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Circulating Inflammatory and Hemostatic Biomarkers are Associated with All-Cause Death and Cancer Death in a Population of Community-Dwelling Japanese: the Tanushimaru Study

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ABSTRACT

BACKGROUND: In patients with cardiovascular diseases, inflammatory and hemostatic biomarkers are significant indicators of prognosis. We investigated whether circulating inflammatory and hemostatic biomarkers were predictive markers for all-cause death and cancer death in a population of community-dwelling Japanese.

METHODS: We studied 1,920 healthy Japanese adults who underwent health examinations in 1999. Those who reported a history of inflammatory diseases and malignancy on a baseline questionnaire were excluded. Inflammatory and hemostatic biomarkers were measured in the remaining 1,862 participants, who were followed up periodically for 10 years. Multivariate proportional hazards regression analysis was used to estimate all-cause and cancer mortality.

RESULTS: A total of 258 participants died during follow-up: 87 from cancer, 38 from cerebro-cardiovascular diseases, and 133 from other diseases. Mean C-reactive protein (CRP) levels at baseline were significantly higher in decedents than in survivors. Mean von Willebrand factor (vWF) levels at baseline were significantly higher in decedents than in survivors. The Cox proportional hazards model after adjustments for age and sex showed that CRP (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.06–1.51) and vWF (HR, 1.01; 95% CI, 1.00–1.01) were independent predictors of all-cause death. CRP (HR, 1.40; 95% CI, 1.06–1.86) and vWF (HR, 1.01; 95% CI, 1.00–1.02) were also independent predictive markers for cancer death.

CONCLUSIONS: Serum CRP and vWF were predictors of all-cause death and cancer death in the population of community dwelling Japanese.

KEYWORDS: biomarker, prospective study, mortality, cancer

SUPPLEMENT: Inflammation, Atherosclerosis and Coronary Artery Disease

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Introduction

Chronic inflammation has been hypothesized to play a role in the pathogenesis of several cancers.[1] Circulating white blood cell (WBC) count, which is a nonspecific marker of inflammation, is significantly associated with the development of cancer mortality.[2,3] Numerous examples suggest an association between C-reactive protein (CRP) and the development of mortality.[4–8] However, except for the Chianti Study,[4] existing reports are

limited to patients with serious conditions, such as those undergoing hemodialysis,[4,5] those with previous premature myocardial infarction[6] or chronic immune-mediated inflammatory disease,[7] and critically ill patients.[8] Increased concentrations of high-sensitivity CRP (hs-CRP) also represent an established, unspecific inflammatory risk marker for mortality resulting from cardiovascular disease,[9] chronic heart failure,[10] and all-cause mortality.[11] Although several hemostatic biomarkers such as von Willebrand factor (vWF), fibrinogen, and tissue factor (TF) are reported as predictors for coronary death[12] and death resulting from ischemic stroke,[13] the role of hemostatic biomarkers for all-cause death, especially cancer death, is not fully understood. Thus, we examined whether inflammatory and hemostatic biomarkers were predictors of all-cause and cancer death among healthy Japanese living in the general population.

Methods

A periodic epidemiologic survey was performed in 1999 in the small farming community of Tanushimaru, Japan. As reported previously, the demographic characteristics of the residents of this area are similar to those of the general Japanese population.[14] A total of 1,920 adults aged 40 years or older underwent health checkups, and a questionnaire was used to ascertain their medical history (particularly cancer), use of alcohol, smoking, and current use of medications for hypertension, hyperlipidemia, and diabetes. Alcohol intake and smoking were classified as current habitual use or not. Use of medication for hypertension, hyperlipidemia, or diabetes was coded using dummy variables. Body mass index was calculated, and blood pressure was measured twice with participants in the supine position. A further blood pressure reading was taken after five 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 A_{1c} (HbA_{1c}; Japan Diabetes Society), lipids profiles (total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides), blood urea nitrogen, creatinine, estimated GFR, uric acid, CRP, hs-CRP, fibrinogen, vWF, plasminogen activator-1 (PAI-1), and TF. PAI-1 was measured in citrated plasma using enzyme-linked immunosorbent assay[15] that is sensitive to free PAI-1, but not to t-PA/PAI-1 complex. A double-antibody enzyme-linked immune-sorbent assay (ELISA) was used to measure vWF, and fibrinogen was measured using high-performance liquid chromatography (HPLC). The plasma TF antigen levels were measured using ELISA kit. Plasma vWF, PAI-1, and TF were measured using ELISA.[15,16] Other chemistry measurements, such as lipid profiles (enzymatic assay method), HbA_{1c} (ion-exchange HPLC), creatinine (enzymatic assay method), CPR (high-sensitivity assay), and hs-CRP (latex method), were done at a commercially available laboratory (Kyodo Igaku Laboratory, Fukuoka, Japan).

