of heavy drinking among the working population.

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Makita S, Onoda T, Ohsawa M, Tanno K, Tanaka F, Omama S, Yoshida Y, Ishibashi Y, Itai K, Sakata K, Ohta M, Kuribayashi T, Ogasawara K, Ogawa A, Okayama A, Nakamura M. Bradycardia is associated with future cardiovascular diseases and death in men from the general population. Atherosclerosis. 2014;236:116-20.

Abstract

BACKGROUND:

Although a higher heart rate is known to be a risk factor for cardiovascular disease (CVD) events, there have been no reports concerning bradycardia. Whether lower and higher resting pulse rates (RPRs) are associated with cardiovascular risk was investigated in subjects from a community-based, prospective cohort study.

METHODS:

After subjects with atrial fibrillation, subjects with a history of CVD, and subjects receiving antihypertensive treatment were excluded, 17,766 subjects (5958 men), aged 40-79 (mean 61.5) years, were analyzed. The RPR at baseline was categorized into four groups (RPR<60, 60-69.5, 70-79.5, ≥80 beats per minute (bpm)) using the average value of two consecutive measurements. The endpoint was set as the composite outcome of myocardial infarction, stroke, or sudden death.

RESULTS:

During a mean follow-up of 5.6 years, there were 213 events in men and 186 events in women. In Cox regression models, increased risks of CVD were found in the men group with RPR<60 bpm, as well as the group with RPR≥80 bpm, compared with the reference group with RPR 60-69.5 bpm (hazard ratio [HR] = 1.73, $p = 0.005$ and HR = 2.01, $p < 0.001$). These increased risks were found even when adjusted for age and other CVD risk factors (HR = 1.55, $p = 0.026$ with RPR<60 bpm and HR = 1.72, $p = 0.009$ with RPR≥80 bpm). In women, there were no significant associations between RPR and CVD risk.

CONCLUSION:

Bradycardia, as well as a higher pulse rate, may be an independent risk factor for future cardiovascular events in apparently healthy men.

Makita S, Tanaka F, Onoda T, Ohsawa M, Tanno K, Omama S, Yoshida Y, Ishibashi Y, Segawa T, Takahashi T, Satoh K, Itai K, Sakata K, Ohta M, Kuribayashi T, Ogasawara K, Ogawa A, Okayama A, Nakamura M. Elevated blood pressure at the first measurement predicts cardiovascular disease independently from the subsequent second reading in men, but not in women. Clin Exp Hypertens. 2015;37:39-44.

Abstract

BACKGROUND AND METHODS:

There have been no investigations concerning the association of each blood pressure (BP) reading with future cardiovascular disease (CVD) when multiple measurements are taken on one occasion. This community-based, prospective cohort study (n = 23 344, mean age = 62.4 years) investigated the associations between the BP obtained from the first and second of two consecutive measurements on one occasion and future cardiovascular events in men and women.

RESULTS:

During the mean follow-up of 5.5 years, 624 CVD events were identified. On the Cox regression analysis of age- and BP-adjusted models, the increased CVD risk of a hypertensive first measurement (systolic BP ≥ 140 mmHg) was independent from the second measurement in men. Even in subjects without a hypertensive second measurement, the CVD risk of the hypertensive first measurement was increased in men. In women, despite a hypertensive first measurement, subjects with a systolic BP < 130 mmHg on the second measurement showed a significantly reduced risk for CVD compared with subjects who retained a hypertensive level during the two measurements.

CONCLUSIONS:

An elevated BP on the first measurement should not be disregarded for CVD risk estimation in men, even if the second BP moves to the normal range. In women, elevated BP on the first measurement may have relatively less meaning for CVD prediction if the second BP shifts to a normal range.

Ando A, Tanno K, Ohsawa M, Onoda T, Sakata K, Tanaka F, Makita S, Nakamura M, Omama S, Ogasawara K, Ishibashi Y, Kuribayashi T, Koyama T, Itai K, Ogawa A, Okayama A. Associations of number of teeth with risks for all-cause mortality and cause-specific mortality in middle-aged and elderly men in the northern part of Japan: the Iwate-KENCO study. Community Dent Oral Epidemiol. 2014;42(4):358-65.

Abstract

OBJECTIVES:

The objective of this study was to determine the associations of number of teeth with all-cause mortality and cause-specific mortality among middle-aged and elderly Japanese men.

METHODS:

A total of 7779 men aged 40-79 years who were free from cardiovascular disease (CVD) were followed up prospectively for 5.6 years. Participants were categorized into four groups (no teeth, 1-9 teeth, 10-19 teeth, and ≥20 teeth) by a self-administered questionnaire. Using Cox's proportional hazard model, multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality from all causes, CVD, cancer, and noncancer, non-CVD according to number of teeth were estimated with adjustments for age, body mass index, systolic blood pressure, total- and HDL-cholesterol, HbA1c, current smoking, current alcohol drinking, and low level of education.

RESULTS:

The numbers (proportions) of participants with no teeth, 1-9 teeth, 10-19 teeth, and ≥20 teeth were 1613 (20.7%), 1650 (21.2%), 1721 (22.1%), and 2795 (35.9%), respectively. During follow-up, a total of 455 deaths (including 175 deaths from cancer, 98 deaths from CVD, and 130 deaths from noncancer, non-CVD) were recorded. In total participants, an inverse relationship between number of teeth and all-cause mortality was found (P for trend = 0.049). Among men aged 40-64 years, inverse relationships were also found in risks for mortality from all causes, CVD, and cancer: multivariate-adjusted HRs (95% CI) for all-cause mortality in men with no teeth, 1-9 teeth, and 10-19 teeth relative to men with ≥20 teeth were 2.75 (1.37-5.49), 1.89 (0.99-3.63), and 1.94 (1.09-3.43), respectively. However, there were no associations of number of teeth with all-cause mortality and cause-specific mortality among men aged 65-79 years.

CONCLUSIONS:

The number of teeth is an important predictive factor for mortality among middle-aged Japanese men.

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Original article

Relationships between the QTc interval and cardiovascular, stroke, or sudden cardiac mortality in the general Japanese population

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ABSTRACT

Background: We attempted to evaluate whether the relationship between the QTc interval and mortality (including sudden cardiac death) is linear or J-shaped in the general Japanese population, who tend to be at greater risk of strokes than cardiac events.
Methods: We classified 10,804 subjects according to their Bazett QTc interval quartiles (determined by electrocardiography) at the baseline and followed them up for a mean period of 141.9 ± 28.3 months (127,712 person-years).
Results: In total, 878 subjects died during the study period, including 104 from cardiovascular events, 100 from stroke, and 46 from sudden cardiac death. In a Cox proportional hazards regression model adjusted for conventional cardiovascular risk factors, the risk of cardiovascular mortality increased progressively with the QTc interval quartile [Q2, hazard ratio (HR) = 0.94 (0.43–2.03); Q3, HR = 1.11 (0.53–2.34); Q4, HR = 2.21 (1.12–4.36); HR are vs. Q1]. A parallel analysis found that the risk of stroke mortality was marginally increased in the highest Bazett QTc interval quartile [HR = 1.93 (0.97–3.85)]. On the other hand, the risk of sudden cardiac death exhibited a J-shaped relationship with the Bazett QTc interval quartile [Q1, HR = 8.58 (1.07–69.05); Q3, HR = 7.17 (0.88–58.73); Q4, HR = 13.18 (1.72–101.03); HR are vs. Q2].
Conclusion: In the general Japanese population, cardiovascular and stroke mortality increase progressively with the Bazett QTc interval quartile, while the risk of sudden cardiac death exhibits a J-shaped relationship with the latter variable.

Introduction

A long QTc interval on an electrocardiogram (ECG) is associated with an increased risk of cardiovascular death [1–4] or sudden cardiac death [5,6]. Ventricular arrhythmia is one of the underlying factors responsible for these associations; however, the association between long QTc intervals and an increased risk of cardiovascular death might also be attributable to the fact that long QTc intervals are associated with cardiovascular risk factors [7] such as high blood pressure and left ventricular hypertrophy [8]. Among the general Japanese population, individuals are more likely to suffer a stroke than a cardiovascular event [9], and the relationships between QTc intervals and the risk of cardiovascular, stroke mortality, or sudden cardiac death could differ from those seen in Western countries. In addition, subjects with extremely short QTc intervals have also been demonstrated to be at increased risk of sudden cardiac death [10,11]; however, previous studies have obtained inconsistent findings regarding whether the associations between the QTc interval and the risk of cardiovascular or sudden cardiac death are J-shaped or linear [2,7,12–14].

