HHS Public Access

Author manuscript

Ann Epidemiol. Author manuscript; available in PMC 2017 August 30.

Published in final edited form as:

Ann Epidemiol. 2008 December ; 18(12): 913–918. doi:10.1016/j.annepidem.2008.09.004.

Risk Factor Effects and Total Mortality in Older Japanese Men in Japan and Hawaii

Robert D. Abbott, PhD, **Hirotsugu Ueshima, MD**, **Atsushi Hozawa, MD**, **Tomonori Okamura, MD**, **Takashi Kadowaki, MD**, **Katsuyuki Miura, MD**, **Nagako Okuda, MD**, **Yasuyuki Nakamura, MD**, **Akira Okayama, MD**, **Yoshikuni Kita, PhD**, **Beatriz L. Rodriguez, MD**, **Katsuhiko Yano, MD**, and **J. David Curb, MD**

Division of Biostatistics and Epidemiology (RDA), University of Virginia School of Medicine, Charlottesville, Virginia, USA; Department of Health Science (RDA, HU, AH, TO, TK, KM, NO, YK, JDC), Shiga University of Medical Science, Otsu, Japan; Department of Preventive Cardiology (TO), National Cardiovascular Center, Suita, Osaka, Japan; Cardiovascular Epidemiology (YN), Kyoto Women's University, Kyoto, Japan; Pacific Health Research Institute (RDA, BLR, KY, JDC), Honolulu, Hawaii, USA; Honolulu Heart Program and Honolulu-Asia Aging Study (RDA, BLR, KY, JDC), Kuakini Medical Center, Honolulu, Hawaii, USA; Department of Geriatric Medicine (RDA, BLR, JDC) and the Office of the Dean (JDC), John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA; The First Institute for Health Promotion and Health Care (AO), Japanese Anti-Tuberculosis Association, Tokyo, Japan

Abstract

Purpose—To identify factors related to total mortality in older Japanese men in Japan and Hawaii.

Methods—Baseline data were collected from 1980 to 1982 in 1,379 men in Hawaii and 954 men in Japan. Ages ranged from 61 to 81 years with mortality follow-up over a 19 year period.

Results—Compared to Japan, men in Hawaii had a 2-fold excess of diabetes and a 4-fold excess of prevalent coronary heart disease ($p<0.001$). Total cholesterol and body mass index were also higher in Hawaii ($p<0.001$). In contrast, men in Japan had higher systolic blood pressure and were nearly 3-times more likely to smoke cigarettes ($p<0.001$). Although each cohort had elements of a poor risk factor profile, there was a 1.4-fold excess in the risk of death in Japan (49.4 vs. 36.2/1,000 person-years, $p<0.001$). While mortality was similar after risk factor adjustment, only blood pressure and cigarette smoking accounted for the higher risk of death in Japan.

Conclusions—Cigarette smoking and hypertension explain much of the excess mortality in Japan versus Hawaii. In this comparison of genetically similar cohorts, evidence further suggests

Address for correspondence: Robert D. Abbott, PhD, Department of Public Health Sciences, University of Virginia School of Medicine, P.O. Box 800717, Charlottesville, Virginia 22908-0717, Telephone: 434-924-1687, Fax: 434-924-8437, rda3e@virginia.edu.

that Japanese in Japan are equally susceptible to develop the same adverse risk factor conditions that exist in Hawaii.

Keywords

Mortality; Japanese; risk factor; epidemiology

Introduction

Risk of death due to stroke began to decline in Japan after 1965 following reductions in blood pressure and in the less frequent use of cigarettes [1]. This occurred in spite of the adverse effects on coronary heart disease through increases in total cholesterol levels and the intake of dietary fat [1]. In contrast, beginning in 1993, lung cancer in Japan became the leading cause of death among all cancers following a period of extensive use of cigarettes between World War II and 1965 [1,2]. In a comparison of Japanese men in Japan, Hawaii, and California, evidence further suggests that increased exposure to Western lifestyles lowers the risk of death due to stroke and increases the risk of death due to coronary heart disease [3–8]. Implications are that stroke, coronary heart disease, and cancer are highly preventable.

