3. Int J Cardiol. 2015 Apr 1;184:692-8.

Relative and absolute risks of all-cause and cause-specific deaths attributable to atrial fibrillation in middle-aged and elderly community dwellers.

Ohsawa M, Okamura T, Ogasawara K, Ogawa A, Fujioka T, Tanno K, Yonekura Y, Omama S, Turin TC, Itai K, Ishibashi Y, Morino Y, Itoh T, Miyamatsu N, Onoda T, Kuribayashi T, Makita S, Yoshida Y, Nakamura M, Tanaka F, Ohta M, Sakata K, Okayama A.

BACKGROUND: The relative and absolute risks of outcomes other than all-cause death (ACD) attributable to atrial fibrillation (AF) stratified age have not been sufficiently investigated.
METHODS: A prospective study of 23,634 community dwellers aged 40 years or older without organic cardiovascular disease (AF=335, non-AF=23,299) was conducted. Multivariate-adjusted rates, rate ratios (RRs) and excess deaths (EDs) for ACD, cardiovascular death (CVD) and non-cardiovascular death (non-CVD), and sex- and age-adjusted RR and ED in middle-aged (40 to 69) and elderly (70 years or older) for ACD, CVD, non-CVD, sudden cardiac death (SCD), stroke-related death (Str-D), neoplasm-related death (NPD), and infection-related death (IFD) attributable to AF were estimated using Poisson regression.
RESULTS: Multivariate-adjusted analysis revealed that AF significantly increased the risk of ACD (RR [95% confidence interval]:1.70 [1.23-2.95]) and CVD (3.86 [2.38-6.27]), but not non-CVD. Age-stratified analysis revealed that AF increased the risk of Str-D in middle-aged (14.5 [4.77-44.3]) and elderly individuals (4.92 [1.91-12.7]), SCD in elderly individuals (3.21 [1.37-7.51]), and might increase the risk of IFD in elderly individuals (2.02 [0.80-4.65], p=0.098). The RR of CVD was higher in middle-aged versus elderly individuals (RRs, 6.19 vs. 3.57) but the absolute risk difference was larger in elderly individuals (EDs: 7.6 vs. 3.0 per 1000 person-years).
CONCLUSIONS: Larger absolute risk differences for ACD and CVD attributable to AF among elderly people indicate that the absolute burden of AF is higher in elderly versus middle-aged people despite the relatively small RR.

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Original Article

Coffee Consumption and Incidence of Subarachnoid Hemorrhage: The Jichi Medical School Cohort Study

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ABSTRACT

Background: Previous studies on the association between coffee consumption and subarachnoid hemorrhage (SAH) have provided inconsistent results. We examine the risk of SAH from coffee consumption in a Japanese population.

Methods: Our analyses were based on the Jichi Medical School Cohort Study, a large-scale population-based prospective cohort study. A total of 9941 participants (3868 men and 6073 women; mean age 55 years) with no history of cardiovascular disease or carcinoma were examined. Participants were asked to choose one of five options to indicate their daily coffee consumption: none, less than 1 cup a day, 1–2 cups a day, 3–4 cups a day, or 5 or more cups a day. The incidence of SAH was assessed independently by a diagnostic committee. Cox proportional hazards models were used to calculate hazard ratios (HRs) and their 95% confidence intervals (CI) after adjustment for age and sex (HR1) and for additional potential confounders (HR2).

Results: During 10.7 years of follow-up, SAH occurred in 47 participants. When compared with the participants who consumed less than 1 cup of coffee a day, the HR of SAH was significantly higher in the group who consumed 5 or more cups a day in both models (HR1 4.49; 95% CI, 1.44–14.00; HR2 3.79; 95% CI, 1.19–12.05).

Conclusions: The present community-based cohort study showed that heavy coffee consumption was associated with an increased incidence of SAH after adjusting for age, sex, and multiple potential cardiovascular confounders.

Key words: coffee consumption; subarachnoid hemorrhage; community-based cohort study

INTRODUCTION

Coffee is one of the most widely consumed beverages in the world,[1] although its effects on health are controversial.[2] As caffeine in coffee elevates blood pressure, coffee drinking has been thought to be a risk factor for incidence of cardiovascular diseases (CVD).[2] However, some epidemiological studies have reported that coffee intake decreases the risk of cardiovascular[3,4] and cerebrovascular diseases.[5–7]

Subarachnoid hemorrhage (SAH) is a type of severe intracranial bleeding that has a fatality rate of almost 50%.[8,9] About 10% of patients die in the prehospital period, and survivors often suffer long-term neurological or cognitive impairments.[8–10] Thus, clarifying the risk factors for SAH remains crucial. To date, high blood pressure,[11–13] smoking,[11–15] and alcohol drinking[15] have been shown to increase the risk of SAH, while a high body mass index (BMI) decreases the risk.[13,15]

Given the cerebrovascular effects of coffee,[5–7,16] studies on incident SAH in relation to coffee consumption are important. However, little information on the association between coffee consumption and SAH is available, and results are mixed.[5,6,11,12] Japan has a nontraditional culture of coffee consumption, with few high-volume consumers of this beverage.[17] Only one Japanese study has assessed the association of coffee consumption with incident SAH, and the study reported no association.[16] With the coffee culture in Japan growing and given the mixed results of previous studies, further Japanese research on this topic would be valuable. The purpose of this study was to evaluate the association of coffee consumption in a Japanese population with the incidence of SAH using data from the Jichi Medical

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School Cohort Study, a large-scale population-based prospective cohort study.[18]

METHODS

Subjects

This study used the data of the Jichi Medical School Cohort Study, which enrolled 12 490 participants (4911 men and 7579 women) from 12 communities in Japan.[18] The Japanese government has conducted mass screening for CVD since 1982 according to a system established by the Health and Medical Service Law for the Aged. The baseline data of the study were obtained during mass screening examinations. The baseline examinations occurred from April 1992 through July 1995, and the examinations included physical examinations, blood tests, and a self-administered questionnaire about socio-demographic status, history of medication use, and diet, including coffee consumption.

Of all participants, 95 declined to participate in follow-up and seven could not be contacted after the baseline examinations. In total, 4869 men and 7519 women were followed up as a complete cohort population. Subjects with a history of CVD or malignant neoplasms and those with missing data on coffee intake were excluded. Ultimately, the data from 9941 participants (3868 men and 6073 women) were used for this study. Further details of the baseline examinations and follow-up methods have been published elsewhere.[18]

Baseline examination

Dietary habits

Dietary habits were assessed using a food frequency questionnaire (FFQ) with 30 items, including an item regarding coffee consumption. Subjects chose one of five options indicating their daily coffee consumption: none, less than 1 cup a day, 1–2 cups a day, 3–4 cups a day, or 5 or more cups a day. The FFQ was already used in the Japan Collaborative Cohort Study, conforming the validity and reproducibility of the frequency assessment.[19] In order to test the reproducibility, the FFQs were distributed twice, at one-year intervals, and validity was assessed using a weighted dietary record.[19]

Lifestyle exposures

The other lifestyle- and health-related exposures were self-reported in semi-structured interviews.[18] Smoking status was classified as never smoker, ex-smoker, or current smoker. Alcohol consumption was categorized as never drinker, ex-drinker, or current drinker.

Physical and blood examinations

Body height was measured without shoes, and weight measured while fully clothed was determined by subtracting 0.5 kg (in the summer) and 1 kg (in other seasons) from the recorded weight values. BMI was calculated as weight in kilograms divided by squared body height in meters. Systolic blood pressure (SBP) was measured using an automated sphygmomanometer on the right arm of the participants after sitting for 5 minutes. Serum concentrations of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) cholesterol were measured using an enzymatic method.

Follow-up

The health status of the participants was followed up each year after the baseline examination. Participants were asked whether they had a diagnosis of CVD and, if so, which hospital they had visited and when they received the diagnosis. Additionally, if the participants did not attend the screening examination each year, they were contacted by mail, telephone, or via a public health nurse's home visit to obtain information on their health status. Death certificates of the participants were collected from public health centers with permission from the Agency of General Affairs and the Ministry of Health, Labour and Welfare. The follow-up of participants who died before the end of the study was stopped at that time. Information on participants who moved out of the study communities during the follow-up period was obtained annually from the relevant municipal governments; these participants ($n = 340$) were no longer followed up from the day they left the study communities. Follow-up of all other participants was continued until the end of 2005.

