Original Article

Association between Cigarette Smoking and Chronic Kidney Disease in Japanese Men

Nobukazu ISHIZAKA[1)], Yuko ISHIZAKA[2)], Ei-ichi TODA[2)], Hiroji SHIMOMURA[2)], Kazuhiko KOIKE[3)], George SEKI[4)], Ryozo NAGAI[1)], and Minoru YAMAKADO[2)]

Cigarette smoking may affect urinary albumin excretion and the glomerular filtration rate in both diabetic and nondiabetic subjects. Here we investigated the association between smoking and decreased or elevated glomerular filtration rate (GFR) and albuminuria by analyzing data from 7,078 Japanese men who had undergone a general health screening between 2005 and 2006. GFR was estimated with the Modified Diet in Renal Disease (MDRD) equation, and low estimated GFR (eGFR) and elevated eGFR were defined, respectively, as eGFR <60 and >90.7 mL/min/1.73 m^2. Albuminuria was considered present when the urinary albumin excretion ratio (UAER), expressed as mg/g creatinine, was ≥30 mg/g. Multivariate logistic regression analysis showed that current smoking was associated inversely with low eGFR, and positively with albuminuria and elevated eGFR. The association between current smoking and low or elevated GFR was dependent on the number of cigarettes smoked per day. Former smoking was also significantly inversely associated with low eGFR, but the association between former smoking and albuminuria or elevated eGFR was not significant, even in individuals who had stopped smoking less than 1 year before. These data suggest that cigarette smoking may increase the prevalence of albuminuria and elevated eGFR or hyperfiltration, traits that might be reversed by smoking cessation. Although this concept should be verified by future longitudinal studies, our data suggest that we may need to take into account an individual's smoking status when assessing the presence or absence of chronic kidney disease because cigarette smoking may transiently increase eGFR. (*Hypertens Res* 2008; 31: 485–492)

***Key Words*: smoking, chronic kidney disease, glomerular filtration rate**

Introduction

Recent studies have shown that a mild decline in renal function, designated as chronic kidney disease (CKD), is associated with substantially higher prevalence of cardiovascular disease and premature death (*1–3*). Screening for CKD, which can be detected by a combination of reduced estimated glomerular filtration rate (eGFR) and microalbuminuria, is thus an important issue from the viewpoint of disease prevention (*4*). Cigarette smoking, an established risk factor for atherosclerotic disease, may increase the prevalence of albuminuria in diabetic and/or nondiabetic populations (*5*, *6*), whereas the effects of smoking on eGFR are controversial (*7*, *8*). In the current study, we investigated whether or not there is an association between cigarette smoking and CKD, its components (low eGFR and albuminuria), or elevated eGFR in Japanese men who had undergone a general health screening.

From the [1)]Department of Cardiovascular Medicine, [3)]Department of Infectious Diseases, and [4)]Department of Nephrology, University of Tokyo Graduate School of Medicine, Tokyo, Japan; and [2)]Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital, Tokyo, Japan.

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Address for Reprints: Nobukazu Ishizaka, M.D., Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Hongo 7–3–1 Bunkyo-ku, Tokyo 113–8655, Japan. E-mail: nobuishizka-tky@umin.ac.jp

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Table 1. Clinical Characteristics and Laboratory Data of All Subjects Enrolled