The follow-up period was 10 years. Causes of death were 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, much attention was paid to identify underlying causes of death. The information was coded independently according to the rules of the Seven Countries Study[17] and the World Health Organization's 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (WHO-ICD).[18] Follow-up data through the end of March 2010 were analyzed. The follow-up rate was 96.7%.

This study was approved by the Ukiha Branch of the Japan Medical Association, by the local citizens' committee of Tanushimaru, and by the Ethics Committee of Kurume University. The research was conducted in accordance with the principles of the Declaration of Helsinki. All participants gave informed consent.

Statistical analysis. Results are presented as mean ± SD. Because of skewed distributions, natural logarithmic transformations were performed for CRP, hs-CRP, and triglycerides. These variables are shown in the original scale in Tables 1 and 2, after analysis using the log (natural)-transformed values. In Tables 1 and 2, the values for CRP, hs-CRP, and triglycerides are presented as geometric mean and range. Mean plasma vWF level was classified into quartiles as follows: ≤116%, 117–151%, 152–177%, and ≥178%. Analysis of variance was used to compare the means of variables, stratified by quartile of vWF levels. Multivariate proportional hazards regression analysis was used to estimate the predictive vWF level for all-cause death and cancer death stratified by vWF quartile. We indicated using hazard ratios (HRs) and 95% confidence intervals (CIs) to two decimals. 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).

Results

Baseline characteristics of the study population, and inflammatory and hemostatic markers are shown in Table 1. Mean age was 62.7 ± 11.0 years and mean systolic blood pressure was 140.1 ± 21.8 mmHg. Most of the subjects were non-obese and non-diabetic, and were also within normal limits of lipids levels. Mean inflammatory and hemostatic markers were within normal limits. A total of 258 participants died during follow-up: 87 from cancer, 38 from cerebro-cardiovascular disease, and 133 from other diseases. Mean CRP levels at baseline were significantly higher in decedents than in survivors. Mean vWF levels at the baseline were significantly higher in the decedents than in the survivors (data not shown).

The Cox proportional hazards model after adjustments for age and sex showed that CRP and vWF were independent predictors of all-cause death. CRP and vWF were independent predictive markers for cancer death (Table 2).

Table 3 presents HRs of all-cause death and cancer death stratified by quartiles of vWF. Subjects were divided into quartiles according to their plasma vWF levels. Increasing

Table 1. Baseline characteristics of subjects.

CHARACTERISTICS	SURVIVORS	ALL-CAUSE DEATH	CANCER DEATH
n (%)	1,600 (83.3)	258 (13.4)	87 (4.5)
Age (ys)	61.0 ± 10.3	73.1 ± 9.3	70.5 ± 9.5
Sex (% male)	794 (41.4)	153 (59.3)	52 (59.8)
Body mass index (kg/m^2)	23.2 ± 3.0	22.4 ± 3.4	23.3 ± 3.4
Systolic blood pressure (mmHg)	139.0 ± 21.3	147.2 ± 23.8	146.1 ± 21.8
Diastolic blood pressure (mmHg)	81.9 ± 12.1	82.5 ± 12.3	84.3 ± 12.4
Hypertensive medication (% yes)	292 (18.3)	74 (28.7)	23 (26.4)
Total cholesterol (mg/dl)	200.6 ± 34.4	197.4 ± 35.5	193.7 ± 33.8
HDL cholesterol (mg/dl)	55.9 ± 14.0	54.5 ± 14.1	54.3 ± 14.3
Triglycerides (mg/dl)*	98.6	98.3	92.9
Range	28–1284	36–843	38–843
Hyperlipidemic medication (% yes)	73 (4.6)	16 (6.2)	5 (5.7)
Fasting plasma glucose (mg/dl)	97.4 ± 18.8	98.9 ± 22.4	98.9 ± 21.9
HbA_{1c} (%)	5.2 ± 0.7	5.7 ± 1.1	5.7 ± 1.4
Diabetic medication (%)	44 (2.8)	14 (5.4)	5 (5.7)
eGFR (ml/min/1.73 m^2)	62.9 ± 16.4	62.5 ± 17.2	63.9 ± 17.7
Uric acid (mg/dl)	4.9 ± 1.4	5.1 ± 1.5	5.1 ± 1.7
Alcohol intake (% yes)	350 (21.9)	63 (24.4)	25 (28.7)
Current smoking (% yes)	247 (15.4)	69 (26.7)	21 (24.1)
Inflammatory and hemostatic markers			
CRP (mg/dl)	0.18	0.21	0.22
Range	0.1–11.5	0.1–5.2	0.1–2.7
High-sensitive CRP (mg/dl)	0.039	0.07	0.07
Range	0.002–11.500	0.002–40.000	0.164–1.227
Fibrinogen (g/l)	312.2 ± 61.9	331.7 ± 70.1	315.4 ± 64.3
von Willebrand factor (%)	142.1 ± 41.7	164.8 ± 33.2	145.1 ± 41.3
Plasminogen activator-1	27.8 ± 20.7	32.6 ± 29.4	28.6 ± 22.3
Tissue factor	234.3 ± 57.1	259.5 ± 48.2	237.6 ± 56.9

