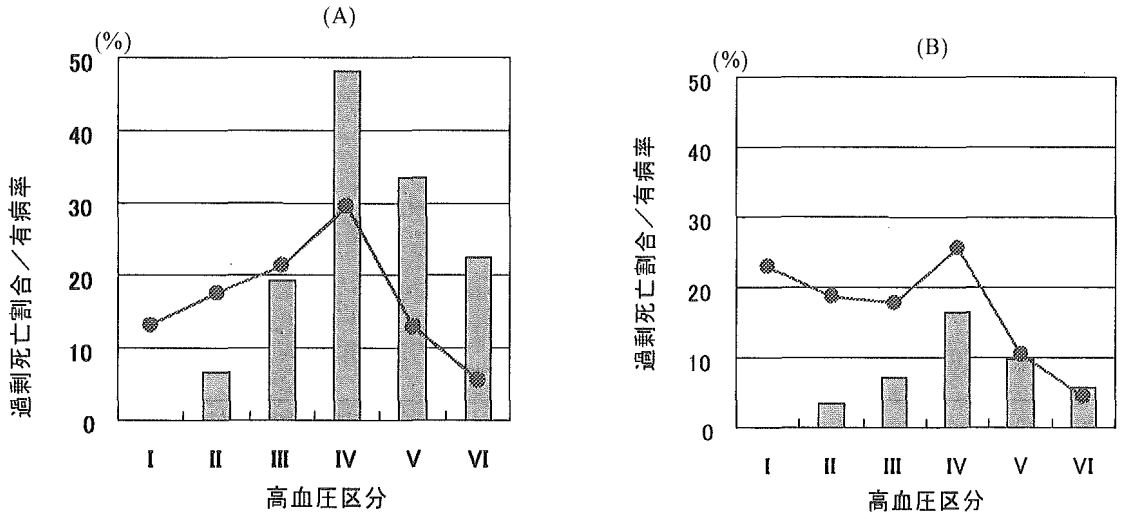
図

最大血圧（SBP）120 mmHg かつ最小血圧（ DBP）<80 mmHg を基準として男性（A）および女性（B）で各群の対象者の有病率（折れ線グラフ）および過剰死亡割合（棒グラフ）を示した。（I: SBP< 120 mmHg and DBP<80 mmHg, II: SBP<130 mmHg and DBP < 85 mmHg, III: SBP<140 mmHg かつ DBP<90 mmHg, IV:SBP<160 mmHg かつ DBP<100 mmHg, V:SBP<180 mmHg かつDBP<110 mmHg, VI: SBP =180 または DBP = 110 mmHg 以上).



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ORIGINAL ARTICLE

# Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese — Nippon data 80

Nippon Data 80 Research Group

The objectives of the study were to clarify the relationship between blood pressure and mortality from stroke, heart disease, cardiovascular diseases and all causes of death among representative population of Japanese and to estimate category-specific excess mortality from stroke due to blood pressure (BP) level. The study design comprised a retrospective cohort study using the 1980 National Survey on Cardiovascular Diseases and identification of underlying causes of death using national vital statistics data. In 1994, a 14-year follow-up cohort study was conducted among participants of the National Survey on Cardiovascular Diseases in 1980, randomly selected from the Japanese population. With a collaboration of 300 public health centres, which had conducted the original survey in 1980, 91.4% of the participants of the original survey could be followed up. Total observed person-years were 53 948 for men and 70 932 for women. During follow-up, 1327 deaths were observed. BP levels were significantly related to mortality from strokes, cardiovascular diseases and all causes of death for both sexes ($P<0.001$). Heart disease mortality was significantly related to BP levels among men ($P<0.05$) while not among women. Estimated excess mortality was 130% for men and 42% for women and chiefly observed among moderate hypertensives (48% for men and 16% for women). In conclusion, high blood pressure was a risk factor for mortality from all causes as well as those from cardiovascular diseases, stroke and heart disease among Japanese. Since the major part of excess mortality was due to mild hypertension, a population strategy to reduce blood pressure should be encouraged.
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Keywords: stroke; retrospective cohort study; blood pressure; Japanese

## Introduction

Japan has low mortality from ischaemic heart disease (IHD) with moderate mortality from stroke and the longest life expectancy in the world. Recent changes in lifestyles may have considerable effects on cardiovascular risk factors. Blood pressure (BP) levels have decreased rapidly and serum cholesterol levels have been increasing.[1,2] Reflecting changes in these risk factors, mortality rates from cardiovascular diseases (CVD) have changed rapidly.[3] During the years from 1969–70 to 1991–92, age-adjusted stroke mortality rate for 30–69 year olds has declined, 77% for men and 78% for women.[4]

Prevalence of risk factors for Japanese are different from those in Western countries, but the relationship of the risk factors to cardiovascular incidence and mortality appears essentially the same as those in Western countries.[5–7] However, since the Japanese data are mainly from small cohorts in rural populations, comprehensive analysis of the effect of risk factors on CVD mortality and mortality from all causes has not been reported from large Japanese populations.

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In 1980, the National Survey on Cardiovascular Diseases was conducted for participants randomly selected from the Japanese population.[8] Since the follow-up study of this representative population will usefully inform the public health policy of Japan, we used these data as the baseline for a retrospective cohort study with the cooperation of 300 public health centres that conducted the National Survey in 1980. We also conducted a survey of activities of daily living of the survivors aged 65 and above at the follow-up in 1994.

We examine the impact of elevated BP on mortality from all causes, CVD, heart disease and stroke.

## Subjects and methods

In the National Survey on Cardiovascular Diseases in 1980, 300 zones were selected using the stratified random sampling method based on the national census in 1975. All residents aged 30 years or more in these zones were invited to this survey. A total of 10 558 participants aged 30 years or more (response rate: 78.5%) were examined with assessment of past and present history of hypertension, stroke and myocardial infarction. Body height and body weight was measured under light clothes and body mass index (BMI) was calculated by body weight (kg) divided by square of body height (m). BP and pulse rates were measured after a 5 min rest by trained public health nurses of each public health centre using a standard mercury sphygmomanometer. Frequency of drinking per week and average number of cigarettes per day were assessed using questionnaires. Serum total cholesterol levels were determined in a laboratory under the quality control programme of the Center for Disease Control in the United States. Casual blood sugar levels were determined in the same laboratory using the deoxidized method. Details of this survey are published elsewhere.[8]

In 1994, we asked the 300 public health centres that took part in the 1980 National Survey to follow-up the original participants by their name and age in 1980, since these were recorded on the participant list. The public health centres reported date of birth, present address and date of death, if dead. We conducted the second follow-up survey for the participants for whom they could not obtain the information ($n=2345$). To identify the participants' address, we used telephone books and residential maps of 1980 stored in the National Library of Parliament. Using this method, we could follow-up 1135 (10.8%) of the original participants.

We requested registration records of the participants in the cities or towns where they lived. If the participants had moved out of the town, we requested their registration record from the cities or towns where they had moved to. We could get information on 9648 participants with a follow-up rate of 91.4%. We found 1327 deaths during the follow-up.

We used computerized vital statistics data to identify the underlying causes of deaths of the participants who died during the follow-up by date of birth, sex, date of death and area code of the place of death with the permission of the Management and Coordination Agency, Japan. Underlying causes of death were assigned centrally from death certificates according to the International Classification of Disease (ICD 9); (Stroke: 430–438, and heart disease: 410–429, CVD 390–459). We could identify the cause of death for 99.5% of the dead participants. Since the observed number of deaths from IHD were small (43 for men and 46 for women), we included these deaths in the heart disease category.

Participants were classified into six BP groups according to JNC-VI[9] (ie, I: SBP < 120 mmHg and DBP < 80 mmHg, II: SBP < 130 mmHg and DBP < 85 mmHg, III: SBP < 140 mmHg and DBP < 90 mmHg, IV: SBP < 160 mmHg and DBP < 100 mmHg, V: SBP < 180 mmHg and DBP < 110 mmHg, VI: SBP = 180 mmHg or more or DBP = 105 mmHg or more). Participants with antihypertensive treatment of SBP < 160 mmHg and DBP < 100 mmHg, of SBP < 180 mmHg and DBP < 110 mmHg and of SBP = 180 mmHg or more or DBP = 110 mmHg were classified into IV, V and VI groups, respectively. Participants with diabetes were assigned by past history of diabetes and/or casual blood sugar = 200 mg/dl or more.

To analyse CVD mortality associations, participants with a past history of myocardial infarction (AMI: $n=45$) or stroke ($n=110$) were excluded. For stroke analyses, participants with a past history of stroke were excluded and for heart disease analyses, participants with a past history of AMI were also excluded.