The purpose of this study was to clarify whether individuals from the general Japanese population with long or short QTc intervals are at increased risk of cardiovascular, stroke, or sudden cardiac death.

Methods

Subjects

The Jichi Medical School (JMS) Cohort Study began in 1992 and aimed to clarify the risk factors for cardiovascular and cerebrovascular disease in the general Japanese population. The details of the

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protocol of the JMS Cohort Study have been reported elsewhere [15]. Baseline data were collected between April 1992 and July 1995 in 12 rural districts of Japan using a government-sponsored mass screening system. In each community, a local government office sent personal invitations to all of the eligible subjects by mail in accordance with the Health and Medical Service Law for the Aged. The individuals that participated in the mass screening examinations were aged 40–69 years in eight regions (Iwaizumi, Tako, Kuze, Sakuma, Sakugi, Okawa, Ainoshima, and Akaike), aged ≥30 years in one area (Wara), and belonged to other age groups in three regions (Hokudan, Yamato, and Takasu). At the baseline, there were a total of 12,490 subjects (4911 males and 7579 females) in the JMS Cohort Study. The selection criteria applied to the subjects in the present study are shown in Fig. 1.

ECG measurements and interpretation

ECG was performed at a paper speed of 25 mm/s and a gain of 10 mm/mV (or 5 mm/mV) using the ECG devices at the participating institutions. Initially, a trained individual who was unaware of the subjects' background data manually measured the QT interval in lead II (or lead I or III if the QT interval could not be measured in lead II), which is the best lead for depicting T waves in 12-lead ECG, according to the reported protocol for the measurement of QTc intervals [16]. The ECG measurements were performed using a ruler with 0.01-mm graduations. The QTc interval for a single beat was measured from the beginning of the QRS complex to the end of the T wave. The end of the QT interval was taken as the last point of the T wave, i.e. where the downsloping limb joined the baseline, while we excluded U waves [17,18]. RR intervals were also measured, and the mean of three RR intervals was calculated. Heart rate-adjusted QT intervals (QTc) were calculated using the Bazett formula [19]: [$QTc = QT/(RR^{1/2})$]. The intraobserver reproducibility of the Bazett QTc interval measurements was confirmed by comparing the pairs of measurements obtained for 98 ECGs. The mean relative error of the QTc interval measurements was 0.5%, and their mean absolute intraobserver error was 2.0 ms (SD: 17.0 ms).

Short QTc intervals were defined as Bazett QTc intervals of <330 ms according to the expert consensus statement on the

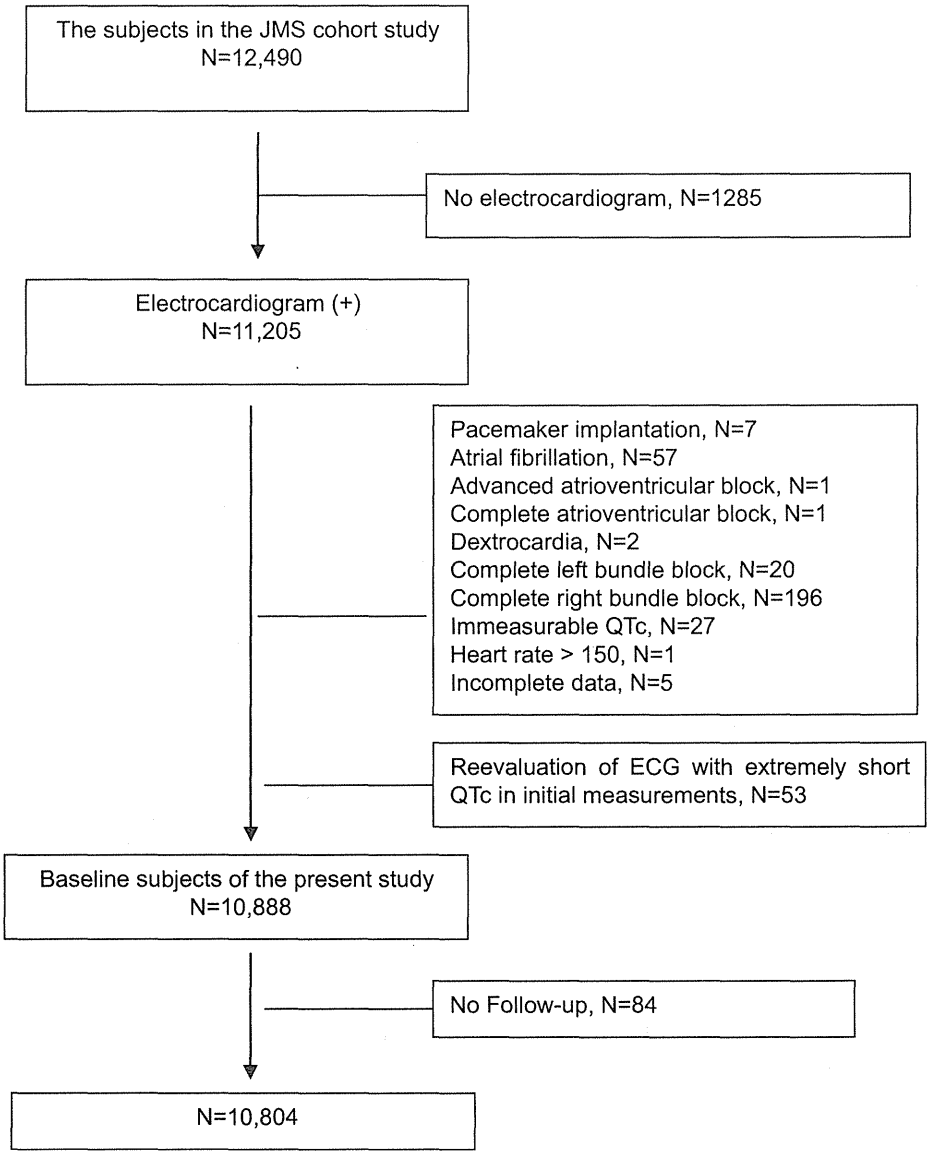

Fig. 1. Selection of subjects. ECG, electrocardiogram.

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diagnosis and management of patients with inherited primary arrhythmia syndromes [20]. Prolonged QTc intervals were defined as Bazett QTc intervals of ≥440 ms in men and ≥460 ms in women.

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 or present illnesses, as well as any heart conditions suffered by the subjects' parents. Age was recorded at the baseline. Smoking status was classified as smoker, ex-smoker, or never smoked. Alcohol drinkers were defined as subjects who drank at least 20 g/alcohol per day. Systolic and diastolic blood pressure were measured at the baseline using a fully automated sphygmomanometer (BP203RV-II, Nippon Colin, Komaki, Japan). Blood pressure was measured once after the subjects had rested for at least 5 min in a sitting position. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or hypertension because of the presence of medication. Diabetes mellitus was defined as a fasting glucose level of >7.0 mmol/L (126 mg/dl), a random nonfasting glucose level of >11.1 mmol/L (200 mg/dl), or because of 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 because of the use of an oral lipid-lowering agent according to the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Disease.

Informed consent

The internal review board at Jichi Medical University School of Medicine approved this study. Written informed consent for the study was obtained from each individual who participated in the mass screening health check-up examinations at the baseline.

Follow-up

We used the mass screening examination system 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 enrollment. If a subject did not undergo a scheduled annual screening examination, we contacted them or their family members by mail or telephone to confirm whether they had suffered any cardiovascular events or had died. In cases in which the subject had visited a medical institution due to a cardiovascular event or had 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 relevant forms and obtained copies of brain computed tomography or magnetic resonance imaging scans (when a cerebrovascular event was suspected) and/or electrocardiograms (when myocardial infarction 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 at the public health centers with the permission of the Agency of General Affairs and the Ministry of Health, Labour and Welfare. Data regarding residence changes during the study were obtained from each municipal government annually.

