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Two risk score models for predicting incident Type 2 diabetes in Japan

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Abstract

Aims Risk scoring methods are effective for identifying persons at high risk of Type 2 diabetes mellitus, but such approaches have not yet been established in Japan.

Methods A total of 1935 subjects of a derivation cohort were followed up for 14 years from 1988 and 1147 subjects of a validation cohort independent of the derivation cohort were followed up for 5 years from 2002. Risk scores were estimated based on the coefficients (β) of Cox proportional hazards model in the derivation cohort and were verified in the validation cohort.

Results In the derivation cohort, the non-invasive risk model was established using significant risk factors; namely, age, sex, family history of diabetes, abdominal circumference, body mass index, hypertension, regular exercise and current smoking. We also created another scoring risk model by adding fasting plasma glucose levels to the non-invasive model (plus-fasting plasma glucose model). The area under the curve of the non-invasive model was 0.700 and it increased significantly to 0.772 ($P < 0.001$) in the plus-fasting plasma glucose model. The ability of the non-invasive model to predict Type 2 diabetes was comparable with that of impaired glucose tolerance, and the plus-fasting plasma glucose model was superior to it. The cumulative incidence of Type 2 diabetes was significantly increased with elevating quintiles of the sum scores of both models in the validation cohort (P for trend < 0.001).

Conclusions We developed two practical risk score models for easily identifying individuals at high risk of incident Type 2 diabetes without an oral glucose tolerance test in the Japanese population.

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Keywords community-dwelling Japanese subjects, oral glucose tolerance test, risk models, Type 2 diabetes

Introduction

The number of individuals with Type 2 diabetes mellitus is rapidly growing worldwide [1], probably because population growth, ageing and urbanization are progressing, and the prevalence of obesity and physical inactivity is also increasing [2]. Thus, the burden of Type 2 diabetes and its complications, including macro- and microvascular diseases, is an important concern in global healthcare systems. A practical and effective scheme for the prevention of Type 2 diabetes should be established without delay. Two randomized clinical trials in Europe and the USA have demonstrated that Type 2 diabetes can largely be prevented through diet and lifestyle modifications in individuals at high risk [3,4]. Similar results were also reported in different ethnic populations, such as Japanese [5], Chinese [6] and Asian Indians [7]. In these researches, the estimation of a person's future risk of Type 2 diabetes has depended primarily on identifying impaired glucose tolerance [3–7]. However, the 75-g oral glucose tolerance test integral to a diagnosis of impaired glucose tolerance is relatively costly and inconvenient, and its reliability has been questioned [8]. These facts have stimulated the development of simple scoring methods involving readily available clinical information capable of predicting Type 2 diabetes with equal or better diagnostic properties than impaired glucose tolerance. To date, risk score models have been derived from several Caucasian populations [9–16] and a few Asians populations [17–19] but none have been developed in Japanese.

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The aim of the present study was to develop and evaluate risk score models for the Japanese population to identify individuals at high risk for incident Type 2 diabetes without an oral glucose tolerance test.

Subjects and methods

Setting and participants

Derivation cohort survey

A population-based prospective study of cardiovascular disease and its risk factors has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. The age and occupational distributions and nutritional intake of the population were almost identical to those of Japan as a whole based on data from the national census and nutrition survey [20]. In 1988, a derivation cohort survey was performed in the town. A detailed description of this survey was published previously [20]. Briefly, of the 3227 residents aged 40–79 years based on the town registry, a total of 2587 residents (participation rate, 80.2%) consented to take part in a comprehensive assessment. After excluding 82 subjects who had already had breakfast, 10 who were on insulin therapy and 15 because of complaints of nausea or general fatigue during the ingestion of glucose, a total of 2480 subjects completed the oral glucose tolerance test. Among these, 297 subjects with diabetes, 52 for whom there was no measurement of waist circumference and two who died before the start of follow-up, were excluded; the remaining 2129 subjects (894 men and 1235 women) were enrolled in the baseline examination.

The baseline subjects were followed up prospectively from December 1988 to November 2002 by yearly health examinations. Of the baseline subjects, 1935 subjects (793 men and 1142 women) who underwent re-examinations were finally selected for the present study (follow-up rate, 90.9%; mean follow-up period, 11.8 years).

Validation cohort survey

A validation cohort survey was conducted in the same town and in a similar fashion in 2002. The study design of the survey has been described in detail elsewhere [21]. In brief, of the 3896 residents aged 40–79 years, 3000 (participation rate, 77.0%) consented to participate in the examination and underwent a comprehensive assessment. Among them, 178 participants were not administered the oral glucose tolerance test: 100 subjects refused the test, 46 had already taken breakfast and another 32 were receiving insulin therapy for diabetes. Consequently, 2822 subjects completed the oral glucose tolerance test. After further excluding 485 subjects with diabetes, one for whom there was no measurement of waist circumference, one who had no information of family history of diabetes and 1044 who were participants of the derivation cohort, the remaining 1291 subjects (550 men and 741 women) were determined to constitute a validation cohort independent of the derivation cohort.

The subjects were followed up prospectively from December 2002 to November 2007 by yearly health examinations. Of the baseline subjects of the validation cohort, 1147 (473 men and 674 women) who underwent re-examinations were finally selected for the present study (follow-up rate, 88.8%; mean follow-up period, 4.7 years).

Clinical evaluation and laboratory measurements

In both the 1988 and 2002 surveys, clinical evaluation and laboratory measurements were performed in a similar manner. The study subjects underwent the oral glucose tolerance tests between 08.00 and 10.30 h after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h post-load and was separated immediately into plasma and blood cells. The glucose tolerance levels were defined by the American Diabetes Association criteria in 2003 as follows [8]—impaired glucose tolerance: fasting plasma glucose concentrations of < 7.0 mmol/l and 2-h post-load glucose concentrations of 7.8–11.0 mmol/l; diabetes mellitus: fasting plasma glucose concentrations of ≥ 7.0 mmol/l and/or 2-h post-load glucose concentrations of ≥ 11.1 mmol/l and/or the use of anti-diabetic medications. At the baseline of each survey, waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Body height and weight were measured in light clothing without shoes and the BMI (kg/m^2) was calculated. Blood pressure was obtained three times using a sphygmomanometer in 1988 and an automated sphygmomanometer (BP-203RV III; Colin, Tokyo, Japan) in 2002 with the subject in a sitting position; the average values were used in the analyses. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current treatment with anti-hypertensive agents.

Each participant completed a self-administered questionnaire covering medical history, anti-diabetic and anti-hypertensive treatments, alcohol intake and smoking habits. Diabetes mellitus in first- or second-degree relatives was taken to indicate a family history of diabetes. Subjects engaging in sports at least three times per week during their leisure time were defined as the regular exercise group.

Follow-up survey of derivation and validation cohorts

An oral glucose tolerance test was performed every year in the follow-up examinations. Subjects from the derivation cohort participated in the follow-up examinations an average of 6.9 times and subjects of the validation cohort an average of 3.2 times. In the follow-up examinations, the diagnosis of incident diabetes was made in a similar way in both cohorts based on the aforementioned American Diabetes Association criteria. During the follow-up, Type 2 diabetes occurred in 286 subjects (145 men and 141 women) in the derivation cohort and 89 subjects (53 men and 36 women) in the validation cohort.

Statistical analysis

SAS version 9.2 (SAS Institute, Cary, NC, USA) and Stata version 10.0 (StataCorp, College Station, TX, USA) software packages were used to perform all statistical analyses. A P-value < 0.05 was considered statistically significant in all analyses.

The Student t-test and χ^2-test were used for the comparison of baseline clinical characteristics between the derivation and validation cohorts. In this study, we used non-invasive risk factors, which were defined as factors that could be measured without taking a blood sample; namely, age (40–44, 45–54, 55–64 and ≥ 65 years), sex, family history of diabetes, central obesity (abdominal circumference ≥ 90 cm in men and ≥ 80 cm in women), BMI (≤ 21.9, 22.0–24.9 and ≥ 25.0 kg/m^2), hypertension, smoking habits (non-smoking, 1–9 and ≥ 10 cigarettes per day), alcohol intake (0, 1–39 and ≥ 40 g of alcohol per day) and regular exercise. Adjusted hazard ratios (HR) and their 95% confidential intervals (CI) were estimated by using the stepwise backward elimination method of Cox proportional hazards model. In the multivariate analysis, we selected independent risk factors for the development of Type 2 diabetes at $P < 0.05$ and composed a non-invasive risk model from these variables. In addition, we created a 'plus-fasting plasma glucose model' in which fasting plasma glucose levels (≤ 5.5, 5.6–6.0 and ≥ 6.1 mmol/l) were added to the non-invasive model. By the use of each scoring model, risk scores for the risk levels of each variable were determined as integral values based on the coefficients (β) of the Cox proportional hazards model, and the sum of the scores was calculated. The probability (P) of incident diabetes for both models was estimated by the following formula: $P = 1 - \{S_0(t)\}^{exp[b0+b1(x1-mx1)+b2(x2-mx2)+.....+bn(xn-mxn)}$ where P was the probability of developing diabetes within time t; $S_0(t)$ was diabetes-free survival probability at the time t in individuals with the profiles corresponding to the means of the explanatory variables; b1, b2 and bn were coefficients estimated by the model for risk factors, such as x1, x2 and xn; mx1, mx2 and mxn were given as the means. The probability was calculated over a 10-year time frame. In addition, a receiver operating characteristic curve was plotted based on the sum of the scores and the probability of incident Type 2 diabetes by each model, and the area under the curve, which indicates the predictive ability of incident Type 2 diabetes, was estimated for each model. The optimal cut-off points of the sum of the scores for predicting Type 2 diabetes were defined as the maximum combination of sensitivity and specificity. The difference in the area under the curve of the receiver operating characteristic curve between models was estimated using DeLong's method [22]. In the derivation cohort, subjects were divided into deciles of the sum scores and predicted risk derived from each model was compared with observed risk. The goodness of fit, which was assessed by the Hosmer–Lemeshow test [23] was calculated according to a χ^2 distribution with eight degrees of freedom.

