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Original Article

Risk Charts Illustrating the 10-year Risk of Stroke among Residents of Japanese Rural Communities: The JMS Cohort Study

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ABSTRACT

Background: Risk charts are used to estimate the risk of cardiovascular diseases; however, most have been developed in Western countries. In Japan, currently available risk charts are based on mortality data. Using data on cardiovascular disease incidence from the JMS Cohort Study, we developed charts that illustrated the risk of stroke.
Methods and Results: The JMS Cohort Study is a community-based cohort study of cardiovascular disease. Baseline data were obtained between 1992 and 1995. In the present analysis, the participants were 12 276 subjects without a history of stroke; the follow-up period was 10.7 years. Color-coded risk charts were created by using Cox's proportional hazards models to calculate 10-year absolute risks associated with sex, age, smoking status, diabetes status, and systolic blood pressure. The risks of stroke and cerebral infarction rose as age and systolic blood pressure increased. Although the risk of cerebral hemorrhage were generally lower than that of cerebral infarction, the patterns of association with risk factors were similar.
Conclusion: These risk charts should prove useful for clinicians and other health professionals who are required to estimate an individual's risk for stroke.

Key words: stroke; blood pressure; smoking; diabetes mellitus; cohort study

INTRODUCTION

Cardiovascular disease (CVD) and cerebrovascular disease are the second and third most common causes of death in Japan.[1] In most Western countries, the incidence of myocardial infarction (MI) is higher than that of stroke.[2,3] However, in Japan the incidence of stroke is much higher than that of MI.[1,4,5] Although stroke mortality[1] and incidence have declined in the last few decades,[1–3] stroke remains a significant healthcare burden for Japan.

Age, sex, blood pressure, smoking status, and diabetes status are considered the major factors in quantifying stroke risk.[4,6–11] Several models to predict the risk of CVD were developed after the Framingham risk estimates were reported.[12–19] However, most of these only assess the risk for coronary heart disease (CHD); only a few address the risk of stroke. Because the incidences of CHD and stroke differ between Japan and Western countries, risk assessment tools from the latter are not ideal for use in Japan.

Recently, a risk assessment chart for CVD was developed using data from the NIPPON DATA80 in Japan.[20,21] However, NIPPON DATA80 investigated stroke mortality only, ie, non-fatal strokes were not included in the analysis. Therefore, a risk chart constructed using these data would not be entirely suitable for predicting stroke incidence. The Jichi Medical School (JMS) Cohort Study is a multi-community prospective study that monitors residents of Japanese rural communities and captures CVD events. We used data from the JMS Cohort Study to develop charts that display the risk of stroke among Japanese.

METHODS

Study population

The JMS Cohort Study began in 1992. Its primary objective was to clarify associations between potential risk factors and CVD in 12 rural districts in Japan.[5,22]

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The baseline data of this cohort study were obtained between April 1992 and July 1995. If several sets of data were obtained for a single identical participant during that period, the first set was used as baseline. The baseline data were collected as a part of a national mass-screening program. In Japan, mass screening for CVD has been conducted since 1982, in accordance with the Health and Medical Service for the Aged Act of 1981. Local government offices in each community issued invitations to residents eligible for the mass screening, and personal invitations were also sent to all potential participants by mail. As a result, 12 490 participants were eligible (4913 males and 7577 females; age range, 19–93 years). The overall response rate among the 12 communities was 65.0%. Written informed consent to participate in the study was obtained individually from all the respondents to the mass screening.

Among the 12 490 participants, 95 (0.8%) who did not sign the agreement to participate in the study, 7 (0.06%) who had no follow-up data, and 112 (0.9%) who had a past history of stroke were excluded. Ultimately, 12 276 participants (4807 men and 7469 women) remained for analysis.

Measurement of baseline variables

To ensure uniform data collection, we established a central committee composed of the chief medical officers from all the participating districts. This committee developed a detailed manual for data collection. Systolic blood pressure and diastolic blood pressure were measured once with a fully automated sphygmomanometer, the BP203RV-II (Nippon Colin, Komaki, Japan), placed on the right arm of a seated participant who had rested in a sitting position for 5 minutes before measurement. Information about medical history and lifestyle was gathered by means of a written questionnaire.

Blood samples were drawn from the antecubital vein of seated participants, with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing a 1/10 volume of 3.8% trisodium citrate for blood glucose, and no additives for lipids. Tubes were centrifuged at 3000g for 15 minutes at room temperature. After separation, the serum samples were stored at 4 °C in refrigerated containers if analysis was to be performed within a few days. Otherwise, the samples were frozen until analysis. Plasma samples were frozen as rapidly as possible to −80 °C for storage, until laboratory examination could be performed.

Total cholesterol was measured by using an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation (CV): 1.5%). Blood glucose was measured via an enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV: 1.9%). In this study, blood samples of 5547 (45.0%) participants were collected after an overnight fast; all other samples were casual samples. Diabetic participants were defined as those with currently treated diabetes, plasma glucose ≥126 mg/dl after an overnight fast, or casual blood glucose ≥200 mg/dl. Participants were also asked whether they were current smokers or not.

Follow-up

A mass screening system was used to obtain baseline data and to follow the participants annually. Those examined were asked whether they had suffered a stroke after enrolling. Participants who did not come to the screening examination were contacted by mail or phone. Public health nurses also visited the participants to obtain pertinent information when necessary. In total, 100% of the participants were contacted. Those with a history of stroke were asked when the stroke had been diagnosed and where (at which hospital) they had been treated. Medical records at hospitals in the study areas were also checked to determine if these participants had been treated. If an incident was suspected, forms were filled out, and duplicates of the CT and/or MRI films of the case were obtained to confirm a diagnosis of stroke. Diagnoses were determined independently by a diagnosis committee comprising 1 radiologist, 1 neurologist, and 2 cardiologists. Stroke was defined as a focal, nonconvulsive neurological deficit of sudden onset that persisted for at least 24 hours. Stroke subtypes, ie, cerebral hemorrhage (CH), cerebral infarction (CI), and subarachnoid hemorrhage (SAH), were determined by using the criteria of the National Institute of Neurological Disorder and Stroke.[23] Symptomatic lacuna infarction was defined as a CI.

Statistical analysis

Statistical analyses were carried out using SAS version 8.2 (SAS Japan). Cox proportional hazards models were used to calculate the 10-year absolute risk of stroke for each risk factor. Under the Cox proportional hazards model, the survival probability S(T:X) of a person with a risk X at time T is defined as $S(T:X) = \{[S0(T)]\exp^{(BX)}\}^{\exp(B(X-Xm))}$, where S0(T) is survival probability corresponding to the standard hazard, B is the regression coefficient, and Xm is the population mean of risk X. The 10-year absolute risk of a person with risk X is thus 1-S(10:X).[21] Risk charts were created based on calculations of the absolute risk associated with 5 conventional cardiovascular risk factors: age, sex, smoking status, diabetes status, and systolic blood pressure. Age was grouped into 5 categories: less than 40, 40–49, 50–59, 60–69, and 70 years or older. Systolic blood pressure was also grouped into 5 categories: less than 120, 120–139, 140–159, 160–179, and 180 mm Hg or higher. The other risk factors were treated as dichotomous variables. The risk charts were color-coded so that users could easily estimate their probability of a stroke.

RESULTS

The mean age of participants at baseline was 55.2 years for men and 55.3 years for women. The mean duration of follow-up was 10.7 years (men: 10.6 years; women: 10.8 years).

Table 1. Participants from JMS Cohort Study included in the analysis of stroke risk

	Men	Women
Total Cohort Participants	4911	7579
Participants with Consent	4869	7519
Study Participants	4406	6817
Duration of follow-up (years)	10.6 ± 2.6	10.8 ± 2.2
Age (years)	55.2 ± 12.0	55.3 ± 11.2
Systolic Blood Pressure (mm Hg)	131.3 ± 20.5	128.0 ± 21.0
Smoker (%)	50.4	5.5
Diabetes (%)	4.5	2.2
Stroke	190	165
Cerebral hemorrhage	41	38
Cerebral infarction	136	87
Subarachnoid hemorrhage	13	39
Unclassified	0	1

Total incidence of stroke was 190 cases for men (CH: 41 [21.6%], CI: 136 [71.6%], SAH: 13 [6.8%]) and 165 cases for women (CH: 38 [23.0%], CI: 87 [52.7%], SAH: 39 [23.6%], Unclassified: 1 (0.6%]) (Table 1).

Figures 1 to 3 show the color-coded 10-year absolute risk for all stroke, CH, and CI for each of the combinations of risk factors. All charts were prepared in the same manner, according to diabetes status, smoking status, and systolic blood pressure in each sex. Initially, total cholesterol was included in the analysis; however, after it was determined that total cholesterol was not associated with stroke in either sex, it was excluded from the model. Figure 1 shows all-stroke risk in both sexes, Figure 2 shows CH risk, and Figure 3 shows the risk for CI. Risk can be read by matching the individual's age to the appropriate age group, and blood pressure to the nearest multiple of 20 mm Hg. The risks rose as systolic blood pressure and age increased. In addition, among men and women, current smokers and participants with diabetes were at higher risk for any stroke event and for CI. Although the 10-year risk of CH was lower than that of CI, the risk patterns were similar in men. The risk of SAH was higher in women than in men, and was positively associated with SBP in women, but not in men. The SAH data in the present study are not shown because the number of cases was small, especially among men, and thus the charts were not likely to be representative.

