ELSEVIER

Atherosclerosis 194 (2007) 498–504

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

γ-Glutamyltransferase predicts cardiovascular death among Japanese women

Atsushi Hozawa [a,*], Tomonori Okamura [a], Takashi Kadowaki [a], Yoshitaka Murakami [a], Koshi Nakamura [a], Takehito Hayakawa [b], Yoshikuni Kita [a], Yasuyuki Nakamura [c], Akira Okayama [d], Hirotsugu Ueshima [a],

The NIPPON DATA90 Research Group

[a] *Department of Health Science, Shiga University of Medical Science, SetaTsukinowa-cho Otsu, 520-2192 Shiga, Japan*
[b] *Department of Public Health, Shimane University School of Medicine, Shimane, Japan*
[c] *Cardiovascular Epidemiology, Faculty of Home Economics, Kyoto Women's University, Kyoto, Japan*
[d] *Department of Preventive Cardiology, National Cardiovascular Center, Osaka, Japan*

Received 9 June 2006; received in revised form 23 August 2006; accepted 28 August 2006
Available online 10 October 2006

Abstract

The clinical importance of γ-glutamyltransferase (GGT) has recently been debated. Although some studies have suggested that the relationship between GGT and cardiovascular disease (CVD) mortality is independent of alcohol consumption, *to our knowledge* no studies have reported the relationship between GGT and CVD mortality in never-drinker subgroups. Since Japanese women are known to have a lower prevalence of alcohol consumption, we examined whether GGT predicts CVD mortality in never-drinkers. We followed 2724 Japanese men and 4122 Japanese women without prior CVD or liver dysfunction for 9.6 years and observed 83 and 82 CVD deaths, respectively. Current alcohol drinkers comprised 59% of men and 7% of women. Among women, the multiple adjusted hazard ratio (HR) for CVD mortality compared with the reference group (GGT: 1–12 U/L) was 2.88 (95% confidence interval (CI), 1.14–7.28) for the elevated group (GGT ≥ 50 U/L). This positive relationship was unchanged in the never-drinkers subgroup (HR for log-transformed continuous GGT, 1.62 (95% CI, 1.11–2.37)). No significant relationships were observed in men. GGT displays a strong positive association with CVD mortality among Japanese women, for whom the prevalence of ever-drinkers is very low. Exploring the significance and biological mechanisms of GGT might provide useful insights into CVD prevention.

Keywords: γ-Glutamyltransferase; Alcohol drinking; Cardiovascular diseases; Prospective studies; Japanese

1. Background

Serum γ-glutamyltransferase (GGT) is a well-known enzyme marker of alcohol consumption and liver disease [1]. However, several recent epidemiological studies have revealed that GGT is a marker of oxidative stress [2], and is associated with several cardiovascular risk factors [3,4]. Furthermore, GGT is predictive of future hypertension, diabetes, stroke and coronary heart disease (CHD) [5–12]. However, most studies investigating relationships between GGT and stroke, CHD and cardiovascular disease (CVD) mortality [9–13] have either not adjusted for alcohol consumption, since GGT was used as a marker of alcohol consumption [10,11] or did not obtain baseline alcohol information [12]. Although GGT might represent an important and independent risk factor for CVD [9,13], little evidence has suggested whether GGT itself is predictive of CVD disease or merely a marker of alcohol consumption. As the prevalence of alcohol drinking and smoking are very

* Corresponding author. Tel.: +81 77 548 2191; fax: +81 77 543 9732.
E-mail address: ahozawa@belle.shiga-med.ac.jp (A. Hozawa).

0021-9150/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.atherosclerosis.2006.08.058

low in Japanese women, particularly in middle to older age, analysis of such individuals should clarify whether GGT levels are predictive of CVD mortality even in never-drinkers.

Our a priori hypothesis was that GGT would predict CVD even in never-drinkers. To test this, we analyzed 9.6-year follow-up data from the National Survey on Circulatory Disorders, Japan, which was initiated in 1990.

