Table 4. Characteristics of Subjects Stratified by the Presence or Absence of Prolonged QTc Interval and Cornell Product Left Ventricular Hypertrophy (n=10 643)

	ECG-LVH Absence			
	Prolonged QTc Interval Absence	Prolonged QTc Interval Presence	ECG-LVH Presence	
Variables	n=9841	n=131	n=671	*P* Value
Age, y	55.1±11.3	60.6±9.1*	58.6±9.7*	<0.001
Men, %	37.6	53.4	34.6	<0.001
Body mass index, kg/m^2	23.1±3.1	22.5±3.0	23.9±3.4*†	<0.001
Current smokers, %	22.7	28.1	19.9	0.086
Alcohol drinking, >20 g/d, %	32.0	27.7	32.1	0.624
Hypertension, %	32.1	45.0	58.4	<0.001
Antihypertensive medication use, %	10.2	11.1	24.4	<0.001
Systolic blood pressure, mm Hg	128.5±20.6	138.7±25.3*	140.5±21.7*	<0.001
Diastolic blood pressure, mm Hg	77.0±12.1	81.3±14.0*	83.4±12.5*	<0.001
Hyperlipidemia, %	35.3	31.0	44.8	<0.001
Total cholesterol, mg/dL	192.4±34.9	188.6±35.3	196.6±34.9*†	0.005
Triglyceride, mg/dL	116.3±76.3	116.3±73.7	132.0±77.9*	<0.001
Diabetes mellitus, %	3.7	2.4	5.5	0.058
Blood glucose, mg/dL	102.5±25.9	104.3±25.2	111.1±31.2*†	<0.001
Heart rate, bpm	66.7±10.6	79.9±15.6*	69.1±11.8*†	<0.001
Bazett QTc interval, ms	386±25	473±27*	400±28*†	<0.001
Cornell product, mV×ms	141.4±46.0	152.9±48.3*	286.0±52.3*†	<0.001
Sokolow–Lyon voltage, mV	2.6±0.8	3.1±1.1*	3.1±0.9*	<0.001

CP-LVH indicates left ventricular hypertrophy diagnosed by Cornell product ≥244 mV×ms; prolonged QTc interval, Bazett QTc interval ≥440 ms in men or ≥460 ms in women. Data are shown as mean±SD or percentage. *P* values were calculated using an ANCOVA test. Intergroup differences were calculated using Tukey honestly significant test. Values of $P<0.05$ were considered statistically significant. QTc, corrected QT.

*$P<0.05$ vs the subjects with neither CP-LVH or prolonged QTc interval presence.

†$P<0.05$ vs the subjects with CP-LVH absence and prolonged QTc interval presence.

subjects without ECG-LVH, which was diagnosed based on the Cornell product. The subjects with prolonged QTc intervals but not ECG-LVH exhibited an increased stroke risk compared with the subjects who had neither prolonged QTc intervals nor ECG-LVH, and the hazard risk was greater than that in the subjects with ECG-LVH. These results suggest that the prolonged QTc interval was associated with stroke risk even among patients without ECG-LVH.

Three previous studies have demonstrated that prolonged QTc intervals are associated with an increased risk of stroke: (1) Cardoso et al[1] detected this association in a Brazilian diabetic population, (2) Maebuchi et al[2] observed it in the general

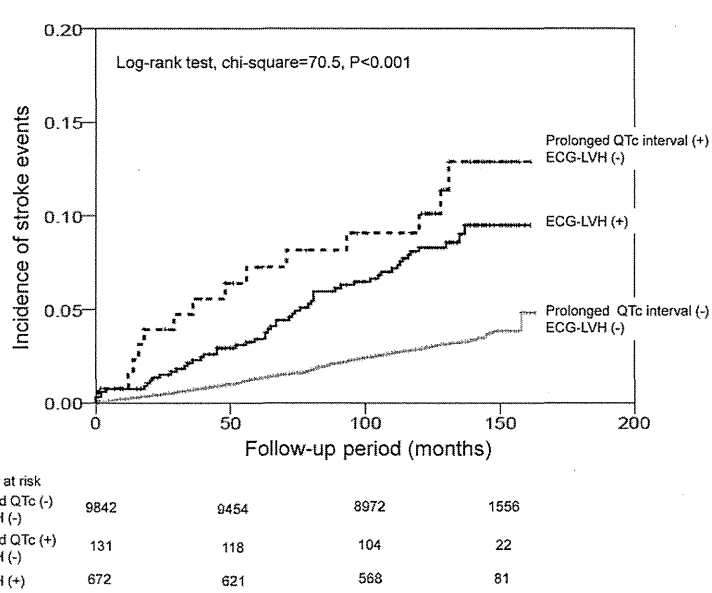

Figure 2. Kaplan–Meier plots of the cumulative incidence of stroke events among subjects stratified according to the presence of prolonged corrected QT (QTc) intervals and ECG-diagnosed left ventricular hypertrophy (LVH).

Table 5. Cox Regression Analysis for Stroke Among the Subjects Stratified by Prolonged QTc Interval and CP-LVH

			Unadjusted Model				Multivariate-Adjusted Model			
Models	No. of events	Incidence, %	HR	95% CI		*P* Value	HR	95% CI		*P* Value
Total stroke events										
Prolonged QTc interval (–) and ECG-LVH (–)	308	3.1	1.00	...	...	...	1.00	...	...	...
Prolonged QTc interval (+) and ECG-LVH (–)	14	10.7	4.13	2.31	7.38	<0.001	2.70	1.48	4.94	<0.001
ECG-LVH (+)	53	7.9	2.74	1.97	3.82	<0.001	1.83	1.31	2.57	<0.001
Cerebral hemorrhage										
Prolonged QTc interval (–) and ECG-LVH (–)	69	0.7	1.00	...	...	...	1.00	...	...	...
Prolonged QTc interval (+) and ECG-LVH (–)	3	2.3	4.78	1.49	15.29	<0.001	3.86	1.16	12.82	0.028
ECG-LVH (+)	13	1.9	2.79	1.37	5.65	<0.001	1.85	0.90	3.82	0.095
Ischemic stroke										
Prolonged QTc interval (–) and ECG-LVH (–)	200	2.0	1.00	...	...	...	1.00	...	...	...
Prolonged QTc interval (+) and ECG-LVH (–)	10	7.6	4.25	2.09	8.64	<0.001	2.53	1.20	5.35	0.015
ECG-LVH (+)	32	4.8	2.49	1.62	3.83	<0.001	1.65	1.07	2.56	0.024
Subarachnoid hemorrhage										
Prolonged QTc interval (–) and ECG-LVH (–)	39	0.4	1.00	...	...	...	1.00	...	...	...
Prolonged QTc interval (+) and ECG-LVH (–)	1	0.8	2.55	0.35	18.63	0.357	1.90	0.25	14.30	0.535
ECG-LVH (+)	7	1.0	3.38	1.49	7.65	0.003	2.38	1.03	5.53	0.043

