Effects of Smoking Habit on the Prevalence of Atrial Fibrillation in Japanese Patients With Special Reference to Sex Differences – Evidence From the Shinken Database –

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**Background:** Tobacco smoking is a well-known risk factor for cardiovascular disease, but controversial results have been reported regarding its relationship with atrial fibrillation (AF). Moreover, no study on the relationship between smoking and AF has yet been undertaken in a Japanese context.

**Methods and Results:** We used data from the Shinken Database 2004–2011 (men/women, n=10,714/6,803, respectively), which included all new patients attending the Cardiovascular Institute between June 2004 and March 2012. AF was diagnosed in 1,698 and 598 men and women, respectively. In men, smokers were more prevalent in the AF than in the non-AF group (54.5% vs. 44.7%), whereas in women the prevalence of smokers was similar between AF and non-AF groups (14.4% vs. 15.4%). This discrepancy between the sexes seems to derive from a characteristic distribution pattern of smoking habit in women. After adjustment for various cofactors, smoking was independently associated with AF (odds ratio 1.54; 95% confidence interval 1.35–1.75; P<0.001) without a significant interaction between sex categories (P=0.195).

**Conclusions:** Smoking was independently associated with AF without a significant interaction between sex categories among Japanese patients visiting a cardiovascular hospital. Further studies using a prospective cohort design are required to confirm a causal link between smoking and AF in Japanese patients. (Circ J 2013; 77: 2948–2953)

**Key Words:** Atrial fibrillation; Epidemiology; Risk factors; Smoking; Tobacco consumption

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in developed countries and is strongly associated with an increase in cardiovascular mortality and morbidity.1–5 Several studies have noted that the prevalence of AF is expected to substantially increase in the future because of the aging of society.6–8 Primary prevention of AF is therefore of great interest, but requires appropriate identification of people at high risk of developing AF. Risk factors for AF include hypertension, type 2 diabetes, obesity, metabolic syndrome and chronic kidney disease.9–15 which are overlapping risk factors for a number of cardiovascular diseases including coronary artery disease.16–19

Tobacco smoking is a well-known risk factor for cardiovascular disease.20,21 Smoking causes endothelial dysfunction and atherosclerosis,22–25 and can also cause cardiac arrhythmias26 through the combined effects of nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons. The studies indicate that tobacco smoking may accelerate atrial remodeling, contributing to the development of AF. Although several case reports have reported the onset of AF following ingestion of nicotine,27,28 the results of population-based studies examining the association between smoking and AF are conflicting. In several cohort studies, the effect of smoking on the incidence of AF was not independent,29–33 but recent large-scale cohort studies with longer-term follow-up periods have demonstrated that smoking is independently associated with the development of AF.34,38

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To date, there have been no studies published on the association between smoking and AF in a Japanese context. We investigated the relationship between smoking and level of tobacco consumption with the prevalence of AF in a Japanese context. We investigated the relationship between smoking and level of tobacco consumption with the prevalence of AF in a Japanese context.

### Methods

#### Data Collection at Initial Visit

After obtaining an ECG and chest X-ray, each patient’s cardiovascular status was evaluated using echocardiography, an exercise test, 24-h Holter recordings and blood laboratory data from the initial visit. In addition to sex, age, height, and weight, we collected data on cardiovascular diseases, including heart failure (New York Heart Association class ≥2), valvular heart disease (moderate or severe stenosis or regurgitation using echocardiography), coronary artery disease (diagnosed by angiography or scintigraphy), hypertrophic and dilated cardiomyopathy (diagnosed by echocardiography or magnetic resonance imaging), left ventricular non-compaction (diagnosed by echocardiography), and history of a disabling cerebral infarction or transient ischemic attack (diagnosed by computed tomography or magnetic resonance imaging). The presence of cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg on admission), diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin ≥6% on admission), dyslipidemia (use of lipid-lowering agents, including statins and fibrates), and history of a disabling cerebral infarction or transient ischemic attack (diagnosed by computed tomography or magnetic resonance imaging). The presence of cardiovascular risk factors was evaluated using echocardiography, an exercise test, 24-h Holter recordings and blood laboratory data from the initial visit. In addition to sex, age, height, and weight, we collected data on cardiovascular diseases, including heart failure, valvular heart disease, coronary artery disease, left ventricular non-compaction, and history of a disabling cerebral infarction or transient ischemic attack.