DISCUSSION

We developed risk charts for stroke based on data from the JMS Cohort Study. The charts show 10-year absolute risk for all stroke events and stroke subtypes associated with sex, age, smoking status, diabetes status, and systolic blood pressure. Because cholesterol was not associated with stroke, it was not

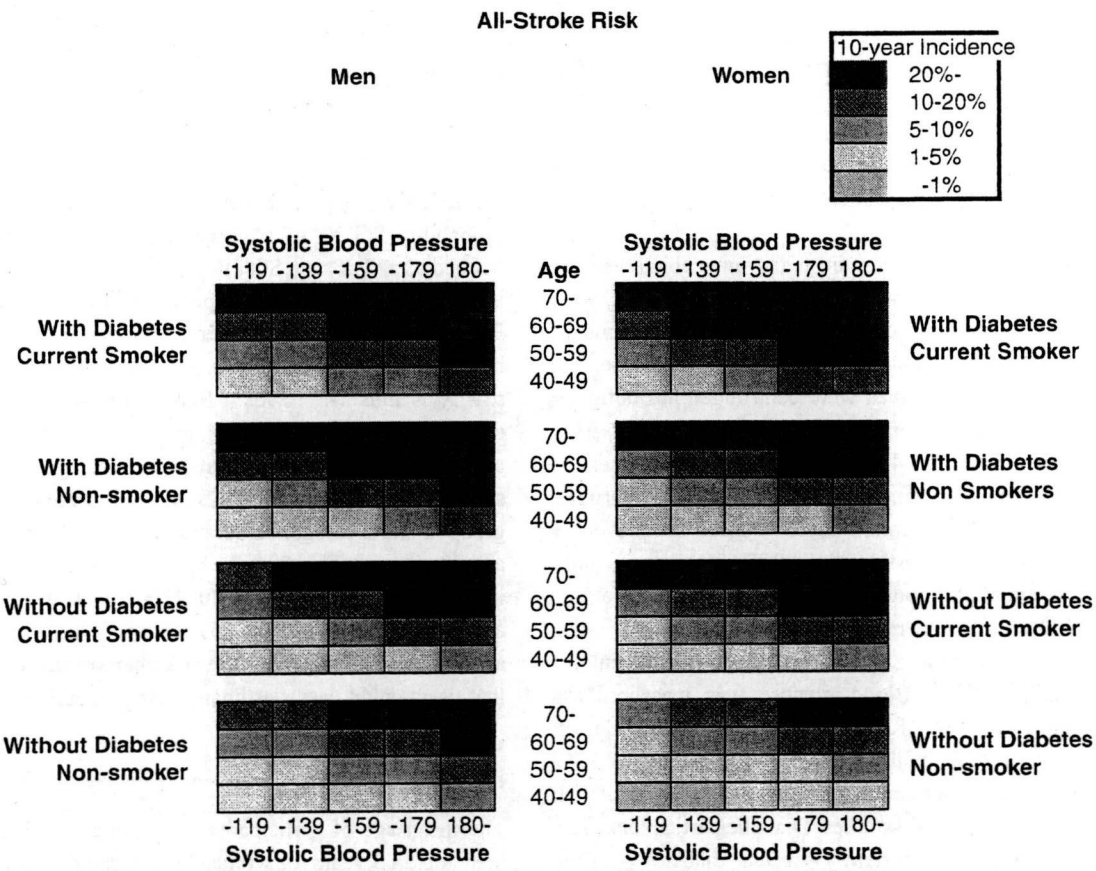

Figure 1. Chart showing 10-year all-stroke risk in men and women

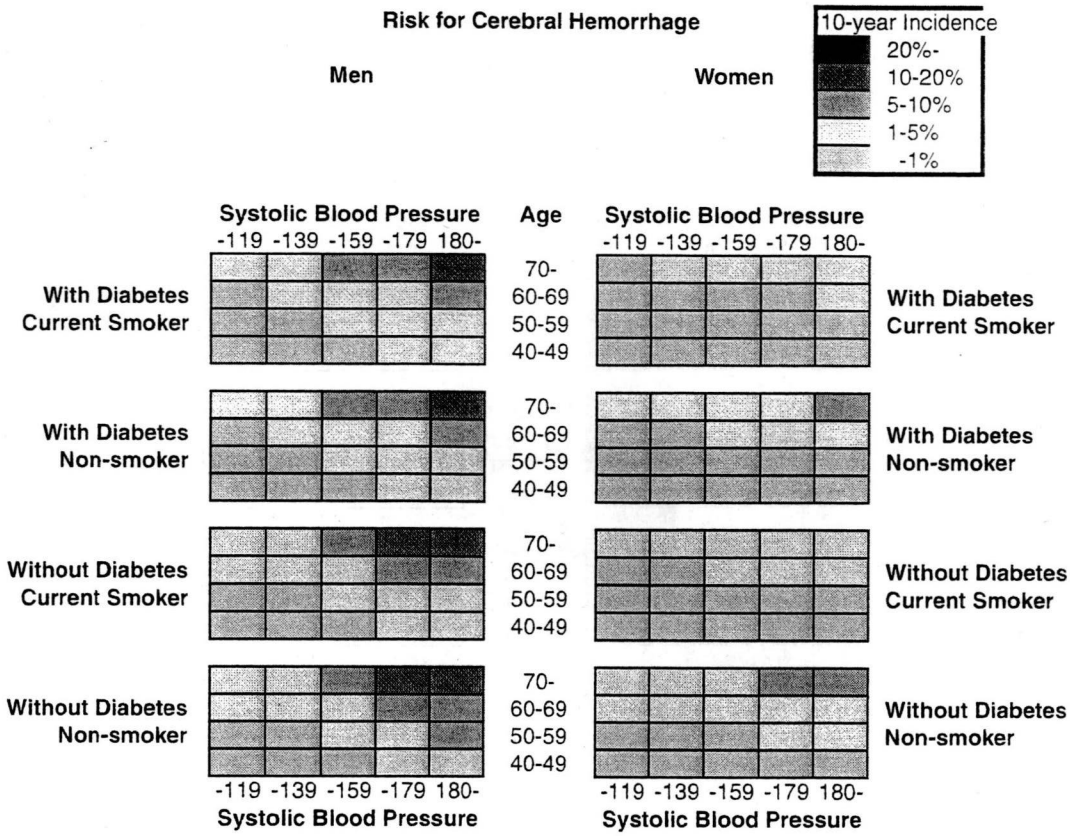

Figure 2. Chart showing 10-year risk for cerebral hemorrhage in men and women

included as an independent variable in the analysis. We believe that these charts will be useful for clinicians and other health professionals who are required to estimate an individual's risk for stroke.

The charts were developed using data from a Japanese community-based cardiovascular cohort study. In the past, a variety of risk charts were developed to estimate the probability of CVD. However, most used data from studies conducted in Western countries.[6,11–13,17–19,24–27] Risk profile charts that estimate the probability of stroke were developed using data from the Framingham Heart Study.[6,27] Although these risk estimates have been widely adopted in the formulation of clinical guidelines in the United States and elsewhere,[28–30] a number of problems in applying these estimates to other populations have been described, the most important of which is that incidences of CVD substantially differ by population.[7,31,32] More recently, tools have been developed that estimate cardiovascular risk in a number of specific populations.[11,13,17–19,25,26]

The Framingham estimates of stroke risk cannot be applied to Japanese because the incidence of stroke differs between the United States and Japan.[33–35] In Asia, tools for CHD risk prediction that are derived from Asian cohorts have been utilized[11]; however, there have been no instruments to predict the risk for stroke in an Asian population. In Japan, cardiovascular risk charts were developed using data from the NIPPON DATA80, which is a representative cohort study. However, the charts were based on mortality data.[20,21] The risk charts developed in the present study should be more accurate in predicting the risk for a stroke event, as opposed to stroke mortality, in Japanese.

We created sex-specific charts that showed risks associated with age, diabetes status, smoking status, and systolic blood pressure. A strong dose-response relationship between systolic blood pressure and stroke has been observed in Japan and other countries.[8–10,36] It is important to note that in the present study total cholesterol was excluded in the estimates of stroke risk because there was no association between total cholesterol and stroke. However, charts for MI risk that are based on data from the JMS Cohort Study have been produced, and these do include total cholesterol as a risk factor for MI.

We developed 10-year charts illustrating CH and CI risk, as well as all-stroke risk. The pattern for all-stroke risk resembled that of CI risk because more than half of the recorded stroke events were CI. The chart patterns for all-stroke, CH, and CI risk were similar, among both men and women.

There were some limitations in this study. The study participants were not randomly selected. The areas in which the study was conducted were primarily rural and the data may therefore not be generalizable to urban populations. In addition, a high-risk population may benefit from more

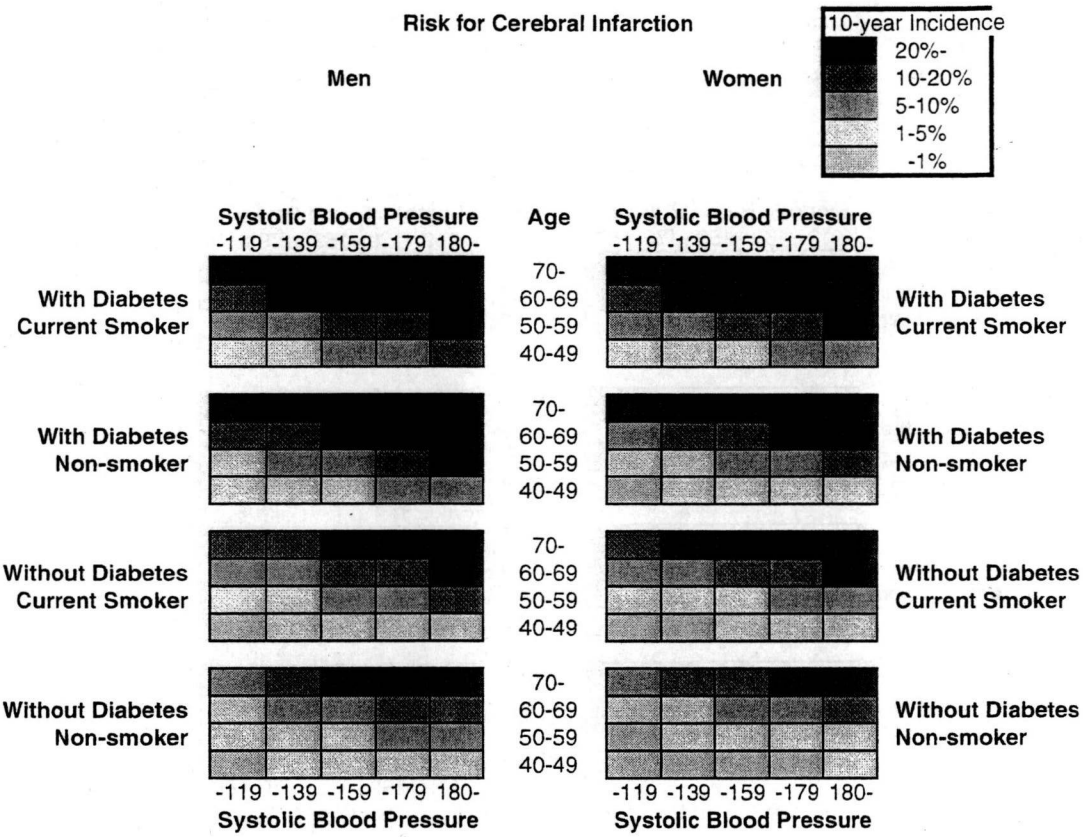

Figure 3. Chart showing 10-year risk for cerebral infarction in men and women

intensive monitoring and intervention than would a population at lower risk. This effect may have led to an underestimation of risks in the present study, because health promotion activities were held in the participating areas.

