Table 1. Comparison of age, body mass index, clinical values, smoking and drinking habits, history of related diseases, and CAVI between the subjects on the Amami islands and the Kagoshima mainland by sex

	Males			Females		
	Amami islands (n=1,853)	Kagoshima mainland (n=240)	p-value	Amami islands (n=2,670)	Kagoshima mainland (n=200)	p-value
Age (years)	55.55 ± 8.14	53.95 ± 8.60	0.004	55.72 ± 7.91	55.11 ± 7.95	0.287
BMI (kg/m^2)	24.92 ± 3.18	23.83 ± 2.89	<0.001	24.12 ± 3.47	22.55 ± 3.23	<0.001
TC (mg/dL)	208.08 ± 36.21	205.81 ± 34.31	0.036	216.20 ± 35.37	213.56 ± 29.69	0.306
TG (mg/dL)	161.90 ± 149.13	129.73 ± 77.52	0.001	103.69 ± 63.60	95.69 ± 56.80	0.084
HDL-C (mg/dL)	57.54 ± 14.50	53.27 ± 13.02	<0.001	63.61 ± 14.02	62.04 ± 13.06	0.125
LDL-C (mg/dL)	120.83 ± 32.72	126.47 ± 32.08	0.013	131.58 ± 32.37	132.27 ± 27.13	0.768
FBS (mg/dL)	104.80 ± 25.24	107.61 ± 21.19	0.099	96.22 ± 18.11	101.13 ± 25.36	<0.001
BUN (mg/dL)	15.57 ± 4.06	16.24 ± 3.95	0.018	14.62 ± 3.57	14.94 ± 3.76	0.234
Cr (mg/dL)	0.80 ± 0.21	0.85 ± 0.21	<0.001	0.60 ± 0.13	0.60 ± 0.10	0.810
UA (mg/dL)	6.15 ± 1.36	5.99 ± 1.17	0.070	4.57 ± 1.03	4.26 ± 0.96	<0.001
HR (beat/min)	63.22 ± 11.62	71.38 ± 11.78	<0.001	65.82 ± 9.89	71.97 ± 9.81	<0.001
SBP (mmHg)	133.94 ± 17.52	128.48 ± 15.34	<0.001	127.15 ± 18.13	125.46 ± 17.40	0.201
DBP (mmHg)	83.19 ± 10.96	84.93 ± 10.65	0.020	77.46 ± 11.11	80.70 ± 10.70	<0.001
MBP (mmHg)	100.95 ± 14.92	100.94 ± 13.60	0.989	95.56 ± 15.20	98.09 ± 14.60	0.023
PP (mmHg)	50.75 ± 10.72	43.55 ± 9.01	<0.001	49.69 ± 10.93	44.76 ± 11.01	<0.001
Never smoked (%)	36.27	35.42	0.847	92.55	93.50	0.858
Ex-smoker (%)	32.38	35.00	0.636	2.40	3.50	0.603
Current smoker (%)	31.25	29.58	0.761	5.02	3.00	0.425
Current drinker (%)	85.70	85.83	0.227	31.35	41.50	<0.001
History of HT (%)	28.12	18.33	0.002	22.40	14.00	0.008
History of stroke (%)	1.83	2.08	0.299	0.90	0.50	0.182
History of CAD (%)	2.32	1.25	0.171	1.99	1.50	0.252
History of diabetes mellitus (%)	8.36	8.33	0.375	4.08	1.50	0.056
History of dislipidemia (%)	10.31	6.67	0.063	10.19	11.50	0.164
CAVI	8.15 ± 0.99	8.63 ± 1.20	<0.001	7.78 ± 0.97	8.52 ± 1.03	<0.001

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBS, fasting blood sugar; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; HT, hypertension; CAD, coronary artery disease; CAVI, cardio-ankle vascular index. Values are mean ± SD, or percentages.

tion with less risk factors for coronary artery disease were examined using an unpaired t-test. Statistical analysis was performed with Stata, Version 8.0 for Windows (StataCorp LP, College Station, Tx).

Results

The clinical and lifestyle characteristics of the subjects differed between the Amami and mainland groups. Body mass index (BMI), TC, TG, HDL-C, SBP, and PP were higher, and LDL-C, BUN, Cr, heart rate (HR), DBP, and CAVI were lower in males in the Amami group than in the mainland group; these differences were statistically significant (**Table 1**). BMI, UA, and PP were significantly higher, while FBS, HR, DBP, MBP, and CAVI were significantly lower in females in the Amami group than in the mainland group. Males and females in the Amami group had a significantly higher prevalence of a history of hypertension. Current smoking and drinking habits were not geographically different except for a higher frequency of drinking in females in the mainland group.

A positive relationship was observed between CAVI values and age, although CAVI values varied widely by subject at each age (**Fig. 1A, 1B**). CAVI values in the mainland group were distributed at higher values than in the Amami group for both sexes. The correlation coefficients were 0.489 in Amami males, 0.547 in mainland males, 0.494 in Amami females, and 0.547 in mainland females.

The frequency of high arterial stiffness (CAVI

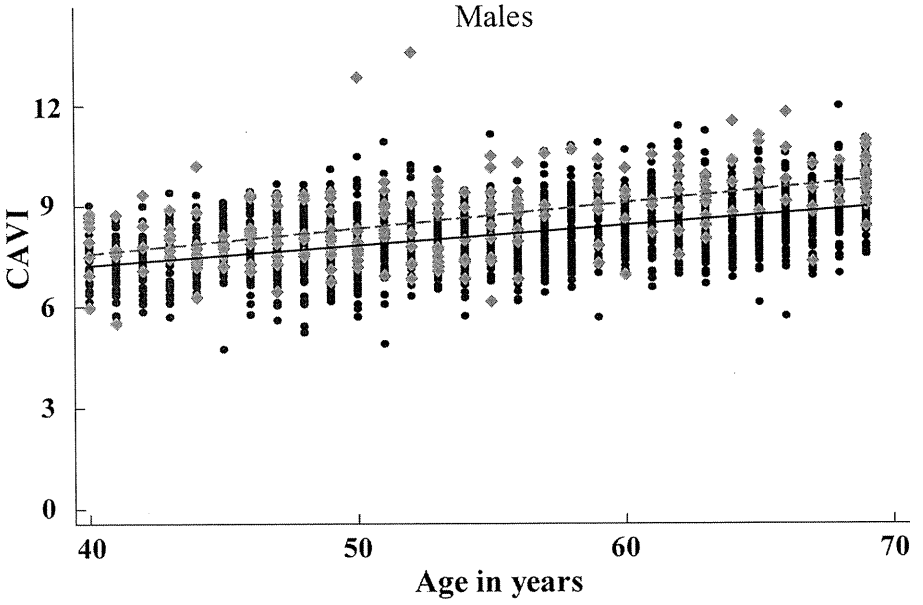

Fig. 1A. Distribution of cardio-ankle vascular index (CAVI) by age in males. The black circle and solid line show each CAVI value and regression line, respectively, on the Amami islands. The dark diamond and broken line show each CAVI value and regression line, respectively, on the Kagoshima mainland. The relation between CAVI and age is expressed as CAVI = 0.06 × age + 4.86 for the Amami islands and CAVI = 0.08 × age + 4.53 for the Kagoshima mainland.

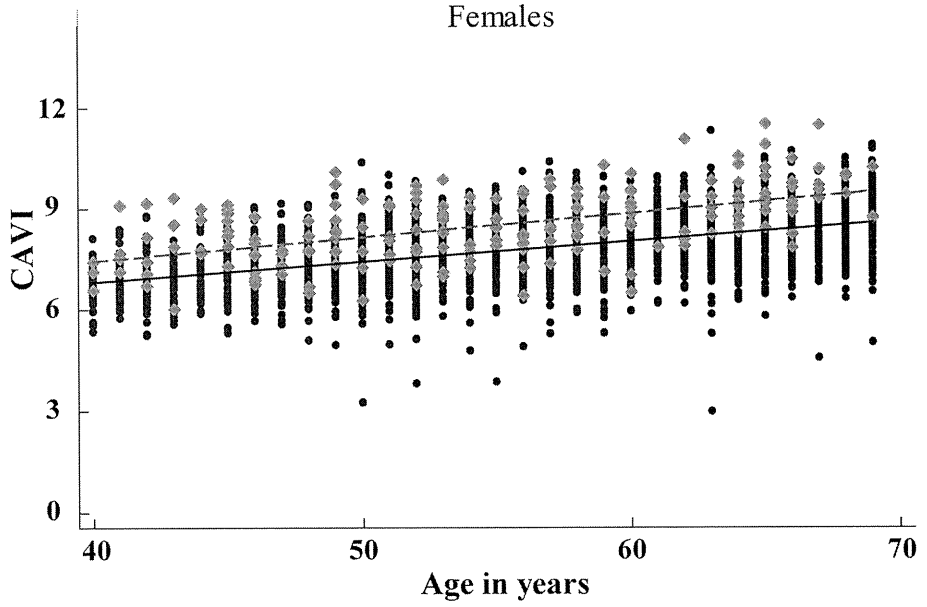

Fig. 1B. Distribution of cardio-ankle vascular index (CAVI) by age in females. The black circle and solid line show each CAVI value and regression line, respectively, on the Amami islands. The dark diamond and broken line show each CAVI value and regression line, respectively, on the Kagoshima mainland. The relation between CAVI and age is expressed as CAVI = 0.06 × age + 4.41 for the Amami islands and CAVI = 0.07 × age + 4.60 for the Kagoshima mainland.

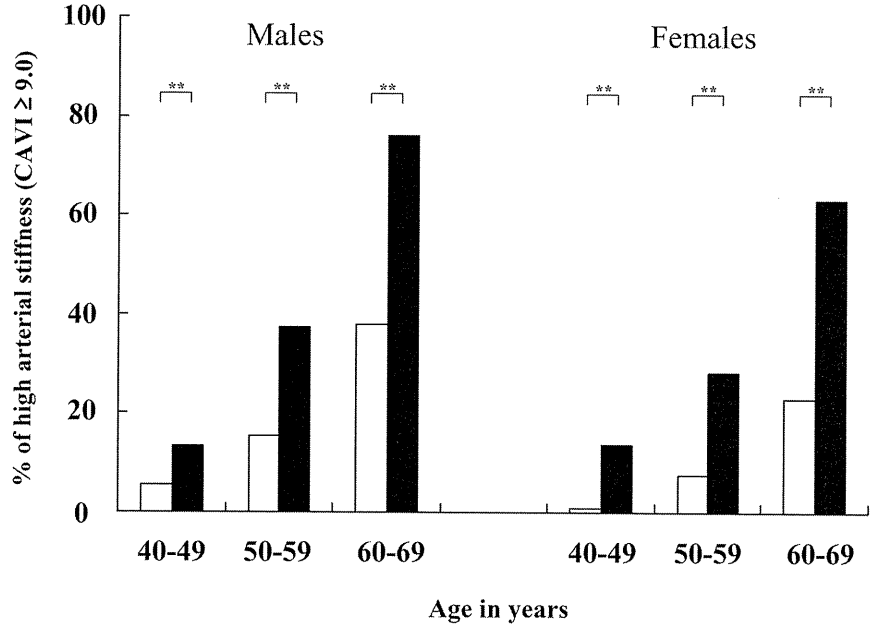

Fig. 2. Geographical comparison of the frequency of high arterial stiffness (cardio-ankle vascular index: CAVI ≥9.0) between the Amami islands and the Kagoshima mainland by age group and sex. White and black squares show the percentage of high arterial stiffness on the Amami islands and the Kagoshima mainland, respectively. $^{*}p<0.05$. $^{**}p<0.01$.