	Never smoker (n=2,669)	Former smoker (n=2,252)	Current smoker (n=2,157)	p value
Age, years	52.8±11.2	56.0±10.0	51.0±9.5	<0.001
Body mass index, kg/m^2	23.5±2.9	23.9±2.7	23.8±3.1	<0.001
Systolic blood pressure, mmHg	125±18	127±18	122±18	<0.001
Diastolic blood pressure, mmHg	79±11	81±11	77±11	<0.001
Antihypertensive medication (n (%))	329 (12)	403 (18)	195 (9)	<0.001
Lipid data				
Total cholesterol, mg/dL	207±32	210±31	206±33	<0.001
HDL-cholesterol, mg/dL	56±13	56±13	52±13	<0.001
LDL-cholesterol, mg/dL	128±29	129±30	126±32	0.002
Triglycerides, mg/dL	101 (73–143)	112 (80–156)	130 (90–189)	<0.001
Glucose metabolism				
Fasting glucose, mg/dL	98±16	101±19	101±24	<0.001
Hemoglobin A1c, %	5.3±0.6	5.4±0.7	5.5±0.9	<0.001
Fasting insulin, μU/mL	5.3 (3.9–7.9)	5.6 (4.0–8.4)	5.4 (3.9–8.4)	0.004
HOMA-IR	1.3 (0.9–1.9)	1.4 (1.0–2.1)	1.3 (0.9–2.1)	<0.001
Diabetes mellitus (n (%))	144 (5.4)	179 (8.0)	219 (10.2)	<0.001
Renal function				
Serum urea nitrogen, mg/dL	15.0±3.4	14.8±3.6	14.0±3.3	<0.001
Serum creatine, mg/dL	0.87±0.13	0.87±0.26	0.83±0.13	<0.001
eGFR, mL/min/1.73 m^2	69.2±9.9	69.2±9.9	73.0±10.3	<0.001
Low eGFR (n (%))	437 (16.4)	369 (16.4)	212 (9.8)	<0.001
Elevated eGFR (n (%))	60 (2.3)	45 (2.0)	99 (4.6)	<0.001
UAER, mg/g	5.2 (3.7–9.5)	6.0 (3.9–12.0)	5.7 (3.9–10.8)	<0.001
Albuminuria (n (%))	200 (7.5)	236 (1,005)	234 (10.8)	<0.001
Uric acid, mg/dL	6.1±1.2	6.2±1.2	6.2±1.3	0.019
Drinking status				
Non-drinkers (n (%))	356 (13.3)	123 (5.5)	167 (7.7)	<0.001
Former drinkers (n (%))	90 (3.4)	228 (10.1)	74 (3.4)	
Current drinkers (n (%))	2,223 (83.3)	1,901 (84.4)	1,916 (88.8)	

Data are means±SD, median (interquartile range), n, or percentage. Diabetes mellitus was diagnosed when the subject had an FPG value of ≥126 mg/dL or current use of anti-diabetic drugs. The Kruskal-Wallis test was used to evaluate differences in triglycerides, fasting insulin, HOMA-IR, and UAER among the different smoking groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance; eGFR, estimated glomerular filtration rate; UAER, urinary albumin excretion rate.

Methods

Study Population

Between April 2005 and August 2006, 8,054 Japanese men underwent such a screening, including the estimation of urinary albumin excretion. Among them, 2,898 were former smokers and 2,487 were current smokers. After 976 subjects were excluded for failing to complete a questionnaire about their smoking habits (the reasons for this failure were unknown), we enrolled a total of 7,078 men, including 2,252 former and 2,157 current smokers. Subjects who had quit smoking for 1 month or less and those who had quit for more than 1 month before the time of the screening were considered to be, respectively, current and former smokers. The mean age of the 8,054 individuals (that is, before exclusion) was 53.7±10.5 years, significantly higher than that of the 7,078 men selected (53.3±10.5 years, p=0.007). Therefore, there may have been some bias in selecting the study subjects; however, this was not the intention of any attending physician. In Japan, regular health check-ups for employees are a legal requirement; all or most of the costs of the screening are paid for either by the employer (accounting for about two-thirds of individuals seen at our institute) or by the subject themselves (the other third). Blood pressure was measured after about 10 min of rest by an automated sphygmomanometer. The study was approved by the Ethics Committee of the Mitsui Memorial Hospital and Faculty of Medicine, University of Tokyo.

