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Original Article

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BACKGROUND: Proteinuria has been considered to be a prognostic marker for persons with diabetes mellitus, but only a limited number of studies about the relationship between proteinuria and mortality among general population has been available.
METHODS: The subjects were 10,897 individuals who participated in the National Cardiovascular Survey conducted in 1980 and who were aged 30 years or older living in 300 districts that had been randomly selected throughout Japan. The vital records were confirmed in 1999 and 7,203 subjects (3,180 males and 4,023 females) without a history of hypertension, stroke, heart disease, renal disease, or diabetes mellitus at the start of the study were investigated.
RESULTS: There were 126,825 person-years of follow-up. During the observed period of time, 371 died of cardiovascular causes, including 171 stroke deaths and 74 coronary deaths. The risk of proteinuria for cardiovascular mortality was greater than unity for those with a normal serum creatinine level, after adjusting for age and other cardiovascular disease risk factors.
CONCLUSIONS: When contrasted with other cardiovascular disease risk factors, urinary protein is an independent risk factor for cardiovascular death among the Japanese population.
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Keywords: Proteinuria, Cardiovascular Diseases, Cohort Studies, Japan, Mortality.

Proteinuria or urinary albumin has been considered to be a prognostic marker for patients with non-insulin-dependent diabetes mellitus[1-14] and those with hypertension[10,15-18] or acute myocardial infarction.[19] However, in general population, knowledge about the relationship between proteinuria and mortality is limited.[14] Proteinuria has been a predictor of mortality in subjects aged 65-79 years[20] but not among those 80 years and older.[21] Urinary albumin is related to risk factors for cardiovascular diseases,[15,22] but in only a few studies has diabetes mellitus or the history of renal diseases been assessed.[23] In addition, most of these studies have been conducted in European countries and in the United States. Studies about the relationship between proteinuria and mortality among non-whites are also limited.[8,10] In this study, we describe the relationship between proteinuria at baseline and death from cardiovascular disease in a nationally representative cohort of the Japanese population.

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METHODS

Study Subjects

The subjects were the participants of The National Cardiovascular Survey of 1980.[24] The procedures of the 1980 National Cardiovascular Survey have already been described.[24-26] In 1980, all household members aged 30 years or older living in 300 districts randomly selected throughout Japan were counted. There were 13,771 eligible subjects, among which 10,897 (79.4%) participated in the national survey.

Baseline Information

Using a standard color tone table, the urine dipstick test for protein was carried out and assessed as: none, trace, +, or ++. Blood samples were obtained during a non-fasting state and the time (in hours) between the last meal and the time of sample collection was recorded. Creatinine was measured by using the Jaffe method. Blood sugar was measured by the Neocaproine-copper method. A Technicon SMA 12-60 (Technicon Instruments, Tarrytown, NY) was used for these measurements. Hyperglycemia was defined as a blood sugar level of 7.7mmol/L or greater when the time from the last meal before blood sampling was two hours or longer and/or 11.1 mmol/L or greater when the elapsed time between the last meal and sampling was less than two hours.

A self-administered questionnaire was used to obtain information on history of gout, hypertension, diabetes mellitus, stroke, heart disease, renal disease, smoking, and alcohol drinking habits. The use of antihypertensive agents was asked to persons with a history of hypertension, although information on specific types of drugs was not obtained. For alcohol drinking habits, the subjects were asked whether they "never drink"; "used to drink"; "occasionally drink"; or "drink daily". For smoking habits, similar questions were posed: whether they "never smoked"; "used to smoke"; or "currently smoke". Both habits were also separated into "current" and "non-current" status. Current drinking included both occasional and daily drinking.

A standard sphygmomanometer was used to measure blood pressure; and the first and the 5th Korotkoff's sounds were recorded as the systolic and diastolic blood pressures. The definition of hypertension was a systolic blood pressure of 160 mmHg or higher and/or a diastolic blood pressure of 95 mmHg or higher. Body weight was measured with light clothes and no shoe.

Follow-up

In 1994, a follow-up study was conducted with the participants of this survey, which was called the 'National Integrated Projects for Prospective Observation of Non-Communicable Diseases and the Trend in the Aged' (NIPPON DATA 80).[25,26]

A total of 10,546 subjects for whom complete information on age, sex, and blood pressure from the 1980 data set was available made up a cohort. The vital status of these subjects was determined by reviewing the resident registry system of 1994 and 1999. The underlying cause of death of those who died during the follow-up period was obtained from death certificates and coded according to the International Classification of Diseases, 9th revision (ICD9) for the period between 1980 and 1994; and 10th revision (ICD10) for the period between 1995 and 1999. Deaths from stroke (ICD9: 430-438, ICD10: I60-I69), cardiovascular diseases (ICD9: 390-459, ICD10: I00-I99), and cancer (ICD9: 140-208, ICD10: C00-C97) were defined as ICD9 or ICD10 codes.

After a follow-up that lasted for 19 years, 908 were lost to follow-up and 759 were excluded because of missing data for potential confounders. For the survival analysis, an additional 1,676 persons with histories of hypertension, stroke, heart disease, renal disease, or diabetes mellitus were excluded because proteinuria or urinary albumin is a predictor of cardiovascular disease mortality for persons with diabetes[9,11,12] or hypertension.[15-18] Finally, 7,203 subjects (3,180 males and 4,023 females) were selected for the study.

Statistical Analysis

Cox's proportional hazards regression models were used to examine the relationship between proteinuria and cardiovascular mortality. First, proteinuria was considered as a categorical variable and hazard ratios (HR) were calculated for each category (trace, +, ++ and more). Next, proteinuria was diagnosed when a subject showed trace, +, or ++ on the urine dipstick test and considered as a dichotomous variable. The subjects were also divided into three categories according to body mass index (BMI, kg/m^2) as follows: "lean" (≤20.0), "standard" (20.1-24.9), and "obese" (25+); and classified according to serum cholesterol (mmol/L) levels as follows: "low" (<4.1), "standard" (4.1-6.1), and "high" (6.2+). The serum creatinine level (μ mol/L) was rated separately for men and women.[27] Male subjects were divided into three categories: "low" (<97), "standard" (97-105), and "high" (106+). For women, the criteria were set as follows: "low" (<71); "standard" (71-79); and "high" (80+).[27]

For comparative purposes, the hazard ratios were calculated with adjustments for age only (grouped by 10-year increments), and with adjustment for age, hypertension (yes/no), hyperglycemia (yes/no), current smoking status (yes/no), current drinking status (yes/no), BMI (lean, standard, or obese), serum cholesterol level (low, standard, or high). To assess the interaction between urinary protein and serum creatinine level, multivariate analyses stratified by the three levels of serum creatinine were conducted. Analyses were performed separately for men and women.

All the analyses was performed with SAS® software (Version 8.2 SAS Institute, Cary, NC). Two-sided values where $p < 0.05$ were considered statistically significant.

