Original Article

Joint Impact of Smoking and Hypertension on Cardiovascular Disease and All-Cause Mortality in Japan: NIPPON DATA80, a 19-Year Follow-Up

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Hypertension and smoking are major risk factors for death due to cardiovascular disease (CVD). These attributions for CVD mortality should be higher in the countries where obesity-related conditions are uncommon. However, the joint effect of these risk factors on CVD and all-cause mortality have not been described. We followed a representative 8,912 Japanese men and women without a history of stroke and heart disease. Participants were categorized into 4 groups as follows: a group of individuals who neither smoked nor had hypertension (HT), a group of current smokers, a group with HT, and a group of current smokers with HT. We further calculated population-attributable fractions (PAF) of CVD and all-cause mortality based on relative hazards assessed by proportional hazard regression models. After 19 years of follow-up, we observed 313 and 291 CVD and 948 and 766 all-cause deaths for men and women, respectively. The PAF of CVD mortality due to smoking or HT were 35.1% for men and 22.1% for women. The PAF of CVD mortality was higher in participants <60 years of age (57.4% for men and 40.7% for women) *vs.* those who were older (26.3% for men and 18.1% for women). Aggressive attempts to discourage smoking and to curb HT could yield large health benefits in Japan and throughout Asia, particularly for those aged <60 years. Efforts to warn about the adverse consequence of HT and smoking during adolescence and youth could yield the greatest health benefits, since positive behaviors adopted early are more easily continued into middle adulthood and later life. (*Hypertens Res* 2007; 30: 1169–1175)

Key Words: hypertension, smoking, population attributable fraction, epidemiology, prospective studies

Introduction

Hypertension (HT) is one of the strongest risk factors for cardiovascular disease (CVD) (*1*). Smoking is also an important risk factor for CVD mortality (*2*). The prevalence of smoking and HT in Japan (*3*, *4*) and in other Asian countries is excessive (*5–9*). Thus, the impact of HT and smoking on CVD mortality should be high in Japanese and throughout Asia.

Although several studies have described the higher population-attributable risk fraction (PAF) of CVD due to HT alone or smoking alone in Japan (*10*, *11*) and in other Asian populations (*8*, *9*), the numbers of CVD and all-cause deaths that could jointly be explained by HT and smoking in Japan have not been examined. Understanding the joint contribution of HT and smoking to CVD could help guide Japan and other Asian countries in formulating programs that warn of the adverse consequences of these risk factors, particularly in areas where obesity-related conditions are relatively uncommon (*12*).

In addition, since previous studies have suggested that the relative risk of smoking alone or HT alone on CVD mortality is stronger in younger than in older individuals (*10*, *11*), the combined impact of HT and smoking on CVD and all-cause mortality might also differ by age group.

Therefore, to describe the amount of CVD and all-cause mortality that could be explained by current smoking and HT in Japan, we calculated the age-specific joint impact of smoking and HT on CVD and all-cause mortality using a representative national survey with a high follow-up rate.

Methods

Study Participants

The subjects of this cohort study participated in the National Cardiovascular Survey of 1980. The standardized procedures used in that survey have been described elsewhere (*13*). All household members ≥30 years of age were surveyed in 300 census tracts that were randomly selected throughout Japan.

The number of individuals selected was 13,771. Among these, 10,546 individuals had completed baseline information regarding age, gender, and blood pressure (BP). The sample comprised the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged (NIPPON DATA80) (*4*, *13–15*). Thus, 76.6% of the overall population was available for analysis. From this sample, we excluded participants with a history of stroke (*N*=117), coronary heart disease (*N*=163) or other heart diseases (*N*=475). An additional 32 were excluded who lacked data on BP, glucose, cholesterol, and smoking and drinking habits. There were 847 participants who were excluded because they had missing residential information and mortality follow-up. The final sample thus included 8,912 participants (3,963 men and 4,949 women). Compared to those not

excluded (*N*=8,912), the excluded group due to loss to follow-up was younger (self-reported age: 46.3 years *vs*. 49.6 years) and less likely to smoke cigarettes (33% *vs*. 39%). These differences, however, appeared to be modest. There were no differences with respect to gender (women comprised 56% of both groups) or age-adjusted BP.

