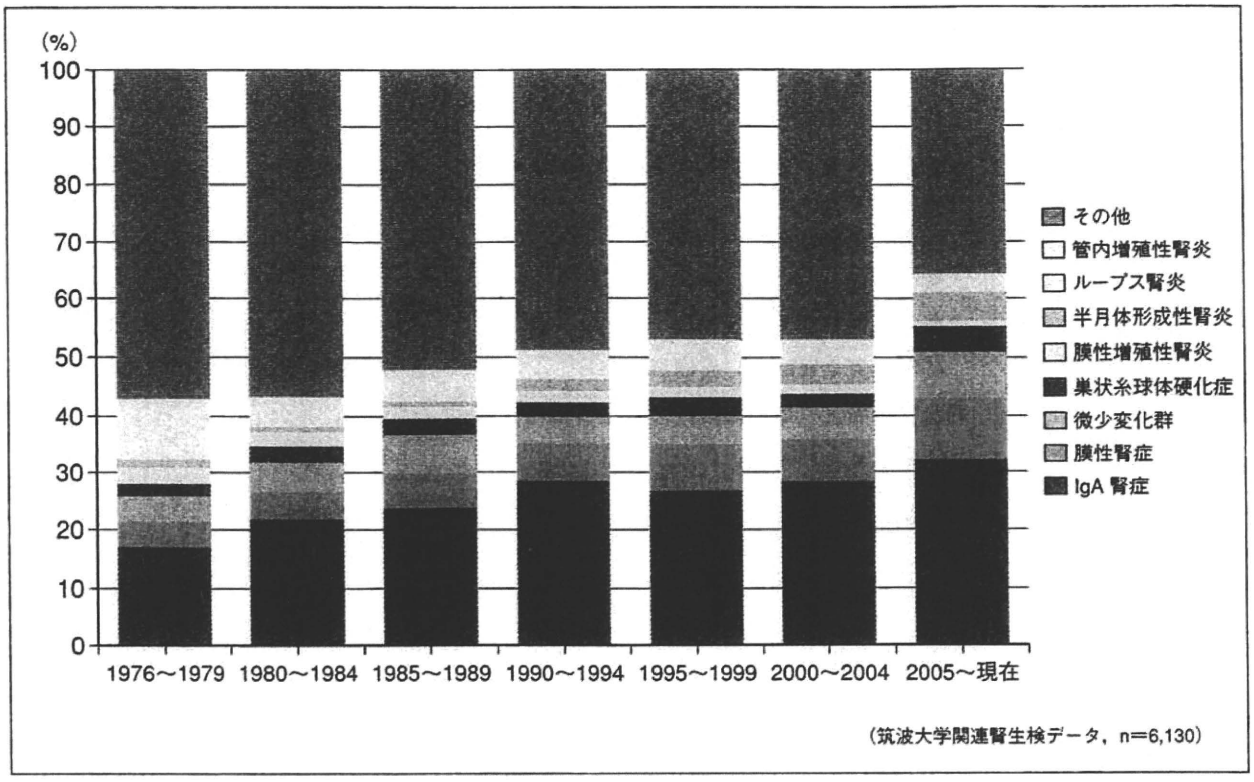
図5　年代別腎生検組織診断頻度



のであろう．このような中で，腎生検組織病型については相変わらずIgA 腎症が最も多く，次いで膜性腎症，微少変化群，巣状糸球体硬化症の順で，大きな変化はない．中でも IgA 腎症の比率は，少子高齢化の影響で腎生検を受ける患者年齢の上昇があるにもかかわらず増加を認め，直近の腎生検例の 32.1％ を占める．また，中高齢者で多い膜性腎症の頻度が上昇しているが，これは中高齢での腎生検施行頻度の上昇の影響も否定できない[9]．