RESULTS

Table 1 shows the number of deaths according to underlying cause of death stratified by baseline proteinuria level. The 19-year

follow-up lasted for 126,825 person-years, during which 1,179 subjects died. Of these, 371 died of cardiovascular causes, including 171 stroke deaths and 71 coronary deaths, and 831 of non-cardiovascular deaths, including 393 who died of cancer and 70 as a result of accidents and injuries. The crude cardiovascular mortality increased with the level of proteinuria for both men and women.

Among the 395 male subjects lost in follow-up, the number of subjects with proteinuria (including trace or more) was 33 (8.4%), as for trace was 16 (4.1%), + was 15 (3.8%), and ++ and more was 2 (0.5%). Among the 513 female subjects lost in follow-up, the number of subjects with proteinuria (including trace or more) was 48(9.4%), as for trace was 26 (5.1%), + was 20 (3.9%), and ++ and more was 2 (0.4%). Among subjects lost in follow-up, the proportion of subjects with proteinuria was higher than that of subjects completed the follow-up for both men and women.

Table 2 shows the baseline characteristics for subjects with and without proteinuria. For both men and women, the mean age, body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol and glucose levels were significantly greater in the subjects with proteinuria. The proportions of subjects with a high serum cholesterol level, obesity, hypertension, or hyperglycemia were significantly greater in the group with proteinuria for both men and women.

Table 3 shows the hazard ratios of proteinuria with all cause and cardiovascular mortality by sex. When examined by using the Cox proportional hazards model adjusted for age only, female subjects with "+" proteinuria significantly associated with all cause mortality. The hazard ratios for male subjects with "++ and more" proteinuria were higher than unity without significance. Proteinuria including trace, +, ++ and more increased the risk with statistical significance with all cause mortality for both men (HR=1.58, 95% confidence interval [CI]: 1.20-2.08) and women (HR=1.75, 95% CI: 1.29-2.38). From the results of multivariate analysis, the hazard ratios of proteinuria with all cause mortality were similar to the models adjusted for age only. The hazard ratios for male subjects with proteinuria including trace, +, ++ and more were higher than unity without significance.

The hazard ratios for cardiovascular mortality increased with the level of proteinuria for both men and women when examined by using the Cox proportional hazards model adjusted for age only. Male subjects with "++" proteinuria and female subjects with "+" proteinuria significantly associated with cardiovascular mortality. The hazard ratios for subjects with "trace" proteinuria were higher than unity for both men and women without significance. Proteinuria including trace, +, ++ and more increased the risk with statistical significance with cardiovascular mortality for both men (HR=2.17, 95% CI: 1.39-3.38) and women (HR=2.41, 95% CI: 1.51-3.84).

From the results of multivariate analysis, the hazard ratios of proteinuria with cardiovascular mortality were similar to the models adjusted for age only. The hazard ratios for female subjects with proteinuria including trace, +, ++ and more were higher than unity with statistical significance. Those for male were higher than unity although they were not statistically significant. Even when the deceased or those lost in the first three years of follow-up were excluded, the risk of proteinuria for cardiovascular mortality among women was significantly higher than unity (HR=2.04, 95% CI: 1.18-3.54). The hazard ratios for male subjects were not statistically significant (HR=1.21, 95% CI: 0.73-2.01).

Table 4 shows the results of stratified analyses by the three levels of serum creatinine. Some of the results from the stratified analysis by serum creatinine level were different from those of age only adjusted models and multivariate analysis. For males, the risk of proteinuria for cardiovascular mortality was significantly higher than unity in the group with standard serum creatinine level. For female subjects, the risk of proteinuria was significantly higher than unity in the group with high creatinine level.

Table 1. The number of deaths according to underlying cause stratified by baseline proteinuria level.

Causes of death	baseline proteinuria level				
	total	negative	trace	+	++ and more
			Male		
cardiovascular	197	175	13	4	5
cancer	237	224	8	4	1
non-cardiovascular, non-cancer	223	203	14	6	0
All-cause	657	602	35	14	6
	(n=3180)	(n=2994)	(n=121)	(n=50)	(n=15)
			Female		
cardiovascular	174	154	9	9	2
cancer	156	145	7	4	0
non-cardiovascular, non-cancer	192	178	10	3	1
All-cause	522	477	26	16	3
	(n=4023)	(n=3804)	(n=150)	(n=57)	(n=12)

Table 2. Baseline characteristics of study subjects in 1980 NIPPON DATA, 3180 men and 4203 women aged 30-91 years.

Proteinuria	Male				Female			
	Negative (n=2994)		Positive* (n=186)		Negative (n=3804)		Positive* (n=219)	
Characteristics	mean	SD	mean	SD	mean	SD	mean	SD
Age (year)	48.6	12.6	52.6	14.0	48.9	12.7	50.2	14.4
Body mass index (kg/m²)	22.4	3.0	23.2	3.2	22.6	3.2	23.3	4.1
Systoric blood pressure (mmHg)	135.4	19.1	141.9	22.3	130.0	18.7	137.8	23.0
Diastolic blood pressure (mmHg)	82.3	11.5	85.3	13.8	78.0	11.0	81.4	12.8
Serum total cholesterol (mmol/L)	4.9	0.9	5.0	0.9	4.9	0.9	5.0	0.9
Serum creatinine (μmol/L)	81.3	14.1	84.9	17.7	80.0	17.7	48.9	12.7
Serum glucose (mmol/L)	7.1	1.7	7.5	2.2	7.0	1.8	7.1	1.8
Follow-up time (year)	17.4	3.9	16.3	5.2	17.9	3.3	16.9	4.8
Current smoker	1915	(64.0%)	123	(66.1%)	328	(8.6%)	24	(11.0%)
Current drinker	2264	(75.6%)	136	(73.1%)	783	(20.6%)	44	(20.1%)
High serum cholesterol	161	(5.4%)	18	(9.7%)	281	(7.4%)	25	(11.4%)
Low serum cholesterol	646	(21.6%)	33	(17.7%)	747	(19.6%)	32	(14.6%)
Leanness (BMI<20)	598	(20.0%)	32	(17.2%)	766	(20.1%)	53	(24.2%)
Obesity (BMI>25)	526	(17.6%)	49	(26.3%)	745	(19.6%)	67	(30.6%)
Hypertension	533	(17.8%)	54	(29.0%)	397	(10.4%)	57	(26.0%)
Hyperglycemia	464	(15.5%)	51	(27.4%)	617	(16.2%)	50	(22.8%)
Creatinine level								
High	1716	(57.3%)	96	(51.6%)	942	(24.8%)	44	(20.1%)
Standard	678	(22.6%)	46	(24.7%)	1311	(34.5%)	65	(29.7%)
Low	600	(20.0%)	44	(23.7%)	1551	(40.8%)	110	(50.2%)

* includes trace, +, ++ and more.

Hyperglycemia was defined as a blood sugar level of 7.7 mmol/L or greater when the time from the last meal before blood sampling was two hours or longer and/or11.1mmol/L or greater when the elapsed time between the last meal and sampling was less than two hours.