2. Methods and population

2.1. Population

Cohort studies of the National Survey on Circulatory Disorders, Japan, were called the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA). NIPPON DATA comprised two cohort studies. Baseline surveys were performed in 1980 and 1990 (NIPPON DATA80 and NIPPON DATA90) [14–16]. The present study analyzed data from NIPPON DATA90 [15,16] as the baseline survey from NIPPON DATA80 did not include any measurement of serum GGT levels. A total of 8384 community residents (3504 men, 4880 women; ≥30-years-old) from 300 randomly selected districts participated in the survey and were followed until November 15, 2000. The overall population of ≥30-years-old in all districts was 10,956, and the participation rate in this survey was 76.5%. Accordingly, these participants were thought to be representative of the Japanese population [16]. Of the 8384 participants, 1538 were excluded for the following reasons: no baseline GGT measurement ($n = 662$), glutamic-oxaloacetic transaminase (GOT) level ≥50 U/L, glutamic pyruvic transaminase (GPT) level ≥50 U/L ($n = 519$), history of coronary heart disease or stroke ($n = 209$), no measurement of confounding factors ($n = 3$) and participants for whom follow-up information could not be obtained because of incomplete residential access information at the first survey ($n = 145$). The remaining 6846 participants (2724 men, 4122 women) were included in the analysis.

2.2. Follow-up survey

Underlying causes of death for the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD-9) for deaths occurring up to the end of 1994 and according to the 10th International Classification of Disease (ICD-10) for deaths occurring from the beginning of 1995. Details of the classification used in the present study have been described elsewhere [14]. Permission to use National Vital Statistics was obtained from the Management and Coordination Agency of the Japanese Government. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12–18, 2000).

2.3. Baseline examination

Non-fasting blood samples were obtained and serum was separated and centrifuged soon after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. All samples were shipped to the same laboratory (SRL, Tokyo, Japan) for blood measurements.

GGT was measured using 3-carboxyl-4-nitroanilide substrate methods. GOT and GPT were measured using ultraviolet methods. Serum total-cholesterol and triglycerides (TG) were measured enzymatically. High-density lipoprotein cholesterol (HDL-C) was measured by the precipitation method using heparin-calcium. Lipid measurements were standardized using the Lipids Standardization Program from the Centers for Disease Control/National Heart, Lung and Blood Institute [17]. Plasma glucose was also measured enzymatically. Diabetes was defined as serum glucose ≥200 mg/dL and/or self-reported history of diabetes. Baseline blood pressures (BP) were measured by trained observers using a standard mercury sphygmomanometer on the right arm of the seated subject. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Public health nurses obtained information on smoking, use of antihypertensive agents and medical histories. For alcohol consumption, public health nurses categorized participants into the following drinking habit categories based on questioning: never-drinkers, ex-drinkers, current drinkers. Current drinkers were defined as drinking ≥3 days/week and consuming ≥1 *gou* per drinking occasion. If the participant was a current drinker, the nurse also asked them the amount of alcohol consumption using *gou*, the traditional Japanese unit of sake, per drinking occasion. For *sake*, 1 *gou* (180 mL) is equivalent to 23 g of alcohol, which is also approximately two measures of whisky (70 mL) or one bottle of beer (633 mL) in terms of alcohol content. Habitual exercise was defined as: (1) exercise ≥2 days/week; (2) duration of exercise per exercise session ≥30 min; (3) continuing the habit for ≥1 year. If participants answered that they did not have any exercise habit, the nurse asked whether exercise was unable to be performed due to health reasons.

2.4. Statistical analysis

To examine associations between GGT and CVD mortality, GGT levels were classified into four groups. These groups were defined as follows: reference, 1–12 U/L; moderate, 13–24 U/L; moderate high, 25–49 U/L; elevated, ≥50 U/L. Basic characteristics were compared among GGT groups using means for continuous variables and percentages for dichotomous variables. As the distribution of TG was positively skewed, geometric mean (antilogarithm of the log-transformed mean) was used instead of arithmetic mean.