3．健診受診者の CKD 原疾患

表3下段に示したごとく[10]，日本腎臓学会の調査による各地の健診結果から，CKD 患者のステージ別の比率は，先述のごとく腎臓内科外来患者の比率と大きく異なり，CKD ステージ3の患者の頻度が極めて高い．この CKD ステージ3の特徴としては，この中の 90％ 以上が尿タンパク陰性であることである．タンパク尿陽性者については，顕性タンパク尿を認める糖尿病性腎症，糸球体腎炎が主体であろう．表4に尿所見が乏しいまま，腎機能の低下を来しうる疾患をまとめた．若年者では腎の発生異常，奇形，先天代謝異常による腎疾患が存在す

表4　尿所見の乏しいCKDの原疾患

先天性・奇形
腎の発生異常
先天性代謝障害
腎血流の異常（糸球体前の血行障害）
慢性心不全
両側腎動脈狭窄
腎梗塞後
高血圧性腎症・腎硬化症
加齢による腎障害（虚血性腎症）
間質性腎障害（糸球体以後の腎実質障害）
加齢による腎障害
慢性間質性腎炎
薬剤性腎障害の一部（鎮痛薬性腎症，シクロスポリン腎症）
寛解後の慢性糸球体腎炎
急性腎不全後
閉塞性尿路疾患
両側水腎症
尿路結石
尿道狭窄
神経因性膀胱
前立腺肥大

る．しかしながら圧倒的に多数を占める中高齢者では，動脈硬化性疾患特に，長期間の高血圧，全身の動脈硬化による虚血性腎症，腎硬化症が挙げられよう．また，長期間の尿路閉塞性疾患なども鑑別の必要がある．これらの疾患については，腎生検の適応となることもまれで，確定診断がつきにくい場合も多い．いずれにしろ，尿所見の乏しい腎機能障害の患者を診たときの腎原疾患の診断には，一部の可逆的障害や積極的な治療による進行防止の可能な疾患も存在することから，単に加齢による腎障害と決めつけずに，慎重に対処することが求められる．

おわりに

CKD患者の原疾患を中心に検討した．我が国の透析療法の現況によると，透析に至った原疾患の中で，原疾患不明の占める割合が10.64％に達し，年々この不明の割合も増加している．これは，原疾

患の3位を占める腎硬化症よりも多い．透析導入後の予後も原疾患により大きく異なることも事実であり，透析導入時点では，腎疾患治療の専門家が施行しているのが主流であろうから，CKD に至る原疾患について，可能な限り追求がなされるべきである．

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Etiology and Primary Kidney Disease of CKD

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糸球体濾過値と尿中アルブミンによる末期腎不全の予測

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はじめに

透析や移植を必要とする末期慢性腎不全(end-stage kidney disease, ESKD)患者数は世界中で顕著に増加しており，1990～2010年の20年間でわが国の透析患者数は10.3万人から30万人，世界では43万人から210万人と，実に5倍に増えると予想されている．ESKD患者では心血管病の合併が多いことが古くから事実として知られていたが，糸球体濾過値(glomerular filtration rate, GFR)の軽度低下や尿蛋白を認める，いわゆる慢性腎臓病(chronic kidney disease, CKD)が心血管イベントのリスクでもある事実が広く知れわたってきた．本稿では，ESKDの予測因子としてGFRと尿蛋白あるいは尿中アルブミンの重要性について概説する．

■ ESKD予測因子としてのGFRの意義

GFRとは，時間当たりの腎糸球体で濾過される血液量を意味し，通常は体表面積で標準化され，ml/分/1.73 m²の単位で表される．わが国でGFRを正確に測定するにはイヌリンによるクリアランス試験を行うことがゴールデンスタンダードである．しかし，この方法はやや煩雑であり，簡易法[1]や，外来などの通常の診療の場においては，血清クレアチニン，年齢，性別により，GFRを推算する式として以下のものが用いられている[2]．この式を用いて算出されたものを“推算GFR(estimated GFR, eGFR)”と呼ぶ．