HR and 95% CI were calculated using Cox hazard models. Age, sex, body mass index, alcohol drinking habit, smoking status, systolic blood pressure, antihypertensive medication use, presence of diabetes mellitus, and presence of hyperlipidemia were also entered in the multivariate-adjusted model. CI, confidence interval; CP-LVH indicates left ventricular hypertrophy diagnosed by Cornell product, >244 mV×ms; HR, hazard ratio; and QTc, corrected QT.

Japanese population, and (3) Soliman et al[3] found it in the general US population. In addition to supporting the findings of these previous studies, our results also suggest that a prolonged QTc interval is a predictor of future stroke events even in individuals without ECG-LVH.

In the analysis of NRI, adding the QTc interval as a continuous variable to the traditional cardiovascular risk factors that included ECG-LVH in the model improved the predictive value of stroke events; however, adding the prolonged QTc interval as a categorical variable did not increase the predictive value. There were no statistical differences in the propensity stroke risk score between the subjects with prolonged QTc interval but not ECG-LVH and those with ECG-LVH; therefore, the predictive value of prolonged QTc interval and ECG-LVH for stroke events did not differ significantly.

The mechanisms responsible for the association between prolonged QTc intervals and a greater risk of stroke events might involve increased arterial stiffness[14] because prolonged QTc intervals have also been reported to be a marker of increased carotid intima media thickness.[15] Therefore, the risk of subarachoid hemorrhage, which is susceptible to elevated blood pressure rather than atherosclerosis, might not be increased by prolonged QTc intervals, but it was increased by ECG-LVH. The QTc interval represents the time required for ventricular excitation and repolarization in the heart, but it was found to be related to stroke events rather than myocardial infarction in this study, probably because of the small number of myocardial infarction events experienced by our subjects (data not shown).

The relationship between prolonged QTc intervals and stroke events might be affected by heart rate. We used the Bazett formula to calculate QTc intervals in this study to make it possible to compare our results with those of a previous study involving a Japanese population.[2] Compared with other QTc interval formulas, such as the Fridericia and Framingham formulas, the Bazett formula is considered to be markedly affected by heart rate.[16] However, it was reported that the stroke risk associated with a prolonged QTc interval was not influenced by the formula used to calculate the interval,[3] and in this study, the relationship between prolonged QTc intervals and stroke events remained significant after adjusting for heart rate.

The QTc interval has also been reported to be associated with the incidence of atrial fibrillation,[17,18] a well-known risk factor for stroke events, and we previously reported that subjects who exhibited atrial fibrillation on ECG at the baseline were at an increased risk of stroke.[18] Therefore, we excluded subjects who displayed atrial fibrillation at the baseline from the present analysis. In addition, the incidence of atrial fibrillation during the follow-up period was not evaluated in this study.

This study had the following limitations: (1) we measured the subjects' QTc intervals manually using lead II (or lead I or III if it was difficult to measure using lead II). Although the mean QTc interval obtained in this study was shorter than that reported in previous studies involving Japanese patients who were referred to a university hospital[19] or a general Japanese population,[2] the Bazett QTc interval cutoff level that was found to be associated with a significantly increased risk of stroke was comparable to that described in a previous report.[2] (2) The QTc interval could be affected by drug use and electrolyte levels; however, these factors were not evaluated in this study. (3) We did not obtain the incidence of atrial fibrillation during the follow-up period.

Perspectives

In the general Japanese population, a prolonged QTc interval is associated with an increased risk of future stroke events even in subjects without ECG-LVH, as diagnosed using the Cornell product. The presence of a prolonged QTc interval on ECG could be a risk marker of future stroke events in subjects without ECG-LVH.

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Disclosures

None.

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Novelty and Significance

What Is New?

- We evaluated whether prolonged corrected QT (QTc) interval was associated with an increased risk of stroke without ECG left ventricular hypertrophy.

What Is Relevant?

- The prolonged QTc interval is not only a risk marker of fatal arrhythmia but also a marker of cardiovascular risk accumulation without ECG left ventricular hypertrophy.

Summary

The subjects with prolonged QTc interval had an increased risk of stroke without ECG left ventricular hypertrophy in the general population.

Online supplemental file

Title

Prolonged QTc interval is predictive of future stroke events even in subjects without electrocardiogram-diagnosed left ventricular hypertrophy

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Methods

Questionnaire and other measurements

Information about each subject's medical history and lifestyle was obtained at the baseline using a questionnaire. The questionnaire included questions about past and present illnesses, as well as any heart conditions suffered by the subjects' parents. The age data shown in this study represent baseline values. Smoking status was judged as current smoker or not. Alcohol drinkers were defined as subjects who drank at least 20 g alcohol/day. Body mass index was calculated as weight (kg)/height $(m)^2$. Systolic and diastolic blood pressure were recorded at the baseline using a fully automated sphygmomanometer (BP203RV-II Nippon Colin, Komaki, Japan). Blood pressure was measured once after the subject had rested for at least 5 minutes in a sitting position. Hypertension was defined as systolic blood pressure of $\geq$140 mmHg and/or diastolic blood pressure of $\geq$90 mmHg, or medicated hypertension. Diabetes mellitus was defined as a fasting glucose level of >7.0 mmol/L (126 mg/dl), a random non-fasting glucose level of >11.1 mmol/L (200 mg/dl), or the use of an oral hypoglycemic agent or insulin. Hyperlipidemia was defined as a total cholesterol level of >5.7 mmol/L (220 mg/dl), a triglyceride level of > 1.7 mmol/L (150 mg/dl), or the use of an oral lipid-lowering agent according to the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases.