Ethical considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research and written informed consent was obtained from all the participants.

Results

Table 1 shows the baseline clinical characteristics of subjects in the derivation and validation cohorts. The derivation cohort was older than the validation cohort, but the proportion of men was not different between the two. The mean values of abdominal circumference and systolic blood pressure, and the frequency of hypertension were higher in the derivation cohort than in the validation cohort, whereas the mean values of fasting plasma glucose and frequencies of family history of diabetes, smoking habits and alcohol intake were higher in the validation cohort. Other variables did not differ between the cohorts.

Table 1 Characteristics of subjects in the derivation and validation cohorts

	Derivation cohort (n = 1935)	Validation cohort (n = 1147)	P-value
Age (years)	57.2 (10.2)	52.2 (8.6)	< 0.001
Men (%)	41.0	41.2	0.89
Fasting plasma glucose (mmol/l)	5.5 (0.5)	5.7 (0.5)	< 0.001
Two-hour post-load glucose (mmol/l)	6.6 (1.6)	6.7 (1.6)	0.07
Family history of diabetes mellitus (%)	7.4	13.8	< 0.001
Abdominal circumference (cm)	81.4 (9.1)	80.5 (9.4)	0.008
BMI (kg/m^2)	22.9 (3.0)	23.0 (3.3)	0.43
Systolic blood pressure (mmHg)	131 (20)	126 (19)	< 0.001
Diastolic blood pressure (mmHg)	78 (11)	77 (12)	0.051
Hypertension (%)	37.0	26.5	< 0.001
Current smoking (%)	23.2	26.9	0.02
Current drinking (%)	33.4	50.6	< 0.001
Regular exercise (%)	10.6	8.6	0.08

All values are given as the mean (standard deviation) or as percentages.

As shown in Table 2, in the derivation cohort, the univariate analysis showed that all non-invasive risk factors—namely, age, sex, family history of diabetes, central obesity, BMI, hypertension, smoking habits, alcohol intake and regular exercise—as well as the fasting plasma glucose levels were significantly associated with incident Type 2 diabetes. In the stepwise backward elimination analysis, non-invasive risk factors other than alcohol intake remained significant, and we constructed the non-invasive model from these risk factors. In the plus-fasting plasma glucose model, fasting plasma glucose was a significant and independent risk factor for Type 2 diabetes, and its risk score was higher than that of other variables. Both models showed no significant difference between predicted and observed Type 2 diabetes incidence, indicating a reasonable fit by the Hosmer–Lemeshow test (non-invasive model: goodness of fit, χ^2 value = 5.76, *P*-value = 0.67; plus-fasting plasma glucose model: goodness of fit, χ^2 value = 6.71, *P*-value = 0.57).

Figure 1 provides a visual presentation of the receiver operating characteristic curves based on the sum of the scores and the probability of incident Type 2 diabetes for the non-invasive and plus-fasting plasma glucose models as well as fasting blood sugar and 2-h post-load glucose values in the derivation cohort. The curve of the sum of the scores was in approximate accordance with that of the probability of incident Type 2 diabetes over 10 years in each model. The area under the curve for the sum of the scores was 0.700 (95% CI 0.667–0.732) and that for the probability of incident Type 2 diabetes was 0.700 (95% CI 0.668–0.733) in the non-invasive model. The optimal cut-off point for the sum of the scores defined by maximizing the sensitivity and specificity to find future Type 2 diabetes was 14 (sensitivity = 62.6% and specificity = 66.5%). In the plus-fasting plasma glucose model, the area under the curve for the sum of the scores and for the probability of incident Type 2 diabetes increased significantly to 0.772 (95% CI 0.742–0.802) and 0.772 (95% CI 0.741–0.802), respectively. The optimal cut-off point for the sum of the scores was 16 (sensitivity = 71.0% and specificity = 69.6%). The area under the curve for the sum scores of the non-invasive model did not significantly differ from that for fasting plasma glucose (AUC = 0.721, *P* = 0.33) and 2-h post-load glucose values (AUC = 0.677, *P* = 0.35), while the

Table 2 Risk scores based on non-invasive and plus-fasting plasma glucose (FPG) models for diabetes incidence in the derivation cohort

	Univariate model				Non-invasive model			Plus-FPG model	
Factors		Hazard ratio	*P*	β	Hazard ratio (95% CI)	Score	β	Hazard ratio (95% CI)	Score
Age (years)	40–44	1			1	0		1	0
	45–54	1.48	0.04	0.41	1.51 (1.03–2.22)	4	0.38	1.47 (0.99–2.17)	4
	55–64	1.57	0.02	0.32	1.38 (0.94–2.04)	3	0.30	1.35 (0.91–2.01)	3
	≥ 65	1.1	0.58	0.14	1.15 (0.72–1.84)	1	−0.09	0.92 (0.57–1.48)	−1
Sex	Women	1			1	0		1	0
	Men	1.59	< 0.001	0.35	1.42 (1.04–1.93)	4	0.16	1.17 (0.86–1.60)	2
Family history of diabetes*	−	1			1	0		1	0
	+	2.17	< 0.001	0.73	2.08 (1.48–2.91)	7	0.70	2.01 (1.43–2.83)	7
Central obesity†	−	1			1	0		1	0
	+	1.54	< 0.001	0.32	1.38 (1.01–1.89)	3	0.26	1.30 (0.94–1.78)	3
BMI (kg/m^2)	≤ 21.9	1			1	0		1	0
	22.0–24.9	1.55	0.004	0.25	1.28 (0.93–1.76)	3	0.19	1.21 (0.88–1.66)	2
	≥ 25.0	2.85	< 0.001	0.67	1.95 (1.36–2.81)	7	0.53	1.69 (1.17–2.46)	5
Hypertension‡	−	1			1	0		1	0
	+	2.23	< 0.001	0.68	1.98 (1.55–2.53)	7	0.51	1.66 (1.30–2.13)	5
Smoking (/day)	0	1			1	0		1	0
	1–9	1.23	0.51	0.16	1.17 (0.63–2.18)	2	0.16	1.17 (0.63–2.17)	2
	≥ 10	1.79	< 0.001	0.46	1.58 (1.16–2.16)	5	0.45	1.56 (1.15–2.96)	5
Alcohol intake (g/day)	0	1							
	1–39	1.40	0.01						
	≥ 40	1.82	0.001						
Regular exercise§	−	1			1	0		1	0
	+	0.59	0.02	−0.51	0.60 (0.37–0.96)	−5	−0.38	0.69 (0.43–1.10)	−4
FPG levels (mmol/l)	< 5.6	1						1	0
	5.6–6.0	2.31	< 0.001				0.68	1.97 (1.46–2.65)	7
	≥ 6.1	8.17	< 0.001				1.89	6.61 (4.89–8.94)	19

*Family history of diabetes was defined as diabetes in first- or second-degree relatives.
†Central obesity was determined by an abdominal circumference of 90 cm or more in men and 80 cm or more in women.
‡Hypertension was defined as blood pressure ≥ 140/90 mmHg and/or current treatment with anti-hypertensive agents.
§Regular exercise was determined as engaging in sports at least three times per week during leisure time.

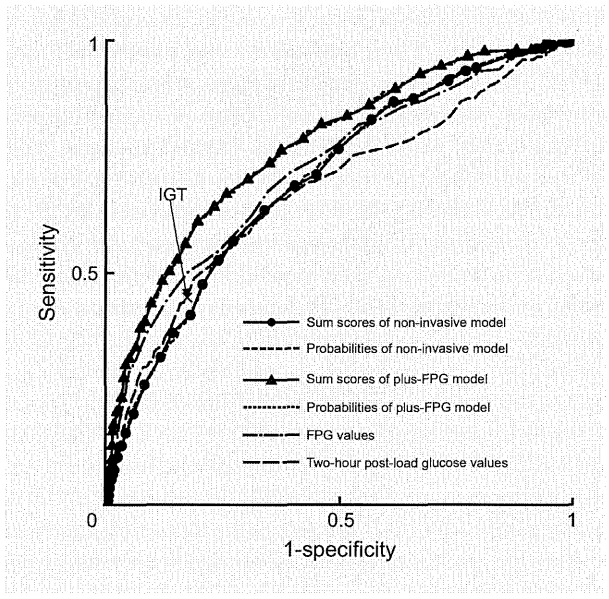

FIGURE 1 Receiver operating characteristics curves of the non-invasive and plus-fasting plasma glucose (FPG) models in the derivation cohort. The cross (×) indicates sensitivity and 1-specificity for impaired glucose tolerance (IGT). The non-invasive model: area under the curve (AUC) for the sum of the scores 0.700 (95% CI 0.667–0.732); AUC for the probability of incident Type 2 diabetes 0.700 (95% CI 0.668–0.733). The plus-FPG model: AUC for the sum of the scores 0.772 (95% CI 0.742–0.802); AUC for the probability of incident Type 2 diabetes 0.772 (95% CI 0.741–0.802). Fasting plasma glucose values: AUC for the probability of incident Type 2 diabetes 0.721 (95% CI 0.687–0.755). Two-hour plasma glucose values: AUC for the probability of incident Type 2 diabetes 0.677 (95% CI 0.687–0.755). The AUCs for the sum of the scores and for the probability of incident Type 2 diabetes of the plus-FPG model increased significantly compared with those of the non-invasive model (both $P < 0.001$).

area under the curve for the sum scores of the plus-fasting plasma glucose model was significantly larger than that for fasting plasma glucose and 2-h post-load glucose values ($P < 0.001$ for both). For impaired glucose tolerance, the sensitivity was 44.8% and the specificity was 82.8%. These findings indicate that the ability of the non-invasive model to predict incident Type 2 diabetes was comparable with that of impaired glucose tolerance, fasting plasma glucose and 2-h post-load glucose values, and the ability of the plus-fasting plasma glucose model was superior to them.