Diagnostic criteria

All diagnoses were determined independently by a diagnostic committee composed of radiologists, neurologists, and cardiologists. Questionnaire responses and copies of the subjects' medical records were used to assess whether myocardial infarction or stroke events had occurred. Detailed definitions of stroke and myocardial infarction events have been reported previously [9]. Sudden cardiac death was defined as a death that occurred within 24 h of symptom onset that did not have an identifiable cause. We could not confirm whether fatal arrhythmia had been responsible for any of the cases of sudden cardiac death. Causes of death were identified using death certificates, which were collected at the respective local public health centers with the permission of the Ministry of General Affairs and the Ministry of Health, Labour and Welfare. Death and events were diagnosed based on the consensus of all members of the diagnostic committee.

Statistical analysis

This study was a retrospective analysis of the ECG data obtained during the JMS Cohort Study. Data are shown as mean ± SD or percentage values. One-way analysis of variance was performed to evaluate the overall differences among the groups, and Tukey's honestly significant difference test was used for inter-group comparisons of mean values. The chi-square test was used to detect differences in percentage values among the groups. Mortality rates are shown as the number of deaths per 10,000 person-years. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality were calculated according to the QTc interval quartiles using Cox proportional hazards regression analysis. In the latter models, we adjusted for the following conventional cardiovascular risk factors: age, gender, body mass index, history of myocardial infarction, history of stroke, smoking status, alcohol intake of >20 g/day, systolic blood pressure, antihypertensive drug use, heart rate, the presence of hyperlipidemia, and the presence of diabetes. A probability <0.05 was considered statistically significant. The software SPSS (version 18.0, Chicago, IL, USA) was used for all analyses.

Results

Subjects

At the baseline, the mean age of the subjects was 55.5 ± 11.2 years, and 37.9% of the subjects were men. The subjects' Bazett QTc intervals ranged from 303 to 563 ms (mean QTc interval: 388 ± 27 ms). In the lowest, second, third, and highest Bazett QTc interval quartiles, the Bazett QTc interval was 303–370 (358) ms, 371–387 (median: 379) ms, 388–405 (395) ms, and 406–563 (418) ms, respectively. In addition, 3.6% of the subjects had Bazett QTc intervals of >440 ms.

Among the 6713 female subjects, 28 (0.4%) had Bazett QTc intervals of <330 ms and 78 (1.2%) had Bazett QTc intervals of ≥460 ms. Among the 4091 male subjects, 64 (1.6%) had Bazett QTc intervals of <330 ms, and 97 (2.4%) had Bazett QTc intervals of ≥440 ms.

Subjects' characteristics classified according to their Bazett QTc interval quartiles

The subjects' baseline characteristics have been classified according to their Bazett QTc interval quartiles in Table 1. Age, body mass index, and the prevalences of hypertension and hyperlipidemia increased progressively with the Bazett QTc interval quartile, while the frequency of male subjects and smokers decreased with the Bazett QTc interval quartile.

The risk of mortality according to the Bazett QTc interval quartile

During the mean follow-up period of 141.9 ± 28.3 months (127,712 person-years), there were a total of 878 deaths, including 92

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Table 1
Subjects' characteristics according to the Bazett QTc interval quartile at the baseline (N = 10,804).

	Q1	Q2	Q3	Q4	p
Range of QTc interval, ms	≤370	371–378	388–405	≥406	
Number of subjects	2701	2702	2700	2701	
Age, years	53.1 ± 12.2	55.3 ± 11.0	56.3 ± 10.6	57.4 ± 10.4	<0.001
Male, %	53.4	40.6	30.8	26.8	<0.001
Body mass index, kg/m^2	22.9 ± 2.9	23.0 ± 3.0	23.2 ± 3.2	23.3 ± 3.3	<0.001
History of stroke, %	0.9	0.8	0.7	1.6	0.012
History of myocardial infarction, %	0.7	0.3	0.5	0.7	0.116
Smoking status					<0.001
Former, %	16.5	13.3	10.8	10.2	
Current, %	29.4	23.9	18.8	17.9	
Alcohol consumption >20 g/day, %	33.3	31.8	30.4	32.1	0.215
Hypertension, %	28.4	31.7	36.1	40.8	<0.001
SBP, mmHg	126.4 ± 20.3	128.2 ± 20.5	130.6 ± 21.1	132.7 ± 21.5	<0.001
DBP, mmHg	75.9 ± 12.2	76.6 ± 12.0	78.2 ± 12.2	79.2 ± 12.5	<0.001
Hyperlipidemia, %	33.4	34.2	37.6	38.1	<0.001
Total cholesterol, mg/dl	189 ± 34	192 ± 35	194 ± 35	195 ± 35	<0.001
Triglycerides, mg/dl	114 ± 76	116 ± 75	117 ± 71	123 ± 83	<0.001
Diabetes, %	3.3	3.9	3.9	4.4	0.227
Blood glucose, mg/dl	100 ± 23	103 ± 27	104 ± 27	105 ± 28	<0.001
Heart rate, beats/min	62 ± 9	65 ± 10	68 ± 10	72 ± 12	<0.001

Data are shown as mean ± SD or percentage values. QTc data are shown as ranges. Overall p values were calculated using an analysis of covariance test. Probability values of <0.05 were considered significant. SBP, systolic blood pressure; DBP, diastolic blood pressure.

due to cardiac events (including 46 sudden cardiac deaths), 12 due to vascular events, and 100 due to stroke. In addition, there were 674 deaths from other causes (i.e., cancer, infection, trauma, suicide, etc.). The total number of cardiovascular and stroke deaths increased according to the Bazett QTc interval quartile (Fig. 2). On the other hand, the relationship between the Bazett QTc interval quartile and the frequency of sudden cardiac death was J-shaped.

Even in the Cox proportional hazards regression model adjusted for conventional cardiovascular risk factors (Table 2), the risk of cardiovascular mortality increased progressively with the QTc interval quartile [Q2, HR = 0.94 (0.43–2.03); Q3, HR = 1.11 (0.53–2.34); Q4, HR = 2.21 (1.12–4.36); HR are vs. Q1]. In a parallel analysis, the risk of stroke mortality was found to be increased in the highest Bazett QTc interval quartile [HR = 1.93 (0.97–3.85)], but the increase was not statistically significant. The risk of sudden cardiac death exhibited a J-shaped relationship with the Bazett QTc interval [Q1, HR = 8.58 (1.07–69.05); Q3, HR = 7.17 (0.88–58.73); Q4, HR = 13.18 (1.72–101.03); HR are vs. Q2].

Even when we entered the presence of the ST–T strain pattern into the model, the results were not changed.