#### Study Participants

The Shinken Database, which was established in June 2004, contains data on all new patients attending the Cardiovascular Institute Hospital in Tokyo, Japan (abbreviated in Japanese as ‘Shinken’), excluding foreign travelers and patients with active cancer. The principal aim of establishing this hospital-based database was to monitor the prevalence and prognosis of cardiovascular diseases in urban areas of Japan. Data on patients’ health status and incidence of cardiovascular events and mortality are linked with hospital medical records and data collected through a postal survey repeated approximately once or twice annually.

The data used in this study were derived from the records for 17,517 new patients between June 2004 and March 2012 (Shinken Database 2004–2011).
women in the burden of the risk of having a smoking habit, we displayed the age-stratified distribution of smoking habit and the tobacco consumption separated by men and women.

Finally, to identify the factors independently associated with AF, multivariate analyses were performed using logistic regression models with stepwise methods. In the multivariate models, smokers, sex category (female vs. male) and their interaction term were forcedly entered; thereafter, the model was adjusted for other covariates and the interaction term between the covariates and the sex category. The covariates in the models were selected from factors that tended to be different between AF and non-AF (P<0.15 in the 2-way analysis of variance or the Mantel-Haenszel test).

Ethical Issues
The ethical committee at the Cardiovascular Institute granted approval for this study and all the patients gave written informed consent.

Results
Characteristics of the Study Participants
Table 1 summarizes the baseline clinical characteristics of the study population, which included 10,714 men and 6,803 women, of whom 1,698 and 598, respectively, were diagnosed as having AF. In both sex categories, AF patients were older and had a higher prevalence of heart failure, valvular heart disease, dilated cardiomyopathy, cerebral infarction or transient ischemic attack, and chronic kidney disease (all, P<0.001). In men, smokers were more prevalent among the AF patients compared with non-AF patients (54.5% vs. 44.7%), but in women, the prevalence of smokers was similar between the AF and non-AF groups (14.4% vs. 15.4%).
Different Age-Stratified Distribution in Smoking Habit and Tobacco Consumption by Sex Category
To understand the difference between men and women in the burden of the risk of having a smoking habit, the age-stratified distribution of smoking habit and tobacco consumption separated by men and women was calculated (Figure). In each age-stratification, lifetime tobacco consumption was estimated for smokers and used to generate a Brinkman Index, and consequently, smokers were separated into 3 groups: Brinkman Index <400, ≥400, and undetermined. The prevalence of high Brinkman Index (≥400) increased according to increment of age, peaked at 60–69 years, and decreased thereafter: the patterns were similar in both sex categories. In addition, we found that the prevalence of smoking habit increased according to increment of age, but peaked at different ages for men and women: 60–69 years in men and 40–49 years in women.

Effect of Smoking on AF Prevalence
To identify the effect of having a smoking habit on AF, unadjusted and adjusted logistic regression analyses were performed (Table 2). The unadjusted OR for presentation of AF indicated a significant effect of being a smoker (OR 1.39; 95% confidence interval (CI) 1.25–1.55; P<0.001) with a negative interaction by female (OR 0.76; 95% CI 0.58–0.99; P=0.044). After adjustment for cofactors that tended to be different between AF and non-AF (P<0.15 in the 2-way analysis of variance or the Mantel-Haenszel test), the covariates included age, body mass index, heart failure, valvular heart disease, coronary artery disease, dilated cardiomyopathy, left ventricular non-compaction, cerebral infarction or transient ischemic attack, hypertension, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease, statin use, renin-angiotensin system inhibitors use, anticoagulant use and antiplatelet use. Smokers × Female represents an interaction term between smokers and female.

