), were 1.0% and 3.0%, respectively. The details of HGF measurement have been previously described. Twenty-four participants who had a history of liver disease, lung disease, or cancer were excluded from the analysis. Ultimately, 1470 participants (595 men and 875 women) were enrolled.

The follow-up period was 10 years. Cause of death was determined on the basis of a review of obituaries, medical records, death certificates, and hospital charts, as well as interviews with primary care physicians, the families of the deceased, and other witnesses. Because many patients with cancer ultimately die from infection or other illnesses, great care was taken to identify underlying cause of death. The information was coded independently according to the rules of the Seven Countries Study and the World Health Organization’s 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (WHO-ICD). Follow-up data through the end of March 2010 were analyzed. The follow-up rate was 92.9%.

This study was approved by the Ukiha Branch of the Japanese Medical Association, by the local citizens’ committee of Tanushimaru, and by the Ethics Committee of Kurume University. All participants gave informed consent.

**Statistical analysis**

Results are presented as mean ± SD. Because of skewed distributions, natural logarithmic transformations were performed for CRP, triglycerides, and γ-GTP. These variables are shown in the original scale in the tables, after analysis using the log (natural)-transformed values. In Tables 1 and 2, the values for CRP, triglycerides, and γ-GTP are presented as geometric mean and range.

Mean HGF level was classified into quartiles as follows: ≤0.16 ng/ml, 0.17–0.21 ng/ml, 0.22–0.27 ng/ml, and ≥0.28 ng/ml. Analysis of variance was used to compare the means of variables, stratified by quartile of HGF levels. Differences between the 2 groups (survivors vs decedents) were assessed using the t test. The χ² test was used to test differences between groups in categorical variables.

Multivariate proportional hazards regression was used to estimate the predictive HGF level for all-cause death and cancer death. We estimated hazard ratios (HRs) and their 95% CIs per 1-unit (approximately 1 SD) increase in the variable. Survival curves for all-cause death and cancer death for each HGF quartile were estimated with the Kaplan-Meier method and interpreted using the log-rank statistic. Statistical significance was defined as a P value less than 0.05. All statistical analyses were performed using SAS software (Release 9.2, SAS Institute, Cary, NC, USA).

**RESULTS**

**Baseline characteristics associated with HGF**

Participants were divided into quartiles according to HGF level. There was a significant positive association between HGF and mortality. In addition, HGF was significantly positively associated with male sex, BMI, systolic and diastolic blood pressures, creatinine, uric acid, CRP, triglycerides, AST, ALT, γ-GTP, smoking, and use of antihypertensive medication and significantly inversely associated with total cholesterol and HDL cholesterol (Table 1).

**Cause of death and characteristics of decedents**

We were able to ascertain cause of death for 92.9% of deaths. There were 169 (103 men and 66 women) deaths: 61 (36.1%) from cancer, 32 (18.9%) from cerebrocardiovascular disease, 27 (16.0%) from infection, and 49 (29.0%) from other causes.

Table 2 shows the characteristics of participants stratified by vital status. Factors positively associated with death were age, male sex, systolic blood pressure, HbA1c, BUN, creatinine, uric acid, CRP, γ-GTP, smoking, use of antihypertensive medication, and HGF, whereas BMI, albumin, and total cholesterol were inversely associated with death.

Regression coefficients for all-cause death in the univariate proportional hazards regression model are shown in Table 3. Age, male sex, systolic blood pressure, HbA1c, BUN, creatinine, uric acid, CRP, γ-GTP, smoking, antihypertensive medication, and HGF were significant positive predictors of all-cause death, whereas BMI, albumin, and total cholesterol were inversely associated with death. Figure 1A shows the cumulative survival curves for all-cause death stratified by HGF quartile in univariate analysis. The HRs by HGF quartile were 1.30 (95% CI, 0.77–2.22) for Q2, 2.18 (1.31–3.62) for Q3, and 2.41 (1.47–3.94) for Q4. Cancer death was positively associated with age, male sex, systolic blood pressure, HbA1c, BUN, creatinine, and smoking and inversely associated with albumin and total cholesterol (Table 4). Figure 1B shows the cumulative survival curves for cancer death stratified by HGF quartile in univariate analysis.
Mortality increased in relation to HGF (log-rank test = 11.3; \( P < 0.001 \)). The HRs by HGF quartile were 1.39 (95% CI, 0.68–2.97) for Q2, 1.19 (0.50–2.83) for Q3, and 2.21 (1.03–4.76) for Q4. For cancer death, mortality increased in relation to HGF (log-rank test = 8.23; \( P = 0.03 \)).