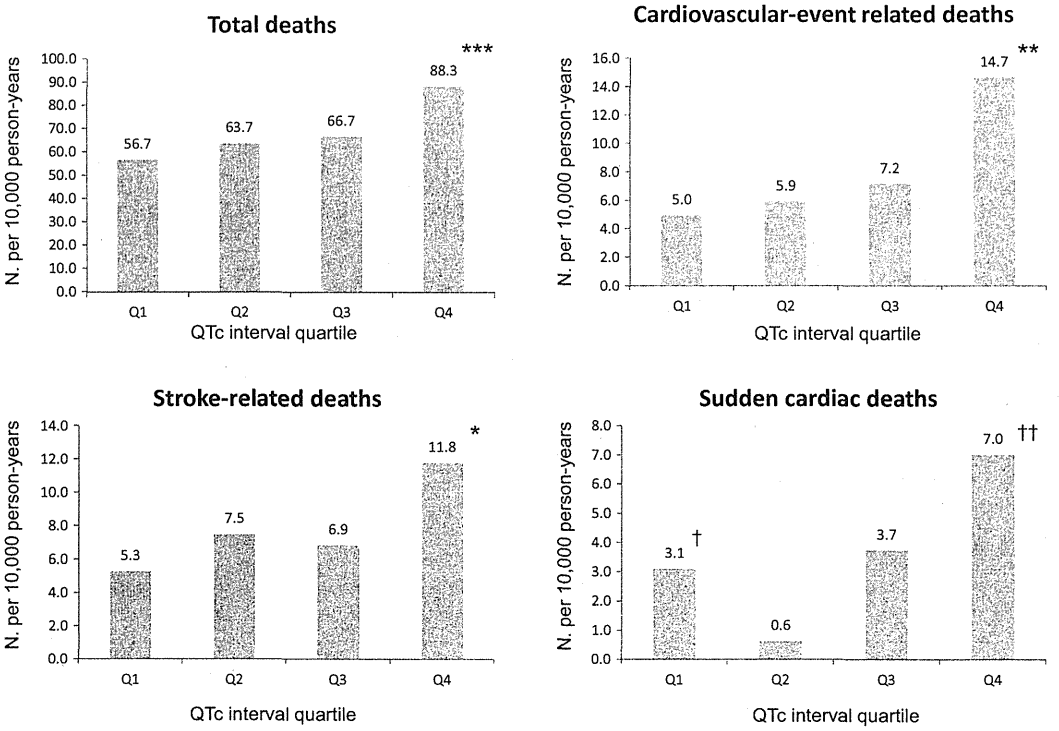

Fig. 2. Total, cardiovascular, stroke, and sudden cardiac deaths according to QTc interval quartile (Q). Data are shown as the number of deaths per 10,000 person-years. The p values were calculated using an unadjusted Cox proportional hazards model. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs. the subjects in the lowest QTc interval quartile; †$p < 0.05$; ††$p < 0.01$ vs. the subjects in the second QTc interval quartile.

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Table 2
Cox proportional hazards regression analyses of mortality according to the QTc interval quartile.

QTc interval quartile	HR	95% CI		p
Total mortality (N=878)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	1.05	0.83	1.31	0.694
Q3, 388–405 ms	1.11	0.89	1.40	0.352
Q4, ≥406 ms	1.29	1.02	1.62	0.030
Combined cardiovascular and stroke mortality (N=204)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	1.18	0.71	1.96	0.533
Q3, 388–405 ms	1.05	0.61	1.78	0.871
Q4, ≥406 ms	2.07	1.28	3.36	0.003
Cardiovascular mortality (N=104)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	0.94	0.43	2.03	0.871
Q3, 388–405 ms	1.11	0.53	2.34	0.782
Q4, ≥406 ms	2.21	1.12	4.36	0.023
Stroke mortality (N=100)				
Q1, ≤370 ms	Reference			
Q2, 371–387 ms	1.39	0.70	2.78	0.345
Q3, 388–405 ms	0.97	0.46	2.08	0.947
Q4, ≥406 ms	1.93	0.97	3.85	0.062
Sudden cardiac death (N=46)				
Q1, ≤370 ms	8.58	1.07	69.05	0.043
Q2, 371–387 ms	Reference			
Q3, 388–405 ms	7.17	0.88	58.73	0.066
Q4, ≥406 ms	13.18	1.72	101.03	0.013

Data are shown as hazard ratios (95% confidence intervals). The hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards model adjusted for age, gender, body mass index, history of stroke, history of myocardial infarction, alcohol consumption of >20 g/day, smoking status, systolic blood pressure, antihypertensive drug use, heart rate, diabetic status, and the presence of hyperlipidemia. HR, hazard ratio; CI, confidence interval; Q, quartile.

The risk of mortality in subjects with short or prolonged QTc intervals

Of the subjects with extremely short QTc intervals (<330 ms), none died from cardiovascular, stroke, or sudden cardiac death during the follow-up period. Data regarding the risk of mortality associated with a prolonged QTc interval (≥440 ms in men and ≥460 ms in women) are shown in Table 3. The risk of cardiovascular mortality was increased in both the male and female subjects with prolonged QTc intervals. However, the increase in the risk of sudden cardiac death detected in the subjects with prolonged QTc intervals did not reach statistical significance.

Table 3
The mortality risks of subjects with prolonged QTc interval in male and female subjects.

	Males (QTc interval ≥440 ms)				Females (QTc interval ≥460 ms)			
	HR	LCI	UCI	p	HR	LCI	UCI	p
Total mortality								
Unadjusted	2.05	1.29	3.24	0.002	2.77	1.37	5.59	0.005
Adjusted	1.28	0.79	2.08	0.313	1.58	0.77	3.24	0.214
Cardiovascular and stroke mortality								
Unadjusted	3.86	1.78	8.36	0.001	5.32	1.94	14.59	0.001
Adjusted	2.23	0.98	5.10	0.056	3.35	1.17	9.58	0.024
Cardiovascular mortality								
Unadjusted	5.37	2.12	13.63	<0.001	5.82	1.39	24.27	0.016
Adjusted	2.75	1.02	7.45	0.046	4.65	1.07	20.22	0.041
Stroke-related mortality								
Unadjusted	2.26	0.55	9.38	0.261	4.91	1.18	20.36	0.028
Adjusted	1.62	0.36	7.25	0.525	2.72	0.61	12.16	0.189
Sudden cardiac death								
Unadjusted	3.30	0.71	15.44	0.129	8.49	1.10	65.81	0.041
Adjusted	1.45	0.30	7.01	0.647	7.60	0.90	64.39	0.063

Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated using Cox hazard model. In the adjusted model, we also entered age, gender, body mass index, history of stroke, history of myocardial infarction, alcohol drinking >20 g/day, smoking status, systolic blood pressure, antihypertensive drug use, heart rate, diabetic status, and presence of hyperlipidemia. LCI, lower confidence interval; UCI, upper confidence interval.

Discussion

In this study, the QTc interval was found to be associated with cardiovascular risk factors, and the risk of cardiovascular mortality increased with the Bazett QTc interval quartile. On the other hand, a J-shaped relationship was detected between the Bazett QTc interval quartile and the risk of sudden cardiac death. When we evaluated the risk of mortality using QTc interval cut-off levels, a prolonged QTc interval was found to be associated with cardiovascular mortality; however, none of the subjects with extremely short QTc intervals of <330 ms suffered sudden cardiac death.

The Rotterdam study [2] reported that a J-shaped relationship exists between the Bazett QTc interval quartile and the risk of cardiovascular mortality (regardless of the formula used to calculate the QTc interval). Moreover, the Third National Health and Nutrition Examination Survey found that shortened and prolonged QT intervals, even those within the reference range, are associated with an increased risk of mortality in the general population [14]. However, our data only support the findings of these previous reports regarding the relationship between the QTc interval and the risk of sudden cardiac death.

In the present study, a J-shaped association was detected between the Bazett QTc interval quartile and the risk of sudden cardiac death in the general Japanese population. It is well established that long QT syndrome is associated with sudden cardiac death attributable to ventricular arrhythmia and that a long QTc interval constitutes a risk factor for sudden cardiac death in the general population. For example, Algra et al. [18] reported that a long QTc interval (>440 ms) was associated with an increased risk of sudden cardiac death, and Straus et al. [6] agreed; although they defined long QTc intervals differently (males: >451 ms; females: >471 ms). In the Framingham study [13], a trend toward an increased risk of sudden cardiac death was detected in the subjects with the shortest QTc intervals (<360 ms) in comparison with those in the second QTc interval quartile. However, when we performed an analysis using the lowest Bazett QTc interval quartile, we found that the increase in the risk of sudden cardiac death observed in the highest Bazett QTc interval quartile was insignificant (data not shown).

There have been reports of familial cases of short QTc interval-associated sudden cardiac death (ventricular arrhythmia) [10,21]; however, some epidemiological studies have found that a short QTc interval is not associated with sudden cardiac death in the general population [12,22]. On the other hand, in the Framingham study [13], the subjects with short QTc intervals (<360 ms) were found to be more likely to suffer sudden cardiac death, and the findings we obtained using a QTc interval cut-off value of <370 ms support these results. In the JMS Cohort Study, there were a total of 46 sudden cardiac deaths, but there were only 10 sudden cardiac deaths among the subjects in the lowest QTc interval quartile (≤370 ms) during a mean follow-up period of 141.9 ± 28.3 months (127,712 person-years). Previous reports of familial cases of short QTc intervals [10,21] defined QTc intervals of <300 ms as short QTc intervals, but there were no subjects with QTc intervals of <300 ms in this study. When we used a cut-off level of <330 ms as a definition of short QTc intervals [20], we found that none of the subjects with such short QTc intervals suffered sudden cardiac death during the follow-up period. When we used the Fridericia or Framingham formula to calculate QTc intervals, the increase in the risk of sudden cardiac death observed in the subjects in the shortest QTc interval quartile

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became insignificant (data not shown). Moreover, the risk of sudden cardiac death associated with a shorter QTc interval did not significantly increase at any cut-off level in the general population.