Crude mortality rates were estimated among groups. Multivariate-adjusted hazard ratio (HR) and 95% confidence intervals (CI) were also estimated among groups. Cox proportional hazard modeling was used to estimate adjusted

HR of CVD mortality. Models were constructed separately for men and women. The reference GGT group was treated as a reference group. Adjustment for confounding factors was performed using three different approaches in this study. First, we adjusted for age only (Model 1). Second, we included other possible confounding factors as follows: age, HDL-C, total-cholesterol, TG (log-transformed), BMI (<18.5, 18.5–24.9 or ≥25), smoking status (never-smoker, ex-smoker or current smoker), drinking status (never-drinker, ex-drinker and current drinker), GOT, GPT and exercise habit (Model 2). For men, we further categorized current smoking and current drinking into two categories each. Cigarette smoking was classified as 1–20 cigarettes/day or ≥21 cigarettes/day. Current drinking was classified as equal to drinking 1 *gou* (23 g of alcohol) per occasion and 2 *gou* or more. Systolic BP, antihypertensive medication and diabetes were not included in Model 2. Since GGT is known to predict future hypertension and diabetes [5–8], adjusting for BP and diabetes might represent an over-adjustment. We therefore created another model (Model 3) using the same factors as Model 2 with the addition of systolic BP, use of antihypertensive medication and diabetes. In each model, the HR of CVD mortality was also estimated using continuous serum GGT values. When GGT levels were used as continuous variables, log-transformed values were used because GGT level is skewed. Values of $P < 0.05$ were considered statistically significant. SAS software (Version 9.1) was used for analyses.

3. Results

Median GGT level was 27 U/L (interquartile range, 18–43 U/L) for men and 14 U/L (interquartile range, 11–21 U/L) for women. Proportions of current, ex- and never-drinkers were 59, 7 and 35% for men and 7, 1 and 93% for women, respectively. Table 1 shows baseline characteristics for study participants according to GGT level. GGT levels were higher in men than in women. For men, mean age was lower in higher GGT groups. Conversely, mean age was higher in GGT groups for women. Mean HDL level was lower in higher GGT groups in women, while no association was observed in men. Otherwise, determinants of GGT were similar in men and women, comprising higher BMI,

Table 1
Mean and prevalence of baseline characteristics stratified by γ-glutamyltransferase (GGT) level at the baseline survey in 1990, NIPPON DATA90

	Men				Women			
	Reference 1–12[a]	Moderate 13–24[a]	Moderate high 25–49[a]	Elevated 50–468[a]	Reference 1–12[a]	Moderate 13–24[a]	Moderate high 25–49[a]	Elevated 50–295[a]
N	183	937	913	691	1538	1812	593	179
Age (years)	57.0	54.5	52.9	51.1	49.8	52.4	55.2	56.0
BMI (kg/m^2)	20.9	21.9	23.1	23.8	22.0	22.9	23.9	23.9
Total-cholesterol (mg/dL)	177.6	191.2	202.5	206.1	197.9	208.1	219.4	221.4
HDL-cholesterol (mg/dL)	50.1	50.3	50.3	51.9	58.0	56.8	56.0	54.5
Triglyceride* (mg/dL)	4.5	4.6	4.9	5.0	4.5	4.7	4.8	5.0
GOT (U/L)	20.2	21.5	23.9	27.1	18.6	20.6	23.4	27.3
GPT (U/L)	15.1	18.3	23.2	28.8	13.8	17.2	23.2	28.1
Systolic BP (mmHg)	131.0	134.8	137.5	142.2	128.7	134.2	138.5	141.0
Diastolic BP (mmHg)	78.9	80.9	83.6	87.2	76.8	80.0	82.2	84.1
Use of antihypertensive medication (mmHg)	7.1	11.1	14.8	13.5	9.2	15.8	25.3	22.9
Diabetes (%)	6.0	5.2	5.5	9.0	2.1	4.0	9.8	10.6
Smoking								
Never (%)	26.8	24.1	21.0	14.8	91.0	87.9	85.3	86.0
Ex-smoker (%)	25.7	23.5	24.0	22.0	2.7	2.4	1.9	2.8
Current (≤1–20 cigarettes/day, %)	15.9	16.7	16.0	14.2	4.9	6.8	7.4	6.7
Current (≥21cigarettes/day, %)	31.7	35.8	39.0	49.1	1.4	3.0	5.4	4.5
Drinking								
Never (%)	61.2	49.2	32.5	12.3	96.0	92.0	88.9	81.0
Ex-drinker (%)	6.6	7.3	5.3	4.3	0.6	1.2	0.8	0.6
Current (=22.8 g per one occasion, %)	24.0	29.7	32.0	31.0	3.0	5.9	7.4	11.2
Current (>22.8 g per one occasion, %)	8.2	13.9	30.2	52.4	0.5	1.0	2.9	7.3
Habitual exercise (not exercising due to ill health, %)	7.1	4.8	4.5	3.3	5.7	6.4	8.3	10.1
Habitual exercise (not exercising for reasons other than ill health, %)	68.9	72.3	71.7	76.1	77.0	74.5	71.0	70.4
Habitual exercise (yes, %)	24.0	23.0	23.8	20.6	17.4	19.1	20.7	19.6