≥9.0) was compared by sex, age group, and region (**Fig. 2**). Its frequency increased with age in both sexes and regions. Males showed a higher frequency of high arterial stiffness than females in each age group and region. Amami residents also had lower percentages of high arterial stiffness than the mainland in each sex and age group. The frequency of high arterial stiffness in the Amami and mainland groups was 5.6% vs. 13.3% ($p=0.009$), 15.4% vs. 37.2% ($p<0.001$), and 37.9% vs. 76.1% ($p<0.001$) in males aged 40-49, 50-59, and 60-69 years, respectively, and 1.0% vs. 13.8% ($p<0.001$), 7.6% vs. 28.4% ($p<0.001$), and 23.0% vs. 63.2% ($p<0.001$) in females in the same respective age groups.

We examined the relationship between CAVI values and clinical characteristics: smoking, drinking, and exercise habits; and a history of clinical status, using multiple linear regression analysis (**Table 2**). A positive relationship was observed for the following: age, SBP, TG, FBS, and history of hypertension and diabetes mellitus in males on Amami; age in males on the mainland; age, SBP, TG, FBS, UA, and history of hypertension in females on Amami; age and history of hypertension in females on the mainland. In contrast, a negative relationship was observed for BUN in males on Amami. The regional effect for differences in CAVI values was also examined using this model after adjusting for traditional cardiovascular risk factors (**Table 3**). The regional factor of Amami, compared with the mainland, was negatively and significantly related to increased CAVI values in both sexes ($p<0.001$ in males and $p<0.001$ in females).

Mean CAVI values of Amami subjects and the healthy Japanese population were similar in all male age groups and were lower in Amami females in their 40s and 50s (**Fig. 3A**, **3B**). In contrast, mean CAVI values of the mainland subjects were higher than those of Amami subjects and the healthy Japanese population in all age groups of both genders.

Discussion

The present study investigated high arterial stiffness using CAVI in relatively large subject groups and compared its distribution and related factors between the Amami islands and the mainland of Japan. We found geographical differences in the mean CAVI values: residents of Amami had lower CAVI values than those of mainland residents. CAVI values in Amami residents were almost equivalent to the healthy Japanese population with less risk factors for coronary arterial diseases; however, differences in lifestyle and clinical characteristics could not explain these geographical variations.

Table 2. The correlation coefficient (coef) for clinical characteristics and lifestyle with CAVI values in multiple linear regression analysis by region and sex

	Males				Females			
	Amami islands		Kagoshima mainland		Amami islands		Kagoshima mainland	
	Multiple coef	*p*-value	Multiple coef	*p*-value	Multiple coef	*p*-value	Multiple coef	*p*-value
Age (years)	0.054	<0.001	0.066	<0.001	0.054	<0.001	0.075	<0.001
Height (cm)	0.038	0.169	0.054	0.500	0.008	0.689	0.092	0.284
Weight (kg)	−0.032	0.340	−0.077	0.435	0.007	0.794	−0.073	0.561
BMI (kg/m^2)	0.016	0.857	0.117	0.674	−0.082	0.196	0.120	0.679
SBP (mmHg)	0.008	0.001	0.006	0.437	0.006	0.002	0.011	0.054
DBP (mmg)	−0.002	0.523	0.017	0.090	−0.001	0.805	−0.007	0.460
HR (beat/min)	0.001	0.563	0.004	0.478	0.001	0.619	0.009	0.153
TG (mg/dL)	0.001	<0.001	0.001	0.539	0.001	0.012	0.001	0.560
HDL-C (mg/dL)	0.002	0.295	−0.002	0.755	0.000	0.945	−0.005	0.429
LDL-C (mg/dL)	0.001	0.060	0.001	0.597	0.001	0.261	0.003	0.283
FBS (mg/dL)	0.003	0.008	0.007	0.060	0.005	<0.001	0.000	0.929
BUN (mg/dL)	−0.019	0.003	0.011	0.490	−0.003	0.610	−0.005	0.783
Cr (mg/dL)	0.270	0.070	0.162	0.618	−0.141	0.330	0.849	0.202
UA (mg/dL)	0.019	0.309	0.035	0.531	0.064	0.003	0.067	0.338
Smoking	0.060	0.213	0.174	0.193	0.036	0.644	0.220	0.368
Drinking	0.008	0.745	0.063	0.333	−0.018	0.557	−0.089	0.394
Exercise	0.010	0.713	−0.032	0.655	0.020	0.406	0.120	0.112
History of HT	0.290	<0.001	0.270	0.119	0.287	<0.001	0.413	0.040
History of stroke	−0.025	0.896	0.240	0.580	0.217	0.315	0.534	0.528
History of CAD	0.134	0.405	0.499	0.363	−0.246	0.073	−0.447	0.412
History of diabetes mellitus	0.358	<0.001	0.162	0.582	0.113	0.336	1.325	0.089
History of dislipidemia	−0.040	0.632	−0.018	0.943	0.116	0.105	−0.089	0.695

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TG, triglycerides; HDL-C, high-density lipoproteincholesterol; LDL-C, low-density lipoprotein-cholesterol; FBS, fasting blood sugar; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; HT, hypertension; CAD, coronary artery disease.

The present study is the first to investigate the geographical variation of high arterial stiffness by CAVI in the same ethnic group of the Japanese general population. A regional difference in aging changes in aortic PWV has been reported by Avolio *et al.*[39], who found that aortic PWV in the residents of an urban Chinese town increased with age to a similar degree as people in Western countries; in contrast, increases in aortic PWV with age in a rural Chinese town was much slower. They reported that salt intake was the main contributor to the regional difference of PWV. Compared with this study, differences in CAVI values in the present study are small, which may be partially due to the different impact of lifestyle and genetic differences between the Japanese and Chinese populations, in addition to methodological differences. The CAVI values of patients with hypertension and diabetes mellitus have been compared between Mongolian and Japanese populations, and the Mongolian CAVI values were higher than those of the Japanese[40, 41]. In the present study, mean CAVI values of the Amami subjects were similar to those of the healthy Japanese population in males, and lower in females. In contrast, those of the mainland subjects were higher in both sexes. These results suggest that Amami subjects have a similar or lower distribution of high arterial stiffness compared with the healthy Japanese population.

Because CAVI is one of the methods to measure high arterial stiffness, its related factors are common to previous risk factors for coronary artery disease[28, 30]. The present study revealed that CAVI was positively correlated with age, SBP, TG, BUN, FBS, and a history of hypertension and diabetes mellitus in Amami males after adjusting for related factors. These results, except for BUN, were concordant with those of previous studies; however, significant findings were not

Table 3. Correlation coefficient (coef) for the region, clinical characteristics and lifestyle with CAVI values in multiple linear regression analysis by sex

	Males		Females	
	Multiple coef	*p*-value	Multiple coef	*p*-value
Region (Amami islands)	−0.518	<0.001	−0.712	<0.001
Age (years)	0.057	<0.001	0.056	<0.001
Height (cm)	0.039	0.122	0.015	0.438
Weight (kg)	−0.037	0.228	0.001	0.957
BMI (kg/m^2)	0.028	0.738	−0.067	0.270
SBP (mmHg)	0.007	0.004	0.007	<0.001
DBP (mmg)	0.002	0.545	−0.001	0.816
HR (beat/min)	0.001	0.653	0.001	0.509
TG (mg/dL)	0.001	<0.001	0.001	0.009
HDL-C (mg/dL)	0.001	0.508	0.000	0.988
LDL-C (mg/dL)	0.001	0.032	0.001	0.187
FBS (mg/dL)	0.003	0.001	0.004	<0.001
BUN (mg/dL)	−0.013	0.023	−0.003	0.604
Cr (mg/dL)	0.248	0.060	−0.096	0.497
UA (mg/dL)	0.018	0.318	0.062	0.002
Smoking	0.086	0.060	0.062	0.396
Drinking	0.022	0.321	−0.025	0.380
Exercise	0.006	0.808	0.030	0.190
History of HT	0.272	<0.001	0.291	<0.001
History of stroke	0.033	0.845	0.249	0.234
History of CAD	0.163	0.293	−0.243	0.065
History of diabetes mellitus	0.365	<0.001	0.141	0.218
History of dislipidemia	−0.058	0.463	0.115	0.087

Region, Kagoshima mainland=0, Amami islands=1; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, lowdensity lipoprotein-cholesterol; FBS, fasting blood sugar; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; HT, hypertension; CAD, coronary artery disease.

apparent in the mainland subjects. The major reason for this small contribution may be the low statistical power in the mainland subjects, but the values of multiple coefficients on the mainland were similar to those on Amami. The regional factor of Amami showed a significant negative relation to increased CAVI values after adjusting for traditional cardiovascular risk factors in the combined analysis of the 2 regions. As BMI in Amami residents was higher than in the mainland group, BMI was also included in this analysis. These results suggest that the geographical variation of high arterial stiffness was independently observed in the present study after controlling for related factors of high arterial stiffness.

We found lower CAVI values in the Amami population than in the mainland population, although established risk factors of coronary artery disease[28, 30], such as BMI, TG, SBP, and a history of hypertension, were more prevalent on Amami. This paradoxical finding requires further consideration. One possible explanation is a birth cohort effect of previous lifestyle. The serum TC level among the general population in 1987 was much lower on Amami than on the mainland according to a report of health checkups by the local government, and the magnitude of each change from 1987 to 2007 was much larger on Amami, although these differences were not apparent for TG, HDL-C, or hypertension[42, 43]. This report suggests that the Amami population ingested more low-cholesterol food than the mainland population 20 years ago, but that they are currently ingesting as much high-cholesterol food as the mainland population. Another potential explanation is the different genetic backgrounds of susceptibility to developing arterial stiffness. Several gene polymorphisms are reported to be associated with the risk of high arterial stiffness[44-46], but only one report has examined the geographical distribution of these polymorphisms in

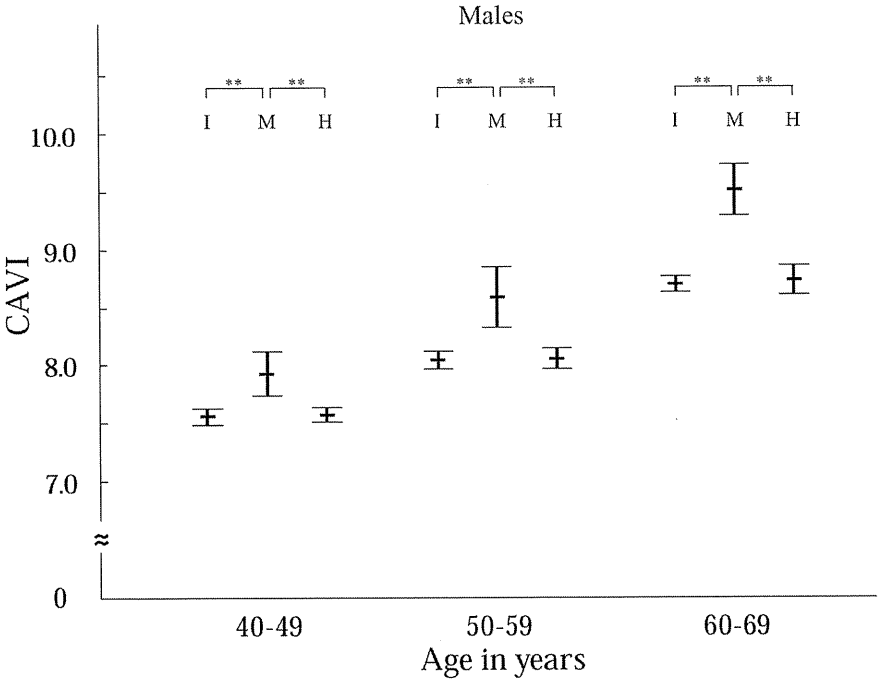

Fig. 3A. Comparison of the mean and 95% confidence interval of the cardio-ankle vascular index (CAVI) among the Amami island subjects (I), the Kagoshima mainland subjects (M), and the healthy population[28] (H) by age group in males. $^{*}p<0.05$, $^{**}p<0.01$.