High serum cholesterol was defined as a serum cholesterol level of 6.2 mmol/L or greater. Low serum cholesterol was defined when a serum cholesterol level was less than 4.1 mmol/L.

The definition of hypertension was a systolic blood pressure of 160 mmHg or greater and/or a diastolic blood pressure of 95 mmHg or greater.

The serum creatinine level (μmol/L) was rated separately for men "low" (serum creatinine<97), "standard" (97-105), and"high"(106+) and women"low"(<71); "standard "(71-79); and "high"(80+).

Table 3. Hazard ratios of proteinuria for all cause and cardiovascular mortality.

	All cause mortality		Cardiovascular mortality	
	Age-adjusted hazard ratio (95% CI)	Multivariate hazard ratio (95% CI)	Age-adjusted hazard ratio (95% CI)	Multivariate hazard ratio (95% CI)
		Male		
negative	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
trace	1.13 (0.77-1.65)	1.13 (0.77-1.65)	1.48 (0.80-2.73)	1.44 (0.78-2.67)
+	0.72 (0.38-1.34)	0.67 (0.35-1.26)	0.46 (0.12-1.87)	0.35 (0.09-1.44)
++ and more	2.07 (0.86-4.98)	1.76 (0.72-4.29)	6.21 (2.29-16.80)	4.20 (1.50-11.72)
p-value for trend	0.1443	0.2083	0.0062	0.0467
trace,+,++ and more*	1.58 (1.20-2.08)	1.22 (0.92-1.61)	2.17 (1.39-3.38)	1.49 (0.95-2.34)
		Female		
negative	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
trace	1.50 (0.98-2.30)	1.48 (0.96-2.28)	1.56 (0.73-3.34)	1.61 (0.75-3.47)
+	1.97 (1.08-3.58)	1.91 (1.04-3.52)	3.42 (1.51-7.75)	3.08 (1.31-7.26)
++ and more*	1.30 (0.42-4.05)	1.19 (0.38-3.74)	2.27 (0.56-9.19)	2.01 (0.48-8.31)
p-value for trend	0.0005	0.0016	0.0002	0.0016
trace,+,++ and more*	1.75 (1.29-2.38)	1.74 (1.27-2.38)	2.41 (1.51-3.84)	2.21 (1.36-3.59)

Age, smoking, drinking, serum cholesterol, hyperglycemia, leanness, obesity, and hypertension were adjusted in multivariate analysis.

* :regrouped

CI: confidence interval

Table 4. Stratified analysis by serum creatinine level for proteinuria for cardiovascular mortality.

serum creatinine level (μ mol/L)	n	Proteinuria positive* (%)	Cardiovascular death (%)	Hazard ratio	(95% CI)
			Male (n=3180)		
106+	644	96 (14.9%)	60 (9.3%)	1.07	(0.45 -2.57)
97-105	724	44 (6.1%)	42 (5.8%)	4.07	(1.80 -9.20)
-96	1812	46 (2.5%)	9 (0.5%)	0.84	(0.36 -1.93)
			Female (n=4023)		
80+	1661	44 (2.6%)	104 (6.3%)	2.36	(1.33 -4.19)
71-79	1376	65 (4.7%)	42 (3.1%)	2.41	(0.77 -7.54)
-70	986	110 (11.2%)	28 (2.8%)	1.03	(0.12 -9.17)

Adjusted for age, smoking, drinking, serum cholesterol, hyperglycemia, leanness, obesity, and hypertension.

Proteinuria includes trace,+,++ and more.

DISCUSSION

Our results indicated that proteinuria is related to an increased risk of death from cardiovascular disease among persons with no history of diabetes mellitus, hypertension, acute myocardial infarction, or stroke. Prospective data on proteinuria and mortality among the general population are limited.[14] A number of prospective epidemiologic studies have reported that proteinuria or urinary albumin is a predictor of death for those with diabetes[1-14] and hypertension.[10,15-18] Most of the prospective studies on urinary protein or albumin and mortality were conducted in European countries[2,5,6,9,12,14,15] and in the United States.[3,11,16] The results of our study are unique because the study subjects were composed of a representative cohort of the Japanese population.

The hazard ratios for cardiovascular mortality increased with the level of proteinuria. The level of proteinuria was proportional to the risk of mortality.[16] In this study, the positive sign of urinary protein is defined according to the urinary dipstick test result (as trace, +, ++ and more). Although without significance, the hazard ratios for cardiovascular mortality in subjects with "trace" proteinuria were higher than unity for both men and women. It is consistent with studies reporting that even lesser degrees of albuminuria predict cardiovascular events even after subjects with dipstick-positive (i.e., less than or equal to +) proteinuria had been excluded.[11,13]

Our results showed that urinary protein, measured by dipstick methods, is an independent risk factor for cardiovascular death. In the most of studies, urinary protein was measured with a dipstick and the positive sign for proteinuria was defined when the test result was + or more,[11,16] 300+mg/24h, 12 or >30mg/dL.[20] Measuring urinary protein with a dipstick is a useful screening test because it is very simple and inexpensive. Finding the optimal cut-off point in the urinary dipstick test requires further consideration.

There are some limitations to be considered in this study. For example, potentially important confounding factors, such as postmenopausal status[14] and waist and hip measurements[28] were not obtained at the initial survey.

Among subjects lost in follow-up, the proportion of subjects with proteinuria was higher than subjects selected for the analysis. The results of this study underestimated true relation between mortality and urine protein because it is presumable that subjects lost in follow-up have higher all cause and cardiovascular mortality. It means that the direction of bias produced by subjects lost in follow-up is toward null value. The observed hazard ratios are probably closer to the null than what it would be if the subjects lost in follow-up were absent.

Urinary protein was measured only once using an available urine sample so that it is possible that it may be misclassified in reading the results. It is also true that urinary protein is determined at the baseline before the survival or cause of death of the surveyed subjects becomes known through follow-up studies; and it is judged that any misclassification, if it occurs, is non-differential. If so, the effect of the risk factor that has been computed must be smaller than the real value and has no bearing on the conclusion of the present study, i.e., urinary protein is an independent risk factor of mortality from cardiovascular diseases.

Microalbuminuria correlates with cardiovascular autonomic dysfunction and insulin resistance in type 2 diabetic patients.[29] In hypertensive subjects, the inflamatory injury in the kidney structures consequent to that of myocardial infarction causes a greater albumin leak.[30] However, precise underlying pathophysiologic mechanisms of the association between proteinuria and unfavorable cardiovascular outcome among persons with no history of diabetes mellitus, hypertension, acute myocardial infarction, or stroke have not been totally given.

The results of the analysis that excluded subjects deceased or lost in the first three years of follow-up and the stratified analysis by serum creatinine level were different with men and women. For males, the risk of proteinuria for cardiovascular mortality was significantly higher than unity in the group with standard serum creatinine level. For female subjects, the risk of proteinuria was significantly higher than unity in the group with high creatinine level. It is reported that a possible difference in the mechanism or significance of urinary albumin excretion between both genders.[31] Future studies on proteinuria should take factors related sex, menopausal status for example, into account.

