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Attributable Risk Fraction of Prehypertension on Cardiovascular Disease Mortality in the Japanese Population: The Ohsaki Study

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BACKGROUND

Although relative risk of prehypertension (pre-HT) on cardiovascular disease (CVD) mortality is modest, prevalence of pre-HT is large, that is, population attributable fraction (PAF) of pre-HT on CVD mortality might be large. However, no studies have reported the fraction.

METHODS

We followed 12,928 Japanese National Health Insurance (NHI) beneficiaries aged 40–79 years without a history of CVD. On the basis of their blood pressure (BP), the participants were categorized as normal BP, pre-HT, and hypertension (HT) (Seventh Report of the Joint National Committee criteria). Multivariate-adjusted Cox proportional hazards model was used to estimate the hazard ratio (HR) of the BP status vs. CVD mortality.

RESULTS

During 12-years of follow-up, 321 participants died of CVD. As positive relation between BP category and CVD mortality

was steeper in middle-aged (40–64 years) than that in elderly (65–79 years), we separately calculated PAF on CVD mortality among middle-aged and elderly. HR (95% confidence interval) for cardiovascular mortality for pre-HT and HT, respectively, was 1.31 (0.59–2.94) and 2.98 (1.39–6.41) in middle-aged, and 1.03 (0.62–1.70) and 1.65 (1.02–2.64) in elderly. Non-normal BP, i.e., pre-HT and HT, accounted for 47 and 26% of the CVD deaths among the middle-aged and elderly participants, respectively. Although the PAF of pre-HT was larger in the middle-aged participants (7%) than that in the elderly ones (0%), neither fraction was considered large.

CONCLUSION

The PAF on CVD mortality in pre-HT was not large compared with that in HT.

Am J Hypertens 2009; 22:267-272 © 2009 American Journal of Hypertension, Ltd.

Blood pressure (BP) is known to relate linearly to cardiovascular disease (CVD) mortality or incidence, and there is no threshold BP value for risk increase. Furthermore, high BP is known as a leading cause of global burden of disease. In light of this, the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure introduced a new category of BP patients, designated as prehypertension (pre-HT). The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure reported that pre-HT category is neither a disease category nor candidate for drug therapy. It also stated that individuals with pre-HT should be advised to reduce their risk of developing hypertension (HT) in the future through lifestyle modification.³

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However, Rose reported that a large number of people at a small risk may give rise to more cases of disease than the small number who are at a high risk;4 individuals with modest risk, such as pre-HT, might have greater impact on CVD mortality or incidence. Furthermore, an intervention study revealed the benefits and feasibility of drug treatment for subjects with pre-HT on HT incidence, indicating a possibility that drug treatment may reduce the risk of CVD mortality/ incidence in subjects with pre-HT.5 Thus, if population attributable fraction (PAF) of pre-HT on CVD were large, individuals with pre-HT should be treated appropriately. The PAF is an indicator of how much of the disease burden in a population could be eliminated if the effects of specific causal factors were eliminated from that population. However, to our knowledge, no studies calculated the excess deaths due to elevated BP and PAF among pre-HT. Therefore, we investigated the relation of BP categories with CVD mortality and estimate PAF.

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Received 26 June 2008; first decision 21 August 2008; accepted 23 October 2008; advance online publication 27 November 2008, doi:10.1038/ajh.2008.335

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METHODS

Study setting and design. The setting and design of the Ohsaki Cohort Study have already been reported in detail.6-8 In brief, this prospective cohort study started in 1994, when we delivered a self-administered questionnaire on various healthrelated lifestyles to all National Health Insurance (NHI) beneficiaries aged 40-79 years living in the catchment areas of Ohsaki Public Health Center, Miyagi Prefecture, Japan. NHI in Japan is used by farmers, the self-employed, pensioners, and their dependents. Ohsaki Public Health Center, which is a local government agency, provides preventive health services for the residents of 14 municipalities. The questionnaires were delivered to and collected from the subjects' residences by public health officials in each municipality. This procedure yielded a high response rate of 94.6% (N = 52.029). We excluded 776 subjects because they had withdrawn from the NHI before 1 January 1995, when we started the prospective collection of NHI claim files. Thus, 51,253 subjects formed the study cohort. Among the participants of the Ohsaki NHI Cohort Study, 16,515 (32.2%) had undergone an annual health checkup between April and December 1995, and they provided their consent for analysis of their results in this study. Among them, 280 participants were withdrawn before undergoing a health checkup. We also excluded those with no history of CVD (N = 502), as well as those in whom BP (N = 31), and other important confounding factors, such as total cholesterol (N = 154), glucose (N = 2,617) and body mass index (BMI) (N=3) were not measured. Consequently, we analyzed 12,928 Japanese men and women in this study. The participants who had undergone an annual health checkup were slightly younger than those who had not (mean age: 60.8 years vs. 61.5 years, P < 0.001). The proportion of women was higher among the participants who underwent the annual checkup than those who did not (57.7% vs. 49.4%).

This study was approved by the ethics committee of the Tohoku University School of Medicine. The participants who had completed the self-administered questionnaires and had signed them were considered to have consented to participate in this study.

Exposure data. Data on the risk factors for CVD in the participants were obtained from results of the annual health checkup that had been organized by the local municipalities and conducted by physicians in 1995. This annual health checkup is provided free, or at low charge, to all people aged ≥40 years in Japan. The checkups include an interview; weight, height, and BP measurements; a physical examination; and blood chemistry tests to determine the serum total cholesterol, plasma glucose, and other parameters. The subjects were not instructed to fast prior to the blood chemistry tests. A single BP measurement was obtained by trained nurses using automated devices after a rest for few minutes, which is standard procedure in annual health checkups in Japan.