To validate the non-invasive and plus-fasting plasma glucose models of the derivation cohort, the scoring methods were ascertained by applying the scores to the validation cohort. The score distribution of the non-invasive model in the derivation cohort (median 11, interquartile range 7–16) was not significantly different from that in the validation cohort (median 11, interquartile range 7–17) ($P = 0.74$), while the score distribution of the plus-fasting plasma glucose model was shifted significantly to higher levels in the validation cohort (median 15, interquartile range 9–23) than in the derivation cohort (median 12, interquartile range 6–19) ($P < 0.001$). As shown in Fig. 2, the 5-year cumulative incidences of Type 2 diabetes increased significantly with elevating quintiles of the sum scores of the non-invasive and plus-fasting plasma glucose models in the validation cohort (both P for trend < 0.001). In this cohort, the area under the curve for the sum scores of the plus-fasting plasma glucose model for incident Type 2 diabetes (AUC = 0.777; 95% CI 0.727–0.827) was significantly larger than that of the non-invasive model (AUC = 0.691; 95% CI 0.633–0.749) ($P < 0.001$), but did not significantly differ from that for fasting plasma glucose (AUC = 0.777; 95% CI 0.720–0.833) ($P = 0.99$) or 2-h post-load glucose values (AUC = 0.843;

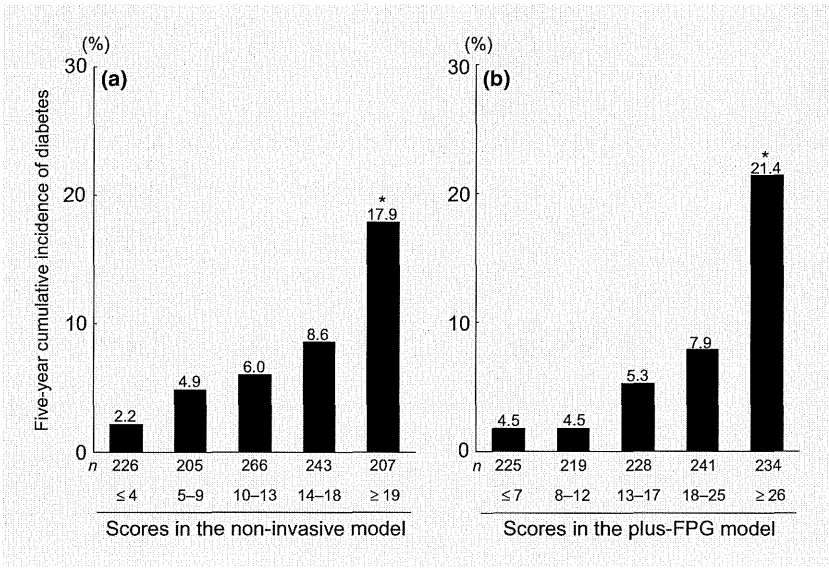

FIGURE 2 Estimated 5-year cumulative incidence of Type 2 diabetes by quintile of prediction scores of the (a) non-invasive and (b) plus-fasting plasma glucose (FPG) models in the independent validation cohort. *P for trend < 0.001.

95% CI 0.800–0.886) ($P = 0.07$). For impaired glucose tolerance, the sensitivity was 70.8% and the specificity was 80.9%.

Discussion

In the present study, we developed two practical risk scoring methods, the non-invasive and plus-fasting plasma glucose models, for prediction of incidence of Type 2 diabetes in Japanese subjects. The variables included in the non-invasive model were age, sex, family history of diabetes, central obesity, BMI, hypertension, smoking and regular exercise, and the plus-fasting plasma glucose model was composed of these factors and fasting plasma glucose levels. The ability of the non-invasive model to predict Type 2 diabetes was comparable with that of impaired glucose tolerance, and the plus-fasting plasma glucose model was superior to the non-invasive model and impaired glucose tolerance as well as fasting plasma glucose and 2-h post-load glucose values. Furthermore, both scoring models were tested in the validation cohort established at a different time, and their utility for identifying persons at high risk of Type 2 diabetes was confirmed. These models could provide an innovative approach for detecting Japanese subjects at high risk of developing Type 2 diabetes in clinical and public health settings.

There are a number of important requirements which must be met by any potential risk assessment model for Type 2 diabetes. First, the risk score model must be appropriately matched to the lifestyle of the ethnic group being studied. The reported risk prediction models for Type 2 diabetes were almost all developed in Caucasians [9–16], with only a few being developed for Asians [17–19] and none being designed specifically for Japanese. Our risk scoring methods are thus the first risk prediction models for incident Type 2 diabetes for Japanese. Second, the scoring method should be appropriate for a primary medical care setting and should allow a non-professional person to perform self-assessment. Some of the reported models have not met this requirement, as the scoring methods were not simplified by using integer point values [10,14,17]. Our two scoring models are easy to use and their scoring methods are simple enough to be calculated using only a pencil and paper through the adoption of integer point scores.

A non-invasive risk prediction model is attractive because it is more convenient and less expensive compared with models that rely on blood tests. Some risk score models for Type 2 diabetes have required the values of biomarkers other than glucose [12,17,19,24]. However, the inclusion of blood test data might not be practical in some situations, as such tests are not easily affordable. Furthermore, it is noteworthy that the ability of our non-invasive model without laboratory tests was almost as good as that of impaired glucose tolerance in predicting the 10-year risk of diabetes. Recent randomized controlled trials have shown that the incidence of diabetes can be decreased significantly by interventions in individuals at high risk of developing Type 2 diabetes; namely, those with impaired glucose tolerance [3–7]. Our non-invasive model would easily identify individuals at high risk of incident Type 2 diabetes without an oral glucose tolerance test in community healthcare and clinical practice.

The predictive performance and discriminative ability of our non-invasive model estimated by the receiver operating characteristic curve was relatively inferior or comparable with those developed among Caucasians (AUC in Caucasian cohorts 0.71–0.85; AUC in our cohort 0.70), although the factors making up the model were similar among these scoring models [9,11–13,16]. It is not clear why the area under the curve in our non-invasive model was smaller than that in the other studies, but the disparity may be related to differences in the aetiology of Type 2 diabetes among races. An epidemiological study has shown that the levels of insulin secretion and resistance differ among various ethnic groups in the USA [25]; Asians had lower levels of insulin secretion compared with other ethnic groups, while Caucasians were more insulin-resistant than Asians. In addition, Japanese individuals with diabetes were found to have lower BMI levels compared with Western individuals with diabetes [26]. Thus, it is speculated that impaired insulin secretion, rather than insulin resistance, plays an important role in the development of Type 2 diabetes among Asian populations. In our risk score models, most of the included factors were predominantly proxy of insulin resistance, and the data on insulin secretion, which is known to be determined mainly by genetic factors [27], were limited. Additionally, the differences in definition of diabetes, distribution of risk factors and changes in risk factors and their distributions over time may contribute to the disparity in the area under the curve among races.

In our study, combining the information on fasting plasma glucose levels with the non-invasive model significantly increased the predictive ability of incident Type 2 diabetes and the fasting plasma glucose concentrations at baseline were the single largest contributor to the risk of diabetes mellitus. Other reports have similarly shown that fasting plasma glucose was a strong predictor of incident Type 2 diabetes [12,16,28]. It is expected that people whose fasting plasma glucose concentration is already close to the diagnostic threshold for Type 2 diabetes are likely to cross the threshold in the near future. Thus, it may be recommended that individuals with higher risk scores in the non-invasive model undergo fasting plasma glucose measurement. However, to date, there is no clear evidence to suggest which strategies are most effective at identifying individuals at high risk and at preventing diabetes in these individuals. Further research into cost-effectiveness for identifying and treating individuals at high risk of diabetes is needed, considering the stepwise strategies incorporating non-invasive risk scores.

Our findings also help to clarify the pathogenesis of incident Type 2 diabetes in Japanese individuals. First, in our study, both BMI and waist circumference independently contributed to risk discrimination for Type 2 diabetes. BMI is an indicator of overall adiposity, whereas waist circumference is highly correlated with visceral adipose tissue, which actively secretes adipocytokines and other vasoactive substances that are associated with the risk of developing Type 2 diabetes [29,30]. Thus, BMI and waist

circumference may each be independent determinants of incident Type 2 diabetes. Second, in our subjects, the risk of diabetes did not increase progressively with age, unlike the risk found in some of the Caucasian cohorts [31,32]. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia Study showed that, in Japanese male subjects, the mean fasting plasma glucose and 2-h post-load glucose concentrations increased with advancing age, reached a peak at 50–59 years, and then remained at an approximate plateau level [33]. A similar phenomenon was observed in Chinese and Indian subjects [33]. The development of Type 2 diabetes might not depend on ageing in the Asian population. Third, regular exercise has a preventive effect on diabetes, with the score of –4 points in the plus-fasting plasma glucose model of the derivation cohort. This means that, according to the plus-fasting plasma glucose model of the validation cohort (Fig. 2), a moderate risk of diabetes in subjects with score values of 13–16 can be reduced to the level of subjects with a low risk by regular exercise. Similar findings were observed in a few prior diabetic risk models [9,11].

The strengths of our study include a longitudinal population-based design, a long duration of follow-up, a sufficient number of individuals developing Type 2 diabetes, a higher follow-up rate and the use of oral glucose tolerance test for the diagnosis of diabetes. However, some limitations should be discussed. First, in the derivation cohort, the predictive ability of the plus-fasting plasma glucose model for future Type 2 diabetes exceeded that of impaired glucose tolerance, fasting plasma glucose and 2-h post-load glucose values, while such superiority of the plus-fasting plasma glucose model was not observed in the validation cohort. The reason for this discrepancy may be different follow-up periods of the two cohorts. Our risk models may be useful for identifying people at high risk of Type 2 diabetes in a relatively long-term follow-up period (the derivation cohort), while glucose parameters may be effective to predict Type 2 diabetes in a short-term period (the validation cohort). Second, the diagnosis of incident Type 2 diabetes was based on a single reading of fasting plasma glucose and 2-h post-load glucose levels, as has been the case in other epidemiological studies. Thus, subjects who had Type 2 diabetes might have been misdiagnosed in our study. Third, it should be noted that self-reporting bias and random error in the measurement of variables used in the scoring models may have limited their ability to obtain accurate risk estimates and may have led to an underestimation of the predictive strength of the score components. In particular, smoking is a value-laden behaviour prone to under-reporting. In spite of these limitations, both risk score models performed similarly well in the validation cohort with acceptable accuracy.