Notes: Data are mean ± standard deviation, geometric mean, range, or percent. *These variables were represented as original scale after analysis by log (natural) transformed values.
Abbreviations: eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.

quartiles of vWF were associated with HRs of all-cause death and cancer death. Compared to quartile 1 of vWF, HR of all-cause death was 1.79 (95% CI, 1.05–3.06) for quartile 4, adjusted for age, sex, systolic blood pressure, glucose, and smoking habit at the baseline. Compared to quartile 1 of vWF, HR of cancer death was 2.25 (95% CI, 1.01–5.09) for quartile 4, adjusted for age, sex, systolic blood pressure, glucose, and smoking habit at the baseline.

Discussion

Significant relationship between mortality or cancer death and inflammatory markers, such as CRP and hs-CRP, or hemostatic markers, such as vWF, was shown in our prospective study.

Inflammatory markers and mortality. Many investigators have suggested that WBC count is a significant factor for predicting cancer.[2,3] Shankar et al.[3] summarized that WBC has been demonstrated in several epidemiologic studies to be a strong and an independent predictor of cancer mortality. CRP has also been demonstrated to be an independent indicator of cardiovascular risk factor in prospective population-based studies.[6,8] Hs-CRP has recently been accepted as an indicator of risk factor for death from coronary artery disease.[9–11] In addition to WBC and CRP, fibrinogen is an acute-phase reactant that is a marker for underlying systemic inflammation. Investigators have reported that fibrinogen is a significant predictor for incidence of coronary heart disease.[12,13]

In general, increasing levels of inflammatory markers correlate with atherosclerosis. A stronger presence of these markers may indicate severe predisposition to atherogenesis, and they may also be correlated with cardio-cerebrovascular diseases. Studies dealing with the relation between these markers and mortality are few, and no studies were found demonstrating this relationship in a Japanese general population

Table 2. Association between inflammatory and hemostatic markers and all-cause death and cancer death.

PARAMETERS	ALL-CAUSE DEATH		CANCER DEATH	
	UNADJUSTED	ADJUSTED FOR AGE AND SEX	UNADJUSTED	ADJUSTED FOR AGE AND SEX
CRP (mg/dl)	1.33** (1.12–1.59)	1.26* (1.06–1.51)	1.47** (1.11–1.94)	1.40* (1.06–1.86)
High-sensitive CRP (mg/dl)	1.36*** (1.22–1.52)	1.25*** (1.13–1.39)	1.29** (1.07–1.56)	1.20 (0.99–1.44)
Fibrinogen (g/l)	1.004*** (1.00–1.01)	1.001 (0.99–1.00)	1.003* (1.00–1.01)	1.002 (0.99–1.01)
von Willebrand factor (%)	1.015*** (1.01–1.02)	1.007** (1.00–1.01)	1.014*** (1.01–1.02)	1.008* (1.00–1.02)
PAI-1	1.01* (1.00–1.02)	1.01** (1.00–1.02)	1.010 (0.99–1.02)	1.01 (0.99–1.02)
Tissue factor	1.01* (1.00–1.01)	1.00 (0.99–1.01)	1.01 (0.99–1.01)	1.00 (0.99–1.01)

Notes: *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.
Abbreviations: CRP, C-reactive protein; PAI-1, Plasminogen activator inhibitor 1.

in which atherosclerosis is rare. It is interesting to note that our study showed that all-cause death and cancer death were significantly related to inflammatory and hemostatic markers.

Hemostatic markers and mortality. Recently, significant associations between hemostatic markers and mortality have been reported.[1,12,13] We also examined the relationship between hemostatic markers and all-cause death or cancer death. Interestingly, increasing vWF levels were related to mortality and cancer death (Table 3).