Follow-up

The mass screening examination system was used to check the subjects every year for 10 years. During these examinations, we asked the subjects directly whether they had suffered a stroke or cardiovascular disease after being enrolled in the present study. If a

subject did not undergo a scheduled annual screening examination, we contacted them or their family by mail or phone to confirm whether they had suffered any cardiovascular events or died. In cases in which the subject had visited a medical institution due to a cardiovascular event or died at a medical institution, doctors or health nurses associated with the JMS Cohort study visited the institution and checked the subject's medical records. When an incident case was suspected, we filled out the appropriate forms and obtained copies of any brain computed tomography or magnetic resonance images (when a cerebrovascular event was suspected). In cases in which a subject died and their family could not be contacted during the follow-up period, death certificates were collected from public health centers with permission of the Agency of General Affairs and the Ministry of Health Labor and Welfare. Information regarding any changes in residence that occurred during the study was obtained from each municipal government annually.

Diagnostic criteria

Diagnoses were determined independently by a diagnosis committee composed of radiologists, neurologists, and cardiologists. Questionnaire responses and copies of the subjects' medical records were used to assess whether any of the following events had occurred: cardiac death, vascular death, stroke death, sudden death, non-fatal myocardial infarction, or non-fatal stroke events. The details of the definitions of stroke events have been reported previously[1].

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Table S1: Net reclassification improvement in the model with and without QTc interval (as a continuous variable)

Model without QTc interval	Stroke event Model with QTc interval			
Frequency Percentage	<2.5%	2.5-5.0%	>5.0%	Total
<2.5%	41	2	0	43
	91.1	3.4	0.0	
2.5-5.0%	4	51	11	66
	8.9	87.9	5.7	
>5.0%	0	5	183	188
	0.0	8.6	94.3	
Total	45	58	194	297

Model without QTc interval	No stroke event Model with QTc interval			
Frequency Percentage	<2.5%	2.5-5.0%	>5.0%	Total
<2.5%	4401	162	2	4565
	95.5	9.2	0.1	
2.5-5.0%	205	1384	165	1754
	4.5	78.2	9.3	
>5.0%	0	224	1613	1837
	0.0	12.7	90.6	
Total	4606	1770	1780	8156

Categorical net reclassification improvement (NRI) = 0.026, P<0.001
Integrated discrimination improvement (IDI) = 0.292, P=0.80

Table S2: Net reclassification improvement in the model with and without ECG-LVH

Model without ECG-LVH	Stroke event Model with ECG-LVH			
Frequency Percentage	<2.5%	2.5-5.0%	>5.0%	Total
<2.5%	41	2	0	43
	95.3	3.2	0.0	14.5
2.5-5.0%	2	56	8	66
	4.7	88.9	4.2	22.2
>5.0%	0	5	183	188
	0.0	7.9	95.8	63.3
Total	43	63	191	297

Model without ECG-LVH	No stroke event Model with ECG-LVH			
Frequency Percentage	<2.5%	2.5-5.0%	>5.0%	Total
<2.5%	4495	70	0	4565
	97.6	4.0	0.0	56.0
2.5-5.0%	110	1551	93	1754
	2.4	88.3	5.2	21.5
>5.0%	0	135	1702	1837
	0.0	7.7	94.8	22.5
Total	4605	1756	1795	8156

Categorical net reclassification improvement (NRI) = 0.020, P<0.001
Integrated discrimination improvement (IDI) = 0.004, P=0.75

Table S3: Net reclassification improvement in the model with and without ECG-LVH and/or QTc interval

Model without ECG-LVH or QTc interval	Stroke event Model with ECG-LVH and QTc interval			
Frequency Percentage	<2.5%	2.5-5.0%	>5.0%	Total
<2.5%	40	3	0	43
	87.0	5.5	0.0	14.5
2.5-5.0%	6	44	16	66
	13.0	80.0	8.2	22.2
>5.0%	0	8	180	188
	0.0	14.5	91.8	63.3
Total	46	55	196	297

Model without ECG-LVH or QTc interval	No stroke event Model with ECG-LVH and QTc interval			
Frequency Percentage	<2.5%	2.5-5.0%	>5.0%	Total
<2.5%	4403	157	5	4565
	94.8	9.0	0.3	56.0
2.5-5.0%	242	1316	196	1754
	5.2	75.9	11.0	21.5
>5.0%	0	262	1575	1837
	0.0	15.1	88.7	22.5
Total	4645	1735	1776	8156

Categorical net reclassification improvement (NRI) = 0.035, P<0.001
Integrated discrimination improvement (IDI) = 0.006, P=0.63

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Prolonged Corrected QT Interval Is Predictive of Future Stroke Events Even in Subjects Without ECG-Diagnosed Left Ventricular Hypertrophy

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Original Article

Hypertension and lifetime risk of stroke

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Background: The lifetime risk (LTR) articulates the probability of disease in the residual lifetime for an index age. These estimates can be useful for general audience-targeted knowledge translation activities against hypertension. There are only a few reports on lifetime of impact of hypertension on stroke events in Asians in whom stroke incidence is higher than Westerners.

Methods: The Suita Study, a cohort study of cardiovascular diseases in Japan, was established in 1989. We included all participants who were stroke free at baseline. Age (in years) was used as the time scale. Age-specific incidence rates were calculated with person-year method within 10-year bands. We estimated the sex and index-age specific LTR of first-ever stroke with taking the competing risk of death into account.

Results: We followed 5783 men and women during 1989–2007 for 74 933 person-years. During the follow-up period, 276 (149 men and 127 women) participants had incident stroke. The majority of them were cerebral infarction; 166 (102 men and 64 women). The LTR of stroke, accounted for competing risk of death, at 45 years of age for men without hypertension was 17.21% and it was 32.79% for hypertensive men. Among the hypertensive patients, participants with stage 2 or greater hypertension had higher LTR of stroke than the participants with stage 1 hypertension. This increased LTR of stroke for hypertensive patients were also observed among women and across all index ages for stroke.

Conclusion: In this urban community-based population, we observed that hypertension has significant effect on the residual LTR of stroke among both men and women of middle age, specifically for ischemic stroke.

Keywords: cohort, hypertension, lifetime risk, stroke

Abbreviations: BP, blood pressure; LTR, lifetime risk

INTRODUCTION

In spite of the declining trend in the stroke mortality since the 1960s [1–3], stroke remains the third most common cause of death in Japan [4]. With the aging of the population and in the backdrop of major dietary changes and worsening some cardiovascular risk factors [1,2], stroke is likely to be still important health burden in Japan. Thus, prevention activities require urgent attention.