$$eGFR = 194 \times Cre^{-1.094} \times 年齢^{-0.287} (女性 \times 0.739)$$

本式を用いる場合には，血清クレアチニンの測定は酵素法であること

GFRは糸球体濾過そのものを評価しており，CKDのステージ5，すなわちGFR 15 ml/分/1.73 m²未満は，ESKDの直前と評価される．したがって，ESKDの予測因子としてGFRをみた場合には，異なる時期におけるGFRからその単位時間当たりの悪化スピードをみることにより，ESKDの予測が可能となる．従来から加齢により腎機能が悪化することは知られてきた．日本人の加齢による腎機能悪化は全年齢平均で0.36 ml/分/1.73 m²であり，欧米人よりも緩除であることが明らかとなった[3]．しかしながら，ひとたびGFRが低下すれば，貧血，高血圧，蛋白尿，電解質代謝異常の頻度が増加し，GFRの悪化スピードが加速する．実際，eGFRの悪化スピードが初期のGFRに影響されることは，国内40～79歳の29万人規模の健診10年間の前向き追跡調査の結果，初期GFRの階層別にGFR低下率を検討して示されており，年齢を問わずGFR 60～69 ml/分/1.73 m²を下回るとき悪化する．さらに，高齢者においては高血圧，糖尿病，肥満，脂質代謝異常による動脈硬化性の危険因子を合併することもGFR低下を加速する(図1)．

またGFR 60 ml/分/1.73 m²以上の健常人において，年1回の血清クレアチニン検査を連続してフォローしたところ，GFR 60 ml/分/1.73 m²未満に至るのは，蛋白尿，血尿，高血圧，加齢，脂質異常症，糖尿病による治療，喫煙などが重要なリスク因子であることがわかった[4]．

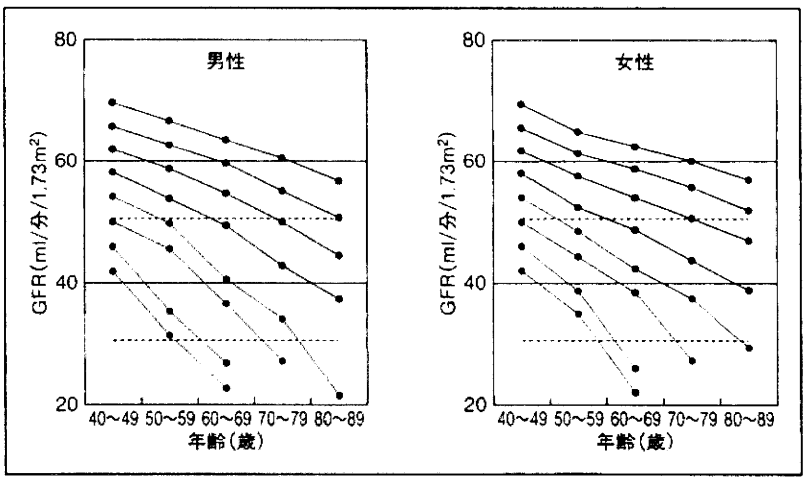

図1 日本人の加齢に伴う腎機能の低下 (文献3から改変して転載)