The strengths of the present study include its very high rates of response and follow-up. Furthermore, the present study was conducted in a standardized fashion in 12 geographically dispersed areas of Japan, and it comprised more than 12 000 men and women. These advantages substantially increased the reliability of the study results.

In conclusion, we used data from Japanese rural populations to develop risk charts that estimate the 10-year risk for stroke in individuals. However, these charts should be used with caution in non-rural populations.

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ORIGINAL INVESTIGATION

Prospective Study on Occupational Stress and Risk of Stroke

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Background: No prospective studies have examined the association between occupational stress according to the job demand–control model and the risk of stroke in Asian populations.

Methods: We conducted a multicenter community-based prospective study of 6553 Japanese male and female workers. Occupational stress was evaluated using a Japanese version of the job demand–control model questionnaire. We used the Cox proportional hazards model to evaluate the association between occupational stress and stroke.

Results: During a mean follow-up of 11 years, we identified 147 incident strokes. Multivariable analysis revealed a more than 2-fold increase in the risk of total stroke among men with job strain (combination of high job demand and low job control) (hazard ratio, 2.73; 95% confidence interval, 1.17-6.38) compared with counterpart men with low strain (combination of low job demand and high job control) after adjustment for age, educational attainment, occupation, smoking status, alcohol consumption, physical activity, and study area. Additional adjustments for biologic risk factors attenuated the hazard ratio, but there continued to be statistical significance (hazard ratio, 2.53; 95% confidence interval, 1.08-5.94). In women, no statistically significant differences were found for any stroke incidence among the job characteristic categories.

Conclusion: Occupational stress related to job strain was associated with incident strokes among Japanese men.

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STRESS IS CONSIDERED A RISK factor for stroke.[1-3] Chronic stress associated with occupations can be avoided; modifiable job characteristics have been conceptualized as stress models, and these may provide clues for concrete interventions.[4] The job demand–control model is the most often used occupational stress model.[4,5] It posits that workers who face high psychological demands in their occupation and have little control over their work (ie, those who have job strain) are at a greater risk of becoming ill than are workers with low psychological demands and a high degree of control in their occupation (ie, those with low-strain occupations). Many prospective studies have supported this hypothesis using the outcome of coronary heart disease.[6,7] Furthermore, stress-reduction approaches based on the model have been shown to be effective.[8]

There is limited prospective evidence showing an association between job strain and the risk of stroke[9-12]; all findings are from studies in Nordic countries. Two Swedish studies that evaluated job strain on the basis of workers' self-reported job characteristics failed to show statistically significant associations.[9,10] Two additional large-scale registry-based studies showed that low levels of job control were significantly associated with death from stroke.[11,12] A crude assessment aggregated to the data by a secondary data source (job exposure matrix) indicated that a more accurate evaluation of occupational stress was warranted.[6] Furthermore, conventional cardiovascular risk factors were not taken into account. In the present study, we sought to estimate the risk of stroke onset associated with job strain in a Japanese working population. We used individual-level data with a valid instrument. We also examined the possible confounding or mediating effects of socioeconomic, behavioral, and biologic risk factors by controlling for them in the analyses.

METHODS

STUDY POPULATION

To investigate the risk factors for cardiovascular diseases in Japan in the Jichi Medical School Cohort Study, data for 12 490 Japanese adults from 12 communities located across Japan were collected between April 1992 and July 1995 using a standardized questionnaire

and physical examination findings.[13] Routine mass screening examinations for cardiovascular diseases in the older adults are held in Japan in accordance with legal regulations and provided the data for the present study. The regulations require municipal governments to offer screenings to all residents who are willing to participate. In each community, potential participants are invited to partake in screenings through letters or public information. Potential participants are told that persons who are treated at a hospital or clinic for a cardiovascular disease do not have to participate in the examination and screening. The overall response rate was 65.4%.

The aim of the present investigation was to explore the effect of job strain on incident stroke, so we limited the study population to 3659 male and 3995 female workers with a baseline age of 65 years or younger. We excluded workers with a history of stroke or myocardial infarction and those without complete information regarding occupational stress. The final study group consisted of 3190 men and 3363 women. The occupations of the participants were manager (759 men and 206 women); professional, technician, or clerk (251 men and 483 women); sales or service worker (280 men and 807 women); farming, forestry, or fishery worker (1055 men and 1110 women); and security, transportation, communications, or craft worker, laborer, or unclassified worker (845 men and 757 woman). Compared with the general working population of Japan, the study population included larger proportions of older workers and workers engaged in nonindustrial occupations (farming, forestry, and fishery).[14] More than 99% of the participants were employed by companies with fewer than 300 employees. Japanese companies are required to provide an annual health examination of employees. For those who are not offered a health examination at their workplace, such as workers in a nonindustrial occupation or who are self-employed, the mass screening examination program is an opportunity to have their health status determined. Employees who are offered a health examination at their workplace may also participate in the mass health examinations. Many small companies (local industry) or local government offices in rural districts such as those constituting our study areas rely on the mass screening examinations to provide their employees with a health examination. We inferred from repeated surveys that changes in occupation or job position were not frequent in the rural settings included in the current cohort.[15] Some part-time employees may have been included in the study population, but this was not confirmed.

SURVEILLANCE OF STROKE AND CLASSIFICATION OF STROKE SUBTYPES

The study follow-up system ensures contact with the participants annually through direct interview or via telephone or letter to determine the participant's current health status. Participants are asked whether they had a stroke or diagnosis of cardiovascular disease that occurred after enrollment in the study. Those who did were asked which hospital they attended and the date of hospitalization. If an incident case was suspected, all the medical records were reviewed and duplicate computed tomography or magnetic resonance imaging films were obtained. Diagnosis of stroke was determined by the presence of a focal and nonconvulsive neurologic deficit lasting 24 hours or longer with a clear onset. Stroke subtype was determined according to the criteria of the National Institute of Neurological Disorder and Stroke.[16] The *International Classification of Diseases, Tenth Revision (ICD-10)*, codes that were applied to study patients were hemorrhagic stroke *ICD-10* codes I60 (subarachnoid hemorrhage) and I61 through I62 (intracerebral hemorrhage) and nonhemorrhagic stroke *ICD-10* code I63 (ischemic stroke). Patients with transient ischemic attack were excluded from the analysis. The diagnosis was determined independently by a diagnosis committee composed of a radiologist, a neurologist, and 2 cardiologists. With the permission of the Agency of General Affairs and the Ministry of Health, Labour, and Welfare, we determined the causes of death for all participants who died between the date of their first health examination and the end of 2005, using the Cause-of-Death Register found at the public health center located in each community.

ASSESSMENT OF OCCUPATIONAL STRESS

Job characteristics were derived at baseline using a Japanese version of the job demand–control model questionnaire from the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (WHO-MONICA) Psychosocial Study Questionnaire. The job characteristics studied were job control and psychological demands. *Job control* was defined as the sum of 2 subscales given equal weight: (1) skill discretion, measured by 4 items (possibility for learning new things, skills required for the job, requirement for creativity, and repetitious nature of the work) and (2) decision authority, measured by 2 items (right to make one's own decisions and freedom to choose the manner in which the work is performed). Psychological job demands were defined by 5 items (speed in completing work, degree of difficulty of the work, excessive workload, insufficient time allowed to complete the work, and conflicting demands). All questions were scored on a Likert scale of 1 to 4. The Cronbach α coefficients for the job control index and psychological demand index were .65 and .69, respectively. Interrelationships among the job characteristic scores, sex, age, educational level, and occupational status were in concordance with the current literature.[17] The job conditions assessed as part of this cohort during the follow-up demonstrated a moderate degree of stability with 5-year–interval intraclass correlation coefficients of 0.63 (n=377) for job control and 0.55 (n=378) for job demands.[15] Cross-classification of the job control and job demand scales according to their sex-specific median values produced a quadrant scheme with 4 exposure categories, with low job demand and high job control representing a low-strain job (reference category), high job demand and high job control representing an active job, low job demand and low job control representing a passive job, and high job demand and low job control representing a strain job.

ASSESSMENT OF RISK FACTORS

We measured the following demographic characteristics and conventional risk factors at baseline: age (18-39, 40-49, 50-59, or 60-65 years), educational attainment (≤15 years [age at completion of compulsory education], 16-18 years [age at completion of senior high school], or ≥19 years [age at entering college or further education]), smoking status (lifetime nonsmoker, ex-smoker, or current smoker), alcohol consumption (nondrinker, <1 *go* daily (*go* is a traditional Japanese alcohol unit; 1 *go*=28.9 g of alcohol), or ≥1 *go* daily), physical activity index[18] (<29, 29-36, or ≥37), body mass index (calculated as weight in kilograms divided by height in meters squared) (<22, 22-24.9, or ≥25), hypertension (physician-diagnosed hypertension or systolic/diastolic blood pressure ≥140/90 mm Hg), diabetes mellitus (under treatment or a fasting/casual blood glucose level of at least 126/200 mg/dL [to convert to millimoles per liter, mutiply by 0.0555]), and hypercholesterolemia (physician-diagnosed hypercholesterolemia or total cholesterol ≥220 mg/dL [to convert to millimoles per liter, multiply by 0.0259]).

