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Original article

Association between smoking habits and the first-time appearance of atrial fibrillation in Japanese patients: Evidence from the Shinken Database

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ABSTRACT

Background: We previously reported a cross-sectional analysis regarding the relationship between smoking and atrial fibrillation (AF) in a single hospital-based cohort with Japanese patients, but the effect of cessation of smoking and/or total tobacco consumption were unclear.
Methods and results: We used data from the Shinken Database 2004–2011 (men/women, n = 10,714/6803, respectively), which included all new patients attending the Cardiovascular Institute between June 2004 and March 2012. After excluding those previously diagnosed with AF (n = 2296), 15,221 patients (men/women, n = 9016/6205) were analyzed. During the follow-up period of 2.0 ± 2.1 years (range 0.0–8.1), the incidence rates of new AF in smokers and non-smokers were 9.0 and 5.0 per 1000 patient-years, respectively. In adjusted models with Cox regression analysis, smokers were independently associated with new AF [hazard ratio (HR) 1.47, 95% confidence interval (CI) 1.09–2.00]. Also, current smokers (HR 1.81, 95% CI 1.17–2.79) and smokers with Brinkman index ≥800 (HR 1.69, 95% CI 1.05–2.70) were independently associated with new AF. However, in current smokers, the HRs were not different by Brinkman index (Brinkman index <800/≥800; HR 1.81/1.82, 95% CI 1.07–3.05/0.94–3.51, respectively).
Conclusions: Smoking was independently associated with the first-appearance of AF in patients in sinus rhythm, especially when the patients continued their smoking habit. However, in patients who continued smoking, difference by total tobacco consumption was not observed, suggesting the significance of cessation of smoking for preventing AF. Our data are limited because of a single hospital-based nature and a relatively short observation period.

Introduction

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 rise in age of society [6–8]. Primary prevention of AF is therefore of great interest. This would require 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 also can cause cardiac arrhythmias [26] through the combined effects of nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons. These studies indicate that tobacco smoking may accelerate atrial remodeling, contributing to

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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 incidence of AF was not independent [29–33], while recent large-scale cohort studies with longer-term follow-up periods have demonstrated that smoking is independently associated with the development of AF [34,35].

To date, there has been only a cross-sectional study published on the association between smoking and AF in a Japanese context, which we reported previously [36]. In this cross-sectional analysis, we demonstrated that smoking habit was independently associated with the prevalence of AF. Notably, although significant interaction between smoking and sex category was observed apparently in the effect of smoking on AF, it was assumed that it was derived from an obvious difference of the distribution of smokers by sex category; women smokers were younger and it might weaken the effect of smoking in women. After adjustment for age and other covariates, interaction between smoking and sex category was diminished. However, we could not make it clear whether cessation of smoking and/or total tobacco consumption were associated with new incidence of AF. It should be ascertained in a longitudinal cohort. Therefore, we analyzed the relationship between smoking habit and the incidence of new AF in a hospital-based cohort in an urban area of Japan (Shinken Database) [37–40] with a longitudinal study design, considering the difference of details regarding smoking habits.

Methods

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 principle aim of establishing this hospital-based database is to monitor the prevalence and prognosis of cardiovascular diseases in urban areas of Japan [37–40]. 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 records from 17,517 new patients between June 2004 and March 2012 (Shinken Database 2004–2011). Excluding 2296 patients who were diagnosed with AF at the initial visit, 15,221 patients were analyzed.

Data collection at initial visit

After obtaining an electrocardiogram and chest X-ray, patients' cardiovascular statuses were evaluated using echocardiography, an exercise test, 24-h Holter recordings, and blood laboratory data from the initial visit. In addition to gender, 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 heart disease (diagnosed by angiography or scintigraphy), hypertrophic and dilated cardiomyopathy (diagnosed by echocardiography or magnetic resonance imaging), and history of a disabling cerebral infarction or transient ischemic attack (diagnosed by computed tomography or magnetic resonance imaging). Cardiovascular risk factors are defined as follows: hypertension (use of antihypertensive agents, systolic blood pressure of ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg), mmHg), diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin $\geq 6.5\%$), dyslipidemia (use of statin or drugs for lowering triglyceride, low-density lipoprotein ≥ 140 mg/dL, high-density lipoprotein < 40 mg/dL, or triglyceride ≥ 150 mg/dL), chronic kidney disease (estimated glomerular filtration rate <60 ml/min/m^2), and chronic obstructive pulmonary disease. Metabolic syndrome (modified) was defined as body mass index (BMI) ≥ 25 kg/m^2 and two or more of the following: hypertension, diabetes mellitus, and dyslipidemia, because we do not have data for abdominal circumference and/or full data for blood pressure, blood sugar, and triglycerides. Information on medical drugs included use of statins, renin–angiotensin system inhibitors, anticoagulants, and antiplatelets. BMI was calculated as weight in kilograms divided by height in meters squared. The glomerular filtration rate was estimated using the Japanese coefficient for the modified isotope dilution mass spectrometry (IDMS)-traceable four-variable Modification of Diet in Renal Disease (MDRD) study equation (glomerular filtration rate = $194 \times \text{serum creatinine}^{-1.004} \times \text{Age}^{-0.287} \times 0.739$ [if female]) [41].

Definition of AF

AF at the initial visit was diagnosed by electrocardiographic recordings, including 12-lead surface electrocardiograms and 24-h Holter recordings. It was also diagnosed by any medical history of AF from referring physicians.

The first-time appearance of AF was determined by electrocardiogram recorded during visits to the outpatient clinic and inpatient stay at our hospital.

Categorization of smoking habits

In the present study, the principal categorization regarding smoking habits was smokers and non-smokers. Next, smokers were separated into former and current smokers. Also, smokers were separated by a Brinkman index. A Brinkman index is an estimation of a lifetime tobacco consumption of each smoker before the initial visit to our hospital which was expressed as the total count of cigarettes-years.

Statistical analysis

All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $p < 0.05$. First, patient backgrounds were compared between smokers and non-smokers, and in smokers, between former and current smokers. The differences of categorical and consecutive variables were tested by unpaired *t*-test and chi-squared test, respectively. Furthermore in smokers, patient backgrounds were compared between different levels of Brinkman index: <400, 400–799, ≥800, and unknown. Unknown was insufficient data which could not be used to calculate Brinkman index.

Next, the incidence rates of new AF in each category of smoking habit were calculated by person-year methods.

Finally, to identify the risk of smoking habits on incidence of AF, unadjusted and adjusted models with Cox regression analysis were determined. In these analyses, four types of parameters regarding smoking habits were evaluated, which were smokers, cessation status (current and former smokers), total tobacco consumption (Brinkman index <400, 400–799, ≥800, and unknown), and combination of cessation status and total tobacco consumption [current and former, and Brinkman index of <800 (or unknown) and ≥800, respectively]. These smoking habit-related parameters were analyzed in different multivariate models, where they were adjusted for all patient backgrounds (except for anticoagulants and antiplatelets) by stepwise methods.