While much is known about the adverse health consequences associated with many risk factors, the purpose of this report is to identify specific characteristics that are important in altering the risk of total mortality in Japanese men in Japan and Japanese men who are more acculturated to Western lifestyles in Hawaii [9,10]. Whether some risk factor combinations are worse than others in promoting early mortality will also be considered. To accomplish this, comparisons will be made between a cohort of men enrolled in the Honolulu Heart Program, and in Japan, a cohort of men enrolled in the National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged (NIPPON-DATA). Both are population-based longitudinal studies with identical periods of follow-up and times of execution.

Methods

Study samples

The Honolulu Heart Program began as a long-term follow-up study of cardiovascular disease in Japanese men who were residing on the island of Oahu, Hawaii. Participants were identified through 11,148 World War II Selective Service records, which at the time, was the most efficient and reliable method that was available for identifying potential cohort members. From 1965 to 1968, 8,006 of these men agreed to participate in the first examination of the Honolulu Heart Program. Subjects were either first generation immigrants or the sons of parents who migrated to Hawaii from Japan. At the time of study enrollment, the men received complete physical examinations when they were aged 45 to 68 years. Cohort members have undergone repeat examinations with follow-up for all-cause mortality. Further details on the recruitment in the Honolulu Heart Program are given elsewhere [9–13].

The NIPPON-DATA sample included participants in the 1980 National Survey on Circulatory Disorders [14]. The cohort consists of 4,244 men age 30 to 92 years who were randomly selected from health districts throughout Japan. As with Hawaii, subjects received complete physical examinations at the time of enrollment with follow-up for total mortality [15–17]. For both cohorts, procedures were in accordance with institutional guidelines and approved by an institutional review committee.

In each sample, follow-up for total mortality began at baseline examinations that were given from 1980 to 1982. In Japan, this corresponded with the time of initiation of the NIPPON-DATA. In Hawaii, it corresponded with repeat examinations that were given to a sample of 1,379 men who were randomly selected to participate in the Cooperative Lipoprotein Phenotyping Study [12,18]. In the Hawaii sample, men ranged in age from 61 to 81 years. In Japan, men who fell outside of this range were excluded from follow-up. The final sample in Japan consisted of 954 men.

Baseline risk factors

Risk factors observed at the baseline examination in each cohort included age, use of cigarettes, alcohol drinking status, hypertension, systolic and diastolic blood pressures, treatment for hypertension, diabetes, total cholesterol levels, body mass index, and prevalent stroke and coronary heart disease. Information on prevalent cancer is not considered in this report since it was not available in the cohort from Japan.

A diagnosis of hypertension was made if a study participant was receiving anti-hypertensive medication or when a systolic or diastolic blood pressure was ≥140 and 90 mm Hg, respectively. Diabetes was defined based on a physician diagnosis or a medical history. Prevalent stroke and coronary heart disease were also based on a physician diagnosis or a self-report of either event. Further description of the remaining risk factors is provided elsewhere [9,11,14–17]. Because the treatment for hyperlipidemia was uncommon when the NIPPON-DATA began, data on lipid altering medications were not collected in the Japan sample. For the 1,379 men in Hawaii, only 17 were receiving lipid altering medications.

Mortality follow-up

In both cohorts, subjects were followed after the baseline examination for 19 years for a mortality outcome. In Hawaii, an underlying cause of death was coded according to the 8th International Classification of Disease (ICD-8). For Japan, the cause of death was coded according to the 9th International Classification of Disease (ICD-9) to the end of 1994 and the 10th International Classification of Disease (ICD-10) beginning in 1995. Because of the use of different coding methods and to differences in the classification of cause-specific death that exist between Japan and the United States, follow-up is limited to total mortality [1,19,20].

Statistical methods

Unadjusted and adjusted rates of total mortality were calculated for each cohort in person-years of follow-up. Standard analysis of covariance techniques and logistic regression models were used to adjust for age and other risk factors [21]. Age-adjusted percents and

risk factor levels were also compared between the two samples using similar methods. To assess cohort effects and the relation between risk factors and the time to death, proportional hazards regression models were used [22]. Estimates of the relative hazard of death that could be associated with important risk factor differences (along with 95% confidence intervals) were based on corresponding regression coefficients and standard errors. Interaction terms between cohort and each risk factor were also examined to determine if effects on death were similar in Japan and Hawaii. All reported *P*-values were based on two-sided tests of significance.