In conclusion, the non-invasive diabetes risk score and plus-fasting plasma glucose models were developed here for Japanese subjects and we confirmed the utility of these scoring models for identifying persons at high risk of Type 2 diabetes over time. These models may help to identify people at risk of Type 2 diabetes from large populations. Individuals with high score values would be encouraged to change to a healthier lifestyle, which would help to eliminate the burden of diabetes in the Japanese population.

Competing interests

Nothing to declare.

Acknowledgments

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Original Article

Impact of lower range of prehypertension on cardiovascular events in a general population: the Hisayama Study

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Objectives: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) defined blood pressure (BP) levels of 120–139/80–89 mmHg as prehypertension. The objective of the present analysis was to examine the impact of prehypertension and its population-attributable fraction for development of cardiovascular events in a general Japanese population.

Methods: Two thousand, six hundred and thirty-four residents of the town of Hisayama aged at least 40 years without cardiovascular disease were followed up for 19 years. BP categories were defined using JNC7, and prehypertension was divided into the lower (120–129/80–84 mmHg) and higher ranges (130–139/85–89 mmHg). During the follow-up period, 449 participants developed cardiovascular disease (305 strokes and 187 coronary heart diseases).

Results: The frequencies of normal BP, prehypertension, and stages 1 and 2 hypertension were 24.9, 37.7, 23.8, and 13.6%, respectively. The age and sex-adjusted incidence of cardiovascular disease rose progressively with elevation of BP levels ($P < 0.001$ for trend). The risks of cardiovascular disease in lower and higher ranges of prehypertension were 58% [95% confidence interval (CI) 11–126%] and 70% (95% CI 18–144%) higher than normal BP even after controlling for other cardiovascular risk factors. The population-attributable fraction of prehypertension was 13.2%, which was similar to those of stages 1 and 2 hypertension.

Conclusions: The risks of cardiovascular disease increased significantly from the lower range of prehypertension in a general Japanese population. Approximately one-third of excess cardiovascular events attributable to elevated BP levels were estimated to occur among individuals with prehypertension.

Keywords: blood pressure, cardiovascular disease, population-attributable fraction, prehypertension, prevention, prospective cohort studies, stroke

Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; JNC7, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; PAF, population-attributable fraction

INTRODUCTION

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) defined the blood pressure (BP) levels of 120–139/80–89 mmHg as prehypertension based on the evidence of a modest increase in cardiovascular risk among individuals with such BP levels [1]. However, current evidence of increased risks of cardiovascular disease (CVD) associated with prehypertension has mainly been reported for its higher range (130–139/85–89 mmHg) [2,3], and it is still unclear about the cardiovascular risks among individuals with the lower range of prehypertension (120–129/80–84 mmHg), particularly in the Japanese. Because the prevalence of prehypertension has been reported to be as high as 31–43% [4–6], a large portion of the burden of CVD is likely attributable to prehypertension. Although a number of large-scale observational studies have shown population-attributable fractions (PAFs) of this BP category for premature deaths or deaths due to cardiovascular causes [7,8], uncertainty remains surrounding the frequency of 'fatal and nonfatal' cardiovascular events attributable to prehypertension.

The Hisayama Study has demonstrated that the incidence rates of stroke significantly increased from BP levels of 140/90 mmHg among participants recruited in 1961 [5].

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However, the effects of BP on the risks of stroke and coronary heart disease might have changed since then because of the substantial changes in lifestyle and the improved awareness, treatment, and control of hypertension [9]. The objective of the present new analysis from the Hisayama Study is to investigate the influence of BP on cardiovascular events among participants recruited in 1988 and to estimate population-attributable risks of prehypertension (lower and higher ranges) and hypertension for incident CVD in a general Japanese population.

METHODS

Study population

The Hisayama Study is a population-based prospective cohort study of CVD established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area in Kyushu Island of Japan. Based on data from the national census, the age and occupational distributions in Hisayama have been almost identical to those in Japan since the 1960s [10]. In 1988, a total of 2742 residents aged at least 40 years consented to participate in the screening examination (participation rate 80.9%). After the exclusion of 106 residents with a history of stroke or coronary heart disease and two residents who died before the start of follow-up, the remaining 2634 residents (1107 men and 1527 women) were enrolled in this study. The study design and characteristics of this cohort population have been described in detail elsewhere [11–13].

Follow-up survey

The participants were followed up prospectively for 19 years, from December 1988 to November 2007, by annual health examinations. The health status of any individual who did not undergo a regular examination or who moved out of town was checked yearly by mail or telephone. We also established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare Office. Using this system, we gathered information on new events of CVD, including suspected cases. When stroke or coronary heart disease occurred or was suspected, physicians in the study team examined the individual and evaluated his/her detailed clinical information. The clinical diagnosis of stroke or coronary heart disease was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. Furthermore, when a patient died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, there was no true loss to follow-up, and 842 patients died, of whom 605 (71.9%) underwent autopsy.

Blood pressure measurements and classification

At the baseline examination, BP was measured three times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 min. Appropriately-sized cuffs were used for BP assessment. Korotkoff phase 5 was taken as the diastolic BP unless the sound persisted at 0, in which case Korotkoff phase 4 was recorded. The mean of the three measurements was used for the analysis. BP levels were classified into four categories according to JNC7: normal BP (<120/80 mmHg), prehypertension (120–139/80–89 mmHg), stage 1 hypertension (140–159/90–99 mmHg), and stage 2 hypertension (≥160/100 mmHg) [1]. Prehypertension was divided into two subcategories: lower (120–129/80–84 mmHg) and higher (130–139/85–89 mmHg) BP ranges. If systolic and diastolic BP readings for a participant were in different categories, that participant was categorized into the higher of the two BP categories. Antihypertensive drug users were classified according to BP levels at baseline.

Other risk factor measurement

At baseline, each participant completed a self-administered questionnaire covering medical history, treatment for hypertension and diabetes, smoking habits, alcohol intake, and exercise. Smoking habits and alcohol intake were classified into currently habitual or not. The participants engaging in sports or other forms of exertion at least three times a week during their leisure time made up a regular exercise group. Body height and weight were measured in light clothing without shoes, and the body mass index (kg/m^2) was calculated. Electrocardiogram (ECG) abnormalities were defined as left-ventricular hypertrophy (Minnesota code 3–1), ST depression (4–1, 2, 3), or atrial fibrillation (8–3).

Serum total and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically. Hypercholesterolemia was defined as total cholesterol at least 5.7 mmol/l. Blood glucose levels were measured by the glucose oxidase method. Diabetes was determined by medical history, plasma glucose levels (fasting glucose level ≥7.0 mmol/l or postprandial glucose level ≥11.1 mmol/l), or a 75-g oral glucose tolerance test using the 1998 World Health Organization criteria [14]. Serum creatinine was measured by the noncompensated Jaffé method. The Jaffé method value was converted to an enzymatic method value by using the following equation [15]:

$$\begin{aligned}&\text{Serum creatinine (enzymatic method [mg/dl])}\\&\quad = 0.9754\\&\qquad \times \text{ serum creatinine (Jaffé method [mg/dl])}\\&\qquad - 0.2802.\end{aligned}$$

Estimated glomerular filtration rate (eGFR) was calculated using the isotope dilution mass spectrometry-traceable 4-variable Modification of Diet in Renal Disease (IDMS-MDRD) Study equation modified with the Japanese correction [16]:

$$\begin{aligned}&\text{eGFR (ml/min per 1.73 m}^2\text{)}\\&\quad = 194\\&\qquad \times \text{serum creatinine (enzymatic method)}^{-1.094}\\&\qquad \times \text{age}^{-0.287} \times 0.742 \text{ (if women).}\end{aligned}$$

Chronic kidney disease was defined as proteinuria (+ or more using the test paper method) or eGFR below 60 ml/min per 1.73 m^2 according to the National Kidney

Foundation Kidney Disease Outcomes Quality Initiative guidelines [17].

Endpoint definition

Cardiovascular disease was defined as first-ever development of stroke or coronary heart disease. In principle, stroke was defined as an acute onset of nonconvulsive and focal neurological deficit lasting more than 24 h. The clinical diagnosis of stroke was determined on the basis of a detailed history, neurological examination, and ancillary laboratory examinations, including computed tomography and magnetic resonance image. Stroke was classified as either ischaemic or haemorrhagic (intracerebral or subarachnoid haemorrhage).

The criteria for a diagnosis of coronary heart disease included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 h after the onset of acute illness, and coronary artery disease followed by coronary intervention or bypass surgery. Acute myocardial infarction was diagnosed when a participant met at least two of the following criteria: typical symptoms, including prolonged severe anterior chest pain; abnormal cardiac enzymes more than twice the upper limit of the normal range; evolving diagnostic ECG changes; and morphological changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars greater than 1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. Clinical diagnoses were corrected by autopsy findings when necessary.