### Statistical analysis

The person-year method of analysis was used and age-adjusted mortality rates were calculated according to the standard population of Japan in 1985. Age-adjusted relative risks and 95% confidence intervals were calculated using the Mantel–Haenszel procedure. The test for linear trends was used to test the overall relationship of blood pressure to mortality rate using the Cox proportional hazard model adjusting for age.

The Cox proportional hazard model was used to calculate multiadjusted relative risks of a BP category increase controlling for age, BMI, serum total cholesterol, presence of diabetes, smoking category and drinking category and then we calculated multiadjusted attributable risk for each BP category. We calculated percentage excess mortality as the product of the multi-adjusted attributable risk and percentage of the participants in the BP category.

## Results

Overall follow-up rate was 91.4%; the rate was significantly lower in the 30–59 years group (90.1%) than for those of the ⩾60 years group (92.4%, $P<0.05$). The number of participants who moved from the original address during the follow-up was 7.8% (9.1% for 30–59 year group and 4.0% for people 60 years or more, $P<0.05$).

Table 1 shows the baseline characteristics of the participants according to BP levels for both sexes. The number of participants in Group IV was the most frequent for both sexes. Mean ages, SBP, DBP, serum total cholesterol and prevalence of antihypertensive treatment were significantly different among BP groups for both sexes. Prevalence of drinking and smoking was significantly different among BP groups among men while not significant for women.

Table 2 shows the number of deaths and age-adjusted rates per 100 000 person-years for all causes and cause-specific mortality. Total observed person-years were 53 948 for men and 70 932 for women. For both sexes, age-adjusted mortality rates from all causes, CVD, heart disease and stroke, increased with BP levels. The mortality from all causes with severe hypertension (Group VI) was 1406 per 100 000 person-years for men and was similar to those for women (1327 per 100 000 person-years), while that in optimal BP level (Group I) was higher in men (790 per 100 000 person-years) than in women (432 per 100 000 person-years). As with the mortality rate from all causes, most increases in cause-specific mortality with increasing BP levels were clearer among men than in women.

Table 3 shows the relative risks and 95-percent confidence interval of mortality from all causes and specific causes according to BP levels for men and women. Relative risk of death from all causes was significantly higher in Group VI for both sexes than in Group I, the test for linear trend shows significant relationship with BP levels and mortality from all causes for men ($P<0.001$) while not significant among women. Relative risk of mortality from CVD, heart disease and stroke increased significantly with BP levels among men. In women, the relative risk of CVD and stroke death similarly increased with BP levels. However, the relationship of heart disease mortality with BP levels was not clear.

Table 4 shows the results of multiadjusted relative risk of a one-level increase of WHO category controlled for age, BMI, smoking habits, drinking habits, serum total cholesterol and presence of diabetes. For both sexes, BP levels were significantly related to mortality from all causes, CVD and stroke. However, the relationship of BP levels to heart disease mortality was different. For men, the relative risk for heart disease was significantly related to BP levels, while not among women.

These data show that elevated blood pressure is an independent risk factor for mortality from all causes as well as from cardiovascular diseases for

**Table 1** Baseline characteristics of participants according to BP categories

| | *I* | *II* | *III* | *IV* | *V* | *VI* | |
|---|---|---|---|---|---|---|---|
| *Men* | | | | | | | |
| No | 560 | 742 | 906 | 1256 | 543 | 238 | |
| Age (year) | 44.5 (10.9) | 45.1 (11.3) | 47.4 (12.4) | 54.0 (12.5) | 58.3 (13.0) | 60.4 (12.3) | ** |
| SBP (mmHg) | 110.8 (5.7) | 122.8 (3.7) | 131.7 (4.9) | 145.0 (7.9) | 163.7 (8.2) | 188.1 (15.3) | ** |
| DBP (mmHg) | 69.7 (7.1) | 75.7 (6.3) | 81.2 (7.3) | 87.3 (8.6) | 95.7 (10.0) | 103.2 (13.4) | ** |
| BMI (kg/m$^2$) | 21.6 (2.7) | 22.2 (2.7) | 22.5 (2.8) | 22.8 (2.8) | 22.9 (2.9) | 22.9 (3.2) | ** |
| Serum cholesterol (mg/dl) | 181.0 (31.7) | 182.8 (31.7) | 186.9 (31.4) | 188.2 (33.4) | 188.8 (34.3) | 186.9 (36.3) | ** |
| Drinking (%) | 39.5 | 41.6 | 45.4 | 51.0 | 53.8 | 61.4 | ** |
| Smoking (%) | 65.5 | 67.1 | 65.4 | 60.6 | 57.6 | 58.6 | ** |
| Diabetes (%) | 3.6 | 3.9 | 3.2 | 6.3 | 8.1 | 8.0 | ** |
| Antihypertensive treatment (%) | 0.0 | 0.0 | 0.0 | 15.7 | 31.3 | 32.4 | ** |
| *Women* | | | | | | | |
| No | 1245 | 1014 | 967 | 1385 | 564 | 218 | |
| Age (year) | 43.1 (10.8) | 45.9 (11.8) | 49.0 (11.6) | 57.1 (11.8) | 61.1 (11.5) | 62.8 (11.2) | ** |
| SBP (mmHg) | 109.4 (6.6) | 122.9 (3.4) | 131.9 (4.3) | 144.5 (8.0) | 165.4 (6.2) | 189.3 (14.4) | ** |
| DBP (mmHg) | 68.1 (7.2) | 74.7 (6.7) | 80.5 (6.8) | 84.7 (8.2) | 92.1 (9.7) | 100.8 (14.8) | ** |
| BMI (kg/m$^2$) | 21.7 (2.9) | 22.2 (3.0) | 23.0 (3.2) | 23.6 (3.5) | 23.9 (3.6) | 24.7 (3.9) | ** |
| Serum cholesterol (mg/dl) | 181.4 (31.5) | 184.2 (31.2) | 191.2 (35.0) | 198.2 (33.4) | 201.0 (35.1) | 205.7 (34.7) | ** |
| Drinking (%) | 2.7 | 2.5 | 2.4 | 3.2 | 3.9 | 1.8 | NS |
| Smoking (%) | 9.7 | 9.5 | 6.5 | 9.0 | 9.0 | 9.1 | NS |
| Diabetes (%) | 0.8 | 1.6 | 2.1 | 4.3 | 3.7 | 6.8 | ** |
| Antihypertensive treatment (%) | 0.0 | 0.0 | 0.0 | 23.8 | 35.8 | 52.8 | ** |

**Significantly different among BP categories ($P<0.01$), NS: not significant.
I: SBP<120 mmHg and DBP<80 mmHg, II: SBP<130 mmHg and DBP<85 mmHg, III: SBP<140 mmHg and DBP<90 mmHg, IV: SBP<160 mmHg, DBP<100 mmHg, V: SBP<180 mmHg and DBP<110 mmHg, VI: SBP=180 mmHg or more or DBP=105 mmHg or more. Participants with antihypertensive treatment of SBP<160 mmHg and DBP<100 mmHg, of SBP<180 mmHg and DBP<110 mmHg and of SBP=180 mmHg or more and DBP=110 mmHg were classified into IV, V and VI groups, respectively.

**Table 2** Person-years, mortalty numbers and age-adjusted mortality rate (per 10000 person-years) according to base-line SBP and DBP levels for deaths from all causes, CVD, heart disease and stroke by 14-year follow-up of the participants of National Survey on Cardiovascular Diseases in 1980 (Nippon Data 80)

| | *Total* | *I* | | *II* | | *III* | | *IV* | | *V* | | *VI* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *No.* | *rate* | *No.* | *rate* | *No.* | *rate* | *No.* | *rate* | *No.* | *rate* | *No.* | *rate* |
| *Men* | | | | | | | | | | | | | |
| *Person-years* | 53948 | *6516* | | *10772* | | *10379* | | *16176* | | *6844* | | *3261* | |
| All causes | | 34 | (790) | 60 | (770) | 99 | (1071) | 219 | (877) | 139 | (1083) | 98 | (1406) |
| CVD | | 3 | (79) | 15 | (208) | 33 | (374) | 77 | (310) | 64 | (474) | 40 | (622) |
| Heart disease | | 1 | (11) | 9 | (111) | 16 | (195) | 39 | (158) | 27 | (220) | 18 | (249) |
| Stroke | | 2 | (67) | 5 | (77) | 15 | (162) | 34 | (135) | 34 | (233) | 22 | (372) |
| *Women* | | | | | | | | | | | | | |
| *Person-years* | 70932 | *15711* | | *14716* | | *11880* | | *18501* | | *7266* | | *2858* | |
| All causes | | 44 | (432) | 72 | (586) | 60 | (448) | 227 | (671) | 114 | (667) | 75 | (1327) |
| CVD | | 13 | (151) | 29 | (265) | 16 | (131) | 91 | (243) | 59 | (390) | 35 | (737) |
| Heart disease | | 8 | (85) | 17 | (144) | 9 | (69) | 40 | (104) | 33 | (160) | 13 | (187) |
| Stroke | | 3 | (45) | 12 | (120) | 6 | (53) | 44 | (122) | 24 | (223) | 18 | (513) |

I: optimal BP, II: normal BP, III: high normal BP, VI: mild hypertension, V: moderate hypertension, VI: severe hypertension.