DATA ANALYSIS

Analysis was based on the stroke incidence rate during the 11 years of follow-up. For each participant, person-years of fol-

Table 1. Baseline Characteristics by Sex and Psychosocial Job Characteristics

	Men (n=3190)					Women (n=3363)				
	Low-Strain Job	Active Job	Passive Job	High-Strain Job	*P* Value[a]	Low-Strain Job	Active Job	Passive Job	High-Strain Job	*P* Value[a]
No. of subjects	499	955	923	813	...	676	947	915	825	...
Mean age, y	51.0	49.1	52.3	50.5	<.001	51.8	49.9	50.6	50.4	.001
Occupation, %[b]										
Manager	27.7	35.2	13.1	20.2	<.001	6.4	12.0	3.5	2.1	<.001
Professional, technician, or clerk	5.8	8.7	8.1	7.9		16.0	16.2	15.7	9.5	
Sales or service worker	11.2	6.4	9.0	9.8		24.7	23.3	27.0	20.8	
Farming, forestry, or fishery worker	41.9	27.2	37.7	29.3		46.9	37.5	26.3	23.9	
Security, transportation, communications, or craft worker, laborer, or unclassified worker	13.4	22.5	32.1	32.8		6.1	11.0	27.4	43.8	
Educational level, age at completion, y, %[b]										
≤15	36.9	33.2	44.0	42.1	<.001	41.9	39.1	44.7	45.0	<.001
16-18	46.5	50.7	44.6	45.6		44.5	44.4	44.2	46.7	
≥19	16.0	15.4	10.9	11.3		13.5	16.5	10.5	7.6	
Unreported	0.6	0.7	0.4	1.0		0.1	0.1	0.7	0.7	
Smoking, %[b]										
Lifetime nonsmoker	21.4	20.7	22.1	22.0	.98	89.5	89.1	89.8	90.5	.71
Ex-smoker	22.8	25.2	24.1	24.7		2.4	2.0	2.6	2.4	
Current smoker	55.5	53.7	53.4	52.8		6.4	6.5	6.4	5.3	
Unreported	0.2	0.3	0.4	0.5		1.8	2.3	1.1	1.7	
Alcohol intake, g/d, %[b]										
Nondrinker	19.2	20.0	24.2	18.0	<.001	68.2	62.4	71.9	65.7	.003
<28.9	31.5	29.5	27.3	26.6		21.9	27.3	20.7	25.8	
≥28.9	46.3	48.6	44.1	53.0		5.6	5.8	4.7	4.2	
Unreported	3.0	1.9	4.4	2.5		4.3	4.4	2.7	4.2	
Physical activity index, MET-h, %[b]										
≤28	18.4	17.0	18.7	19.9	<.001	24.0	22.2	27.7	27.3	<.001
29-36	38.7	34.3	43.8	32.1		49.0	46.0	53.4	50.4	
≥37	42.3	47.7	36.5	46.9		26.0	30.3	16.8	21.0	
Unreported	0.6	0.9	1.0	1.1		1.0	1.5	2.1	1.3	
Mean BMI[b]	23.2	23.4	22.8	23.1	.001	23.2	23.1	23.0	22.9	.16
Hypertension, %[b]	28.9	32.3	35.0	35.1	.07	30.0	24.7	27.2	25.7	.15
Diabetes mellitus, %[b]	5.2	5.7	6.7	5.3	.54	1.5	1.7	2.6	2.8	.18
Hypercholesterolemia, %[b]	19.2	16.0	17.7	17.0	.68	19.7	21.3	21.3	20.0	.72

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET-h, metabolic equivalent task per hour.
[a] Calculated using the χ^2 test for heterogeneity.
[b] Because of rounding, percentages may not total 100.

low-up were allocated according to the dates of her or his health examinations until death, date of movement outside the study community, the endpoint of stroke, or December 31, 2005, whichever occurred first. Data regarding the movements of the study population were obtained every year from the participant's municipal government, which records movements of residents in and out of the particular community. A total of 193 subjects (2.9% of the analytic cohort) moved out of their community during the study period and were treated as censored cases. The total observed person-years was 71 385. Cox's proportional hazard regression analysis was used to examine the association between psychosocial job characteristics and an incident stroke. The hazard ratios were estimated first after adjusting for age and study area (community), and then after adjusting for age, educational attainment, occupation, smoking status, alcohol consumption, physical activity index, and study area. Body mass index, hypertension, diabetes, and hypercholesterolemia were also included in the multivariable model as intermediate variables to examine how the inclusion of these variables influenced the association between psychosocial job characteristics and the risk of stroke. Ordinal variables were represented by dummy variables. All probability values were 2-tailed, and values of $P < .05$ were considered statistically significant. All analyses were conducted with SPSS for Windows, release 15 (SPSS Inc, Chicago, Illinois).

The study design and procedures were reviewed and approved by each municipal government and the Ethics Committee for Epidemiological Research at Jichi Medical School. Written informed consent was obtained from all prospective participants.

RESULTS

Table 1 shows the relationships between psychosocial job characteristics and the examined variables at baseline. Men reporting active jobs were younger than those reporting passive jobs. The socioeconomic status was lower for men with passive or strain jobs than for those with active or low-strain jobs; the former group was more likely to be engaged in blue-collar work and to have less education. Nonindustrial occupations were more prevalent among men with low-strain jobs, while managerial positions were prevalent among men with active jobs. Men exposed to high-strain jobs were more likely to be heavy drinkers than

Table 2. Associations of Psychosocial Job Characteristics With Incident Stroke

	Person-Years	No. of Events	Hazard Ratio (95% CI)		
			Adjusted for Age and Area	Adjusted for Age, Area, and Sociodemographic[a] and Behavioral[b] Risk Factors	Adjusted for Age, Area, Sociodemographic, Behavioral, and Biologic[c] Risk Factors
Men (n=3190)					
Total stroke					
Low-strain job	5311	7	1 (Reference)	1 (Reference)	1 (Reference)
Active job	10 446	23	2.00 (0.86-4.67)	2.04 (0.86-4.81)	1.72 (0.73-4.05)
Passive job	9788	33	2.27 (0.99-5.20)	2.35 (1.02-5.43)	2.17 (0.93-5.06)
High-strain job	8808	28	2.62 (1.13-6.04)	2.73 (1.17-6.38)	2.53 (1.08-5.94)
Ischemic stroke					
Low-strain job	5311	4	1 (Reference)	1 (Reference)	1 (Reference)
Active job	10 446	17	2.62 (0.88-7.83)	2.43 (0.80-7.38)	2.14 (0.71-6.49)
Passive job	9788	25	2.93 (1.01-8.52)	2.89 (0.98-8.59)	2.76 (0.93-8.20)
High-strain job	8808	18	2.87 (0.96-8.57)	2.76 (0.91-8.39)	2.69 (0.89-8.16)
Hemorrhagic stroke					
Low-strain job	5311	3	1 (Reference)	1 (Reference)	1 (Reference)
Active job	10 446	6	1.18 (0.30-4.75)	1.23 (0.30-5.00)	1.12 (0.20-6.38)
Passive job	9788	8	1.38 (0.36-5.32)	1.33 (0.34-5.23)	1.28 (0.23-7.00)
High-strain job	8808	10	2.32 (0.63-8.57)	2.43 (0.64-9.21)	2.33 (0.46-11.90)
Women (n=3363)					
Total stroke					
Low-strain job	7440	11	1 (Reference)	1 (Reference)	1 (Reference)
Active job	10 498	15	1.15 (0.53-2.53)	1.18 (0.53-2.61)	1.17 (0.53-2.59)
Passive job	10 069	15	1.08 (0.49-2.35)	1.21 (0.54-2.72)	1.22 (0.54-2.74)
High-strain job	9026	15	1.25 (0.56-2.78)	1.47 (0.63-3.40)	1.46 (0.63-3.38)
Ischemic stroke					
Low-strain job	7440	5	1 (Reference)	1 (Reference)	1 (Reference)
Active job	10 498	9	1.89 (0.63-5.72)	2.02 (0.65-6.24)	1.99 (0.64-6.21)
Passive job	10 069	7	1.24 (0.39-3.94)	1.39 (0.42-4.63)	1.40 (0.42-4.68)
High-strain job	9026	5	1.28 (0.36-4.54)	1.42 (0.38-5.27)	1.38 (0.37-5.16)
Hemorrhagic stroke					
Low-strain job	7440	6	1 (Reference)	1 (Reference)	1 (Reference)
Active job	10 498	6	0.67 (0.21-2.09)	0.67 (0.21-2.16)	0.60 (0.18-1.94)
Passive job	10 069	8	0.96 (0.33-2.79)	1.00 (0.33-2.99)	0.95 (0.32-2.85)
High-strain job	9026	10	1.16 (0.41-3.26)	1.31 (0.42-4.03)	1.32 (0.43-4.12)

Abbreviation: CI, confidence interval.

[a]Sociodemographic risk factors include educational attainment (≤15 years [age at completion of compulsory education], 16-18 years [age at finishing senior high school], or ≥19 years [age at entering college or further education]) and occupation (5 strata: manager; professional, technician, or clerk; sales or service worker; farming, forestry, or fishery worker; and security, transportation, communications, or craft worker, laborer, or unclassified worker).

[b]Behavioral risk factors include smoking status (lifetime nonsmoker, ex-smoker, or current smoker), alcohol consumption (nondrinker, <28.9 g/d or ≥28.9 g/d), and physical activity index (≤28, 29-36, or ≥37).