N, numbers of participants; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BP, blood pressure; '*', log-transformed; participants were not fasting when the blood samples were drawn.

[a] GGT (U/L).

Table 2
Relative hazards (95% confidence interval (CI)) for CVD mortality according to γ-glutamyltransferase (GGT) level in women

	Reference 1–12[b]	Moderate 13–24[b]	Moderate high 25–49[b]	Elevated 50–295[b]	Continuous[a]
Person-years	14982	17548	5682	1707	39918
N of CVD mortality	27	32	17	6	82
CVD mortality rate/1000 person-years	1.80	1.82	2.99	3.52	2.05
Model 1	1	1.10 (0.66–1.84)	1.59 (0.86–2.93)	2.20 (0.90–5.40)	1.50 (1.06–2.12)
Model 2	1	1.17 (0.69–1.98)	1.86 (0.98–3.53)	2.88 (1.14–7.28)	1.71 (1.18–2.47)
Model 3	1	1.16 (0.68–1.98)	1.89 (0.95–3.75)	2.97 (1.06–8.34)	1.73 (1.13–2.63)

NIPPON DATA90, 1990–2000. *N*, numbers of participants; HDL, high-density lipoprotein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BP, blood pressure; Model 1, adjusted for age; Model 2, adjusted for age, alcohol consumption (never, past and current), cigarette smoking (never, past and current), HDL-cholesterol, total-cholesterol, triglyceride*, GOT, GPT, body mass index (<18.5, 18.5–24.9 and ≥25 kg/m^2) and habitual exercise (yes, not exercising for reasons other than ill health, not exercising due to ill health); Model 3, Model 2 + systolic BP, use of antihypertensive medication and diabetes.
[a] Log-transformed.
[b] GGT (U/L).

total-cholesterol, log-transformed TG, GOT, GPT, systolic and diastolic BP, use of antihypertensive medication and prevalence of diabetes in higher GGT groups. Prevalence of never-drinkers and never-smokers was lower in higher GGT groups. For men, the prevalence of current drinkers was >80% in the highest GGT groups. Conversely, for women, the prevalence of current drinkers was <20% even in the highest GGT groups.

Table 2 shows follow-up information and risk of GGT for CVD mortality in women. From a total of 39,918 person-years, 82 CVD deaths were observed (stroke, $n = 38$; CHD, $n = 12$; other heart disease, $n = 27$; other CVD, $n = 5$). CVD mortality rates according to GGT category were 1.80/1000 person-years for the reference group, 1.82/1000 person-years for moderate, 2.99/1000 person-years for moderate-high and 3.52/1000 person-years for elevated. Compared with the reference group, multivariate adjusted HRs (Model 2) were significantly higher in the elevated category (HR, 2.88; 95% CI, 1.14–7.28). These findings were unchanged when quartiles of GGT were used. These positive significant relationships between GGT and CVD mortality were also apparent when log-transformed GGT level was used as a continuous variable (HR, 1.71; 95% CI, 1.18–2.47). These relationships were unchanged even after adjusting for systolic BP, use of antihypertensive medication and diabetes (Model 3). A significant relationship was also identified between GGT and CVD mortality among never-drinkers (HR, 1.62; 95% CI, 1.11–2.37; Model 2). These results were unchanged when we excluded the few subjects with very high GGT (GGT ≥100 U/L). The relationship between GGT and overall mortality in women (274 deaths) was also investigated. Overall mortality was significantly increased in elevated category (Model 2) (HR, 2.07; 95% CI, 1.20–3.59) compared with the reference category. Positive significant relationships between log-transformed continuous GGT and overall mortality were also observed (HR, 1.36; 95% CI, 1.10–1.68).