**Table 3** Age-adjusted relative risk and 95 percent confidence interval for deaths from all causes, CVD, heart disease and stroke according to BP categories by Mantel–Haenszel method for 14-year follow-up of the participants of National Survey on Cardiovascular Disease in 1980. *P*-values of the test for linear trends were calculated using the Cox proportional hazard model

| | *I* | *II* | *III* | *IV* | *V* | *VI* | P |
|---|---|---|---|---|---|---|---|
| *Men* | | | | | | | |
| All causes | 1 | 1.01 (0.66–1.53) | 1.21 (0.82–1.79) | 1.07 (0.74–1.56) | 1.38 (0.95–2.00) | 1.63 (1.06–2.51) | <0.001 |
| CVD | 1 | 2.80 (0.87–9.05) | 3.97 (1.32–11.94) | 3.88 (1.30–11.63) | 6.65 (2.49–17.73) | 7.66 (2.71–21.70) | <0.001 |
| Heart disease | 1 | 5.25 (0.83–33.01) | 6.38 (0.88–46.26) | 7.68 (1.07–55.23) | 19.27 (2.86–130.00) | 32.28 (3.14–332.00) | 0.024 |
| Stroke | 1 | 1.36 (0.27–6.82) | 2.62 (0.68–10.11) | 2.27 (0.60–8.63) | 3.70 (1.11–12.28) | 4.69 (1.42–15.50) | <0.001 |
| *Women* | | | | | | | |
| All causes | 1 | 1.33 (0.92–1.93) | 1.11 (0.75–1.63) | 1.58 (1.15–2.18) | 1.40 (0.97–2.03) | 2.36 (1.62–3.45) | 0.076 |
| CVD | 1 | 1.73 (0.91–3.29) | 0.92 (0.44–1.92) | 1.82 (1.03–3.20) | 2.17 (1.23–3.85) | 3.22 (1.86–5.60) | 0.005 |
| Heart disease | 1 | 1.62 (0.70–3.72) | 0.87 (0.35–2.18) | 1.23 (0.58–2.61) | 1.94 (0.89–4.24) | 1.87 (0.77–4.53) | 0.24 |
| Stroke | 1 | 3.00 (0.95–9.44) | 1.28 (0.32–5.14) | 3.48 (1.29–9.34) | 3.28 (1.30–8.26) | 6.06 (2.80–13.12) | 0.004 |

I: optimal BP, II: normal BP, III: high normal BP, VI: mild hypertension, V: moderate hypertension, VI: severe hypertension.

**Table 4** Multivariate-adjusted relative risk (RR) and 95% confidence interval (95% CI) with one-level increase of WHO category (I: optimal BP, II: normal BP, III: high normal BP, VI: mild hypertension, V: moderate hypertension, VI: severe hypertension) for mortality from all causes CVD, heart disease and stroke[a]

| | *Men* | | *Women* | |
|---|---|---|---|---|
| | *RR* | *(95% CI)* | *RR* | *(95% CI)* |
| All causes | 1.16 | (1.09–1.23) | 1.09 | (1.03–1.17) |
| CVD | 1.37 | (1.23–1.52) | 1.18 | (1.07–1.31) |
| Heart disease | 1.29 | (1.11–1.51) | 1.12 | (0.97–1.28) |
| Stroke | 1.45 | (1.24–1.69) | 1.27 | (1.09–1.49) |

[a]A multivariate proportional hazard model (Cox) was used to adjust for age, BMI, serum total cholesterol, DM status, smoking category and drinking category.

both sexes. Figure 1a and b show the percentage of excess stroke mortality (bar) calculated by multi-adjusted relative risks (Table 4) and the prevalence of participants in the 1980 survey (lines) in each BP category for men and for women. The overall percentages of excess mortality of elevated BP

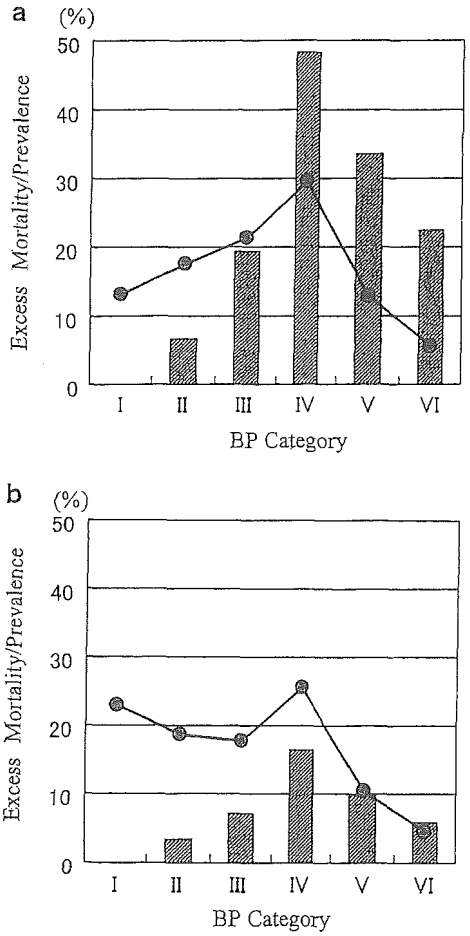


**Figure 1** Prevalence of participants (line) according to SBP levels in 1980 survey and estimated percentage excess mortality from stroke (Bar) using multivariate-adjusted relative risks considering the less than 120 mmHg SBP and DBP <80 mmHg (group I) as the reference among men (a) and women (b) (I: SBP<120 mmHg and DBP<80 mmHg, II: SBP<130 mmHg and DBP<85 mmHg, III: SBP<140 mmHg and DBP<90 mmHg, IV: SBP<160 mmHg and DBP<100 mmHg, V: SBP<180 mmHg and DBP<110 mmHg, VI: SBP=180 mmHg or more or DBP=105 mmHg or more). Participants with antihypertensive treatment of SBP<160 mmHg and DBP<100 mmHg, of SBP<180 mmHg and DBP<110 mmHg and of SBP=180 mmHg or more or DBP=110 mmHg were classified into IV, V and VI groups, respectively.

considering the group I (optimal BP level) as reference group were 130% for men and 42% for women. Although relative risk was highest in the group VI (severe hypertension), the prevalence of this BP group was only 5.6% for men and 4.5% women. Thus, estimated excess stroke mortality was chiefly due to the group IV (mild hypertension) for both sexes: 48% for men and 16% for women.

## Discussion

### Major findings from this study

This is the follow-up study in Japan using the participants randomly selected in 300 districts throughout Japan in 1980 (NIPPON DATA 80). We analysed the comprehensive effect of elevated BP on mortality from stroke, heart disease, CVD and all causes of death using BP categories according to *JNC-VI*.[9] For men, elevated BP level was an independent risk factor for mortality from all causes as well as CVD, heart disease and stroke mortality before and after controlling for other major cardiovascular risk factors. For women, a significant relationship of BP levels to mortality from all causes, CVD and stroke was also observed but not for heart disease.

In the analysis of excess stroke mortality according to BP levels, the major contribution was from the group IV (mild hypertension) for both sexes rather than from the highest BP group. The prevalence of hypertension was much lower than that in 1965 survey (15% for men and 14% for women).[1]

The observed relationships of elevated BP to CVD and stroke mortality are consistent with other studies.[5,7,10–14] The relative risks are relatively smaller than those from other studies in Japan.[5,7,14] These differences may be explained by the difference of the age of the target population, since this study includes older participants who are 80 years and above with smaller relative risk than the younger generation.

### Design of this study

Although well-designed cross-sectional surveys can be used for the baseline data for the follow-up study, it is difficult to perform the follow-up with a high performance rate after 14 years. At the beginning of this study, we had information only on name, age and sex for the participants of the National Survey on Cardiovascular Disease in 1980. However, with the cooperation of most of the 300 public health centres involved in the original survey in 1980, we could get the date of birth, present address and, if the person was dead, date and place of death for most of participants. We also used computerized telephone lists in 1994, telephone books and residential maps in 1980 to get more information on the participants. In this study, we had a high follow-up rate (91.4%) and could specify the underlying causes of deaths in 98.3% of participants.