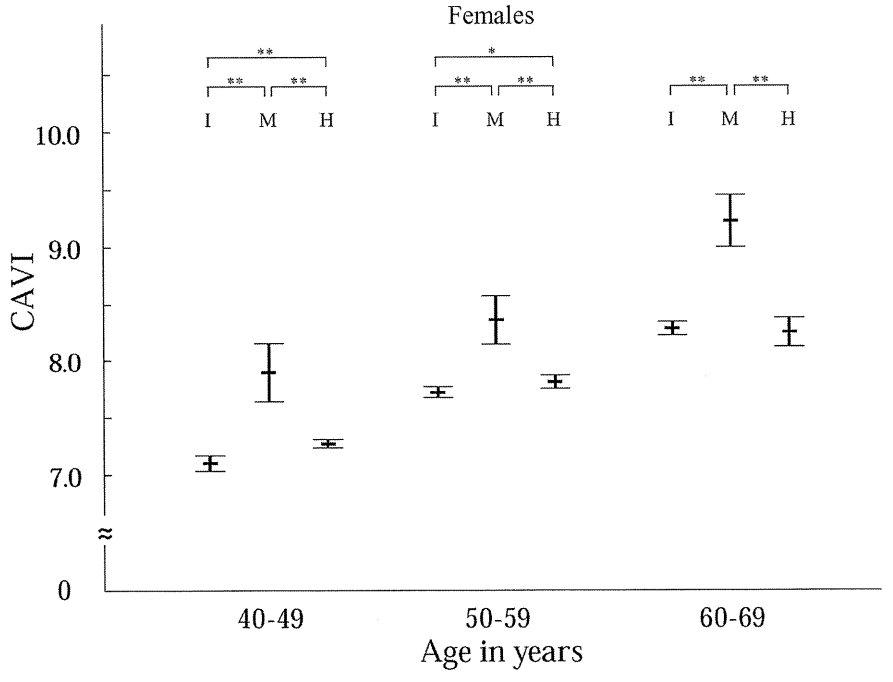

Fig. 3B. Comparison of the mean and 95% confidence interval of the cardio-ankle vascular index (CAVI) among the Amami island subjects (I), the Kagoshima mainland subjects (M), and the healthy population[28] (H) by age group in females. $^{*}p<0.05$, $^{**}p<0.01$.

this study region. SNP genotypes with frequency differences between the Hondo and Ryukyu clusters among 7003 Japanese have been reported[47]. The Amami islands neighbor Okinawa, which includes the Ryukyu cluster. Further studies are needed to clarify the role of environmental and genetic factors in the observed geographical variation. A methodological issue should also be discussed with regard to the geographical variation. We used the same equipment to examine the CAVI in both study regions. Quality control for the biochemical examination was also conducted, and the results were found to be appropriate.

Several limitations have to be considered. First, the present subjects may not be completely representative of the general population, but were comparable between the 2 studied regions because subjects in both groups were recruited from health checkup examinees in the general population. The present study may still include some selection bias because the Amami subjects were recruited through a routine health checkup program at the local governmental level, whereas the mainland subjects were recruited at a health checkup center that they visited. This selection bias, however, may not be large and can be controlled since both subject groups were recruited from the general population and the prevalence of a history of stroke, coronary artery disease, and diabetes mellitus did not differ between them. Since some health status markers, such as SBP, LDL-C, and FBS levels, differed by region, we also adjusted for these factors to evaluate geographical variation. Second, the CAVI data quality was not compared between the 2 regions; however, we used the same method to examine CAVI, and those with potential misclassification due to arrhythmias and low ABI were excluded. Third, the number of subjects on the mainland was not large compared with those on Amami, but the statistical power was enough to clarify the difference in the mean CAVI values and the regional factor between regions. Fourth, for calculating CAVI values, the CAVI system uses estimated aortic path length by height, not the real distance, and several researchers have proposed concerns about the use of this estimation[48, 49]. Finally, no studies have reported the ability of CAVI to predict cardiovascular end points in prospective observation studies or interventional trials. These limitations should be evaluated in the future.

Conclusion

CAVI values in Amami residents were significantly lower than in mainland residents; however, differences in lifestyle and clinical characteristics could not explain these geographical variations. It is suggested that other environmental or genetic factors might improve the arterial stiffness of people on Amami. Further molecular epidemiological studies are required to clarify these factors.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgments

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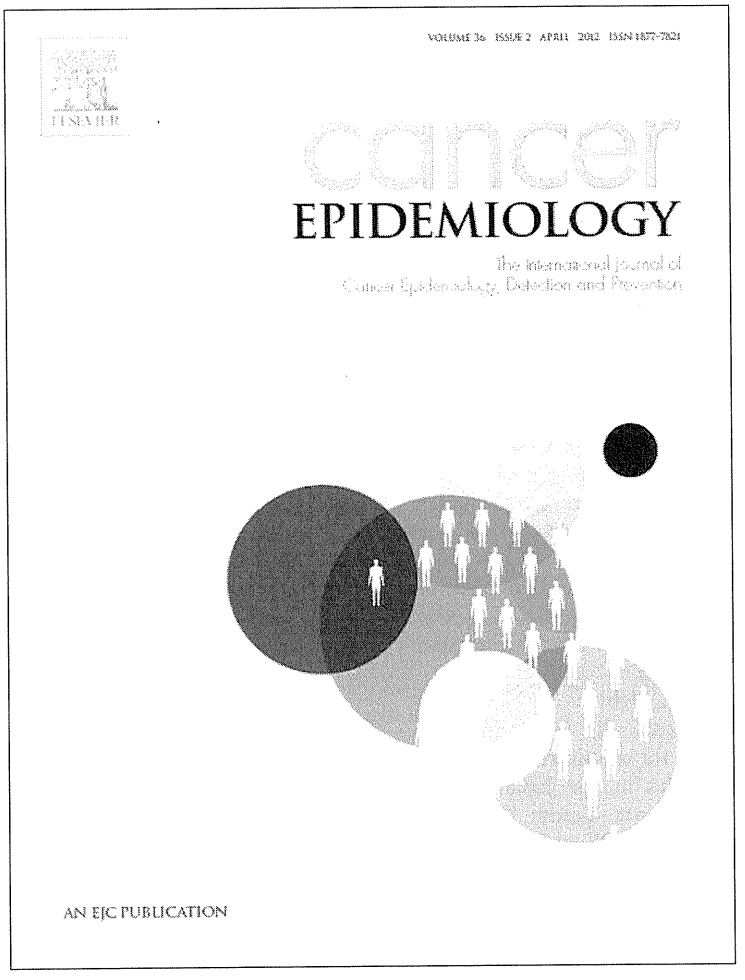
References

1) Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare: Vital statistics of Japan 2006, Vol 3. Health and Welfare Statistics Association, Tokyo, 2007 (in Japanese)
2) World Health Organization: WHO Statistical Information System (WHOSIS) Mortality Profiles. Available at: http://www.who.int/whosis/mort/profiles/en/index.html. Accessed 14 March 2010
3) Tanaka H, Nishino M, Ishida M, Fukunaga R, Sueyoshi K: Progression of carotid atherosclerosis in Japanese patients with coronary artery disease. Stroke, 1992; 23: 946-951
4) Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S: Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension, 2002; 39: 10-15
5) Jones EF, Kalman JM, Calafiore P, Tonkin AM, Donnan GA. Proximal aortic atheroma: An independent risk factor for cerebral ischemia. Stroke, 1995; 26: 218-224

6) Dijk JM, van der Graaf Y, Grobbee DE, Banga JD, Bots ML; SMART Study Group: Increased arterial stiffness is independently related to cerebrovascular disease and aneurysms of the abdominal aorta: the Second Manifestations of Arterial Disease (SMART) Study. Stroke, 2004; 35: 1642-1646
7) Fujiwara T, Saitoh S, Takagi S, Ohnishi H, Ohata J, Takeuchi H, Isobe T, Chiba Y, Katoh N, Akasaka H, Shimamoto K: Prevalence of asymptomatic arteriosclerosis obliterans and its relationship with risk factors in inhabitants of rural communities in Japan: Tanno-Sobetsu study. Atherosclerosis, 2004; 177: 83-88
8) Ogawa O, Hayashi C, Nakaniwa T, Tanaka Y, Kawamori R: Arterial stiffness is associated with diabetic retinopathy in type 2 diabetes. Diabetes Res Clin Pract, 2005; 68: 162-166
9) Yokoyama H, Hirasawa K, Aoki T, Ishiyama M, Koyama K: Brachial-ankle pulse wave velocity measured automatically by oscillometric method is elevated in diabetic patients with incipient nephropathy. Diabet Med, 2003; 20: 942-945
10) Tomochika Y, Tanaka N, Ono S, Murata K, Muro A, Yamamura T, Tone T, Iwatate M, Ueda K, Morikuni K, Matsuzaki M: Assessment by transesophageal echography of atherosclerosis of the descending thoracic aorta in patients with hypercholesterolemia. Am J Cardiol, 1999; 83: 703-709
11) Dernellis J, Panaretou M: Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension, 2005; 45: 426-431
12) Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S; Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Group: Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: the JPHC Study Cohort I. Stroke, 2004; 35: 1248-1253
13) Yanez ND, Burke GL, Manolio T, Gardin JM, Polak J; CHS Collaborative Research Group: Sibling history of myocardial infarction or stroke and risk of cardiovascular disease in the elderly: the Cardiovascular Health Study. Ann Epidemiol, 2009; 19: 858-866
14) Laskarzewski P, Morrison JA, Horvitz R, Khoury P, Kelly K, Mellies M, Glueck CJ: The relationship of parental history of myocardial infarction, hypertension, diabetes and stroke to coronary heart disease risk factors in their adult progeny. Am J Epidemiol, 1981; 113: 290-306
15) O'Rourke M: Mechanical principles in arterial disease. Hypertension, 1995; 26: 2-9
16) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. Circulation, 1998; 97: 1837-1847
17) Kodama K, Sasaki H, Shimizu Y: Trend of coronary heart disease and its relationship to risk factors in a Japanese population: a 26-year follow-up, Hiroshima/Nagasaki study. Jpn Circ J, 1990; 54: 414-421
18) O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE: Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens, 2002; 15: 426-444
19) Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries: Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J, 2006; 27: 2588-2605
20) Hasegawa, M: Fundamental research on human aortic pulse wave velocity. Jikei Med J, 1970; 85: 742-760 (in Japanese)
21) Kubo T, Miyata M, Minagoe S, Setoyama S, Maruyama I, Tei C: A simple oscillometric technique for determining new indices of arterial distensibility. Hypertens Res, 2002; 25: 351-358
22) Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res, 2002; 25: 359-364
23) Shirai K, Utino J, Otsuka K, Takata M: A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb, 2006; 13: 101-107
24) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Matsuda T, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is a new noninvasive parameter of arterial stiffness. Circ J, 2007; 71: 1710-1714
25) Ibata J, Sasaki H, Kakimoto T, Matsuno S, Nakatani M, Kobayashi M, Tatsumi K, Nakano Y, Wakasaki H, Furuta H, Nishi M, Nanjo K: Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pract, 2008; 80: 265-270
26) Shirai K, Song M, Suzuki J, Kurosu T, Oyama T, Nagayama D, Miyashita Y, Yamamura S, Takahashi M: Contradictory Effects of β1- and α1- Aderenergic Receptor Blockers on Cardio-Ankle Vascular Stiffness Index (CAVI). J Atheroscler Thromb, 2011; 18: 49-55
27) Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O, Tei C: Clinical significance and reproducibility of new arterial distensibility index. Circ J, 2007; 71: 89-94
28) Suzuki K, Ishizuka N, Miyashita H, Shirai K: Standardization of CAVI as a non-invasive and blood-pressure-independent method for the examination of arterial stiffness: an epidemiological investigation on standard values and its plausibility. The Niigata Journal of Medical Technology, 2008; 48: 2-10 (in Japanese)
29) Okura T, Watanabe S, Kurata M, Manabe S, Koresawa M, Irita J, Enomoto D, Miyoshi K, Fukuoka T, Higaki J: Relationship between cardio-ankle vascular index (CAVI) and carotid atherosclerosis in patients with essential hypertension. Hypertens Res, 2007; 30: 335-340
30) Kadota K, Takamura N, Aoyagi K, Yamasaki H, Usa T, Nakazato M, Maeda T, Wada M, Nakashima K, Abe K, Takeshima F, Ozono Y: Availability of cardio-ankle vascular index (CAVI) as a screening tool for atherosclerosis. Circ J, 2008; 72: 304-308
31) Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H: Cardio-ankle vascular index is a candidate