[c]Biologic risk factors include body mass index (calculated as weight in kilograms divided by height in meters squared: <22, 22-24.9, or ≥25), hypertension, diabetes mellitus, and hypercholesterolemia.

were men with low-strain occupations. Men with active jobs had a higher level of physical activity than did men with passive jobs. Body mass index was lowest in men with passive jobs. Women with low-strain jobs were older and more obese than women with job strain. The relationship between psychosocial job characteristics and socioeconomic status of women was similar to that of men. Active jobs for women were associated with alcohol consumption and a high level of physical activity.

During the follow-up period, we identified 147 incident strokes: 91 in men and 56 in women. There were 90 ischemic strokes (64 in men and 26 in women), 33 intracerebral hemorrhages (21 in men and 12 in women), and 24 subarachnoid hemorrhages (6 in men and 18 in women). Due to the small number of cases in each category, we pooled intracerebral and subarachnoid hemorrhage cases into the category of hemorrhagic stroke.

Age- and area-adjusted hazard ratios showed that men with high-strain jobs had a more than 2-fold higher risk of total stroke than did men with low-strain jobs. Further adjustment for socioeconomic status and behavioral risk factors strengthened the associations. The hazard ratio for job strain decreased after biologic risk factors were added to the model but continued to be statistically significant. Multivariable analyses of stroke subtypes revealed that men with high-strain jobs had more than 2-fold higher risks of ischemic and hemorrhagic strokes than men with low-strain jobs, but the associations were not statistically significant due to large confidence intervals. Although women with high-strain jobs tended to have a higher risk of stroke than women with low-strain jobs, no statistically significant differences were found for any stroke incidence among the job characteristic categories for women (**Table 2**).

COMMENT

To our knowledge, the present study is the first to demonstrate a significant association between job strain and the risk of an incident stroke. A more than 2-fold increase in the risk of incident total stroke was found among men with high-strain jobs compared with men with low-strain jobs. The association remained statistically significant after adjustment for various conventional risk factors. The more than 2-fold higher risks of job strain for ischemic and hemorrhagic strokes suggested that the association between job strain and stroke was attributable to increased incidences of both subtypes, although the effects of job strain on the risks of these subtypes separately were uncertain due to the limited number of cases. Our evidence was based on the largest available Japanese cohort of its kind, and data were obtained in a standardized fashion. Information about exposure to job strain was obtained from self-reports with a validated instrument rather than by assigning scores based on job description. Hence, each score more accurately represents the individual work environment.[6] Diagnosis of stroke was ascertained by an independent committee using accepted diagnostic criteria. Self-reporting bias is unlikely to be important due to the hard end point and prospective study design, while bias attributable to sample attrition is thought to be implausible because the follow-up rate was high.

Most of the literature regarding job strain and cardiovascular diseases relates to white populations, with health outcomes fairly restricted to coronary heart diseases. Only large-scale prospective studies with aggregated job characteristics data have demonstrated associations between low job control and stroke mortality.[11,12] The relatively higher incidence of stroke among Japanese men may produce sufficient statistical power to detect associations that have not previously been well addressed. Differences in the predominant lesions and their pathologic condition, or the most attributable risk factors, between Japanese and white populations may provide other explanations for race/ethnicity differences. Lacunar infarcts and small intracerebral artery lesions appear to be important for stroke pathogenesis among Japanese populations, in contrast to the large-artery occlusive infarctions found in white populations.[19] Blood pressure appears more strongly associated with stroke in Asian populations, whereas dyslipidemia and a cholesterol-rich diet seem to be more strongly associated with stroke in white populations.[19,20]

Our findings did not show any statistically significant associations in women. Low statistical power among the women is obvious due to the limited number of outcome cases. The power analysis revealed that the minimal hazard ratio required to achieve statistical significance with 80% power among the women was around 2.5. Although this may be possible, it is hard to achieve based on the current literature.[6,7] Furthermore, the characteristics of our female sample indicate that further research is necessary in women. Specifically, the labor force participation rate of Japanese women is lower than that in Western societies and, therefore, with the exception of large enterprises, the attitudes of Japanese women toward work may be less proactive. In addition, the possible inclusion of part-time workers, most of whom are assumed to be women, may have affected the results.

We found that adjustments for biologic risk factors slightly attenuated the association between job strain and an incident stroke. These findings suggest that the association between job strain and cardiovascular diseases is mediated by the presence of 1 or more chronic diseases, such as obesity, hypertension, glucose intolerance, and dyslipidemia.[21] However, adjustments for such variables did not fully account for the associations between job strain and stroke. Other than the studied variables, possible mechanisms through which job strain leads to stroke may include poor adaptation to stress,[1,22] enhanced sympathetic activation,[22] and hemostatic or inflammatory conditions.[23]

The participants in this study were relatively older adults and thus a considerable number may have sustained a long career in the same job. Several studies regarding the association between job strain and cardiovascular disease risk have encountered the problem that many participants cease gainful employment during the follow-up period, such that exposure would have stopped and the associations become attenuated.[6] Around the time when the study population was recruited, the average retirement age of Japanese employees was 63 years,[24] but some workers in the cohort are thought to have retired later because of the rural study setting. A stratified analysis by age at the end of the follow-up ($\leq$63 or $>$63 years) showed elevated risks of job strain among both strata, but the association was stronger among men who were followed up until an older age ($\leq$63 years: age- and area-adjusted hazard ratio, 2.23; 95% confidence interval, 0.59-8.98; $>$63 years: 3.23; 1.09-9.59). Most subjects probably continued to work until an older age, and, therefore, would also have reached an age when there really is a risk of developing stroke (greater duration of exposure). Alternatively, the clinical manifestation could become overt after retirement due to the pathophysiological changes anticipated by job-strain exposure during their working life. Because we did not capture the exact length of job-strain exposure or the actual retirement age, these hypotheses need to be examined in a future study.

The study population was composed of relatively healthy Japanese adults. The mass screening examination program is not mandatory and employees who undergo health checks at their workplaces do not have to participate. Thus, participants may have a more health-oriented predisposition than do nonparticipants. Furthermore, the invitation to participate in screenings did not insist that those receiving care for cardiovascular diseases sign up. All these conditions probably accounted for the small number of outcome events.[13] In addition, the relatively low response rate may imply that those with the worst work conditions chose to opt out of the study. The age-adjusted incidence rates for total stroke per 100 000 population (calculated using the Japanese employed population in 1995 as the standard population) were 229.7 for men and 107.4 for women, and slightly lower than those of a contemporary community-based cohort that used the comprehensive stroke registration system (268.7 for men and 167.5 for women).[25] These findings may indicate that our ob-

servations reflect a profile of stroke incidence among community-dwelling Japanese workers. Nevertheless, because underrepresentation of those with access to occupational health care limits the ability to generalize the findings, future replication is needed among representative samples of employed workers.

The Cronbach α coefficient of job control was somewhat low, and our exposure assessment was limited to 1 point in time; both of these aspects probably caused associations toward the null. As with all observational studies, residual and unmeasured confounders remain an alternative explanation for our findings. For example, employment status (full-time vs part-time) and income level were not measured. Furthermore, the prevalence of negative emotions, such as depression, was not ascertained at baseline. However, recent studies indicate that the impact of a tendency toward negative affectivity should not be overstated.[26]

In conclusion, job strain was associated with incident stroke among Japanese men. Because modification of work structures based on the job demand–control model can be useful for stress reduction, our study has implications regarding the prevention of incident strokes among male workers.

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Cornell Product Left Ventricular Hypertrophy in Electrocardiogram and the Risk of Stroke in a General Population

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Abstract—Left ventricular hypertrophy (LVH), assessed by ECG, is associated with an increased risk for cardiovascular events among hypertensive subjects. We evaluated the risks of LVH in a Japanese general population including normotensive and prehypertensive subjects. We measured ECG and blood pressure in 10 755 subjects at baseline. The Cornell product (CP) and Sokolow-Lyon (SL) voltage were calculated as markers of LVH (CP ≥2440 mm×ms and SL voltage ≥38 mm). Follow-up was performed for 10 years, and the incidence of stroke and myocardial infarction was evaluated. The prevalence of CP-LVH was 2.7% for normotensives, 5.2% for prehypertensives, and 11.0% for hypertensives, and the prevalence of SL-LVH was 5.0%, 8.2%, and 15.2%, respectively. In all of the subjects, CP-LVH and SL-LVH were both predictors of stroke (CP-LVH: hazard risk: 1.62, 95% CI: 1.19 to 2.20, $P=0.002$; SL-LVH: hazard risk: 1.29, 95% CI: 0.98 to 1.71, $P=0.07$) after adjustment for confounding factors but were not predictors of myocardial infarction. The adjusted hazard ratio of CP-LVH predicting stroke was especially high in the normotensives (hazard risk: 7.53; 95% CI: 3.39 to 16.77). In the normotensives, diabetes mellitus and hyperlipidemia were significant determinants of CP-LVH but not of SL-LVH. In all of the hypertensive subgroups (normotensives, prehypertensives, and hypertensives), the c-statistic for the equation predicting stroke increased when CP-LVH was added to the model but not when SL-LVH was added. In conclusion, both CP-LVH and SL-LVH are risk factors for stroke in the Japanese general population. CP-LVH is related to glucose abnormality, and its predictive value for stroke is seen even in normotensives and prehypertensives. (***Hypertension.* 2009;53:00-00.**)

Key Words: Cornell product ■ left ventricular hypertrophy ■ stroke event ■ cohort study

Left ventricular hypertrophy (LVH), a measure of hypertensive target organ damage in the heart, has been reported to be associated with increased morbidity and mortality.[1,2] LVH can be evaluated by echocardiography (Echo) and/or a 12-lead ECG. LVH defined by ECG (ECG-LVH) has been evaluated using standard voltage criteria reported by Sokolow and Lyon (SL)[3] and more recently using the Cornell product (CP) criteria.[4] LVH detected by CP (CP-LVH) is reported to have a higher sensitivity for the presence of LVH evaluated by echocardiography (Echo-LVH) than the Sokolow-Lyon criteria (SL-LVH).[5] CP-LVH and SL-LVH were independently associated with Echo-LVH[6] and with stroke events, cardiovascular morbidity, and mortality[7] in subjects with essential hypertension. These data show that evaluation of CP-LVH is beneficial in Western hypertensive subjects; however, in Japanese populations, the incidence of stroke is higher than that of ischemic heart disease,[8] and there are no data on the cardiovascular risk in Japanese subjects with CP-LVH.