A prolonged QTc interval was reported to be associated with increased arterial stiffness [23] and left ventricular hypertrophy [8]. In other reports [24,25], a prolonged QTc interval was found to be associated with an increased risk of stroke events, suggesting that the association between the risk of cardiovascular mortality and the QTc interval can not only be derived from the risk of ventricular arrhythmia, but must also be affected by the associations between the QTc interval and cardiovascular risk factors. In this study, the relationship between the QTc interval and stroke mortality disappeared after we adjusted for conventional cardiovascular risk factors.

The current study had the following limitations: (1) We measured the QT interval manually in lead II (or lead I or III if it was difficult to measure in lead II), and the mean QTc interval was about 20 ms shorter than the value obtained in a previous report involving 12,149 Japanese patients who were referred to a university hospital [26]. Moriya et al. [27] studied 19,153 subjects who were exposed to the atomic bombs dropped on Nagasaki and Hiroshima and found that only two subjects had QTc intervals of <350 ms, while about 6.9% of subjects ($N = 741$) exhibited QTc intervals of <350 ms in the JMS Cohort Study, in which we enrolled subjects from rural districts across Japan. In addition, the incidence of fatal cardiovascular and stroke events in the present study was much lower than those described in previous reports involving other general Japanese populations [9], suggesting that the subjects in the JMS Cohort Study had relatively few cardiovascular risk factors, which might explain why the mean QTc interval of the subjects of the JMS Cohort Study was shorter than those obtained in previous studies involving general Japanese populations. (2) The QTc interval can also be affected by drug use and electrolyte levels; however, these factors were not evaluated in this study. (3) We should have measured the RR interval between the beat for which the QT interval was calculated and the previous beat, whereas we actually calculated the mean of three RR intervals in this study. (4) We were unable to confirm whether fatal arrhythmia had been responsible for any of the cases of sudden cardiac death. (5) We enrolled the subjects during annual health examinations. Therefore, a greater number of female than male subjects participated in this study. In addition, the QTc interval was found to have a more significant effect on mortality risk in women, which was probably attributable to the larger number of female subjects enrolled.

Conclusion

The QTc interval is associated with cardiovascular risk factors in the general Japanese population. Among the general Japanese population examined in this study, the risk of cardiovascular and stroke mortality increased progressively with the Bazett QTc interval quartile, while a J-shaped relationship was observed for the effect of the latter parameter on the risk of sudden cardiac death.

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ORIGINAL ARTICLE

Relationship between screening plasma glucose concentrations and cancer- and all-cause mortality: the Jichi Medical School (JMS) cohort study

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Abstract
Aim Whether plasma glucose concentrations at the screening level in the public health care setting can predict mortality remains to be determined in Japanese people. The aim of this study was to investigate the relationships between screening plasma glucose concentrations and cause- and all-cause mortality in a general Japanese cohort.
Subjects and methods The current study investigated 11,998 community-dwelling participants from 12 Japanese communities who had been registered in the Jichi Medical School Cohort Study (a population-based prospective cohort study) between 1992 and 1995. Mortality was documented as the primary outcome. The relationships between screening plasma glucose concentrations and outcomes were analyzed using Cox proportional hazard models.
Results In all, 1,050 deaths (men/women = 631/419) were identified during a follow-up period of 10.7 years. Compared with the lowest glucose concentration (<5.22 mmol/L), multivariate-adjusted hazard ratios for the highest glucose concentration (≥6.11 mmol/L) were 1.52 (95 % confidence interval [CI], 1.25–1.85) for all-cause mortality and 1.76 (95 % CI, 1.29–2.41) for cancer-cause mortality in men and 4.65 (95 % CI, 1.69–12.78) for myocardial infarction mortality in women.
Conclusions The current Japanese population-based cohort study suggests that high screening plasma glucose concentrations can predict cancer- and all-cause mortality, particularly in men.

Keywords Diabetes mellitus · Cancer mortality · All-cause mortality · Mass screening

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Introduction

Patients with diabetes are at increased risk of cardiovascular disease (CVD) (Haffner et al. 1998). Recent evidence further suggests that patients with diabetes have an increased risk of developing cancer (Giovannucci et al. 2010; Emerging Risk Factors Collaboration 2011). The prevalence of diabetes is increasing worldwide (Thomas et al. 2009). The total number of people with diabetes was estimated to be 382 million (8.3 %) worldwide in 2013 (Guariguata et al. 2014). In Japan, the estimated number of individuals with diabetes was approximately 7.2 million in 2013 (International Diabetes Federation 2013).

To reduce diabetes-related deaths, it is crucial for community mass-screening systems to identify individuals with high mortality associated with these disorders of glucose metabolism (Borch-Johnsen et al. 2003). Screening such people at an earlier phase has also been recommended by the American Diabetes Association (American Diabetes Association 2004). While several studies have already reported the usefulness of community mass screening for detecting subjects with impaired glucose tolerance and diabetes (Ealovega et al. 2004; Nucci et al. 2004; Ziemer et al. 2008; van den Donk et al. 2011), these studies were research-based and used less than optimal methods to identify such individuals in health care settings, casual blood glucose measurement being the optimal

means of achieving high rates of participation in screening programs. In Japan, general screening programs in non-health care settings currently take samples from participants under both fasting and non-fasting conditions (Takahara et al. 2013). Previous cohort studies have reported that casual blood glucose concentrations are predictive of CVD- and all-cause mortality in the general Japanese (Kadowaki et al. 2008) and USA populations (Port et al. 2005), fasting blood glucose concentrations predict cancer-cause mortality in the general Korean populations (Jee et al. 2005), and oral glucose tolerance tests (OGTT) can predict cancer-cause mortality in the general USA populations (Saydah et al. 2003). Because cancer is the leading cause of death in Japan (Katanoda et al. 2013), prevention of diabetes and glucose disorders would contribute to preventing cancer and related deaths. Accurate screening of glucose disorders requires an OGTT; however, this test takes at least 2 h and is costly. Screening plasma glucose (SPG) is an easily obtainable and less costly measure and is already familiar to subjects in public-health-care settings because samples for blood glucose measurement are obtained during general mass screening. Although studies using SPG are therefore preferable, a relationship between SPG concentrations and mortality, particularly cancer-related mortality, has not yet been established in Japanese people. The current prospective cohort study investigated the ability of SPG to predict cause-specific and all-cause mortality in the general Japanese population.

Methods

The Jichi Medical School (JMS) Cohort Study, which was approved by the institution's Ethics Committee and began in 1992, was designed to clarify the risk factors for health and diseases, CVD in particular (Ishikawa et al. 2002). A community government office sent personal invitations to prospective subjects by mail and all participants in the study provided informed consent. Baseline data of subjects free-living in 12 Japanese communities were collected through health examinations (April 1992–July 1995) in accordance with the Health and Medical Service Law in Japan (Ishikawa et al. 2002). The end date of follow-up was 31 December 2005. The study had an overall response rate of 65 % and included 12,490 subjects (4,911 men, 7,579 women; ages, 19–93 years). In the current study, 93 of the participants in the original study were excluded because no follow-up data were available, a further 174 because no baseline glucose values were available and another 225 because they were receiving treatment for diabetes (treatment would have significantly altered their glucose values). Dates of the remaining 11,998 subjects were analyzed in the study.

Based on height in stocking-clad feet and weight in light clothing, each subject's body mass index (BMI) was calculated. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured using a fully automated sphygmomanometer (BP203RV-II, Nippon Colin Co., Ltd., Komaki, Japan). Questionnaires were used to assess the percentages of subjects who smoked tobacco and/or consumed alcohol. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and plasma glucose (PG) concentrations were measured enzymatically (SRL Inc., Tokyo, Japan). Blood samples were collected in the morning in tubes containing sodium fluoride for PG or tubes without anticoagulant for the other variables, and then centrifuged at 3,000 × g for 15 min at room temperature. Those for PG were then stored at 4 °C in refrigerated containers with dry ice for a maximum of 6 h, after which they were analyzed or frozen as rapidly as possible to −80 °C until use. The serum samples were stored at 4 °C in refrigerated containers until measurement, which occurred within 1 or 2 days. Information regarding cause of deaths was collected using data from death certificates and national vital statistics with the permission of the Agency of General Affairs.