We categorized our study participants into three groups according to the criteria provided in the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria.² Participants with a systolic BP of ≥140 mm Hg and/or a diastolic BP of ≥90 mm Hg and/or those who were taking antihypertensive medication were regarded as HT; those who did not satisfy the HT criteria and those with a systolic BP of ≥120 mm Hg and/or a diastolic BP of ≥80 mm Hg were regarded as pre-HT; and those who did not satisfy either the HT or pre-HT criteria were regarded as normal BP. We defined hyperglycemia as either a self-reported history of diabetes or a casual plasma glucose level of ≥140 mg/dl.⁹ The BMI of the participants was calculated as the ratio of the body weight (kg) to the height (m)². We defined underweight and overweight/obesity as a BMI of <18.5 kg/m² and ≥25 kg/m², respectively.¹⁰

Follow-up. We prospectively collected NHI claim files from the local NHI Association for all individuals in the cohort for the period from date when they received annual health check up between April 1995 and December 1995, to the date of withdrawal from the NHI because of death or emigration, or until 31 December 2006. When a beneficiary withdraws from the NHI, the date and reason are entered in the NHI withdrawal files. Both the NHI claim and withdrawal files were linked to our baseline survey data and the annual health checkup data by using each beneficiary's identification number as the key code. For decedents identified as described herein, we investigated the cause of death by reviewing the death certificates filed at Ohsaki Public Health Center. Cause of death was coded by trained physicians according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. We identified deaths from CVD according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes 100-199. None of the participants died of unknown causes. Because the Family Registration Law in Japan requires registration of death, death certificates confirmed all deaths that occurred in the study area. except participants who died after emigration from the area.

Statistical analysis. We described baseline characteristics according to BP categories using means for continuous variable and percentages for dichotomous variables. P for trends was calculated by Pearson's correlation for continuous variable and by logistic regression model for categorized variable. We estimated the age-sex or multivariate-adjusted hazard ratios (HRs) and the 95% confidence intervals for the relation of BP categories with CVD and all-cause mortality using Cox proportional hazard models. We treated participants with normal BP as a reference group. The multivariate-adjusted model included the following possible confounding factors: age, sex, BMI category (underweight, normal, and overweight/obesity). hyperglycemia, total cholesterol, and smoking (never, past, and current). We also tested the interaction of age group, i.e., middle-aged (years 40-64) and elderly (years ≥65), or sex with BP category for CVD mortality. The numbers of excess CVD or all-cause deaths due to non-normal BP were calculated as (number of cases exposed to the BP category) × (multiple adjusted HR - 1)/multiple adjusted HR, and the percentage of

excess CVD or all-cause deaths due to non-normal BP (PAF) was calculated as follows: $P \times (\text{multiple adjusted HR} - 1)$ / multiple adjusted HR, where P = proportion of cases exposed to the BP category.¹¹

RESULTS

Baseline characteristics

The mean age of the study participants was 61.2 years (s.d. 9.4 years). The prevalence of pre-HT and HT was 41.8% and 40.1%, respectively. Table 1 shows the baseline characteristics of the study participants according to the BP categories. Higher BP categories related to older age, lower prevalence of current smoking, higher prevalence of hyperglycemia, higher total cholesterol level, and higher BMI. The proportion of women in the high-BP categories was low.

Follow-up data

There were 130,782 person-years of follow-up (up to 11.7 years per person), corresponding to a follow-up rate of 88.3%. During the follow-up period, 1,227 participants died and 321 participants of them died due to CVD.

Overall, a positive relation was observed between the BP status and CVD mortality (Table 2). Since relation between BP categories and CVD mortality in middle-aged was stronger than that in elderly (Table 2, P for interaction = 0.07), we analyzed middle-aged and elderly separately. Whereas, since no sex interaction between sex and BP category for CVD mortality was observed in both age groups, we combined men and women together ($P \ge 0.18$).

Among the middle-aged patients, 8, 24, and 48 of them in the normal BP, pre-HT, and HT categories, respectively, died of CVD. Among the elderly patients, 20, 64 and 157 died of CVD in these respective categories. Thus, 30% (24/80) and 27% (64/241) of CVD deaths were observed from pre-HT categories.

PAF

The number of excess CVD deaths due to high BP was 5.7 and 31.9 in middle-aged participants with pre-HT and HT, respectively, and the corresponding PAF for CVD mortality was 7.1% and 39.9%, respectively (Figure 1). Non-normal BP explained 47.0% of CVD deaths among middle-aged. The PAF for CVD mortality in the elderly participants with pre-HT and HT was 0.1% and 25.7%, respectively (Figure 1). The sum of the excess CVD deaths (PAF) due to pre-HT and HT was 7.6 (2.4%) and 93.7 (29.2%),

Table 1 | Baseline characteristics of study participants according to blood pressure (BP) category: the Ohsaki study 1995