Data Collection

The baseline survey included medical examinations, BP measurements, blood tests, and a self-administered questionnaire about lifestyle. Trained staff at local health centers in the respective districts performed the examinations in community centers. A history of heart disease, stroke and diabetes, as well as smoking and drinking habits was obtained from the questionnaire. Height and weight were measured with the subjects wearing light clothing and no shoes. The subjects were asked to note whether they were current smokers, had quit smoking, or had never smoked, and smokers were asked to note the number of cigarettes smoked each day. We treated ex-smokers and those who had never smoked as nonsmokers in this study. Single measurements of systolic and diastolic BP (SBP and DBP) were obtained after a 5 min rest by trained public health nurses at each public health center using a standard mercury sphygmomanometer. HT was defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medication (*1*). Non-fasting blood samples were collected. The precision and accuracy of the assay for measuring serum total cholesterol (TC) were certified by the Lipid Standardization Program administered by the Centers for Disease Control and Prevention, Atlanta, USA (*16*). Diabetes was defined as a serum glucose value ≥200 mg/dL or a self-reported history of diabetes. For alcohol consumption, subjects were asked whether they were never drinkers, past drinkers, occasional drinkers, or regularly drinkers on a daily basis.

Follow-Up Survey

NIPPON DATA80 has completed follow-up surveys until 1999. The underlying causes of death were coded for the Japanese National Vital Statistics according to the 9th International Classification of Disease (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the beginning of 1995. Details of the classification used in the present study have been described elsewhere (*13*). Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency of the Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Statistical Analysis

To examine the association of the combined effects of smok-

Table 1. Baseline Characteristics According to the Combination of Blood Pressure and Smoking Status: NIPPON DATA80, 1980, Japan

Characteristics	Younger (age <60 years)					Older (age ≥60 years)				
	Normotensive		Hypertensive			Normotensive		Hypertensive		
	Non-smoker	Current smoker	Non-smoker	Current smoker	*p*-value*	Non-smoker	Current smoker	Non-smoker	Current smoker	*p*-value*
Men										
N	580	1,178	450	829		90	161	320	355	
Age	42.6	42.2	46.7	47.2	<0.01	68.9	67.5	69.9	68.1	<0.01
BMI (kg/m²)	22.6	22.1	23.7	23.2	<0.01	21.4	20.9	22.5	21.6	<0.01
Diabetes (%)	4	4	6	8	<0.01	8	11	9	15	0.054
Total cholesterol (mg/dL)	186.8	183.3	196.7	188.5	<0.01	184.3	176.5	187.0	180.6	<0.01
Drinking status										
Never (%)	24	19	19	12	<0.01	33	34	26	22	<0.01
Past (%)	5	4	3	3		16	7	11	8	
Occasional (%)	36	29	30	22		27	19	20	17	
Daily (%)	35	48	48	63		24	40	43	52	
Women										
N	2,403	216	1,060	92		312	41	741	84	
Age	42.3	42.1	49.4	48.8	<0.01	67.4	67.1	69.1	69.1	<0.01
BMI (kg/m²)	22.3	21.9	24.1	24.0	<0.01	21.8	21.7	23.4	22.1	<0.01
Diabetes (%)	1	1	6	4	<0.01	10	10	8	8	0.92
Total cholesterol (mg/dL)	182.5	185.6	195.8	199.7	<0.01	199.6	190.6	202.4	197.6	<0.01
Drinking status										
Never (%)	79	46	84	48	<0.01	81	71	84	67	<0.01
Past (%)	1	5	1	3		1	5	2	5	
Occasional (%)	19	36	13	35		15	15	10	19	
Daily (%)	2	13	2	14		2	10	4	10	

N, number of participants; BMI, body mass index; non-smoker, never smoked and ex-smoker. *Test by analysis of variance for continuous variable and χ^2 test for categorical variables.

ing and HT on mortality, participants were categorized as: 1) neither smokers nor HT, 2) smokers only, 3) HT only, and 4) smoker with HT. We compared basic characteristics among the four groups using means for continuous variables and percentages for dichotomous variables. We separately analyzed men and women and those <60 years and ≥60 years of age. We estimated the multivariate adjusted relative hazards (RH) and the 95% confidence intervals (95% CI) for the effect of the combination of smoking and HT on CVD and on all-cause mortality using Cox proportional hazard models. We treated those who were neither smokers nor HT as a reference group. The multivariate adjusted model included the following possible confounding factors: age, body mass index, diabetes, TC, and alcohol consumption category (never, past, occasional, and daily). We also calculated the PAF of CVD and all-cause mortality due to the combination of smoking and HT using methods described elsewhere (*17*). The PAF was also recalculated for comparison with other Japanese studies (*4*, *10*).