predictor of coronary atherosclerosis. Circ J, 2008; 72: 598-604
32) Ueyama K, Miyata M, Kubozono T, Nagaki A, Hamasaki S, Ueyama S, Tei C: Noninvasive indices of arterial stiffness in hemodialysis patients. Hypertens Res, 2009; 32: 716-720
33) Takenaka T, Hoshi H, Kato N, Kobayashi K, Takane H, Shoda J, Suzuki H: Cardio-ankle vascular index to screen cardiovascular diseases in patients with end-stage renal diseases. J Atheroscler Thromb, 2008; 15: 339-344
34) Kubozono T, Miyata M, Ueyama K, Nagaki A, Hamasaki S, Kusano K, Kubozono O, Tei C: Association between arterial stiffness and estimated glomerular filtration rate in the Japanese general population. J Atheroscler Thromb, 2009; 16: 840-845
35) Noike H, Nakamura K, Sugiyama Y, Iizuka T, Shimizu K, Takahashi M, Hirano K, Suzuki M, Mikamo H, Nakagami T, Shirai K: Changes in cardio-ankle vascular index in smoking cessation. J Atheroscler Thromb, 2010; 17: 517-525
36) Hamajima N; J-MICC Study Group: The Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study) to detect gene-environment interactions for cancer. Asian Pac J Cancer Prev, 2007; 8: 317-323
37) Naito M, Eguchi H, Okada R, Ishida Y, Nishio K, Hishida A, Wakai K, Tamakoshi A, Hamajima N; J-MICC Study Group: Controls for monitoring the deterioration of stored blood samples in the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study). Nagoya J Med Sci, 2008; 70: 107-115
38) Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 1972; 18: 499-502
39) Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF: Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation, 1985; 71: 202-210
40) Uurtuya S, Taniguchi N, Kotani K, Yamada T, Kawano M, Khurelbaatar N, Itoh K, Lkhagvasuren T: Comparative study of the cardio-ankle vascular index and ankle-brachial index between young Japanese and Mongolian subjects. Hypertens Res, 2009; 32: 140-144
41) Uurtuya S, Kotani K, Taniguchi N, Yoshioka H, Kario K, Ishibashi S, Yamada T, Kawano M, Khurelbaatar N, Itoh K, Lkhagvasuren T: Comparative study of atherosclerotic parameters in Mongolian and Japanese patients with hypertension and diabetes mellitus. J Atheroscler Thromb, 2010; 17: 181-188
42) Health and Environmental Department, Kagoshima Prefecture: Adult diseases of Kagoshima Prefecture, 1987. Health and Environmental Department, Kagoshima Prefecture, Kagoshima, 1988 (in Japanese)
43) Health and Social Welfare Department, Kagoshima Prefecture: Basic Health Checkup/Cancer Screening Results, 2007. Available at: http://www.pref.kagoshima.jp/kenko-fukushi/kenko-iryo/seikatusyukan/seikatusyukan/kennshinnkekka-ken19.html. Accessed 19 May 2010 (in Japanese)
44) Lacolley P, Challande P, Osborne-Pellegrin M, Regnault V: Genetics and pathophysiology of arterial stiffness. Cardiovasc Res, 2009; 81: 637-648
45) Medley TL, Kingwell BA, Gatzka CD, Pillay P, Cole TJ: Matrix metalloproteinase-3 genotype contributes to age-related aortic stiffening through modulation of gene and protein expression. Circ Res, 2003; 92: 1254-1261
46) Pojoga L, Gautier S, Blanc H, Guyene TT, Poirier O, Cambien F, Benetos A: Genetic determination of plasma aldosterone levels in essential hypertension. Am J Hypertens, 1998; 11: 856-860
47) Yamaguchi-Kabata Y, Nakazono K, Takahashi A, Saito S, Hosono N, Kubo M, Nakamura Y, Kamatani N: Japanese population structure, based on SNP genotypes from 7003 individuals compared to other ethnic groups: effects on population-based association studies. Am J Hum Genet, 2008; 83: 445-456
48) Safar ME, O'Rourke MF: The brachial-ankle pulse wave velocity. J Hypertens, 2009; 27: 1960-1961
49) Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T: Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. J Hypertens, 2009; 27: 2022-2027



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Metabolic syndrome and incidence of liver and breast cancers in Japan

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ABSTRACT

Aim of the study To clarify the relationship between the presence of metabolic syndrome and the incidence of cancer in a general Japanese population. *Methods* A retrospective cohort study was conducted among 8329 male and 15,386 female subjects between 1992 and 2000. The analysis used five definitions of metabolic syndrome. The information on the site-specific cancer was obtained from the population-based cancer registry. A Cox proportional hazard model was adapted for the statistical analyses. The average follow-up period was 9.1 years. *Results* The National Cholesterol Education Program Adult Treatment Panel III 2001 criteria of metabolic syndrome revealed that the hazard ratio of metabolic syndrome for liver cancer was 1.89 (95% confidence interval (CI) 1.11–3.22) for males, and 3.67 (CI 1.78–7.57) for females. The hazard ratio for female breast cancer was 2.87 (CI 1.67–4.94). When the analysis was limited to postmenopausal women (55 years of age or older), the ratio increased to 6.73 (CI 2.93–15.43). The NCEP-ATPIII 2001 criteria were superior to the other four proposed criteria for predicting the incidence of cancer. In the statistical model, which included all components of the metabolic syndrome and the metabolic syndrome (present or absent), high blood glucose was a significant associated factor for all sites and liver cancers, whereas the metabolic syndrome was found to be a significant associated factor for breast cancer. *Conclusion* Metabolic syndrome may play an important role in the incidence of breast cancer. High fasting plasma glucose level is considered to be useful as an associated factor for the incidence of all-sites and liver cancer.

1. Introduction

Metabolic syndrome is an important risk factor for the development of circulatory diseases such as ischemic heart disease or cerebrovascular diseases based on arteriosclerosis [1–3]. This syndrome comprises various clinical conditions, such as hypertension, dyslipidemia, and impaired glucose tolerance, which are associated with abdominal obesity. Interventions that resolve metabolic syndrome are essential for preventing the subsequent circulatory diseases. Various criteria have been proposed to define metabolic syndrome, but there is still no international consensus [4–8].

On the other hand, hyperinsulinemia due to insulin resistance is the primary clinical condition of metabolic syndrome; it induces cell proliferation and apoptotic suppression, and influences cell proliferation signals. In addition, the low level of adiponectin due to abdominal obesity may increase the probability of carcinogenesis through inflammatory promotion or apoptotic suppression [9]. Therefore, metabolic syndrome may be a risk factor for cancer as well as for circulatory diseases. In particular, several groups have reported that metabolic syndrome may be a risk factor for several types of cancer [10–14]. However, there are few available studies from Asian countries [15–17].

A retrospective cohort study was conducted to determine whether metabolic syndrome is a risk factor for specific sites of cancers in Japan. Furthermore, five proposed criteria of metabolic syndrome were compared to determine which is a factor associated with cancer incidence. The subsequent analyses were conducted to compare the components of the metabolic syndrome with the metabolic syndrome as an associated factor for the incidence of certain cancers.

2. Participants and methods

2.1. Subjects

The present study design was a retrospective cohort study. The subjects consisted of general health examinees by the municipalities' government in the Tottori Prefecture (population of approximately 600,000 in 2007) from January 1, 1992 to March 31, 2000. The government informed the residents of the municipalities about the health examination through a public information

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magazine. The cohort included 13,048 males and 25,784 females. Individuals who were under 20 year of age at the time of the health examination, those who already had cancer, those who contracted cancer within 2 years after the follow-up, and those with missing data related to the diagnosis of metabolic syndrome – body mass index (BMI) for five participants, blood pressure (systolic pressure for five and diastolic pressure for seven), high density lipoprotein (HDL) for 56, triglycerides for 59, and fasting plasma glucose (FPG) for 14,397 – were excluded from the study. In total, 8239 males and 15,386 females (total 23,625) were included in the current analyses.

2.2. Criteria of the metabolic syndrome

Metabolic syndrome has been defined by five recently proposed sets of criteria [4–8]. The criteria vary depending on whether abdominal circumference or obesity was an essential item, whether the cut-off point of the value was used, and whether each item included people taking medication. In many cases the criteria used abdominal circumference, whereas the WHO criteria for the waist-to-hips ratio were adopted for the definition of obesity [4–8].