In addition, hypertension is the major cause of LVH, and the cardiovascular risks in normotensive and prehypertensive subjects with CP-LVH and/or SL-LVH remain unknown. It is reported that hypertensive patients with diabetes mellitus have a higher prevalence and greater severity of LVH than those without diabetes mellitus.[9,10] Okin et al[11] reported that diabetes mellitus, per se, attenuates the regression of hypertensive LVH during antihypertensive treatments. However, there are no data examining whether cardiovascular risk factors such as diabetes mellitus might contribute to an increase of ECG-LVH in normotensive subjects or whether LVH in normotensive and prehypertensive subjects can be a risk factor for cardiovascular events.

The purpose of the present study was to evaluate the cardiovascular risks of CP-LVH and SL-LVH in the Japanese

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general population and to explore the differences in backgrounds and prognostic factors that predict the presence of CP-LVH and SL-LVH, especially in normotensive and prehypertensive subjects.

Methods

Subjects

The Jichi Medical School Cohort Study was begun in 1992, with the primary aim of clarifying the risk factors for cardiovascular and cerebrovascular diseases in the Japanese general population. The details of the protocol of the Jichi Medical School Cohort Study have been reported previously.[12] Baseline data were collected between April 1992 and July 1995 in 12 rural districts using a government-sponsored mass screening system. In each community, a local government office sent personal invitations by mail to all of the subjects in accordance with the health and medical service law for the aged. The subjects for the mass screening examinations were residents aged 40 to 69 years in 8 areas (Iwaizumi, Tako, Kuze, Sakuma, Sakugi, Okawa, Ainoshima, and Akaike). Subjects included those aged ≥30 years in 1 area (Wara), and other age groups were also included in 3 areas (Hokudan, Yamato, and Takasu). The total number of subjects in the Jichi Medical School Cohort Study at baseline was 12 490 (4911 men and 7579 women). The participation rate varied in each community (26.0% to 90.0%), and the overall participation rate of those invited to the mass screening examination program was 65.4%.[13]

ECG Measurement and Interpretation

ECG was measured at a paper speed of 25 mm/s, at a gain of 10 mm/mV (or 5 mm/mV), using ECG devices that the institutes had (FCP130-A9, FCP145-M4, and FCP270-M5, Fukuda Denshi, etc). A trained person, who did not know the subjects' backgrounds, measured ECGs at a central laboratory using a ruler with 0.01-mm graduations. Both SL voltage (SV1+RV5) and Cornell voltage (RaVL+SV3, with 6 mm added for women)[4,5] were measured. QRS duration was measured manually from lead II (or lead I or III if the measurement of QRS duration was difficult from lead II) on a single heart beat. CP was calculated as the product of Cornell voltage times QRS duration afterward. SL-LVH was defined as ≥38 mm (3.8 mV), and CP-LVH was defined as 2440 mm×ms according to a previous report of the Losartan Intervention for Endpoint Reduction in Hypertension Study.[7]

Questionnaire and Other Measurements

Information about medical history and lifestyle was obtained with a questionnaire at baseline. Age is the value at baseline. Smoking status was reported as current smoker, ex-smoker, or never smoked. Alcohol drinkers were defined as those who were reported consuming ≥20 g/d. Body mass index (BMI) was calculated as weight (kilograms)/height (meters squared). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline were measured using a fully automated and validated upper arm cuff-oscillometric device, the BP203RV-II (Nippon Colin).[14] Blood pressure was measured once after resting for ≥5 minutes while seated. Hypertension was defined as either a SBP/DBP of ≥140/90 mm Hg or taking antihypertensive medications. Prehypertension was defined as SBP/DBP 120/80 to 139/89 mm Hg. Normotension was defined as SBP/DBP <120/80 mm Hg. Diabetes mellitus was defined by a fasting glucose level ≥7.0 mmol/L (126 mg/dL), a casual glucose level >11.1 mmol/L (200 mg/dL), or the use of an oral hypoglycemic agent or insulin. Impaired fasting glucose was defined as a fasting glucose level of 110 to 125 mg/dL. Hyperlipidemia was defined as a total cholesterol level ≥5.7 mmol/L (220 mg/dL), a triglyceride level ≥1.7 mmol/L (150 mg/dL), or the use of an oral lipid-lowering agent, according to the Japanese Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases.

Informed Consent

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained individually from all of the subjects during the mass screening examination health checkup.

Follow-Up and Diagnostic Criteria

The mass screening examination system was used to check the subjects every year for 10 years. The details of follow-up are shown in the online supplemental data file (please see http://hyper.ahajournals.org). The diagnosis was determined independently by an end points committee, which included radiologists, neurologists, and cardiologists, in accordance with the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease Project.[15] The details of diagnostic criteria are also shown in the online supplemental data file.

Statistical Analysis

Among the 12 490 subjects who were initially enrolled in the Jichi Medical School Cohort Study, we analyzed 10 755 subjects who had adequate follow-up, after excluding 1735 subjects with no ECG recording (n=1285), immeasurable ECG findings (n=28), complete left bundle branch block (n=20), complete right bundle branch block (n=189), atrial fibrillation (n=53), or no blood pressure data (n=160).

Data are shown as means±1 SDs for continuous variables and as percentages for dichotomous variables. Differences in characteristics between subjects with and without CP-LVH and SL-LVH were evaluated using Student *t* test or χ^2 test. Because the prevalence of LVH varied among the hypertensive subgroups (normotension, prehypertension, and hypertension), we performed analyses of characteristics of the subjects with CP-LVH in the hypertensive subgroups. Determinants of CP-LVH and SL-LVH in all of the subjects and separately for each hypertensive subgroup were evaluated using multivariate logistic regression analysis including age, gender, BMI, smoking status, alcohol drinking, SBP, antihypertensive medication use (only in the hypertensives), presence of hyperlipidemia, and status of diabetes mellitus. The incidence risks of stroke and myocardial infarction in both unadjusted models and those adjusted for significant covariates were evaluated using Cox regression analysis in the total sample and separately for each hypertension subgroup. The c-statistic was calculated, according to the method of Pencina and D'Agostino,[16] for the baseline model that included the unmodifiable cardiovascular risk factors (age and gender) and then for a series of models in which each cardiovascular risk factor was added separately to the baseline model. Computer software SPSS 16.0 (SPSS Inc) and SAS 9.1 (SAS Institute) were used for the analysis, and a *P* value <0.05 was considered statistically significant.

Results

Study Subjects

The mean age was 55.6±11.2 years (men: 37.8%). The average SBP/DBP was 130±21/78±12 mm Hg. The percentages of subjects with normotension, prehypertension, and hypertension were 32.9%, 32.6%, and 34.5%, respectively. The characteristics of the study subjects were as follows: history of stroke, 1.0%; history of myocardial infarction, 0.5%; antihypertensive medication use, 11.1%; former smoker, 12.4%; current smoker, 21.8%; alcohol drinker, 27.6%; hyperlipidemia, 35.3%; impaired fasting glucose, 2.5%; and diabetes mellitus, 3.6%. The prevalences of CP-LVH and SL-LVH in the full sample were 6.4% were 9.5%, respectively.

Table 1. Characteristics of Subjects With/Without CP-LVH and SL-LVH

	CP >2440 mm×ms			SL Voltage ≥38 mm		
Characteristic	LVH (−) (N=10 069)	LVH (+) (N=686)	*P*	LVH (−) (N=9723)	LVH (+) (N=1027)	*P*
Age, y	55.4±11.2	58.7±9.7	<0.001	55.3±11.2	57.8±10.4	<0.001
Male, %	38.0	35.0	0.12	35.2	62.0	<0.001
BMI, kg/m^2	23.1±3.1	23.9±3.4	<0.001	23.2±3.1	22.8±2.9	<0.001
Smokers			0.13			<0.001
Former, %	12.8	11.3		12.1	18.6	
Current, %	22.6	20.2		21.4	32.9	
Alcohol drinkers, %	27.7	26.1	0.36	27.7	26.4	0.36
History of stroke, %	0.9	2.2	0.002	0.9	2.3	<0.001
History of myocardial infarction, %	0.5	0.8	0.33	0.5	0.9	0.056
Hypertension, %	33.7	61.1	<0.001	33.3	56.2	<0.001
Antihypertensive therapy, %	10.6	25.5	<0.001	10.7	19.9	<0.001
SBP, mm Hg	129±21	141±22	<0.001	128±21	140±23	<0.001
DBP, mm Hg	77±12	83±13	<0.001	77±12	83±13	<0.001
Hyperlipidemia, %	35.0	43.2	<0.001	35.8	32.7	0.049
Total cholesterol, mg/dL	192±35	196±34	0.004	193±35	188±35	<0.001
Triglyceride, mg/dL	116±76	131±77	<0.001	117±77	115±68	0.41
Status of diabetes			0.056			0.078
Impaired fasting glucose, %	2.5	3.1		2.4	3.5	
Diabetes, %	3.5	5.1		3.6	3.2	
Blood glucose, mg/dL	103±26	112±34	<0.001	103±27	106±26	<0.001
SL-LVH, %	8.8	21.3	<0.001	. . .	. . .	. . .
CP-LVH, %	. . .	. . .	. . .	5.6	14.2	<0.001

CP-LVH indicates LVH defined by CP (≥2440 mm×ms); SL-LVH, LVH defined by SL (≥38 mm); . . ., no data. *P* values were calculated using Student *t* test or χ^2 test. *P* value <0.05 was considered statistically significant.

Characteristics and Determinants of CP-LVH and SL-LVH in All Subjects

Comparisons of subjects with and without CP-LVH and SL-LVH are shown in Table 1. Subjects with CP-LVH and those with SL-LVH were older and had a higher prevalence of hypertension and antihypertensive medication use; however, there were differences in characteristics such as gender, BMI, and hyperlipidemia, and diabetes mellitus depended on whether we grouped subjects by CP-LVH or SL-LVH.