0301-2611/10/¥250/論文/JCOPY

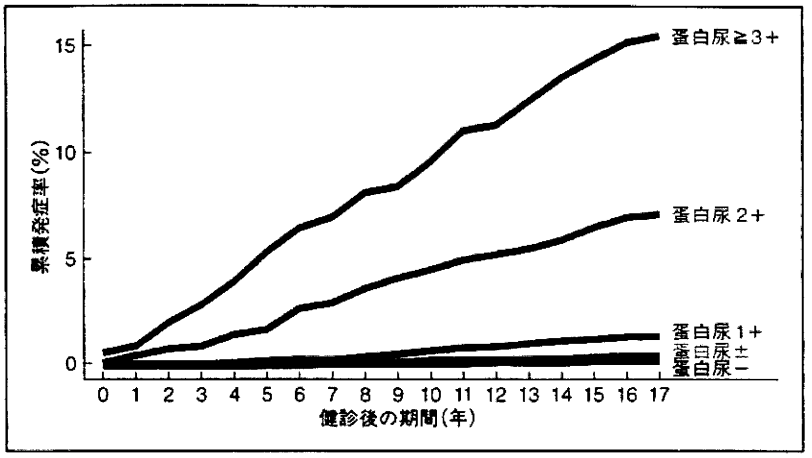

図2　健診時の蛋白尿の程度(試験紙法)別のESKD発症率(沖縄県)
(文献5から改変して転載)

■ESKD予想因子としての蛋白尿・尿中アルブミンの意義

検尿異常，特に蛋白尿の存在が腎機能の悪化スピード加速と大きな関係があり，将来のESKDへの進展を予測するために最も重要である．実際，沖縄県の検討では，蛋白尿の程度が透析導入発症率の17年間の観察期間においては尿蛋白3+以上で16%，2+で7%であり，蛋白尿が多ければ多いほどESKDに至ることが示され，試験紙法の有用性は明らかである(図2)[5]．

これらのわが国の検討では尿蛋白の評価は基本的に試験紙法の定性検査で評価されてきた．尿試験紙法は主に尿中のアルブミンと反応し，尿細管障害や多発性骨髄腫などのグロブリン尿では陰性となるので注意が必要である．詳細な尿蛋白量の評価は蓄尿に検討すべきである．蓄尿が不可能な場合には尿中クレアチニン濃度(mg/dl)を尿蛋白濃度(mg/dl)で除して，1gクレアチニン(成人の1日のクレアチニン排泄量と仮定)当たりの尿蛋白量から1日の尿蛋白量を推定することが可能である．

さらに微量アルブミン尿として尿中アルブミン30～300 mg/日もしくは30～300 mg/1gクレアチニンを定義することが多い．微量アルブミン尿は酸化ストレスなどによる血管内皮細胞障害，心血管イベントの予測因子として重視されている．この微量アルブミン尿そのものが直接的にESKDの予測因子として捉えるよりも，糖尿病性腎症患者においては微量アルブミン尿が将来の顕性蛋白尿に進行する患者のリスク因子であることは間違いなく，蛋白尿(アルブミン尿)としてESKDへと進展する危険性は大きく上昇する．

海外の報告ではStage 3～4のCKDからESKDに移行する予測にはアルブミン尿単独，eGFR単独，アルブミン尿とeGFRの組み合わせの順で正確であることが示され[6]この場合，eGFRの低下した，CKDステージ3以降であっても，微量アルブミン尿が有意な予後予測因子となることが示されている．わが国においても，従来の糸球体腎炎によるESKD患者は減少し，糖尿病，高血圧，動脈硬化によるESKD患者が増加してきており，顕性蛋白尿だけでなく，微量アルブミン尿の意義付けについてもさらなる検討が必要であろう．

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Cigarette Smoking and Progression of IgA Nephropathy

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Background: Multiple community-based cohort studies of mainly middle-aged and elderly populations have shown that cigarette smoking is a risk factor for chronic kidney disease. However, little information is available about an effect of cigarette smoking on progression of primary kidney diseases, including immunoglobulin A (IgA) nephropathy.

Study Design: Retrospective cohort study.

Setting & Participants: 971 of 1,001 patients with a diagnosis of IgA nephropathy in 3 major nephrology centers in Osaka, Japan, between 1992 and 2005 who enrolled in the Study of Outcome and Practice Pattern of IgA Nephropathy (STOP-IgAN).

Predictors: Smoking status and number of cigarettes smoked at the time of diagnosis using kidney biopsy. Dose-dependent associations between cigarette smoking and outcomes were assessed in multivariate Cox proportional hazards models. Significantly different clinical characteristics between non-/past and current smokers were controlled for using propensity score–based adjustment, stratification, and matching.