Since the original survey in 1980 was not designed for follow-up, several limitations should be kept in mind in interpreting the results. Risk factors were only observed once at the baseline survey, and changes in lifestyles or risk factor levels were not considered. Therefore, the risk of high blood pressure may be underestimated. We conducted a cause-specific mortality-based study using centrally coded national vital statistic data, which was not validated. This may also reduce the relationship between risk factors and disease occurrence since nonspecific causes occasionally appear on the death certificate.[15]

Our study design is a retrospective cohort study and some deaths in the early stage of the follow-up period may have been missed since the residential record is usually discarded 5 years after death or moving out. However, the follow-up rate was significantly higher in those who were 60 years or above in 1980 than those under 60 years reflecting the high moving out rate among the younger age group. Thus, loss of follow-up seems to be due to moving from the original address rather than to death in the early follow-up period. Moreover, mortality was similar in the Japanese population and the influence of loss of follow-up seems to be minimal.

The treatment rates with anti-hypertensive drugs among participants with hypertension (SBP $\geqslant$ 160 mmHg or DBF $\geqslant$ 95 mmHg or with anti-hypertensive treatment) were 45% for men and 57% for women.[8] Since BP may change with treatment and the same BP level with or without treatment may not imply the same mortality rate, the observed relationship between BP levels and mortality may be diluted, especially in women.

### Effect of elevated BP on heart disease mortality

In this study, we used heart disease mortality as a category to estimate the overall effect of elevated BP on heart-related mortality since IHD mortality numbers were very small for both sexes. Since mortality from heart disease includes other non specific causes (ie, mortality from heart failure), the observed relationships may be diluted. Among men, the relationship of SBP levels to heart disease mortality was significant before and after adjustment of other risk factors, in good agreement with other reports on IHD incidence in Japan.[5,6,16]

However, among women, no significant relationship was observed between elevated BP and mortality from heart disease. The percentage of heart failure in the heart disease was 70% in women (1987) while 66% among men (1987) in Japan, and this high percentage of nonspecific causes among women may be related to the lack of a relationship of elevated BP to heart disease mortality among women.[4]

### Public health implication

Mortality from stroke among Japanese has decreased by 80% during the last 30 years with the continuous decline of BP levels and has now reached moderate rates. Their decline may be due to changes in lifestyles such as reduction in salt intake[3] as well as an increasing treatment rate among hypertensives.[8,17] As shown in this report, elevated BP is still one of the leading causes of death among Japanese, while the impact of high BP shown in this study may be overestimated because of continuous declining trends after this baseline survey.[2,3]

Excess stroke mortality due to elevated BP is still high and efforts to reduce the BP level among Japanese should continue. Since mild hypertension is a major source of excess stroke death (Figure 1), lifestyle modification should be emphasized for the whole population. We should also pay more attention to reducing other risk factors such as smoking and the continuing increase of serum total cholesterol levels among Japanese.[18]

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研究成果の要約

喫煙習慣の全死因、がん、肺がん死亡への影響に関する研究: NIPPON DATA80

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2003;57:669-673.

【目　的】我が国における喫煙とがん、肺がんとの関係を、全国的な前向き研究で明らかにしたものは平山ら1)による厚生省コホート研究しかなく、他の研究によりこの関係を示すデータはなかった。今回は、1980 年に厚生省により実施された循環器疾患基礎調査の対象者約 1 万人を基に 14 年間追跡調査し、追跡結果より喫煙状況と前死因、がん、肺がんによる死亡との関係を分析した。
【方　法】対象は、1980 年に厚生省により実施された第 4 回循環器疾患基礎調査客体を追跡対象とした。調査客体は同年度国民栄養調査対象者 10,546 人であった。本調査では 1980～1999 年 11 月に追跡できた対象者について、全死亡者、がん死亡者、肺がん死亡者における喫煙状況(非喫煙、禁煙、現在喫煙、現在喫煙については 1 日の平均喫煙本数別に分類)別 10 万人年あたりの年齢調整死亡率を求めた。追跡人年および死亡数を 5 歳階級ごとに計算し直接法による年齢調整を行った。さらに、比例ハザードモデルにより年齢、飲酒習慣及び BMI などを調整した相対危険度(95%信頼区間)及び傾向性の検定結果を求めた。計算された相対危険度と本研究対象者の喫煙状況を基に、各疾患(全死因、全がん、肺がん)による死亡者のうち、現在喫煙者が禁煙に転じた場合に、社会全体に起こる各疾患による死亡を予防できる割合：人口寄与割合(PAF: population attributable fraction)を求めた。

Table2 Mortality from cancer by smoking habit

| | | | smokers | | | | total | |
|---|---|---|---|---|---|---|---|---|
| cancer site | non-smokers | ex-smokers | total(3) | -20 cig/day | 21-40 cig/day | 41- cig/day | subjects | |
| All sites: | | | | | | | | |
| Male | | | | | | | | |
| No of deaths | 48 | 67 | 230 | 150 | 70 | 10 | 345 | |
| Mortality(1) | 335 | 423 | 543 | 515 | 586 | 551 | | |
| Relative risk(2) | 1.00 | 1.17(0.80-1.70) | 1.62 | 1.39(0.99-1.93) | 1.77(1.21-2.58) | 1.70(0.85-3.40) | | trend(+) |
| PAF(%) | | | 29.5 | 10.0 | 13.0 | 6.5 | | |
| Female | | | | | | | | |
| No of deaths | 205 | 5 | 23 | 22 | 1 | 0 | 233 | |
| Mortality(1) | 247 | 170 | 268 | 275 | 134 | - | | |
| Relative risk(2) | 1.00 | 0.79(0.32-1.94) | 1.09 | 1.15(0.73-1.81) | 0.75(0.10-5.45) | - | | |
| PAF(%) | | | 2.7 | 2.8 | -0.05 | - | | |
| Lung: | | | | | | | | |
| Male | | | | | | | | |
| No of deaths | 3 | 8 | 68 | 40 | 24 | 4 | 79 | |
| Mortality(1) | 23 | 51 | 158 | 129 | 225 | 221 | | |
| Relative risk(2) | 1.00 | 2.35(0.62-8.91) | 6.76 | 5.99(1.84-19.51) | 11.16(3.31-37.66) | 13.10(2.88-59.70) | | trend(+) |
| PAF(%) | | | 42.9 | 23.3 | 16.5 | 3.1 | | |
| Female | | | | | | | | |
| No of deaths | 20 | 0 | 7 | 6 | 1 | 0 | 27 | |
| Mortality(1) | 24 | - | 88 | 80 | 134 | - | | |
| Relative risk(2) | 1.00 | - | 3.67 | 3.40(1.29-8.93) | 10.25(1.19-88.26) | - | | trend(+) |
| PAF(%) | | - | 7.1 | 6.3 | 0.8 | - | | |

(1)Rate/100,000 person-years adjusted for age according to the person-year distribution of the entire cohort
(2)Relative risk and 95% confidence intervals adjusted for age, body mass index, place of residence and alcohol drinking habit
(3)Relative risk was not adjusted for body mass index, place of residence or alcohol drinking habit
PAF: population attributable fraction

【結　果】本調査では 1980～1999 年 11 月に追跡できた対象者は 9,629 人、追跡率 91.3%であった。その中で全死亡者数は 2,011 人、がん死亡者数 579 人、肺がん死亡者数 106 人であった。喫煙状況別全死因及びがん年齢調整死亡率の相対危険度については、女性の全がんを除いて、現在喫煙者が非喫煙者に比べて死亡リスクが高く、喫煙本数が多くなるほど死亡リスクが高くなる傾向であった。肺がんについても、男女とも同様の傾向がみられた。各疾患（全死因、全がん、肺がん）による死亡者のうち、現在喫煙者が禁煙に転じた場合による Population approach 効果は、全死因については禁煙することにより男性：9%、女性：2%、がんでは男性：30%、女性：3%、肺がんでは最も高く男性：43%、女性：7%死亡を予防・回避することができると、本研究結果から明らかとなった（上記表を参照）。

【メッセージ】喫煙の影響を PAF により判断したコホート研究は少なく、分娩時における死産への人口寄与危険度の評価や、HDL cholesterol 値における虚血性心疾患死亡の危険度、喫煙による若年者での入院による労働損失の危険度を評価するにとどまっている。また、日本において喫煙と肺がんとの関係を人口寄与危険度を用いて分析した患者対照研究もある。しかし、コホート研究で日本を代表するサンプルデータを用いて、喫煙の影響を人口寄与危険度で評価した研究報告はなく、本研究結果の意義は高いと考えられる。

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# 喫煙習慣の全死因，がん，肺がん死亡への影響に関する研究：NIPPON DATA80

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# An Association (Population Attributable Fraction) between Smoking Habit and Mortality from all Causes, Cancer and Lung Cancer: NIPPON DATA80, 1980-1999. National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in the Aged