Statistical analysis

The age and sex-adjusted mean values of risk factors were calculated and tested by the analysis of covariance. Frequencies of risk factors were adjusted for age and sex by the direct method and were compared using the logistic regression analysis. The age and sex-adjusted cumulative incidence of CVD was estimated, and the differences among BP categories were tested using the Cox proportional hazards model. The incidence rate was calculated by the person-year method and adjusted for age and sex by the direct method. Differences in age and sex-adjusted incidences among BP levels were tested by the Cox proportional hazards model. The adjusted hazard ratio and its 95% confidence interval (CI) were also calculated using the Cox proportional hazards model. The heterogeneity in the relationship between subgroups was estimated by adding an interaction term to the Cox model. The PAF of each BP category was calculated using the following equation with the observed multivariate-adjusted hazard ratio of each category and its frequency in event cases (Pe) [18].

$$\mathrm{PAF} = \mathrm{Pe}(\mathrm{HR} - 1)/\mathrm{HR}$$

The CI of the PAF was estimated by the method proposed by Greenland [19]. All statistical analyses were performed with the SAS program package version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). P values of less than 0.05 were considered statistically significant.

Ethical considerations

The study protocol was approved by Kyushu University Institutional Review Board for Clinical Research, and the procedures followed were in accordance with national guidelines. The participants provided written informed consent.

RESULTS

The frequencies of normal BP, prehypertension, stage 1 hypertension, and stage 2 hypertension were 24.9, 37.7, 23.8, and 13.6%, respectively. The age and sex-adjusted mean values or frequencies of cardiovascular risk factors are listed according to BP categories in Table 1. Individuals with higher BP levels were older and more likely to be men. The mean values of body mass index and total cholesterol, and frequencies of diabetes, chronic kidney disease, ECG abnormalities, and alcohol intake increased with elevating BP levels, whereas the mean value of HDL cholesterol and frequency of smoking habits decreased. Such trends were not observed for regular exercise.

During the 19-year follow-up, 449 individuals developed CVD events (229 men and 220 women). These CVD cases had 305 first-ever stroke (213 ischaemic and 92 haemorrhagic strokes), and 187 first-ever coronary events. Figure 1 shows the age and sex-adjusted cumulative incidence curves of CVD according to BP categories. The incidence of CVD significantly increased with elevating BP categories; compared with normal BP, the incidence of CVD became significantly higher from the 6th year in lower range of prehypertension, the 6th year in higher range of prehypertension, the 4th year in stage 1 hypertension, and the 5th year in stage 2 hypertension. Table 2 shows the age and sex-adjusted incidence of CVD and its subtypes according to BP categories. The age and sex-adjusted incidence of CVD rose progressively with elevation of BP levels: normal BP 7.5 per 1000 person-years, lower range of prehypertension 12.6, higher range of prehypertension 12.1, stage 1 hypertension 13.7, and stage 2 hypertension 24.6. The incidence rates were significantly higher from the lower range of prehypertension compared to normal BP. Similar associations were observed in both sexes ($P = 0.62$ for heterogeneity). The age and sex-adjusted incidence of stroke increased continuously with elevating BP levels, and the difference in the incidence between normal BP and lower range of prehypertension was significant. A similar tendency was observed for both ischaemic and haemorrhagic strokes. The association between BP levels and the incidence of coronary heart disease was somewhat weak, and the incidence was significantly elevated only in stage 2 hypertension. The associations of BP categories with the risks of CVD, stroke, and coronary heart disease were substantially unchanged even after adjusting for potential confounding factors such as age, sex, body mass index, total and HDL cholesterol, diabetes, chronic kidney disease, ECG abnormalities, smoking, drinking, and regular exercise (Table 3). There was a continuous relationship of BP levels with total CVD, and a significant increase was observed from the

TABLE 1. Age and sex-adjusted mean values or prevalence of risk factors according to blood pressure categories at baseline

Variable	Blood pressure category					
		Prehypertension				
	Normal BP ($n=657$)	Lower range ($n=545$)	Higher range ($n=447$)	Stage 1 HT ($n=626$)	Stage 2 HT ($n=359$)	*P* for trend
Age (years)	55.1±0.4	56.4±0.5	58.8±0.5	61.8±0.5	66.2±0.6	<0.001
Men (%)	32.4	42.9	45.4	47.8	44.0	<0.001
Systolic blood pressure (mmHg)	110.8±0.3	123.5±0.3	133.8±0.4	145.9±0.3	170.3±0.4	<0.001
Diastolic blood pressure (mmHg)	66.7±0.3	73.7±0.3	78.6±0.4	84.2±0.3	91.9±0.4	<0.001
Antihypertensive medication (%)	3.1	7.5	13.2	23.4	32.6	<0.001
Body mass index (kg/m^2)	21.4±0.1	22.6±0.1	23.4±0.1	23.6±0.1	23.9±0.2	<0.001
Total cholesterol (mmol/l)	5.24±0.04	5.31±0.05	5.49±0.05	5.38±0.04	5.34±0.06	0.02
HDL cholesterol (mmol/l)	1.33±0.01	1.29±0.01	1.30±0.01	1.28±0.01	1.28±0.02	0.009
Diabetes (%)	5.1	12.6	14.7	15.1	19.5	<0.001
Chronic kidney disease (%)	7.0	12.1	11.7	16.2	23.5	<0.001
Electrocardiogram abnormalities (%)	10.6	12.8	15.5	18.6	29.3	<0.001
Current drinking (%)	20.9	30.4	30.4	34.5	39.5	<0.001
Current smoking (%)	29.7	24.4	25.2	21.6	22.7	0.004
Regular exercise (%)	9.2	12.0	9.2	9.7	10.7	0.78

BP, blood pressure; HT, hypertension; HDL, high-density lipoprotein. All values are given as means±SE or as percentages. Neither age nor sex was adjusted for covariates.

lower range of prehypertension (hazard ratio 1.58, 95% CI 1.11–2.26). When lower and higher ranges of prehypertension were combined, multivariate-adjusted hazard ratio of total prehypertension (120–139/80–89 mmHg) for the development of CVD was 1.64 (95% CI 1.18–2.26). Similar findings were obtained after excluding those taking antihypertensive agents at baseline from the study participants (Table 4).

As shown in Table 3, the PAFs of prehypertension, stage 1 hypertension, and stage 2 hypertension for development of CVD were 13.2, 13.6, and 16.5%, respectively. Approximately one-third of excess cardiovascular events attributable to elevated BP occurred among participants with prehypertension. PAFs for stroke incidence (16.1, 17.8, and 17.8 for prehypertension, stage 1 hypertension, and stage 2 hypertension, respectively) were larger than those for coronary heart disease (5.8, 8.0, and 12.6%).

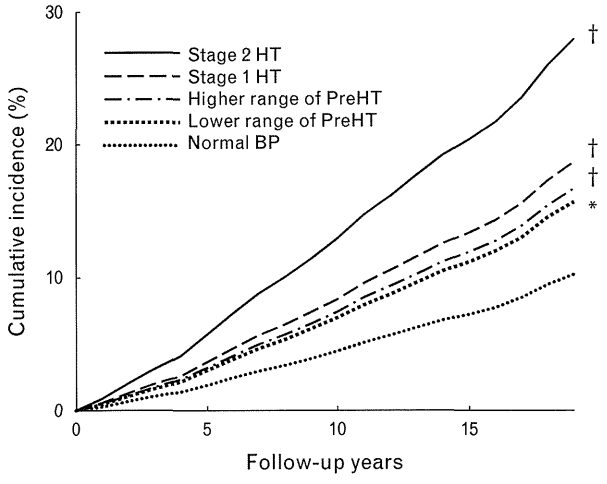


FIGURE 1 Age and sex-adjusted cumulative incidence of cardiovascular disease according to blood pressure categories. Cardiovascular disease was defined as stroke or coronary heart disease. BP, blood pressure; HT, hypertension. $^*P<0.05$, $^\dagger P<0.01$ vs. normal BP.

Figure 2 shows the association of BP categories with the risk of CVD between two groups defined by the number of other cardiovascular risk factors (diabetes, hypercholesterolaemia, smoking, and chronic kidney disease). The multivariate-adjusted hazard ratio of CVD continuously increased with BP levels both among participants with 0–1 risk factor and those with 2–4 risk factors. However, stronger associations of prehypertension and hypertension with CVD were observed for participants with 2–4 risk factors compared to those with 0–1 risk factor ($P=0.04$ for heterogeneity).

DISCUSSION

In a long-term prospective study of a general Japanese population, we demonstrated that higher BP levels were associated with increased risks of CVD, and significantly higher incidence of CVD was observed from the lower range of prehypertension compared to normal BP. This association remained unchanged even after adjustment for other cardiovascular risk factors such as age, sex, body mass index, total and HDL cholesterol, diabetes, ECG abnormalities, chronic kidney disease, smoking, drinking, and regular exercise. Because the prevalence rate of prehypertension was high, about one-third of the burden of CVD attributable to elevated BP was likely to occur from prehypertension. Furthermore, the effects of BP on the risks of CVD were stronger among 'high-risk' participants with multiple cardiovascular risk factors than among participants with 0–1 risk factor.

A number of large-scale cohort studies have demonstrated that prehypertension, particularly higher-range prehypertension, was associated with increased risks of CVD and death [4,20,21]. However, these studies were mainly conducted in Western populations, and it has been unclear to what extent these findings apply to Japanese populations. The Ohsaki study did not show significant effects of prehypertension on cardiovascular or total deaths in a general Japanese population [7]. The Evidence for

TABLE 2. Age and sex-adjusted incidence of cardiovascular disease according to blood pressure categories, 1988–2007

Endpoint	Blood pressure category					
		Prehypertension				
	Normal BP ($n=657$)	Lower range ($n=545$)	Higher range ($n=447$)	Stage 1 HT ($n=626$)	Stage 2 HT ($n=359$)	*P* for trend
Cardiovascular disease						
Total: no. of events/person-years	53/11148	76/8954	77/7142	127/9075	116/4440	
Age and sex-adjusted incidence	7.5	12.6*	12.1†	13.7‡	24.6‡	<0.001
Male: no. of events/person-years	24/3385	37/3747	47/3074	65/4108	56/1867	
Age-adjusted incidence	9.5	15.8	16.7†	17.8†	32.6‡	<0.001
Female: no. of events/person-years	29/7763	39/5207	30/4068	62/4968	60/2573	
Age-adjusted incidence	6.1	10.4*	8.5	10.9†	19.5‡	<0.001
Stroke						
No. of events/person-years	31/11238	50/9048	53/7262	92/9183	79/4535	
Age and sex-adjusted incidence	4.1	8.2*	8.5†	9.9‡	16.8‡	<0.001
Ischaemic stroke						
No. of events/person-years	25/11238	36/9048	39/7262	66/9183	47/4535	
Age and sex-adjusted incidence	3.4	6.3	6.5*	6.9†	9.4†	<0.001
Haemorrhagic stroke						
No. of events/person-years	6/11238	14/9048	14/7262	26/9183	32/4535	
Age and sex-adjusted incidence	0.7	1.8*	2.0*	2.9†	7.4‡	<0.001
Coronary heart disease						
No. of events/person-years	26/11267	32/9225	29/7381	52/9596	48/4754	
Age and sex-adjusted incidence	3.7	5.1	4.0	5.2	8.7†	0.002

Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension. Incidence, per 1000 person-years.
*$P<0.05$.
†$P<0.01$.
‡$P<0.001$ vs. normal BP.

Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) has reported a significant increase in all-cause mortality associated with prehypertension only among participants aged 50–69 [22]. The Jichi Medical School Cohort Study has shown a clear association between the higher range of prehypertension and incident CVD, but not for lower range of prehypertension [23]. In contrast, the Japan Atherosclerosis Longitudinal Study (JALS) and the

TABLE 3. Age and sex-adjusted and multivariate-adjusted hazard ratios and population-attributable fractions for cardiovascular disease according to blood pressure categories, 1988–2007

Endpoint	Blood pressure category					
		Prehypertension				
	Normal BP ($n=657$)	Lower range ($n=545$)	Higher range ($n=447$)	Stage 1 HT ($n=626$)	Stage 2 HT ($n=359$)	*P* for trend
Cardiovascular disease						
Age and sex-adjusted HR	1.00	1.58 (1.11–2.25)	1.69 (1.19–2.40)	1.92 (1.39–2.65)	3.04 (2.17–4.25)	<0.001
Multivariate-adjusted HR	1.00	1.58 (1.11–2.26)	1.70 (1.18–2.44)	1.93 (1.37–2.72)	2.78 (1.93–4.01)	<0.001
PAF (%)		6.2 (1.3–10.9)	7.0 (2.1–11.7)	13.6 (6.9–19.8)	16.5 (11.0–21.7)	
Stroke						
Age and sex-adjusted HR	1.00	1.80 (1.15–2.81)	2.05 (1.31–3.19)	2.44 (1.62–3.69)	3.54 (2.31–5.44)	<0.001
Multivariate-adjusted HR	1.00	1.79 (1.14–2.82)	2.05 (1.30–3.24)	2.44 (1.59–3.75)	3.21 (2.03–5.08)	<0.001
PAF (%)		7.2 (1.5–12.6)	8.9 (3.2–14.3)	17.8 (10.0–24.9)	17.8 (11.3–23.9)	
Ischaemic stroke						
Age and sex-adjusted HR	1.00	1.57 (0.94–2.61)	1.76 (1.06–2.92)	1.99 (1.25–3.17)	2.27 (1.37–3.75)	<0.001
Multivariate-adjusted HR	1.00	1.48 (0.88–2.49)	1.63 (0.97–2.73)	1.80 (1.10–2.94)	1.77 (1.02–3.05)	0.03
PAF (%)		5.5 (−1.9 to 12.3)	7.0 (−0.6 to 14.1)	13.8 (2.8–23.5)	9.6 (0.7–17.7)	
Haemorrhagic stroke						
Age and sex-adjusted HR	1.00	2.74 (1.05–7.15)	3.18 (1.22–8.31)	4.38 (1.79–10.74)	10.06 (4.13–24.53)	<0.001
Multivariate-adjusted HR	1.00	2.96 (1.13–7.74)	3.76 (1.42–9.98)	5.26 (2.10–13.18)	11.97 (4.73–30.32)	<0.001
PAF (%)		10.1 (0.8–18.4)	11.2 (2.4–19.1)	22.9 (11.3–32.9)	31.9 (20.6–41.6)	
Coronary heart disease						
Age and sex-adjusted HR	1.00	1.27 (0.76–2.14)	1.17 (0.69–1.99)	1.42 (0.88–2.29)	2.28 (1.40–3.72)	0.002
Multivariate-adjusted HR	1.00	1.23 (0.72–2.10)	1.11 (0.64–1.94)	1.35 (0.81–2.25)	1.97 (1.14–3.41)	0.02
PAF (%)		3.2 (−6.5 to 8.9)	1.6 (−8.8 to 7.5)	7.2 (−5.3 to 18.1)	12.6 (2.8–21.5)	

Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction.
Multivariate analyses were adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, chronic kidney disease, electrocardiogram abnormalities, smoking, drinking, and regular exercise.

TABLE 4. Age and sex-adjusted and multivariate-adjusted hazard ratios and population-attributable fractions for cardiovascular disease according to blood pressure categories in participants without antihypertensive medication, 1988–2007

	Blood pressure category					
		Prehypertension				
Endpoint	Normal BP ($n=642$)	Lower range ($n=510$)	Higher range ($n=388$)	Stage 1 HT ($n=474$)	Stage 2 HT ($n=227$)	*P* for trend
Cardiovascular disease						
No. of events	47	67	64	92	70	
Age and sex-adjusted HR	1.00	1.67 (1.15–2.42)	1.83 (1.26–2.67)	2.03 (1.42–2.89)	3.41 (2.33–4.98)	<0.001
Multivariate-adjusted HR	1.00	1.72 (1.17–2.51)	1.85 (1.25–2.74)	2.06 (1.42–3.01)	3.31 (2.19–4.99)	<0.001
PAF (%)		8.2 (2.3–13.8)	8.7 (3.0–14.0)	13.9 (6.9–20.4)	14.4 (9.2–19.3)	
Stroke						
No. of events	29	44	42	65	50	
Age and sex-adjusted HR	1.00	1.78 (1.16–2.85)	1.99 (1.24–3.20)	2.38 (1.53–3.71)	4.02 (2.51–6.43)	<0.001
Multivariate-adjusted HR	1.00	1.81 (1.13–2.91)	2.00 (1.22–3.25)	2.41 (1.52–3.83)	3.82 (2.31–6.32)	<0.001
PAF (%)		8.6 (1.5–15.1)	9.1 (2.4–15.3)	16.5 (8.1–24.2)	16.0 (9.7–22.0)	
Ischaemic stroke						
No. of events	23	31	32	47	25	
Age and sex-adjusted HR	1.00	1.56 (0.91–2.68)	1.83 (1.07–3.14)	2.01 (1.21–3.34)	2.23 (1.25–4.00)	0.003
Multivariate-adjusted HR	1.00	1.54 (0.89–2.65)	1.69 (0.97–2.95)	1.84 (1.07–3.14)	1.84 (0.98–3.45)	0.04
PAF (%)		6.8 (−2.3 to 15.1)	8.3 (−0.8 to 16.5)	13.5 (1.8–23.9)	7.2 (−0.5 to 14.4)	
Haemorrhagic stroke						
No. of events	6	13	10	18	25	
Age and sex-adjusted HR	1.00	2.63 (1.00–6.94)	2.51 (0.91–6.93)	3.75 (1.48–9.55)	12.37 (4.99–30.66)	<0.001
Multivariate-adjusted HR	1.00	2.83 (1.07–7.51)	3.00 (1.07–8.45)	4.60 (1.76–11.99)	15.28 (5.88–39.74)	<0.001
PAF (%)		11.7 (0.3–21.8)	9.3 (−0.4 to 17.9)	19.6 (7.1–30.3)	32.4 (19.9–43.1)	
Coronary heart disease						
No. of events	22	27	27	37	25	
Age and sex-adjusted HR	1.00	1.34 (0.76–2.35)	1.51 (0.86–2.65)	1.55 (0.91–2.63)	2.34 (1.31–4.20)	0.008
Multivariate-adjusted HR	1.00	1.38 (0.77–2.46)	1.46 (0.80–2.65)	1.47 (0.83–2.62)	2.25 (1.19–4.28)	0.03
PAF (%)		5.3 (−4.8 to 14.5)	6.1 (−4.0 to 15.3)	8.6 (−4.4 to 20.0)	10.1 (1.7–17.7)	

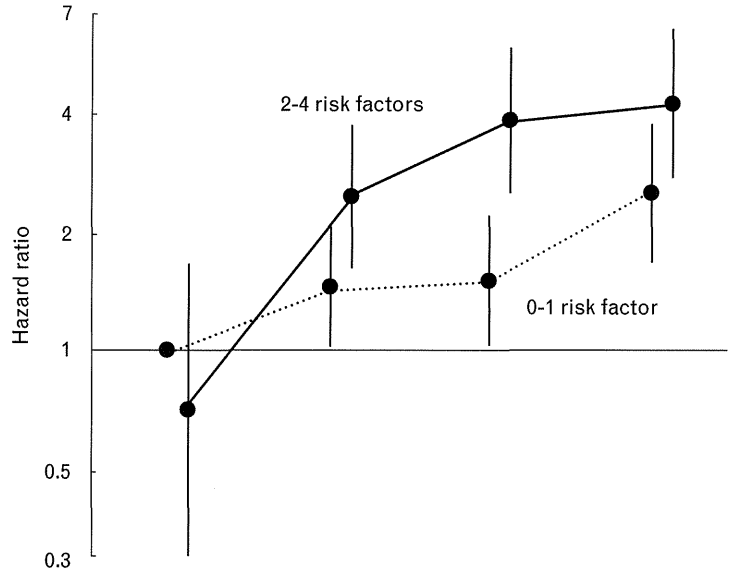
Cardiovascular disease was defined as stroke or coronary heart disease.
BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction.
Multivariate analyses are adjusted for age, sex, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, chronic kidney disease, electrocardiogram abnormalities, smoking, drinking, and regular exercise.