Outcomes: 50% increase in serum creatinine level as primary outcome. A composite outcome of a 100% increase in serum creatinine level or end-stage renal disease (ESRD) and ESRD alone as secondary outcomes.

Results: During the median 5.8 years (interquartile range, 2.6-10.2) of the observational period, 117 participants progressed to a 50% increase in serum creatinine level and 47 advanced to ESRD. Multivariate Cox proportional hazards models identified current smokers (HR, 2.03 [95% CI, 1.33-3.10] for primary outcome) and number of cigarettes at kidney biopsy (HR, 1.21 [95% CI, 1.06-1.39] per 10 cigarettes per day) as significant predictors of outcomes. Propensity score–based models confirmed these results. Tests for interaction showed that the association of current smoking with adverse outcomes was stronger in those with lower compared with higher estimated glomerular filtration rates.

Limitation: Baseline smoking status was not verified using biochemical tests. Smoking status during the observational period was unavailable.

Conclusions: Cigarette smoking, in a dose-dependent manner, was identified as a key prognostic factor in IgA nephropathy. Smoking cessation should be encouraged as part of the treatment for IgA nephropathy.

Am J Kidney Dis 56:313-324.

INDEX WORDS: Immunoglobulin A (IgA) nephropathy; cigarette smoking; dose-dependent effect; progression; end-stage renal disease (ESRD); propensity score, interaction.

Immunoglobulin A (IgA) nephropathy was described first by J. Berger in 1969 and is now generally considered to be the most common primary glomerulonephritis in the world.[1-3] Although multiple long-term observational studies reported a wide range of kidney survival rates for IgA nephropathy,[4-19] approximately 15%-25% of patients with IgA nephropathy advance to

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0272-6386/10/5602-0012$36.00/0
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end-stage renal disease (ESRD) within 10 years of diagnosis. Impaired kidney function, proteinuria, hypertension, and advanced histologic lesions have been identified as major prognostic factors of progressive kidney failure.[20] In addition to these conventional risk factors, several recent studies have shown that atherosclerotic metabolic factors, such as obesity,[21] fasting triglyceride level,[22] insulin resistance,[23] and uric acid level,[22] are significant predictors of progressive IgA nephropathy.

Cigarette smoking, which is a well-known risk factor for atherosclerotic diseases, also has been identified as a risk factor for the development and progression of chronic kidney disease (CKD) in community-based longitudinal cohort studies.[24-33] In these studies, causes of CKD were heterogeneous, including patients with diabetes, nephrosclerosis, and other diseases, and it consequently was uncertain whether every kidney disease was equally vulnerable to cigarette smoking. Some studies implied that the relationship between cigarette smoking and kidney impairment varied among underlying kidney diseases.[34]

When it comes to primary glomerulonephritides, little information is available about an influence of cigarette smoking on their renal prognosis. Although Orth et al[35] reported a dose-dependent association of smoking and ESRD in a matched case-control study of 108 patients with IgA nephropathy and 96 patients with autosomal dominant polycystic kidney disease, their analyses did not control for critical confounding factors, such as urinary protein excretion and estimated glomerular filtration rate (eGFR). Therefore, they failed to demonstrate an independent association of cigarette smoking and renal prognosis in IgA nephropathy. Because previous community-based cohort studies were based entirely on middle-aged and older participants with normal or nearly normal kidney function, it remains to be confirmed that their result also is true in IgA nephropathy, which occurs most commonly in the second and third decades of life[36] and has a wide range of kidney function at diagnosis. Few reports showed a relevant association between cigarette smoking and renal prognosis in IgA nephropathy, and if so, another point that remains to be elucidated is whether patients with IgA nephropathy with early and advanced stages are equally vulnerable to cigarette smoking.