Table 3 shows the relationship between GGT level and CVD mortality among men. During 25,830 person-years, we observed 83 CVD mortality cases (stroke, $n = 29$; CHD, $n = 23$; other heart disease, $n = 26$; other CVD, $n = 5$). In contrast to women, no significant associations were observed. This is true even after adjusting for alcohol consumption using more detailed definitions. Analysis of the small number of never-drinker men revealed no significant findings (HR of log-transformed continuous GGT with CVD mortality, 0.58 (95% CI, 0.29–1.13). No significant association was identi-

Table 3
Relative hazards (95% confidence interval (CI)) for CVD mortality according to γ-glutamyltransferase (GGT) level in men

	Reference 1–12[b]	Moderate 13–24[b]	Moderate high 25–49[b]	Elevated 50–468[b]	Continuous[a]
Person-years	1651	8787	8706	6687	25830
N of CVD mortality	10	39	24	10	83
CVD mortality rate/1000 person-years	6.06	4.44	2.76	1.50	3.21
Model 1	1	1.03 (0.51–2.06)	0.77 (0.37–1.61)	0.61 (0.25–1.49)	0.80 (0.58–1.09)
Model 2	1	1.14 (0.56–2.35)	0.95 (0.43–2.10)	0.87 (0.33–2.33)	0.95 (0.67–1.36)
Model 3	1	0.99 (0.48–2.04)	0.77 (0.34–1.76)	0.84 (0.30–2.39)	0.93 (0.62–1.41)

NIPPON DATA90 1990–2000. *N*, numbers of participants; HDL, high-density lipoprotein; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; BP, blood pressure; Model 1, adjusted for age; Model 2, adjusted for age, alcohol consumption (never, past, 1 go, 2 go or more), cigarette smoking (never, past, current: ≤1–20 cigarettes/day and current: ≥21cigarettes/day), HDL-cholesterol, total-cholesterol, triglyceride*, GOT, GPT, body mass index (<18.5, 18.5–24.9 and ≥25 kg/m^2) and habitual exercise (yes, not exercising for reasons other than ill health, not exercising due to ill health); Model 3, Model 2 + systolic BP, use of antihypertensive medication and diabetes.
[a] Log-transformed.
[b] GGT (U/L).

fied between log-transformed continuous GGT and overall mortality (292 deaths) in men (HR, 1.14; 95% CI, 0.95–1.37).

4. Discussion

This prospective study tested the hypothesis that GGT would predict CVD mortality even in never-drinkers in the Japanese population. For Japanese women, for whom the prevalence of drinking is very low, GGT was independently and positively associated with CVD mortality. In contrast, we did not identify any relationship between GGT and CVD mortality among Japanese men, for whom the prevalence of smoking and drinking is high.

The strengths of the present study are as follows: (1) study participants were selected randomly from a representative sample of the Japanese population with a high participation rate (76.5%); (2) because most Japanese women at that time did not drink (93% in this study), the effects of alcohol consumption did not need to be considered; (3) we excluded participants who might have potential liver dysfunction such as chronic hepatitis, that is high GOT or GPT, to focus on the risks associated with GGT.

Previous studies have reported a positive significant relationship between GGT and CVD incidence or mortality [9–13]. However, such studies have typically used GGT as a marker of alcohol consumption [10–12], and thus did not adjust for alcohol consumption. However, findings using self-reported alcohol consumption and CVD mortality differ from findings using GGT, with the former showing a U- or J-shaped relationship and the latter showing a linear relationship [12]. A Finnish study that directly compared relationships between self-reported alcohol consumption and stroke incidence with the relationship between GGT and stroke showed that stroke incidence was not predicted by self-reported alcohol consumption, but was strongly predicted by GGT [10]. These findings suggest that GGT is not only a marker of alcohol consumption, but also has an independent role in CVD mortality. Findings from a British study showed that GGT predicts ischemic heart disease independent of alcohol consumption or other factors relating to GGT, supporting this finding [9]. Similarly, a recent report confirmed a positive relationship between GGT and coronary events after adjusting for alcohol consumption, with positive relationships observed for both <20 and ≥20 g/day [13]. However, to the best of our knowledge, no studies have investigated the pathological importance of GGT among never-drinkers and our study of Japanese women might be the first to clarify that GGT predicts CVD mortality in never-drinkers.