Diagnostic criteria of CVD, including SAH

In this study, CVD was defined as stroke, myocardial infarction, and sudden cardiac death, whichever occurred first. In participants with an event suspected to be related to CVD, computed tomography (CT) scans or magnetic resonance images in cases of stroke or electrocardiograms in cases of myocardial infarction was duplicated. A set of the image copy was sent to the diagnostic committee. CVD events were diagnosed independently by a diagnosis committee, which was composed of a neurologist, a radiologist, and two cardiologists. Stroke was diagnosed according to the diagnostic criteria of the National Institute of Neurological Disorders and Stroke (ie, in cases with a sudden onset of a focal, non-convulsive, and neurological deficit persisting longer than 24 hours).[20] SAH was diagnosed with a cranial CT scan performed to confirm the hyperdense appearance of extravasated blood in the subarachnoid space and/or basal cisterns. Myocardial infarction was diagnosed according to the criteria of the World Health Organization Multinational Monitoring of the Trends and Determinants in Cardiovascular Disease (MONICA) Project.[21]

Statistical analysis

The Statistical Package for Social Science (SPSS) for Windows, version 21.0 (IBM SPSS Japan Inc., Tokyo, Japan) was used for all analyses. General characteristics of participants were analyzed by frequency of coffee consumption and reported as proportions and means

Table 1. Baseline characteristics of participants by frequency of coffee intake

	Frequency of coffee intake						
	None	Less than 1 cup a day	1–2 cups a day	3–4 cups a day	5 or more cups a day	Total	*P*-value[a]
Number of subjects	2631	3198	2924	883	305	9941	
Female, %	65.1	60.6	60.9	56.9	44.6	61.1	<0.001
Age, years	59.8 (9.8)	56.1 (10.8)	51.2 (11.9)	48.1 (12.2)	52.3 (12.5)	54.8 (11.7)	<0.001
Body mass index, kg/m^2	23.1 (3.2)	23.1 (3.0)	23.0 (3.0)	22.8 (3.0)	22.8 (3.1)	23.0 (3.1)	0.011
Systolic blood pressure, mm Hg	132.2 (20.9)	129.9 (20.7)	126.3 (20.6)	123.6 (19.8)	126.1 (21.7)	128.8 (20.9)	<0.001
Serum cholesterol concentration							
Total cholesterol, mg/dL	192.5 (34.5)	191.7 (34.8)	191.1 (35.4)	189.5 (35.3)	188.1 (32.4)	191.5 (34.9)	0.078
HDL cholesterol, mg/dL	51.0 (12.9)	50.9 (12.7)	51.3 (12.8)	51.1 (12.9)	49.4 (13.6)	51.0 (12.8)	0.150
Triglycerides, mg/dL	122.0 (77.2)	118.1 (74.1)	110.0 (71.7)	109.3 (77.1)	117.4 (74.4)	115.9 (74.7)	<0.001
Current smoker, %	16.4	20.2	26.2	38.5	50.5	23.5	<0.001
Current alcohol drinker, %	36.4	44.0	48.2	54.8	54.2	44.5	<0.001

HDL, high-density lipoprotein.
[a]Values were calculated using one-way analysis of variance for continuous variables or the chi-square test for categorical variables and are reported as mean (standard deviation) unless otherwise noted.

(standard deviations). The associations between the frequency of coffee consumption and the confounders were analyzed by one-way analysis of variance and the chi-square test. A Cox proportional hazards model was used for calculating the hazard ratios (HRs) and 95% confidence intervals (CIs) of the incidence of SAH in relation to categories of coffee consumption, with adjustment for age and sex (HR1) or adjustment for age, sex, BMI, SBP, TC, smoking status, and alcohol consumption (HR2). Age, BMI, SBP, and TC were entered in the model as continuous variables; sex, smoking (current, ex-, or never smoker), and alcohol drinking (current, ex-, or never drinker) were entered as categorical variables.

Ethical considerations

This study was approved by the Institutional Review Board of Jichi Medical School (Epidemiology 03-01) and the Ethics Committee of Saitama Prefectural University (524716). Written informed consent was obtained from each participant.

RESULTS

The baseline characteristics by frequency of coffee intake are shown in Table 1. High-frequency drinkers were more likely to be young, smokers, and alcohol drinkers and less likely to be female and obese. The group who drank 3–4 cups of coffee a day had lower SBP and TG.

During an average follow-up of 10.7 years, we documented 488 CVD events (270 in men and 218 in women): 360 strokes (187 in men and 173 in women) including 47 SAHs (13 in men and 34 in women), 84 hemorrhagic strokes (42 in men and 42 in women), and 228 cerebral infarctions (132 in men and 96 in women). The incidence of SAH was 4.4 per 10 000 person-years.

Adjusted HRs and 95% CIs by frequency of coffee intake are shown in Table 2. HRs of SAH incidence were significantly higher among those who drank 5 or more cups a day than in those who drank less than 1 cup a day (HR1 4.49; 95% CI, 1.44–14.00 and HR2 3.79; 95% CI, 1.19–12.05).

DISCUSSION

The present study found that subjects who consumed 5 or more cups of coffee a day had a significantly higher risk of SAH incidence, while no significant risk increase was observed among those who drank less than 5 cups a day. To our knowledge, this is the first report of a significant increase of SAH incidence among heavy coffee drinkers in Japan. Given the mixed epidemiological research results on the cerebrovascular effects of coffee,[5–7,11,12,16] this finding is valuable.

Among our subjects, those who consumed 5 or more cups of coffee a day can be regarded as extremely high consumers. Such individuals might have other unhealthy nutrition-taking behaviors, meaning that the magnitude of the risk could be exaggerated. Further nutritional study is needed.

The Miyagi cohort study in Japan reported that frequent coffee intake was not significantly correlated with SAH mortality.[16] The Miyagi study categorized the frequency of coffee intake into three groups (never, occasionally, and one or more cups a day) while our analysis used five groups. This different categorization of coffee consumption could explain the different results.

Table 2. Hazard ratios and 95% confidence intervals for the incidence of subarachnoid hemorrhage by frequency of coffee intake adjusted for potential cardiovascular confounders

	Frequency of coffee intake				
	None	Less than 1 cup a day	1–2 cups a day	3–4 cups a day	5 or more cups a day
Person-years	27 719	34 682	31 629	9442	3200
Number of cases					
Total	15	12	13	3	4
Men	5	1	4	2	1
Women	10	11	9	1	3
Incidence rate, per 10 000 person-years	5.4	3.5	4.1	3.2	12.5
HR1 (95% CI)	1.29 (0.60–2.77)	1.00	1.44 (0.65–3.17)	1.28 (0.36–4.60)	4.49 (1.44–14.00)
HR2 (95% CI)	1.31 (0.61–2.82)	1.00	1.28 (0.57–2.87)	1.16 (0.32–4.23)	3.79 (1.19–12.05)

CI, confidence interval; HR1, Hazard ratio adjusted for age and sex; HR2: Hazard ratio adjusted for age, sex, body mass index, systolic blood pressure, total cholesterol concentration, smoking status, and alcohol consumption.

Most previous studies of the association between coffee intake and SAH were conducted in Western countries; two of these were incidence studies. Swedish women with high coffee intake showed significantly lower SAH incidence,[6] but coffee intake was not significantly associated with SAH incidence among Finnish male smokers.[5] Subjects in the Swedish study were about 60 years old and were participants in a mammography program. Their measured coffee intake was similar to that of our subjects, but they were older than our subjects by about 5 years on average and had a lower incidence of SAH (2.2 per 10 000 person-years). Compared with the subjects in our study, they may represent a healthier population. Age and incidence of SAH (5.4 per 10 000 person-years) of the Finnish men were similar to those of our subjects, but they were smokers and heavier coffee drinkers, and 21% reported consuming 8 or more cups of coffee a day. These differences in characteristics between the Scandinavian subjects and our own may help explain the differences in the findings.

A Colombian case-control study found no significant association between coffee intake and SAH.[12] Our results appear to be consistent with those of a Norwegian study[11] that showed significantly increased SAH mortality among subjects who drank more than 6 cups of coffee a day.

Findings from the present epidemiological study cannot fully explain the underlying mechanisms of the relation between coffee consumption and incidence of SAH. Many experimental and clinical studies have reported both protective and harmful effects of coffee. Excess intake of caffeine, the most investigated component in coffee, may elevate blood pressure by increasing systemic vascular resistance.[16] Hydroxyhydroquinone generated by roasting coffee beans could interfere with the vasodilatory effect of chlorogenic acids,[2] which have antioxidant functions[17] that benefit vascular health.[22,23] Another possibility is that the addition of sugar, milk, and cream to coffee leads to high energy intake that may induce oxidative stress and insulin resistance. However, when our study results were adjusted to account for factors related to oxidative stress and insulin resistance, including smoking, BMI, and blood pressure, the adjustments did not attenuate the statistical significance of the findings.