One of the major modifiable risk factor for stroke is high blood pressure (BP) or hypertension. The impact of hypertension on the burden of stroke needs to be presented in an easily understandable way to the lay audience, including at-risk population, patient population, health policy makers, and health educators. For example, clinical and scientific bodies are using this index in their knowledge translation materials [5]. Traditionally, measures of disease burden or risk estimates have primarily focused on the concepts of prevalence, incidence, or relative risk. Estimation of the lifetime risk (LTR) of stroke, which provides an absolute risk assessment, can be an important tool for knowledge translation because it would be more easily comprehensible by lay audience who are not that numerically savvy to apprehend the conventional measures of disease burden. This index would be helpful for public health education in motivating beneficial changes in lifestyle or health-related behaviors as well as social security policy such as health planning. In this study, we estimated the impact of hypertension on the short, intermediate-term risk and LTR of stroke in an urban population in central Japan.

POPULATION AND METHOD

Study sample

The Suita study, a cohort study for cardiovascular diseases among urban residents, was established in 1989. The details of this study have been described elsewhere [6–9]. Briefly, the cohort was formed from randomly sampled Suita city residents aged 30–79 years, stratified by sex and age class (10-year increments). From this sample, 6483 participated in a baseline survey at the National Cardiovascular Center between September 1989 and March 1994. After excluding

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participants with a previous history of stroke ($n = 98$) and those lost to follow-up ($n = 602$), data from the remaining 5783 participants (2722 men and 3061 women) were included in the analysis (Fig. 1). This cohort study was approved by the Institutional Review Board of the National Cardiovascular Center, Suita, Osaka, Japan.

Measurement of blood pressure and categories

Measurement of BP has been described elsewhere [10]. In brief, well trained physicians measured the BP of each individual three times in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff, and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 min. SBP and DBP were recorded as the average of the second and third measurements, which were taken more than 1 min apart. Hypertension was defined as SBP of at least 140 mmHg and/or DBP of at least 90 mmHg and/or on antihypertensive medication. Participants with SBP below 140 mmHg and DBP below 90 mmHg were defined as normotensive. We further categorized the hypertensive patients without regard to the use of antihypertensive medication according to the classification by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [11] as follows: stage 1 hypertension, SBP 140–159 mmHg and/or DBP 90–99 mmHg; and stage 2 hypertension, SBP of at least 160 mmHg and/or DBP of at least 100 mmHg. We decided not to consider treatment of hypertension in this categorization in our analyses because we wanted to evaluate the effect of increased BP levels, which can also arise in hypertensive patients under treatment.

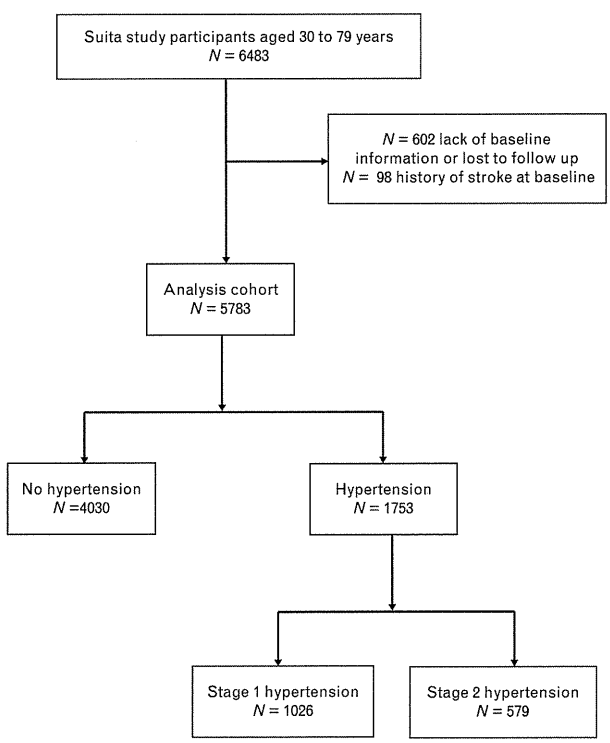

FIGURE 1 Cohort creation.

When SBP and DBP fell into different categories, the higher category was selected for the purposes of classification.

Endpoint ascertainment

The endpoints of the present study were the first stroke; death; or December 31, 2007. The first step in the survey involved checking the health status of all participants by repeated clinical visits every 2 years and yearly questionnaires by mail or telephone. In the second step, registered hospital physicians or research physicians reviewed in-hospital medical records of participants who were suspected of having a stroke. The reviewers were blinded to the baseline information. The criteria for stroke were defined according to the US National Survey of Stroke criteria [12]. For each stroke subtype (i.e. cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhagic), a definite diagnosis was established based on the computed tomography, MRI, or autopsy.

Statistical analysis

Age (in years) was used as the time scale [13,14]. Follow-up began at baseline or study entry age. Participants who were below 40 years of age at the beginning of the study period entered the sample on attainment of 40 years of age. The age categories began at the age of 40 years and the highest age category was set at age 90 years and over. The likelihood of failing from a particular cause at a given time is simply the product of the overall survival to that time. The follow-up ended either at stroke occurrence, on death, or on 31 December 2007, whichever came first.

We estimated cumulative stroke incidence conditional on survival to ages of 45, 55, 65, and 75 years. The estimation of cumulative incidence (the outcome of interest) is affected by the competing risk of death (death because of other causes). Participants who die of other causes of death during the observation period are treated as censored in traditional survival analytic technique, and their potential contribution to the outcome of interest is distributed among patients still at risk. Cause-specific survival is traditionally a net survival measure representing survival of a specified cause of event in the absence of other causes of death. However, the potential contribution of a participant who has died should not be zero, because to be at risk of event occurrence at a particular time, one must first survive from all causes until that time. Treating such participants as censored inflates the estimates of cumulative incidence. Therefore, to examine the actual risk during one's lifetime, we estimated cumulative stroke incidence conditional on survival to ages of 45, 55, 65, and 75 by executing double decrement taking into consideration both occurrence of outcome of interest and all-cause death [13–17].

Sex-specific 10, 20, 30, and 40-year risks and the LTR were estimated for stroke-free participants at different index ages for all stroke, cerebral infarction, and cerebral hemorrhage. The estimates were calculated using a modified technique of survival analysis from previously reported analyses methods [13,18]. All statistical analyses were done using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

We had 74932.7 person-years of observation. During the follow-up period, 276 (149 men and 127 women) participants had incident stroke. The majority of them were cerebral infarction; 166 (102 men and 64 women). There were only 52 cerebral hemorrhage (27 men and 25 women) and 58 subarachnoid hemorrhage (25 men and 33 women). Owing to the very small number of cerebral hemorrhage and subarachnoid hemorrhage events, we could not estimate the short, intermediate, and LTR for these stroke subtypes.