The BMI was used for the definition of obesity because abdominal circumference was not measured at the beginning of the follow-up. The BMI was calculated as follows: (weight in kg)/(height in m^2). Subjects with a BMI ≥ 25 were regarded as obese in both sexes [18]. This criterion was equivalent to the global definition of being overweight; however, the prevalence of subjects with a BMI ≥ 30 was only 1.8%, and therefore being overweight was defined as being obese in the present study. The five criteria of the metabolic syndrome were used for this analysis (Table 1). A new criterion of metabolic syndrome based on the National Cholesterol Education Program's Adults Treatment Panel III (NCEP-ATPIII) 2001 criteria was devised, replacing the criterion of the blood pressure according to the WHO (BP > 140/90) because the prevalence of normal high blood pressure (>130/85) as a component of metabolic syndrome was relatively high. In this way we evaluated six different criteria regarding metabolic syndrome. Subjects that lacked one item in a criterion were concluded to have pre-metabolic syndrome.

The components of the metabolic syndrome were measured as follows. The blood pressure was measured by manual operation by trained nurses using a mercury manometer. Blood pressure was measured twice when the value was ≥140/90, and the lower value was recorded. Blood pressure was also measured twice when the maximal blood pressure was <100, and the higher value was recorded. The body weight was measured by using an authorized scale (Tanita Corporation). Blood specimens were refrigerated using a refrigeration box for 2–3 h and were analyzed. The serum triglyceride (TG) levels were measured by the enzymatic method and high-density-lipoprotein (HDL) cholesterol levels were measured by the direct method using a 7700 Hitachi automatic-analyzer (Hitachi Co. Ltd., Tokyo, Japan). Fasting plasma glucose (FPG) levels were measured by the enzymatic method (hexokinase method) using a DM-Jack Ex automatic-analyzer (Kyowa Medex Co. Ltd., Tokyo, Japan). Participants were asked about their use of medications for hypertension, diabetes, and dyslipidemia in a face-to-face interview at their health examination by trained public health nurses.

2.3. Other factors used in the analysis

Information about subjects' smoking and drinking habits was obtained by trained public health nurses. Smoking status was classified into three categories: namely current smokers, ex-smokers and never-smokers. Drinking behavior was classified according to the average amount of pure alcohol consumed in an average day. The available data used in the analysis were categorized into two categories, namely heavy drinkers (≥60 g pure alcohol) and non-heavy drinkers.

2.4. Endpoint detection

The endpoint of the follow-up was the occurrence of cancer. The incidence of cancer was detected using the database of the Tottori prefectural cancer registry. The event times of the participants who died before the end of the follow-up were censored. The follow-up period was from the day of the health examination until the end of January of 2007, and the average follow-up period was 9.1 years.

2.5. Statistical analysis

The statistical analyses were performed using the Cox proportion hazard regression model. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated for the associations between the presence of metabolic or pre-metabolic syndrome and its components and the risk of cancer. The statistical analyses were stratified by sex. The HRs were calculated after adjusting for age, smoking status (never, former, and current smoker) and heavy drinking (≥60 g of daily alcohol).

In the first analyses, we analyzed the association of six criteria for metabolic syndrome with cancer by site. Hazard ratios were calculated for each criterion related to metabolic syndrome using participants without metabolic syndrome or pre-metabolic syndrome as the reference status. For each cancer site, we repeated the same statistical model for the six criteria of metabolic syndrome.

Table 1
Evolving definitions of metabolic syndrome.

	Japan 2005	Modified NECP 2001	Modified NECP 2004	Modified IDF 2006	Modified WHO 1999
Criteria	Obesity plus at least 2 other items	At least 3 of the following	At least 3 of the following	Obesity plus at least 2 other items	Hyperglycemia plus at least 2 other items
Essential item	Obesity			Obesity	Hyperglycemia
Obesity	BMI ≥ 25	BMI ≥ 25	BMI ≥ 25	BMI ≥ 25	BMI ≥ 25
High blood pressure	≥130/85 mmHg or medication	≥130/85 or medication	≥130/85 or medication	≥130/85 or medication	≥140/90 or medication
Serum lipids	HDL < 40 mg/dl or TG ≥ 150 mg/dl or medication	HDL < 40 in males, HDL < 50 in females	HDL < 40 in males, HDL < 50 in females or medication	HDL < 40 in males, HDL < 50 in females or medication	HDL < 35 in males (HDL < 39 in females) or TG ≥ 150
		TG ≥ 150	TG ≥ 150 or medication	TG ≥ 150 or medication	
Hyperglycemia	FPG ≥ 110 mg/dl or medication	FPG ≥ 110	FPG ≥ 100	FPG ≥ 100 or medication	FPG ≥ 110

J-MeS: Japanese definition of metabolic syndrome; NCEP: National Cholesterol Education Program's Adults Treatment Panel III; IDF: International Diabetes Federation; WHO: World Health Organization; BMI: body mass index; HDL: serum high density lipoprotein cholesterol; TG: serum triglycerides; FPG: fasting plasma glucose.

An additional analysis was performed for breast cancer, limiting subjects' age to ≥55 years, because some studies have reported that the results differ between premenopausal and postmenopausal females [19,20]. Most Japanese females achieve postmenopausal status at 55 years of age [21], and therefore 55 years of age was considered to be the menopausal age.

In the second analyses, models determining the associations with the cancer incidence of all metabolic syndrome components as covariates were generated. These analyses were performed for all sites, liver, and breast cancer because statistically significant results were obtained in the first analyses.

We tested the proportional hazards assumption for each categorical variable in relation to cancer risk using Kaplan–Meier plots. For the continuous variable, we checked after making a dummy variable. A time-dependent variable was not found in the analyses. No evidence was found of violation of the proportional hazards assumption. We also analyzed co-linearity among covariates, and did not find any co-linearity. The DFbeta plots for the residual analysis were tested and no remarkable outliner plot was identified.

The statistical analyses were conducted using the SPSS computer software program (SPSS version 18.0). The Tottori University Ethical Review Board approved the present study. In addition, the Tottori prefectural government and municipality governments also approved the study. This study was supported by the Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour and Welfare [20–22].

3. Results

The annual death certificate notification (DCN), a precision index of the cancer registry, was 5.9% during the follow-up period of the present series. A DCN is the proportion of cases for which the information was received first via a death certificate notification among all registered cases. This value was sufficiently precise for detecting the outcomes of this study. There were 215,847 total follow-up person-years, 72,553 for male subjects and 143,295 for female subjects. The observed number of cancers was 1056 for male subjects, 875 for female subjects, and a total of 1931 cases were recorded. The most prevalent sites of cancer included the stomach (males 226, females 167, a total of 393), lung (males 130, females 81, a total of 211), colon (males 64, females 94, a total of 158), prostate (males 152), liver (males 82, females 47, a total of 129), breast (male 1, females 77, a total of 78), rectum (males 34, females 42, a total of 76). The average of the components of metabolic syndrome and the proportion of subjects who were applicable to the criteria of each component are shown in Table 2.

The proportion of subjects with BMI ≥ 25 was 20.2%, that with BMI ≥ 30 was only 1.8%, that with blood pressure ≥130/85 was 45.2%, that of subjects with a blood pressure ≥140/90 was 32.2%; the proportion of subjects with HDL levels <40 or TG levels ≥150 (Japanese criteria of dyslipidemia) was 22.5%, and that of subjects with FPG levels of ≥110 was 20.7%. The subjects with cancer were significantly older, the smoking rate was high for male subjects, and the patient BMI was low, blood pressure high, and plasma glucose relatively high for female subjects who later developed cancer.

The prevalence of metabolic syndrome and pre-metabolic syndrome according to the criteria is shown in Table 2. The proportion of subjects with applicable WHO criteria was the lowest, and subsequently that with the Japanese criteria, the IDF criteria, were low. These are criteria requiring an essential item for diagnosing metabolic syndrome. The criteria that showed the highest prevalence of the metabolic syndrome were the criteria of the NCEP-ATPIII 2004.

The Cox proportional hazard regression analyses showed that metabolic syndrome was a significant risk factor for the incidence of several types of cancer. Pre-metabolic syndrome is associated with an elevated likelihood of developing cancer in male subjects. Several criteria showed that metabolic syndrome was a significant risk factor for the later development of liver cancer for both sexes. The presence of metabolic syndrome was a significant risk factor for overall cancer and for liver and breast cancer development, whereas it was not a significant risk factor for colon, rectal or prostate cancer. Metabolic syndrome was a strong risk factor for breast cancer, and the magnitude of the hazard ratio was elevated in postmenopausal female subjects (≥55 years of age). A relationship with graded increased risks from pre-metabolic syndrome to metabolic syndrome was observed in female subjects (Table 3).

In a model considering all components of the metabolic syndrome as defined by the NCEP-ATPIII 2001, high glucose was a significant associated factor for the incidence of overall cancer development and liver cancer development, whereas obesity (BMI ≥ 25) was a significant associated factor for breast cancer even after adjusting for all components of metabolic syndrome (Table 4). The hazard ratio for high triglycerides was significant below a value of 1.0.

4. Discussion

The present study demonstrated that metabolic syndrome increased the risk of cancers at several sites. The hazard ratio of metabolic syndrome was statistically significant, and it increased in the order of pre-metabolic syndrome, metabolic syndrome for liver cancer in males and females, total cancer in females, and female breast cancer. In particularly, metabolic syndrome was found to be a strong risk factor for female breast cancer in subjects ≥55 years of age. On the other hand, when all individual components of the metabolic syndrome were included in the statistical model, a high glucose level was a significant risk factor for the development of overall cancer and liver cancer in particular.

Metabolic syndrome has attracted interest as a new risk factor for the circulatory diseases. Epidemiological studies conducted in Western countries show that metabolic syndrome is an independent risk factor for hospitalization, or for death due to heart disease and cerebral infarction, and the hazard ratio was approximately 2 [1–3]. Several studies from Asian countries have shown a similar hazard ratio [22–25]. The current results indicate that metabolic syndrome is a risk factor for the incidence of cancer, especially for cancers in females, and therefore metabolic syndrome may be an important clinical factor not only for preventing circulatory diseases but also for preventing cancers.

The relationship between the site-specific occurrence of cancer and metabolic syndrome have not yet reached consistent conclusions [10,11,26]; however, several types of cancer – such as colon, prostate, and pancreatic cancers – have a positive association with metabolic syndrome according to many studies [10–14,27,28]. The current study observed a significant relationship between metabolic syndrome and some sites of cancer, especially liver and breast cancers, but no such relationship was observed for colon, prostate, stomach, or lung cancer. These results were not thought to be coincidental, because the person–years in this study were relatively high (approximately 216,000). Therefore, the difference between the findings obtained in this study and those of previous studies may be due to racial or environmental factors between Asian people and Western populations.

Conventionally, obesity is considered to be a risk factor for several types of cancer, including breast cancer. A meta-analysis on BMI and cancer found that obesity is a risk factor for esophageal, colon, thyroid, and renal cancer in male subjects, and endometrial,

Table 2
The baseline characteristics and prevalence of metabolic syndrome of the total cohort and cancer incident cases by sex.