The strengths of this study are the large size, use of a community-based cohort study design with incident disease outcomes, and careful case review by an independent diagnostic committee. However, our study has several limitations. First, the group with a significantly increased risk of SAH included only four cases. While the results were statistically significant after adjusting for sex, age, and five major CVD risk factors, the robustness of the observed association is probably limited, and the finding could be a chance observation. No statistically significant trend in risk was observed among those who drank less than 5 cups a day. Statistical power may be low due to the small number of SAH cases ($n = 47$) in the cohort population, while the incidence of SAH in this study is almost three times as high as the mortality of SAH (1.46 per 10 000 person-years) reported in a previous Japanese study.[16] Second, a high prehospital mortality rate could make SAH diagnosis difficult. During follow-up, we documented 41 cases of sudden death defined as death within 24 hours after the onset of symptoms. All cases of sudden death were reviewed carefully by the diagnostic committee to rule out SAH. However, considering difficulty in identifying cause of out of hospital death, it is possible that some SAH cases could not be diagnosed. Finally, the FFQ was self-administered and implemented only once at baseline, so the evaluation of dietary habits might not be accurate. We did not clarify whether dietary habits changed during the follow-up period, although the validity and reliability of the FFQ are known to be acceptable.[19] Types of coffee and its additives were not assessed by the FFQ.

In conclusion, the present study from the Jichi Medical School Cohort Study showed that, compared with subjects who consumed less than 1 cup a day, those who consumed 5 or more cups of coffee a day had a significantly higher risk of incident SAH, while no significant increase in risk was observed among those who drank less than 5 cups a day. This suggests that heavy coffee consumption is a risk factor for incident SAH.

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Conflicts of interest: None declared.

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Original Article

Accuracy of Death Certificates and Assessment of Factors for Misclassification of Underlying Cause of Death

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ABSTRACT

Background: Cause of death (COD) information taken from death certificates is often inaccurate and incomplete. However, the accuracy of Underlying CODs (UCODs) recorded on death certificates has not been comprehensively described when multiple diseases are present.

Methods: A total of 450 consecutive autopsies performed at a geriatric hospital in Japan between February 2000 and August 2002 were studied. We evaluated the concordance rate, sensitivity, and specificity of major UCODs (cancer, heart disease, and pneumonia) reported on death certificates compared with a reference standard of pathologist assessment based on autopsy data and clinical records. Logistic regression analysis was performed to assess the effect of sex, age, comorbidity, and UCODs on misclassification.

Results: The concordance rate was relatively high for cancer (81%) but low for heart disease (55%) and pneumonia (9%). The overall concordance rate was 48%. Sex and comorbidity did not affect UCOD misclassification rates, which tended to increase with patient age, although the association with age was also not significant. The strongest factor for misclassification was UCODs ($P < 0.0001$). Sensitivity and specificity for cancer were very high (80% and 96%, respectively), but sensitivity for heart disease and pneumonia was 60% and 46%, respectively. Specificity for each UCOD was more than 85%.

Conclusions: Researchers should be aware of the accuracy of COD data from death certificates used as research resources, especially for cases of elderly patients with pneumonia.

Key words: accuracy; autopsy; death certificates; outcome misclassification; underlying cause of death

INTRODUCTION

Cause of death (COD) data from death certificates are often used in epidemiological studies to estimate mortality rates or risk of death from certain diseases. However, the accuracy and utility of COD data from death certificates are uncertain and often questionable.[1–5] For cancer mortality statistics in particular, uncertainty regarding the information on death certificates has been discussed for more than 100 years. For example, in early 1900s, Riechelmann reported differences in the number of cancer cases between autopsy and vital statistics reports,[6] and Wells discussed the degree of this influence on vital statistics.[7] In the late 20th century, Hoel et al reviewed the effect of death certificate error on cancer mortality statistics and found a consistent 18% underestimation of total cancer mortality, with an especially large influence on the elderly population (75 years or older).[8] Since around 2000, site-specific analyses for misclassification have been investigated. For example, Percy et al reported on misclassification in colorectal cancer, finding that colon cancer

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was over-reported while rectal cancer was underreported on death certificates.[9] Similarly, Yin et al indicated that 82% of misclassified rectal cancer deaths were coded as colon cancer deaths.[10]

For diseases other than cancer, Cheng et al reported death certificate sensitivity and specificity for diabetes of 34.7% and 98.1%, respectively. In their 30-year study, they also reported cardiovascular disease-related diabetes sensitivity stratified by decade of death and showed a time trend of improved sensitivity that reflected increased recognition of cardiovascular disease risk factors.[11] In Japan, Saito et al reported the validity of death certificates for ischemic heart diseases after the ICD-10 code revision. They compared death certificates and the diagnosis examined by a review of the medical records and/or interviews with physicians and reported that the sensitivity and specificity for ischemic heart disease certified as the cause of death was 86.5% and 64.7%, respectively.[12] Ravakhah compared death certificate diagnoses with autopsy report diagnoses in 223 cases and reported that myocardial infarction was more likely to be unsuspected in women and those with advanced age.[13] Kohn reviewed autopsy findings in 200 persons older than 85 years, indicating that the autopsy data were in strong disagreement with the causes of death listed in the vital statistics and proposing that 'senescence' be accepted as a cause of death.[14]

These studies underscore the difficulty in specifying underlying COD (UCOD), especially among elderly people, who tend to have multiple diseases before death. However, the accuracy of UCODs recorded on the death certificates of elderly people has not yet been comprehensively examined for multiple diseases using consecutive autopsy studies. Here, we evaluated the accuracy of UCODs of elderly people recorded on death certificates compared to a reference standard of autopsy findings.

METHODS

Study subjects

Of 532 consecutive autopsies performed at the Tokyo Metropolitan Geriatric Hospital (Tokyo, Japan) between February 2000 and August 2002, 450 (84.6%) were included in the present study. No medico-legal cases were included. The average autopsy rate during this period was 32%. All subjects were registered in the geriatric autopsy database (GEAD) at the Tokyo Metropolitan Geriatric Hospital, which contains clinical information (presence or absence of 26 geriatric diseases, as follows: ischemic heart disease, atrial fibrillation, degenerative valvular diseases, hypertension, aneurysm, arteriosclerosis obliterans, dementia, cerebrovascular disorder, Parkinson's disease, diabetes mellitus, hyperlipidemia, malnutrition, osteoporosis, degenerative osteoarthritis, aspiration, chronic obstructive pulmonary disease, idiopathic interstitial pneumonia, urinary tract infection, prostatic hypertrophy, decubital ulcer, lung cancer, gastric cancer, colon cancer, hematopoietic malignancy, cataract, and glaucoma, as well as clinical dementia ratings and histories of smoking and alcohol consumption) and pathological findings (720 items frequently encountered in autopsy examinations of elderly subjects). Details on the GEAD have been reported elsewhere.[15]

COD data

All CODs recorded on death certificates based on clinical and autopsy records were first evaluated by M.S., a pathologist and co-author of this study, for reporting consistency and adherence to instructions for proper completion of the death certificate. The CODs were subsequently evaluated by T.A., also a pathologist and co-author of this study, to confirm the accuracy of the findings and were entered into the database using the International Classification of Diseases, Tenth Revision (ICD-10) codes. UCODs based on death certificates were defined as the diagnoses listed last in Part I of death certificates according to guidelines published by the Ministry of Health, Labour and Welfare in Japan.[16] UCODs based on postmortem examination in conjunction with clinical information were diagnosed by the same two pathologists, M.S. and T.A., as the reference standard. UCODs specified for each subject were coded using Simcode as well as ICD-10. Simcode is the classification code developed by the Japanese Ministry of Health, Labour and Welfare to define vital statistics.[17] The overall agreement between UCOD identified on death certificates and the reference standard was classified into the following categories: 1. Perfect ICD-10 code agreement; 2. Disagreement involving the same organ system; 3. Disagreement, but listed as a COD on death certificate; and 4. Complete disagreement. We defined these agreement proportions as the concordance rates, sensitivity as the proportion of the cases positively identified using both methods (UCOD identified on death certificate [+] and UCOD identified using the reference standard [+]) to the cases positively identified using the reference standard, and specificity as the proportion of the cases negatively identified using both methods (UCOD identified on death certificate [−] and UCOD identified using the reference standard [−]) to the cases negatively identified using the reference standard.

Statistical analysis

McNemar's test was used to evaluate differences between UCOD proportions estimated based on data solely from the death certificates and those estimated based on reference standard data. We also calculated the 95% Wald confidence intervals (CIs) with Bonett-Price Laplace adjustment for differences between proportions.[18] Multivariate unconditional logistic regression analyses assessed the effect of age at death (<80 vs 80–89 and ≥90 years), sex, comorbidity, and major UCODs identified on death certificates (cancer, heart disease, pneumonia, and others) on UCOD misclassification.

Comorbidity was defined as the number of clinical findings present among the 26 findings registered in the GEAD. In the logistic regression model, we had classified the number of comorbidity into three groups: no or low comorbidity (0–1 finding), moderate comorbidity (2–4 findings), and high comorbidity (≥5 findings).

Sensitivity and specificity with 95% Clopper-Pearson exact CIs were calculated for UCODs estimated to be present in at least 5% of the study population. We used SAS and JMP software for Windows (versions 9.3 and 10, respectively; SAS Institute, Cary, NC, USA) for all statistical analyses. Statistical significance was set at $P < 0.05$.