Results

The baseline risk factors observed at the beginning of follow-up (1980–1982) in each cohort are described in table 1. Except for alcohol drinking and the prevalence of stroke, all other risk factors differed significantly between Japan and Hawaii. The most noteworthy difference was in the use of cigarettes. In Hawaii, 19.1% smoked cigarettes, while in Japan, 55.8% were smokers ($p<0.001$). Men in Japan were also more likely to have hypertension than men in Hawaii (73.7 vs. 61.3%, $p<0.001$). On average, systolic blood pressure in Japan was 11 mm Hg higher ($p<0.001$), while diastolic blood pressure was 4 mm Hg higher ($p<0.001$). Although men in Japan were significantly less likely to be treated for hypertension than men in Hawaii, the difference was modest. The less frequent use of hypertensive medication in Japan also failed to explain the elevated blood pressure and the greater frequency of hypertension that existed in Japan.

While men in Japan were more likely to smoke cigarettes and were more often hypertensive than men in Hawaii, men in Japan were half as likely to have prevalent diabetes (6.5 vs. 13.0%). Total cholesterol in Japan was also 28 mg/dl lower than in Hawaii. In addition, body mass index in men in Japan was significantly lower by an average of 1.7 kg/m^2. Men in Japan were noticeably shorter by an average of 5 cm. For the overall average height (161 cm), a 1.7 kg/m^2 difference corresponds to a weight difference of 4.4 kg. Compared to men in Japan, men in Hawaii had a 4-fold excess in the prevalence of coronary heart disease (11.4 vs. 2.6%, $p<0.001$).

Among the 1,379 men in the Hawaii, there were 738 deaths (36.2/1,000 person-years). In the 954 men in Japan there were 643 deaths (49.4/1,000 person years). The excess risk of death in Japan was significantly higher than in Hawaii ($p<0.001$).

Table 2 describes how several of the risk factors in table 1 are related to the risk of death within and between the study cohorts. Here, the effects of age, systolic blood pressure, total cholesterol, body mass index, and alcohol intake on mortality were similar between the samples. In both cohorts, age and high systolic blood pressure were significantly related to an increased risk of death, while there was no association with total cholesterol. Alcohol consumption appeared protective against total morality, although its effect was significant only in Japan. A test for an interaction between alcohol intake and cohort was not significant.

In contrast, while cigarette smoking and prevalent stroke were associated with an increased risk of death in both cohorts, there were significant cohort by risk factor interaction effects. Here, the effects of cigarette smoking and stroke on the risk of death were stronger in Hawaii. In both cohorts, where prevalent cancer could be an important confounder, body mass index had a significant inverse relationship with mortality.

Among the other risk factors, treatment for hypertension, prevalent diabetes, and prevalent coronary heart disease had a marked difference in their effects on death between the study samples. In Hawaii, men with diabetes or prevalent coronary heart disease experienced a near 1.5-fold excess in the risk of death as compared to when the condition was absent ($p<0.001$). In Japan, an association involving diabetes was less apparent, although a significant cohort interaction effect was absent. For prevalent coronary heart disease, there was a significant cohort interaction effect where the effect of prevalent coronary heart disease on mortality in Japan was weaker. In contrast, treatment for hypertension was associated with an increased risk of death in Japan but not in Hawaii. For the latter, a cohort by treatment interaction was not significant. While the findings in Table 2 were risk factor adjusted, unadjusted results are similar.

Table 3 provides additional details on the risk of death in each of the study cohorts. Here, attempts were made to identify an explanation for the excess risk of death in Japan versus Hawaii that could be attributed to risk factor differences and effects that are shown in tables 1 and 2. While there was a 1.4-fold excess in the risk of death in Japan versus Hawaii (49.4 vs. 36.2/1,000 person-years, $p<0.001$), the risk of death between the cohorts became similar after accounting for the combined effects of the baseline risk factors (41.8 vs. 40.9/1,000 person years, $p=0.760$). Among the risk factors, however, only elevated blood pressure and the use of cigarettes explained the excess risk of death in Japan. When adjusted for combinations of the other factors, differences in the risk of death became insignificant only when adjustments were made for the joint (not individual) effects of systolic blood pressure and cigarette smoking. To help mitigate confounding from prevalent cancer and subclinical disease on the effects of body mass index, total cholesterol, and other factors, deaths that occurred early in the course of follow-up were also excluded. After removing deaths that occurred within 2 and 10 years of follow-up, findings were unchanged.