Three groups were defined according to SPG as follows: high group ≥6.11 mmol/L; middle group 5.22≤6.10 mmol/L; and low group SPG <5.22 mmol/L, as defined in a previous study (Janssen et al. 2007). Descriptive variables are presented as mean ± standard deviation (SD), median (interquartile range) or percentage. One-way analysis of variance and the χ^2 test were used for statistical comparisons. The relationship between SPG concentrations and mortality was examined using the Cox proportional hazards model. After adjustment for age and confounding factors (BMI, SBP, TC, HDL-C, TG, smoking and alcohol consumption; Leys et al. 2002; Patel et al. 2004), hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated for mortality. Statistical significance was defined as $p<0.05$. These analyses were carried out using the SPSS program, version 11 (SPSS Inc., Tokyo, Japan).

Results

The mean duration of follow-up was 10.7±2.4 years. Table 1 shows the baseline characteristics of subjects grouped by SPG category and gender. The mean ages of men and women were 55.0±12.1 and 55.2±11.2 years, respectively. In men, age, BMI, SBP, DBP, and TG values were significantly positively correlated with SPG concentrations, whereas in women, age, BMI, SBP, DBP, TC, HDL-C, and TG values were significantly positively correlated with SPG concentrations. The prevalence of smoking in men and women and drinking habits in women were significantly related to SPG concentrations; drinking habits in men were not significantly related to SPG concentrations.

Table 2 shows the number and proportion of deaths according to cause of death. In total, 631 men and 419 women

Table 1 Baseline characteristics of participants by screening plasma glucose concentration and gender

	Screening plasma glucose concentrations (mmol/L)									*P*
	<5.22			5.22–6.10			≥6.11			
Men										
	N	Mean	(SD)	*N*	Mean	(SD)	*N*	Mean	(SD)	
Age (years)	1,943	54.4	(13.1)	1,524	54.9	(11.8)	1,229	56.3	(10.5)	<0.001
BMI (kg/m^2)	1,853	22.6	(2.7)	1,466	23.1	(2.9)	1,189	23.4	(3.1)	<0.001
SBP (mm Hg)	1,952	122.5	(31.8)	1,538	128.4	(32.0)	1,310	130.8	(31.0)	<0.001
DBP (mm Hg)	1,952	74.0	(19.1)	1,538	77.6	(19.2)	1,310	78.2	(18.6)	<0.001
TC (mmol/L)	1,952	4.8	(0.9)	1,538	4.8	(0.9)	1,310	4.7	(0.9)	0.017
HDL-C (mmol/L)	1,952	1.3	(0.3)	1,538	1.3	(0.3)	1,310	1.2	(0.4)	0.012
TG (mmol/L)[a]	1,952	1.1	(0.8–1.5)	1,538	1.2	(0.8–1.7)	1,310	1.3	(0.9–2.0)	<0.001
Smoking	*N*	%		*N*	%		*N*	%		
Current	986	53.7		662	46.1		613	50.8		<0.001
Former	480	26.2		454	31.6		331	27.4		
Never	369	20.1		319	22.2		263	21.8		
Drinking										
Current	1,340	74.0		1,072	76.7		858	74.8		<0.218
Former	60	3.3		48	3.4		51	4.4		
Never	412	22.7		278	19.9		238	20.7		
Women										
	N	Mean	(SD)	*N*	Mean	(SD)	*N*	Mean	(SD)	
Age (years)	3,559	53.4	(12.0)	2,266	56.5	(10.8)	1,477	57.9	(9.2)	<0.001
BMI (kg/m^2)	3,409	22.6	(3.0)	2,210	23.5	(3.2)	1,452	23.7	(3.4)	<0.001
SBP (mm Hg)	3,564	120.4	(29.9)	2,273	127.3	(28.0)	1,580	131.6	(27.0)	<0.001
DBP (mm Hg)	3,564	72.0	(17.7)	2,273	75.7	(16.4)	1,580	77.6	(15.6)	<0.001
TC (mmol/L)	3,564	5.0	(0.9)	2,273	5.1	(0.9)	1,580	5.2	(0.9)	<0.001
HDL-C (mmol/L)	3,564	1.4	(0.3)	2,273	1.3	(0.3)	1,580	1.3	(0.3)	<0.001
TG (mmol/L)[a]	3,564	0.9	(0.7–1.3)	2,273	1.1	(0.8–1.5)	1,580	1.2	(0.9–1.8)	<0.001
Smoking	N	%		N	%		N	%		
Current	216	7.2		105	5.0		60	4.2		<0.001
Former	121	3.6		51	2.4		23	1.6		
Never	2,991	89.9		1,951	92.6		1,354	94.2		
Drinking										
Current	938	28.3		477	23.3		257	19.0		<0.001
Former	47	1.4		31	1.5		24	1.8		
Never	2,326	70.3		1,542	75.2		1,069	79.2		

BMI body mass index; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *TC* total cholesterol; *HDL-C* high-density lipoprotein cholesterol; *TG* triglyceride. Except for TG, data are shown as mean ± standard deviation for quantitative data and as percentages for qualitative data.

[a] Data are shown as median and interquartile range. *P* values were compared between groups by one-way analysis of variance or the χ^2 test. Cut-offs for the lowest and highest tertiles were <5.22 and ≥6.11 mmol/L, respectively

died during the study. The death rates for stroke, heart disease and cancers were 10.5 % (1.2/1,000 person-years), 11.4 % (1.3/1,000 person-years) and 38.0 % (4.4/1,000 person-years), respectively, in men, and 14.3 % (0.7/1,000 person-years), 14.1 % (0.7/1,000 person-years) and 36.8 % (1.8/1,000 person-years), respectively, in women.

Table 3 shows the number of deaths, crude incidence rates, and HRs and 95 % CIs for all-cause mortality according to SPG concentrations. Compared with the lowest SPG group (<5.22 mmol/L), the multivariate-adjusted HRs of the highest SPG group (<6.11 mmol/L) were 1.52 (95 % CI, 1.25–1.85) for men and 1.24 (0.96–1.61) for women.

Table 4 shows HRs and 95 % CIs for mortality from stroke, heart disease and cancer according to SPG concentrations. For mortality of stroke, compared with the

Table 2 Incidence and proportional rate of causes of deaths

Causes	Men			Women		
	N	%	Incidence[a]	*N*	%	Incidence[a]
Stroke	66	10.5	1.2	60	14.3	0.7
SAH	7	1.1	0.1	16	3.8	0.2
Infarction	36	5.7	0.7	28	6.7	0.3
Hemorrhage	18	2.9	0.3	12	2.9	0.1
Other	5	0.8	0.1	4	1.0	0.05
Heart disease	72	11.4	1.3	59	14.1	0.7
Infarction	30	4.8	0.5	27	6.4	0.3
Heart failure	20	3.2	0.4	13	3.1	0.2
Other	22	3.5	0.4	19	4.5	0.2
Cancer	240	38.0	4.4	154	36.8	1.8
Lung	68	10.8	1.2	21	5.0	0.2
Stomach	26	4.1	0.5	21	5.0	0.2
Colon	17	2.7	0.3	18	4.3	0.2
Other	129	20.4	2.3	94	22.4	1.1
Others	253	40.1	4.6	146	34.8	1.7
Pneumonia	68	10.8	1.2	25	6.0	0.3
Suicide	24	3.8	0.4	17	4.1	0.2
Accident	29	4.6	0.5	7	1.7	0.1
Other	132	20.9	2.4	97	23.2	1.1
Total	631	100	11.4	419	100	4.9

SAH subarachnoid hemorrhage

[a] Incidence expressed per 1,000 person-year

lowest SPG group, the multivariate-adjusted HRs of the highest SPG group were 1.47 (95 % CI, 0.80–2.69) for