Table 1 shows the basic characteristics of the participants with different hypertension statuses at the baseline. The proportion of hypertensive participants in the baseline survey was 33.36% for men and 27.61% for women. In men, 60.02% of the participants had stage 1 hypertension and 33.26% of the participants had stage 2 hypertension. In women, the respective proportions were 56.92 and 32.78%. Hypertensive patients were generally older and had higher mean plasma glucose and higher total blood cholesterol levels. This difference was observed in both men and women.

Figure 2 (and Supplementary Table 1, http://links.lww.com/HJH/A530) presents the 10, 20, 30, and 40-year risks and LTR of stroke by presence of hypertension in men and women of various index ages. The LTR of stroke, accounted for competing risk of death, for 45-year-old men without hypertension was 17.21% and was 32.79% for hypertensive men of the same index age. There was a graded increase in stroke risk with increasing time span. For stroke, 10-year risk at the age of 45 for normotensive patients was 0.34% and this increased across 20, 30, and 40-year risk categories as 1.74, 5.34, and 11.62%, respectively. This phenomenon was observed in both sexes and all index ages. Figure 3 (and Supplementary Table 2, http://links.lww.com/HJH/A530) presents the short, intermediate, and LTR of stroke by level of hypertension among hypertensive men and women. The LTR of stroke, accounted for competing risk of death, at 45 years of age for men with stage 1 hypertension was 20.21%, whereas the LTR of stroke for stage 2 hypertensive men of 45 years age was 48.33%. The graded increase in stroke risk with increasing time span was observed for both sexes and all index ages.

Table 2 presents the short, intermediate, and LTR of cerebral infarction by presence of hypertension in men and women of various index ages. The LTR of cerebral

TABLE 1. Baseline characteristics of Suita study participants with different hypertension status

		Blood pressure categories			
		No hypertension	Hypertension	Hypertension	
Sex	Variables			Stage 1	Stage 2
Men	Age (years) (s.d)	53.1 (13.2)	61.0 (11.6)	60.3 (11.8)	61.8 (11.3)
	BMI (kg/m^2) (s.d)	22.5 (2.8)	23.4 (3.1)	23.3 (3.0)	23.6 (3.3)
	Height (cm) (s.d)	165.9 (6.2)	164.0 (6.0)	164.2 (6.2)	163.8 (5.5)
	Weight (kg) (s.d)	62.1 (8.9)	63.1 (10.0)	63.1 (10.1)	63.5 (10.2)
	Plasma glucose (mg/dl) (s.d)	99.7 (18.8)	103.7 (21.2)	103.8 (22.3)	103.8 (17.0)
	Total cholesterol (mg/dl) (s.d)	199.6 (33.5)	204.9 (35.2)	205.5 (36.4)	204.5 (34.2)
	Serum creatinine (mg/dl) (s.d)	0.9 (0.2)	0.9 (0.2)	0.9 (0.3)	0.9 (0.2)
	Smoking, *n* (%)				
	Never smoker	338 (18.6)	169 (18.6)	105 (19.3)	58 (19.2)
	Current smoker	969 (53.4)	386 (42.5)	235 (43.1)	121 (40.1)
	Ex-smoker	485 (26.7)	334 (36.8)	194 (35.6)	116 (38.4)
	Unknown	22 (1.2)	19 (2.1)	11 (2.0)	7 (2.3)
	Drinking, *n* (%)				
	Never drinker	401 (22.1)	170 (18.7)	110 (20.2)	49 (16.2)
	Current drinker	1328 (73.2)	683 (75.2)	406 (74.5)	236 (78.2)
	Ex-drinker	64 (3.5)	40 (4.4)	22 (4.0)	10 (3.3)
	Unknown	21 (1.2)	15 (1.7)	7 (1.3)	7 (2.3)
Women	Age (years) (s.d)	51.2 (12.6)	62.6 (9.6)	61.8 (9.6)	63.3 (9.7)
	BMI (kg/m^2) (s.d)	21.8 (3.0)	23.5 (3.5)	23.2 (3.3)	23.8 (3.9)
	Height (cm) (s.d)	153.4 (5.7)	150.5 (5.7)	150.7 (5.7)	150.5 (5.5)
	Weight (kg) (s.d)	51.2 (7.6)	53.3 (9.0)	52.8 (8.5)	53.9 (9.8)
	Plasma glucose (mg/dl) (s.d)	94.4 (14.7)	101.6 (20.6)	100.8 (19.7)	102.7 (22.0)
	Total cholesterol (mg/dl) (s.d)	208.3 (37.6)	225.1 (37.0)	226.6 (36.4)	224.6 (38.8)
	Serum creatinine (mg/dl) (s.d)	0.7 (0.2)	0.7 (0.3)	0.7 (0.4)	0.7 (0.3)
	Smoking, *n* (%)				
	Never smoker	1794 (81.0)	705 (83.4)	408 (84.8)	231 (83.4)
	Current smoker	296 (13.4)	68 (8.1)	32 (6.7)	25 (9.0)
	Ex-smoker	78 (3.5)	35 (4.1)	23 (4.8)	7 (2.5)
	Unknown	48 (2.2)	37 (4.4)	18 (3.7)	14 (5.1)
	Drinking, *n* (%)				
	Never drinker	1392 (62.8)	571 (67.6)	316 (65.7)	194 (70.0)
	Current drinker	740 (33.4)	232 (27.5)	139 (28.9)	71 (25.6)
	Ex-drinker	38 (1.7)	14 (1.7)	10 (2.1)	4 (1.4)
	Unknown	46 (2.1)	28 (3.3)	16 (3.3)	8 (2.9)