In all of the subjects, significant determinants of both CP-LVH and SL-LVH were SBP (CP-LVH: odds ratio [OR]: 1.20 per 10 mm Hg, 95% CI: 1.15 to 1.25; SL-LVH: OR: 1.26 per 10 mm Hg, 95% CI: 1.21 to 1.30) and antihypertensive medication use (CP-LVH: OR: 1.79, 95% CI: 1.45 to 2.20; SL-LVH: OR: 1.71, 95% CI: 1.41 to 2.08). Additional determinants of only CP-LVH were age (OR: 1.16 per 10 years; 95% CI: 1.07 to 1.27) and higher BMI (OR: 1.03 per 1 kg/m^2; 95% CI: 1.00 to 1.06) and of only SL-LVH were male gender (OR: 3.00; 95% CI: 2.47 to 3.65) and lower BMI (OR: 0.92 per 1 kg/m^2; 95% CI: 0.89 to 0.93).

Characteristics and Determinants of Subjects With CP-LVH and SL-LVH in the Hypertensive Groups

The characteristics of subjects with and without CP-LVH and those with and without SL-LVH in the 3 hypertensive subgroups (normotensives, prehypertensives, and hypertensives) are shown in the online supplemental data file (Tables S1 and S2).

In the normotensives, the significant determinants of both CP-LVH and SL-LVH were male gender (CP-LVH: OR: 2.15, 95% CI: 1.22 to 3.78; SL-LVH: OR: 3.55, 95% CI: 2.30 to 5.48) and lower BMI (CP-LVH: OR: 0.90 per 1 kg/m^2, 95% CI: 0.83 to 0.98; SL-LVH: OR: 0.93 per 1 kg/m^2, 95% CI: 0.87 to 0.99). The additional determinants of only CP-LVH were nonsmokers (ex-smokers: OR: 0.45, 95% CI: 0.24 to 0.87; current smokers: OR: 0.24, 95% CI: 0.09 to 0.66), the presence of hyperlipidemia (OR: 1.66; 95% CI: 1.05 to 2.61), and diabetes mellitus (OR: 3.26; 95% CI: 1.24 to 8.53), and that of only SL-LVH was age (OR: 1.15 per 10 years; 95% CI: 1.01 to 1.32).

In the prehypertensives, the significant determinants of both CP-LVH and SL-LVH were SBP (CP-LVH: OR: 1.38 per 10 mm Hg, 95% CI: 1.07 to 1.79; SL-LVH: OR: 1.27 per 10 mm Hg, 95% CI 1.03 to 1.57). The significant determinant of only CP-LVH was age (OR: 1.22 per 10 years; 95% CI: 1.04 to 1.42), and those of only SL-LVH were male gender (OR: 2.88; 95% CI: 2.00 to 4.14) and lower BMI (OR: 0.90 per 1 kg/m^2; 95% CI: 0.86 to 0.95).

In the hypertensives, the significant determinants of both CP-LVH and SL-LVH were antihypertensive medication use (CP-LVH: OR: 1.51, 95% CI: 1.20 to 1.89; SL-LVH: OR: 1.59, 95% CI: 1.28 to 1.96) and SBP (CP-LVH: OR: 1.07 per

Table 2. Incidence of Stroke and Myocardial Infarction in Subjects With CP-LVH and SL-LVH

	Stroke (N=391)						Myocardial Infarction (N=79)					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
Characteristic	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Total samples												
CP-LVH	2.25	1.67 to 3.05	<0.001	1.62	1.19 to 2.20	0.002	0.55	0.17 to 1.76	0.32	0.43	0.14 to 1.39	0.16
SL-LVH	1.93	1.47 to 2.54	<0.001	1.29	0.98 to 1.71	0.07	2.80	1.61 to 4.89	<0.001	1.53	0.86 to 2.75	0.15
Hypertensive subgroups												
Normotensives												
CP-LVH	7.48	3.48 to 16.07	<0.001	7.65	3.40 to 17.21	<0.001	0.00	. . .	0.99	0.00	. . .	0.99
SL-LVH	1.32	0.47 to 3.69	0.60	0.89	0.30 to 2.60	0.82	6.65	1.34 to 32.97	0.020	2.96	0.47 to 18.56	0.25
Prehypertensives												
CP-LVH	1.47	0.64 to 3.41	0.37	1.39	0.60 to 3.23	0.45	0.00	. . .	0.98	0.00	. . .	0.99
SL-LVH	1.83	0.96 to 3.48	0.066	1.66	0.86 to 3.17	0.13	1.47	0.34 to 6.37	0.61	1.52	0.34 to 6.77	0.59
Hypertensives												
CP-LVH	1.43	1.00 to 2.05	0.047	1.38	0.97 to 1.98	0.076	0.52	0.16 to 1.69	0.28	0.53	0.16 to 1.73	0.29
SL-LVH	1.50	1.09 to 2.05	0.012	1.23	0.89 to 1.69	0.22	2.06	1.07 to 3.97	0.031	1.50	0.76 to 2.98	0.24

CP-LVH indicates left ventricular hypertrophy defined by CP (≥2440 mm×ms); SL-LVH, LVH defined by SL (≥38 mm); . . ., no data. HR and 95%CI were calculated using Cox regression analysis including CP-LVH and SL-LVH together. Adjusted model includes covariates age, gender, body mass index, history of stroke, history of myocardial infarction, alcohol drinking >20 g/d, status of smoking, SBP, antihypertensive medication use, presence of hyperlipidemia, and status of diabetes mellitus.

10 mm Hg, 95% CI: 1.01 to 1.14; SL-LVH: OR: 1.17 per 10 mm Hg; 95% CI: 1.11 to 1.24). The significant determinants of only CP-LVH were female gender (male: OR: 0.68; 95% CI: 0.49 to 0.95) and higher BMI (OR: 1.04 per 1 kg/m^2; 95% CI: 1.00 to 1.07), and those of only SL-LVH were male gender (OR: 2.82; 95% CI: 2.14 to 3.71), lower BMI (OR: 0.91 per 1 kg/m^2; 95% CI: 0.88 to 0.94), nonsmokers (current smokers: OR: 0.71; 95% CI: 0.51 to 0.99), and absence of impaired fasting glucose or diabetes mellitus (diabetes: OR: 0.53; 95% CI: 0.33 to 0.86).

Follow-Up

We followed up the subjects for an average of 127.5±30.3 months (total: 114 270 person-years). There were 391 clinical stroke events (cerebral hemorrhage: n=91; cerebral infarction: n=252; subarachnoid hemorrhage: n=47; and unknown: n=1) and 79 myocardial infarction events. In separate Cox hazard models, both CP-LVH (hazard ratio [HR]: 1.67; 95% CI: 1.23 to 2.26; *P*=0.001) and SL-LVH (HR: 1.35; 95% CI: 1.02 to 1.78; *P*=0.035) were significant risk factors for stroke after adjustment for the following potential confounding factors: age, gender, BMI, history of stroke, history of myocardial infarction, smoking status, alcohol drinking, antihypertensive medication use, SBP level, presence of hyperlipidemia, and status of diabetes mellitus. The results of Cox regression analyses that included CP-LVH and SL-LVH together are shown in Table 2. In the total sample, CP-LVH and SL-LVH were both significant predictors of stroke risk in the unadjusted model; CP-LVH, but not SL-LVH, remained a significant predictor after adjustment for the confounding factors. In the unadjusted Cox regression analysis predicting myocardial infarction, SL-LVH was associated with an increased risk, whereas CP-LVH was not. However, the increased risk for subjects with SL-LVH disappeared after adjustment for the confounding factors (Table 2). When we divided the subjects into 4 groups based on presence/absence of CP-LVH and SL-LVH, the incidence of stroke was significantly higher in subjects with CP-LVH alone and those with both CP-LVH and SL-LVH compared to those with neither CP-LVH nor SL-LVH (Figure 1), and SL-LVH increased the risk for stroke in addition to CP-LVH.

Incidence of Stroke in Subjects With CP-LVH and SL-LVH in the Hypertension Subgroups

The incidences of stroke in subjects with CP-LVH and those with SL-LVH in the 3 hypertension subgroups are shown in Figure 2. In the normotensives, the incidence of stroke was

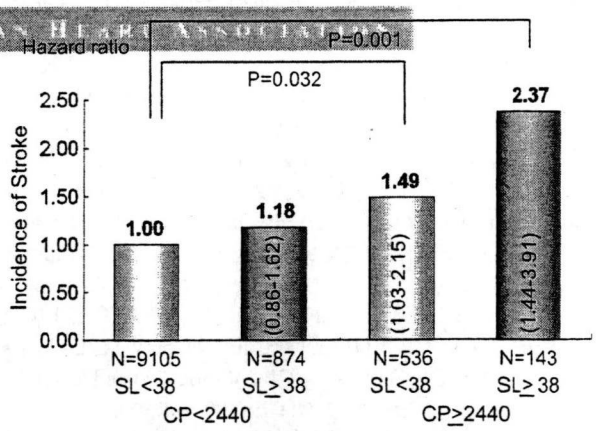

Figure 1. Incidence of stroke in subjects with either or both CP-LVH and SL-LVH (total samples). Adjusted HR was estimated using Cox regression analysis after adjustment for known covariates: age, gender, BMI, smoking status and alcohol drinking, history of stroke, history of myocardial infarction, status of diabetes mellitus, presence of hyperlipidemia, SBP, and antihypertenisve medication use.