Ethical considerations

The Japanese Postmortem Examination and Corpse Preservation Act generally permits use of autopsy materials for medical education and research. This study was approved by the ethics committee of Tokyo Metropolitan Geriatric Hospital (#240423).

RESULTS

Table 1 shows subject characteristics. The average age at death was 79.8 years (range, 46–100 years; median, 80 years). Median number of major clinical findings was 3 (range, 0–8).

UCOD distributions by sex are shown in Table 2. Simcodes generally conformed to ICD-10 codes, which are also shown in Table 2. The results indicate that cancer mortality would be underestimated (the absolute difference between death certificate information and the reference standard was 5.3% in women [95% CI, 0.49–10.0%; $P = 0.025$] and 6.1% in men [95% CI, 2.2–9.9%; $P = 0.0017$]), whereas the mortality for respiratory system diseases, especially pneumonia, would be overestimated (the absolute difference between death certificate information and the reference standard was 6.4% [95% CI, 1.6–11.1%; $P = 0.0073$] in women and 8.7% [95% CI, 4.1–13.3%; $P = 0.0002$] in men).

Of 450 UCODs identified on death certificates, 214 (47.6%) agreed completely with UCODs identified based on clinical and post-autopsy reports at ICD-10 three-digit code levels. When we applied Simcode (broader categories than the ICD-10 code categories shown in Table 2) to UCODs, the concordance rate increased to 59.3% and was further improved to 69.6% when major Simcodes (largest CODs category, indicated by boldface in Table 2, used for rough national mortality statistics) were used (Figure). Of 236 instances of UCOD disagreement, 83 (35.2%) cases were assigned to the same organ system, 38 (16.1%) were assigned as CODs but not UCODs on the death certificates, and 115 (48.7%) disagreed completely.

We also explored how concordance rates varied depending on UCODs. The concordance rate for cancer was 80.8% at the ICD-10 code level and increased to 93.6% at the major Simcode level. The concordance rate at the ICD-10 code level for heart disease was not high (54.7%); however, it improved to 83.0% at the major Simcode level. Among major UCODs, pneumonia, which is the third leading COD in Japan in 2012,[19] had the lowest concordance rate (8.8% at the ICD-10 code level) (Figure).

We next examined the effects of sex, age, comorbidity, and UCODs on misclassification of UCODs identified on death certificates (Table 3). We found that sex, comorbidity, and age did not affect the UCOD misclassification rate ($P = 0.53$, $P = 0.75$, and $P = 0.13$, respectively), although the misclassification rate showed an increasing trend, especially for cases >90 years old (adjusted odds ratio [vs <80 years old] 1.44; 95% CI, 0.72–2.88). The strongest factor for misclassification was UCODs ($P < 0.0001$); the results also show that cancer and heart disease were less often misclassified than other minor UCODs (adjusted odds ratio 0.10; 95% CI, 0.06–0.16 and adjusted odds ratio 0.34; 95% CI, 0.18–0.65, respectively), whereas pneumonia was significantly misclassified compared to other minor UCODs (adjusted odds ratio 4.44; 95% CI, 1.66–11.8) (Table 3). On exploring the factors influencing accuracy of sensitivity and specificity for each disease, we found that age (>90 years) had a profound influence on specificity for pneumonia (odds ratio 3.23; 95% CI, 1.50–6.69; $P = 0.0016$), although the sample size was relatively small for such disease-specific analyses.

Finally, we evaluated the sensitivity and specificity of UCODs estimated to be present in at least 5% of the population (Table 4). Statistics were calculated for each UCOD identified on death certificates compared with the reference standard of assessment by two pathologists based on autopsy data and past clinical records. Overall, specificity for each UCOD was at least 85%. Sensitivity for any cancer was high (80%), although values varied according to organ. Sensitivity for heart disease was 60%, and sensitivity for pneumonia was very low (46%). Results also suggested that diseases of the digestive system were difficult to specify as UCOD (sensitivity, 51.9%). Among 13 deaths attributable to digestive diseases, 5 (38%) were reported as deaths due to unknown causes, 3 (23%) as deaths due to infectious diseases, and 3 (23%) as deaths due to heart disease.

Table 1. Patient characteristics

Sex	Female (n = 187)	Male (n = 263)	Total (n = 450)
Mean (SD) age at death, years	81.9 (8.7)	78.2 (8.6)	79.8 (8.8)
frequency (%)			
<70 years	9 (5%)	33 (13%)	42 (9%)
70–79 years	61 (33%)	118 (45%)	179 (40%)
80–89 years	75 (40%)	83 (32%)	158 (35%)
≥90 years	42 (23%)	29 (11%)	71 (16%)
Mean (SD) number of major clinical findings	3.1 (1.7)	3.1 (1.6)	3.1 (1.7)
frequency (%)			
0–1	34 (18%)	50 (19%)	84 (19%)
2–4	117 (63%)	164 (62%)	281 (62%)
≥5	36 (19%)	49 (19%)	85 (19%)

Table 2. Patients proportion of UCOD measured by death certificates only or by clinical and autopsy reports

Disease category	ICD-10 codes	Females (n = 187)			Males (n = 263)		
		UCOD on the death certificates	UCOD based on clinical and autopsy-derived information	absolute difference[a]	UCOD on the death certificates	UCOD based on clinical and autopsy-derived information	absolute difference[a]
Certain infectious and parasitic diseases	A00–B99	6 (3.2%)	4 (2.1%)	−1.1%	10 (3.8%)	11 (4.2%)	0.4%
Malignant neoplasms	C00–C97	**62 (33.2%)**	**72 (38.5%)**	**5.3%**	**94 (35.7%)**	**110 (41.8%)**	**6.1%**
Malignant neoplasms of lip, oral cavity, and pharynx	C00–C14	0 (0.0%)	0 (0.0%)	0.0%	0 (0.0%)	1 (0.4%)	0.4%
Malignant neoplasm of esophagus	C15	0 (0.0%)	0 (0.0%)	0.0%	1 (0.4%)	1 (0.4%)	0.0%
Malignant neoplasm of stomach	C16	1 (0.5%)	2 (1.1%)	0.6%	14 (5.3%)	17 (6.5%)	1.2%
Malignant neoplasm of colon	C18	4 (2.1%)	4 (2.1%)	0.0%	2 (0.8%)	2 (0.8%)	0.0%
Malignant neoplasm of rectum and rectosigmoid junction	C19–C20	1 (0.5%)	1 (0.5%)	0.0%	2 (0.8%)	2 (0.8%)	0.0%
Malignant neoplasm of liver and intrahepatic bile ducts	C22	2 (1.1%)	5 (2.7%)	1.6%	4 (1.5%)	5 (1.9%)	0.4%
Malignant neoplasm of gallbladder and unspecified parts of biliary tract	C23–C24	5 (2.7%)	8 (4.3%)	1.6%	3 (1.1%)	5 (1.9%)	0.8%
Malignant neoplasm of pancreas	C25	4 (2.1%)	3 (1.6%)	−0.5%	4 (1.5%)	5 (1.9%)	0.4%
Malignant neoplasm of trachea, bronchus, and lung	C33–C34	14 (7.5%)	13 (7.0%)	−0.5%	26 (9.9%)	31 (11.8%)	1.9%
Malignant neoplasm of cervix uteri, corpus uteri, and uterus	C53–C55	1 (0.5%)	1 (0.5%)	0.0%	—	—	—
Malignant neoplasm of prostate	C61	—	—	—	1 (0.4%)	0 (0.0%)	−0.4%
Malignant neoplasm of bladder	C67	3 (1.6%)	1 (0.5%)	−1.1%	1 (0.4%)	1 (0.4%)	0.0%
Malignant lymphoma	C81–C85	11 (5.9%)	13 (7.0%)	1.1%	8 (3.0%)	11 (4.2%)	1.2%
Leukemia	C91–C95	10 (5.3%)	16 (8.6%)	3.3%	23 (8.7%)	24 (9.1%)	0.40%
Other malignant neoplasms	Others in C00–C97	6 (3.2%)	5 (2.7%)	−0.5%	5 (1.9%)	5 (1.9%)	0.0%
Non-malignant neoplasms	D00–D48	**6 (3.2%)**	**1 (0.5%)**	**−2.7%**	**3 (1.1%)**	**5 (1.9%)**	**0.8%**
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50–D89	**1 (0.5%)**	**2 (1.1%)**	**0.6%**	**3 (1.1%)**	**3 (1.1%)**	**0.0%**
Endocrine, nutritional, and metabolic diseases	E00–E90	**1 (0.5%)**	**6 (3.2%)**	**2.7%**	**5 (1.9%)**	**5 (1.9%)**	**0.0%**
Diabetes mellitus	E10–E14	1 (0.5%)	2 (1.1%)	0.6%	2 (0.8%)	3 (1.1%)	0.3%
Other endocrine, nutritional, and metabolic diseases	Others in E00–E90	0 (0.0%)	4 (2.1%)	2.1%	3 (1.1%)	2 (0.8%)	−0.3%
Mental and behavioral disorders	F00–F99	**0 (0.0%)**	**1 (0.5%)**	**0.5%**	**0 (0.0%)**	**0 (0.0%)**	**0.0%**
Diseases of the nervous system	G00–G99	**5 (2.7%)**	**6 (3.2%)**	**0.5%**	**4 (1.5%)**	**7 (2.7%)**	**1.2%**
Diseases of the circulatory system	I00–I99	**46 (24.6%)**	**52 (27.8%)**	**3.2%**	**41 (15.6%)**	**45 (17.1%)**	**1.5%**
Hypertensive diseases	I10–I15	1 (0.5%)	0 (0.0%)	−0.5%	2 (0.8%)	0 (0.0%)	−0.8%
Heart disease	I01–I02, I05–I09, I20–I25, I27, I30–I52	26 (13.9%)	34 (18.2%)	4.3%	27 (10.3%)	33 (12.5%)	2.2%
Cerebrovascular diseases	I60–I69	9 (4.8%)	6 (3.2%)	−1.6%	4 (1.5%)	2 (0.8%)	−0.7%
Aortic aneurysm and dissection	I71	5 (2.7%)	6 (3.2%)	0.5%	4 (1.5%)	6 (2.3%)	0.8%
Diseases of the circulatory system other than aortic aneurysm and dissection	Others in I00–I99	5 (2.7%)	6 (3.2%)	0.5%	4 (1.5%)	4 (1.5%)	0.0%
Diseases of the respiratory system	J00–J99	**29 (16.5%)**	**17 (9.1%)**	**−7.4%**	**70 (26.6%)**	**51 (19.3%)**	**−7.3%**
Pneumonia	J12–J18	20 (10.7%)	8 (4.3%)	−6.4%	37 (14.1%)	14 (5.3%)	−8.8%
Chronic obstructive pulmonary disease	J41–J44	2 (1.1%)	0 (0.0%)	−1.1%	11 (4.2%)	11 (4.2%)	0.0%
Other diseases of the respiratory system	Others in J00–J99	7 (3.7%)	9 (4.8%)	1.1%	22 (8.4%)	26 (9.9%)	1.5%
Diseases of the digestive system	K00–K93	**16 (8.6%)**	**14 (7.5%)**	**−1.1%**	**15 (5.7%)**	**13 (4.9%)**	**−0.8%**
Diseases of the skin and subcutaneous tissue	L00–L99	**0 (0.0%)**	**1 (0.5%)**	**0.5%**	**1 (0.4%)**	**0 (0.0%)**	**−0.4%**
Diseases of the musculoskeletal system and connective tissue	M00–M99	**1 (0.5%)**	**5 (2.7%)**	**2.2%**	**1 (0.4%)**	**1 (0.4%)**	**0.0%**
Diseases of the genitourinary system	N00–N99	**7 (3.7%)**	**5 (2.7%)**	**−1.0%**	**4 (1.5%)**	**6 (2.3%)**	**0.8%**
Other cause of death	Others	**7 (3.7%)**	**1 (0.5%)**	**−3.2%**	**12 (4.6%)**	**6 (2.3%)**	**−2.3%**