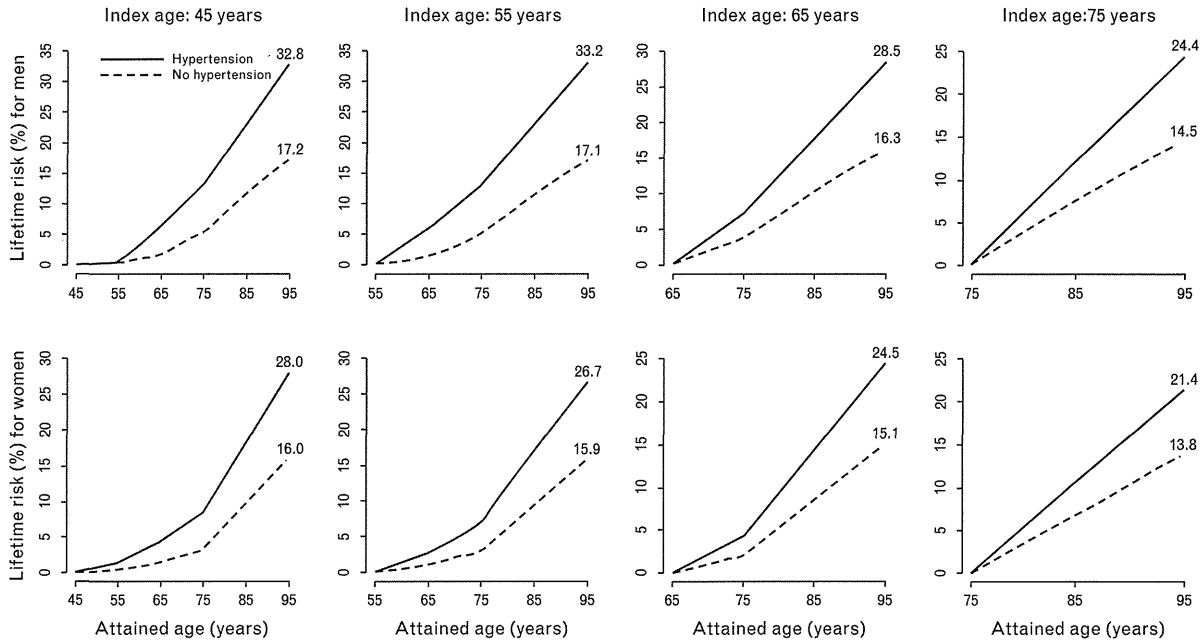

FIGURE 2 Lifetime risk estimates for stroke by presence of hypertension (adjusted for competing risk of death) across different index ages for men and women. The black line represents hypertension and the dotted line represents no hypertension.

infarction, accounted for competing risk of death, at 45 years of age for men without hypertension was 8.25%, whereas the LTR of cerebral infarction for hypertensive men aged 45 years was 19.01%. Table 3 presents the short, intermediate, and LTR of cerebral infarction by level of hypertension among hypertensive men and women. The LTR of cerebral infarction, accounting for competing risk of death, at 45 years of age for men with stage 1 hypertension was 14.75%, whereas the LTR of stroke for stage 2 hypertensive men of 45 years of age was 25.43%.

DISCUSSION

In this urban community-based population, we observed that hypertension has significant effect on the residual LTR of stroke among both men and women of middle age. Individuals with normal BP have significantly lower LTR for stroke in comparison with the individuals with hypertension. Among the hypertensive patients, though the differences were not that large, the individuals with stage 1 hypertension had a lower LTR of stroke in comparison with the individuals with

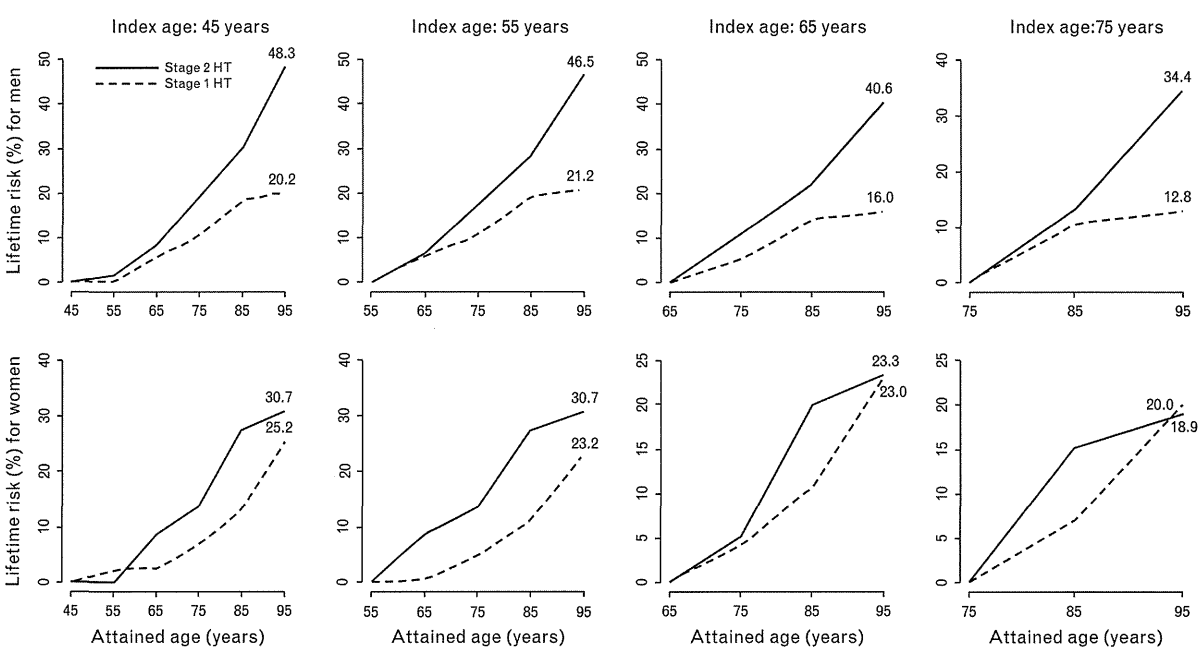

FIGURE 3 Lifetime risk estimates for stroke by level hypertension (adjusted for competing risk of death) across different index ages for men and women. The black line represents stage 2 hypertension and the dotted line represents stage 1 hypertension.