Using the significant factors shown in Tables 3 and 4, we performed multivariate proportional hazards regression analysis (Tables 5 and 6). Age, systolic blood pressure, HGF, albumin (inversely), smoking, and creatinine remained significantly associated with all-cause death (Table 5): the HRs by HGF quartile after adjustment for confounding factors were 1.15 (95% CI, 0.68–1.93) for Q2, 1.49 (0.91–2.44) for Q3, and 1.77 (1.10–2.97) for Q4. For cancer death, age, HGF, and total cholesterol (inversely) remained significant (Table 6): after adjustment for confounding factors, the HRs by HGF quartile were 1.22 (95% CI, 0.53–2.83) for Q2, 1.19 (0.50–2.83) for Q3, and 2.21 (1.03–4.76) for Q4.

There was no significant association between HGF and cerebrocardiovascular death (data not shown).

DISCUSSION

We investigated whether plasma HGF predicted cancer death among a population of Japanese adults. Our results showed that plasma HGF level was predictive of both all-cause death and cancer death.

We made every effort in this prospective study to ascertain cause of death, and the death rates among this population were comparable to those of the Japanese general population. Multivariate proportional hazards regression analysis revealed that age, systolic blood pressure, HGF, albumin (inversely), smoking, and creatinine were independently associated with all-cause death (Table 5). Age, blood pressure, and smoking are known causes of cerebrocardiovascular death. Thus, it is feasible that these factors contributed to all-cause death in this population.

The number of deaths from cerebrocardiovascular disease was too small to analyze, and we were thus unable to identify the factors responsible for cerebrocardiovascular death in this study. In addition to the above-mentioned factors, low albumin and HGF were significant predictors of all-cause death (Table 5). Low albumin may indicate poor nutritional status. The predictive power of HGF was comparable to that of systolic blood pressure (Table 5). At present, it is unclear why HGF was a significant predictor of all-cause death.
We investigated whether HGF was a predictor of cancer death in this apparently healthy population because cancer is the most common cause of death in this population and because HGF level was found to be a predictor of death in patients with cancer. Multivariate proportional hazards regression analysis revealed that age, HGF, and cholesterol (inversely) were predictors of cancer death. Although baseline HGF was associated with cholesterol (inversely) and some other factors, as shown in Table 1, the data in Table 6 show that HGF was a significant independent factor for cancer death, which indicates that HGF is a predictor for cancer death in apparently healthy community-dwelling Japanese adults.

The pathophysiologic mechanisms for the association between HGF and cancer death in this population were not investigated in this epidemiologic study. Because we excluded patients with history of cancer at baseline, it is natural to assume that the remaining study participants developed cancer during follow-up. To confirm this, we divided cancer deaths into those that occurred during the first 5 years of follow-up and those that occurred in the second 5 years of follow-up. There were 30 cancer deaths during the first 5 years and 31 during the second 5 years. As mentioned above, serum HGF is elevated in individuals with cancer and stimulates not only tumor cell invasion but also neovascularization as a potent endothelial growth factor. If participants who died within 5 years had subclinical cancer at baseline, they might have had higher baseline HGF levels. However, we found that baseline HGF was similar in the early and late study periods among participants who died of cancer. Thus, the increase in the risk of cancer death associated with high HGF was not due to the presence of subclinical cancer. It is possible that participants with high baseline HGF levels experienced rapid growth and spread of cancer once they developed cancer. However, this hypothesis cannot be confirmed in an observational study.