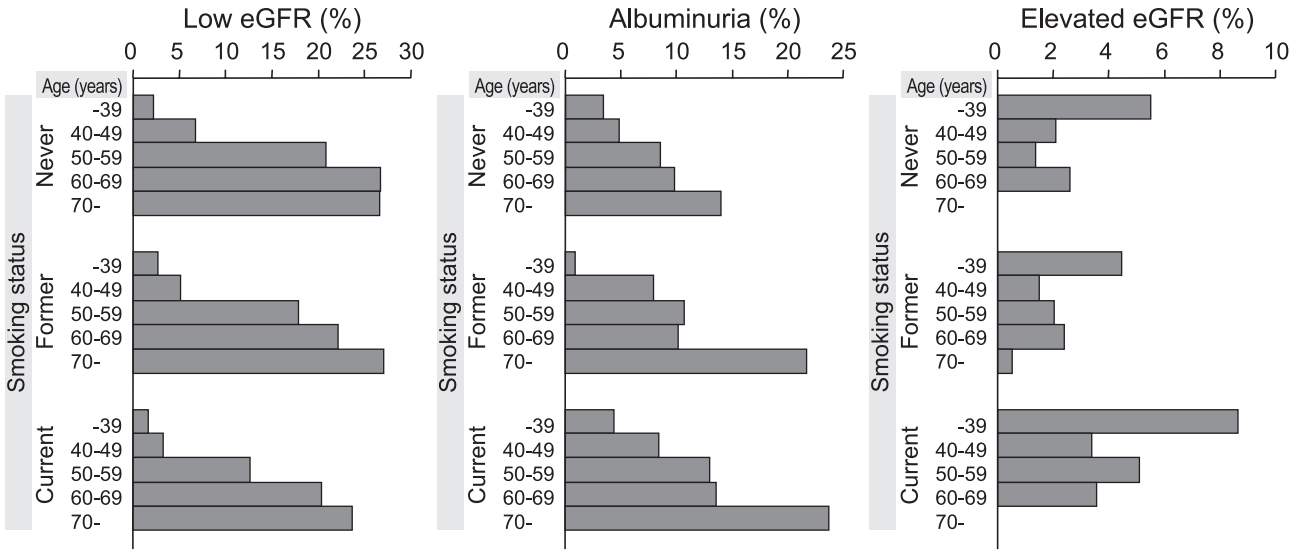

Fig. 1. *Prevalence of low eGFR, albuminuria, and elevated eGFR according to smoking status and age.*

Examination

Blood samples were taken and spot-urine specimens were obtained from the subjects in the morning after an overnight fast. Serum levels of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method, hemoglobin A1c was determined using the latex agglutination immunoassay, and creatinine was determined by the enzymatic method. Plasma glucose was measured by the hexokinase method, and serum insulin was measured by enzyme immunoassay. Homeostasis model assessment insulin resistance (HOMA-IR) was calculated in these individuals according to the following formula: HOMA-IR = [fasting immunoreactive insulin (μU/mL) × fasting plasma glucose (FPG; mg/dL)]/405. Creatinine and urine albumin were measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) and by Accute (Toshiba Medical Systems), respectively, using commercially available kits, Accuras Auto CRE (Shino-test, Tokyo, Japan) and IATRO U-ALB (TIA) (Mitsubishi Kagaku Iatron, Tokyo, Japan) respectively, according to the manufacturers' instructions. Accuracy was monitored every day by constructing X-bar and R charts using commercially available standards. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by an automated sphygmomanometer, BP-203RVIII (Omron Colin, Tokyo, Japan). Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg or current treatment with any antihypertensive drug.

Estimated GFR, Albuminuria, and Definition of CKD

Serum creatinine was calibrated by using the following formula: serum creatinine (Jaffe method) = 0.2 + serum creatinine (enzyme method). Serum creatinine was measured in mg/dL and age in years; glomerular filtration rate (GFR) was estimated by using the following equation from a simplified version of the Modification of Diet in Renal Disease (MDRD) (*9*): eGFR (mL/min/1.73 m^2) = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 0.881 (× 0.742 if female). In this MDRD formula, 0.881 is a coefficient for eGFR specific to the Japanese population (*10*). An eGFR of <60 mL/min/1.73 m^2 was designated as low eGFR. For the diagnosis of albuminuria, spot urine samples were collected and analyzed; albuminuria was considered present when the urinary albumin excretion ratio (UAER) expressed in mg/g creatinine, was ≥30 mg/g. Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as UAER of <30 mg/g, 30–299 mg/g, and ≥300 mg/g, respectively (*11*). Individuals were said to have CKD when they had low eGFR and/or albuminuria (*12*). Elevated eGFR was defined as an eGFR value that exceeded twice the SD of the mean eGFR value in the individuals enrolled, which was an eGFR value of >90.73 mL/min/1.73 m^2.