Japan Public Health Center-based Prospective (JPHC) Study have demonstrated clear associations between BP and stroke incidence, with significant increase from the lower range of prehypertension [6,24]. The Suita Study has also reported that both higher and lower ranges of prehypertension were associated with increased risks of stroke and total CVD among Japanese men [25]. The present analysis from the Hisayama Study confirmed the hypothesis generated from previous cohort studies that prehypertension is not innocent even in the lower range of 120–129/80–84 mmHg, and that this level of BP definitely promotes systemic arteriosclerosis, resulting in incident stroke, coronary heart disease, and other manifestations of cardiovascular events. These findings could also be supported by our previous findings that prehypertension increased the risk of renal arteriosclerosis and arteriolar hyalinosis in an autopsy series of Hisayama residents [26].

In the present study, the highest risks of CVD were observed among patients with stage 1 and 2 hypertension. The third highest risk was among patients with higher range of prehypertension, and the fourth highest among those with lower range of prehypertension. These findings are directly in line with the results of large-scale cohort studies [6,24,25]. They confirm that the risks of CVD is slightly higher among patients with higher range of prehypertension than among those with lower range of prehypertension and support the European and Japanese guidelines for management of hypertension [27,28] which distinguish these two groups as high-normal and normal BP.

In the present analysis, the prevalence of prehypertension was as high as 38% of the total population. As a result, the PAF of prehypertension for development of CVD was similar to those of stage 1 and 2 hypertension. This finding is compatible with the results of several other cohort studies [6,25]. These results suggest that approximately one-third of the burden of excess CVD attributable to elevated BP levels comes from prehypertension. Therefore, in order to reduce the enormous burden of CVD, a high-risk strategy to treat patients with hypertension should be complemented with population strategies to lower BP levels which include lifestyle modifications such as weight loss in the overweight, physical activity, moderation of alcohol intake, a diet with increased fresh fruit and vegetables and reduced saturated fat content, reduction of dietary sodium intake, and increased dietary potassium intake [1,27,28].

Another important finding from the present analysis of the Hisayama Study is that the effects of prehypertension on the risks of CVD were larger among 'high-risk' participants with multiple cardiovascular risk factors than among 'lower-risk' participants with only a few risk factors. Furthermore, the risk of CVD among these 'high-risk' participants with prehypertension was equivalent to that among participants with stage 2 hypertension who have only a few risk factors. Therefore, a pharmaceutical



N of events/person-years				
0-1 risk factor	47/9785	107/13 142	81/7315	66/3122
2-4 risk factors	6/1363	46/2954	46/1760	50/1300

FIGURE 2 Multivariate-adjusted hazard ratios for cardiovascular disease according to blood pressure categories and the number of risk factors. Risk factors included diabetes, hypercholesterolaemia, smoking, and chronic kidney disease. Cardiovascular disease was defined as stroke or coronary heart disease. BP, blood pressure; HT, hypertension. Hazard ratios were adjusted for age, sex, body mass index, high-density lipoprotein cholesterol, electrocardiogram abnormalities, drinking, and regular exercise. $P=0.04$ for heterogeneity in the effects of blood pressure categories between participants groups defined by the number of risk factors.

treatment to lower BP may be necessary for participants with prehypertension who are at high risk of CVD as well as for hypertensive patients. In fact, several randomized controlled trials of BP-lowering have demonstrated that patients with high cardiovascular risk benefit from BP-lowering treatment regardless of whether they were hypertensive or not [29–32]. These findings support the concept of treating patients with high cardiovascular risk who have BP levels of prehypertension, which is recommended by current national and international guidelines [27,28].

The strengths of our study include its longitudinal population-based study design, no true loss to follow-up for a long period, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD subtypes. In contrast, the present study was limited by the fact that BP was only measured at baseline and that BP during the follow-up period was not considered for the analysis. However, this limitation is not likely to invalidate the findings observed in the present study, because a random misclassification of this nature would tend to cause an underestimation of the true relationship. The participants of the present analysis were leaner compared to more westernized populations that exist today. Further studies are required to determine whether the findings obtained from the present study are applicable to more westernized populations.

In conclusion the present study confirmed the strong and continuous associations between BP levels and the incidence of CVD in a general Japanese population. The lowest incidence of CVD was observed among individuals with normal BP, and even a slight increase in BP (e.g. lower range of prehypertension) was associated with significantly higher risks of CVD. Approximately one-third of excess CVD events attributable to elevated BP were likely to occur among individuals without hypertension. These results support the current guidelines for management of hypertension which recommend lifestyle modification with/without BP-lowering agents for moderate to high-risk patients with prehypertension as well as hypertensive patients [1,27,28].

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Conflicts of interest

There are no conflicts of interest.

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Smoking cessation improves mortality in Japanese men: the Hisayama study

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ABSTRACT

Background Although the smoking rate among Japanese men has been the highest in developed countries, the epidemiological evidence about whether smoking cessation can extend their lifespan is not well established.

Methods A total of 1083 Japanese men aged ≥40 years were classified by their smoking status and followed up prospectively for 18 years (1988–2006).

Results Current smoking was a significant risk factor for all-cause death: the multivariate-adjusted HRs of all-cause death for current smokers of 1–19, 20–39 and ≥40 cigarettes per day were 1.61 (95% CI 1.16 to 2.22), 1.56 (95% CI 1.08 to 2.23) and 3.15 (95% CI 1.59 to 6.24), respectively. Former smokers did not have an increased risk of all-cause death compared with never smokers. The excess risk of all-cause death for current smokers tended to decrease within 5 years after smoking cessation, eventually reaching a level almost equivalent to that of never smokers. The risk of cancer death decreased by 53% in subjects who had quit smoking for ≥10 years, while the risk of cardiovascular death decreased by 56% in subjects with the cessation period of <10 years.

Conclusions Our findings suggest that even a modest smoking habit significantly increases the risk of death among Japanese men, and the risk of death diminishes soon after cessation of smoking. These results imply the importance of smoking cessation to extend life in Japanese men.

INTRODUCTION

A considerable number of epidemiological studies in Western[1 2] and Asian countries[3 4] have reported that cigarette smoking is an important risk factor for many types of diseases and premature death. Therefore, tobacco control is currently a key target of prevention strategies in all parts of the world. In Japan, cigarette smoking is an important public health problem. Even though the proportion of smokers has decreased gradually since 1966,[5] Japanese men still have the highest habitual smoking rate in the developed world.[6] In fact, the latest smoking rate among Japanese men is around 40%.[5] Meanwhile, evidence for the influence of smoking cessation has been accumulating in Western countries.[1 7 8] Data show that stopping smoking contributes to the risk reduction for total mortality. Therefore, the effect of smoking cessation on the risk of mortality among Japanese men would be of value for formulating public health recommendations. To our knowledge, however, few studies have examined whether smoking cessation can improve life expectancy among the Japanese, especially in recent years.[3 9–11] Since a smoking habit is often accompanied by an unhealthy lifestyle, appropriate control for confounding factors is necessary to estimate the hazard of cigarette smoking. The aims of the present study were to clarify the relation of smoking status and time since smoking cessation with total and cause-specific mortalities in an 18-year cohort study of Japanese men.

METHODS

Study population

A population-based prospective study of cardiovascular disease and malignancy has been under way since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area of Kyushu Island in southern Japan. The age and occupational distributions for Hisayama have been almost identical to those of Japan as a whole from 1961 to the present, based on national census data.[12] In 1988, a screening survey for the present study was performed in the town. A total of 2742 Hisayama residents (1165 men and 1577 women) aged ≥40 years (80.9% of the total population of this age group) consented to participate. Subjects were limited to men because the prevalence of smoking was low (6.9%) among women. After the exclusion of 81 individuals with a prior history of cancer, coronary heart disease or stroke and one individual who died during the screening period, a total of 1083 men (mean age 58.2 years) were enrolled in this study.

Follow-up survey

The subjects were followed up prospectively for 18 years from December 1988 to November 2006 by repeated health examinations or by a daily monitoring system established by the study team and local physicians or members of the health and welfare office of the town. Information about death was received from this system. Vital status was also checked once yearly by mail or telephone for any subjects who moved out of town. When the subject died, all medical information related to their illness and death, including hospital charts, physicians' records and death certificate were collected. Moreover, an autopsy was performed at the Kyushu University Department of Pathology if consent for autopsy was obtainable. All participants were followed up completely over 18 years. During the follow-up, 380 subjects died, of whom 278 (73.2%) underwent autopsy. All the medical data including autopsy findings were scrutinised, and the

underlying causes of death were classified according to the International Classification of Diseases, 10th revision (ICD-10). Cause-specific mortality was defined for cancer death (ICD-10: C00-C97), cardiovascular death (ICD-10: I00-I99) and deaths from 'other' causes. External causes of death were censored at the date of death.

Risk factor measurement

At the baseline examination, each participant completed a self-administered questionnaire on lifestyle, medical history and family history of cancer, coronary heart disease and stroke. The questionnaire was checked by trained interviewers. Smoking status was initially classified as never, former or current based on responses to two questions: 'Do you smoke cigarettes regularly now?' and 'Did you ever smoke cigarettes regularly?' Current smokers were those who were currently smoking at least one cigarette per day regularly. They were then asked about the age at which they started smoking and the average number of cigarettes they were currently smoking per day. Subsequently, current smokers were subclassified into three categories of 1–19, 20–39 and ≥40 cigarettes per day on the basis of the average number of cigarettes they smoked. Pack-years among current smokers were calculated by multiplying the number of packs of cigarettes per day by the number of years of smoking. The subjects were divided into three categories of ≤39, 40–59 and ≥60 pack-years. Former smokers were asked the ages at which they started and quit smoking. Participants were also asked the frequency of their alcohol intake and the kinds and amounts of alcoholic beverages they had consumed over the previous several months. Habitual drinkers were defined as those who drank alcoholic beverages at least once a month. The measurements were converted into daily amounts of alcohol (g per day) and participants were classified into three categories: none, <30 and ≥30 g per day. Subjects engaging in sports or other forms of exercise ≥3 times a week during their leisure time were assigned to a regular exercise group.