Item	Total subjects (n=23,625)	Males (n=8239)	Females (n=15,386)	Cancer cases (n=1931)	Male cases (n=1056)	Female cases (n=875)	p-Value Male versus female	p-Value Cancer versus non-cancer cases
Age, mean (SD), y	58.6 (11.8)	60.5 (10.8)	57.6 (12.1)	63.9 (8.7)	65.3 (7.4)	62.3 (9.8)	0.000	0.000
Current smokers, No (%)	3150 (13.3)	2945 (35.7)	205 (1.3)	443 (22.9)	431 (40.8)	12 (1.4)	0.000	0.000
Ex-smokers, No (%)	1663 (7.0)	1607 (19.5)	56 (0.4)	258 (13.4)	255 (24.1)	3 (0.3)	0.000	0.000
Heavy drinkers, No (%)	438 (1.9)	428 (5.2)	10 (0.1)	47 (2.4)	47 (4.5)	0	0.000	0.060
Body mass index (BMI), mean (SD)	22.7 (3.1)	22.7 (2.8)	22.6 (3.2)	22.6 (3.0)	22.3 (2.8)	22.9 (3.2)	0.000	0.200
BMI ≥ 25, No (%)	4781 (20.2)	1648 (20.0)	3133 (20.4)	376 (19.5)	165 (15.6)	211 (24.1)	0.522	0.399
BMI ≥ 30, No (%)	432 (1.8)	91 (1.1)	341 (2.2)	21 (1.1)	6 (0.6)	15 (1.7)	0.000	0.014
Systolic blood pressure, mean (SD), mmHg	132.1 (18.3)	134.7 (17.7)	130.7 (18.5)	135.7 (18.1)	136.5 (17.7)	134.6 (18.6)	0.000	0.000
Diastolic blood pressure, mean (SD), mmHg	77.9 (10.9)	80.3 (10.6)	76.6 (10.8)	79.3 (10.8)	80.4 (10.7)	78.0 (10.7)	0.145	0.000
Medication for hypertension, No (%)	3011 (12.7)	1030 (12.5)	1981 (12.9)	315 (16.3)	16.3 (15.4)	152 (17.4)	0.423	0.000
Blood pressure ≥ 130 and or 85, No (%)	10,690 (45.2)	4277 (51.9)	6413 (41.7)	959 (49.7)	559 (52.9)	400 (45.7)	0.000	0.000
Serum HDL cholesterol, mean (SD) mg/dl	57.6 (15.4)	55.1 (16.0)	59.0 (15.0)	55.6 (15.6)	54.3 (16.1)	57.1 (14.9)	0.000	0.000
Serum triglycerides, mean (SD), mg/dl	109.3 (71.7)	121.0 (85.5)	103.0 (62.2)	108.6 (65.8)	112.8 (70.3)	103.5 (59.5)	0.000	0.648
Medication for dyslipidemia, No (%)	517 (2.2)	81 (1.0)	436 (2.8)	31 (1.6)	10 (0.9)	21 (2.4)	0.000	0.081
HDL < 40 and or TG ≥ 150, No (%)	5319 (22.5)	2497 (30.3)	2822 (18.3)	468 (24.2)	291 (27.6)	177 (20.2)	0.000	0.237
Fasting blood glucose (FBS), mean (SD)	104.0 (29.8)	109.9 (35.7)	101.1 (25.6)	108.7 (34.0)	110.9 (35.0)	106.0 (32.6)	0.000	0.000
Medication for diabetes, No (%)	557 (2.4)	273 (3.3)	284 (0.8)	59 (3.1)	33 (3.1)	26 (3.0)	0.000	0.042
FBS ≥ 110 mg/dl, No(%)	4894 (20.7)	2269 (27.5)	2625 (17.1)	503 (26.0)	320 (30.3)	183 (20.9)	0.000	0.000
Japanese metabolic syndrome (%)	2214 (9.4)	920 (11.2)	1294 (8.4)	178 (9.29)	89 (8.4)	89 (10.2)	0.000	0.841
Japanese pre-metabolic syndrome (%)	1877 (7.9)	577 (7.0)	1300 (8.4)	155 (8.0)	61 (5.8)	94 (10.7)	0.000	0.924
Modified NECP 2001 (%)	4031 (17.1)	1549 (18.8)	2482 (16.1)	360 (18.6)	170 (16.1)	190 (21.7)	0.000	0.058
Pre modified NECP 2001 (%)	5657 (23.9)	2122 (25.8)	3535 (23.0)	542 (28.1)	301 (28.5)	241 (27.5)	0.000	0.000
Modified NCEP 2004 (%)	5272 (22.3)	1971 (23.9)	3301 (21.5)	472 (24.4)	222 (21.0)	250 (28.6)	0.000	0.021
Pre modified NCEP 2004 (%)	6417 (27.2)	2516 (30.5)	3901 (25.4)	606 (31.4)	358 (33.9)	248 (28.39)	0.000	0.000
Modified IDF 2005 (%)	3078 (13.0)	1142 (13.9)	1936 (12.6)	252 (13.1)	109 (10.3)	143 (16.3)	0.006	1.000
Pre modified IDF 2005 (%)	1251 (5.3)	391 (4.7)	860 (5.6)	98 (5.1)	46 (4.4)	52 (5.9)	0.006	0.691
Modified WHO 1999 (%)	1596 (6.8)	761 (9.2)	835 (5.4)	142 (7.4)	82 (7.8)	60 (6.9)	0.000	0.296
Pre modified WHO 1999 (%)	2144 (9.1)	1007 (12.2)	1137 (7.4)	261 (13.5)	168 (15.9)	93 (10.6)	0.000	0.000
NCEP 2001 BP 140/90 (%)	3293 (13.9)	1247 (15.1)	2046 (13.3)	296 (15.3)	141 (13.4)	155 (17.7)	0.000	0.071
Pre NCEP 2001 BP 140/90 (%)	4768 (20.2)	1805 (21.9)	2963 (19.3)	474 (24.5)	261 (24.7)	213 (24.3)	0.000	0.000

HDL: high density lipoprotein.
p-Value: comparisons between means were evaluated using a t-test, and comparisons between proportions were evaluated with the chi-square test.

gallbladder, esophageal, renal cancer in female subjects [29]. Obesity is a weak risk factor for postmenopausal breast cancer. The meta-analysis pointed out that obesity may be a strong risk factor for breast cancer in Asian females. In the present study, high glucose rather than high BMI was the most important associated factor for the incidence of overall and liver cancer among the Japanese population. Recently, a study reported that high fasting serum glucose levels are predictive for the incidence of some sites of cancer, including liver cancer [30]. We also found that high BMI among the components of metabolic syndrome was a significant risk factor for female breast cancer. This suggests that the importance of components of metabolic syndrome for developing a cancer differ by cancer site. Since the number of events was insufficient for these analyses including the components of metabolic syndrome by the Cox proportional hazard model, we should therefore extend the follow-up, and analyze again.

Numerous studies have investigated the relationship between obesity and breast cancer, especially postmenopausal breast cancer [29,31]. Furthermore, there are several reports concluding that some components of metabolic syndrome, diabetes, or insulin resistance are associated with breast cancer [32,33]. The current study used the incidence of cancer as the endpoint in a cohort study of Asian subjects. Furthermore, the magnitude of the hazard ratio in the present study was larger than that in the previous studies. In particular, the hazard ratio to postmenopausal breast cancer was high. The presence of metabolic syndrome was a significant factor associated with breast cancer, particularly in younger subjects. In this way, for Asian populations, metabolic syndrome may be a more important risk factor for breast cancer than it is for Western populations. Therefore, metabolic syndrome is important for predicting not only circulatory diseases but also cancer, and this information should be utilized for implementing breast cancer prevention.

Various mechanisms have been proposed to explain the relationship between metabolic syndrome and cancer development, but the mechanisms associated with breast cancer development are currently poorly understood. Postmenopausal breast cancer is likely to be affected by estrogen secreted from adipose tissue. In addition, hormone-like substances secreted from abdominal adipose tissue may be also related to developing cancers [9]. The present results may suggest additional effects of metabolic syndrome for breast cancer development rather than its components. High glucose or diabetes may cause hepatic inflammation, oxidative stress, and a lipid peroxidation response, leading to liver damage, fibrosis, cirrhosis, and finally liver cancer.

The present study also compared five proposed criteria of metabolic syndrome. According to the values of the significant hazard ratios and the consistency of the relationship, i.e., the dose–response relationship of the results, NCEP 2001 appeared to be the optimal criteria for cancer prediction. The criteria have no essential items, and are based on the accumulation of components, based on test values regardless of medication. Observing the applicable prevalence of each component of metabolic syndrome showed that only the prevalence of elevated blood pressure was high. New criteria were created, replacing 130/85 in the NCEP 2001 criteria with the 140/90 of the WHO criteria for blood pressure, and a Cox proportional-hazards model was applied. However, the results of the analysis were inferior to the model using the original NCEP 2001 criteria. Therefore, the NCEP 2001 criteria were the optimal

Table 3
The association between metabolic syndrome and cancer incidence according to the Cox proportional hazard model.