Results

Baseline Characteristics

The mean age±SD was 50.0±13.0 years for men and 50.2±13.1 years for women. The prevalence of HT was 49.3% for men and 40.0% for women. The prevalence of current smoking was 63.7% for men and 8.8% for women. Table 1 shows the baseline characteristics according for each of the four smoking and HT groups. For both men and women, the hypertensive groups were older, more obese, more likely to have diabetes, more likely to have higher TC levels, and more likely to consume alcohol on a daily basis than the normotensive groups. The differences were statistically significant. Male current smokers were leaner, had lower TC levels, and were more likely to consume alcohol on a daily basis than male nonsmokers. Female current smokers were more likely to consume alcohol and to have a lower body mass index than female nonsmokers. No other differences in risk factors were found to be significant.

Table 2. Relative Hazard (RH) and 95% Confidence Interval (CI) for Cardiovascular Disease (CVD) or All Cause Mortality According to the Combination of Blood Pressure (BP) and Smoking Status by Age Group: NIPPON DATA80, 1980–1999

| | Younger (age <60 years) | | | | | Older (age ≥60 years) | | | | |
| | Normotensive | | Hypertensive | | | Normotensive | | Hypertensive | | |
	Non-smoker	Current	Non-smoker	Current	Total	Non-smoker	Current	Non-smoker	Current	Total
Men										
Person-year	10,623	21,437	8,232	14,692	54,984	1,295	2,260	4,165	4,708	12,428
CVD death	6	19	13	51	89	17	29	78	100	224
CVD mortality rate (per 1,000 person-years)	0.6	0.9	1.6	3.5	1.6	13.1	12.8	18.7	21.2	18.0
RH (95% CI) for CVD mortality*	1	1.58 (0.63–3.97)	1.96 (0.73–5.22)	3.86 (1.62–9.19)		1	1.02 (0.56–1.87)	1.27 (0.74–2.17)	1.72 (1.02–2.89)	
Excess CVD death		7.0	6.4	37.8	51.1		0.7	16.4	41.8	58.9
PAF for CVD death (%)		7.8	7.1	42.4	57.4		0.3	7.3	18.6	26.3
All cause death	40	115	50	143	348	47	99	209	245	600
All cause mortality rate (per 1,000 person-years)	3.8	5.4	6.1	9.7	6.3	36.3	43.8	50.2	52.0	48.3
RH (95% CI) for all cause mortality*	1	1.40 (0.98–2.01)	1.21 (0.79–1.84)	1.69 (1.17–2.42)		1	1.24 (0.87–1.76)	1.32 (0.95–1.82)	1.47 (1.07–2.02)	
Excess all cause death		33.0	8.5	58.1	99.6		18.9	50.2	78.3	147.4
PAF for all cause death (%)		9.5	2.4	16.7	28.6		3.2	8.4	13.1	24.6
Women										
Person-year	44,630	3,990	19,427	1,656	69,703	4,947	601	10,971	1,133	17,652
CVD death	16	3	28	5	52	49	3	160	27	239
CVD mortality rate (per 1,000 person-years)	0.4	0.8	1.4	3.0	0.7	9.9	5.0	14.6	23.8	13.5
RH (95% CI) for CVD mortality*	1	2.58 (0.75–8.93)	2.19 (1.13–4.22)	5.88 (2.07–16.72)		1	0.46 (0.14–1.48)	1.23 (0.88–1.71)	2.01 (1.25–3.23)	
Excess CVD death		1.8	15.2	4.1	21.2		0.0	29.6	13.6	43.2
PAF for CVD death (%)		3.5	29.2	8.0	40.7		0.0	12.4	5.7	18.1
All cause death	100	13	85	10	208	117	19	373	49	558
All cause mortality rate (per 1,000 person-years)	2.2	3.3	4.4	6.0	3.0	23.7	31.6	34.0	43.2	31.6
RH (95% CI) for all cause mortality*	1	1.63 (0.90–2.94)	1.07 (0.79–1.47)	1.77 (0.91–3.46)		1	1.23 (0.75–2.01)	1.28 (1.03–1.59)	1.61 (1.15–2.26)	
Excess all cause death		5.0	5.8	4.4	15.2		3.5	80.7	18.6	102.9
PAF for all cause death (%)		2.4	2.8	2.1	7.3		0.6	14.5	3.3	18.4

PAF, population attributable fraction; non-smoker, never smoked and ex-smoker. *Adjusted for age, body mass index, diabetes, total cholesterol, and drinking status.