Blood pressure was measured three times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 minutes. The mean value of the three measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. Height and weight were measured with the subject in light clothes without shoes, and the body mass index was calculated (kg/m^2). Diabetes was determined by medical history, plasma glucose levels (fasting glucose level ≥7.0 mmol/l or postprandial glucose level ≥11.1 mmol/l), or a 75-g oral glucose tolerance test (using the 1998 WHO criteria), with plasma glucose measured by the glucose-oxidase method. Serum cholesterol levels were determined by an enzymatic auto-analyser.

Table 1 Age-adjusted mean values or prevalences of risk factors according to smoking status at baseline

Risk factor	Never smoker	Former smoker	Current smoker
Number at risk	221	322	540
Age (years)	57.3 (11.6)	60.8 (11.5)**	57.0 (11.5)
Systolic blood pressure (mm Hg)	136 (19)	137 (19)	133 (19)
Diastolic blood pressure (mm Hg)	83 (11)	83 (11)	79 (11)**
Hypertension	44.1	52.2	40.6
Antihypertensive medication	10.3	18.6**	11.7
Body mass index (kg/m^2)	23.2 (2.8)	23.4 (2.8)	22.3 (2.8)**
Diabetes	10.5	18.2*	14.5
Medication for diabetes	0.8	3.5	2.9
Total cholesterol (mmol/l)	5.09 (1.06)	5.23 (1.06)	5.02 (1.06)
Alcohol intake			
None	47.8	34.7**	39.3*
<30 g/day	34.7	38.4	33.4
≥30 g/day	17.5	26.9**	27.3**
Regular exercise	11.8	13.7	11.2
Family history of cancer, coronary heart disease and stroke	18.5	19.4	16.1

Values and prevalences are expressed as means (SD) and percentages, respectively.
*p<0.05; **p<0.01 compared with never smoker.

Table 2 Age-adjusted and multivariate-adjusted risks for total and cause-specific death by smoking status

	Smoking status		
	Never	Former	Current
Person-years of follow-up	3405	4736	7816
All-cause death			
Number	56	109	191
Age-adjusted HR (95% CI)	1.00	1.04 (0.75 to 1.43)	1.68 (1.25 to 2.27)*
Multivariate-adjusted HR (95% CI)	1.00	1.05 (0.76 to 1.46)	1.63 (1.20 to 2.20)*
Cancer death			
Number	18	43	79
Age-adjusted HR (95% CI)	1.00	1.36 (0.78 to 2.35)	2.04 (1.22 to 3.41)*
Multivariate-adjusted HR (95% CI)	1.00	1.40 (0.80 to 2.45)	1.99 (1.19 to 3.33)*
Cardiovascular death			
Number	18	29	55
Age-adjusted HR (95% CI)	1.00	0.86 (0.48 to 1.54)	1.49 (0.87 to 2.54)
Multivariate-adjusted HR (95% CI)	1.00	0.80 (0.44 to 1.46)	1.48 (0.86 to 2.53)
Death from other causes			
Number	20	37	57
Age-adjusted HR (95% CI)	1.00	0.94 (0.55 to 1.62)	1.52 (0.91 to 2.53)
Multivariate-adjusted HR (95% CI)	1.00	1.04 (0.59 to 1.81)	1.45 (0.86 to 2.43)

*p<0.01 compared with never smoker.
Multivariate adjustment was made for age, hypertension, body mass index, diabetes, total cholesterol, alcohol intake, regular exercise and family history of cancer, coronary heart disease and stroke.

Statistical analysis

The age-adjusted mean values of possible risk factors taken as continuous variables—namely, systolic and diastolic blood pressures, body mass index and total cholesterol, were estimated and compared between smoking status using analysis of covariance. The prevalences of risk factors taken as categorical variables, such as a history of hypertension or diabetes, use of antihypertensive or antidiabetic medication, current alcohol intake, regular exercise and family history of cancer, coronary heart disease and stroke, were adjusted for age by the direct method and tested with logistic regression analysis. All subjects enrolled in the study were used as the standard population for age adjustment. The age-adjusted or multivariate-adjusted HRs and their 95% CIs were estimated using the Cox proportional hazards model. In the multivariate analysis, the risk estimates were adjusted for potential confounding factors at baseline—namely, age, hypertension, body mass index, diabetes, serum total cholesterol level, current habitual alcohol intake, regular exercise and family history of cancer, coronary heart disease and stroke. The proportions of missing values were less than 1% for all the variables included in the model. Two-sided $p<0.05$ was considered as statistically significant. Statistical analyses were conducted using Statistical Analysis Software (SAS), version 9.2 (SAS Institute Inc, Cary, North Carolina).

Ethical considerations

This study protocol was approved by the Kyushu University Institutional Review Board for Clinical Research, and written informed consent for medical research was obtained from the study subjects. The procedures were in accordance with the national guideline for epidemiological studies.

RESULTS

Table 1 shows the mean values or prevalences of potential risk factors by smoking status. Compared with never smokers, former smokers were older and showed higher prevalence of antihypertensive medication, diabetes and alcohol intake, while current smokers had lower levels of diastolic blood pressure and body mass index and higher prevalence of alcohol intake.

During the 18-year follow-up, 356 subjects died from all causes except for external causes of death (n=24). Of the dead, 140 subjects died of cancer, 102 of cardiovascular disease and 114 of other causes. The age-adjusted and multivariate-adjusted hazard ratios (HRs) for total and cause-specific death by smoking status are shown in table 2. Compared with never smokers, the risk of death from any cause did not significantly increase in former smokers, while the risks of all-cause death and cancer death were significantly higher in current smokers: the age-adjusted HR was 1.68 (95% CI 1.25 to 2.27; $p<0.001$) for all-cause death and 2.04 (95% CI 1.22 to 3.41; $p=0.006$) for cancer death in current smokers. The risks of cardiovascular death for current smokers tended to increase but did not reach statistical significance. The age-adjusted and multivariate-adjusted risks for total and cause-specific death by number of cigarettes per day and pack-years smoked among current smokers are presented in table 3. When current smokers were classified according to the daily amount of smoking, the age-adjusted risk of all-cause death significantly increased with elevating smoking levels. A similar trend was observed for cancer death and cardiovascular death. These associations were substantially unchanged even after adjusting for other risk factors—namely, hypertension, body mass index, diabetes, total cholesterol, alcohol intake, regular exercise and family history of cancer, coronary heart disease and stroke. On the other hand,

Table 3 Age-adjusted and multivariate-adjusted risks for total and cause-specific death by number of cigarettes per day and pack-years smoked in current smoker

		Number of cigarettes/day smoked in current smoker			Pack-years smoked in current smoker		
	Never smoker	1–19	20–39	≥40	≤39	40–59	≥60
Person-years of follow-up	3405	3913	3463	441	2789	2614	2334
All-cause death							
Number	56	113	68	10	27	90	70
Age-adjusted HR (95% CI)	1.00	1.73 (1.25 to 2.38)**	1.52 (1.07 to 2.17)*	2.98 (1.51 to 5.90)**	1.35 (0.83 to 2.17)	2.00 (1.43 to 2.79)**	1.50 (1.05 to 2.13)*
Multivariate-adjusted HR (95% CI)	1.00	1.61 (1.16 to 2.22)**	1.56 (1.08 to 2.23)*	3.15 (1.59 to 6.24)**	1.29 (0.80 to 2.09)	1.87 (1.34 to 2.62)**	1.51 (1.06 to 2.15)*
Cancer death							
Number	18	41	34	4	14	32	32
Age-adjusted HR (95% CI)	1.00	1.88 (1.08 to 3.28)*	2.21 (1.25 to 3.92)**	2.80 (0.94 to 8.35)	1.59 (0.78 to 3.27)	2.18 (1.23 to 3.89)**	2.18 (1.22 to 3.88)**
Multivariate-adjusted HR (95% CI)	1.00	1.78 (1.02 to 3.12)*	2.23 (1.25 to 3.98)**	2.74 (0.92 to 8.19)	1.55 (0.75 to 3.19)	2.06 (1.15 to 3.69)*	2.18 (1.21 to 3.90)**
Cardiovascular death							
Number	18	34	17	4	9	25	20
Age-adjusted HR (95% CI)	1.00	1.60 (0.90 to 2.83)	1.17 (0.60 to 2.28)	3.62 (1.20 to 10.91)*	1.37 (0.59 to 3.16)	1.71 (0.93 to 3.13)	1.32 (0.70 to 2.51)
Multivariate-adjusted HR (95% CI)	1.00	1.54 (0.86 to 2.74)	1.19 (0.61 to 2.33)	4.13 (1.36 to 12.56)*	1.36 (0.58 to 3.15)	1.68 (0.91 to 3.10)	1.33 (0.70 to 2.54)
Death from other causes							
Number	20	38	17	2	4	33	18
Age-adjusted HR (95% CI)	1.00	1.75 (1.02 to 3.02)*	1.13 (0.59 to 2.16)	2.57 (0.59 to 11.24)	0.95 (0.31 to 2.92)	2.16 (1.24 to 3.77)**	1.04 (0.55 to 1.97)
Multivariate-adjusted HR (95% CI)	1.00	1.55 (0.90 to 2.69)	1.19 (0.61 to 2.33)	2.72 (0.62 to 11.96)	0.89 (0.29 to 2.74)	1.93 (1.10 to 3.40)*	1.05 (0.55 to 2.01)

*p<0.05; **p<0.01 compared with never smoker.
Multivariate adjustment was made for age, hypertension, body mass index, diabetes, total cholesterol, alcohol intake, regular exercise and family history of cancer, coronary heart disease and stroke.
The information on pack-years was missing for six subjects.

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