A strength of the present study is that it is the first prospective cohort study to show that HGF is a predictor of cancer death in apparently healthy adults. Moreover, the follow-up rate was high (92.9%).

A limitation of this study is that, because of the relatively small number of cancer deaths, we were unable to investigate the association between HGF and particular malignancies. Second, the cancer endpoint was not incidence but mortality. Third, the association between HGF and cancer death might be confounded by several factors. However, this association remained significant after adjustment for confounders.

### Table 2. Characteristics of participants stratified by vital status

| Variables                              | Survivors |      |      | Decedents |      |      |      | P value |
|----------------------------------------|-----------|------|------|-----------|------|------|------|---------|
|                                        | No. | % | Mean (SD) | No. | % | Mean (SD) |
| Total No.                              | 1291 | 88 | 0.23 (0.09) | 169 | 12 | 0.26 (0.11) | 0.009 |
| HGF, ng/ml                             |       |    | 0.23 (0.09) |       |    | 0.26 (0.11) |
| Age, years                             | 61 (10) |       |       | 72 (9) |       |       | <0.0001 |
| Male sex                               | 487 | 38 |       | 103 | 61 |       | <0.0001 |
| Blood urea nitrogen, mmol/l            | 5.7 (1.4) |       |       | 6.4 (1.9) |       |       | <0.0001 |
| Creatinine, µmol/l                     | 74 (15) |       |       | 85 (22) |       |       | <0.0001 |
| Triglycerides, mmol/l                  | 1.10 |       |       | 1.09 |       |       | 0.837 |
| Total cholesterol, mmol/l              | 5.2 (0.9) |       |       | 4.9 (0.9) |       |       | <0.0001 |
| HDL cholesterol, mmol/l                | 1.5 (0.4) |       |       | 1.5 (0.4) |       |       | 0.485 |
| AST, units/l                           | 28 (5) |       |       | 28 (6) |       |       | 0.485 |
| ALT, units/l                           | 26 (4) |       |       | 26 (3) |       |       | 0.460 |
| γ-GTP, units/l                         | 18 |       |       | 22 |       |       | 0.043 |
| Smoking                                | 187 | 15 |       | 47 | 28 |       | <0.0001 |
| Alcohol                                | 268 | 21 |       | 40 | 24 |       | 0.429 |
| Antihypertensive medication            | 234 | 18 |       | 48 | 28 |       | 0.02 |
| Antihyperlipidemic medication          | 60 | 5 |       | 12 | 7 |       | 0.228 |
| Antidiabetic medication                | 32 | 2 |       | 8 | 5 |       | 0.148 |

Data are mean (SD), geometric mean, range, or percent. Abbreviations: HGF, hepatocyte growth factor; SD, standard deviation; BP, blood pressure; HbA1c, glycosylated hemoglobin A1c; HDL, high density lipoprotein; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase. 

*Weight (kg)/height (m)*.

*These variables are shown in the original scale after analysis using log (natural)-transformed values.
Table 3. Univariate regression coefficients for all-cause death from a Cox proportional hazards regression model