Follow-Up Data

There were 67,412 and 87,355 person-years of follow-up in men and women, respectively (up to 19 years per person). During this time, a total of 948 men and 766 women died, and 313 and 291 of these deaths were due to CVD, respectively.

In this study, we combined never smokers and ex-smokers into one category because of the small number of ex-smokers. In addition, the risk factor–adjusted RH for deaths due to CVD for ex-smokers *vs*. never smokers was nearly one (RH=1.09 for men and RH=1.18 for women). This was also true for all-cause deaths (RH=1.14 for men and RH=1.18 for women).

Since CVD mortality in smokers with HT was higher in those <60 years of age than in those ≥60 years (*p* for interaction: <0.01 for men and 0.03 for women), we analyzed these groups separately. Table 2 further shows that the age-stratified joint impact of smoking and HT on CVD mortality was stronger in participants <60 years old *vs*. participants who were older.

For younger men, the risk factor–adjusted RH for CVD mortality was significantly higher in smokers with HT *vs*. the reference value (RH=3.86; 95% CI: 1.62–9.19). This value tended to be higher, but not significantly so, in the smoking only (RH=1.58; 95% CI: 0.63–3.97) and HT only (RH=1.96; 95% CI: 0.73–5.22) groups. Compared to the reference group, the risk factor–adjusted RH for CVD mortality among younger women was significantly higher in smokers with HT (RH=5.88; 95% CI: 2.07–16.72) and participants with HT only (RH=2.19; 95% CI: 1.13–4.22). The PAFs of CVD mortality in the smoking only, HT only, and smoking with HT groups were 7.8%, 7.1%, and 42.4%, respectively. Smoking and HT accounted for 57.4% of CVD deaths among younger men. Smoking and HT also accounted for 40.7% of CVD deaths among younger women. These proportions were higher than those observed in older participants (26.3% in men and 16.6% in women). However, the number of excess CVD deaths due to smoking and HT among men were similar between the younger and older subgroups (51.1 for younger and 58.9 for older male participants). In contrast, the excess deaths due to CVD among young women was half that in those who were older (21.2 for younger and 43.2 for older female participants). The overall sum of excess CVD deaths (PAF) due to smoking and HT was 110.0 (35.1%) for men and 64.4 (22.1%) for women.

Similar to the CVD findings, the risk factor–adjusted RH for all-cause mortality was higher in the smoking only, HT only, and smoking plus HT groups than in the group with neither factor. The PAFs of all-cause mortality due to smoking combined with HT were 28.6% for younger men, 24.6% for older men, 7.3% for younger women, and 18.4% for older women. The sum of the excess of all-cause deaths (PAF) due to smoking and HT were 247.0 (26.1%) for men and 118.1 (15.4%) for women.

Discussion

Evidence suggests that smoking and HT account for a large proportion of CVD and all-cause mortality in Japan. In the present report, although the number of excess CVD deaths due to smoking and HT were similar between younger and older men, the PAF was more than double in those who were younger. The number of excess deaths due to CVD among young women was half the number among older women. Because of the exceptionally high RHs, the PAF was also more than doubled in those who were younger. These findings confirm the importance of discouraging smoking and eliminating HT. They further suggest that aggressive attempts to warn about the adverse consequences of smoking and HT at an early age could yield significant health benefits in Japan, particular for those <60 years. Similar findings may also apply to other Asian countries where smoking and HT are highly prevalent.

It is well known that smoking has an important effect on CVD and all cause mortality in Japan (*4*, *10*). The NIPPON DATA80 (*4*) showed that the PAF of CVD mortality due to smoking was 27.5% for men and 5.0% for women, while the PAF for all-cause mortality was 15.0% for men and 4.0% for women. These values were similar to those of Iso *et al*. (*10*), who found that 23.5% and 6.0% of CVD mortality could be explained by smoking status. Other Japanese studies have also reported similar values for the PAF for all-cause mortality (*18–20*) due to smoking (range of PAF: 22–34% for men and 0–5% for women), and other Asian studies have yielded PAFs that are comparable to those in Japan (*8*).