TABLE 2. Age and sex-specific 10, 20, 30, and 40-year and lifetime risk estimates for cerebral infarction by presence of hypertension (adjusted for competing risk of death)

Sex	Index age (years)	Short, intermediate term and lifetime risk (years)	No hypertension	Hypertension
Men	45	10	0.16 (0.00–0.48)	0.60 (0.00–1.77)
		20	1.1 (0.29–1.91)	5.29 (2.53–8.05)
		30	3.71 (2.22–5.2)	9.54 (6.28–12.81)
		40	7.24 (4.98–9.5)	17.95 (13.72–22.17)
		LTR	8.25 (5.28–11.22)	19.01 (14.35–23.68)
	55	10	0.95 (0.19–1.7)	4.84 (2.21–7.46)
		20	3.6 (2.12–5.07)	9.22 (6–12.44)
		30	7.17 (4.9–9.45)	17.89 (13.6–22.18)
		LTR	8.2 (5.2–11.2)	18.99 (14.25–23.74)
	65	10	2.75 (1.42–4.09)	4.57 (2.5–6.64)
		20	6.47 (4.22–8.72)	13.6 (9.86–17.34)
		LTR	7.54 (4.5–10.57)	14.75 (10.44–19.06)
	75	10	4.30 (2.16–6.43)	10.45 (6.7–14.2)
		LTR	5.52 (2.34–8.71)	11.78 (7.27–16.29)
Women	45	10	0.12 (0.00–0.34)	0.00 (0.00–0.00)
		20	0.48 (0.01–0.94)	0.83 (0.00–1.97)
		30	1.34 (0.51–2.18)	3.37 (1.51–5.22)
		40	4.33 (2.38–6.28)	9.94 (6.76–13.12)
		LTR	6.15 (3.01–9.29)	15.32 (7.59–23.06)
	55	10	0.37 (0.00–0.78)	0.83 (0.00–1.98)
		20	1.24 (0.43–2.06)	3.39 (1.52–5.25)
		30	4.28 (2.32–6.24)	10.00 (6.8–13.2)
		LTR	6.12 (2.95–9.3)	15.42 (7.64–23.19)
	65	10	0.90 (0.18–1.63)	2.62 (1.09–4.15)
		20	4.03 (2.05–6.01)	9.42 (6.32–12.52)
		LTR	5.93 (2.68–9.17)	14.98 (7.06–22.9)
	75	10	3.27 (1.33–5.21)	7.19 (4.27–10.11)
		LTR	5.26 (1.94–8.58)	13.08 (4.81–21.34)

LTR, lifetime risk.

stage 2 hypertension. These were observed across all the studied index ages as well as on both sexes.

Our estimates of LTR of stroke in the Suita study are also consistent with the reported LTR of stroke from the Netherlands [19], United States [20], United Kingdom [21], as well as another study from Japan [22]. The LTRs of stroke for middle-aged men and women were substantial. The observed probabilities from the Rotterdam [19], Framingham [20], Radiation Effects Research Foundation Adult Health [22], and Cardiovascular research using linked bespoke studies and electronic health records [21] studies illustrate that approximately one in five men and women of middle age will experience stroke in their remaining lifetime.

Although there are a number of reports regarding the LTR of cardiovascular diseases, including stroke [16,17, 23–26], only a few prior reports have presented the effect of hypertension on the LTR of stroke [20–22,27]. A recent publication from the UK, based on an analysis on electronic records of 1.25 million people during 1997 to 2010, reported that people aged 30 years or older with hypertension have a LTR for strokes compared with those with normal BP [21]. For ischemic stroke, the LTR was 7.6% among the hypertensive patients whereas the normotensive patients had a LTR of 6.5%. For intracerebral hemorrhage, the LTR was 1.3% among the hypertensive patients whereas the normotensive patients had a LTR of 0.9%. Another study from seven US cohorts pooled together estimated that increase or decrease in BP in middle age was associated with higher and lower remaining LTR of stroke [27]. Studying 61 585 men and women for 700 000 person-years, it was reported that LTR of stroke increased with increasing baseline BP categories for both men and women (normal BP, prehypertension, stage 1 hypertension, and stage 2 hypertension) [27]. Also, it was observed that individuals who maintained or decreased their BP to normal levels had the lowest remaining LTR for stroke, compared with individuals who had or developed hypertension by 55 years of age [27]. Authors from Japan, studying the Radiation Effects Research Foundation Adult Health Study cohort, showed that the LTR of stroke and its subtypes differed across the categories in BP among men and women of index age of 55 years [22]. The LTR of stroke for normotensive men and women was 13.8 and 16.0%, respectively, whereas the LTR of stroke for stage 2 hypertensive men and women were 25.8 and 30.5%, respectively [22]. Seshadri *et al.* [20], using Framingham study, reported that participants with a normal BP had a significantly lower LTR of stroke than participants with a high BP [20]. In men, these risks were 10 and 21%, respectively, whereas in women, these were 15 and 26% [20].

In our study, similar to other studies, the LTR for stroke was higher for the younger index ages (e.g. 45 years) in comparison to the older index ages (e.g. 65 years). This phenomenon was observed for both participants with and without hypertension. This finding is of very much importance because this points to the fact that the population-level stroke prevention activities need to be initiated early, especially among the patients with hypertension. This definitely provides supports for efforts to identify hypertension early and start treatment as early as possible.

TABLE 3. Age and sex-specific 10, 20, 30, and 40-year and lifetime risk estimates for cerebral infarction among the hypertensive patients by stages of hypertension (adjusted for competing risk of death)

Sex	Index age (years)	Short, intermediate term and lifetime risk (years)	Hypertension	
			Stage 1 hypertension	Stage 2 hypertension
Men	45	10	0.00 (0.00-0.00)	0.00 (0.00-0.00)
		20	4.65 (1.47–7.84)	7.42 (1.54–13.3)
		30	7.65 (3.95–11.36)	12.69 (5.97–19.4)
		40	14.75 (9.73–19.77)	21.88 (13.88–29.88)
		LTR	14.75 (9.73–19.77)	25.43 (15.26–35.61)
	55	10	4.88 (1.52–8.24)	5.60 (0.68–10.52)
		20	8.02 (4.11–11.93)	10.87 (4.79–16.95)
		30	15.47 (10.19–20.75)	20.06 (12.33–27.8)
		LTR	15.47 (10.19–20.75)	23.61 (13.57–33.66)
	65	10	3.31 (1.05–5.56)	5.38 (1.47–9.29)
		20	11.14 (6.62–15.67)	14.76 (8.24–21.29)
		LTR	11.14 (6.62–15.67)	18.39 (9.08–27.7)
	75	10	9.09 (4.45–13.74)	10.79 (4.43–17.16)
		LTR	9.09 (4.45–13.74)	14.96 (4.94–24.99)
Women	45	10	0.00 (0.00–0.00)	0.00 (0.00–0.00)
		20	0.00 (0.00–0.00)	2.71 (0.00–6.41)
		30	2.41 (0.5–4.31)	5.51 (1.00–10.01)
		40	4.92 (2.05–7.79)	16.94 (9.69–24.19)
		LTR	13.00 (0.00–26.32)	20.29 (11.98–28.6)
	55	10	0.00 (0.00–0.00)	2.71(0.00–6.41)
		20	2.43 (0.51–4.35)	5.51 (1.00–10.01)
		30	4.96 (2.07–7.86)	16.94 (9.69–24.19)
		LTR	13.12 (0.00–26.56)	20.29 (11.98–28.6)
	65	10	2.45 (0.51–4.39)	2.97 (0.10–5.84)
		20	5.01 (2.09–7.93)	15.11 (8.22–21.99)
		LTR	13.25 (0.00–26.82)	18.66 (10.49–26.83)
	75	10	2.72 (0.35–5.08)	12.73 (5.94–19.52)
		LTR	11.45 (0.00–25.73)	16.46 (8.21–24.72)