		Males					Females				
		Cases	Pre-metabolic syndrome		Metabolic syndrome		Cases	Pre-metabolic syndrome		Metabolic syndrome	
			HR	CI	HR	CI		HR	CI	HR	CI
All sites	J-MeS	1056	0.89	(0.68–1.15)	0.88	(0.71–1.10)	875	1.21	(0.97–1.50)	1.24	(1.00–1.55)
	NCEP-ATPIII 2001		1.18	(1.02–1.35)	1.01	(0.85–1.20)		1.21	(1.03–1.42)	1.37	(1.15–1.63)
	NCEP-ATPIII 2004		1.18	(1.02–1.35)	1.05	(0.89–1.23)		1.17	(1.00–1.38)	1.35	(1.15–1.59)
	IDF 2005		1.10	(0.74–1.35)	0.87	(0.71–1.06)		1.21	(0.91–1.61)	1.23	(1.03–1.48)
	WHO 1999		1.38	(1.17–1.63)	1.03	(0.82–1.29)		1.49	(1.20–1.85)	1.30	(1.00–1.69)
	NCEP 2001 BP ≥ 140/90		1.22	(1.05–1.40)	1.00	(0.83–1.20)		1.25	(1.06–1.47)	1.29	(1.07–1.55)
Stomach	J-MeS	226	0.82	(0.47–1.43)	0.47	(0.26–0.86)	167	0.65	(0.35–1.21)	1.26	(0.78–2.04)
	NCEP-ATPIII 2001		0.94	(0.69–1.28)	0.74	(0.50–1.10)		1.13	(0.79–1.61)	0.98	(0.65–1.49)
	NCEP-ATPIII 2004		1.02	(0.76–1.38)	0.84	(0.59–1.20)		1.30	(0.91–1.85)	1.02	(0.69–1.50)
	IDF 2005		0.75	(0.37–1.52)	0.62	(0.38–1.00)		1.06	(0.54–2.08)	0.90	(0.58–1.41)
	WHO 1999		1.08	(0.73–1.59)	0.79	(0.46–1.33)		1.35	(0.81–2.25)	1.78	(1.06–2.99)
	NCEP 2001 BP ≥ 140/90		0.96	(0.69–1.32)	0.79	(0.53–1. 20)		1.01	(0.69–1.47)	0.95	(0.61–1.46)
Lung	J-MeS	130	0.76	(0.33–1.73)	0.51	(0.22–1.15)	81	0.70	(0.28–1.74)	1.27	(0.64–2.56)
	NCEP-ATPIII 2001		1.05	(0.71–1.54) 1	0.48	(0.26–0.91)		1.05	(0.63–1.77)	1.05	(0.58–1.89)
	NCEP-ATPIII 2004		0.99	(0.67–1.45)	0.62	(0.37–1.04)		1.37	(0.83–2.27)	1.09	(0.62-1.92)
	IDF 2005		0.75	(0.28–2.04)	0.54	(0.27–1.11)		0.70	(0.22–2.24)	0.99	(0.52–1.87)
	WHO 1999		1.12	(0.68–1.84)	0.50	(0.20–1.22)		0.91	(0.39–2.10)	1.06	(0.43–2.63)
	NCEP 2001 BP ≥ 140/90		1.01	(0.67–1.53)	0.48	(0.24–0. 95)		0.85	(0.48–1.48)	0.92	(0.49–1.73)
Colon	J-MeS	64	0.94	(0.34–2.62)	0.83	(0.49–2.40)	94	0.79	(0.36–1.71)	0.71	(0.31–1.62)
	NCEP-ATPIII 2001		1.01	(0.57–1.79)	0.80	(0.44–1.78)		1.02	(0.63–1.67)	1.08	(0.63–1.85)
	NCEP-ATPIII 2004		1.13	(0.64–2.00)	1.12	(0.60–2.10)		0.77	(0.45–1.31)	1.29	(0.80–2.07)
	IDF 2005		0.71	(0.17–2.91)	1.11	(0.55–2.26)		0.39	(0.10–1.59)	0.90	(0.49–1.65)
	WHO 1999		0.78	(0.33–1.83)	0.51	(0.71–3.20)		1.57	(0.83–2.98)	1.17	(0.51–2.69)
	NCEP 2001 BP ≥ 140/90		0.93	(0.50–1.74)	1.09	(0.54–2.17)		1.21	(0.74–1.97)	1.10	(0.62–1.96)
Liver	J-MeS	82	0.95	(0.38–2.37)	1.36	(0.70–2.65)	47	1.25	(0.48–3.22)	1.93	(0.86–4.37)
	NCEP-ATPIII 2001		1.30	(0.77–2.20)	1.89	(1.11–3.22)		2.66	(1.30–5.43)	3.67	(1.78–7.57)
	NCEP-ATPIII 2004		1.17	(0.69–1.97)	1.54	(0.90–2.63)		2.02	(0.95–4.28)	2.93	(1.43–6.00)
	IDF 2005		1.12	(0.41–3.09)	1.19	(0.62–2.26)		3.59	(1.58–8.18)	1.69	(0.80–3.57)
	WHO 1999		2.93	(1.78–4.81)	1.17	(0.50–2.72)		3.84	(1.86–7.91)	3.03	(1.26–7.29)
	NCEP 2001 BP ≥ 140/90		1.79	(1.08–2.98)	1.95	(1.10–3.44)		3.11	(1.59–6.06}	3.00	(1 .42–6.33)
Rectum	J-MeS	34	0.97	(0.23–4.13)	2.33	(1.01–5.40)	42	2.28	(1.04–4.98)	0.61	(0.15–2.53)
	NCEP-ATPIII 2001		2.20	(1.02–4.75)	2.04	(0.84–4.93)		1.38	(0.69–2.76)	0.86	(0.35–2.14)
	NCEP-ATPIII 2004		1.95	(0.88–4.31)	1.73	(0.72–4.19)		1 22	(0.59–2.56)	1.27	(0.60–2.72)
	IDF 2005		1.48	(0.35–6.28)	1.84	(0.79–4.27)		2.59	(1.00–6.68)	1.39	(0.60–3.20)
	WHO 1999		0.80	(0.24–2.65)	2.36	(0.97–5.79)		0.61	(0.15–2.55)	0.39	(0.05–2.83)
	NCEP 2001 BP ≥ 140/90		1.03	(0.43–2.43)	1.57	(0.66–3 .72)		1.69	(0.85–3.33)	0.69	(0.24–2.02)
Prostate	J-MeS	152	0.97	(0.49–1.91)	1.32	(0.80–2.16)					
	NCEP-ATPIII 2001		1.21	(0.83–1.76)	1.22	(0.79–1.87)					
	NCEP-ATPIII 2004		1.33	(0.92–1.92)	1.37	(0.91–2.06)					
	IDF 2005		1.28	(0.63–2.63)	1.18	(0.74–1.90)					
	WHO 1999		1.32	(0.84–2.07)	1.14	(0.64–2.03)					
	NCEP 2001 BP ≥ 140/90		1.35	(0.93–1.96)	0.96	(0.59–1.58)					
Breast	J-MeS						77	2.66	(1.44–4.94)	3.54	(1.96–6.38)
	NCEP-ATPIII 2001							1.45	(0.80–2.62)	2.87	(1.67–4.94)
	NCEP-ATPIII 2004							1.39	(0.76–2.54)	2.57	(1.50–4.40)
	IDF 2005							1.93	(0.83–4.51)	3.09	(1.84–5.17)
	WHO 1999							1.12	(0.45–2.79)	0.55	(0.13–2.24)
	NCEP 2001 BP ≥ 140/90							1.06	(0.55–2.02)	2.42	(1.39–4.22)
Breast ≥55 years	J-MeS						42	5.38	(2.56–11.32	5.80	(2.79–12.06
	NCEP-ATPIII 2001							3.68	(1.56–8.69)	6.73	(2.93–15.43
	NCEP-ATPIII 2004							2.74	(1.08–6.96)	5.80	(2.48–13.58
	IDE 2005							4.21	(1.56–11.37)	5.57	(2.89–10.73)
	WHO 1999							1.57	(0.61–4.02)	0.85	(0.20–3.54)
	NCEP 2001 BP ≥ 140/90							1.66	(0.75–3.67)	3.80	(1.89–7.65)

Hazard ratios were calculated for each criterion of metabolic syndrome using participants without metabolic syndrome or pre-metabolic syndrome as the reference status. Adjusted for age, smoking status (current smoker, ex-smoker), heavy drinking (more the 60 g pure alcohol), presence of metabolic syndrome or pre-metabolic syndrome of each definition.

criteria of metabolic syndrome as an associated factor of cancer incidence.

The present study had several limitations. The records of general health examination did not contain data on abdominal circumference, which is one of the essential criteria of metabolic syndrome, and therefore BMI was used as the index for obesity. This increased the prevalence of female obesity and thus metabolic syndrome may have been over-represented. However, metabolic syndrome was a significant associated factor for the incidence of cancer with a higher hazard ratio in the current study. The criteria using the BMI may be useful for preventive measures. A prospective cohort study measuring abdominal circumference is required in the future.

There was also a lack of information on well-known risk factors on cancer, including age at menopause, dietary factors, hepatitis antibody, and sociodemographic factors. This study design was a retrospective cohort study, and the information of menopausal age was not available and therefore a specific age was uniformly used. Moreover, there was no information on lifestyle factors other than smoking and alcohol. The additional potential confounders, such as reproductive risk factors and infections (related to breast and liver cancers, respectively), were not measured. It is also necessary to

Table 4
The hazard ratio of metabolic syndrome and its components on cancer incidence according to the Cox proportional hazard model.

	Components	Total			Males			Females		
		Hazard ratio	95% C.I.	*p*-Value	Hazard ratio	95% C.I.	*p*-Value	Hazard ratio	95% C.I.	*p*-Value
All sites	High blood pressure (versus not)	1.04	(0.94–1.14)	0.480	1.01	(0.89–1.15)	0.887	1.06	(0.92–1.23)	0.403
	High triglycerides (versus not)	1.00	(0.88–1.14)	0.976	1.04	(0.89–1.23)	0.614	0.93	(0.77–1.13)	0.473
	Low HDL cholesterol (versus not)	0.93	(0.83–1.04)	0.189	0.95	(0.80–1.13)	0.534	1.06	(0.91–1.23)	0.453
	High glucose (versus not)	1.32	(1.19–1.46)	0.000	1.29	(1.09–1.42)	0.001	1.32	(1.12–1.54)	0.001
	High BMI (≥25) (versus not)	1.03	(0.92–1.16)	0.574	0.89	(0.75–1.06)	0.179	1.17	(1.00–1.38)	0.058
Liver	High blood pressure (versus not)	1.20	(0.82–1.78)	0.352	1.09	(0.67–1.78)	0.719	1.28	(0.66–2.47)	0.469
	High triglycerides (versus not)	0.52	(0.30–0.88)	0.016	0.73	(0.39–1.34)	0.302	0.21	(0.06–0.70)	0.011
	Low HDL cholesterol (versus not)	1.49	(1.01–2.21)	0.046	1.51	(0.87–2.62)	0.142	2.02	(1.12–3.65)	0.019
	High glucose (versus not)	2.34	(1.64–3.36)	0.000	1.90	(1.21–2.97)	0.005	2.99	(1.64–5.44)	0.000
	High BMI (≥25) (versus not)	1.36	(0.90–2.06)	0.146	1.00	(0.56–1.79)	0.993	1.94	(1.04–3.62)	0.039
Breast	High blood pressure (versus not)							1.37	(0.82–2.28)	0.232
	High triglycerides (versus not)							0.82	(0.42–1.59)	0.553
	Low HDL cholesterol (versus not)							1.27	(0.78–2.08)	0.340
	High glucose (versus not)							0.86	(0.46–1.61)	0.636
	High BMI (≥25) (versus not)							2.39	(1.47–3.91)	0.000

Adjusted for age, smoking status (current smoker, ex-smoker), heavy drinking (more than 60 g pure alcohol), and every component of metabolic syndrome (high blood pressure, high triglycerides, low HDL, high glucose, and high BMI).
The metabolic syndrome and components of the metabolic syndrome were as defined by the National Cholesterol Education Program Adult Treatment Panel III.

conduct a future prospective study and include other lifestyle factors.

An additional limitation was the small number of incident cancers for several sites. The prolongation of the follow-up will be necessary in the future to obtain a sufficient number of cases. Therefore, regarding the result for breast cancer in subjects ≥55 years of age, colon cancer, or rectal cancer, we should extend the follow-up, and also fully analyze the reproducibility of results.

In conclusion, this study has demonstrated that the metabolic syndrome is a risk factor for some types of cancer and may yield useful information about cancer prevention and prediction of individuals at risk for certain cancers in the general population in Japan as well as the prevention of circulatory diseases. When all components of the metabolic syndrome together with the presence of metabolic syndrome were included in the model, a high glucose level rather than the metabolic syndrome was the significant associated factor for overall cancer and liver cancer development, whereas the metabolic syndrome was a significant associated factor for breast cancer, even after adjusting for other components. The comparison of the five criteria of the metabolic syndrome demonstrated that the NCEP 2001 criteria were a superior associated factor for the later development of cancer.

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Conflict of interest statement

The authors declared that there are no conflicts of interest and financial disclosures.