UCOD, underlying cause of death.
[a]The difference between the proportion of UCOD based on clinical and autopsy-derived information and that of UCOD on the death certificates.

Table 5 also shows that deaths due to cancer and heart disease were underestimated regardless of true UCODs, and 18 (38%) of 47 deaths due to pneumonia and 28 (55%) of 51 deaths due to respiratory diseases would be considered deaths due to cancer or heart disease.

DISCUSSION

We evaluated the accuracy of UCODs, particularly major UCODs, recorded on the death certificates of elderly patients in Japan. To our knowledge, this is the first report to quantitatively estimate accuracy for several UCODs specified on death certificates. Data from death certificates are used for many clinical and population-based studies and national vital statistics, although the difficulties in properly completing the COD section of the death certificate to ensure accuracy of COD data have been well documented.[1–5] Several recently proposed statistical methods to account for outcome variable misclassification enable bias correction of effect estimates due to misclassified outcomes, such as those measured by death certificates.[20–23] However, it is difficult to quantitatively evaluate the accuracy of data from death certificates, as we have done here, because reference standard data is not easily obtainable, especially in studies that utilize large national databases. Our results might be informative either for applying bias correction methods or sensitivity analyses to assess effect estimate bias in studies using data from death certificates.

According to national vital statistics' reports, the four leading UCODs in Japan in 2000 were malignant lymphoma (29.6% of deaths among 80- to 84-year-olds), heart disease (16.1% of deaths among 80- to 84-year-olds), cerebrovascular disease (11.6% of deaths among 80- to 84-year-olds), and

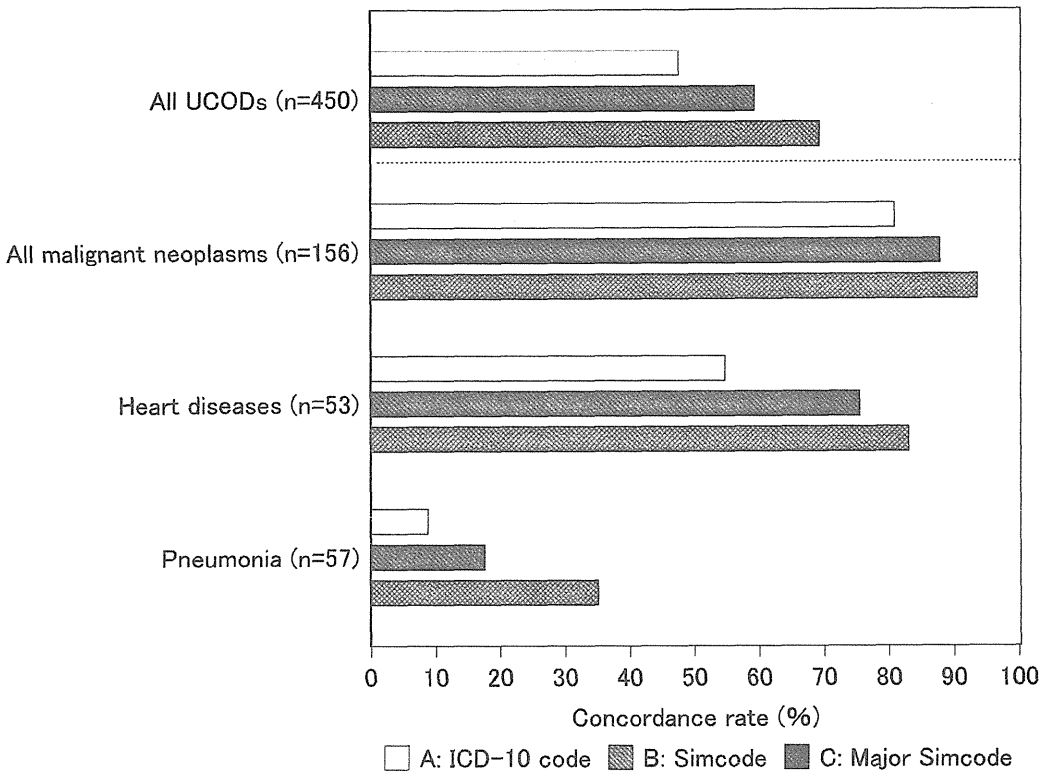

Figure. Concordance rates for UCOD recorded on the death certificates and judgment from clinical and pathological records by coding methods for CODs.

Table 3. Multivariate logistic regression analysis for agreement between UCODs evaluated by death certificates only and clinical and autopsy-based UCODs

Variables in the model	Adjusted OR	95% CI	*P* value[a]
Gender (female vs male)	1.16	0.73, 1.84	0.53
UCOD in death certificates			<0.0001
Cancer (vs others)	0.10	0.06, 0.16	<0.0001
Heart Disease (vs others)	0.34	0.18, 0.65	0.018
Pneumonia (vs others)	4.44	1.66, 11.8	<0.0001
Age			0.134
80–89 (vs <80) years	0.73	0.44, 1.21	0.050
≥90 (vs <80) years	1.44	0.72, 2.88	0.114
Number of clinical findings (Comorbidity)			0.75
2–4 (vs 0–1)	0.79	0.44, 1.45	0.59
≥5 (vs 0–1)	0.81	0.39, 1.70	0.76

CI, confidence interval; OR, odds ratio; UCOD, underlying cause of death.
[a]*P* value was from Wald Chi-Square test.

pneumonia (11.4% of deaths among 80- to 84-year-olds). In our study, the top four UCODs were malignant lymphoma (28.5% among individuals in their 80s), pneumonia (16.5% among individuals in their 80s), heart disease (13.3% among individuals in their 80s), and digestive system disease (7.6% among individuals in their 80s). Thus, except for death due to cerebrovascular disease, the distribution of UCODs in our population was similar. This is because the Tokyo Metropolitan Geriatric Hospital is not an acute care hospital, and most cases had chronic diseases. The population analyzed here is not representative of the whole population of elderly people in Japan, and we could not assess the accuracy of UCODs for acute diseases in this study. However, our data showed that deaths due to cancer and heart disease based solely on death certificate records would be underestimated, a finding that has also been reported in previous studies.[9,12] Hu et al assessed the reliability of COD for the Surveillance, Epidemiology, and End Results (SEER) database using a relative survival approach and showed that the number of cancer-specific deaths documented in SEER was over-coded for early stage cancers or cancers with favorable prognoses, whereas SEER tended to undercode the number of cancer-specific deaths for cancers with generally poor prognosis or advanced-stage cancers.[24] In our study data, most cancer-specific deaths were of poor prognosis or advanced-stage cancer, so our observation is consistent with previous research.