Other mechanisms are considered to explain the relationship between GGT and CVD. First, GGT is known to be increased in participants with high TG, cholesterol and glucose levels [3,4]. However, adjusting for these factors did not attenuate the relationship in the present study. Second, recent experimental work has reported that active GGT is present in atherosclerotic plaques of coronary and cerebral arteries [18,19]. GGT could thus be considered as a marker of subclinical atherosclerosis. Third, recent epidemiological studies have reported that GGT level is inversely associated with antioxidant levels [2]. The Coronary Artery Risk Development in Young Adults Study reported that GGT level within the normal range is inversely associated with serum carotenoid levels [20], and positively associated with future F2-isoprostane [7]. Following these study series, several epidemiological investigations have confirmed these findings, such as NHANES III [21] and various Japanese studies [22,23]. GGT is thus thought to be a marker of oxidative stress and enhanced lipid oxidization can be more enhanced in participants with high GGT than in those with lower GGT. Although the biological mechanisms remain unclear, some experimental evidence indicates that GGT is directly involved in the generation of reactive oxygen species under physiological conditions [2].

To date, most studies have shown a positive association between GGT and CVD mortality or CVD incidence in both men and women [9–13]. However, our findings are inconsistent in this regard. We considered that we did not find a positive association between GGT and CVD mortality in men because of the difficulty in controlling for the effects of alcohol consumption, and reverse causality may be present. Participants who had problems with health or liver conditions might display reduced alcohol consumption. Conversely, participants might drink more when they have less concern for their health. However, we could not find any significant results even in the few male participants without any drinking history. Thus, the lack of relationship between GGT and CVD mortality in Japanese men might not be fully explained by the confounding to alcohol consumption. Further studies should be needed to clarify whether a relation of GGT with CVD mortality is observed in Japanese men.

Some methodological limitations were present in this study. Since we did not have incidence data, the possibility exists that GGT does not predict CVD incidence, but instead represents a marker of prognosis after the CVD event. However, relationships between risk factors and CVD mortality and CVD incidence are usually similar. We thus did not consider this limitation as critical. Second, we had only 83 and 82 cases of CVD mortality for women and men, respectively, and thus could not analyze cause-specific relationships between GGT and CVD mortality.

In conclusion, GGT displays a strong positive association with CVD mortality among Japanese women, for whom the prevalence of ever-drinkers is very low. Exploring the significance and biological mechanisms of GGT might provide useful insights into CVD prevention.

Acknowledgements

This study was supported by a Grant-in-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-cardiovascular Disease Control, a

Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003 and H17, 18-chouju-012). The authors thank all members of Japanese Association of Public Health Center Directors and all staffs of the public health centers that cooperated with our study.

Appendix A

List of the NIPPON DATA90 Research group:

NIPPON DATA90: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged".
Chairman: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).
Consultant: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).
Participating Researchers: Akira Okayama (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka), Kazunori Kodama, Fumiyoshi Kasagi (Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura, Yoshikuni Kita (Department of Heath Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa, Shinichi Tanihara (Department of Public Health, Shimane University School of Medicine, Izumo, Shimane), Shigeyuki Saito (Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yosikazu Nakamura (Department of Public Health, Jichi Medical University School of Medicine, Shimotsuke, Tochigi) and Fumihiko Kakuno (Higashiomi Public Health Center, Higashiomi, Shiga).
Participating Research Associates: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano, Takahisa Kawamoto and members of 300 Public Health Centers in Japan, Masumi Minowa (Faculty of Humanities, Seitoku University, Matsudo, Chiba), Minoru Iida (Kansai University of Welfare Sciences, Kashiwara, Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa), Shigemichi Tanaka (Department of Cardiology, Cardiovascular Center, Teine Keijinkai, Sapporo, Hokkaido), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama), Koryo Sawai (The Japanese Association for Cerebrocardiovascular Disease Control, Tokyo) and Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama).