Table 3 All-cause mortality by screening plasma glucose concentration

	Screening plasma glucose concentrations (mmol/L)		
	<5.22	5.22–6.10	≥6.11
Men			
N (Incidence[a])	238 (10.5)	178 (13.3)	215 (15.0)
Crude HR	1	0.98 (0.80–1.19)	1.46 (1.20–1.76)
Age-adjusted HR	1	1.04 (0.85–1.27)	1.54 (1.27–1.86)
Multi-adjusted HR[b]	1	1.09 (0.89–1.33)	1.52 (1.25–1.85)
Women			
N (Incidence[a])	179 (4.3)	127 (4.8)	113 (6.5)
Crude HR	1	1.14 (0.91–1.43)	1.35 (1.05–1.72)
Age-adjusted	1	0.99 (0.79–1.24)	1.19 (0.93–1.52)
Multi-adjusted HR[b]	1	1.05 (0.83–1.32)	1.24 (0.96–1.61)

[a] Incidence expressed per 1,000 person-year

[b] Adjusted for age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglyceride, and current smoking and alcohol consumption

Table 4 Cause-specific mortality by screening plasma glucose concentration

	Screening plasma glucose concentrations (mmol/L)		
	<5.22	5.22–6.10	≥6.11
Men			
Stroke			
N (Incidence[a])	21 (0.9)	18 (1.2)	24 (1.7)
Crude HR	1	1.01 (0.54–1.87)	1.68 (0.94–3.00)
Age-adjusted HR	1	1.08 (0.58–2.01)	1.81 (1.01–3.24)
Multi-adjusted HR[b]	1	1.01 (0.54–1.90)	1.47 (0.80–2.69)
Ischemic stroke			
N (Incidence[a])	11 (0.5)	11 (0.6)	14 (1.0)
Crude HR	1	1.41 (0.60–3.31)	2.15 (0.94–4.91)
Age-adjusted HR	1	1.54 (0.65–3.64)	2.42 (1.05–5.59)
Multi-adjusted HR[b]	1	1.53 (0.64–3.69)	2.23 (0.93–5.32)
Hemorrhagic stroke			
N (Incidence[a])	9 (0.4)	4 (0.5)	5 (0.3)
Crude HR	1	0.57 (0.18–1.85)	0.91 (0.31–2.72)
Age-adjusted HR	1	0.59 (0.18–1.91)	0.91 (0.30–2.72)
Multi-adjusted HR[b]	1	0.53 (0.16–1.73)	0.67 (0.22–2.09)
Heart disease			
N (Incidence[a])	27 (1.2)	23 (1.5)	22 (1.5)
Crude HR	1	1.11 (0.63–1.96)	1.45 (0.82–2.57)
Age-adjusted HR	1	1.22 (0.69–2.16)	1.62 (0.91–2.89)
Multi-adjusted HR[b]	1	1.32 (0.74–2.37)	1.57 (0.87–2.84)
Myocardial infarction			
N (Incidence[a])	10 (0.4)	10 (0.6)	6 (0.4)
Crude HR	1	1.29 (0.51–3.24)	1.85 (0.75–4.56)
Age-adjusted HR	1	1.48 (0.59–3.75)	2.30 (0.92–5.78)
Multi-adjusted HR[b]	1	1.91 (0.73–4.99)	2.63 (1.01–6.86)
Heart failure			
N (Incidence[a])	10 (0.4)	4 (0.6)	6 (0.4)
Crude HR	1	0.55 (0.17–1.75)	1.09 (0.39–3.03)
Age-adjusted HR	1	0.62 (0.19–2.00)	1.29 (0.45–3.66)
Multi-adjusted HR[b]	1	0.59 (0.18–1.93)	1.11 (0.38–3.27)
Stroke + Heart disease			
N (Incidence[a])	48 (2.1)	41 (2.7)	46 (3.2)
Crude HR	1	1.06 (0.70–1.62)	1.56 (1.04–2.34)
Age-adjusted HR	1	1.15 (0.76–1.76)	1.71 (1.13–2.58)
Multi-adjusted HR[b]	1	1.18 (0.77–1.80)	1.54 (1.01–2.36)
Cancer			
N (Incidence[a])	86 (3.8)	65 (4.8)	89 (6.2)
Crude HR	1	1.00 (0.73–1.39)	1.73 (1.28–2.34)
Age-adjusted HR	1	1.05 (0.76–1.47)	1.76 (1.30–2.38)
Multi-adjusted HR[b]	1	1.12 (0.81–1.56)	1.76 (1.29–2.41)
Women			
Stroke			
N (Incidence[a])	23 (0.6)	20 (0.8)	14 (0.8)
Crude HR	1	1.22 (0.68–2.19)	0.94 (0.45–1.94)
Age-adjusted HR	1	1.07 (0.60–1.93)	0.86 (0.41–1.79)
Multi-adjusted HR[b]	1	1.17 (0.65–2.12)	0.97 (0.46–2.04)
Ischemic stroke			
N (Incidence[a])	12 (0.3)	9 (0.3)	7 (0.4)
Crude HR	1	1.19 (0.50–2.81)	0.81 (0.26–2.50)

Table 4 (continued)

	Screening plasma glucose concentrations (mmol/L)		
	<5.22	5.22–6.10	≥6.11
Age-adjusted HR	1	1.09 (0.46–2.60)	0.83 (0.26–2.60)
Multi-adjusted HR[b]	1	1.15 (0.48–2.78)	0.83 (0.26–2.66)
Hemorrhagic stroke			
N (Incidence[a])	2 (0.05)	6 (0.2)	4 (0.2)
Crude HR	1	4.86 (0.98–24.11)	5.10 (0.93–27.88)
Age-adjusted HR	1	4.30 (0.87–21.36)	4.78 (0.86–26.45)
Multi-adjusted HR[b]	1	4.89 (0.97–24.72)	6.19 (1.09–35.14)
Heart disease			
N (Incidence[a])	24 (0.6)	17 (0.6)	18 (1.0)
Crude HR	1	1.19 (0.64–2.23)	1.75 (0.92–3.31)
Age-adjusted HR	1	1.10 (0.58–2.05)	1.85 (0.96–3.56)
Multi-adjusted HR[b]	1	1.06 (0.56–2.02)	1.67 (0.84–3.27)
Myocardial infarction			
N (Incidence[a])	8 (0.2)	7 (0.3)	12 (0.7)
Crude HR	1	1.59 (0.56–4.52)	4.19 (1.65–10.64)
Age-adjusted HR	1	1.49 (0.52–4.26)	4.66 (1.79–12.11)
Multi-adjusted HR[b]	1	1.48 (0.50–4.33)	4.65 (1.69–12.78)
Heart failure			
N (Incidence[a])	7 (0.2)	3 (0.1)	3 (0.2)
Crude HR	1	0.69 (0.18–2.65)	0.71 (0.15–3.44)
Age-adjusted HR	1	0.60 (0.16–2.32)	0.67 (0.14–3.28)
Multi-adjusted HR[b]	1	0.56 (0.14–2.21)	0.53 (0.10–2.76)
Stroke + Heart disease			
N (Incidence[a])	47 (1.2)	37 (1.4)	32 (1.8)
Crude HR	1	1.21 (0.79–1.85)	1.31 (0.82–2.11)
Age-adjusted HR	1	1.08 (0.71–1.66)	1.28 (0.79–2.07)
Multi-adjusted HR[b]	1	1.12 (0.72–1.72)	1.28 (0.79–2.10)
Cancer			
N (Incidence[a])	58 (1.4)	52 (2.0)	13 (0.8)
Crude HR	1	1.42 (0.98–2.07)	1.60 (1.06–2.41)
Age-adjusted HR	1	1.25 (0.86–1.81)	1.36 (0.90–2.04)
Multi-adjusted HR[b]	1	1.28 (0.87–1.87)	1.37 (0.90–2.09)

[a] Incidence expressed per 1,000 person-year

[b] Adjusted for age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglyceride, and current smoking and alcohol consumption

men and 0.97 (0.46–2.04) for women. For mortality of heart disease, compared with the lowest SPG group, the multivariate-adjusted HRs of the highest SPG group were 1.57 (95 % CI, 0.87–2.84) for men and 1.67 (0.84–3.27) for women. For mortality of myocardial infarction, compared with the lowest SPG group, the age-adjusted HR of the highest SPG group was 4.66 (95 % CI, 1.79–12.11) and the multivariate-adjusted HR of the highest SPG group was 4.65 (1.69–12.78) for women. For cancer-cause mortality, compared with the lowest SPG group, the multivariate-adjusted HRs of the highest SPG group were 1.76 (95 % CI, 1.29–2.41) for men and 1.37 (0.90–2.09) for women.