In general, COD in elderly patients is subject to speculation because of the competing effects of comorbidity-associated mortality. However, while our data showed neither significant comorbidity nor age effects, we observed that the misclassification rate in very old patients tended to be higher than in younger patients even after adjusting for UCOD and comorbidity. This suggests that "more likely"

Table 4. Sensitivity and specificity of major UCODs evaluated by death certificates only

UCOD	*n* of UCOD on the death certificates	*n* of UCOD based on clinical and autopsy-derived information	*n* of both UCODs truly classified (+)	Sensitivity (%)		Specificity (%)	
				Point estimate	95% CI	Point estimate	95% CI
Certain infectious and parasitic diseases	16	15	6	40.0	16.3, 67.7	97.7	95.8, 98.9
Malignant neoplasms	**156**	**182**	**146**	80.2	73.7, 85.7	96.3	93.3, 98.2
Stomach	15	19	14	73.7	48.8, 90.9	99.8	98.7, 100
Trachea, bronchus, and lung	40	44	38	86.4	72.7, 94.8	99.5	98.2, 99.9
Malignant lymphoma	19	24	18	75.0	53.3, 90.2	99.8	98.7, 100
Leukemia	33	40	30	75.0	58.8, 87.3	99.3	97.9, 99.9
Diseases of the circulatory system	**87**	**97**	**74**	71.1	61.1, 79.9	94.9	92.1, 97.0
Heart disease	53	67	40	59.7	47.0, 71.5	96.6	94.3, 98.2
Diseases of the respiratory system	**99**	**68**	**48**	70.6	58.3, 81.0	86.7	82.8, 89.9
Pneumonia	57	22	10	45.5	24.4, 67.8	89.0	85.7, 91.8
Diseases of the digestive system	**31**	**27**	**14**	51.9	32.0, 71.3	96.0	93.6, 97.6

CI, confidence interval; UCOD, underlying cause of death.

CODs without detailed investigation are recorded on death certificates regardless of patient history, particularly if the patient was more than 90 years of age and died of old age.

To our knowledge, there have been no previous reports on the accuracy of COD data from death certificates for pneumonia, despite being a leading COD in many countries. As discussed above, the UCOD recorded for elderly patients could be the "more likely" COD, and pneumonia would be a most likely UCOD in very elderly patients because many of them are likely to die of pneumonia. Another reason for the high pneumonia misclassification rate was that many cases of aspiration pneumonia were reported as deaths due to pneumonia. In contrast to the misclassified cases of death due to digestive or other minor diseases, misclassified death due to pneumonia is likely to be caused by misjudgment and not by errors in diagnostic techniques. Myers et al showed that the accuracy of death certificates could be improved by implementation of a simple educational intervention.[25] In Japan, many medical doctors previously reported heart failure as the UCOD on death certificates regardless of the true UCOD.[12,26] However, this poor practice has improved in the past several decades by adding a note on death certificates according to a revised ICD-10 code, which states, "Do not enter the mode of dying, such as cardiac or respiratory arrest, shock, or heart failure." Therefore, the pneumonia misclassification rate could be reduced by education or by including notes or instructions in the guidelines for completing death certificates when pneumonia appears as a condition on the death certificate.

Study limitations

Although having multiple-cause autopsy mortality data was a strength of this study, the potential for autopsy bias limits our ability to generalize the results to the rest of the population. As mentioned above, we could not assess the accuracy of UCODs for acute diseases, such as cerebrovascular death. Additionally, we were unable to measure the accuracy of UCOD for minor diseases and diseases for which only clinical diagnoses were available, such as diabetes or some psychiatric diseases. To assess the validity of death certificate data for such diseases, additional disease-specific studies modeled on previous reports are necessary.[3,4,27] The data we investigated were collected more than 10 years ago. If the medical record training for doctors had been well-established during the period, we might have obtained more accurate sensitivities and specificities. However, to our knowledge, the situation has not changed much, so improvements in medical recordkeeping may have little effect on the interpretation of our results.

Conclusion

Researchers should be aware of the accuracy of COD data on death certificates used as research resources, particularly for elderly research subjects who died from diseases other than cancer (especially pneumonia).

ONLINE ONLY MATERIAL

Abstract in Japanese.

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Conflicts of interest: None declared.

Author contributions

Study design: NT and MNM. Autopsy data retrieval: MS and TA. Statistical analyses: MNM and NT. Data management: MNM, TK, and AK. Manuscript review: AK, TK, TA, and SI. Manuscript preparation: MNM, NT, and MS.

Table 5. List of major UCODs misclassified on death certificates

UCOD specified with the death certificate	UCOD specified with clinical and autopsy records								
Certain infectious and parasitic diseases (*n* = 10)	Diseases of the digestive system (3)	Diseases of the respiratory system other than pneumonia (2)	Cancer (2)	Pneumonia (1)	Diseases of the genitourinary system (1)	Diseases of the skin and subcutaneous tissue (1)			
Malignant neoplasms (*n* = 10)	Heart disease (3)	Diseases of the genitourinary system (2)	Non-malignant neoplasms (1)	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (1)	Diseases of the circulatory system other than aortic aneurysm and dissection (1)	Pneumonia (1)	Diseases of the respiratory system other than pneumonia (1)		
Stomach (*n* = 1)	Pneumonia (1)								
Trachea, bronchus, and lung (*n* = 2)	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (1)	Heart disease (1)							
Malignant lymphoma (*n* = 1)	other cancer (1)								
Leukemia (*n* = 3)	other cancer (1)	Non-malignant neoplasms (1)	Diseases of the genitourinary system (1)						
Diseases of the circulatory system (*n* = 13)	Diseases of the digestive system (4)	Cancer (3)	Certain infectious and parasitic diseases (2)	Pneumonia (2)	Diseases of the respiratory system other than pneumonia (2)	unknown (2)	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (1)	Diabetes mellitus (1)	Diseases of the genitourinary system (1)
Heart disease (*n* = 13)	Diseases of the circulatory system other than heart disease (4)	Diseases of the digestive system (3)	Certain infectious and parasitic diseases (1)	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (1)	Diabetes mellitus (1)	Pneumonia (1)	Diseases of the genitourinary system (1)	unknown (1)	
Diseases of the respiratory system (*n* = 51)	Cancer (17)	Heart disease (11)	Certain infectious and parasitic diseases (6)	Endocrine, nutritional and metabolic diseases other than diabetes (4)	Diseases of the nervous system (4)	Diseases of the musculoskeletal system and connective tissue (3)	Non-malignant neoplasms (2)	unknown (2)	Cerebrovascular diseases (1)	Diseases of the genitourinary system (1)
Pneumonia (*n* = 47)	Diseases of the respiratory system other than pneumonia (10)	Cancer (9)	Heart disease (9)	Certain infectious and parasitic diseases (4)	Endocrine, nutritional and metabolic diseases other than diabetes (4)	Diseases of the nervous system (4)	Diseases of the musculoskeletal system and connective tissue (2)	Cerebrovascular diseases (1)	Diseases of the genitourinary system (1)	unknown (1)
Diseases of the digestive system (*n* = 17)	cancer (5)	Heart disease (4)	Non-malignant neoplasms (2)	Pneumonia (2)	Diseases of the genitourinary system (2)	Diseases of the respiratory system other than pneumonia (1)	unknown (1)			

UCOD, underlying cause of death.