Discussion

Life-expectancy in Japan is among the highest in the world [1]. In the current comparison of samples from Japan and Hawaii, however, risk of death in Hawaii is significantly less. The longer life-expectancy in Hawaii occurred in spite of a greater frequency of diabetes and prevalent coronary heart and higher levels of total cholesterol and body mass index. Given that the men in Japan had higher blood pressure and were more likely to smoke cigarettes, these data suggest that blood pressure and the use of cigarettes in Japan have a greater impact on mortality than does the adverse risk factor profile that exists in Hawaii.

Similar findings have been noted elsewhere [1,2]. Declines in stroke mortality in Japan since 1965 have followed closely with reductions in blood pressure and in the use of cigarettes, overcoming adverse effects on coronary heart disease through increases in total cholesterol

levels and the intake of dietary fat [1]. From 1965 to 1990, average systolic blood pressure has dropped nearly 15 mm Hg in men aged 60 years and older. Increases in the risk of death due to lung cancer have also followed patterns of excessive use of cigarettes during the 20 year period following the close of World War II [2]. While use of cigarettes in Japan has declined since this time, cigarette smoking remains a major public health concern. In 1965, 82.3% of men smoked cigarettes while in 2005, the prevalence was 45.5%.

Unfortunately, among the risk factors considered in this report, efforts to control cigarette smoking and hypertension in Japan have not been successful [2,23,24]. Although treatment for hypertension is only slightly less frequent in Japan versus Hawaii (25.3 vs. 29.2%, see table 1), therapeutic intervention in Japan begins later in life [23]. In a recent report based on data collected from 2001 to 2005, only 5.5% of younger Japanese men in Japan aged 40 to 50 years were being treated for hypertension while over 20% were being treated in Hawaii [23].

Efforts to control cigarette smoking in Japan are more disheartening. When follow-up began in the current study in 1980, 55.8% of men in Japan smoked cigarettes versus 19.1% in Hawaii. In contrast to Hawaii, little has changed in Japan. From 2001 to 2005, 49.5% of Japanese men in Japan aged 40 to 50 years smoked cigarettes as compared to 12.7% of those in the same age range in Hawaii [23]. In 2002, Japan Tobacco, the third largest tobacco company in the world asserted that 49% of Japanese men smoked cigarettes [2]. While providing protection for its commercial interests, Japan Tobacco is largely owned by the Japanese government [2]. Frequency of cigarette smoking in Japan is now among the highest in the industrialized world [2,24]. In 2006, 37% of boys in the 12^{th} grade of high school were reported to be current cigarette smokers [24]. Three quarters purchased their cigarettes through highly accessible vending machines [2], the number of which has increased steadily since 1973 [24].

It seems interesting that among the risk factors considered in this report, that an adverse risk factor profile in Japan is more often characterized by a high frequency of cigarette smoking and elevated blood pressure levels, while in Hawaii, risk factors cluster around higher body mass index and associated conditions (diabetes and high total cholesterol). Based on a comparison of cohorts with genetically similar origins, these findings suggest that with increased Westernization, Japanese in Japan have the same susceptibility for developing diabetes, obesity, high total cholesterol, and coronary heart disease as Japanese in Hawaii. Equally important is that Japanese men in Hawaii may be capable of reversing their high susceptibility to elements of a poor risk factor profile that are less common in Japan. Attention to these latter risk factors holds promise for increasing longevity in Hawaii. In an earlier report from the NIPPON-DATA cohort, findings further suggest that longevity in Japan can be increased through efforts to lower blood pressure and discourage smoking [25].

With a direct comparison between Japanese men in Japan and Hawaii, it seems unlikely that genetic variation could provide more than a partial explanation for the findings observed in this report. While this assumes that gene distributions and susceptibilities are similar between the samples being compared, similarities are more likely in the current study than in comparisons between different ethnicities. Genetics, however, may still be important. An

excess of non-genetic risk factors in one sample could alter disease risk by providing an environment for genetic effects to operate on disease processes.

Between the study samples, there are also noticeable differences associated with the effects of diabetes, prevalent coronary heart disease, and the treatment for hypertension. For diabetes, there was a significant effect on mortality in Hawaii that was absent in Japan. Effects in Hawaii, however, could have been stronger due to higher body mass indices and an association with earlier onset and a greater severity of diabetes. The effect of prevalent coronary heart disease on mortality was also stronger in Hawaii, although its association with mortality is poorly estimated due to its infrequent occurrence in Japan (25 men vs. 156 in Hawaii). In contrast, treatment for hypertension was associated with an increased risk of death in Japan but not in Hawaii. The latter could possibly be due to different treatment practices in Japan where only the more severe forms of hypertension receive therapeutic intervention.