		Total			Age 40-64					Age≥65			
		Normal BP	Pre-HT	нт	P for trend	Normal BP	Pre-HT	нт	Pfor trend	Normal BP	Pre-HT	HT	P for trend
Numbers of participants		2,350	5,398	5,180		1,723	3,648	2,637		627	1,750	2,543	
Age (years)	mean (s.d)	57.9 (9.8)	60.0 (9.5)	64.0 (8.2)	<0.01	53.6 (7.6)	55.1 (7.2)	57.9 (6.2)	< 0.01	69.7 (3.4)	70.2 (3.8)	70.5	<0.01
Women	N (%)	1,528 (65.0%)	3,013 (55.8%)	2,869 (55.4%)	<0.01	1,169 (67.9%)	2,104 (57.7%)	1,497 (56.8%)	<0.01	359 (57,3%)	909 (51,9%)	1,372 (54.0%)	0.54
Current smoking	N (96)	543 (26.5%)	1,222 (26.4%)	1,085 (25.0%)	0.02	401 (26.2%)	824 (25.9%)	589 (26.0%)	0.49	142 (27.6%)	398 (27.4%)	496 (23.8%)	0.01
Past smoking	N (%)	216 (10.6%)	695 (15.0%)	729 (16.8%)	<0.01	123 (8.0%)	380 (12.0%)	279 (12.3%)	< 0.01	93 (18.1%)	315 (21.7%)	450 (21.6%)	0.22
Neversmoker	N (%)	1,287 (62.9%)	2,718 (58.6%)	2,534 (58.3%)	<0.01	1,008 (65.8%)	1,977 (62.2%)	1,394 (61.6%)	<0.01	279 (54.3%)	741 (51.0%)	1,140 (54.7%)	0.42
Hyperglycemia	N (%)	175 (7.5%)	503 (9.3%)	682 (13.2%)	< 0.01	112 (6.5%)	285 (7.8%)	292 (11.1%)	<0.01	63 (10.1%)	218 (12.5%)	390 (15.3%)	<0.01
Total cholesterol (mg/dl)	mean (s.d)	200.6 (34.7)	204.1 (34.6)	207.3 (36.1)	<0.01	200.0 (34.5)	204.2 (34.6)	208.7 (36.8)	<0.01	202.1 (35.3)	203.8 (34.7)	205.9 (35.2)	<0.01
Body mass index (kg/m²)	mean (s.d)	22.9 (2.8)	23.7 (2.9)	24.6 (3.2)	< 0.01	23.0 (2.8)	23.9 (2.9)	24.9 (3.1)	< 0.01	22.6 (3.0)	23.2 (2.9)	24.3 (3.3)	< 0.01
Systolic BP (mm Hg)	mean (s.d)	108.9 (6.5)	128.0 (7.2)	145.6 (16.1)	< 0.01	108.6 (6.6)	127.4 (7.3)	144.9 (15.7)	< 0.01	109.4 (6.3)	129.3 (6.9)	146.4 (16.5)	< 0.01
Diastolic BP (mm Hg)	mean (s,d)	67.7 (6.9)	78.4 (7.7)	85.7 (10.3)	< 0.01	67.9 (6.7)	79.0 (7.4)	87.8 (9.5)	<0.01	67.0 (7.3)	77.1 (8.2)	83.5 (10.5)	<0.01
Antihypertensive medication	N (%)	0	0	2,548 (49.2%)	<0.01	0	0	1,154 (43.8%)	< 0.01	0	0	1,394 (54.8%)	< 0.01

BP, blood pressure; N, numbers of participants.

Clinic BP category: HT, hypertension (systolic BP≥140 mm Hg and/or diastolic BP≥90 mm Hg and/or taking antihypertensive medication); Pre-HT, prehypertension (BP level less than HT and systolic BP≥120 mm Hg and/or diastolic BP≥80 mm Hg). Normal BP, BP level less than pre-HT.

Table 2 | Relation of blood pressure category with cardiovascular disease and all-cause mortality, the Ohsaki study, 1995–2006

		Total				Age 40-64		Age ≥65			
		Normal BP	Pre-HT	HT	Normal BP	Pre-HT	HT	Normal BP	Pre-HT	HT	
	Numbers of participants	2,350	5,398	5,180	1,723	3,648	2,637	627	1,750	2,543	
	Person-years	23,709	55,040	52,033	17,413	37,611	26,886	6,296	17,429	25,146	
CVD death	Numbers of CVD deaths	28	88	205	8	24	48	20	64	157	
	CVD mortality rate (/1,000 person- years)	1.2	1.6	3.9	0.5	0.6	1.8	3.2	3.7	6.2	
	Age-sex adjusted HR	1	1.07 (0.70-1.64)	1.93 (1.29-2.87)	1	1.18 (0.53-2.64)	2.71 (1.27-5.78)	1	1.02 (0.61-1.68)	1.70 (1.06-2.71)	
	Multiple adjusted HR ^a	1	1.10 (0.72-1.69)	1.91 (1.28-2.85)	1	1.31 (0.59-2.94)	2.98 (1.39-6.41)	1	1.03 (0.62–1.70)	1.65 (1.02-2.64)	
All-cause death	Numbers of all-cause deaths	153	417	657	48	126	164	105	291	493	
	All-cause mortality rate (/1,000 person-years)	6.5	7.6	12.6	2.8	3.4	6.1	16.7	16.7	19.6	
	Age-sex adjusted HR	1	0.93 (0.77-1.12)	1,16 (0.97–1.38)	1	1.02 (0.73-1.42)	1,52 (1.10-2.10)	1	0.89 (0.71-1.11)	1.04 (0.85-1.29)	
	Multiple adjusted HR ^a	1	0.97 (0.80-1.17)	1.20 (0.995-1.43)	1	1.06 (0.76-1.49)	1.53 (1.10-2.13)	1	0.93 (0.75-1.17)	1.09 (0.88-1.35)	

Clinic BP category: HT, hypertension (systolic BP \geq 140 mm Hg and/or diastolic BP \geq 90 mm Hg and/or taking antihypertensive medication); Pre-HT, prehypertension (BP level less than HT and systolic BP \geq 120 mm Hg and/or diastolic BP \geq 80 mm Hg); Normal BP, BP level less than pre-HT.

*Adjusted for age, sex, smoking (current, past, never), hyperglycemia, total cholesterol, BMI (underweight, normal, overweight).

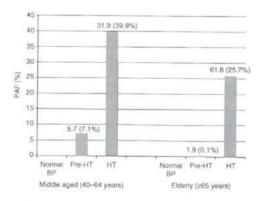


Figure 1 | Population attributable fraction (PAF) for cardiovascular diseases (CVDs) mortality in each blood pressure (BP) category. Excess CVD deaths (PAF) are shown at the top of the bars. The excess CVD mortality due to non-normal BP was calculated as (HR - 1)/HR \times number of CVD deaths observed for each BP category. The PAF was calculated as the excess of CVD deaths for each BP category divided by the total number of CVD deaths. Pre-HT, prehypertension; HT, hypertension.

respectively, i.e., non-normal BP accounted for 31.6% of the CVD deaths in this Japanese population. These values remained essentially unchanged when PAF was calculated using age-sex adjusted HR instead of multiple adjusted HR (4.6% and 37.9% for middle-aged participants with pre-HT and HT and 0.5% and 26.8% for elderly participants with pre-HT and HT).