In conclusion, urinary protein is an independent risk factor for cardiovascular death among the Japanese population especially in relation to their medical histories, blood pressure status and blood sugar level. Measuring urinary protein by the dipstick method is useful in locating persons with a high risk for cardiovascular mortality because it is simple and easy to conduct during a mass screening.

REFERENCES

1. Morrish NJ, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H. A prospective study of mortality among middle-aged diabetic patients (the London Cohort of the WHO Multinational Study of Vascular Disease in Diabetics) II: Associated risk factors. Diabetologia 1990; 33: 542-8.
2. Stiegler H, Standl E, Schulz K, Roth R, Lehmacher W. Morbidity, mortality, and albuminuria in type 2 diabetic patients: a three-year prospective study of a random cohort in general practice. Diabet Med 1992; 9: 646-53.
3. Neil A, Hawkins M, Potok M, Thorogood M, Cohen D, Mann J. A prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. Diabetes Care 1993; 16: 996-1003.
4. Bianchi S, Bigazzi R, Quinones Galvan A, Muscelli E, Baldari G, Pecori N, et al. Insulin resistance in microalbuminuric hypertension. Sites and mechanisms. Hypertension 1995; 26: 789-95.
5. Standl E, Balletshofer B, Dahl B, Weichenhain B, Stiegler H, Hormann A, et al. Predictors of 10-year macrovascular and

overall mortality in patients with NIDDM: the Munich General Practitioner Project. Diabetologia 1996; 39: 1540-5.
6. Pontiroli AE, Pacchioni M, Camisasca R, Lattanzio R. Markers of insulin resistance are associated with cardiovascular morbidity and predict overall mortality in long-standing non-insulin-dependent diabetes mellitus. Acta Diabetol 1998; 35: 52-6.
7. Mattock MB, Barnes DJ, Viberti G, Keen H, Burt D, Hughes JM, et al. Microalbuminuria and coronary heart disease in NIDDM: an incidence study. Diabetes 1998; 47: 1786-92.
8. Chen KT, Chen CJ, Fuh MM, Narayan KM. Causes of death and associated factors among patients with non-insulin-dependent diabetes mellitus in Taipei, Taiwan. Diabetes Res Clin Pract 1999; 43: 101-9.
9. Hanninen J, Takala J, Keinanen-Kiukaanniemi S. Albuminuria and other risk factors for mortality in patients with non-insulin-dependent diabetes mellitus aged under 65 years: a population-based prospective 5-year study. Diabetes Res Clin Pract 1999; 43: 121-6.
10. Sievers ML, Bennett PH, Roumain J, Nelson RG. Effect of hypertension on mortality in Pima Indians. Circulation 1999; 100: 33-40.
11. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med 2000; 160: 1093-100.
12. Casiglia E, Zanette G, Mazza A, Donadon V, Donada C, Pizziol A, et al. Cardiovascular mortality in non-insulin-dependent diabetes mellitus. A controlled study among 683 diabetics and 683 age- and sex-matched normal subjects. Eur J Epidemiol 2000; 16: 677-84.
13. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286: 421-6.
14. Roest M, Banga JD, Janssen WM, Grobbee DE, Sixma JJ, de Jong PE, et al. Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. Circulation 2001; 103: 3057-61.
15. Pontremoli R, Viazzi F, Martinoli C, Ravera M, Nicolella C, Berruti V, et al. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. Nephrol Dial Transplant 1999; 14: 360-5.
16. Grimm RH Jr, Svendsen KH, Kasiske B, Keane WF, Wahi MM. Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Kidney Int Suppl 1997; 63: S10-S14.
17. Segura J, Campo C, Ruilope LM. Effect of proteinuria and glomerular filtration rate on cardiovascular risk in essential hypertension. Kidney Int Suppl 2004; S45-S49.
18. Tsioufis C, Dimitriadis K, Antoniadis D, Stefanadis C, Kallikazaros I. Inter-relationships of microalbuminuria with the other surrogates of the atherosclerotic cardiovascular disease in hypertensive subjects. Am J Hypertens. 2004; 17: 470-6.
19. Berton G, Cordiano R, Palmieri R, Cucchini F, De Toni R, Palatini P. Microalbuminuria during acute myocardial infarction; a strong predictor for 1-year mortality. Eur Heart J 2001; 22: 1466-75.
20. Casiglia E, Pauletto P, Mazza A, Ginocchio G, Di Menza G, Pavan L, et al. Impaired glucose tolerance and its co-variates among 2079 non-diabetic elderly subjects. Ten-year mortality and morbidity in the CASTEL study. CArdiovascular STudy in the ELderly. Acta Diabetol 1996; 33: 284-90.
21. Casiglia E, Spolaore P, Ginocchio G, Colangeli G, Di Menza G, Marchioro M, et al. Predictors of mortality in very old subjects aged 80 years or over. Eur J Epidemiol 1993; 9: 577-86.
22. Nakanishi N, Takatorige T, Fukuda H, Shirai K, Li W, Okamoto M, et al. Components of the metabolic syndrome as predictors of cardiovascular disease and type 2 diabetes in middle-aged Japanese men. Diabetes Res Clin Pract 2004; 64: 59-70.
23. Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Go OT, et al. Rising tide of cardiovascular disease in American Indians. The Strong Heart Study. Circulation 1999; 99: 2389-95.
24. Ministry of Health and Welfare. National Survey on Circulatory Disorders 1980. Tokyo: Japan Heart Foundation, 1982.
25. Hayakawa T, Okayama A, Ueshima H, Kita Y, Choudhury SR, Tamaki J. Prevalence of impaired activities of daily living and the impact of stroke and lower limb fracture in elderly persons in Japan. CVD prevention 2000; 3: 187-194.
26. Sakata K, Hashimoto T, Ueshima H, Okayama A. Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980-1994. National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in the Aged. Eur J Epidemiol 2001; 17: 461-8.
27. Kanai S, Sekiguchi M, Nomoto S. Cleatinine and Cleatine. In: Kanai S, eds. Kanai's Manual of Clinical Laboratory Medicine, 31th ed. Kanahara, Tokyo. (in Japanese)
28. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, et al. Body weight and mortality among women. N Engl J Med 1995; 333: 677-85.
29. Takahashi N, Anan F, Nakagawa M, Yufu K, Ooie T, Nawata T, et al. Microalbuminuria, cardiovascular autonomic dysfunction, and insulin resistance in patients with type 2 diabetes mellitus. Metabolism 2004; 53: 1359-64.
30. Gosling P, Hughes EA, Reynolds TM, Fox JP. Microalbuminuria is an early response following acute myocardial infarction. Eur Heart J 1991; 12: 508-13.
31. Verhave JC, Hillege HL, Burgerhof JG, Navis G, de Zeeuw D, de Jong PE for the PREVEND Study Group. Cardiovascular risk factors are differently associated with uri-

nary albumin excretion in men and women. J Am Soc Nephrol 2003; 14: 1330-5.