Similarly, HT is also a potent CVD risk factor (*9*, *11*, *13*, *21*). However, few studies have described the PAF of CVD deaths due to HT defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medication in Japan (*9*). A few studies have described the PAF for CVD death due to non-optimal BP (SBP ≥120 mmHg or DBP ≥80 mmHg or current use of antihypertensive medication) (*11*, *14*). These studies found that the PAF of non-optimal BP was very high. Thus, both HT and smoking definitely contribute to a large proportion of CVD or all-cause deaths. These findings should be applied to other Asian populations, most of which have a high prevalence of smoking and HT and few obesity-related CVD risk factors, such as diabetes or hypercholesterolemia (*4–6*). In fact, a recent study has reported that a large fraction of CVD was attributable to HT (*9*).

However, the joint impact of smoking and HT on CVD and all-cause mortality is relatively unknown. Since Rothman described that the sum of disease attributable to various causes in reality has no upper limit (*22*), simple addition of these PAFs might not express the true contributions of the risk factors. Thus, it makes sense that the PAF should be calculated using a combination of smoking and HT when trying to determine their joint impact.

We found that the PAF for CVD mortality was higher in

younger than in older populations. This is consistent with previous findings. Iso *et al*. reported that excess CVD mortality associated with cigarette smoking is more evident in middle-age (40–64 years of age) than in the elderly (65–79 years) (*10*). Sairenchi *et al*. also reported that the PAF for CVD mortality due to non-optimal BP is higher in younger than in elderly persons (*11*). Although we could not conclude why the PAF for CVD mortality was higher in the younger than in the older population in the present work, this difference might be partly explained by an age-related increase in the risk for CVD in nonsmoking elderly individuals without HT; the crude CVD mortality rate in nonsmoking elderly participants without HT was more than 20 times as large as that in nonsmoking younger persons without HT. The PAF is defined by both RH and the prevalence. Since the prevalence of HT was greater in older than in younger participants, the difference in the PAF for CVD mortality between younger and older participants observed in our study could be explained by the higher RH in the younger participants. Thus, earlier intervention to discourage smoking and warn against the hazard of HT should have a greater benefit in those who are young, with continued carry-over into later life. Similar interventions in the elderly are also important, because the number of excess CVD deaths due to smoking and HT were higher among those aged 60 or older *vs*. those who were younger.

The strength of our study was the use of a representative population with a high response rate and long follow-up period. Thus, our results could be applicable to the entire Japanese population. The study also has several limitations that should be considered. First, these data were based on participants who lived 25 years ago. Since Japanese lifestyles have recently undergone dramatic changes, it may be that these data are less applicable today. However, the 2003 National Health and Nutrition Survey in Japan showed that the prevalence of current smoking among younger men (30–59 years) has remained high (54.4–56.8%) and that the prevalence is increasing among younger women (10.7–18.1%). These values were also rather high when compared with the sample in the present study (*23*). The prevalence of HT remained similarly high in the 2003 survey (10.1% for the age group of 30–39 years, 30.8% for 40–49 years, 36.4% for 50–59 years, 52.4% for 60–69 years and 57.5% for those aged ≥70 years, with men and women combined) (*23*). Thus, the prevalence of both smoking and HT continues to be a major public health problem, and developing intervention strategies to warn of the adverse health consequence of smoking and HT should be a top priority. Secondly, we defined HT as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or the current use of antihypertensive medications. Therefore, our results might underestimate the true PAF due to HT compared with other studies that used optimal BP levels (SBP <120 mmHg and DBP <80 mmHg) as a reference. Furthermore, since we obtained only single BP values for each participant, some measurement error may have occurred. Such error could have resulted in conservative findings. Finally, we combined never and ex-smokers into one category because of the small number of deaths that were observed in the ex-smoker group, particularly among those who were young. Although combining never and ex-smokers into a single group could have resulted in an underestimation of the impact of smoking on our PAFs, this may not have been the case in this instance because, after adjusting for risk factors, the rate of all-cause and CVD mortality were nearly identical in never and ex-smokers.

In conclusion, our results suggest that eliminating two major CVD risk factors, namely, smoking and HT, would prevent 35% of CVD deaths in men and 22% of CVD deaths in women. Moreover, eliminating these factors would prevent 26% of all-cause deaths in men and 15% of all cause deaths in women. Intervention programs that discourage smoking and warn of the adverse consequences of HT in adolescence might eventually yield the greatest health benefits for men and women <60 years of age, since the increased capacity for healthy behaviors would be carried over into later life. It seems likely that the benefits from initial intervention programs as early in life as possible will increase longevity, not just in Japan, but throughout Asia.

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