The aim of the present study is first, to examine whether cigarette smoking had a deleterious impact on the progression of IgA nephropathy in a dose-dependent manner independent of conventional prognostic factors, and if so, second, to assess whether cigarette smoking was a predictor of progression of IgA nephropathy at both early and advanced stages. This multicenter observational cohort study was organized by a research group for the Study of Outcome and Practice Patterns of Primary IgA Nephropathy (STOP-IgAN) based on 3 major nephrology centers in Osaka, Japan.

METHODS

Study Population

Between January 1992 and December 2005, a total of 1,001 patients 15 years or older were given a diagnosis of IgA nephropathy using kidney biopsy in Osaka University Hospital, Osaka General Medical Center, and Osaka Rosai Hospital. The diagnosis of IgA nephropathy was made by detection of mesangial deposits staining predominantly for IgA in immunofluorescence studies in patients without evidence of systemic lupus erythematosus, Henoch-Schönlein purpura, chronic liver diseases, and rheumatoid arthritis. After excluding 30 patients (3.0%) with missing data for the covariates of interest except for the number of cigarettes smoked at the time of diagnosis using kidney biopsy, 971 patients with IgA nephropathy were enrolled in the present study and followed up until June 2009. The study protocol was approved by the ethics committees in Osaka University Hospital, Osaka General Medical Center, and Osaka Rosai Hospital.

Covariates

Baseline clinical data at diagnosis using kidney biopsy, including age, sex, body mass index, hypertension (systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or any antihypertensive medication), serum creatinine level, CKD stage[37] based on GFR estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation (eGFR = 175 $\times$ Creatinine [mg/dL]$^{-1.154}$ $\times$ Age [y]$^{-0.203}$ [$\times$ 0.742 if female]),[38] serum total cholesterol level, serum uric acid level, urinary protein excretion, smoking status (current, past, or nonsmokers), and, in the case of current smokers, number of cigarettes smoked daily at the time of the kidney biopsy, were collected from medical records. In 2 facilities, serum creatinine was measured using the enzymatic method during the entire observational period, whereas creatinine measurement was changed from the Jaffé method to the enzymatic method in November 1995 in 1 facility. Using sera from 648 patients in the facility, the correlation coefficient r between creatinine values measured using the Jaffé method and the enzymatic method was 0.998,

and the least squares method determined the predictive equation: creatinine (enzymatic method) = 0.94 × creatinine (Jaffé method) − 0.25. Thus, creatinine values for 205 patients with a diagnosis of IgA nephropathy before November 1995 in the facility were calibrated using this equation. CKD stage[37] was classified into 3 subgroups: stage 1, eGFR ≥90 mL/min/1.73 m^2; stage 2, eGFR of 60-89 mL/min/1.73 m^2; and stages 3-5, eGFR <60 mL/min/1.73 m^2. Antihypertensive drugs were renin-angiotensin-aldosterone system (RAAS) blockers (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone receptor blockers), calcium channel blockers, α-blockers, β-blockers, and thiazides. Smoking status was based on a questionnaire filled in at admission for kidney biopsy. According to the number of cigarettes smoked at the time of diagnosis using kidney biopsy, current smokers were classified into 2 groups: those smoking 1 pack daily or less (1-20 cigarettes daily) and those smoking more than 1 pack daily (>20 cigarettes daily). Nonsmokers and past smokers were combined into a single group (non-/past smokers) because the number of past smokers were very small (n = 31) and one of the main interests of the present study was a dose-dependent association between kidney outcomes and number of cigarettes smoked at time of diagnosis using kidney biopsy. Considering the relatively high recurrence rate of smoking,[39-41] combining the groups of past and nonsmokers will tend to bias toward the null.

Therapeutic interventions, including use of RAAS blockers and immunosuppressants, including corticosteroid and other agents that were initiated within 1 year of kidney biopsy, also were collected from the medical records.