APPENDIX

List of the NIPPON DATA80 Research group

NIPPON DATA80: "National Integrated Projects for Prospective Observation of Non-communicable Diseases And its Trends in the Aged"

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白血球数と総死亡、心血管事故死亡、がん死亡リスク

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要旨

白血球数と総死亡、心血管事故死亡、がん死亡との関連を明らかにするために、心血管事故の既往のない 6944 名の日本人（男性 2806 名、女性 4138 名）を対象に平均 9.6 年間の追跡調査を行った。各死亡に対する白血球数の相対危険度及び 95%信頼区間は、コックスの比例ハザードモデルを用いて算出した。追跡期間中、604 の死亡（男性 316、女性 288）が観察され、そのうち、168（男性 81、女性 87）が心血管事故死亡、232（男性 124、女性 108）ががん死亡であった。男女合わせた解析では、白血球の増加は総死亡リスクの上昇と関連していた（白血球数 4000-5900 個/mm^3 群を基準とした白血球数 8000-10000 個/mm^3 群の相対危険度：95%信頼区間、1.33：1.04-1.70)。性別の解析では、女性において白血球数が増加するほど心血管事故死亡リスクが有意に上昇する傾向がみられた（傾向性検定 p 値＝0.048、白血球数 4000-5900 個/mm^3 群を基準とした白血球数 8000-10000 個/mm^3 群の相対危険度：95%信頼区間、2.37：1.29-4.36)。さらに興味深いことに、白血球数の減少ががん死亡リスクの上昇と有意に関連していた（白血球数 4000-5900 個/mm^3 群を基準とした白血球数 4000 個/mm^3 未満群の相対危険度：95%信頼区間、2.15：1.07-4.31)。男性では、ともに関連は認められなかった。これらの結果は、白血球数の死亡予測因子として有用性を示唆している。

はじめに

白血球数は炎症マーカーとして広く周知されているが、白血球数の増加が心血管事故危険因子例えば喫煙、肥満、高血圧・糖尿病・脂質異常を含む代謝異常と関連するとの報告がある。さらには、白血球数の増加している人では、虚血性心疾患、脳卒中、総死亡のリスクが高いとの報告もある。また、がんとの関連においても、白血球数の増加が発生リスクを高めるとの報告がある。しかしながら、これらの報告は、欧米人を対象としたものが殆どであり、生活習慣、体格の違う日本人での報告はない。特に、生活習慣の中でも、喫煙率の差は顕著であり、欧米人と比して日本人男性の喫煙率は高く、逆に女性の喫煙率は低い（男性・女性の喫煙率：日本、52.3%・13.4%；米国、25.7%・21.5%、英国、27.0%・26.0%、フランス、38.6%・30.3%)。上述したように、喫煙、肥満は白血球数と強く関連しており、白血球数と死亡リスクとの関連を確固たるものにするためには、背景が違う日本人において検証する必要がある。そこで、我々は、日本全域から形成されたコホート集団である NIPPON DATA90 を用いて、白血球数と総死亡、心血管疾患死亡、がん死亡リスクとの関連について検討した。

方法

対象集団

NIPPON DATA90 に関する詳しい内容は、他の報告を参照していただきたい。NIPPON DATA90 では、1990 年、日本全国 300 地域から 30 歳以上の男女 10956 名が登録された。そのうち健診成績、血液検査成績、生活習慣のアンケートが得られ、2000 年 11 月まで追跡された人は、8384 名（男性 3504 名、女性 4880 名）であった。今回の検討では、結果を確かなものにするため、以下の基準に当てはまる者を対象から除外した：脳卒中の既往歴（159 名）、冠血管疾患の既往歴（230 名）、生活習慣に関する検討項目あるいは身長・体重の欠損（122 名）、臨床的に明らかに炎症が存在すると考えられる白血球数が 10000 個/mm^3 を越える人（306 名）。最終的に、1440 名が除外され、研究対象者は 6944 名（男性 2806 名、女性 4138 名）となった。

検査項目

非凝固剤を含んだ非空腹時の血液を室温で保存した後、自動血球計数装置にて白血球数（100 個/mm^3 単位）を計測した。

統計解析

対象者を白血球数にしたがって、白血球数 4000 個/mm^3 未満、4000 個/mm^3 以上 6000 個/mm^3 未満、6000 個/mm^3 以上 8000 個/mm^3 未満、8000 個/mm^3 以上 10000 個/mm^3 以下の 4 群に分けた。今回特に、我々は白血球数が少ない場合の影響を検討するため、4000 個/mm^3 未満の群を作った。

先ず、白血球数 4 群間で、交絡要因と考えられる年齢、BMI、喫煙状況、飲酒状況、運動習慣、高血圧の病歴、糖尿病の病歴、脂質異常症の病歴を比較した。次に、コックスの比例ハザードモデルを用いて総死亡、心血管事故死亡、がん死亡に対する相対危険度（RR）と 95%信頼区間（95%CI）を算出した。観察期間は、生存者は最終確認日をもとに算出し、死因別の解析では他の要因で死亡した人はその死亡日を最終確認日とした。相対危険度と 95%信頼区間は、白血球数 4000 個/mm^3 以上 6000 個/mm^3 未満群を基準とし、調整要因として年齢（連続数）、性（男、女）、BMI（連続数）、喫煙状況（現喫煙、過去喫煙、喫煙経験無し）、飲酒状況（現飲酒、過去飲酒、飲酒経験なし）、運動習慣（有、無）、高血圧の病歴（有、無）、糖尿病の病歴（有、無）、脂質代謝異常症の病歴（有、無）を用いた。上記の解析を、全対象者と男女別に行った。さらに、観察期間が 1 年未満の者を除外して同様の解析を行った。

全ての統計解析には、SPSS　11.0 を使用し、p 値が 0.05 未満を統計学的に有意と判断した。

結果

観察開始時の平均年齢±標準偏差は52.5±13.6歳であった（男性53.1±13.4歳、女性）。白血球数は女性に比して男性が有意に多かった（男性：6770±1471個/mm^3、女性：6700±1413個/mm^3）。

表1に白血球数群別の観察開始時における対象者の特性を示す。白血球数減少群に比して、増加群は年齢が低く、BMIが高く、喫煙者が多かった。現在飲酒している者も白血球数が増加していた。

総観察人年は66523人年（男性26520人年、女性40003人年）、平均観察期間は9.6年（男性9.5年、女性9.7年）であった。観察期間中、604の死亡が確認され、そのうち168（28%）が心血管事故死、232（38%）ががん死であった。

表2に白血球数と総死亡との関連を示す。対象者全体では、多要因調整後の相対危険度に傾向性は認められなかったものの、白血球数最多群（8000個/mm^3以上10000個/mm^3以下）は有意に高い死亡リスクを有していた（RR、95%CI=1.33、1.04-1.70）。白血球数と総死亡との関連には男女差が認められ、男性では関連が認められなかったが、女性では白血球数最多群（8000個/mm^3以上10000個/mm^3以下）が基準群に比して有意に高い死亡リスクを有していた（RR、95%CI=1.51、1.02-2.24）。また、女性では、白血球数最少群（4000個/mm^3未満）も高いリスクを有する傾向がみられた（RR、95%CI=1.30、0.81-2.10）。即ち、女性では白血球数と総死亡リスクにJ字形の関連が認められた。