| Variable (increment)          | Beta   | SE     | Hazard ratio | 95% CI       | P value |
|-------------------------------|--------|--------|--------------|--------------|---------|
| HGF (0.09 ng/ml)              | 3.271  | 0.721  | 1.35         | 1.19, 1.54   | <0.0001 |
| Age (10 years)                | 0.103  | 0.008  | 2.95         | 2.49, 3.49   | <0.0001 |
| Male sex                      | 0.835  | 0.185  | 2.31         | 1.60, 3.32   | <0.0001 |
| Body mass indexb (3 kg/m²)     | -0.067 | 0.025  | 0.81         | 0.69, 0.95   | 0.009   |
| Systolic BP (20 mmHg)         | 0.021  | 0.003  | 1.57         | 1.38, 1.79   | <0.0001 |
| Diastolic BP (11 mmHg)        | 0.012  | 0.006  | 1.15         | 0.99, 1.34   | 0.060   |
| HbA1c (0.7%)                  | 0.210  | 0.069  | 1.18         | 1.06, 1.31   | 0.002   |
| Blood urea nitrogen (1.4 mmol/l) | 0.089 | 0.016  | 1.44         | 1.26, 1.65   | <0.0001 |
| Creatinine (16.4 µmol/l)      | 1.452  | 0.168  | 1.30         | 1.22, 1.38   | <0.0001 |
| Uric acid (59.4 µmol/l)       | 0.244  | 0.050  | 1.40         | 1.22, 1.61   | <0.0001 |
| C-reactive proteinb (1.8 times) | 0.328 | 0.104  | 1.39         | 1.13, 1.70   | 0.002   |
| Albumin (2 g/l)               | -2.253 | 0.268  | 0.56         | 0.49, 0.64   | <0.0001 |
| Total cholesterol (0.87 mmol/l)| -0.011 | 0.002  | 0.68         | 0.58, 0.80   | <0.0001 |
| HDL cholesterol (0.36 mmol/l) | -0.003 | 0.005  | 0.99         | 0.82, 1.11   | 0.557   |
| Triglyceridesb (1.1 times)    | -0.038 | 0.153  | 0.96         | 0.71, 1.30   | 0.804   |
| AST (5 units/l)               | 0.011  | 0.014  | 1.06         | 0.91, 1.24   | 0.447   |
| ALT (3 units/l)               | -0.020 | 0.027  | 0.93         | 0.77, 1.13   | 0.463   |
| γ-GTPb (2.2 times)            | 0.224  | 0.102  | 1.25         | 1.03, 1.53   | 0.030   |
| Smoking                       | 0.175  | 0.172  | 1.29         | 1.07, 1.55   | <0.0001 |
| Alcohol                       | 0.172  | 0.181  | 1.19         | 0.83, 1.69   | 0.341   |
| Antihypertensive medication   | 0.545  | 0.170  | 1.73         | 1.23, 2.41   | 0.001   |
| Antihyperlipidemic medication | 0.428  | 0.299  | 1.54         | 0.85, 2.76   | 0.152   |
| Antidiabetic medication       | 0.592  | 0.362  | 1.81         | 0.89, 3.68   | 0.102   |

Abbreviations: HGF, hepatocyte growth factor; BP, blood pressure; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase.

bWeight (kg)/height (m)².

bThese variables are shown in the original scale after analysis using log (natural)-transformed values. These values indicate hazard ratios per times increase.

---

Figure 1. (A) Kaplan-Meier survival curves for all-cause death, stratified by quartile of hepatocyte growth factor (HGF), after adjustment for age and sex. (B) Kaplan-Meier survival curves for cancer death, stratified by quartile of hepatocyte growth factor (HGF), after adjustment for age and sex.

---

Otsuka M, et al. J Epidemiol 2012;22(5):395-401
### Table 4. Univariate regression coefficients for cancer death from a Cox proportional hazards regression model