Statistical Analysis

Skewed variables, such as TG, fasting serum insulin, HOMA-IR, and UAER, are presented as medians (interquartile range). Other data are expressed as means±SD unless stated otherwise. Analyses of variance with Bonferroni post-hoc test, Kruskal-Wallis test, or χ^2-test were conducted as appropriate to assess the statistical significance of differences between groups. The association of smoking with CKD components (low eGFR and albuminuria) or with elevated eGFR was analyzed with a logistic regression model adjusted for all or some of the following variables: age, body mass index (BMI), SBP, FPG, HDL-C, TG, fasting serum insulin, and

current use of antihypertensive medication. Statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, USA). A value of $p<0.05$ was taken to be statistically significant.

Results

Baseline Characteristics

The mean eGFR was 70.4±10.2 mL/min/1.73 m^2, and the median UAER was 5.6 mg/g (interquartile range 3.8 to 10.6 mg/g). The mean age of former smokers was significantly higher ($p<0.001$), and that of current smokers was significantly lower ($p<0.001$), than that of never smokers (Table 1). Antidiabetic treatment was being administered to 47 (1.8%) never smokers, 85 (3.8%) former smokers, and 72 (3.3%) current smokers. The prevalence of diabetes mellitus, defined as a fasting glucose level greater than 126 mg/dL and/or taking antidiabetic medication, was significantly greater in both current and former smokers ($p<0.001$) than in never smokers. The prevalence of low eGFR was significantly lower and that of elevated eGFR was significantly higher in current than in never smokers ($p<0.001$). The prevalence of albuminuria in both former and current smokers was greater than that in never smokers ($p<0.001$).

Prevalence of Low eGFR, Albuminuria, and Elevated eGFR According to Smoking Status after Stratification by Age

As mean age differed significantly among the three groups, we plotted the prevalence of the components of CDK and elevated eGFR after stratification by age (Fig. 1). The number of individuals in the age categories of <39, 40–49, 50–59, 60–69, and ≥70 years were 7, 52, 170 155, and 53, respectively, in never smokers; 3, 24, 158, 129, and 55 in former smokers; and 4, 22, 104, 69, and 13 in current smokers. The prevalence of low eGFR and albuminuria both increased with age irrespective of smoking status.

Prevalence of Low eGFR According to Smoking Status

After adjusting for age, SBP, and FPG, logistic regression analysis revealed that current smoking showed a dose-dependent inverse association with the prevalence of low eGFR (Table 2). The prevalence of low eGFR was found to be significantly lower in current smokers who had been smoking for 10 years or longer and former smokers who had smoked for 20 years or longer. An inverse association between former smoking and low eGFR was observed in those individuals who had stopped smoking <1 year ago, but not in those who had stopped ≥1 year ago. Similar results were obtained after further adjustment for BMI, TG, HDL-C, serum insulin, and use of antihypertensive drugs; however, the association between former smoking and low eGFR was statistically significant in individuals who had stopped smoking ≥1 year ago as well as in those who had stopped <1 year ago. After adjusting for these variables, current and former smoking as a whole was associated with low eGFR, with odds ratios of 0.60 (95% confidence interval [CI] 0.50–0.73, $p<0.001$) and 0.80 (0.68–0.94, $p=0.005$), respectively.