表3に白血球数と心血管事故死亡との関連を示す。全体では、白血球数最多群が高い心血管事故死亡リスクを有する傾向がみられたが、統計学的には有意ではなかった（RR、95%CI=1.49、0.96-2.33）。男女別の検討では、女性において白血球数が多いほど心血管事故死亡リスクが有意に上昇する傾向がみられた（白血球数が少ない群から順に、RR：95%CIは0.89：0.38-2.49、1.00、1.01：0.62-1.65、2.37：1.29-4.36、傾向性検定p値＝0.048）。男性では関連は認められなかった。

表4に白血球数とがん死亡との関連を示す。全対象者では関連が認められなかったが、性別の分析では白血球数最少群が有意に高いがん死亡リスクを有していた（RR、95%CI=2.15、1.07-4.31）。男性では関連は認められなかった。

観察期間が1年未満の対象者を除いても白血球数と総死亡、心血管事故死亡、がん死亡リスクとの関連は上述と同様であった。

考察

日本人を対象とした本研究においても、白血球数増加は総死亡リスクの上昇と関連していた。そして、その関連は女性において顕著であった。加えて、白血球数減少も女性において総死亡リスクの上昇と関連しているようだった。興味深いことに、この白血球数と総死亡リスクとのJ字形の関連は、白血球数減少とがん死亡リスク上昇との関連と白血球数増加と心血管死亡リスク上昇との関連から成り立っていた。これら

の関連は何れも喫煙状況や肥満と独立していた。

先ず、本研究においては何故女性のみで関連が認められたのかを考える必要がある。その理由として、喫煙は白血球数と強い正の関連を示すことから、日本人における喫煙率の男女差が関わっているのではないかと推測される。本研究の対象者では、現在喫煙している人の割合は、男性 54.2%、女性 8.7%と大きな違いがあり、この男性の喫煙率は、白血球数と死亡リスクとの関連を報告した過去の欧米での研究対象者に比して高率である。韓国も日本同様男性の喫煙率は高いが、Jee ら [1] は喫煙状況で層別化した結果、白血球数と死亡リスクとの正の関連は喫煙者より非喫煙者で強く認められたと報告している。残念ながら、本研究では死亡例が少なかったため、層別化の解析は行えなかったが、喫煙率の高さが本来の関連を修飾している可能性がある。

本研究では、白血球数増加と総死亡リスクとの正の関連が女性において強く観察されたが、過去に性別に検討あるいは女性のみを対象とした研究は少ない。Jee ら [1]、Mergolis ら [2]、Leng ら [3] の 3 つの報告のみが白血球数増加と総死亡リスクとの正の関連を報告している。白血球数は急性あるいは慢性の炎症性刺激に対する宿主の反応として知られているが、本研究では高血圧、糖尿病、脂質代謝異常などの慢性疾患を考慮しても、白血球数増加と総死亡リスクとの正の関連が観察された。また、白血球数が 10000 個/mm^3 を越える明らかに炎症を有すると考えられる者は対象者から除いたことから、正常域での白血球数増加は他の要因と独立して死亡リスクと関連している可能性が示唆された。また、下記に示すように、この関連の一部は白血球数増加と心血管事故死亡リスクとの正の関連に因るものかもしれない。

本研究では、日本人女性において、白血球数増加は心血管事故死亡の独立した予測因子であった。女性を対象とした研究は男性に比して少ないが、幾つか過去に報告がある。The first National Health and Nutrition Examination Survey (NHANES I) では、8100 個/mm^3 以上の白血球を有する白人女性は、6600 個/mm^3 以下の女性と比べて有意に冠血管疾患罹患リスクが高かった (RR、95%CI=1.31、1.05-1.63)。[4] しかしながら、脳卒中との関連は示されなかった。[5] NHANES II においても、3 分位で最高位の白血球数 (7700-18400 個/mm^3) を有する女性は、最下位の群 (2200-6000 個/mm^3) に比して有意に高い冠血管事故死亡リスクを示した (RR、95%CI=1.7、1.1-2.6)。[6] 脳卒中死亡に関しても、最高位の白血球数(8200 個/mm^3 以上)を有する女性は最下位の群(5700 個/mm^3 未満) 比して有意に高いリスクを示した (RR、95%CI=2.7、1.4-5.0)。[7] The Women's Health Initiative Observational Study (WHI-OS)では、最高位の白血球数 (6710-15000 個/mm^3) を有する女性は最下位の群 (2500-4700 個/mm^3) 比して有意に高い冠血管疾患 (RR、95%CI=2.367、1.51-3.68)、脳卒中 (RR、95%CI=1.46、1.17-1.81)、心血管事故 (RR、95%CI=1.47、1.26-1.72) 罹患リスクが示された。[2] この研究では、心血管事故罹患リスクに関して、白血球数が 4 分位の最高位である 6710 個/mm^3 以上で閾値効果が認められた (白血球数 4 分位値の低い順に RR は、1.00(基準)、1.01、1.12、

1.47)。同様な関連が本研究でも観察された（白血球数の少ない順に RR は、0.89、1.00(基準)、1.01、2.37)。

白血球が心血管事故の病態に直接関与しているのか、あるいは原因となる要因の単なるマーカーなのかは分からない。本研究において、心血管事故の危険因子を調整しても尚両者の間に関連が見られたことは、因果関係を示唆する結果かもしれない。白血球と心血管事故を繋ぐ病態としては、白血球の血液動態に対する影響、血管内皮細胞へ接着することによる内皮への障害、NO 産生や蛋白分解酵素による内皮への障害などが考えられる。このことから、健常人における白血球数は動脈硬化形成の兆候であり、それ故に心血管事故の予測が可能であるのかもしれない。

我々が知る限り、本研究は、白血球減少とがん死亡リスクとの関連を報告した初めての研究である。我々は、過去の他のどの研究よりも少ない白血球数の群（4000 個/mm^3 未満）を作り、同群の女性が白血球数 4000 個/mm^3 以上 6000 個/mm^3 未満の群の女性に比して高いがん死亡リスクを有することを見出した。この結果を支持する報告として、白血球分画と死亡リスクとの関連を検討した報告がある。Huang ら[8] は 19—61 歳の台湾女性を対象にリンパ球数が少ない女性はがんの死亡リスクが高いと報告している。また、Leng ら[3] と Izaks[9] らは、リンパ球数が少ない高齢女性は総死亡リスクが高いと報告している。免疫能の低下が原因として推測されるが、白血球減少とがん死亡リスクとの関連についてはさらに研究が必要であろう。

本研究の最たる限界点としては、一度きりの測定である白血球数を用いて死亡リスクとの関連を検討していることである。しかし、白血球数を経年測定し、その変化が将来の死亡予測に対してより正確で詳しい情報を供するのであれば、今回の我々の結果は本来の関連を過小評価していることになる。その他には、分画がないこと、症例数が少なく部位別の心血管事故やがん死亡との関連が検討できなかったことなどが限界点として挙げられる。

結論

本研究では、日本人においても白血球数の増加は総死亡と心血管事故死亡の独立した予測因子であり、その関連は女性において顕著であった。さらに、白血球の少ない女性（4000 個/mm^3 未満）ではがん死亡リスクが高かった。白血球数は測定も標準化されている上、広く健診や臨床でも測定されており、コストも安い検査である。それ故に、我々は白血球の持つ生理学的意義に着目し、予防や臨床の分野で白血球数を死亡予測因子として活用すべきである。

文献

1. Jee SH, Park JY, Kim HS, Lee TY, Samet JM. White blood cell count and risk for all-cause, cardiovascular, and cancer mortality in a cohort of Koreans.