| Dependent variable (increment) | Beta  | SE   | Hazard ratio² | 95% CI          | P value |
|--------------------------------|-------|------|---------------|-----------------|--------|
| HGF (0.09 ng/ml)               | 3.949 | 1.185| 2.03          | 1.39, 2.87      | <0.0001|
| Age (10 years)                 | 0.072 | 0.013| 1.02          | 1.01, 1.03      | 0.007  |
| Male sex                       | 0.919 | 0.295| 2.51          | 1.41, 4.47      | 0.001  |
| Body mass index³ (3 kg/m²)     | -0.005| 0.042| 0.98          | 0.76, 1.27      | 0.894  |
| Systolic BP (20 mm Hg)         | 0.013 | 0.005| 1.31          | 1.04, 1.66      | 0.024  |
| Diastolic BP (11 mm Hg)        | 0.009 | 0.011| 1.11          | 0.87, 1.43      | 0.413  |
| HbA1c (0.7%)                   | 0.260 | 0.100| 1.24          | 1.07, 1.45      | 0.005  |
| Blood urea nitrogen (1.4 mmol/l)| 0.058 | 0.029| 1.27          | 1.01, 1.61      | 0.044  |
| Creatinine (16.4 µmol/l)       | 1.042 | 0.409| 2.84          | 1.27, 6.32      | 0.011  |
| Uric acid (59.4 µmol/l)        | 0.101 | 0.090| 1.15          | 0.90, 1.47      | 0.259  |
| C-reactive protein² (1.8 times)| 0.320 | 0.174| 1.38          | 0.98, 1.94      | 0.066  |
| Smoking                        | -1.828| 0.471| 0.63          | 0.49, 0.79      | <0.0001|
| Total cholesterol (0.87 mmol/l)| -0.015| 0.004| 0.58          | 0.44, 0.76      | <0.0001|
| HDL cholesterol (0.36 mmol/l)  | -0.009| 0.009| 0.87          | 0.67, 1.14      | 0.327  |
| Triglycerides² (1.1 times)     | -0.019| 0.257| 0.93          | 0.59, 1.62      | 0.940  |
| AST (5 units/l)                | -0.007| 0.031| 0.96          | 0.69, 1.33      | 0.813  |
| ALP (3 units/l)                | -0.033| 0.051| 0.89          | 0.63, 1.26      | 0.508  |
| γ-GTP² (2.2 times)             | 0.123 | 0.181| 1.13          | 0.79, 1.61      | 0.496  |
| Smoking                        | 0.828 | 0.288| 2.29          | 1.30, 4.03      | 0.004  |
| Alcohol                        | 0.422 | 0.287| 1.53          | 0.87, 2.68      | 0.141  |
| Antihypertensive medication    | -0.127| 0.347| 0.88          | 0.54, 1.54      | 0.161  |
| Antihyperlipidemic medication  | 0.621 | 0.467| 1.86          | 0.75, 4.66      | 0.183  |
| Anabolic medication            | 0.951 | 0.517| 2.59          | 0.94, 7.15      | 0.066  |

Abbreviations: HGF, hepatocyte growth factor; SE, standard error; BP, blood pressure; γ-GTP, γ-glutamyl transpeptidase. ³Weight (kg)/height (m)².

Table 5. Multivariate proportional hazards regression analysis of all-cause death

| Dependent variable (increment) | Beta  | SE   | Hazard ratio² | 95% CI          | P value |
|--------------------------------|-------|------|---------------|-----------------|--------|
| Age (10 years)                 | 0.088 | 0.013| 2.53          | 1.90, 3.37      | <0.0001|
| Systolic BP (20 mm Hg)         | 0.013 | 0.005| 1.32          | 1.06, 1.63      | 0.007  |
| HGF (0.09 ng/ml)               | 2.593 | 1.006| 1.27          | 1.06, 1.52      | 0.009  |
| Albumin (2 g/l)                | -1.019| 0.460| 0.77          | 0.61, 0.97      | 0.026  |
| Smoking                        | 0.654 | 0.091| 1.93          | 1.67, 2.24      | 0.028  |
| Creatinine (16.4 µmol/l)       | 0.706 | 0.311| 2.03          | 1.10, 5.73      | 0.033  |
| γ-GTP² (2.2 times)             | 0.072 | 0.110| 1.19          | 0.96, 1.48      | 0.109  |
| C-reactive protein² (1.8 times)| 0.160 | 0.106| 1.17          | 0.96, 1.44      | 0.128  |
| Hypertensive medication        | -0.382| 0.263| 0.68          | 0.41, 1.14      | 0.146  |
| Blood urea nitrogen (1.4 mmol/l)| 0.038 | 0.147| 1.11          | 0.94, 1.34      | 0.161  |
| HbA1c (0.7%)                   | 0.133 | 0.114| 1.11          | 0.93, 1.32      | 0.242  |
| Total cholesterol (0.87 mmol/l)| -0.002| 0.003| 0.91          | 0.71, 1.17      | 0.455  |
| Uric acid (59.4 µmol/l)        | 0.040 | 0.086| 1.06          | 0.84, 1.34      | 0.639  |
| Male sex                       | 0.107 | 0.296| 1.11          | 0.62, 1.99      | 0.716  |
| Body mass index³ (3 kg/m²)     | 0.003 | 0.038| 2.01          | 0.80, 1.28      | 0.524  |

