

# 学位論文の要旨

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

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## 論文内容の要旨

### **INTRODUCTION**

Dietary salt intake has been reported to be associated with cardiovascular disease (CVD). The Japanese are known to have higher salt intake than many other populations. Daily salt intake may be estimated by a food frequency questionnaire or by measurement of 24 hour urinary sodium excretion. 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. However, there were few studies that assessed the relationship of salt preference with CVD.

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.

### **MATERIALS AND METHODS**

The Jichi Medical School (JMS) Cohort Study is a population-based prospective study that was started 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. We excluded participants with a history of CVD and those with missing data on salt preference. Ultimately, 11,394 subjects were analyzed in the present study. The study protocol was approved by the Ethics Committee of Jichi Medical School and written informed consent was obtained from all subjects.

The subject's height, weight, serum cholesterol concentration, and blood pressure were measured at the baseline physical examination. Body mass index (BMI) was calculated as weight (kg)/height (m)<sup>2</sup>. Information on age, smoking habit, alcohol drinking habit, histories of hypertension, diabetes, and hyperlipidemia, and years of education 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".

Subjects were asked whether they had a history of CVD after enrolling. Follow-up was conducted from 1995 to 2005. 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. We requested duplicate images from computed tomography or magnetic resonance imaging (in cases of stroke) or electrocardiograms (in cases of MI). 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. MI was diagnosed according to the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project.

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.

## **RESULTS AND DISCUSSION**

During a mean follow-up period of 10.7 years, we documented 485 CVD events: 415 strokes, including 264 cerebral infarctions, 94 hemorrhagic strokes, and 56 SAHs, and 76 MIs. In

both men and women, favor salt preference was positively associated with smoking and alcohol drinking.

Among the men, the multivariable adjusted HRs (HR-all\*) for incidence of myocardial infarction and subarachnoid hemorrhage for favor versus so-so salt preference were 0.34 (95% CI, 0.17 - 0.71) and 7.10 (0.88 - 56.84), respectively. There were no significant associations between salt preference and CVD or total stroke. 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. There were no significant associations between salt preference and myocardial infarction or subarachnoid hemorrhage.

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. To our knowledge, this study is the first prospective study to provide evidence of the relationship of salt preference with the incidence of stroke.

In our study, favor salt preference was positively associated with smoking and alcohol drinking in both men and women. Despite these results, salt preference was not associated with CVD risk factors such as SBP, DBP, and a history of hypertension. Our results suggest that salt preference may be one of the risk factors of premature CVD.

For men, the decreased risk of MI associated with high salt preference might reflect the beneficial cardiovascular effects of the intake of n-3 polyunsaturated fatty acids and isoflavones. The low incidence of MI and the high incidence of SAH were based on a small number of incident cases. Thus, there was wide range of 95% CIs for the point estimates. For women, high salt preference tended to be less well educated. Therefore, subjects with high salt preference may have behavioral risk factors, leading to higher risk of CVD in the women. Accordingly, women with a high salt preference may intake much more salt than those with a low salt preference.

Especially in women, early assessment of salt preference may be effective in reducing the incidence of CVD. For subjects with high salt preference, early intervention may be able to prevent excessive salt intake in the future.

## **CONCLUSION**

We found that salt preference was positively associated with an increased risk of the incidence of SAH in men after multivariate adjustment and in CVD in women after adjustment for age. As with other common risk factors for CVD, assessing salt preference may lead to the prevention of CVD. These tendencies may apply especially to women.

論文審査及び最終試験又は学力の確認の結果の要旨

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論文審査の結果の要旨

心血管疾患の発症に、栄養を含め生活習慣が強く関与している。近年、食の嗜好と疾患の発症や死亡に関連する疫学研究結果が報告され始めた。しかし、追跡研究で塩分嗜好と心血管疾患の発症との関連を検討した研究はみられない。そこで、本研究は、全国規模のコホート集団を用いて、塩分嗜好と心血管疾患発症の関連を明らかにすることを目的とした。対象は、全国12地区の一般住民が参加したコホート研究（Jichi Medical School (JMS) コホート）において、1992年から1995年のベースライン調査に参加し有効な回答が得られた11,394人とした。塩分嗜好は、自記式質問票を用いて塩分の好みを5区分で尋ね、回答から、好き、まあまあ、嫌いの3群に区分した。心血管疾患は、脳卒中（脳梗塞、脳出血、くも膜下出血）または急性心筋梗塞と定義した。心血管疾患の発症は1995年から2005年の間（平均追跡期間10.7±2.4年）に、健診時の問診、郵送、電話、家庭訪問により把握し、医療機関に情報開示を依頼した。開示された医療情報を基にJMSコホート内の独立した4人の医師により最終診断を行った。分析には、塩分嗜好群別の検討に一元配置分散分析または $\chi^2$ 検定を、塩分嗜好に対する多変量解析としてCox比例ハザードモデルを用いた。結果、追跡期間中485人の心血管疾患発症がみられた。女性では、塩分が好きな群はまあまあな群と比較して、年齢調整において心血管疾患発症と有意に正の関連がみられ、脳梗塞、脳出血、急性心筋梗塞の発症でも、有意ではないが同様の関連を示す傾向がみられた。男性で同様の検討を行ったところ、年齢調整において塩分が好きな群でもくも膜下出血発症と有意に正の関連がみられた。一方で、男性の塩分が好きな群で、心筋梗塞発症と有意に負の関連がみられた。この関連には、他のリスク因子にマスクされた可能性や調査対象数、追跡期間などの影響が考えられた。

本研究は、塩分嗜好が、特に女性で心血管疾患発症のリスクである可能性を示唆したものであり、予防医学分野の発展に寄与すると考えられた。

最終試験又は学力の確認の結果の要旨

申請者は、全国12地域1万人以上を対象に食塩嗜好性と心血管疾患発症との関連を10年以上にわたって追跡調査を行い、女性においては有意な発症リスクになるが、男性では他の危険因子の影響が強いことを示した。このことは、嗜好性によっても心血管疾患発症の警鐘になり得ることを示し、生活習慣指導の貴重な情報となると評価できる。基礎知識、関連情報収集も十分であり学位授与に値すると判断した。  
(主査) 石橋 豊

申請者は、1万人を越えるコホートを10年に渡って追跡したデータを元に、食塩嗜好性が心血管疾患のリスクになり得るかという仮説について検討し、女性においてのみ、全心血管疾患に対して年齢調整後に有意な危険因子となることを示した。このことは今後同様の疫学的研究を進める上で有益な知見である。背景の知識もあり、質疑においてはデータについての的確な解釈が出来ており、学位に値すると判断した。  
(副査) 並河 徹

申請者は、全国規模で11,394人の塩分嗜好別に平均10年間の心血管イベントを追跡し、塩分嗜好とイベント発症の男女差、特に女性において塩分嗜好がイベント発症のリスクになる可能性をつきとめた。今後の心血管イベント予防に寄与する研究と評価できる。周辺の知識も豊富で学位授与に値すると判断した。  
(副査) 田邊 一明

(備考) 要旨は、それぞれ400字程度とする。