All-cause mortality

We also analyzed the relation between BP categories and all-cause mortality, and we estimated the PAF for all-cause mortality. Among middle-aged, positive relation between BP category and all-cause mortality was observed (Table 2). The relation was modest in elderly (Table 2). The excess all-cause deaths due to high BP (PAF) in middle-aged were 7.1 (2.1%) for pre-HT and 56.8 (16.8%) for HT. Similarly, the excess all-cause deaths (PAF) due to pre-HT and HT in elderly were 0 (0%) and 40.7 (4.6%), respectively. Thus, non-normal BP explained 18.9 and 4.6% of all-cause deaths among middle-aged and elderly, respectively.

DISCUSSION

In this study, based on 130,000 person-years of follow-up, we calculated the attributable risk fraction of pre-HT on CVD mortality in Japanese population. Although 25–30% CVD deaths were observed from pre-HT category, relative risk in pre-HT was modest and PAF of pre-HT on CVD mortality was not large, i.e., 7, 0, and 2% of CVD deaths were explained by pre-HT categories in middle-aged, elderly, and overall, respectively.

Our results indicate that a high BP is positively related with CVD mortality.^{1,3} In addition, we found that the relation between the BP categories and CVD mortality was stronger among younger participants. These results were consistent with those from many previous studies. ^{1,12–14}

In our study, prevalences of pre-HT were 45.5% in middleaged and 35.6% in elderly and 30 and 27% of CVD deaths were

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observed from this category. That is, pre-HT category can be considered as one category with "large number of people at a low risk". In the National Health and Nutrition Examination Survey that was conducted in 1999–2000, the prevalence of pre-HT was found to be 34.7% in the population aged 40–59 years and 23.1% in that aged 60 years and more. 15 Thus, the proportion of pre-HT is reported to be high in the United States.

In our study, the HR for CVD mortality among the middle-aged subjects with pre-HT was 1.31 (95% confidence interval: 0.59–2.94). Previous studies have reported this value to range from 1.08 to 1.80 among the pre-HT individuals. ^{16–20} Although the point estimate determined in this study was relatively lower than that reported previously, we considered that the HR determined here is largely consistent with that determined in previous studies. Although the risk of CVD mortality showed no increase (HR = 1.03; 95% confidence interval: 0.62–1.70) among the elderly pre-HT patients, this finding was also consistent with the results of the follow-up survey performed by National Health and Nutrition Examination Survey III. ¹⁹ Gu et al. reported that the risk of CVD mortality did not increase among pre-HT subjects aged 65–74 years and ≥75 years.

We investigated the PAF of high BP with regard to CVD mortality. Non-normal BP, i.e., combination of pre-HT and HT, explained 47% of CVD deaths in middle-aged and 26% of CVD deaths in elderly. This proportion was similar to the previous reports from Japan. Sairenchi et al. reported that PAF of non-normal BP was 60, 28, 15, and 7% of in middle-aged men, elderly men, middle-aged women, and elderly women, respectively. 14 Our findings that the PAF of non-normal BP for all-cause mortality was higher in middle-aged than that in elderly were also consistent with those of a recent report describing that the PAF of non-normal BP for all-cause mortality was higher in the 50s or 60s age group than in the 70s or 80s.21 However, to the best of our knowledge, no study reported the fraction specific to pre-HT category. The PAF of pre-HT on CVD mortality was 7, 0, and 2% in the middle-aged, elderly, and total study population, respectively. We do not consider this proportion to be very large.

In recent years, the effects of drug treatment for prehypertensive patients to avoid progression to HT have been reported. Participants with repeated measurements of systolic pressure of 130-139 mm Hg and diastolic pressure of ≤89 mm Hg, or systolic pressure of ≤139 mm Hg, and diastolic pressure of 85-89 mm Hg were randomly assigned to receive 2 years of candesartan (N = 409) or placebo (N = 400), and followed by 2 years of placebo for all.5 The result revealed that pre-HT patients tolerated treatment with candesartan well and that the risk of incident HT (relative risk = 0.58) reduced during the study period. Therefore, it was concluded that candesartan treatment is feasible and effective for pre-HT patients. After this trial, the topic whether pre-HT should be treated or not was debated.^{22,23} However, as we have shown in this study, population impact of treatment pre-HT should not be large and HT categories explained a large proportion of excess CVD death. Furthermore, only a quarter of hypertensive is

known to be well controlled, i.e., a half of hypertensives were treated and a half of treated hypertensives were well controlled at best.^{3,24-27} Thus, we believe that the primary target population that should receive antihypertensive medication is that of HT patients. Further researches also should be required to estimate the burden in other population.

Our study has some limitations. First, the study population consisted of participants who underwent an annual health checkup. As this population was likely to be health conscious, the distribution of pre-HT may have been overestimated. Second, as most of Japanese annual health checkups, single measurement of BP was used for analyses. Due to regression dilution effect, relative risks might be underestimated. Finally, our data were based on mortality data but not morbidity data. Although the relationship between BP categories and CVD morbidity, risk profiles of morbid and mortal events sometimes differ. Thus, further studies using morbidity data might be required to corroborate our findings.

In conclusion, large amount of CVD deaths were accounted for non-normal BP categories in this Japanese population. We found that the PAF of pre-HT with regard to CVD mortality was not high, while that of HT was high. Therefore, we concluded that the primary target population that should receive antihypertensive medication is that of HT patients.

Acknowledgment: We thank Yoshiko Nakata, Mika Wagatsuma, and Hiroko Okajima from the Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendal, Japan, for their research assistance. This study was supported by a Health Sciences Research Grant for Health Services (H19-Seisaku-Ippan-026, H20-Junkankitou (Seisyu)-Ippan-013), Ministry of Health, Labour and Welfare, Japan.