Prevalence of Albuminuria According to Smoking Status

After adjusting for age, SBP, and FPG, logistic regression analysis showed that current smoking was statistically significantly associated with albuminuria irrespective of the amount of smoking, although the association just missed statistical significance when the amount of smoking was ≥20 cigarettes per day (Table 3). The association was also statistically significant in current smokers when the duration of smoking was ≥10 years. Former smoking tended to be associated with albuminuria when the duration of smoking was ≥10 years. Similar results were obtained after further adjustment for BMI, TG, HDL-C, serum insulin, and use of antihypertensive drugs. After adjusting for these variables, current smoking as a whole was associated with albuminuria, with an odds ratio of 1.63 (95% CI 1.34–2.03, $p<0.001$), although former smoking as a whole was not (odds ratio 1.16, 95% CI 0.94–1.44, $p=0.155$).

Prevalence of Elevated eGFR According to Smoking Status

After adjusting for age, SBP, and FPG, logistic regression analysis revealed that current smoking had a dose-dependent positive association with elevated eGFR (Table 4). In contrast, former smoking was not significantly associated with elevated eGFR irrespective of the amount or duration of smoking, or even when the cessation period was <1 year. Similar results were obtained after further adjustment for BMI, TG, HDL-C, serum insulin, and use of antihypertensive drugs. After adjusting for these variables, current smoking as a whole was associated with albuminuria with an odds ratio of 1.98 (95% CI 1.41–2.78, $p<0.001$), although former smoking as a whole was not (odds ratio 0.97, 95% CI 0.65–1.44, $p=0.878$).

Discussion

This study showed that current smoking was inversely associated with low eGFR when the amount smoked was ≥10 cigarettes per day. This association remained statistically significant after adjustment for age, SBP, and other metabolic parameters related to metabolic syndrome (BMI, HDL-C, TG, FPG, serum insulin, antihypertensive treatment) (Table 2). After adjusting for these variables, current smoking also showed a graded positive association with elevated eGFR

Table 2. Logistic Regression Analysis for Low eGFR as a Dependent Variable and Smoking Status as Independent Variables

Smoking status	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Amount of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (cigarettes/day)						
<10	0.78 (0.55–1.11)	0.171	0.78 (0.55–1.11)	0.164	0.77 (0.54–1.09)	0.143
10–19	0.93 (0.75–1.14)	0.478	0.93 (0.76–1.14)	0.491	0.90 (0.73–1.11)	0.336
20–39	0.77 (0.61–0.96)	0.020	0.77 (0.61–0.96)	0.023	0.72 (0.57–0.91)	0.005
≥40	0.84 (0.60–1.19)	0.332	0.84 (0.60–1.19)	0.334	0.80 (0.57–1.14)	0.222
Current smoking* (cigarettes/day)						
<10	1.12 (0.81–1.54)	0.499	1.13 (0.82–1.56)	0.465	1.07 (0.77–1.48)	0.708
10–19	0.55 (0.43–0.72)	<0.001	0.56 (0.43–0.73)	<0.001	0.53 (0.40–0.69)	<0.001
20–39	0.61 (0.47–0.80)	<0.001	0.63 (0.49–0.83)	<0.001	0.55 (0.42–0.73)	<0.001
≥40	0.29 (0.12–0.72)	0.008	0.32 (0.13–0.79)	0.014	0.26 (0.10–0.65)	0.004
Duration of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (years)						
<5	0.71 (0.42–1.20)	0.200	0.70 (0.42–1.19)	0.189	0.72 (0.42–1.21)	0.213
5–9	0.87 (0.63–1.20)	0.383	0.86 (0.63–1.19)	0.371	0.82 (0.59–1.14)	0.232
10–19	1.00 (0.79–1.25)	0.965	0.99 (0.79–1.25)	0.947	0.97 (0.77–1.22)	0.789
≥20	0.76 (0.62–0.93)	0.007	0.77 (0.63–0.94)	0.010	0.72 (0.59–0.89)	0.002
Current smoking* (years)						
<5	0.94 (0.31–2.79)	0.904	1.00 (0.33–2.99)	0.999	1.12 (0.37–3.37)	0.837
5–9	1.11 (0.48–2.56)	0.805	1.15 (0.50–2.64)	0.750	1.18 (0.51–2.71)	0.701
10–19	0.53 (0.32–0.89)	0.017	0.54 (0.32–0.91)	0.021	0.50 (0.30–0.84)	0.009
≥20	0.64 (0.53–0.78)	<0.001	0.66 (0.55–0.80)	<0.001	0.60 (0.49–0.73)	<0.001
Years of cessation						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking*						
Last smoked <1 year ago	0.51 (0.29–0.88)	0.015	0.52 (0.30–0.89)	0.018	0.51 (0.29–0.88)	0.015
Last smoked ≥1 year ago	0.87 (0.74–1.02)	0.079	0.87 (0.74–1.02)	0.081	0.83 (0.71–0.98)	0.025