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Salt Preference and the Incidence of Cardiovascular Disease in a Japanese General Population: The Jichi Medical School Cohort Study

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Abstract

Dietary salt intake has been reported to be associated with cardiovascular disease (CVD). However, there were few studies that assessed the relationship of salt preference with CVD. We examined the association between salt preference and the incidence of CVD and its subtypes in a Japanese general population. Based on the prospective Jichi Medical School Cohort Study, data were analyzed from 11,394 eligible participants. A baseline survey of the preference for salt was obtained by questionnaire and health examinations from April 1992 through July 1995 in 12 communities in Japan. The participants were followed up until December 2005 (mean follow-up period, 10.7 ± 2.4 years). Subjects were divided into three categories according to their preference for salt: favor, so-so, and disfavor. A Cox proportional hazards model was used to calculate hazard ratios (HRs) of the incidence of CVD according to the preference categories. We observed 485 cardiovascular events (258 in men and 227 in women). Among the men, the multivariable adjusted HRs for incidence of myocardial infarction and subarachnoid hemorrhage for favor versus so-so salt preference were 0.34 (95% confidence interval, 0.17 - 0.71) and 7.10 (0.88 - 56.84), respectively.

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Among the women, age-adjusted HRs for the incidence of CVD, total stroke, cerebral hemorrhage, and cerebral infarction for the favor preference were 1.41 (1.02 - 1.95), 1.36 (0.97 - 1.91), 1.79 (0.87 - 3.71), and 1.40 (0.89 - 2.19), respectively. The data indicated that preference for salt may be associated with an increase in the incidence of CVD in women.

Keywords

Salt Preference, Cardiovascular Disease, Cohort Study, Japanese

1. Introduction

Cardiovascular diseases (CVD), such as coronary heart disease (CHD) and stroke, are common causes of death and disabilities for elders in developed countries, including Japan, after hypertension and atherosclerosis. An estimated 17.5 million people died from CVD in 2012 (31% of all global deaths). Tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, diabetes and hyperlipidemia, hypertension and atherosclerosis are established risk factors for CVD. One of main causes on hypertension is much more salt intakes. Salt intakes influence individual salt preferences strongly [1].

Excessive salt intake affects the incidence and prevalence of hypertension, and subsequently influences the prevalence of cardiovascular disease (CVD) [2]. High salt intake has also been associated with increased CVD mortality and incidence [3]-[6]. The Japanese are known to have higher salt intake than many other populations [7]. In Japan, the mean salt intake among adults was 10.2 g per day (men, 11.3 g per day; women, 9.4 g per day) according to a national nutrition survey in 2013 [8]. Now, a new goal has been set to improve the level of salt intake among Japanese to within 8 g per day [9]. Therefore, dietary sodium restriction must be recommended to a considerable number of people. It is important to estimate salt intake and advice participants who consume excessive amounts of salt to reduce their salt intake. In general, daily salt intake may be estimated by a food frequency questionnaire or by measurement of 24 hour urinary sodium excretion [10]. However, both methods seem inconvenient for general use in mass screening. For these reasons, at health check-up centers or outpatient clinics, salt intake is usually estimated by a questionnaire on salt preference [11] [12].

Salt preference is thought to be associated with salt intake [13]. In a prospective study that examined the relationship between salt preference and CVD, salt preference was significantly positively associated with dietary sodium intake. Compared to the low salt preference group, the high salt preference group showed a relation to higher mortality from stroke [11]. However, few researches have attempted to assess the effects of salt preference on CVD. We could find no studies that clarified the relationships between salt preference and mortality from subtypes of CVD. As far as we know, no previous studies have reported an association of salt preference with the incidence of CVD and its subtypes.

Therefore, the aim of this study was to clarify the relationships between salt preference and the incidence of CVD and CVD subtypes using about 10 years of follow-up data from a large-scale prospective population-based cohort study conducted in Japan.

2. Subjects and Methods

2.1. Subjects

The Jichi Medical School (JMS) Cohort Study is a population-based prospective study that was started in 1992 to investigate the risk factors for CVD in 12 rural areas in Japan. A total of 12,490 people (4911 men and 7579 women) were enrolled in this study. Mass screening examinations for CVD have been conducted in Japan since 1982 under the direction of the Health and Medical Service Law for the Aged, and we used this system to collect the data. The baseline data were obtained from April 1992 through July 1995. Baseline examinations consisted of physical and blood examinations and a self-administered questionnaire. A detailed description of the standardized collection of baseline examinations was published previously [14].

Among the 12,490 participants, 95 (0.8%) declined follow-up and 7 (0.06%) could not be contacted after baseline examination, after which 12,388 subjects (4869 men and 7519 women) remained. We excluded partic-

ipants with a history of CVD (96 men and 74 women) and those with missing data on salt preference (356 men and 468 women). Ultimately, 11,394 subjects (4417 men and 6977 women) were analyzed in the present study. Written informed consent to participate in the study was obtained individually from all of the participants in the mass screening. This study was approved by the Institutional Review Board of Jichi Medical School.

2.2. Baseline Examination

The health checkup was carried out in all 12 communities using same protocols. The body height of all participants was measured without shoes. Body weight while fully clothed was recorded; 0.5 kg in summer or 1 kg in other seasons was subtracted from the recorded weight. Body mass index (BMI) was calculated as weight (kg)/ height $(m)^2$. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline were measured with a fully automated sphygmomanometer (BP203RV-II; Nippon Colin, Komaki, Japan), which was placed on the right arm of the participant after resting for at least 5 minutes in a sitting position. Serum cholesterol concentration was measured by taking a blood sample from the antecubital vein of the seated participants. Total cholesterol was measured using an enzymatic method, and high density lipoprotein cholesterol (HDL-C) was measured using the phosphotungstate precipitation method (Wako, Osaka, Japan; inter-assay coefficient of variation, 1.5%).

Information on age, lifestyle, and medical history was obtained from responses to the baseline questionnaire. Salt preference was ascertained with the following question: "Do you like salty foods?" Participants answered with 1 of 5 multiple choice options: "highly favor", "favor", "so-so", "moderately disfavor", or "disfavor". Subjects were divided into three categories of salt preference according to their response: favor: "highly favor" or "moderately favor"; so-so: "so-so"; and disfavor: "moderately disfavor" or "disfavor".

Smoking habit and alcohol drinking habit were determined from the baseline questions on current smoking and current drinking. Histories of hypertension, diabetes, and hyperlipidemia were determined from questions on the medical history of each illness. Response to the number of years of education was in terms of consecutive years; the response was then categorized as $\geq$9 years or <9 years.

2.3. Follow-Up

The national mass screening system used to obtain the baseline data for the JMS Cohort Study was also used to follow the subjects each year. Subjects were asked whether they had a history of CVD after enrolling. Follow-up was conducted from 1995 to 2005. The mean follow-up period ± standard deviation (SD) was 10.7 ± 2.4 years. Subjects who did not attend a follow-up examination were contacted by mail or telephone. If an incident case of stroke or myocardial infarction (MI) was suspected, those subjects with such histories were asked when and which hospital they visited. Medical records pertaining to stroke and MI were checked if the subjects were hospitalized for any reason, and incident cases were recorded. If both MI and stroke had occurred during the follow-up period, each of the endpoints of stroke and MI was counted as the first for each disease. The CVD endpoint was defined as stroke or MI, whichever occurred first. Death from CVD was also included in the CVD incidence data. Information on death was obtained from death certificates, which were collected at public health centers with the official permission from the Japanese Ministry of General Affairs and the Ministry of Health, Labour and Welfare until the end of 2005. Data on subjects who moved out of the study area during the follow-up period were obtained annually from the municipal government.

2.4. Diagnostic Criteria

If a CVD event was suspected, we requested duplicate images from computed tomography or magnetic resonance imaging (in cases of stroke) or electrocardiograms (in cases of MI). The diagnoses were determined independently by a diagnosis committee in the JMS Cohort Study Group composed of a radiologist, a neurologist, and two cardiologists. Criteria for stroke were a focal and nonconvulsive neurological deficit of sudden onset persisting longer than 24 hours. Stroke subtypes were categorized as cerebral hemorrhage, cerebral infarction, or subarachnoid hemorrhage (SAH) according to the criteria of the National Institute of Neurological Disorder and Stroke [15]. MI was diagnosed according to the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project [16].

2.5. Statistical Analysis

All analyses were conducted according to subject gender. Descriptive parameters are shown as the mean, standard deviation, or proportion (%). We compared characteristics between salt preference groups by the chi-square test or one-way analysis of variance. Finally, Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the incidence of CVD according to salt preference, after adjusting for age, smoking habit, alcohol drinking habit, history of hyperlipidemia, and years of education (HR-all[*]) for men, and after adjusting for age, smoking habit, and alcohol drinking habit, BMI, HDL-C, and years of education (HR-all[†]) for women, which were considered to be potential confounding factors. HRs of each incidence of stroke, stroke subtypes, and MI were calculated by same statistical models. All p values were two-tailed, and a probability value < 0.05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Science (SPSS) for Windows, version 16.0 (SPSS Inc., Japan).

3. Results

During a mean follow-up period of 10.7 years, we documented 485 CVD events (258 in men, 227 in women): 415 strokes (210 in men, 205 in women), including 264 cerebral infarctions (150 in men, 114 in women), 94 hemorrhagic strokes (47 in men, 47 in women), and 56 SAHs (13 in men, 43 in women), and 76 MIs (52 in men, 24 in women).