Disclosure: The authors declared no conflict of interest.

- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903–1913.
- Lawes CM, Vander Hoorn S. Rodgers A: International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. Lancer 2008; 371: 1513–1518.
- 3 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jt, Jones DW, Materson BJ, Opani S, Wright JT Jt, Roccella EJ, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program Coordinating Committee Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Hypertension 2003; 42:1206–1252.
- Rose G. Sick individuals and sick populations. Int J Epidemiol 2001; 30:427–432.
 Julius S. Nesbitt SD. Egan BM. Weber MA, Michelson EL, Kaciroti N, Black HR. Grimm RH Jr. Messerlii FH, Oparil S. Schork MA: Tral of Preventing Hypertension (TROPHY) Study Investigators. Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med 2006; 354:1685–1697.
- Tsuji I, Nishino Y, Ohkubo T, Kuwahara A, Ogawa K, Watanabe Y, Tsubono Y, Bando T, Kanemura S, Izumi Y, Sasaki A, Fukao A, Nishikori M, Hisamichi S, A prospective cohort study on National Health Insurance beneficiaries in Ohsaki, Miyagi Prefecture. Japan: study design, profiles of the subjects and medical cost during the first year. J Epidemiol 1998; 8:258–263.
- Kuriyama S, Shimazu T, Ohmori K, Kikuchi N, Nakaya N, Nishino Y, Tsubono Y, Tsuji I. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 2006; 296:1255–1265.
- Ohmori-Matsuda K, Kuriyama S, Hozawa A, Nakaya N, Shimazu T, Tsuji I. The joint impact of cardiovascular risk factors upon medical costs. Prev Med 2007; 44: 349–355.

- Kadowaki S, Okamura T, Hozawa A, Kadowaki T, Kadota A, Murakami Y, Nakamura K, Saitoh S, Nakamura Y, Hayakawa T, Kita Y, Okayama A, Ueshima H, for the NIPPON DATA Research Group. Relationship of elevated casual blood glucose level with coronary heart disease, cardiovascular disease and all-cause mortality in a representative sample of the Japanese population. NIPPON DATA80. Diabetologia 2008; 51:575–582.
- World Health Organization, Obesity, Preventing and Managing the Global Endemic, WHO Technical Report Series no 894, WHO, Geneva, 2000.
- Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998; 88:15–19.
- Franklin SS, Larson MG, Khan SA, Wong ND, Lelp EP, Kannel WB, Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001; 103:1245–1249.
- Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H, The NIPPON DATA80. Research Group. Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). J Hyperters 2006; 24:459–462.
- Sairenchi T, Iso H, Irie F, Fukasawa N, Yamagishi K, Kanashiki M, Saito Y, Ota H. Nose T. Age: specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. Hypertens Res 2005; 28:901–909.
- Greenlund KJ, Croft JB, Mensah GA. Prevalence of heart disease and stroke risk factors in persons with prehypertension in the United States, 1999–2000. Arch Intern Med 2004; 164:2113–2118.
- Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001; 345:1291–1297.
- Mainous AG 3rd, Everett CJ, Uszka H, King DE, Egan BM. Prehypertension and mortality in a nationally representative cohort. Am J Cardiol 2004; 94:1496–1500.
- Zhang Y, Lee ET, Devereux RB, Yeh J. Best LG, Fabsitz RR, Howard BV. Prehypertension, diabetes, and cardiovascular disease risk in a population-based sample: the Strong Heart Study. Hypertension 2006; 47:410–414.
- Gu Q, Burt VI., Paulose-Ham R, Yoon S, Gillum RF, High blood pressure and cardiovascular disease mortality risk among U.S. adults: the third National Health

- and Nutrition Examination Survey mortality follow-up study. Ann Epidemiol 2008; 18:302–309.
- Hsia J, Margolis KL, Eaton CB, Wenger NK, Allison M, Wu L, LaCroix AZ. Black HR. Women's Health Initiative Investigators. Prehypertension and cardiovascular disease risk in the Women's Health Initiative. Circulation 2007; 115:855–860.
- Murakami Y, Hozawa A, Okamura T, Ueshima H; Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group (EPOCH-JAPAN). Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Phyper Tession* 2008; 51:1483–1491.
- Pitt B. Prehypertension. To treat, or not to treat: that is the question. Am J Hypertens 2007: 20:492.
- Nilsson PM, High-normal blood pressure and future risks a new concern for clinicians? Eur Heart J 2007; 28:2832–2833.
- Joffres MR, Harnet P, MacLean DR, Litalien GJ, Fodor G. Distribution of blood pressure and hypertension in Canada and the United States. Am J Hypertens 2001; 14:1099–1105.
- 25 Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodriguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003: 289:2363–2369.
- Hozawa A, Ohkubo T, Kikuya M, Yamaguchi J, Ohmori K, Fujiwara T, Hashimoto J. Matsubara M, Kitaoka H, Nagai K, Tsuji I, Satoh H, Hisamichi S, Imai Y, Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. Pryperters Res 2002; 25:57–63.
- Obara T, Ohkubo T, Funahashi J, Kikuya M, Asayama K, Metoki H, Oikawa T, Hashimoto J, Totsune K, Imal Y, Isolated uncontrolled hypertension at home and in the office among treated hypertensive patients from the J-HOME study. J Hypertens 2005; 23:1653–1660.
- MacMahon S, Peto R, Cutier J. Collins R. Sorlie P. Neaton J, Abbott R. Godwin J, Dyer A. Stamler J. Blood pressure, stroke, and coronary heart disease Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335:765–774.