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**Abstract** **Objectives: The authors examined the relationship and the population attributable fraction (PAF) between smoking habit and death from all causes, including cancer and lung cancer.**

**Methods: The baseline data were collected in the National Cardiovascular Survey in 1980 carried out for all household members aged 30 years or older in 300 districts, which were randomly selected throughout Japan. The number of participants in the survey was 10,546. The vital status was ascertained in 1999, and he calculated the adjusted relative risk of mortality and the PAF of mortality attributable to stopping smoking.**

**Results: A total of 9,629 subjects were available for the final analyses. There were 165,190 person-years of follow-up, and 2,011 deaths from all causes, including 579 deaths from cancer and 106 deaths from lung cancer. After adjustment for age and other cancer risk factors, smoking habit was associated with mortality from all causes, cancer and lung cancer. These associations had positive trends.**

**The PAF (%) from all causes was 9.0 (male), 1.6 (female). The PAF (%) from cancer was 29.5 (male), 2.7 (female) and that from lung cancer was 42.9 (male), 7.1 (female).**

**Conclusions: After adjustment for age and other cancer risk factors, smoking habit was associated with mortality from all causes, cancer and lung cancer. These associations had positive trends.**

**The PAF (%) from all causes was 9.0 (male), 1.6 (female). The PAF (%) from cancer was 29.5 (male), 2.7 (female) and that from lung cancer was 42.9 (male), 7.1 (female).**

**Key words:** smoking habit（喫煙習慣），mortality rate（死亡率），lung cancer（肺がん），population attributable fraction（人口寄与割合）

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## 目　　的

たばこは，肺がんをはじめとする多くのがんや，虚血性心疾患，脳血管疾患，慢性閉塞性肺疾患，歯周疾患など多くの疾患，低出生体重児や流・早産など妊娠に関連した異常の危険因子である (1-8)。また，たばこに含まれるニコチンには依存性があり，自分の意志だけでは，やめたくてもやめられないことが多い (9-10)。しかし，禁煙に成功すれば，喫煙を継続した場合に比べて，これらの疾患の危険性は減少する (11-13)。

最新の疫学データに基づく推計では，たばこによる超過死亡数は，1995年には日本では9万5000人であり (14)，全死亡数の12%を占めている。また，人口動態統計によると，近年急増している肺がん死亡数が1998年に初めて胃がんを抜き，がん死亡の中で首位となった。

喫煙の影響に関する研究については，平山らによる日本人を対象としたコホート研究によると，喫煙量と肺がんリスクとの間に明瞭な量反応関係があることが示されている (15)。

また，山口らの推計によると，2010年に男女の喫煙率が半減した場合，74歳までの肺がんによる累積死亡確率は，2020年の段階で，男性では若干減少することが明らかとなった (16)。

このように，我が国における喫煙とがん，肺がんとの関係を，全国的な前向き研究で明らかにしたものは平山ら (2, 15) による厚生省コホート研究しかなく，他の研究によりこの関係を示すデータはなかった。今回は，1980年に厚生省により実施された循環器疾患基礎調査の対象者約1万人を基に19年間追跡調査し，追跡結果より喫煙状況と全死因，がんと肺がんによる死亡との関係を分析した。

## 方　　法

対象は，1980年に厚生省により実施された第3回循環器疾患基礎調査客体を追跡対象とした。調査客体は同年度国民栄養調査対象者10,546人であった。追跡方法について，詳しくは文献 (17) に記述されているが，概略としては，調査対象者の住所・生年月日を同定し，対象者の居住地域を管轄する保健所に対して，対象者の生存確認調査（在籍，転出，死亡，不明）を依頼した。さらに，調査対象者の住民票請求を行い，人口動態調査死亡票をリンクさせ，生死追跡及び死亡者の死因同定を行った。本研究は，主任研究者の所属する滋賀医科大学の倫理審査委員会にて承認されている。今回利用した第3回循環器疾患基礎調査及び人口動態調査死亡票の調査票データは，滋賀医科大学が厚生労働省及び総務省に利用申請し許可されたものである。

本調査では1980～1999年11月に追跡できた対象者について，全死亡者，がん死亡者，肺がん死亡者における喫煙状況（非喫煙，禁煙，現在喫煙，現在喫煙については1日の平均喫煙本数別に分類）別10万人年あたりの年齢調整死亡率を求めた。追跡人年および死亡数を5歳階級ごとに計算し直接法による年齢調整を行った。さらに，比例ハザードモデルにより年齢，飲酒習慣及びBMIなどを調整した相対危険度（95%信頼区間）及び傾向性の検定結果を求めた。計算された相対危険度と本研究対象者の喫煙状況を基に，各疾患（全死因，全がん，肺がん）による死亡者のうち，現在喫煙者が禁煙に転じた場合に，社会全体に起こる各疾患による死亡を予防できる割合：人口寄与割合（PAF: population attributable fraction）を下式のとおり求めた (18)。

$$PAF(\%)= \frac{P2 \times (RR2 - RR1) \times 100}{RR2}$$

P0：1980年循環器疾患基礎調査客体での非喫煙者割合
P1：1980年循環器疾患基礎調査客体での禁煙者割合
P2：1980年循環器疾患基礎調査客体での現在喫煙者割合
RR1：非喫煙者を対照とした禁煙者の調整済み相対危険度
RR2：非喫煙者を対照とした現在喫煙者の調整済み相対危険度
ただし，$P0 + P1 + P2 = 1$

## 結　　果

本調査では1980～1999年11月に追跡できた対象者は9,629人，追跡率91.3%であった。その中で全死亡者数は2,011人，がん死亡者数579人，肺がん死亡者数106人であった。全死因における喫煙状況別10万人あたりの年齢調整死亡率（Table 1: Entire Cohort の Mortality）は非喫煙者（男性：1151，女性：949），禁煙者（男性：1438，女性：999），現在喫煙者（男性：1663，女性：1179）と，現在喫煙者の死亡率が高い結果であった。脳卒中，心筋梗塞，狭心症，糖尿病といった既往歴のある人を除いた場合の全死因における喫煙状況別年齢調整死亡率（Table 1: Excluding those with selected serious diseases の Mortality）もほぼ上記と同様の結果であった。

がん死亡者については，喫煙状況別10万人あたりのがん年齢調整死亡率（Table 2: All sites の Mortality）は非喫煙者（男性：335，女性：247），禁煙者（男性：423，女性：170），現在喫煙者（男性：543，女性：268）と，現在喫煙者のがん死亡率が高い結果であった。女性は有意な結果ではなかった。特に肺がんについては，喫煙状況別10万人あたりの肺がん年齢調整死亡率（Table 2: Lung の Mortality）は非喫煙者（男性：23，女性：24），禁煙者（男性：51），現在喫煙者（男性：158，女性：88）と，現在喫煙者の肺がん死亡率が高い結果であった。

喫煙状況別全死因及びがん年齢調整死亡率の相対危険度（Table 1: Entire Cohort の Relative risk, Table 2: All sites の Relative risk）については，女性の全がんを除いて，現在喫煙者が非喫煙者に比べて死亡リスクが高く，喫煙本

**Table 1 Total mortality by smoking habit**

| | all subjects | non-smokers | ex-smokers | smokers | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | total (3) | –20 cig/day | 21–40 cig/day | 41–cig/day | |
| Entire cohort: | | | | | | | | |
| Male | | | | | | | | |
| No of deaths | 1091 | 177 | 240 | 672 | 472 | 174 | 26 | |
| Mortality (1) | | 1151 | 1438 | 1663 | 1620 | 1658 | 1332 | |
| Relative risk (2) | | 1.00 | 1.19 (0.98–1.45) | 1.45 | 1.31 (1.10–1.56) | 1.52 (1.23–1.89) | 1.58 (1.04–2.41) | trend (+) |
| PAF (%) | | | | 9.0 | 3.5 | 4.5 | 0.9 | |
| Female | | | | | | | | |
| No of deaths | 920 | 782 | 30 | 105 | 95 | 10 | 0 | |
| Mortality (1) | | 949 | 999 | 1179 | 1149 | 1551 | — | |
| Relative risk (2) | | 1.00 | 1.10 (0.75–1.59) | 1.24 | 1.27 (1.02–1.58) | 1.98 (1.05–3.74) | — | trend (+) |
| PAF (%) | | | | 1.6 | 1.2 | 0.4 | — | |
| Excluding those with selected serious diseases (4): | | | | | | | | |
| Male | | | | | | | | |
| No of deaths | 879 | 145 | 190 | 544 | 384 | 138 | 22 | |
| Mortality (1) | | 1077 | 1285 | 1529 | 1491 | 1498 | 1348 | |
| Relative risk (2) | | 1.00 | 1.15 (0.92–1.43) | 1.42 | 1.32 (1.08–1.60) | 1.50 (1.18–1.91) | 1.74 (1.11–2.75) | trend (+) |
| PAF (%) | | | | 11.1 | 4.9 | 4.9 | 1.3 | |
| Female | | | | | | | | |
| No of deaths | 774 | 656 | 27 | 91 | 83 | 8 | 0 | |
| Mortality (1) | | 879 | 1055 | 1086 | 1069 | 1344 | — | |
| Relative risk (2) | | 1.00 | 1.22 (0.82–1.81) | 1.24 | 1.31 (1.03–1.65) | 1.89 (0.93–3.84) | — | trend (+) |
| PAF (%) | | | | 0.9 | 0.6 | 0.3 | — | |

(1) Rate/100,000 person-years adjusted for age according to the person-year distribution of the entire cohort.
(2) Relative risk (95% confidence intervals) adjusted for age, body mass index, place of residence and alcohol drinking habit.
(3) Relative risk was not adjusted for body mass index, place of residence or alcohol drinking habit.
(4) History of stroke, angina pectoris, myocardial infarction and diabetes.
PAF: population attributable fraction.