Model 1, adjusted for age; model 2, age, SBP, and FPG; model 3, age, SBP, FPG, BMI, HDL-C, TG, fasting serum insulin, and current use of antihypertensive drug. *Never smoking was used as reference. eGFR, estimated glomerular filtration rate; CI, confidence interval; SBP, systolic blood pressure; FPG, fasting blood glucose; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride.

(Table 4). On the other hand, former smoking showed a statistically significant inverse association with low eGFR, whereas the association with either albuminuria or elevated eGFR did not reach statistical significance irrespective of the duration of smoking (Tables 3, 4). Interestingly, the association between cigarette smoking and elevated eGFR lost statistical significance even within 1 year after quitting (Table 4). These findings collectively suggest that cigarette smoking decreases the prevalence of low eGFR and increases the prevalence of albuminuria and elevated eGFR—an association that is markedly weakened (for low eGFR and albuminuria) or abolished (for elevated eGFR) after quitting smoking.

Several studies have demonstrated a positive association between smoking and albuminuria, some of which showed statistically significant associations in both current and former smokers (*13*), while others demonstrated only in current smokers (*5*, *6*). In the current study, after adjusting for age and variables related to metabolic syndrome, current smoking as a whole showed a statistically significant inverse association with low eGFR and positive ones with albuminuria and elevated eGFR. On the other hand, former smoking, as a whole, showed a statistically significant inverse association with low eGFR, but the association between former smoking and albuminuria was not significant. These findings are in agreement with the results of the third National Health and Nutrition Examination Survey, which showed that the cessation of smoking weakens or abolishes the increase in albuminuria (*5*).

Table 3. Logistic Regression Analysis for Albuminuria as a Dependent Variable and Smoking Status as Independent Variables

Smoking status	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Amount of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (cigarettes/day)						
<10	0.65 (0.39–1.11)	0.112	0.73 (0.42–1.24)	0.239	0.70 (0.41–1.21)	0.203
10–19	1.49 (1.16–1.91)	0.002	1.46 (1.12–1.90)	0.005	1.45 (1.12–1.89)	0.006
20–39	1.26 (0.96–1.65)	0.102	1.08 (0.81–1.44)	0.601	1.03 (0.77–1.37)	0.857
≥40	1.56 (1.05–2.33)	0.029	1.27 (0.84–1.92)	0.261	1.16 (0.77–1.77)	0.482
Current smoking* (cigarettes/day)						
<10	1.57 (1.08–2.30)	0.019	1.72 (1.15–2.56)	0.008	1.67 (1.12–2.51)	0.012
10–19	1.61 (1.24–2.08)	<0.001	1.64 (0.25–2.16)	<0.001	1.70 (1.28–2.24)	<0.001
20–39	1.66 (1.27–2.18)	<0.001	1.56 (1.17–2.08)	0.002	1.53 (1.14–2.06)	0.005
≥40	2.43 (1.37–4.32)	0.003	1.88 (0.99–3.55)	0.053	1.81 (0.96–3.41)	0.068
Duration of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (years)						
<5	0.52 (0.23–1.20)	0.124	0.57 (0.25–1.31)	0.184	0.55 (0.24–1.29)	0.169
5–9	0.69 (0.43–1.13)	0.137	0.72 (0.44–1.18)	0.193	0.70 (0.42–1.15)	0.159
10–19	1.57 (1.19–2.06)	0.001	1.36 (1.02–1.81)	0.035	1.33 (1.00–1.77)	0.050
≥20	1.45 (1.14–1.84)	0.003	1.33 (1.04–1.71)	0.025	1.27 (0.99–1.64)	0.060
Current smoking* (years)						
<5	1.53 (0.46–5.14)	0.491	1.03 (0.24–4.52)	0.965	1.19 (0.28–5.04)	0.809
5–9	0.88 (0.27–2.88)	0.838	0.84 (0.25–2.81)	0.773	0.89 (0.27–2.96)	0.843
10–19	1.83 (1.21–2.78)	0.004	1.82 (1.17–2.83)	0.008	1.73 (1.10–2.72)	0.017
≥20	1.66 (1.35–2.04)	<0.001	1.64 (1.32–2.05)	<0.001	1.66 (1.32–2.08)	<0.001
Years of cessation						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking*						
Last smoked <1 year ago	1.41 (0.83–2.37)	0.204	1.28 (0.74–2.22)	0.374	1.28 (0.74–2.22)	0.382
Last smoked ≥1 year ago	1.29 (1.05–1.58)	0.014	1.20 (0.97–1.48)	0.097	1.16 (0.93–1.43)	0.184