The results of this study show that smoking was independently associated with AF prevalence without an interaction by sex categories among patients in a cardiovascular hospital in an urban area of Japan. Interestingly, the age-dependent distribution of smoking habit and tobacco consumption varies according to sex category, which may explain the apparent interaction between smoking and sex category in the effect on the prevalence of AF. To best of our knowledge, this is the first report regarding the relationship between smoking habit and the prevalence of AF in a large cohort in Japan.

In the present study, the effect of smoking habit on AF was apparently different between men and women: significantly and positively associated with AF in men, but not in women. The difference can also be observed as an interaction between smoking and sex category in the effect on the prevalence of AF. Although the reasons of the difference in the effect between men and women are unclear, we can assume several correlations between smoking habit and sex category that would affect the risk for AF.

In general, habitual tobacco use is highly prevalent in men, and is a major cause of hypertension, chronic obstructive pulmonary disease, and chronic kidney disease. And notably, these cofactors have been reported as independent risk factors for development of AF. Therefore, the relationship between smoking and AF might be partially explained by an indirect linkage via these confounding factors. However, such an indirect linkage only cannot fully explain the relationship between smoking habits and AF in the present study, because the relationship was independent in a multivariate model.

Several recent large-scale cohort studies with longer follow-up periods have reported that smoking is an independent predictor for the development of AF. Smoking was independently associated with AF prevalence without an interaction by sex categories among patients in a cardiovascular hospital in an urban area of Japan. Interestingly, the age-dependent distribution of smoking habit and tobacco consumption varies according to sex category, which may explain the apparent interaction between smoking and sex category in the effect on the prevalence of AF. To best of our knowledge, this is the first report regarding the relationship between smoking habit and the prevalence of AF in a large cohort in Japan.

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atrial fibrosis via downregulation of atrial microRNAs in atrial fibroblasts, alongside upregulation of transforming growth factors β1 and βRII.48-62

It is assumed that, if smoking-related remodeling of the atrium truly exists, the promotion of the remodeling depends on the total amount of tobacco consumed. Actually, a previous report has suggested a relationship between tobacco consumption and AF.63 However, there is another view: tobacco consumption is inherently linked to age, because a large consumption of tobacco requires a long-term smoking habit. In the present study, tobacco consumption showed a clear age-dependent distribution: the prevalence of high tobacco consumption (Brinkman index ≥400) increased according to increment of age. This age-dependent distribution of tobacco consumption might explain the difference between men and women in the contribution of smoking habit to AF, because in women, smokers were more prevalent in the younger population and thus they would have a low tobacco consumption. Consequently, for both of the reasons of the distribution of smoking habit in younger age groups and subsequent low tobacco consumption, the effect of smoking habit on AF in women is apparently weaker than that in men. It might be, at least in part, the basis of the interaction between smoking and sex category in the effect on the prevalence of AF. However, it should be emphasized that, after adjustment by various cofactors, the effect of smoking habit on AF was independent of an interaction by sex category, which indicates that the effect of smoking habit truly exists beyond sexual specificity.

Study Limitations

In the present study of Japanese patients in a cardiovascular hospital, an obvious discrepancy was observed between men and women in the distribution of smoking habit in women in the present study is similar to that in the Japanese general population. The distribution of smoking habit in women in the present study is similar to that in the Japanese general population, but different from that in Western populations. Therefore, the discrepancy between men and women observed in the present study might be unique to a Japanese population, and cannot be extrapolated to populations in other countries. The presence of AF was determined using both the patient’s medical histories and clinical examinations using ECG and Holter recordings. This diagnostic method is known to underestimate AF prevalence, because of its low sensitivity for detecting asymptomatic AF.63

Conclusions

Smoking was independently associated with AF prevalence without a significant interaction between sex categories among patients visiting a cardiovascular hospital. Although an apparent discrepancy in the role of smoking on AF was observed between men and women, it seems to derive from a characteristic age-dependent distribution pattern of smoking habit and tobacco consumption in women, which might be unique to a Japanese population. Further studies using a prospective cohort design are required to confirm a causal link between smoking and AF in Japanese patients.

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Disclosures

None declared.

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