会議で麻生首相は以下のような 昨年11 月20日の経済財政諮問

議事録要旨より)。 するとごそっと減る」(同会議の ティブがないといけない。予防 れるとか、そういうインセン 健康を保った人には何かしてく が払うんだ。だから、 何もしない人の分の金を何で私 3 ある。私の方が税金は払ってい 朝歩いたり何かしているからで 療費がかかってない。それは毎 なるとこちらの方がはるかに医 代はとても元気だったが、 いる者がいる。彼らは、学生時 いる、医者にやたらにかかって に行くと、よほどよぼよぼして たらたら飲んで、 68歳になって同窓会 努力して 食べて、

はないか。 に失望した国民も多かったので まった。思いやりに欠ける言葉 この発言に大きな批判が集

論

抱える矛盾について考えてみた これを契機に現在の医療保険が あることも直視すべきである。 が、この発言には一面の真実が しかし言い方に問題はある 平等のなかの不平

東北大学教授

郎

等という矛盾である。

生 活習慣と医療費との関係

5万人を対象に、生活習慣アン り異なる。医療費の個人差は、 その給付(医療費)は、 して、平等に徴収される。 者コホート研究)。 て調査している(大崎国保加入 療費データを10年以上にわたっ ケートを実施した後、各人の医 管内の40歳以上の国保加入者約 クの個人差などにより生じる。 生活習慣を始めとする疾病リス に対する一定率または一定額と 筆者らは、宮城県大崎保健所 公的保険での保険料は、 人に上 一方、

> 煙によるものと換算される。こ 千億円のうち1兆4千億円が喫 5年の40歳以上の医療費26兆9 データに当てはめると、 ることが分かった。これを全国 そして、この集団全体が使う医 している の費用の一部を非喫煙者が負担 療費のうち、 は、非喫煙者より10%も高 それによると、 約5%が喫煙によ 喫煙者の医療 200

全体が使う医療費のうち、 すべて該当する者の医療費は 代表的な生活習慣リスクのどれ 13%がこれら3つの生活習慣リ も該当しない者に比べて、 4%も高い。そして、 喫煙・肥満・運動不足という この集団 3 約

している。 ち3兆6千億円が喫煙・肥 0 重で運動に励む非喫煙者が負 る。この費用の一部を、 スクによる。ということは、 動不足によるものと換算され 05年の4歳以上医療費 適正

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けでも、これほどのインパクト とは、文字通り桁が違う。 障費の圧縮目標「2200億円 最も基本的な生活習慣リスクだ を医療費に与えている。 喫煙・肥満・運動不足という 社会保

医療保険の平等と不平等

う矛盾である。 療費の使い方は平等でないと は平等に徴収されているが、 考えてみよう。つまり、 保険の平等と不平等について この現実を踏まえたうえで医 保険料

平等に負担増を強いられる。 剰分は、 のようなシステムは公正と言え 迫すると、喫煙者も非喫煙者も いる。そして医療保険財政が逼 擦費を多く使っている。 先述のように喫煙者の方が医 保険料として負担して 喫煙者だけでなく非喫 その過

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K 会は介入できない。 ば、よほどの危害でなければ社 好も 一方、本人だけでなく他者に 供ぐらいしか手はない。 る現代社会では、 ある習慣・嗜好により本人 分かったうえでの選 択の自由が最大限に尊 が加わることが明白 個人の選択に任せられ 実際、 生活習慣や 択なら 重

00 喫 と、介入は正当化される。受動 to 決するだけでなく、 なかの不平等」という矛盾が解 か。これが実現すると、「平等の ば「リスクに応じた負担」を医 ステムが求められている。なら ている。そして今、 いう点で、 ベルは上がり、 保険に導入しようではない は危機に瀕し、 保険料負担まで増大させると だけでなく、 飲酒運転禁止などである。 分煙化、交通事故を防ぐため 煙による健康被害を防ぐため 危害が及ぶことが証明される 生活習慣リスクは本人の医療 他者に影響を及ぼし リスクのない者 持続可能なシ 医療保険財 険財政も改 民の健康

予防 保険 のインセンティ ブを

のだろうか?

をタバコ価格に上乗せし、その が喫煙による。同年の紙巻きタ ように、1兆4千億円の医療費 単なのはタバコである。 による健康被害も減る。 も減るだろう。そうなれば喫煙 タバコ価格が上がれば、 者がすべて支払うことになる。 れで喫煙による医療費は、 収入を医療保険に拠出する。こ たり4円75銭となる。この金額 で割り算すると、タバコ一本あ べて負担してもらおう。先述の よる超過医療費は、 コの総販売本数2800億本 体策を提案しよう。 喫煙者にす 喫煙者 喫煙に 最も 喫煙

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際に肥満者の医療費は高いのだ保険料を設定してはどうか。実 らうのである。 よる超過医療費分を負担しても を上げればよい。 重を測定して、 保険証の更新の度に身長と体 その程度に応じて保険料 肥満度に応じた そして肥満に

早期がんが多いので医療費も安 がん検診で発見され では、 がん検診で発見され た場 合

善するだろう。

発見が増えて、がん死亡は減 ば受診率は上がり、 低くしてはどうか。 がん医療費の自 がんの早期 そうなれ 己負担

うし、レセプト情報を使えば精 検受診率・がん発見率・偽陰性 は飛躍的に向上する。 きるので、がん検診の 率などが容易かつ正確に把握で これにより受診率は上がるだろ るように、がん検診を医療保険 医療費も減るだろう。 ここまで言うと、(自 予防給付で行うべきである。 欧米各国ですでに行 わ 動 車保険

きだと言われることがある。 12 費も増大する恐れがある。 健康が損なわれるとともに医 たら、病状は重症化 らである。早期受診が避けられ 受診抑制を来す可能性があるか かし、これは行うべきでない。 で無事故の者の保険料が優遇さ 被保険者に優遇措置を施すべ るように) 一定期間受診しな 国民 0