Because dietary intake data were not uniformly collected, the effect of differences in the types of food consumed on mortality between the two cohorts could not be assessed. Such effects could be important since it has been well documented that the Japanese men in Hawaii have become more Westernized in their lifestyle and biologic characteristics as compared to men in Japan [9,10].

Unfortunately, because systems of disease classification (ICD-8, 9, and 10) were not uniformly applied, the current study is unable to examine differences in risk factor effects on specific causes of death between the study cohorts. Others have noted that the use of death certificate data is insufficient for comparing cause-specific fatality between cultures that adhere to different diagnostic practices [19,20], particularly in the diagnosis of coronary heart disease [1,19]. In the current report, discrepancies in the diagnosis of stroke raise concerns about the validity of a stroke comparison. Based solely on death certificate data, 57.7% of strokes in Hawaii were classified as unknown, while only 12.9% were classified as unknown in Japan. Whether differences in the classification of death based on death certificate data are largely due to differences in diagnostic convention rather than clinical evidence remains to be determined.

Failure to exclude prevalent cancer in the current report is also a limitation. It may be that the difference in the risk of death between Japan and Hawaii is unexplained by body mass index, total cholesterol levels, and the other factors because of coexisting relationships with cancer or subclinical disease. The latter appears unlikely, however, since when deaths that occurred within 2 and 10 years of follow-up were excluded, mortality continued to be higher in Japan than in Hawaii. As before, only blood pressure and cigarette smoking explained the excess risk of death in Japan.

Generalizations of findings to the population of Japanese men in Hawaii and Japan is also uncertain. Large epidemiologic studies, even those that attempt to rely on the principles of randomization, often attract bias through the unavoidable recruitment of healthier members of a target community [26–29]. Both samples from Japan and Hawaii, however, are characterized by a broad range of physiologic and clinically important risk factors that

include cigarette smoking, blood pressure, diabetes, total cholesterol, body mass index, and prevalent coronary heart disease and stroke. As a result, findings are likely representative of a large component of each of the targeted populations. Adjustments for confounders that were collected at the same time and with identical periods of follow-up also improves the validity of the comparisons that were made between the cohorts.

Whether findings from the current study can be applied to other population segments also remains to be determined. It is especially uncertain for Japanese women where cigarette smoking is infrequent and geographic differences in the use of cigarettes can be modest [1,30]. Fewer than 6% of women in Japan older than 60 years smoke cigarettes [1]. Since 1970, however, smoking among women younger than 30 years has more than doubled to 20% in 2005 [1]. If this pattern continues, it is likely that investments in smoking cessation programs among women in Japan will overtake other public health initiatives that are currently more important. Whether other risk factor clusters emerge as having a more meaningful public health impact within ethnicities exposed to different cultural environments warrants consideration.

Acknowledgments

Supported by a contract (N01-AG-4-2149) and grant (1-R01-AG17155-01A1) from the National Institute on Aging, a contract (N01-HC-05102) from the National Heart, Lung, and Blood Institute, a grant (1-R01-NS41265-01) from the National Institute of Neurological Disorders and Stroke, a grant from the United States Department of the Army (DAMD17-98-1-8621), by a Grant-In-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-Cardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare, a Japan Health and Labour Sciences Research Grant (Comprehensive Research on Aging and Health: H11-Chouju-046, H14-Chouju-003, H17-Chouju-012), the Japan Cardiovascular Research Foundation, and by the Japan Society for the Promotion of Science.

Abbreviations

NIPPON DATA	National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged
CI	confidence interval

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Table 1

Average Age and Age-adjusted Percents and Averages for the Baseline Risk Factor Levels (1980–1982) in Japanese Men Aged 61 to 81 Years in Japan and Hawaii.