Am J Epidemiol 2005;162:1062-1069.

2. Margolis KL, Manson JE, Greenland P, Rodabough RJ, Bray PF, Safford M, et al. Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. Arch Intern Med 2005;165:500-508.
3. Leng SX, Xue QL, Huang Y, Ferrucci L, Fried LP, Walston JD. Baseline total and specific differential white blood cell counts and 5-year all-cause mortality in community-dwelling older women. Exp Gerontol 2005;40:982-987.
4. Gillum RF, Ingram DD, Makuc DM. White blood cell count, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. Am Heart J 1993;125:855-863.
5. Gillum RF, Ingram DD, Makuc DM. White blood cell count and stroke incidence and death. The NHANES I epidemiologic follow-up study. Am J Epidemiol 1994;139:894-902.
6. Brown DW, Giles WH, Croft JB. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. J Clin Epidemiol 2001;54:316-322.
7. Brown DW, Ford ES, Giles WH, Croft JB, Balluz LS, Mokdad AH. Associations between white blood cell count and risk for cerebrovascular disease mortality: NHANES II Mortality Study, 1976-1992. Ann Epidemiol 2004;14:425-430.
8. Huang ZS, Chien KL, Yang CY, Wang CH, Chang TC, Chen CJ. Peripheral differential leukocyte counts and subsequent mortality from all diseases, cancers, and cardiovascular diseases in Taiwanese. J Formos Med Assoc 2003;102:775-781.
9. Izaks GJ, Remarque EJ, Becker SV, Westendorp RG. Lymphocyte count and mortality risk in older persons. The Leiden 85-Plus Study. J Am Geriatr Soc 2003;51:1461-1465.

表1. 白血球数別の対象者の特性

	白血球数（個/mm^3）				差のp値
	<4000	4000-5900	6000-7900	8000-10000	
男性					
人数	43	835	1264	664	
年齢：平均（標準偏差）	61.6 (14.6)	55.8 (142)	52.8 (13.0)	50.0 (12.5)	<0.001
Body mass index (kg/m^2	21.7 (2.78)	22.5 (2.91)	23.1 (2.97)	23.3 (3.12)	<0.001
喫煙状況					
喫煙経験なし（%）	48.8	30.3	20.9	11.3	<0.001
過去に喫煙（%）	18.6	30.2	24.8	15.4	
現在喫煙（%）	32.6	39.5	54.3	73.3	
飲酒状況					
飲酒経験なし（%）	34.9	35.4	34.5	34.0	<0.05
過去に飲酒（%）	11.6	7.9	5.1	4.8	
現在飲酒（%）	53.5	56.6	60.5	61.1	
定期的な運動あり	16.3	26.0	22.7	19.0	<0.05
病歴					
高血圧（%）	32.6	20.0	21.4	21.1	0.25
糖尿病（%）	11.6	6.2	6.6	5.0	0.24
脂質代謝異常（%）	0.0	4.0	7.4	5.7	<0.01
女性					
人数	158	1723	1756	501	
年齢：平均（標準偏差）	57.0 (14.8)	53.4 (13.8)	50.9 (13.6)	49.0 (13.2)	<0.001
Body mass index (kg/m^2	22.1 (2.92)	22.6 (3.18)	23.0 (3.27)	23.2 (3.47)	<0.001
喫煙状況					
喫煙経験なし（%）	93.7	91.8	88.0	80.0	<0.001
過去に喫煙（%）	1.9	2.6	2.6	2.0	
現在喫煙（%）	4.4	5.6	9.4	18.0	
飲酒状況					
飲酒経験なし（%）	96.8	92.7	92.6	91.6	0.39
過去に飲酒（%）	0.0	1.1	0.8	1.0	
現在飲酒（%）	3.2	6.2	6.6	7.4	
定期的な運動あり	19.6	18.8	18.5	19.0	0.98
病歴					
高血圧（%）	24.1	20.5	20.7	18.6	0.49
糖尿病（%）	1.3	4.0	3.2	3.0	0.21
脂質代謝異常（%）	5.1	7.4	7.9	4.4	<0.05

表2. 白血球数と総死亡リスクとの関連

観察開始時の白血	死亡数	人年	年齢調整相対危険度	多要因調整相対危険度*
全体				
<4000	30	1857	1.10 (0.75-1.61)	1.13 (0.77-1.65)
4000-5900	242	24403	1.00 (基準)	1.00 (基準)
6000-7900	235	29118	1.12 (0.93-1.34)	1.04 (0.86-1.24)
8000-10000	97	11146	1.63 (1.28-2.06) †	1.33 (1.04-1.70) ‡
傾向性検定p値			0.001	0.118
男性				
<4000	10	374	0.98 (0.51-1.87)	0.92 (0.47-1.76)
4000-5900	121	7736	1.00 (基準)	1.00 (基準)
6000-7900	121	12094	0.91 (0.70-1.17)	0.88 (0.68-1.14)
8000-10000	64	6316	1.34 (0.98-1.82)	1.21 (0.88-1.67)
傾向性検定p値			0.21	0.416
女性				
<4000	20	1482	1.30 (0.81-2.09)	1.30 (0.81-2.10)
4000-5900	121	16667	1.00 (基準)	1.00 (基準)
6000-7900	114	17025	1.26 (0.97-1.63)	1.24 (0.96-1.61)
8000-10000	33	4830	1.60 (1.09-2.36) ‡	1.51 (1.02-2.24) ‡
傾向性検定p値			0.052	0.094