Models as in Table 2. *Never smoking was used as reference. CI, confidence interval.

We also showed here that current smoking dose-dependently reduced the prevalence of low eGFR. In agreement with our result, some studies have shown that current smoking is associated with higher creatinine clearance or GFR in the general population (*14*) and in type 2 diabetic patients (*7*). On the other hand, however, some other studies have shown that current smoking decreases GFR in community-dwelling subjects (*8*) and type 2 diabetic patients (*15*). What causes these conflicting results has not been fully clarified; however, insulin resistance, which might be enhanced by smoking (*16*), may have a role in these discrepant observations, as it may lead to a decrease (*17*) or an elevation (*18*) of eGFR.

In the current study, current smoking, but not former smoking, was dose-dependently positively associated with elevated eGFR (Table 2). Ekberg *et al*. reported that glomerular hyperfiltration was more prevalent in smokers than in nonsmokers (*19*). In addition, in a substudy of the PREVEND study (Prevention of Renal and Vascular End-stage Disease), Pinto-Sietsma *et al*. reported that current smoking showed a dose-dependent association with elevated eGFR in nondiabetic subjects, which disappeared after smoking ceased (*13*). We cannot conclude the mechanism by which smoking elevates GFR in the Japanese population from this type of cross-sectional study; however, it is possible that pre-glomerular vessels and glomerular obsolescence lead to hypertrophy and hyperfiltration of remnant glomeruli after repeated transient decreases in renal plasma flow and GFR induced by smoking, which eventually result in elevated GFR (*14*, *20*). It is recognized that glomerular hyperfiltration is not a rare occurrence in individuals with impaired glucose metabolism (*21*, *22*) or even in apparently healthy young men (*23*). It should be noted that glomerular hyperfiltration represents a new marker of clustering of metabolic risk factors even before overt features of cardiovascular disease are manifest (*23*). Thus, the increase

Table 4. Logistic Regression Analysis for Elevated eGFR as a Dependent Variable and Smoking Status as Independent Variables