References

[1] Teschke R, Brand A, Strohmeyer G. Induction of hepatic microsomal γ-glutamyltransferase activity following chronic alcohol consumption. Biochem Biophys Res Commun 1977;75:718–24.
[2] Lee DH, Blomhoff R, Jacobs DR. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Rad Res 2004;38:535–9.
[3] Sakuta H, Suzuki T, Yasuda H, Ito T. Gamma-glutamyl transferase and metabolic risk factors for cardiovascular disease. Intern Med 2005;44(6):538–41.
[4] Kim DJ, Noh JH, Cho NH, et al. Serum gamma-glutamyltransferase within its normal concentration range is related to the presence of diabetes and cardiovascular risk factors. Diab Med 2005;22:1134–40.
[5] Lee DH, Ha MH, Kim JH, et al. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. Diabetologia 2003;46:359–64.
[6] Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. Diabetes Care 1998;21:732–7.
[7] Lee DH, Jacobs DR, Gross M, et al. γ-Glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Clin Chem 2003;49:1358–66.
[8] Nakanishi N, Suzuki K, Tatara K. Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care 2004;27:1427–32.
[9] Wannamethee G, Ebrahim S, Shaper A. γ-Glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol 1995;142:699–708.
[10] Jousilahti P, Rastenyte D, Tuomilehto J. Serum γ-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. Stroke 2000;31:1851–5.
[11] Bots ML, Salonen JT, Elwood PC, et al. Gamma-glutamyltransferase and risk of stroke: the EUROSTROKE project. J Epidemiol Commun Health 2002;56(Suppl. 1):i25–9.
[12] Ruttmann E, Brant LJ, Concin H, et al., Vorarlberg Health Monitoring and Promotion Program Study Group. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005;112:2130–7.
[13] Meisinger C, Doring A, Schneider A, Lowel H, For The KORA Study Group. Serum gamma-glutamyltransferase is a predictor of incident coronary events in apparently healthy men from the general population. Atherosclerosis 2006;(February (14)) [Epub ahead of print].
[14] Okamura T, Kadowaki T, Hayakawa T, et al. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003;253:169–80.
[15] Okamura T, Hayakawa T, Kadowaki T, et al., NIPPON DATA90 Research Group. The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. Atherosclerosis 2006;184:143–50.
[16] Nakamura K, Okamura T, Hayakawa T, et al. NIPPON DATA90 Research Group: Electrocardiogram screening for left high R-wave predicts cardiovascular death in a Japanese community-based population. Hypertens Res 2006;29:353–60.
[17] Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL cholesterol by the US Cholesterol Reference Method Laboratory Network. J Atheroscler Thromb 2003;10:145–53.

[18] Paolicchi A, Emdin M, Ghliozeni E, et al. Images in cardiovascular medicine. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. Circulation 2004;109:1440.
[19] Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum gamma-glutamyltransferase in cardiovascular diseases. Clin Chem Lab Med 2004;42:1085–91.
[20] Lee DH, Gross MD, Jacobs Jr DR, Cardiovascular Risk Development in Young Adults Study. Association of serum carotenoids and tocopherols with gamma-glutamyltransferase: the Cardiovascular Risk Development in Young Adults (CARDIA) Study. Clin Chem 2004;50:582–8.
[21] Lim JS, Yang JH, Chun BY, et al. Is serum gamma-glutamyltransferase inversely associated with serum antioxidants as a marker of oxidative stress? Free Rad Biol Med 2004;37:1018–23.
[22] Yamada J, Tomiyama H, Yambe M. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Atherosclerosis 2006 [Epub ahead of print].
[23] Sugiura M, Nakamura M, Ikoma Y, et al. High serum carotenoids are inversely associated with serum gamma-glutamyltransferase in alcohol drinkers within normal liver function. J Epidemiol 2005;15:180–6.