新新しし いい 矢 時 療代の

とは異なり、 間 の自 動車保険や医療保険 公的医療保険にイ

とし、人々の相互扶助と連帯 性と個人責任の免除を基本理念 異を唱える方も多 的医療保険とは、疾病の不確実 センティブを導入することに

精度(質 れてい

されているからであろう。

から

依拠して、受診機会の平等化を

図るシステムであると広く認

身を守れなかった頃に考えられ 病の原因が不明で、 たものである。 人に平等であり、 主体だった時代に生まれた。 しかし、この理念は感染症 自助努力では リスクが万 疾

と連帯が試練に立 怪しくなっている。 る。そして受診機会の らかになるにつれて、 のなかの不平等という実態が明 分 慣ごとの発病確率や医 葉に代表されるように、 今は、「生活習慣病」と ればならない。 かる時代である。一 たされてい 何とかし 相 方、 「療費まで 平等すら 生活習 宣扶助 いう言 平等

代の疾病構造と予防・治 活習慣病の 果の程度により規定される。 するものでありた 医療保険のあり方は、 疾病予 時代における医療保 防と健康増 その 療の効 進を推 生 時

週刊社会保障 No.2519[2009. 2.23]

「学会発表」

1. 永井雅人,栗山進一,寶澤 篤,辻 一郎。 年齢階級別のBMIと全死因死亡リスクを検討した前向きコホート研究。(口演) 第29回日本肥満学会,大分,2008年.

0-025

年齢階級別の BMI と全死因死亡リスクを検討した前向きコホート研究

東北大学 公衆衛生学

〇永井雅人、栗山進一、寶澤 篤、辻 一郎

【目的】

Body Mass Index (BMI) と全死因死亡リスクの関係は Uカープや Jカーブを描くなど、未だ一致した結論が得られていない。一方、諸外国から BMI と全死因死亡リスクの関係は、年齢階級ごとに異なる可能性が示されている。そこで、本研究では BMI と全死因死亡リスクの関係を年齢階級別に検討した。

【方法】

対象は 1994 年にベースライン調査に参加した 40 ~ 79 歳の男性 24,895 名、女性 27,134 名の計 52,029 名で、 生存状況を 11 年間追跡した。

BMI を<18.5、18.5-20.9、21.0-22.9、23.0-24.9、25.0-27.4、27.5-29.9、30.0 \leq の 7 つに分類し、男女別、年齢階級別に全死因死亡リスクとの関連を Cox 比例ハザードモデルより求めた。共変量は喫煙習慣や飲酒習慣などである。

【結果】

BMI23.0-24.9 を基準としたときの、BMI < 18.5 の痩身者のハザード比 (HR) は男性の 40-54歳、55-64歳、65-79歳の群でそれぞれ、0.84 (95%信頼区間;0.38-1.86)、1.37 (0.96-1.94)、1.49 (1.26-1.76) であった。女性の 40-54、55-64、65-79歳の群では、1.93 (0.87-4.31)、1.29 (0.79-2.10)、1.47 (1.19-1.82) であった。一方、 $30 \le$ BMI の肥満者の HR は男性の 40-54歳、55-64歳、65-79歳の群でそれぞれ、1.28 (0.59-2.79)、2.03 (1.27-3.24)、1.25 (0.87-1.79)、女性の 40-54、55-64、65-79歳の群で、2.45 (1.13-5.30)、1.15 (0.67-1.99)、1.26 (0.95-1.68) であった。

[まとめ]

BMI < 18.5 の痩身者のリスクは、65 歳以上の男女の高齢者で有意に上昇した。一方、30.0 \le BMI の肥満者のリスクは、55 \sim 64 歳の男性、40 \sim 54 歳の女性で有意に上昇した。以上より、65 歳以上の男女における全死因死亡リスクは、肥満者よりも痩身者で高かった。

2. 寶澤 篤, 栗山進一, 柿崎真沙子, 大森 芳, 大久保孝義, 辻 一郎. 健診受診と死亡リスクの関連―大崎国保コホート―. (ポスター) 第67回日本公衆衛生学会総会, 福岡, 2008年.

07-044

健診受診と死亡リスクの関連-大崎国保コホートー ○寳澤 篤¹¹、栗山 進一¹¹、柿崎 真沙子¹¹、大森 芳¹¹、大久保 孝義²¹、 辻 一郎¹¹ 東北大学 大学院 医学系研究科 公衆衛生学分野¹¹、東北大学 医薬開発 権租寄附諸座²¹

【背景】大崎国保コホートは1994年にベースライン調査を実施した宮城県 大崎保健所管内の国保加入者に対するコホート研究で、高い参加率 (95%) と詳細な生活習慣の調査が特徴である。さらに基本健康診査(健診)受診者の 結果も結合しており、健診データとその後の死亡リスクの関連の調査も可能 である。本研究ではこの健診受診者と非受診者を比較し、1.健診受診者と非 受診者の生活習慣の違い、2.健診受診者と非受診者のその後の死亡リスクの 違い、3.もし死亡リスクに差があるとすれば、その差は生活習慣で説明が可 能か、について検討を行う。【方法】本研究では1995年度健診の最終日ま で国保に加入していた 48775 名 (男性 23451 名、女性 25324 名) を対象とし た。検討した項目は喫煙、飲酒、既往歷(脳卒中、心筋梗塞、高血圧、がん)、 スポーツ、歩行時間、生きがい、主観的健康度、身体活動能力、食物摂取頻 度 (肉類、魚類、緑黄色野菜)、学歴、がん検診の受診歴である。また健診 非受診者に対する健診受診者の死亡リスク比はコックス比例ハザードモデル を用いて推定し、多変量モデルでは上記の要因を調整した。【結果】健診の 受診者は男性で 6814 名 (29.1%)、女性で 9171 名 (36.2%) であった。男 女とも健診受診者で喫煙率、脳卒中、心筋梗塞、がんの既往歴が低かった。 「生きがいがある」と答えた者、主観的健康度が「非常に健康/まあ健康」と 答えた者、中一高強度の活動に問題がない者、緑黄色野菜の摂取頻度が多い 者の割合、各種がん検診の受診率は健診受診者で高かった。12年間の追跡 で男性 4641 名、女性 2644 名の死亡が観察された。総死亡、循環器疾患死亡、 がん死亡、その他の死亡のリスク比はいずれも健診受診者で有意に低かった (年齢調整ハザード比は男性でそれぞれ 0.56、0.47、0.66、0.53、女性でそれ ぞれ 0.47、0.47、0.56、0.41)。これらの死亡リスク比は多変量調整後に若干 上昇(多変量調整ハザード比は男性でそれぞれ0.70、0.60、0.74、0.66、女 性でそれぞれ 0.60、0.59、0.64、0.51) するものの、いずれも有意に低下し ていた。【考察】健診受診者は健診非受診者よりも健康的な生活習慣であっ た。健診受診者の死亡リスクは非受診者よりも低く、今回の調整項目ではこ の死亡リスクの低下は十分に説明されなかった。特に循環器疾患以外の死亡 リスクも低下していることから残余交絡の影響が考えられる。