Some studies have reported that higher levels of hemostatic factors were associated with increased mortality.[1,12,19,20] Anderson et al reported that participants with lower levels of vWF had better survival rates after 26 years than those with higher levels.[20] An association between vWF and increased risk of coronary heart disease has been reported.[20,21] Our study indicated that vWF levels were independent predictors of all-cause death and cancer death (Table 2). Since the number of deaths resulting from cardiovascular disease was too small

Table 3. Odds ratios of all-cause death and cancer death stratified by quartiles of vWF levels.

ALL-CAUSE DEATH	QUARTILE OF PLASMA vWF			
	Q1	Q2	Q3	Q4
vWF (%) Total No. No. of death	≤116 464 22	117–151 465 40	152–177 473 75	≥178 460 90
Unadjusted	1.00	1.91* (1.12–3.27)	3.83*** (2.33–6.28)	4.93*** (1.71–4.26)
Model 1[a]	1.00	1.31 (0.75–2.32)	1.90* (1.12–3.22)	2.02** (1.19–3.40)
Model 2[b]	1.00	1.31 (0.73–2.33)	1.71 (0.99–2.94)	1.79* (1.05–3.06)
CANCER DEATH	**QUARTILE OF PLASMA vWF**			
	Q1	Q2	Q3	Q4
vWF (%) Total No. No. of death	≤116 464 8	117–151 465 14	152–177 473 29	≥178 460 30
Unadjusted	1.00	1.79 (0.74–4.30)	3.75** (1.70–8.30)	3.99*** (1.81–8.81)
Model 1[a]	1.00	1.36 (0.56–3.31)	2.14 (0.94–4.88)	2.30* (1.02–5.21)
Model 2[b]	1.00	1.35 (0.55–3.29)	1.98 (0.87–4.54)	2.25* (1.01–5.09)

Notes: [a]Adjusted for age and sex at baseline. [b]Adjusted for age, sex, SBP, total cholesterol, glucose and smoking habit at baseline. *$P < 0.05$ vs. Q1. **$P < 0.01$ vs. Q1. ***$P < 0.001$ vs. Q1. There are 31 subjects who could not measure vWF in all-cause death. There are 6 subjects who could not measure vWF in cancer death.
Abbreviations: vWF; von Willebrand factor; Q, quartile; SBP, systolic blood pressure.

to analyze, we were unable to identify the factors responsible for cardiovascular death in this study. Accordingly, we investigated whether higher levels of vWF were related to higher ratio of cancer death. Our results showed that higher levels of vWF did not indicate a higher HR of cancer death (Table 3).

The pathophysiologic mechanisms for the association between vWF, haemostatic marker, and cancer death were reported. The vWF is a glycoprotein essential for normal hemostasis by mediating platelet adhesion and aggregation. It is involved in inflammation and has a novel link with angiogenesis.[21] Terraube et al suggested that vWF plays a role in tumor metastasis, independent of its role in hemostasis.[22] The vWF leads to the adhesion of platelets to the exposed subendothelium. In cancer development, tumor cells interact with platelets, leading to angiogenesis. A correlation of vWF levels with advanced disease in cancer patients has been reported.[23]

In Japan, there are many cancer deaths compared to that in the Caucasian. Also, there are small number of cardiovascular deaths in Japan when compared to the Caucasian. Similarly, racial differences do exist in the association between inflammatory and hemostatic biomarkers and mortality.

Study limitation and strength. Our study has some limitations. First, the cancer end point was not incidence but mortality. Second, only a single measurement of inflammatory markers and hemostatic markers was examined. Third, we were unable to investigate the association between vWF and cardiovascular disease, because of the small number of cardiovascular deaths in the study population. To increase the prognostic impact of these markers, more large-scale epidemiological studies are needed. Fourth, we did not have any information of ABO blood type, which may effect on vWF levels. Finally, only a single measurement data were available.

The strengths of the present study are its prospective design and relatively long follow-up period.

Summary. In conclusion, our prospective study showed that both all-cause death and cancer death were significantly related to hemostatic markers. High levels of CRP and vWF were a predictor of mortality in a community-dwelling Japanese population. Our findings suggest that vWF may be a novel predictive marker for cancer death in a general population.

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Author Contributions

ME was responsible for performance of the study and statistical analysis, and HA was responsible for study design. Conceived and designed the experiments: ME, HA, AF, AY, AO, SN, YN, EN, YU, KH, YF. Analyzed the data: ME, HA. Wrote the first draft of the manuscript: HA, YF. Contributed to the writing of the manuscript: ME, HA. Agree with manuscript results and conclusions: AF, AY, AO, SN, YN, EN, YU, KH, YF. Jointly developed the structure and arguments for the paper:AF, AY, AO, SN, YN, EN, YU, KH, YF. Made critical revisions and approved final version: AF, AY, AO, SN, YN, EN, YU, KH, YF. All authors read and approved the final manuscript.

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