Abbreviations: HGF, hepatocyte growth factor; SE, standard error; BP, blood pressure; γ-GTP, γ-glutamyl transpeptidase. ³Weight (kg)/height (m)².

Table 6. Multivariate proportional hazards regression analysis of cancer death

| Dependent variable (increment) | Beta  | SE   | Hazard ratio² | 95% CI          | P value |
|--------------------------------|-------|------|---------------|-----------------|--------|
| Age (10 years)                 | 0.065 | 0.017| 1.39          | 1.29, 1.87      | <0.001 |
| HGF (0.09 ng/ml)               | 2.929 | 1.267| 2.86          | 1.94, 4.03      | 0.065  |
| Total cholesterol (0.87 mmol/l)| -0.010| 0.005| 0.68          | 0.48, 0.97      | 0.034  |
| Blood urea nitrogen (1.4 mmol/l)| 0.059 | 0.034| 1.02          | 0.97, 1.09      | 0.982  |
| HbA1c (0.7%)                   | 0.193 | 0.123| 1.16          | 0.96, 1.41      | 0.116  |
| Male sex                       | 0.547 | 0.408| 1.73          | 0.78, 3.85      | 0.180  |
| Albumin (2 g/l)                | -0.787| 0.630| 0.43          | 0.29, 0.65      | 0.211  |
| Smoking                        | 0.472 | 0.383| 1.60          | 0.76, 3.40      | 0.217  |
| Creatinine (16.4 µmol/l)       | 0.506 | 0.567| 1.66          | 0.55, 5.04      | 0.371  |
| Systolic BP (20 mm Hg)         | 0.003 | 0.007| 1.08          | 0.81, 1.45      | 0.608  |

Abbreviations: HGF, hepatocyte growth factor; SE, standard error; BP, blood pressure. ³Hazard ratio per 1-increment increase in variable.
In conclusion, serum HGF was a predictor of cancer death in an apparently healthy community-dwelling Japanese population. Our findings suggest that serum HGF may be a predictive marker for cancer death in the general population.

ACKNOWLEDGMENTS

We are grateful to the members of the Ukiha Branch of the Japan Medical Association, the elected officials and residents of Tanushimaru, and the team of cooperating physicians for their help in performing the health examinations. We also thank Professor Hiroki Inutsuka, Kurume University School of Nursing, for developing the SAS system.

Conflicts of interest: None declared.