*年齢、性、BMI、喫煙状況、飲酒状況、定期的な運動、高血圧の病歴、糖尿病の病歴、脂質代謝異常の病歴で調整. †p <0.01. ‡p <0.05

表3. 白血球数と心血管事故死亡リスクとの関連

観察開始時の白血	死亡数	人年	年齢調整相対危険度	多要因調整相対危険度*
全体				
<4000	8	1857	0.95 (0.46-1.97)	0.96 (0.46-2.01)
4000-5900	72	24403	1.00 (基準)	1.00 (基準)
6000-7900	58	29118	0.96 (0.68-1.36)	0.89 (0.62-1.26)
8000-10000	30	11146	1.81 (1.18-2.79)†	1.49 (0.96-2.33)
傾向性検定p値			0.052	0.274
男性				
<4000	3	374	1.06 (0.33-3.47)	1.04 (0.31-349)
4000-5900	33	7736	1.00 (基準)	1.00 (基準)
6000-7900	30	12094	0.84 (0.51-1.38)	0.78 (0.47-1.30)
8000-10000	15	6316	1.18 (0.63-2.21)	1.01 (0.53-1.92)
傾向性検定p値			0.900	0.765
女性				
<4000	5	1482	0.97 (0.38-2.45)	0.89 (0.38-2.49)
4000-5900	39	16667	1.00 (基準)	1.00 (基準)
6000-7900	28	17025	1.01 (0.62-1.65)	1.01 (0.62-1.65)
8000-10000	15	4830	2.42 (1.33-4.40)†	2.37 (1.29-4.36)†
傾向性検定p値			0.040	0.048

*年齢、性、BMI、喫煙状況、飲酒状況、定期的な運動、高血圧の病歴、糖尿病の病歴、脂質代謝異常の病歴で調整. †p <0.01.

表4. 白血球数とがん死亡リスクとの関連

観察開始時の白血	死亡数	人年	年齢調整相対危険度	多要因調整相対危険度*
全体				
<4000	10	1857	1.05 (0.54-2.01)	1.13 (0.59-2.18)
4000-5900	90	24403	1.00 (基準)	1.00 (基準)
6000-7900	101	29118	1.23 (0.92-1.63)	1.08 (0.81-1.44)
8000-10000	31	11146	1.26 (0.84-1.91)	0.95 (0.62-1.45)
傾向性検定p値			0.172	0.885
男性				
<4000	0	374	-	-
4000-5900	49	7736	1.00 (基準)	1.00 (基準)
6000-7900	52	12094	0.94 (0.64-1.40)	0.87 (0.58-1.30)
8000-10000	23	6316	1.15 (0.69-1.91)	0.97 (0.57-1.62)
傾向性検定p値			0.26.	0.661
女性				
<4000	10	1482	2.11 (1.05-4.22)†	2.15 (1.07-4.31)†
4000-5900	41	16667	1.00 (基準)	1.00 (基準)
6000-7900	49	17025	1.47 (0.97-2.23)	1.39 (0.91-2.12)
8000-10000	8	4830	1.01 (0.47-2.16)	0.87 (0.40-1.88)
傾向性検定p値			0.983	0.630

*年齢、性、BMI、喫煙状況、飲酒状況、定期的な運動、高血圧の病歴、糖尿病の病歴、脂質代謝異常の病歴で調整. †$p < 0.05$.

日本人の代表集団における循環器疾患死亡に対する心電図左胸部高 R 波によるスクリーニングの有用性；NIPPON DATA90 における 10 年間の追跡による検討

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【 目的 】慢性的な血圧上昇は左室肥大などの高血圧性臓器障害をきたし、これを有するものはハイリスク者として充分な治療が必要なため、スクリーニングで早期に発見する必要がある。血圧による循環器疾患死亡のリスク評価は可能だが、健診における一時点の測定では正確な評価ができない恐れがあり、臓器障害の有無の評価が必要であろう。日本全国から無作為に選ばれた対象集団において、心電図検査によって診断された左室肥大（左高 R 波）が将来の循環器疾患の予測に対してどの程度有用なのかを評価することを試みた。

【 方法 】高血圧未治療で循環器疾患の既往のない日本人 6,688 名（平均年齢 50.7 歳、女性の割合 57%）を 10 年間（1990 年-2000 年）追跡した。左高 R 波の循環器疾患死亡のハザード比を評価した。

【 結果 】心電図左高 R 波（ミネソタ・コード 3-1 または 3-3）は、全対象者 6,688 名中 9.4%、高血圧（収縮期血圧≥140mmHg または拡張期血圧≥90mmHg）者 2,413 名中 14.6%および正常血圧（収縮期血圧<140mmHg かつ拡張期血圧<90mmHg）者 4,275 名中 4.1%に見られた。追跡期間に、128 名の対象者が循環器疾患によって死亡した。収縮期血圧および他の危険因子を調節しても、左高 R 波は循環器疾患死亡の増加と関係があった。全対象者におけるハザード比は 1.88（95%CI, 1.22-2.89）、高血圧者においては 1.97（95%CI, 1.20-3.24）、正常血圧者においては 1.66（95%CI, 0.69-3.98）であった。左高 R 波の循環器疾患死亡に対する集団寄与危険割合は、全対象者において 7.6%、高血圧者において 12.4%、正常血圧者において 4.1%であった。

【 結論 】地域在住の日本人集団において、心電図左高 R 波は収縮期血圧値とは独立して循環器疾患死亡を予測するマーカーとなり得る。一時点の血圧測定によって正常血圧と評価された者の中にも、左室肥大を有すると思われるハイリスク者は存在し、心電図によってその者を同定できることは有用である。健診においては血圧測定だけではなく、 心電図左胸部高 R 波の有無を評価すべきである。

表. 心電図左高R波と循環器疾患死亡の関連（NIPPON DATA90）

	全対象者		高血圧者		正常血圧者	
	心電図左高R波		心電図左高R波		心電図左高R波	
	なし (n=6,061)	あり (n=627)	なし (n=2,060)	あり (n=353)	なし (n=4,001)	あり (n=274)
追跡人年	58,476	5,863	19,509	3,235	38,967	2,629
循環器疾患死亡						
ケース数	105	28	68	22	37	6
死亡率 (/1,000人年)	1.8	4.8	3.5	6.8	0.9	2.3
ハザード比 *	1.00	1.88 (1.22-2.89)	1.00	1.97 (1.20-3.24)	1.00	1.66 (0.69-3.98)
脳卒中死亡						
ケース数	43	12	33	9	10	3
死亡率 (/1,000人年)	0.7	2.0	1.7	2.8	0.3	1.1
ハザード比 *	1.00	1.93 (0.99-3.74)	1.00	1.64 (0.77-3.50)	1.00	3.74 (0.98-14.25)
心臓病死亡						
ケース数	57	16	33	13	24	3
死亡率 (/1,000人年)	1.0	2.7	1.7	4.0	0.6	1.1
ハザード比 *	1.00	2.06 (1.16-3.64)	1.00	2.40 (1.23-4.68)	1.00	1.22 (0.36-4.11)

* 年齢、性、BMI、喫煙、飲酒、糖尿病、高コレステロール血症、収縮期血圧を調整
高血圧： 収縮期血圧≥140mmHg または 拡張期血圧≥90mmHg
正常血圧： 収縮期血圧<140mmHg かつ 拡張期血圧<90mmHg

【 研究成果の公表 】

Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Ueshima H. Electrocardiogram Screening for Left High R-Wave Predicts Cardiovascular Death in a Japanese Community-Based Population: NIPPON DATA90. Hypertens Res (in press).