数が多くなるほど死亡リスクが高くなる傾向であった。肺がん（Table 2: Lung の Relative risk）についても，男女とも同様の傾向がみられた。

各疾患（全死因，全がん，肺がん）による死亡者のうち，現在喫煙者が禁煙に転じた場合に，社会全体に起こる各疾患による死亡を予防できる割合：人口寄与割合 PAF（%）については，全死因（男性：9.0，女性：1.6），がん（男性：29.5，女性：2.7），肺がん（男性：42.9，女性：7.1）であった（Table 1 の Entire Cohort and Table 2: PAF（%））。

## 考　　察

我が国における喫煙とがん及び肺がんとの関係を，全国的な前向き研究で明らかにしたものは平山ら (2, 15) による厚生省コホート研究しかなく，他の研究によりこの関係を示すデータはなかった。平山らによるコホート研究の結果である「非喫煙」に対する「毎日喫煙」の相対危険度，全がん（男性：1.65，女性：1.32），肺がん（男性：4.45，女性：2.34）を本研究結果と比較すると，全がんは同程度であったが，肺がんは本研究結果（男性：6.76，女性：3.67）で男女ともに高い値を示していた。祖父江らの報告 (19) では，我が国における喫煙による肺癌相対リスクは男で4～5倍，女で2～3倍と報告されているが，これよりも本研究結果は高い値を示していた。同様の報告では，我が国における肺癌死亡数は一貫して増加しているが，この主な原因は高齢者人口の増加にあるとしている。このような近年における肺がん死亡率の上昇と，本研究結果の肺がん相対危険度が男女ともに高い値を示していたこととは，何らかの関係があると考えられ，喫煙による肺がんリスクが高まったことが一要因ということも推測される。

次に，喫煙の影響を PAF により判断したコホート研究は少なく，分娩時における死産への人口寄与危険度の評価 (20) や，HDL cholesterol 値における虚血性心疾患死亡の危険度 (21)，喫煙による若年者での入院による労働損失の危険度 (22) を評価するにとどまっている。また，日本において喫煙と肺がんとの関係を人口寄与危険度を用いて分析した患者対照研究 (23) もある。しかし，コホート研究で日本を代表するサンプルデータを用いて，喫煙の影響を人口寄与危険度で評価した研究報告はなく，本研究結果の意義は高いと考えられる。

**Table 2 Mortality from cancer by smoking habit**

| cancer site | non-smokers | ex-smokers | smokers | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | total (3) | –20 cig/day | 21–40 cig/day | 41– cig/day | total subjects | |
| All sites: | | | | | | | | |
| Male | | | | | | | | |
| No of deaths | 48 | 67 | 230 | 150 | 70 | 10 | 345 | |
| Mortality (1) | 335 | 423 | 543 | 515 | 586 | 551 | | |
| Relative risk (2) | 1.00 | 1.17 (0.80–1.70) | 1.62 | 1.39 (0.99–1.93) | 1.77 (1.21–2.58) | 1.70 (0.85–3.40) | | trend (+) |
| PAF (%) | | | 29.5 | 10.0 | 13.0 | 6.5 | | |
| Female | | | | | | | | |
| No of deaths | 205 | 5 | 23 | 22 | 1 | 0 | 233 | |
| Mortality (1) | 247 | 170 | 268 | 275 | 134 | — | | |
| Relative risk (2) | 1.00 | 0.79 (0.32–1.94) | 1.09 | 1.15 (0.73–1.81) | 0.75 (0.10–5.45) | — | | |
| PAF (%) | | | 2.7 | 2.8 | –0.05 | — | | |
| Lung: | | | | | | | | |
| Male | | | | | | | | |
| No of deaths | 3 | 8 | 68 | 40 | 24 | 4 | 79 | |
| Mortality (1) | 23 | 51 | 158 | 129 | 225 | 221 | | |
| Relative risk (2) | 1.00 | 2.35 (0.62–8.91) | 6.76 | 5.99 (1.84–19.51) | 11.16 (3.31–37.66) | 13.10 (2.88–59.70) | | trend (+) |
| PAF (%) | | | 42.9 | 23.3 | 16.5 | 3.1 | | |
| Female | | | | | | | | |
| No of deaths | 20 | 0 | 7 | 6 | 1 | 0 | 27 | |
| Mortality (1) | 24 | — | 88 | 80 | 134 | — | | |
| Relative risk (2) | 1.00 | — | 3.67 | 3.40 (1.29–8.93) | 10.25 (1.19–88.26) | — | | trend (+) |
| PAF (%) | | — | 7.1 | 6.3 | 0.8 | — | | |

(1) Rate/100,000 person-years adjusted for age according to the person-year distribution of the entire cohort.
(2) Relative risk and 95% confidence intervals adjusted for age, body mass index, place of residence and alcohol drinking habit.
(3) Relative risk was not adjusted for body mass index, place of residence or alcohol drinking habit.
PAF: population attributable fraction.

近年，我が国では，健康日本21(24)が策定され，基本指針である「対象集団への働きかけ」の中で，健康障害の危険因子を持つ集団のうち，より高い危険度を有する者に対して，その危険を削減することによって疾病を予防する方法：高リスクアプローチ（High risk approach）とともに，さらに集団全体で疾病を予防する方法：集団アプローチ（Population approach）を提唱している。例えば，高血圧の場合，臨床的高血圧のグループを見つけ出し，強力な治療，例えば降圧剤で血圧を下げることによって，そのグループの合併症の頻度は低下させることができる。しかし，将来，脳卒中などの重大な合併症に罹る実際の人数は，現在高血圧域の人より境界域の人数の方が圧倒的に多い。従って全体の血圧を下げた方が，合併症への罹患を大きく予防することができるのである。

高リスクアプローチは方法論も明確で対象も明確にしやすいが，影響の量は限られている。一方，集団全体の予防効果からすれば，集団アプローチが必要である。しかし，一般に集団アプローチは社会全体への働きかけを必要とし，効果を定量化しにくいことが多い。

この集団全体で疾病を予防する方法：集団アプローチ（Population approach）において，効果を定量化していく手段の一つとして人口寄与割合がある。喫煙に関しては，健康日本21の運動目標の一つに「禁煙希望者に対する禁煙支援」が掲げられており，禁煙によって罹患・死亡を予防できる人口寄与割合を本研究では算出した。本研究結果は，集団アプローチ（Population approach）に対する効果を数値化するものであり，健康日本21を進める上で基礎的かつ重要な研究となると推測される。

禁煙による Population approach 効果は，現在喫煙者が禁煙に転じた場合に，社会全体に起こる各疾患による死亡を予防できる割合 PAF の比較により判断され，全死因については禁煙することにより男性：9%，女性：2%，がんでは男性：30%，女性：3%，肺がんでは最も高く男性：43%，女性：7%死亡を予防・回避することができると，本研究結果から明らかとなった。祖父江らの報告（19）では，喫煙による人口寄与危険割合（喫煙が原因と考えられる肺癌の割合）は男で70%，女で15～25%と報告されている。本研究結果と比較すると，男女とも低い結果であった。これは近年における喫煙率の減少による影響が考えられるが，修正PAF(18)を求めているため，その影響とも考えられた。

なお，本研究の一部は，第11回日本疫学会学術総会

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研究成果の要約

## 日本人における総コレステロール値と死因別死亡の関連

**Okamura T, Kadowaki T, Hayakawa T, et al. What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med 2003; 253: 169-180.**

【研究の目的】総コレステロール値が低い集団では、総コレステロールのスクリーニングによって、どのような疾患の死亡が予測できるかが不明確である。日本では総コレステロールの測定が広く行われているため、その意義を明らかにしておく必要がある。