3. 永井雅人, 柿崎真沙子, 栗山進一, 大森 芳, 菅原由美, 曽根稔雅, 寶澤 篤, 辻 一郎. 性別にみた BMI と死因別死亡リスクに関する前向きコホート研究 - 大崎国保コホート研究 - 、(口演) 第 19 回日本疫学会学術総会, 金沢, 2009 年.

03-07

性別にみたBMIと死因別死亡リスクに関する前向きコホート研究一大崎国保コホート研究—

永井雅人、柿崎真沙子、栗山進一、大森 芳、菅原由美、曽根稔雅、寶澤 篤、辻 一郎 東北大学大学院医学系研究科公衆衛生学分野

【目的】我々は本研究データにおいて、Body Mass Index (BMI)と全死因死亡リスクとの関連が男女ともUカーブを描くこと、男性では痩せと肥満のリスクは同程度であるのに対して、女性では痩せのリスクは肥満よりも高いことを以前に報告した。本研究ではこの男女差の要因を解明するため、BMI と死因別死亡リスクとの関連を性別に検討した。

【方法】対象者は、宮城県大崎保健所管内の 40~79 歳の国民健康保険加入者全員(54,996 名)を対象とする平成6年のベースライン調査に回答した52,029名(回収率:95%)のうち、がん・心筋梗塞・脳卒中の既往歴がある者、BMI を算出できない者を除外した43,984名(男性:21,042名、女性:22,942名)である。12年間の追跡で、5,709名の死亡が観察された(虚血性心疾患(IHD)::376名、脳卒中、766名、がん:1,966名、肺炎:434名)。BMI を<18.5(痩せ)、18.5-24.9、25.0-29.9(過体重)、≥30.0(肥満)に分類し、死因別死亡リスクをCox 比例ハザードモデルより算出した。

【結果】IHD 死亡リスクは、男女とも痩せ及び肥満で上昇した。痩せでのリスク上昇は女性で顕著であった。一方、肥満でのリスク上昇は男女とも同様であった。脳卒中死亡リスクは、男女とも肥満で上昇する傾向を示し、男性で顕著だった。がん死亡リスクは、男女とも有意な関連はみられなかったが、肥満で上昇する傾向があり、それは女性でやや強かった。肺炎死亡リスクは、男女とも痩せで有意に上昇した。一方、肥満でのリスク上昇は男性でしかみられなかった(表)。

【結論】BMI と全死因死亡リスクとの関連でみられた男女差は、痩せでの IHD 死亡リスクが男性より女性、 肥満での脳卒中、肺炎死亡リスクが女性より男性で顕著であったことによることが示唆された。

表 BMI と死因別死亡リスクの HR と 95%CI

	Body Mass Index							
	<18.5	18.5-24.9	25.0-29.9	≥30				
虚血性心疾患(IHD))							
男性 HR(95%CI)	1.56 (0.94 - 2.56)	1.00 (reference)	1.09 (0.75 - 1.59)	1.88 (0.66 - 5.36)				
女性 HR(95%CI)	2.12 (1.23 - 3.63)	1.00 (reference)	1.56 (1.02 - 2.39)	1.61 (0.66 - 3.97)				
脳卒中								
男性 HR(95%CI)	1.11 (0.73 - 1.68)	1.00 (reference)	1.05 (0.80 - 1.37)	1.67 (0.85 - 3.28)				
女性 HR(95%CI)	1.28 (0.84 - 1.95)	1.00 (reference)	0.93 (0.69 - 1.23)	1.28 (0.75 - 2.18)				
がん								
男性 HR(95%CI)	1.13 (0.89 - 1.44)	1.00 (reference)	0.97 (0.83-1.13)	1.35 (0.88 - 2.08)				
女性 HR(95%CI)	1.00 (0.68 - 1.46)	1.00 (reference)	1.03 (0.84 - 1.28)	1.44 (0.97 - 2.15)				
肺炎								
男性 HR(95%CI)	2.28 (1.61 - 3.23)	1.00 (reference)	0.93 (0.65 - 1.34)	1.48 (0.57 - 3.83)				
女性 HR(95%CI)	2.34 (1.37 - 4.00)	1.00 (reference)	1.22 (0.76 - 1.97)	0.81 (0.28 - 2.40)				

HR: ハザード比、95%CL 95%信頼区間

補正項目: 年齢、20歳からの体重変化、学歴、配偶者の有無、喫煙習慣、飲酒習慣、歩行時間、 身体活動時間、腎疾患の既往歴、肝疾患の既往歴

厚生労働科学研究費補助金(政策科学総合研究事業(政策科学推進研究事業)) 「生活習慣・健診結果が生涯医療費に及ぼす影響に関する研究」 (H19-政策-一般-026)

平成 20 年度総括·分担研究報告書 (平成 21 年 3 月)

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