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Similarities and differences between coronary heart disease and stroke in the associations with cardiovascular risk factors: The Japan Collaborative Cohort Study

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ABSTRACT

Background and aims: Coronary heart disease (CHD) and stroke have common risk factors, but some of these differ in the magnitude or direction of associations between CHD and stroke. We assessed whether the impact of each risk factor differed between CHD and stroke mortality in Asians.
Methods: In total, 104 910 subjects aged 40–79 years without histories of cancer, CHD and stroke at baseline were followed between 1988 and 2009. Competing-risks analysis was used to test for differences in the associations of each risk factor with two endpoints (CHD and stroke). Population attributable fractions (PAFs) were also calculated for these endpoints to estimate the population impact of each risk factor.
Results: During a median 19.1-year follow-up, 1554 died from CHD and 3163 from stroke. The association of hypertension with CHD was similar to that with stroke in terms of the magnitude and direction (multivariable-adjusted hazard ratio for CHD: 1.63 *vs.* stroke: 1.73 in men and 1.70 *vs.* 1.66 in women). Conversely, the magnitude of these associations differed for smoking (CHD: 1.95 *vs.* stroke: 1.23 in men and 2.45 *vs.* 1.35 in women) and diabetes (1.49 *vs.* 1.09 in men and 2.08 *vs.* 1.39 in women). The highest PAF for CHD was caused by smoking in men and by hypertension in women; that for stroke was caused by hypertension in both sexes.
Conclusions: Hypertension associations and PAFs were consistent between CHD and stroke, but not for other risk factors. These findings may be useful to optimize public health intervention strategies.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and disease burden worldwide. Hypertension [1], smoking [2], diabetes [3], alcohol intake [4], obesity [5], and physical inactivity [6] are well-known risk factors for CVD. In terms of the magnitude or direction, some of these risk factors are common to coronary heart disease (CHD) and stroke, while others are not.

Hypertension, for example, was similarly associated with CHD and stroke mortality [1]. Light to moderate alcohol intake was associated with a decreased risk of CHD mortality but not of stroke

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[4]. However, these possible similarities and differences between CHD and stroke mortality associated with CVD risk factors have not been systemically documented, especially in Asians, where the case mix of CHD and stroke differs significantly from that in Caucasians [7].

Therefore, we assessed whether the magnitude or direction of the association of each CVD risk factor with CHD mortality was different from that with stroke mortality in a large community-based cohort of Japanese men and women. We also assessed population attributable fractions (PAFs) of CHD or stroke related to each risk factor to recommend appropriate preventive strategies and policies from a public health viewpoint.

2. Materials and methods

2.1. Study population

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks, sponsored by the Ministry of Education, Sports, Science, and Technology of Japan, started between 1988 and 1990 and enrolled subjects living in 45 areas throughout Japan. Subjects (n = 110 585; 46 395 men and 64 190 women) aged 40–79 years completed self-administered questionnaires about their lifestyles and medical histories. See the online Supplementary Materials and references for sampling methods and other details of the JACC study. For the present analysis, we excluded subjects with histories of cancer, coronary heart disease (CHD) or stroke (n = 5675; 2488 men and 3187 women). Thus, 104 910 subjects (43 907 men and 61 003 women) were included. The study was approved by the Ethics Review Committee of Hokkaido University School of Medicine and Nagoya University School of Medicine.

2.2. Follow-up and mortality surveillance

The participants were followed up until death or up to the end of 2009 for most communities (follow-up concluded at the end of 1999 for four communities, 2003 for four communities and 2008 for two communities). In total, 20 017 subjects (11 407 men and 8610 women) were censored because of death secondary to causes other than CHD and stroke, and 5818 were censored because they were lost to follow-up. The median follow-up period of subjects was 19.1 (interquartile range, 11.4–21.0) years.