REFERENCES

1. Nakamura T, Nawa K, Ichihara A. Partial purification and characterization of hepatocyte growth factor from serum of hepatotomized rats. Biochem Biophys Res Commun. 1984; 122:1450–9.
2. Nakamura T, Teramoto H, Ichihara A. Purification and characterization of a growth factor from rat platelets for mature parenchymal hepatocytes in primary cultures. Proc Natl Acad Sci USA. 1986;83:6489–93.
3. Nakamura T, Nawa K, Ichihara A, Kaise N, Nishino T. Purification and subunit structure of hepatocyte growth factor from rat platelets. FEBS Lett. 1987;224:311–6.
4. Higashio K, Shima N, Goto M, Itagaki Y, Nagao M, Yasuda H, et al. Identity of a tumor cytotoxic factor from human fibroblasts and hepatocyte growth factor. Biochem Biophys Res Commun. 1990;170:397–404.
5. Stoker M, Gherardi E. Regulation of cell movement: the motogenic cytokines. Biochim Biophys Acta. 1991;1072:81–102.
6. Nakamura T. Structure and function of hepatocyte growth factor. Prog Growth Factor Res. 1991;3:67–85.
7. Edakuni G, Sasatomi E, Satoh T, Tokunaga O, Miyazaki K. Expression of the hepatocyte growth factor/c-Met pathway is increased at the cancer front in breast carcinoma. Pathol Int. 2001;51:172–8.
8. Taniguchi T, Kitamura M, Arai K, Iwasaki Y, Yamamoto Y, Igar A, et al. Increase in the circulating level of hepatocyte growth factor in gastric cancer patients. Br J Cancer. 1997; 75:673–7.
9. Niki M, Isozuki H, Toyoda M, Ishibashi T, Fujii K, Nomura E, et al. Serum human hepatocyte growth factor (hHGF) is elevated in patients with metastatic gastric carcinoma. Hepatogastroenterology. 1999;46:568–73.
10. Toiyama Y, Miki C, Inoue Y, Okugawa Y, Tanaka K, Kasunoki M. Serum hepatocyte growth factor as a prognostic marker for stage II or III colorectal cancer patients. Int J Cancer. 2009;125:1657–62.
11. Siegfried JM, Weissfeld LA, Luketch JD, Weyant RJ, Gubish CT, Landreneau RJ. The clinical significance of hepatocyte growth factor for non-small cell lung cancer. Ann Thorac Surg. 1998;66:1915–8.
12. Yamashita J, Ogawa M, Yamashita S, Nomura K, Karamoto M, Saishoji T, et al. Immunoreactive hepatocyte growth factor is a strong and independent predictor of recurrence and survival in human breast cancer. Cancer Res. 1994;54:1630–3.
13. Toi M, Taniguchi T, Ueno T, Asano M, Funata N, Sekiguchi K, et al. Significance of circulating hepatocyte growth factor level as a prognostic indicator in primary breast cancer. Clin Cancer Res. 1998;4:659–64.
14. Hino A, Adachi H, Toyomasu K, Yoshida N, Enomoto M, Hiratsuka A, et al. Very long chain N-3 fatty acids intake and carotid atherosclerosis: an epidemiological study evaluated by ultrasonography. Atherosclerosis. 2004;176:145–9.
15. Yamada A, Matsumoto K, Iwahori H, Sekiguchi K, Kawata S, Matsuzawa Y, et al. Rapid and sensitive enzyme-linked immunosorbent assay for measurement of HGF in rat and human tissues. Biomed Res. 1995;16:105–14.
16. Hiratsuka A, Adachi H, Fujirua Y, Yamagishi S, Hirai Y, Enomoto M, et al. Strong association between serum hepatocyte growth factor and metabolic syndrome. J Clin Endocrinol Metab. 2005;90:2927–31.
17. Koga Y, Hashimoto R, Adachi H, Tsuruta M, Tashiro T, Toshima H. Recent trends in cardiovascular disease and risk factors in the Seven Countries Study. Lessons for science from the Seven Countries Study: A 35-year collaborative experience in cardiovascular disease epidemiology. Springer Verlag; 1994. p. 63–74.
18. International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Geneva: World Health Organization; 2003.
19. Health and Welfare Statistics Association. Journal of Health and Welfare Statistics. 2009;56 (in Japanese).
20. Zarnegar R, Michalopoulos GK. The many faces of hepatocyte growth factor: from hepatopoiesis to hematopoiesis. J Cell Biol. 1995;129:1177–80.
21. Tuck AB, Park M, Sterna EE, Boag A, Eliott BE. Coexpression of hepatocyte growth factor and receptor (Met) in human breast carcinoma. Am J Pathol. 1996;148:225–32.
22. Bussolino F, Di Renzo MF, Ziche M, Bocchietto E, Olivero M, Naldini L, et al. Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. J Cell Biol. 1992;119:629–41.
23. Grant DS, Kleiman HK, Goldberg ID, Bhargava MM, Nickeloff BJ, Kinsella JL, et al. Scatter factor induces blood vessel formation in vivo. Proc Natl Acad Sci USA. 1993;90:1937–41.