【研究方法】1980年の循環器疾患基礎調査受検者 10,546人から循環器疾患の既往歴やデータ欠損のある460人を除外した 10,086人を1994年まで追跡した。途中追跡不能となった 870人を除く、男性 4,035 人、女性 5,181 人を解析対象とした。ベースライン時の総コレステロール値(mg/dl)で 160 未満、160-199、200-239、240 以上の4群に分けて、160-199 を基準とした死因別の相対危険度を、年齢、高血圧、糖尿病、BMI、喫煙、飲酒、血清アルブミン(男女計の場合は性別も追加)を調整して求めた。

【研究結果】

160 未満群で総死亡率が高い傾向を認めたが、この関連はベースラインから 5 年以内の死亡を除くと消失した。総コレステロールと脳卒中、肝臓がん以外の悪性新生物、非がん非循環器疾患死亡には有意な関連を認めなかった。総コレステロール値は、虚血性心疾患と正の関連を示し、男性の240以上で有意差を認めた。また160未満群では有意に肝臓がん死亡が高く、これらの関連は5年以内の死亡を除いても同様であった。

表. 血清総コレステロール値と虚血性心疾患、肝臓がん死亡

| 総コレステロール値 (mg/dl) | 虚血性心疾患 RR (95% CI) | 肝臓がん RR (95% CI) |
|---|---|---|
| | 男性 | 男女計 |
| 160未満 | 0.93 (0.35, 2.48) | 2.40 (1.11, 5.18) |
| 160-199 | 1.00 | 1.00 |
| 200-239 | 1.83 (0.81, 4.13) | 0.60 (0.19, 1.88) |
| 240以上 | 4.76 (1.91, 11.9) | 0.90 (0.20, 4.09) |
| | 女性 | |
| 160未満 | 0.89 (0.29, 2.73) | |
| 160-199 | 1.00 | |
| 200-239 | 1.16 (0.55, 2.43) | |
| 240以上 | 1.99 (0.79, 5.03) | |

注)RRは相対危険度。総コレステロール値が160-199のグループの死亡率を1として計算している。

【メッセージ】

日本人集団でも総コレステロール値の測定は虚血性心疾患死亡の危険因子であった。なお肝臓がんと低コレステロールの関連は、肝硬変や慢性肝炎の存在による因果の逆転によると考えられた。

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# What cause of mortality can we predict by cholesterol screening in the Japanese general population?

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**Abstract.** Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H (Shiga University of Medical Science, Shiga, Japan; Iwate Medical University, Morioka, Iwate, Japan). What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med* 2003; **253**: 169–180.

**Objective.** In a population with a markedly lower coronary mortality such as in Japan, the benefit of cholesterol screening may be different from Western populations. We attempted to assess the importance of cholesterol screening in Japan.

**Design.** A 13.2-year cohort study for cause-specific mortality.

**Setting.** Three hundred randomly selected districts throughout Japan in which the National Survey on Circulatory Disorders 1980 was performed.

**Subjects.** A total of 9216 community dwelling persons aged 30 years and over, with standardized serum cholesterol measurement and without a past history of cardiovascular disease.

**Results.** There were 1206 deaths, which included 462 deaths due to cardiovascular disease with 79 coronary heart diseases. Hypercholesterolemia (>6.21 mmol $L^{-1}$) showed a significant positive relation to coronary mortality (relative risk; 2.93, 95% confidence interval; 1.52–5.63) but not to stroke. Although hypocholesterolemia (<4.14 mmol $L^{-1}$) was significantly associated with an increased risk of liver cancer, noncardiovascular, noncancer disease and all-cause mortality, these associations, except for liver cancer, disappeared after excluding deaths in the first 5 years of the follow-up. The multivariate adjusted attributable risk of hypercholesterolaemia for coronary disease was 0.98 per 1000 person-years, which was three-fold higher than that of hypocholesterolemia for liver cancer: 0.32 per 1000 person-years. The attributable risk percentage of hypercholesterolaemia was 66% for coronary heart disease.

**Conclusion.** Similar to Western populations, it is recommended to provide screening for hypercholesterolaemia in Japan, especially for males, although its attributable risk for coronary disease might be small.

**Keywords:** attributable risk, cholesterol, cohort, coronary, mortality, screening.

## Introduction

A high level of serum total cholesterol (TC) is an important causal risk factor for coronary heart disease. Some studies have shown that a high cholesterol concentration contributes to the development of other cardiovascular diseases [1–3]. A basic principle of prevention requires the measurement of blood cholesterol to assess the risk status [2, 3]. After the Health and Medical Service Law for the Elderly was enacted in 1982, all Japanese citizens aged 40 and over have the opportunity to undergo screening for TC, and those with hypercholesterolaemia are provided with health services such as health education or guidance to prevent coronary disease [4].

In contrast, low TC level has also been reported to raise the mortality. The National Heart, Lung, and

*Investigators and members of the research group are listed in the Appendix.

Blood Institute (NHLBI) Conference in 1990 reviewed and discussed previous observational studies that had reported a U- or J-shaped association between blood cholesterol level and noncoronary mortality [5], and concluded that these associations were explainable by confounding factors such as pre-existing cancers or respiratory diseases, but further researches were recommended. Since this conference, many studies have been reported on this issue [6–17]. Some did not support any causal contribution of low blood cholesterol to the risk of death from noncoronary diseases [8, 11–13, 15], but other studies, especially performed in the East Asian subjects, showed contrary results suggesting low mortality with a high blood cholesterol level compared with Western populations [9, 10, 16, 17].

In populations with a low mean cholesterol level such as in Japan, which has a markedly lower coronary mortality or morbidity compared with Western populations [18], the benefit of cholesterol screening may be different. Pignone *et al.* suggested that further research would be needed to estimate the benefits of cholesterol screening in people of non-European descent [19]. The purpose of this study is to investigate the benefit of cholesterol screening as a prediction marker for all-cause or cause-specific mortality in the Japanese general population through a 13.2-year prospective study.

## Subjects and methods

### *Subjects*

The subjects of this cohort were the participants of the National Survey on Circulatory Disorders 1980 [20]. A total of 10 546 community-based subjects aged 30 years and over in 300 randomly selected areas all over Japan participated in the survey. It included medical examinations, blood pressure measurements, blood tests and a self-administered questionnaire about lifestyle.

The cohort was followed until 1994 (NIPPON DATA 80; The National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged, 1980) [21, 22]. In order to clarify the cause of death, we used the National Vital Statistics. In accordance with Japan's Family Registration Law, all death certificates issued by medical doctors were to be forwarded centrally to the Ministry of Health and Welfare via the public health centres in the area of residency. The underlying causes of death were to be coded according to the 9th International Classification of Disease for the National Vital Statistics. We confirmed death in each area by computer matching of data from the Vital Statistics, using the area, sex, and date of birth and death as key codes.

Of 10 546 subjects, a total of 1330 were excluded for the following reasons: past histories of coronary disease or stroke, $n = 280$, some missing information at the baseline survey, $n = 180$; and lost to follow-up, $n = 870$. We analysed the rest of 9216 subjects (4035 males and 5181 females). There was no significant difference between subjects who were lost to follow-up and censored in sex-specific mean TC; 4.89 vs. 4.81 mmol $L^{-1}$ for males, 4.98 vs. 4.93 mmol $L^{-1}$ for females, respectively. Therefore, the potential bias of the 870 subjects lost to follow-up may be negligible.

Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, the Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 12–18, 2000).

### *Biochemical and physical examinations*

The baseline surveys were conducted by public health centres. Nonfasting blood samples were drawn and centrifuged within 60 min of collection. They were stored at −70°C until analyses. Serum albumin and TC were analysed in a sequential autoanalyser (SMA12; Technicon, Tarrytown, USA) with the Lieberman-Burchard direct method for TC and bromcresol-green method for albumin at one specific laboratory (formerly, Center for Adult diseases; Osaka, present name, Osaka Medical Center for Health Science and Promotion). The laboratory is a member of the Cholesterol Reference Method Laboratory Network (CRMLN) [23], and the Measurement precision and accuracy for serum cholesterol were certified in the Lipid Standardization Program administered by the Center for Disease Control and Prevention, Atlanta.

Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated subjects after at least 5 min rest. Hypertension was defined

as systolic blood pressure being 140 mmHg or higher, diastolic blood pressure being 90 mmHg or higher, use of antihypertensive agents or any combination of these. The serum level of glucose was measured by a deoxidization method. Diabetes was defined as a serum glucose level being 11.1 mmol $L^{-1}$ or greater, a past history of diabetes, or both. Height in stocking feet and weight in light clothing were measured. The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Public health nurses confirmed information on smoking and drinking habits, and present and past medical histories.