The date and cause of death were confirmed with the official death certificates, with permission of the Director-General of the Prime Minister's Office. The cause-specific mortality was adjusted for the transition to the International Classification of Diseases (10th revision), and was determined for CHD (I20–I25), stroke (I60–I69), CVD (including CHD and stroke), intracerebral hemorrhage (I61), and ischemic stroke (I63). The Hisayama Study reported that concordance between causes of death in death certificates and those in autopsy reports were 0.84 for stroke and 0.66 for CHD [8].

2.3. Statistical analysis

A self-administered questionnaire assessed sociodemographic information, smoking and alcohol-drinking status, exercise/sports activities, and self-reported past histories of hypertension and diabetes. The definition and coding of CVD risk factor variables, as well as information (references) regarding their reliability and validity, are provided in the Supplementary Materials. Sociodemographic characteristics, medical histories, and health behaviors of participants at baseline were summarized using the number and frequency percentages for each sex.

The percentage of missing values across eight variables ranged from 5.9% to 26.6% (Supplementary Table 1). In total, 54 161 out of 104 910 subject records (51.6%) were incomplete. We imputed the missing data using the Missing Values option of SPSS. Briefly, it constructed multiple regression models including age, sex, study area, and CVD risk factors and confounding variables. Using Rubin's rules [9], the results from 20 imputed data sets were combined by averaging, and standard errors were adjusted to reflect both within-imputation variability and between-imputation variability.

We used a Cox proportional cause-specific hazards model [10] to examine whether the associations with a risk factor (e.g., smoking status, alcohol intake, physical activity, body mass index [BMI], history of hypertension and history of diabetes) differed according to the outcomes.

The summary influence of each variable was estimated by constructing a series of minimally adjusted models that included the variable of interest, age, and education level (for women, menopausal and hormone replacement therapy were also included in the models). The independent influence of each variable was estimated using a multivariable model that was the same as the minimally adjusted model above, but that was also mutually adjusted for the other remaining variables.

There were different follow-up periods among study areas. We defined three subgroups: cohort 1 included subjects enrolled through 1999 (n = 13 569), cohort 2 included subjects enrolled through 2003 (n = 6165), and cohort 3 included subjects enrolled through 2008 or 2009 (n = 81 914). These cohorts were treated as strata in the Cox models to avoid potential confounding by the length of follow-up. The proportional hazard assumption was tested by plotting the logarithm of the estimated cumulative hazard function for each variable against time and then checking for parallelism; it was found not to be violated.

We tested whether Cox regression coefficients (i.e., hazard ratio: HR) of each risk factor variable differed between CHD and stroke mortality and calculated a p-value for the difference (p_{diff}) (see Supplementary Materials for details).

Although dyslipidemia is a well-established risk factor for CVD [11,12], it was not included in the main analyses because of the high percentage of missing values (total cholesterol [TC]: 72.4%, high-density lipoprotein cholesterol [HDL-C]: 90.6%, and triglycerides: 87.8%). However, we conducted supplementary analyses using imputed TC and HDL-C (see Supplementary Materials for details).

Additionally, the following sensitivity analyses were performed: a complete dataset, excluding early deaths occurring within 5 years of baseline (n = 3345; 1943 men and 1402 women), and excluding current smokers. Furthermore, additional analyses were performed by stratifying subjects according to age (40–64 and 65–79 years), and using different endpoints (CVD or stroke subtype). PAF was calculated to express the contribution of each CVD risk factor in the population (Supplementary Materials). Analyses were performed using SPSS ver.24 (IBM Corporation, Chicago, IL, USA).

3. Results

Participating men and women had a mean age of 57.2 and 57.6 years, respectively. During the follow-up period, 1554 died from CHD (874 men and 680 women) and 3163 from stroke (1587 men and 1576 women). Stroke mortality rates (2.27/1000 person-years in men and 1.56/1000 in women) were higher than CHD mortality rates (1.25/1000 in men and 0.67/1000 in women). Table 1 shows the crude mortality rates according to CVD risk factors.

History of hypertension was associated with both CHD and stroke mortality in a similar magnitude and direction in both men (p_{diff} = 0.525) and women (p_{diff} = 0.834) (Tables 2 and 3). Conversely, positive associations of current smoking with CHD mortality were considerably stronger than those with stroke

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