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References

[1] Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–16.
[2] Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 2004;164:1092–7.
[3] McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28:385–90.
[4] Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 1999;16:442–3.
[5] Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.
[6] Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–39.
[7] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469–80.
[8] Matsuzawa Y. Metabolic syndrome – definition and diagnostic criteria in Japan. J Atheroscler Thromb 2005;12:301.
[9] Cowey S, Hardy RW. The metabolic syndrome: a high-risk state for cancer? Am J Pathol 2006;169:1505–22.
[10] Lund Håheim L, Wisløff TF, Holme I, Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. Am J Epidemiol 2006;64:769–74.
[11] Laukkanen JA, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A, Salonen JT. Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. Cancer Epidemiol Biomarkers Prev 2004;13:1646–50.
[12] Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. Cancer 2006;107:28–36.
[13] Kim JH, Lim YJ, Kim YH, Sung IK, Shim SG, Oh SO, et al. Is metabolic syndrome a risk factor for colorectal adenoma? Cancer Epidemiol Biomarkers Prev 2007;16:1543–6.
[14] Kabat GC, Kim M, Chlebowski RT, Khandekar J, Ko MG, McTiernan A, et al. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2009;18:2046–53.
[15] Lee JS, Cho SI, Park HS. Metabolic syndrome and cancer-related mortality among Korean men and women. Ann Oncol 2009. doi: 10.1093/annonc/mdp344.
[16] Inoue M, Noda M, Kurahashi N, Iwasaki M, Sasazuki S, Iso H, et al. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. Eur J Cancer Prev 2009;18:240–7.

[17] Inoue M, Kurahashi N, Iwasaki M, Tanaka Y, Mizokami M, Noda M, et al. Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). Cancer Causes Control 2009;20:741–50.
[18] International association for the study of obesity, international obesity task force. The Asia-Pacific perspective: redefining obesity and its treatment. World Health Organization Western Pacific Reason; 2000.
[19] Garmendia ML, Pereira A, Alvarado ME, Atalah E. Relation between insulin resistance and breast cancer among Chilean women. Ann Epidemiol 2007; 17:403–9.
[20] Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of current evidence. Am J Clin Nutr 2007;86(Suppl.):823–35.
[21] Hiroi M. Natural menopause. Sanka to Fujinka (Obstet Gynecol) 2006;11: 1653–60.
[22] Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. Stroke 2006;37:1060–4.
[23] Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke 2007;38:1744–51.
[24] Asia Pacific Cohort Studies Collaboration, Patel A, Barzi F, Woodard M, Ni Mhurchu C, Ohkubo T, et al. An evaluation of metabolic risks for coronary death in the Asia Pacific region. Diabetes Res Clin Pract 2006;74:274–81.
[25] Chien KL, Hsu HC, Sung FC, Su TC, Chen MF, Lee YT. Metabolic syndrome as a risk factor for coronary heart disease and stroke: an 11-year prospective cohort in Taiwan community. Atherosclerosis 2007;194:214–21.
[26] Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol 2006;164:1094–102.
[27] Russo A, Autelitano M, Bisanti L. Metabolic syndrome and cancer risk. Eur J Cancer 2008;44:293–7.
[28] Pelucchi C, Negri E, Talamini R, Levi F, Giacosa A, Crispo A, et al. Metabolic syndrome is associated with colorectal cancer in men. Eur J Cancer 2010. doi: 10.1016/j.ejca.2010.03.010.
[29] Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569–78.
[30] Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202.
[31] Zhu K, Caulfield J, Hunter S, Roland CL, Payne-Wilks K, Texter L. Body mass index and breast cancer in African American women. Ann Epidemiol 2005;15:123–8.
[32] Furberg AS, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst 2004;96:1152–60.
[33] Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. Diabetes mellitus and breast cancer: a retrospective population-based cohort study. Breast Cancer Res Treat 2006;98:349–56.

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LETTER TO THE EDITOR

Lower fasting plasma glucose criteria and high triglycerides are effective for screening diabetes mellitus in the rural Japanese population: the Tottori-Kofu Study

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Lower fasting plasma glucose criteria and high triglycerides are effective for screening diabetes mellitus in the rural Japanese population: the Tottori-Kofu Study

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Dear Editor

The Tottori–Kofu Study was intended to assist in preventing stroke in the rural town of Kofu, Tottori Prefecture, Japan (Fig1), where the incidence of cerebral stroke was 3 times higher than the national average. One aim of the study was to develop an effective screening method for diabetes mellitus (DM), a major risk factor for stroke.

In Japan, the diagnostic criteria for glucose intolerance has been defined as a fasting plasma glucose (FPG) level of ≥6.1 mmol/L (110 mg/dL). The cutoff point for FPG was found to be optimal at 6.2 mmol/L in the urban area of Hisayama (sensitivity 78-81%); however, in rural Funagata the sensitivity was found to be low at 6.1 mmol/L (64%)[1,2]. Based on these results it was hypothesized that the rural Japanese population requires different FPG criteria and measures of other risk factors compared with their urban counterparts. This was tested in the town of Kofu.

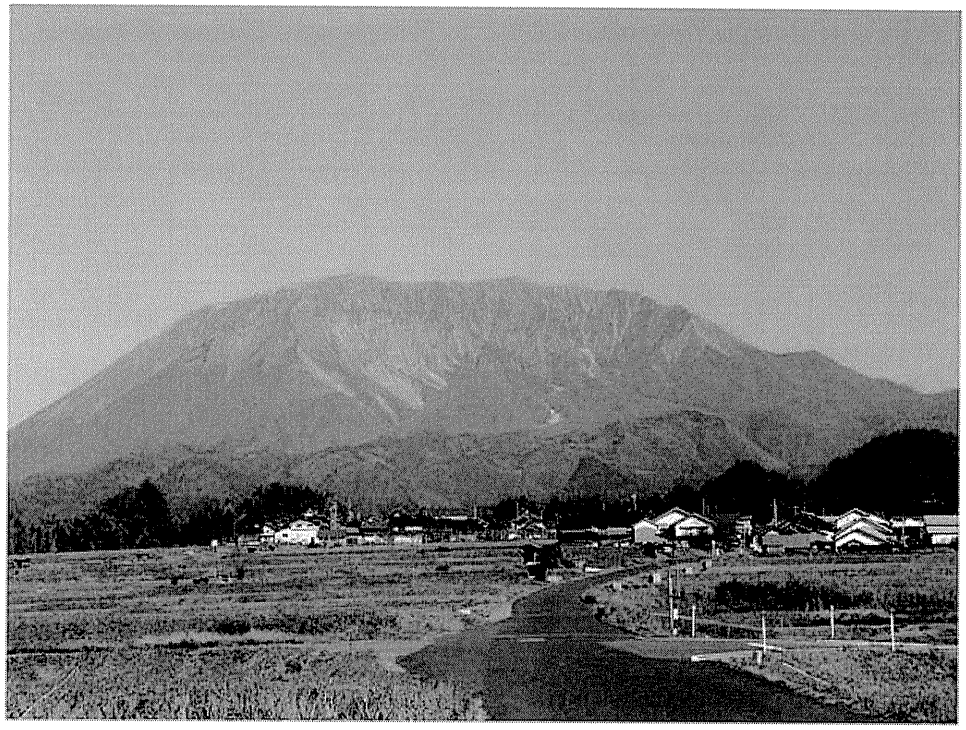

Figure 1: The rural town, Kofu, Japan - site of the research.

In 2005, 734 residents of the town of Kofu received a basic medical examination. Their mean age was 66.4 years; mean BMI was 22.7 kg/m^2; FPG 5.07 mmol/L; HbA1c (NGSP) 5.59%; and fasting triglycerides 1.16 mmol/L (all mean values). Residents who met any of the following criteria underwent an oral glucose tolerance test (OGTT): FPG ≥5.5 mmol/L or HbA1c (NGSP) ≥5.9%, BMI ≥25 kg/m^2, triglycerides ≥1.69 mmol/L (150 mg/dL), currently being treated for hypertension, or a family history of DM.

The authors performed a multiple regression analysis and receiver operating characteristic (ROC) analysis of the data. It was presumed that non-DM subjects were individuals with normal glucose tolerance and impaired glucose tolerance in OGTT. From a past report[3], subjects believed to have an extremely low probability of having DM at examination were individuals with FPG <5.5 mmol/L and HbA1c (NGSP) <5.9%, BMI <25 kg/m^2, triglycerides <1.69 mmol/L, no family history of DM, and no reported treatment for hypertension.

Only 4 subjects were newly diagnosed with DM (FPG ≥7.0 mmol/L [126 mg/dL]) following the basic medical examination. Of the 220 persons who underwent OGTT, 20 subjects were detected to have DM. Multiple regression analysis indicated that elevated FPG (per 1 mg/dL) and triglycerides (≥1.69 mmol/L) were significant risk factors for DM (FPG: OR=1.20, 95%CI:1.13-1.28; triglycerides: OR=3.63, 95%CI: 1.06-12.4) (Table 1). The optimal FPG cut-off for DM was 5.2 mmol/L (94 mg/dL), based on ROC analysis (sensitivity 85%, specificity 78%, area under the curve [AUC] 0.880). Consumption of alcohol was significantly higher (>23 g ethanol >3 times/week) in the DM group compared with the non-DM group (65% vs 33.7%, $p<0.005$, χ^2 test). The mean triglycerides level was significantly higher in the group of drinkers compared with non-drinkers (1.22 mmol/L vs 1.13 mmol/L, $p<0.05$, unpaired *t*-test).

Table 1: Odds ratios for diabetes mellitus by multiple logistic regression analysis

Risk factors	Odds ratio	*P*-value	95% CI
Age	0.97	0.233	0.92-1.02
Sex (male)	0.78	0.667	0.25-2.40
Fasting plasma glucose (1mg/dL)	1.20	<0.001	1.13-1.28
BMI ≥25 kg/m^2	1.08	0.906	0.32-3.63
Triglycerides ≥1.69 mmol/L	3.63	0.040	1.06-12.4
Hypertension treatment	0.68	0.562	0.18-2.52
Family history of diabetes mellitus	1.79	0.430	0.42-7.65

Data are the dependent variable (diabetes mellitus [DM]) vs the explanatory variable (non-DM): DM in 20 persons; non-DM in 548 persons. Adjusted for all explanatory variables.

These results suggest that FPG of ≥6.1 mmol/L alone is insufficient to detect early-stage DM. The combination of FPG ≥5.2 mmol/L and triglycerides ≥1.69 mmol/L was found to be useful as a screening to detect early-stage DM in the group studied. While the suggested FPG criteria may have been too low, it was useful to also consider OGTT results, especially in those with hypertriglyceridemia. It is speculated that moderate alcohol consumption induced diabetes and hypertriglyceridemia in the population studied[4,5].

The study results should, however, be interpreted with care as it was cross-sectional rather than a cohort study, and the subset of residents who underwent the OGTT was biased. Moreover, the Kofu town residents were an elderly population, so the criteria may not be applicable to other rural areas in Japan. However, it is predicted that the screening criteria established in the present study will contribute to the prevention of stroke in the specific population studied, and may also be useful to consider for other rural residents in the vicinity of the rural town of Kofu.

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References

1. Doi Y, Kubo M, Yonemoto K, Ninomiya T, Iwase M, Kiyohara Y et al. Fasting plasma glucose cutoff for diagnosis of diabetes in a Japanese population. *Journal of Clinical Endocrinology and Metabolism* 2008; **93(9):** 3425-3429.

2. Nakagami T, Tominaga M, Nishimura R, Daimon M, Oizumi T, Tajima N. Is the measurement of glycated hemoglobin A1c alone an efficient screening test for undiagnosed diabetes? Japan National Diabetes Survey. *Diabetes Research and Clinical Practice* 2007; **76(2):** 251-256.

3. Ko GT, Chan JC, Li JK. Combined use of a fasting plasma glucose concentration and HbA1c or fructosamine predicts the likelihood of having diabetes in high-risk subjects. *Diabetes Care* 1998; **21(8):** 1221-1225.