The baseline characteristics of the subjects by salt preference group are shown in Table 1. In both men and women, favor salt preference was positively associated with smoking ($p < 0.01$ for men; $p = 0.01$ for women) and alcohol drinking ($p < 0.01$ for men; $p = 0.02$ for women). Among the men, those in the favor salt preference group tended to be younger, more highly educated (both, $p < 0.01$), and less likely to have hyperlipidemia ($p = 0.04$). Among the women, those in the favor salt preference group tended to be older, less well educated (both, $p < 0.01$) and more likely to have both a higher incidence of CVD ($p = 0.046$) and higher BMI ($p < 0.01$) and a lower serum concentration of HDL-C ($p < 0.01$).

The incidence and HRs for CVD by salt preference category are shown in Table 2. After adjustment for age, there were no significant associations between salt preference and CVD or total stroke among the men. Our data showed 11 MIs, and the HR for MI was significantly lower in the favor salt subjects compared with so-so subjects (HR, 0.34; 95% CI, 0.17 - 0.68). After further multiple adjustment for smoking status, alcohol drinking status, history of hyperlipidemia, and years of education, the HR for MI was 0.35 (0.17 - 0.71). Among women, the HR for CVD was significantly higher in the favor salt subjects compared with the so-so subjects (HR, 1.41; 95% CI, 1.02 - 1.95) after adjustment for age. After further adjustment for smoking status, alcohol drinking status, BMI, HDL-C, and years of education, the HR was 1.15 (0.81 - 1.63). The HR for total stroke was also high (1.36; 95% CI, 0.97 - 1.91) in the favor salt subjects among women. After multivariate adjustment (HR-all[†]), HR was 1.08 (0.74 - 1.57). No significant association was found between salt preference and MI in the women, although a significant association was found in the men.

We also analyzed the respective association between salt preference and the incidences of stroke subtypes (Table 3). Among the men, there were 9 SAHs, and the HR was 8.09 (1.02 - 63.84) in the favor salt subjects after adjustment for age. After multivariate adjustment (HR-all[*]), the HR of SAHs was 7.10 (0.88 - 56.84). Among the women, age-adjusted HRs for cerebral hemorrhage and cerebral infarction were 1.79 (0.87 - 3.71) and 1.40 (0.89 - 2.19), respectively, in the favor salt subjects. After multivariate adjustment (HR-all†), HRs were 1.59 (0.74 - 3.44) and 1.07 (0.65 - 1.78), respectively.

4. Discussion

We investigated the association between salt preference and the incidence of CVD in a Japanese general population. We found that salt preference was positively associated with an increased risk of SAH and a decreased risk of MI in men. For women, salt preference was positively associated with an incidence of CVD after age-adjustment. HRs for incidences of cerebral hemorrhage and cerebral infarction were also higher, although not with significance. To our knowledge, this study is the first prospective study to provide evidence of the relationship of salt preference with the incidence of stroke.

We found that salt preference was associated with an increased incidence of CVD in the women. We examined CVD incidence data rather than mortality data as endpoints. Because the incidence of CVD occurs earlier

Table 1. Baseline characteristics of study participants by salt preference categories.

	Favor	So-so	Disfavor	
(Men) number (n)	1813	1585	1019	p-value[a]
Number of CVD incidence	91 (5.0)	102 (6.4)	65 (6.4)	0.15
Number of Stroke incidence	81 (4.5)	76 (4.8)	53 (5.2)	0.68
Number of MI incidence	11 (0.6)	29 (1.8)	12 (1.2)	<0.01**
				p-value[b]
Age (year)	54.5 (11.5)	54.6 (12.1)	56.7 (12.4)	<0.01**
Systolic blood pressure (mmHg)	131.6 (20.6)	131.1 (21.0)	131.0 (21.0)	0.66
Diastolic blood pressure (mmHg)	79.3 (12.3)	79.0 (12.1)	79.0 (12.6)	0.71
Total-cholesterol (mg/dl)	183.8 (34.4)	186.3 (33.7)	185.3 (34.7)	0.10
HDL-cholesterol (mg/dl)	49.3 (13.6)	49.0 (13.6)	48.1 (13.0)	0.08
Body mass index (kg/m^2)	23.0 (2.9)	23.0 (2.9)	22.9 (2.9)	0.51
Current Smokers	55.8	49.2	43.4	<0.01**
Current Drinkers	78.2	75.5	70.4	<0.01**
History of hypertension	8.8	9.8	10.7	0.27
History of diabetes mellitus	1.9	2.7	3.0	0.12
History of hyperlipidemia	0.7	1.4	1.8	0.04*
Education years (over 9 years)	88.5	88.7	83.4	<0.01**
(Women) number (n)	1618	2885	2474	p-value[a]
Number of CVD incidence	67 (4.1)	80 (2.8)	80 (3.2)	0.046*
Number of stroke incidence	60 (3.7)	74 (2.6)	71 (2.9)	0.09
Number of MI incidence	7 (0.4)	8 (0.2)	9 (0.4)	0.68
				p-value[b]
Age (year)	55.8 (11.0)	54.8 (11.0)	55.5 (11.5)	<0.01*
Systolic blood pressure (mmHg)	128.9 (21.5)	127.9 (20.9)	127.6 (21.0)	0.15
Diastolic blood pressure (mmHg)	76.8 (12.3)	76.2 (12.0)	76.0 (12.1)	0.08
Total-cholesterol (mg/dl)	196.5 (34.1)	197.2 (35.5)	197.1 (34.5)	0.81
HDL-cholesterol (mg/dl)	51.5 (12.0)	52.5 (12.5)	53.8 (12.7)	<0.01**
Body Mass Index (kg/m^2)	23.5 (3.3)	23.1 (3.1)	23.0 (3.2)	<0.01**
Current smokers	6.9	5.1	5.0	0.01*
Current drinkers	26.9	25.6	23	0.02*
History of hypertension	12.9	11.6	12.4	0.39
History of diabetes mellitus	1.2	1.6	2.0	0.14
History of hyperlipidemia	1.5	2.3	2.1	0.16
Education years (over 9 years)	75.9	81.2	80.0	<0.01**

Data are expressed as a mean (standard deviation) for variables or as a percentage of the population. [a]Chi-square test; [b]Analysis of variance (ANOVA); *p values were < 0.05; **p values were < 0.01.

Table 2. Hazard ratios and 95% CIs of incidence from cardiovascular disease and myocardial infarction with gender difference by salt preference categories.

	Salt preference category		
	Favor	So-so	Disfavor
Men			
Cardiovascular disease[§]			
N	91	102	65
HR-age	0.80 (0.60 - 1.06)	1.00	0.83 (0.61 - 1.13)
HR-all[*]	0.75 (0.57 - 1.01)	1.00	0.84 (0.61 - 1.17)
Total-stroke			
N	81	76	53
HR-age	0.97 (0.71 - 1.33)	1.00	0.9 (0.63 - 1.28)
HR-all[*]	0.90 (0.64 - 1.25)	1.00	0.89 (0.62 - 1.28)
Myocardial infarction			
N	11	29	12
HR-age	0.34 (0.17 - 0.68)	1.00	0.55 (0.28 - 1.09)
HR-all[*]	0.35 (0.17 - 0.71)	1.00	0.64 (0.33 - 1.24)
Women			
Cardiovascular disease[§]			
N	67	80	80
HR-age	1.41 (1.02 - 1.95)	1.00	1.11 (0.81 - 1.51)
HR-all[†]	1.15 (0.81 - 1.63)	1.00	1.14 (0.83 - 1.57)
Total-stroke			
N	60	74	71
HR-age	1.36 (0.97 - 1.91)	1.00	1.06 (0.78 - 1.47)
HR-all[†]	1.08 (0.74 - 1.57)	1.00	1.09 (0.78 - 1.52)
Myocardial infarction			
N	7	8	9
HR-age	1.44 (0.52 - 3.98)	1.00	1.38 (0.54 - 3.50)
HR-all[†]	1.37 (0.49 - 3.82)	1.00	1.29 (0.50 - 3.36)

HR-age: hazard ratios adjusted for age. HR-all[*]: hazard ratios adjusted for age, smoking status and drinking status, history of hyperlipidemia, and education years. HR-all[†]: hazard ratios adjusted for age, smoking status and drinking status, BMI, HDL-choesterol, and education years. [§]: The case which occurred both stroke and myocardial infarction is included.

than that of mortality, our study was significant in that we captured the risk of CVD at an earlier stage. With respect to Japanese studies, the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) reported an association between salt preference and mortality from stroke among Japanese men and women [11]. In that study, subjects were divided into three categories according to their preference answer. Compared to the low salt preference group, the salt preference group was associated with higher mortality from stroke after 16.4 years of follow-up: The multivariable HRs for CVD were 1.05 (0.92 - 1.20) for men and 1.05 (0.92 - 1.19) for