*Statistical analysis*

The relation between TC and risk characteristics at the baseline survey or cause-specific mortality was described by dividing the subjects into four groups stratified by the TC level. We used 4.14 mmol $L^{-1}$ (160 mg $dL^{-1}$), 5.18 mmol $L^{-1}$ (200 mg $dL^{-1}$) and 6.21 mmol $L^{-1}$ (240 mg $dL^{-1}$) of serum TC as cut-off points. The category of TC < 4.14 mmol $L^{-1}$ was defined as hypocholesterolemia because such low levels was reported to be associated with excess mortality risk in the NHLBI Conference on low cholesterol, based on cohort studies form Europe, the United States and Japan, and in some previous studies [5, 6, 9]. The other cut-off points were selected in accordance with the manual for health examinations under Japan's Health and Medical Service Law [4]. In the manual, the TC of 5.18–6.20 mmol $L^{-1}$ was defined as a level that required lifestyle modification, and 6.21 mmol $L^{-1}$ and over as a level that required referral to a doctor. These criteria agree with that of Adult Treatment Panel III [3]. The group with TC level of 4.14–5.17 mmol $L^{-1}$ was defined as having the normal level.

Age-adjusted mean values were estimated with analyses of covariance. Age-adjusted prevalences with adjustment for 5-year age categories by the Mantel–Haenszel method were estimated by comparing with the prevalence in the standard group. The multivariate adjusted relative risk (RR) for all-cause or cause-specific mortality was calculated using a Cox's proportional hazard model adjusted for age, serum albumin, BMI, hypertension, diabetes, cigarette smoking category (never-smoker, ex-smoker, current smoker ≤ 20 cigarettes $day^{-1}$ and current smoker >20 cigarettes $day^{-1}$) and alcohol intake category (never-drinker, ex-drinker, occasional drinker and daily drinker). Sex was adjusted, whilst a sex-combined analysis was also performed. For some cause-specific mortality that reached statistical significance in the Cox's proportional hazard model, the multivariate adjusted RR was calculated again excluding deaths within the first 5 years of follow-up because subjects who had a severe but subclinical disease might have had a low cholesterol level. We estimated the multivariate-adjusted mortality rates of some cause-specific mortalities that showed a significant relation in the described analysis in the hyper- or hypo-cholesterolemia group; it was estimated by multiplying the multivariate adjusted RR by the crude mortality rate of the standard group. We estimated the multivariate-adjusted attributable risk and attributable risk percentage, [1 − (1/adjusted RR)]*100%, for hyper- or hypo-cholesterolemia compared with the standard group.

All probability values were two-tailed and all confidence intervals were estimated at the 95% level. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 10.0 J Tokyo, Japan) was used for the analyses.

## Results

Figure 1 shows the age distribution of the present study population. There was no significant difference between males and females ($\chi^2 = 5.2$, $P = 0.389$). The mean age in this population was 50.0 ± 13.2 (mean ± SD) in all, 49.7 ± 13.1 for males and 50.1 ± 13.3 for females. The mean serum TC in this population was 4.88 mmol $L^{-1}$ (4.81 mmol $L^{-1}$ for males and 4.93 mmol $L^{-1}$ for females).

Table 1 shows age-adjusted mean values or prevalences of the baseline characteristics of all subjects in each cholesterol level category. There were significant differences in the mean values for albumin and BMI; they were higher in a higher cholesterol group in both sexes. Compared with the normal group, the hypercholesterolaemia (>6.21 mmol $L^{-1}$) group had a significantly higher prevalence of hypertension in both sexes, a higher prevalence of diabetes in females and a lower prevalence of daily drinker and current smoker in males. In males, the hypocholesterolemia (<4.14 mmol $L^{-1}$) group for TC showed a significantly lower prevalence of hypertension compared with the normal group and

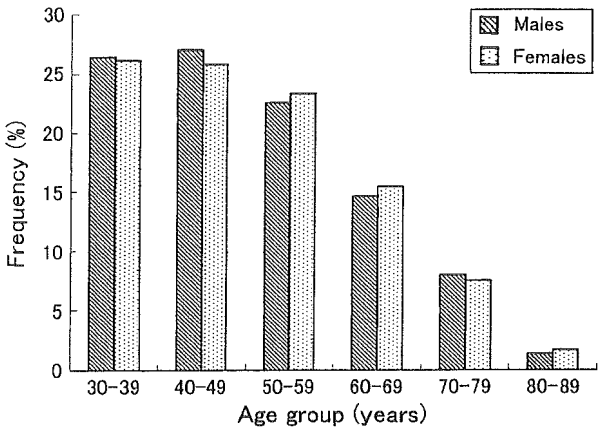


Fig. 1 Distribution of age amongst 4035 males and 5181 females at the baseline survey in a 13.2-year follow-up study.

the highest prevalence of current smokers, although it did not reach statistical significance.

Total person-years were 121 392 and mean follow-up period was 13.2 years. During the follow-up, there were 1206 deaths (638 for males and 568 for females). The number of total and cause-specific deaths is shown in Table 2. Amongst them, 38% ($n = 462$, 36% for males and 41% for females) were due to cardiovascular diseases. There were 79 coronary heart disease deaths, which represented 17% of deaths due to cardiovascular disease. There were 216 stroke deaths, which represented 47% of deaths due to cardiovascular disease and this proportion was threefold higher than that of coronary heart disease. Deaths from cerebral haemorrhage were about one half to one-third of cerebral infarction deaths.

Amongst the total deaths, 29% ($n = 353$, 32% for males and 26% for females) were due to cancers. There were 92 stomach cancers, 65 lung cancers and 33 liver cancers, a total of which represented 54% of deaths due to cancer. Age distribution of cancer deaths was skewed towards younger population than that of cardiovascular diseases. Of all the deaths, 32% ($n = 391$, 32% for males and 33% for females) were due to noncardiovascular and noncancer diseases. There were 80 pneumonias and 64 'accidents, poisoning and suicide' which represented 37% of deaths due to noncardiovascular and noncancer diseases.

In most diseases, 60–90% of deaths occurred after 60 years. However, concerning liver cancer,

Table 1 Age and age-adjusted mean values and prevalences of baseline characteristics stratified by cholesterol level at the baseline survey

| | Baseline serum cholesterol level (Stratum mean), mmol $L^{-1}$ | | | | |
|---|---|---|---|---|---|
| Risk characteristics | <4.14 (3.75) | 4.14–5.17 (4.65) | 5.18–6.20 (5.59) | 6.21– (6.70) | *P*-values |
| Male | | | | | |
| Number of subjects | 851 | 1937 | 1002 | 245 | |
| Age (years) | 51.4 (14.3) | 49.9 (13.5) | 48.9 (12.7) | 49.5 (11.7) | <0.001 |
| Albumin (g $L^{-1}$) | 43.3 (0.08) | 44.2 (0.05) | 43.3 (0.07) | 43.3 (0.15) | <0.001 |
| BMI (kg $m^{-2}$) | 21.7 (0.10) | 22.3 (0.07) | 23.3 (0.10) | 24.0 (0.19) | <0.001 |
| Hypertension (%) | 38.0* | 48.2 | 58.9* | 75.0* | |
| Diabetes (%) | 1.2 | 1.0 | 1.6 | 1.2 | |
| Daily drinker (%) | 45.3 | 49.2 | 47.5 | 33.3* | |
| Current smoker (%) | 73.2 | 65.2 | 45.4* | 44.7* | |
| Heavy smoker (>20 cigarettes $day^{-1}$) (%) | 21.1 | 24.8 | 25.0 | 30.1 | |
| Female | | | | | |
| Number of subjects | 952 | 2325 | 1453 | 451 | |
| Age (years) | 44.6 (13.1) | 48.6 (13.2) | 53.7 (12.8) | 56.3 (11.9) | <0.001 |
| Albumin (g $L^{-1}$) | 42.9 (0.01) | 43.4 (0.01) | 44.1 (0.01) | 44.5 (0.01) | <0.001 |
| BMI (kg $m^{-2}$) | 22.1 (0.11) | 22,6 (0.07) | 23.4 (0.09) | 24.0 (0.16) | <0.001 |
| Hypertension (%) | 32.9 | 35.1 | 47.9* | 53.9* | |
| Diabetes (%) | 0.3 | 0.6 | 1.0 | 1.6* | |
| Daily drinker (%) | 3.6 | 2.8 | 2.9 | 1.9 | |
| Current smoker (%) | 8.0 | 8.9 | 9.6 | 6.5 | |
| Heavy smoker (>20 cigarettes $day^{-1}$) (%) | 1.3 | 1.0 | 2.0 | 1.1 | |

*$P < 0.05$.
Numbers in parentheses are standard deviation for age and standard errors for other variables.