Smoking status	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Amount of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (cigarettes/day)						
<10	0.57 (0.20–1.57)	0.276	0.61 (0.22–1.70)	0.348	0.61 (0.22–1.70)	0.342
10–19	0.81 (0.46–1.44)	0.477	0.77 (0.43–1.38)	0.379	0.78 (0.45–1.40)	0.405
20–39	1.40 (0.93–2.37)	0.207	1.21 (0.71–2.06)	0.477	1.32 (0.77–2.25)	0.310
≥40	1.50 (0.63–3.57)	0.358	1.24 (0.53–3.05)	0.592	1.41 (0.58–3.41)	0.447
Current smoking* (cigarettes/day)						
<10	0.72 (0.31–1.67)	0.438	0.70 (0.30–1.63)	0.403	0.71 (0.30–1.69)	0.440
10–19	2.03 (1.37–3.01)	<0.001	1.87 (1.25–2.81)	0.002	1.93 (1.28–2.90)	0.002
20–39	2.50 (1.67–3.75)	<0.001	2.35 (1.56–3.54)	<0.001	2.56 (1.68–3.91)	<0.001
≥40	3.10 (1.30–7.39)	0.011	2.46 (1.01–6.00)	0.049	2.81 (1.13–6.99)	0.026
Duration of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (years)						
<5	0.95 (0.34–2.66)	0.924	1.02 (0.37–2.87)	0.965	1.01 (0.36–2.83)	0.986
5–9	0.48 (0.17–1.32)	0.154	0.50 (0.18–1.38)	0.181	0.50 (0.18–1.39)	0.183
10–19	1.01 (0.57–1.80)	0.963	0.91 (0.51–1.64)	0.762	0.95 (0.53–1.70)	0.853
≥20	1.36 (0.80–2.29)	0.254	1.18 (0.69–2.00)	0.548	1.28 (0.75–2.19)	0.365
Current smoking* (years)						
<5	2.54 (0.59–11.04)	0.214	2.03 (0.43–0.96)	0.369	1.89 (0.38–9.45)	0.439
5–9	2.06 (0.71–5.97)	0.186	2.05 (0.71–5.96)	0.188	1.97 (0.67–5.77)	0.216
10–19	1.70 (0.99–2.92)	0.053	1.59 (0.92–2.74)	0.097	1.68 (0.97–2.92)	0.065
≥20	2.10 (1.48–2.98)	<0.001	1.94 (1.36–2.78)	<0.001	2.04 (1.42–2.95)	<0.001
Years of cessation						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking*						
Last smoked <1 year ago	1.49 (0.63–3.50)	0.364	1.32 (0.55–3.15)	0.534	1.37 (0.57–3.29)	0.479
Last smoked ≥1 year ago	0.97 (0.64–1.47)	0.871	0.90 (0.59–1.37)	0.628	0.94 (0.62–1.43)	0.768

Abbreviations and models as in Table 2. *Never smoking was used as reference. CI, confidence interval.

in eGFR caused by cigarette smoking may not simply be a preferable or an innocuous observation. In addition, current smoking may increase the prevalence of both low GFR and elevated GFR in the same population (*13*, *15*), which suggests the possibility that a simple comparison of the eGFR between smokers and nonsmokers may lead to an inappropriate conclusion.

Our study has some limitations. First, we used the MDRD formula with the Japanese coefficient of 0.881 for the estimation of GFR (*10*), and a recent study has shown that this formula may underestimate GFR in the inulin clearance range of over 60 mL/min/1.73 m^2 in the Japanese population. Second, in the MDRD formula used, muscle mass was not taken into consideration for GFR estimation. Because the serum creatinine value is the balance of the release from skeletal muscle and removal by the kidneys, both muscle mass and renal function are important determinants. Recent studies have shown that anthropometric/demographic variables, such as age, gender, height, and weight, may not adequately account for variance in muscle mass, and that measures of muscle mass, which can be clinically obtainable (*24*), may improve the estimation of GFR (*25*). Third, owing to the cross-sectional nature of the current study, we cannot determine whether or not elevation of eGFR in smokers modulates long-term renal prognosis.

In conclusion, by analyzing the cross-sectional data of Japanese men who underwent a general health screening, we showed that current smoking was dose-dependently associated inversely with low eGFR and positively with albuminuria and elevated eGFR—associations that were weakened or abolished after quitting. We may need to take into account an individual's smoking status when assessing the eGFR and

thus the presence of CKD, especially when urine data are not available, as smoking may increase the prevalence of not only albuminuria but also hyperfiltration. Whether or not elevation of eGFR owing to cigarette smoking acts protectively for renal function in the long term, and whether or not elevation of eGFR by current smoking is an acute and transient phenomenon that does not modulate long-term renal prognosis, need to be investigated in future longitudinal studies.

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