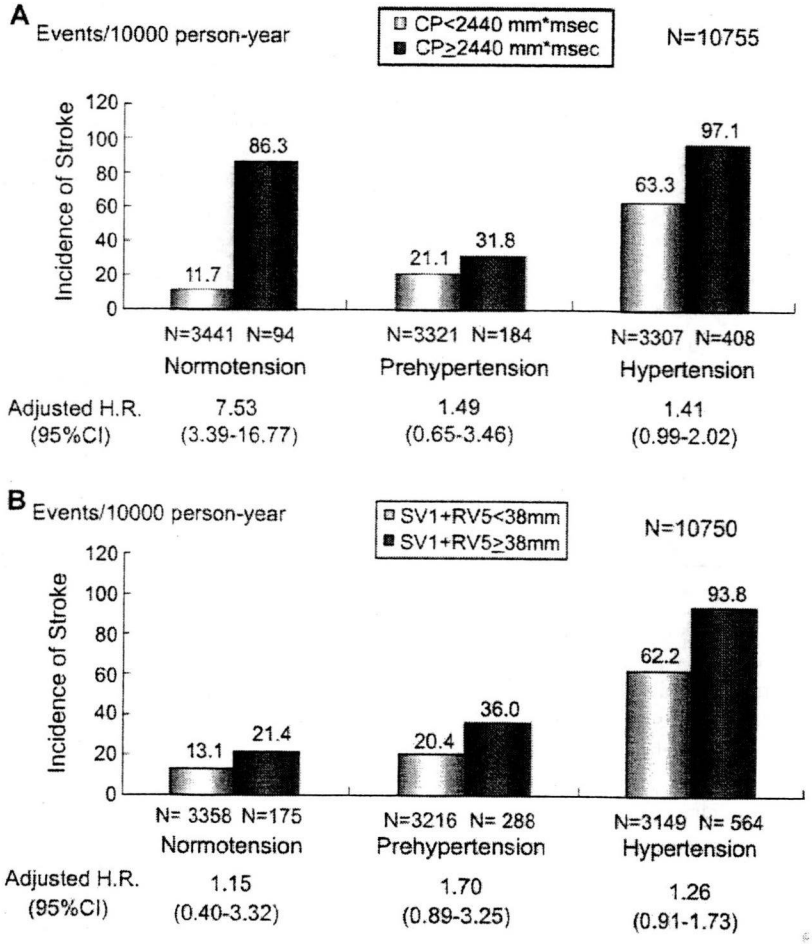

Figure 2. Incidence of stroke in subjects with CP-LVH (A) and in subjects with SL-LVH (B) by hypertension subgroup. Adjusted HRs of subjects with CP-LVH (vs those without CP-LVH) and of subjects with SL-LVH (vs those without SL-LVH) in each hypertension subgroup were calculated using Cox regression analysis after adjustment for known covariates: age, gender, BMI, smoking status and alcohol drinking, history of stroke, history of myocardial infarction, status of diabetes mellitus, presence of hyperlipidemia, and SBP.

higher in subjects with CP-LVH than in those with SL-LVH, although it was similar for subjects with CP-LVH and SL-LVH within prehypertensives and hypertensives. In separate Cox regression analyses for the 3 groups, the HR for stroke events in subjects with CP-LVH was higher in the normotensives (HR: 7.53; 95% CI: 3.39 to 16.77) than in the prehypertensives (HR: 1.49; 95% CI: 0.65 to 3.46) and hypertensives (HR: 1.41; 95% CI: 0.99 to 2.02; Figure 2A), after adjustment for age, gender, BMI, smoking status and alcohol drinking, history of stroke, history of myocardial infarction, diabetes mellitus status, hyperlipidemia, and SBP. However, the HR for stroke events in subjects with SL-LVH was not a significant predictor of stroke in subjects for any of the hypertensive groups (normotensives: HR: 1.15, 95% CI: 0.40 to 3.32; prehypertensives: HR: 1.71, 95% CI: 0.89 to 3.25; hypertensives: HR: 1.26, 95% CI: 0.91 to 1.73; Figure 2B).

C-Statistics of LVH for Predicting Stroke Event in Hypertensive Groups

The c-statistics for the models that separately contain ECG-LVH and each of the other cardiovascular risk factors for the Cox regression models predicting stroke in hypertensive groups are shown in Table 3. The inclusion of CP-LVH increased the c-statistic in all of the hypertensive groups, but the inclusion of SL-LVH did not. Inclusion of CP-LVH resulted in similar c-statistic values to that of status of diabetes mellitus in prehypertensives and resulted in the highest c-statistic value in normotensives.

Discussion

Both CP-LVH and SL-LVH were risk factors for the incidence of stroke in the Japanese general population. Screening of ECG using CP-LVH, in addition to SL-LVH, is beneficial for detecting individuals who are at high risk for stroke. The predictive value of CP-LVH was seen even in normotensive subjects, where those with CP-LVH were more likely to have hyperlipidemia and diabetes mellitus. In normotensive subjects, the presence of CP-LVH is the strongest predictor of future stroke events compared with the conventional cardiovascular risk factors. In addition, in prehypertensive subjects, for whom antihypertensive medication is controversial, the presence of CP-LVH independently predicted stroke as did the status of diabetes mellitus, history of stroke, history of myocardial infarction, and smoking status.

CP-LVH and SL-LVH were related to different risk factors, although they were both ECG markers of LVH. Okin et al[17] reported in hypertensive patients for whom the presence of CP-LVH was predominantly associated with higher BMI, whereas SL-LVH was predominantly related to lower BMI and male gender. The determinants of CP-LVH in the present study of community-dwelling Japanese individuals were sim-

Table 3. C-Statistics of Presence ECG-LVH for Stroke Event in Hypertensive Groups

	Normotensives			Prehypertensives			Hypertensives		
Variable	C-statistics	95% CI		C-statistics	95% CI		C-statistics	95% CI	
Baseline model									
Age and gender	0.808	0.799	0.817	0.737	0.729	0.744	0.688	0.680	0.696
Added variables									
History of stroke	0.819	0.810	0.827	0.742	0.734	0.749	0.694	0.686	0.702
History of myocardial infarction	0.809	0.800	0.818	0.739	0.732	0.747	0.688	0.680	0.696
BMI	0.811	0.803	0.820	0.737	0.730	0.745	0.687	0.679	0.695
Smoking	0.808	0.799	0.816	0.744	0.736	0.752	0.690	0.682	0.698
Alcohol intake >20 g/d	0.809	0.800	0.817	0.737	0.729	0.744	0.686	0.678	0.694
Hyperlipidemia	0.807	0.798	0.815	0.737	0.729	0.745	0.687	0.679	0.695
Status of diabetes mellitus	0.818	0.810	0.827	0.740	0.733	0.748	0.693	0.686	0.701
SBP	0.813	0.804	0.821	0.737	0.729	0.745	0.690	0.682	0.698
Presence of SL-LVH	0.808	0.799	0.817	0.735	0.728	0.743	0.688	0.680	0.696
Presence of CP-LVH	0.820	0.812	0.828	0.740	0.732	0.747	0.693	0.685	0.701

ilar to the results in the Losartan Intervention for Endpoint Reduction in Hypertension Study (hypertensive subjects).[17]

CP-LVH was related to metabolic factors (hyperlipidemia and diabetes mellitus), especially in normotensive subjects, but SL-LVH was not. Okin et al[6] reported that abnormal left ventricular geometry was more common in patients with only CP-LVH than in patients with only SL-LVH, and Shirai et al[18] reported that CP-LVH is a better marker of relative wall thickness (RWT) than SL-LVH. We reported previously that hypertensive patients with type 2 diabetes mellitus had greater RWT (but not increased left ventricular mass index) than those without diabetes mellitus.[19] Therefore, CP-LVH might reflect increased RWT related to diabetes mellitus. In diabetic patients, RWT is a better marker of cardiovascular events than left ventricular mass index,[20] and the higher predictive value of CP-LVH for stroke might be derived from that of diabetes-associated RWT. It is reported that protein glycation can cause myocardial damage in diabetes mellitus, and receptor binding of advanced glycation products induces proinflammatory cytokines, inflammation, growth factor release, and fibrosis.[21] On the other hand, the presence of diabetes mellitus was a negative predictor of SL-LVH in the hypertensive group of the present study. Diabetic subjects are more often overweight, which can reduce the SL product and, thus, SL-LVH on ECG. SL-LVH was more strongly associated with hypertension than with metabolic factors such as diabetes mellitus and hyperlipidemia compared with CP-LVH.

Evaluation of both CP-LVH and SL-LVH may be useful for detecting subjects at an increased risk of stroke events. The subjects with both CP-LVH and SL-LVH had an increased risk for stroke (Figure 1). In the present study, the predictive value of SL-LVH for stroke lost the significance when we adjusted for CP-LVH and conventional risk factors (Table 2); however, the risks of both CP-LVH and SL-LVH were significant when we preformed a parallel analysis excluding the subjects with history of stroke and myocardial infarction (data not shown).

In prehypertensives, the c-statistic increased when CP-LVH, history of stroke, history of myocardial infarction, status of diabetes, and smoking were each added to a baseline model that included only age and gender; however, the c-statistic did not increase when SBP was added. Therefore, a prehypertensive with these risk factors should be monitored cautiously and may be a candidate for lifestyle modification (especially cessation of smoking and glycemic control if needed). Moreover, CP-LVH was the strongest predictor of stroke in normotensives. Evaluation of CP-LVH may be useful for detecting normotensive diabetic subjects at greatest risk for stroke.

Study Limitations

The specificity of ECG-LVH for detecting Echo-LVH is higher than its sensitivity,[5] and it is difficult to apply the results of the present study to Echo-defined LVH. Okin et al[22] reported that the use of ECG-LVH for detecting increased left ventricular mass index varies by race. Sundstrom et al[23] reported that Echo-LVH and CP-LVH have independent predictive values for mortality. ECG-LVH ("electronic" LVH) is clearly an imperfect proxy measure of Echo-LVH (structural LVH) for the prediction of cardiovascular events. Finally, there are no data with which to determine whether the adjustment of Cornell voltage (6 mm) for women is appropriate for Japanese people.

Perspectives

Both CP-LVH and SL-LVH predicted future stroke in a Japanese population. The prediction of stroke by the CP-LVH is high even in normotensive subjects, in whom CP-LVH is related to the presence of diabetes mellitus and hyperlipidemia. In prehypertensives, CP-LVH predicts future stroke events, as do history of stroke, history of myocardial infarction, smoking status, and presence of diabetes mellitus.

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