Risk factor‡	Hawaii (1,379)*	Japan (954)
Excess adverse risk factors in Japan		
Age (y)	67.8 (5.0)†	68.9 (5.2)
Cigarette smoker (%)	19.1	55.8
Hypertension (%)	61.3	73.7
Systolic blood pressure (mm Hg)	139 (18)	150 (22)
Diastolic blood pressure (mm Hg)	81.2 (9.2)	85.2 (12.6)
Excess adverse risk factors in Hawaii		
Diabetes (%)	13.0	6.5
Total cholesterol (mg/dl)	211 (38)	183 (32)
Body mass index (kg/m^2)	23.5 (2.9)	21.8 (3.0)
Prevalent coronary heart disease (%)	11.4	2.6
Other characteristics		
Prevalent stroke (%)	3.5	5.0
Treatment for hypertension (%)	29.2	25.3
Height (cm)	163 (6)	158 (6)
Alcohol drinker (%)	66.4	62.5

*Sample size.

†Mean (standard deviation).

‡Risk factors differ significantly between Japan and Hawaii except for the percent of men who drank alcohol and the percent of men with prevalent stroke. For treatment of hypertension, p=0.037. For the other significant differences, p<0.001.

Table 2

Risk Factor Adjusted Relative Hazards of Total Mortality After 19 Years of Follow-up According to Baseline (1980–1982) Risk Factor Differences in Japanese Men Aged 61 to 81 Years in Japan and Hawaii.

		Hawaii		Japan	
Risk factor	**Risk factor difference***	**Relative hazard†**	**95% CI**	**Relative hazard†**	**95% CI**
Age	10 years	2.68‖	2.32, 3.09	2.97‖	2.54, 3.48
Cigarette smoker	Yes vs. no	1.67‖	1.40, 2.00	1.23≠	1.05, 1.45
Systolic blood pressure	20 mm Hg	1.16‖	1.07, 1.26	1.13§	1.05, 1.21
Treatment for hypertension	Yes vs. no	1.04	0.88, 1.22	1.39‖	1.16, 1.67
Diabetes	Yes vs. no	1.43‖	1.17, 1.75	1.22	0.90, 1.65
Total cholesterol	40 mg/dl	0.95	0.87, 1.04	0.94	0.84, 1.04
Body mass index	3 kg/m^2	0.91≠	0.84, 0.99	0.85‖	0.78, 0.93
Alcohol drinker	Yes vs no	0.95	0.82, 1.11	0.81≠	0.69, 0.96
Prevalent stroke	Yes vs no	2.56‖	1.85, 3.54	1.56§	1.14, 2.15
Prevalent coronary heart disease	Yes vs no	1.51‖	1.22, 1.87	0.85	0.51, 1.40

*For continuous risk factors, estimated relative hazards compare the risk of all-cause mortality in men with a high versus low risk factor level where risk factors differ by the amount specified and between men with and without a risk factor condition.

†Adjusted for other risk factors in the table.

Significant risk factor effect:

≠p<0.05,

§p<0.01,

‖p<0.001.

Note: The effects of smoking, prevalent stroke, and prevalent coronary heart disease were significantly different between Japan and Hawaii after risk factor adjustment (p<0.05).

Abbreviation: CI, confidence interval.

Table 3

Unadjusted and Adjusted Deaths/1,000 Person-years Based on 19 Years of Follow-up in Japanese Men Aged 61 to 81 Years in Japan and Hawaii.

	Deaths/1,000 person-years			
Adjusted risk factors	**Hawaii (1,379)***	**Japan (954)**	**Relative hazard‡**	**95% CI**
No adjustment	36.2 (738)†	49.4// (643)	1.44	1.29, 1.60
Age	36.4	48.8//	1.36	1.22, 1.51
Age and systolic blood pressure	37.3	47.2//	1.28	1.15, 1.43
Age and cigarette smoking	38.4	45.3¶	1.19	1.06, 1.33
All risk factors except systolic blood pressure and cigarette smoking§	37.8	46.4//	1.24	1.10, 1.40
Age, systolic blood pressure, and cigarette smoking	39.6	43.6	1.11	0.98, 1.25
All risk factors§	40.9	41.8	1.02	0.90, 1.16

*Sample size.

†Number of deaths.

‡Japan versus Hawaii.

§All risk factors include age, cigarette smoking, systolic blood pressure, treatment for hypertension, diabetes, total cholesterol, body mass index, alcohol drinking, and prevalent stroke and coronary heart disease.

//Significant excess risk of death in Japan versus Hawaii ($p<0.001$).

¶Significant excess risk of death in Japan versus Hawaii ($p<0.01$).

Abbreviation: CI, confidence interval.