Discussion

The Japanese population-based study, the JMS Cohort Study, has shown that high SPG concentrations are predictors of cancer- and all-cause mortality in the general Japanese population, particularly in men. High SPG concentrations also predicted CVD mortality in men (myocardial infarction and stroke) and in women (myocardial infarction). The results of this study are important because the ability of SPG, a simple measure, to predict major outcomes has not previously been conclusively proven in Japanese people.

Subjects with diabetes have higher all-cause mortality than those without diabetes (Campbell et al. 2012). In the current study, SPG concentrations ≥6.11 mmol/L were predictors of high risk of all-cause mortality, particularly in men. This SPG concentration is lower than that required to diagnose diabetes (American Diabetes Association 2004). Thus, our findings suggest that this risk may be increased even in individuals with pre-diabetes. Additionally, in the current study, total death rates were higher in men than in women, and all-cause mortality was more clearly related to SPG concentrations in men than in women. This difference between the sexes may be, in part, linked to gender-specific socio-biological factors, namely, the more frequent development of lifestyle-related diseases and shorter lifespan of men than of women (Fodor and Tzerovska 2004; Manuel and Schultz 2004; Pinkhasov et al. 2010).

In Japan, cancer and CVD are the major causes of deaths (Murray and Lopez 2013; Katanoda et al. 2013). Epidemiologic evidence suggests that diabetes is associated with higher cancer incidence (Giovannucci et al. 2010) and cancer mortality in the USA (Gregg et al. 2012). Diabetes and cancer are common diseases with tremendous impacts on health worldwide. Hyperglycemia itself may promote carcinogenesis by increasing oxidative stress by Abe and Yamagishi (2008). Hyperglycemia is linked with several conditions that are associated with increased risk of cancer, namely insulin resistance, obesity, chronic inflammation, and antidiabetic agents (Pandey et al. 2011). In the current study, like the risk of all-cause mortality, a lower SPG concentration than that required to diagnose diabetes (American Diabetes Association 2004) predicted an increased risk of cancer, particularly in men. Even individuals with pre-diabetes may be thus at increased risk of cancer mortality in men. Cancer death rates were higher in men than in women in the current study. Further investigation is necessary for identifying gender-related factors (i.e., socio-biological factors, Pinkhasov et al. 2010) that can affect cancer mortality.

As for CVD, glucose exposure induces endothelial impairment with reduced nitric oxide function and thrombotic progression, thereby leading to an increased incidence of CVD (Folli et al. 2011). Subjects with increased glucose

concentrations (including those with not very high concentrations) are reported to have increased CVD mortality (Fisman et al. 2001; Saaristo et al. 2010). In population-based screening, high casual blood glucose concentrations are reported to predict CVD mortality (Port et al. 2005; Kadowaki et al. 2008). The current study finding of a significant association between SPG concentrations and CVD mortality seems to support the results of these earlier studies.

This study has some limitations. The duration of follow-up may have been too short to accurately evaluate the incidence of deaths, and the recorded incidence of deaths was too low to accurately evaluate an association between SPG concentrations and risk of mortality. This study did not investigate cause-specific cancer mortality. These limitations need to be addressed in future studies.

In conclusion, this cohort study of the general Japanese population showed that high SPG concentrations can predict cancer- and all-cause mortality, particularly in men, and CVD mortality in men and women. Mass screening of SPG may make a useful contribution to public health measures. Further evidence is necessary.

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Conflict of interest The authors have no conflicts of interest to declare.

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Article

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Soy and Soy Products Intake, All-Cause Mortality, and Cause-Specific Mortality in Japan: The Jichi Medical School Cohort Study

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Abstract

Soy and soy products are popular ingredients in the Japanese diet. This study aimed to determine whether soy or soy products intake was associated with all-cause mortality in a community-based cohort in Japan. A total of 11 066 participants were obtained from an annual community-based health examination program. A self-administered questionnaire was used to collect information concerning soy and soy products intake and potential confounding factors. Associations between soy and soy products intake and all-cause mortality were assessed using hazard ratios (HRs). After adjusting for all factors, morality was significantly higher in men with infrequent soy intake (HR = 1.53; 95% confidence interval [CI] = 1.13-2.07) and with almost daily intake (HR = 1.55; 95% CI = 1.19-2.03) compared with intake 1 to 2 times per week. Cancer mortality was higher among men who reported rarely eating soy (HR = 1.74; 95% CI = 1.08-2.79). Soy products intake was not statistically significantly associated with all-cause mortality in both sexes.

Keywords

all-cause mortality, cardiovascular disease, cancer, dietary intake, soy or soy products

Background

Japanese men and women have a mean soy intake that is generally higher than that of Western individuals,[1,2] reflecting the use of soy products in the traditional Japanese diet. Soy contains high quantities of the isoflavones daidzein and genistein. It has been reported that soy itself exhibits antiatherosclerotic and anticarcinogenic activities and that it can prevent hypertension.[3-5] Some meta-analyses have also reported an impact of soy intake on risk factors for cardiovascular disease.[6,7] In epidemiological studies, populations with a higher intake of soy proteins have been

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reported to have a lower incidence of cardiovascular events[8] and stomach cancer.[9] In contrast, a Japan Public Health Center-based (JPHC) study suggested that the intake of isoflavones and soy food had no substantial effect on the risk of colorectal cancer in Japanese men and women.[10] Moreover, the JPHC study reported that isoflavone consumption may be associated with an increased risk of hepatocellular carcinoma in women.[11] However, the Gifu Takayama study reported that soy intake was associated with a moderate but statistically significant inverse association with all-cause mortality in women. A similar reduction in all-cause mortality was observed for men. However, there was no statistically significant association of soy intake with specific causes of death or all-cause mortality, except for a reduction in cardiovascular mortality in women.[12] A systematic review reported that soy products appear to be protective against ischemic stroke in Japanese populations, but the numbers in the individual studies were too small to draw definite conclusions.[13] Thus, the association between soy or soy products intake and all-cause mortality remains controversial. The aim of the present study was to determine whether soy or soy products intake was associated with all-cause mortality, cardiovascular mortality, or cancer mortality in a community-based population cohort in Japan.

Methods

Study Population

The Jichi Medical School Cohort Study was a multicenter study that investigated risk factors for cardiovascular disease in Japanese populations. Details of the study design have been described previously.[14] In brief, baseline data were obtained between 1992 and 1995. The study participants comprised 12 490 Japanese individuals who attended health examination programs for cardiovascular disease in 12 communities across Japan and who were followed up until 2005. Among the 12 490 participants, we excluded individuals who refused to be followed up (n = 95), lived outside the study areas at the baseline survey (n = 2), did not respond to questions about soy and soy product intake (n = 755), or had a past medical history of myocardial infarction, stroke, or neoplasm (n = 572). Finally, 11 066 participants (4309 men, 6757 women; age range = 19-93 years) were included in the analysis.

Assessment of Soy and Soy Products Intake

At baseline, information about soy and soy products intake was assessed using a food frequency questionnaire (FFQ) that contained 30 items, including soy and soy products such as bean curd, fried soy, and *natto*.[15] The soy products are usually produced in a variety of different methods. Therefore, we analyzed soy and soy products separately in this study. The FFQ was based on a questionnaire used in the Japan Collaborative Cohort (JACC) Study, which had demonstrated acceptable reproducibility and validity. In the FFQ, the frequency of intake of each food was assessed by a 5-level scale: 1, seldom; 2, 1 to 2 times per month; 3, 1 to 2 times per week; 4, 3 to 4 times per week; and 5, almost every day. Soy products intake was classified into 3 categories: less than 1 to 2 times per month, 1 to 4 times per week, and almost every day because of the small number of individuals in the "rarely" category. In addition, according to a study conducted by the Japanese Ministry of Health, Labour and Welfare, *miso* was classified as seasoning, so miso soup was not included in the determination.

Behavioral Profiles and Education and Laboratory Data

Education status and behavioral variables that were considered to be potential confounding factors were ascertained by a standardized questionnaire. Smoking habits were classified as "never