LTR, lifetime risk.

From a methodological standpoint, our study includes the use of a population-based cohort, the prospective ascertainment of endpoints using rigorous standardized and previously validated clinical diagnostic criteria, and the completeness of stroke event and mortality ascertainment. Thus, our estimates are based on simultaneously gathered data on both stroke incidence and other-cause mortality attributable to competing risk of death in the same cohort. Interpreting our observed estimates, few things need to be kept in mind. The Suita cohort is based on urban population, so the estimates might not represent Japanese population in general. But Japan has a high urbanization rate and in the urban environment changes in the lifestyle factors associated with the risk with stroke would be more prominent. Therefore, we believe that the LTR of stroke points toward risk in urban setting that itself also represents a large part of the population. On the contrary, time period and birth cohort effects could limit the external validity of our results. Temporal trends in life expectancy, risk factor prevalence and control among the study population, disease awareness, and the sensitivity of diagnostic tests could potentially alter the LTR of stroke. We also could not, because of the lack of enough number of outcomes, estimate the effect of hypertension on the LTRs of cerebral hemorrhage and subarachnoid hemorrhage.

Our findings have important clinical implications. Recently published clinical practice guidelines from the United States [28] and the United Kingdom [29] agree that the primary purpose of assessment of cardiovascular risk is to provide the basis of a risk discussion with the patient. These LTR estimates are specifically useful for public education because they are easier to comprehend than measures such as incidence, prevalence, or relative risk [30]. This will be a more commonsense approach to health education because problems with numeracy or low quantitative literacy are common [31]. A recent study using focus group discussions concluded that patients preferred health risks to be framed in absolute terms and lifetime estimate with a scale to 'x out of 100' [32]. In younger individuals with low short-term risks, the high LTR might be more useful to motivate lifestyle modifications with appropriate health education efforts aimed at prevention of stroke, thereby reducing the population burden of stroke.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

Strengths: Stroke risk is usually calculated as relative risk. Estimation of the lifetime risk of stroke, as done in this study, provides an absolute risk assessment and seems to be more easily understandable by a lay audience. Therefore, it may improve adherence to preventive procedures. The current paper has therefore important clinical implications.

Weaknesses: The main limitation of the current study lies in its confirmatory role. Furthermore, as the study is based on a Japanese cohort, the number of ischemic stroke events is relatively small (276 patients with a stroke with only 166 with ischemic stroke), whereas the impact of ischemic stroke is largely the most relevant in western populations. This limits the potential clinical implications of the study.

Reviewer 2

The main strengths of this paper are its longitudinal follow-up for close to 20 years and its novel mode of quantifying the increase in the risk of stroke in people with hypertension. The main limitations are firstly, that the notion that hypertension increases the risk of stroke is not really new, and secondly that the number of subjects with stroke was small (276).

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Original Article

Changes in Waist Circumference and the Incidence of Type 2 Diabetes in Community-Dwelling Men and Women: The Suita Study

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ABSTRACT

Backgrounds: The association between weight gain and the incidence of type 2 diabetes is well known. The aim of our study was to investigate the relationship between change in waist circumference (WC) and type 2 diabetes incidence.

Methods: The participants in the Suita Study, a population-based cohort study in an urban area of Japan, underwent a baseline survey between 1989 and 1994 (Exam 1) and were examined at follow-up every 2 years. We performed a 9.3-year cohort study of 946 men and 1327 women with no history of diabetes who underwent Exam 1 and Exam 2 (between 1997 and 1999). Participants were stratified by sex and median WC at Exam 1, and, in each stratum, participants were further classified into three categories by tertile of WC change per year between Exam 1 and Exam 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for type 2 diabetes incidence were calculated by Cox proportional hazard models. The endpoints were first diagnosis of type 2 diabetes or March 2011.

Results: During follow-up, 287 participants developed type 2 diabetes. In both sexes with median WC or higher, participants in the highest tertile of WC change had a significantly higher risk of developing type 2 diabetes. Multivariable adjusted HRs were 1.84 (95% CI, 1.10–3.08) in men and 2.30 (95% CI, 1.31–4.04) in women. No significant association was observed among participants with WC below median.

Conclusions: Preventing WC gain is important in preventing type 2 diabetes in the Japanese population, especially among individuals with a relatively high WC.

Key words: waist circumference; type 2 diabetes mellitus; prospective cohort study

INTRODUCTION

The worldwide prevalence of type 2 diabetes is alarmingly high. The International Diabetes Federation (IDF) has reported that the global prevalence of diabetes has reached 8.3% (382 million people), and that the prevalence will be 10% by 2035.[1] In particular, of IDF regions, the Western pacific region, which includes China, Indonesia, and Japan, has a high prevalence of diabetes (8.6%) and is home to 36% of the total number of people with diabetes in the world.[2] At the same time, the prevalence of obesity is escalating worldwide. The mean body mass index (BMI) worldwide has increased by 0.4 kg/m^2 per decade in men and 0.5 kg/m^2 per decade in women.[3] Although the prevalence of obesity or overweight in Asia is relatively low compared with other parts of the world, the drastic increase in BMI in Asia is similar to that in other regions. Many studies have reported significant associations between weight gain and the incidence of type 2 diabetes.[4–10] Therefore, it is anticipated that this increase in obesity will lead to increased rates of type 2 diabetes.

It is well known that higher waist circumference (WC), as well as higher BMI, is associated with elevated risks of type 2

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