Outcomes

The primary outcome measures of the present study were time from kidney biopsy to 50% increase in baseline serum creatinine level before ESRD. Secondary outcomes consisted of a composite outcome of 100% increase in baseline serum creatinine level (namely, doubling of serum creatinine level) or development of ESRD requiring renal replacement therapy and development of ESRD alone. Death before these outcomes was regarded as being censored. Serum creatinine was measured as required according to the clinical needs for each patient. Patients were followed up until June 2009 and censored at death before ESRD or on the last day of serum creatinine measurement before June 2009.

Statistical Analysis

Differences in clinical characteristics between non-/past smokers and current smokers were compared using *t* test, Wilcoxon rank-sum test, or χ^2 test, and those between matched pairs of non-/past smokers and current smokers were compared using paired *t* test, Wilcoxon signed rank test, or Mantel-Haenszel test, as appropriate. Cumulative probability of the outcomes was estimated using the Kaplan-Meier method. To determine prognostic factors independently associated with outcomes, potential covariates were examined using log-rank test and/or univariate and multivariate Cox proportional hazards models. Potential confounding by facility was accounted for by stratifying on facilities. The assumption of proportional hazards for covariates was tested formally by calculating the slope of the scaled Schoenfeld residuals on time.

To control for significant differences in clinical characteristics between non-/past smokers and current smokers, we used a propensity score, an estimated probability of being a current smoker, given the observed confounding variables.[42] The propensity score for each patient was calculated in a separate multivariate logistic regression model including baseline clinical characteristics: facility, age, sex, body mass index, hypertension, serum creatinine level, urinary protein excretion, serum total cholesterol level, and serum uric acid level as independent variables. Calibration was assessed using Hosmer-Lemeshow goodness-of-fit test. The area under the receiver operating characteristic curve was calculated to assess the predictive ability of the propensity model. After calculating the propensity score for each patient, 3 kinds of propensity score–based models were constructed to assess associations between current smokers and outcomes. (1) Adjustment for propensity score: propensity score was incorporated as an independent variable into the multivariate Cox proportional hazards models stratified on facilities. (2) Stratification on propensity score: propensity score was categorized into quartiles and hazard ratios (HRs) for covariates were calculated using the multivariate Cox proportional hazards model stratified on the quartiles of propensity score. (3) Matching by propensity score: each current smoker was matched to non-/past smokers with the closest propensity score at a ratio of 1:1 without replacement, using a standard greedy matching algorithm with a caliper width of 0.2 standard deviation of the logit of the propensity score.[43] Survival curves of current and non-/past smokers were compared using log-rank tests and univariate Cox proportional hazards models stratified on matched pairs.

To assess whether an association between smoking status and outcomes was different in patients at earlier and advanced stages of IgA nephropathy, effect modification between smoking status and serum creatinine level at kidney biopsy was explored by inclusion of interaction terms in the multivariate Cox proportional hazards models stratified on facilities.

Normally distributed continuous variables are expressed as mean ± standard deviation, and non–normally distributed continuous variables, as median and interquartile range. Categorical variables are expressed as number and proportion. $P < 0.05$ is considered statistically significant. All statistical analyses were performed using STATA, version 10 (STATA Corp, www.stata.com).

RESULTS

Total numbers of non-, past, and current smokers were 714 (73.5%), 31 (3.2%), and 226 (23.3%), respectively. For 844 patients 20 years or older, numbers of non-, past, and current smokers were 203 (55.8%), 22 (6.0%), and 139 (38.2%) in 364 male patients and 391 (81.5%), 9 (1.9%), and 80 (16.7%) in 480 female patients, respectively. Clinical characteristics of all 971 patients are listed in Table 1. Compared with

Table 1. Clinical Characteristics of 971 Patients With IgA Nephropathy

	Non-/Past Smokers	Current Smokers	*P*
Sample	745 (76.7)	226 (23.3)	
Baseline characteristics			
Facility A	217 (29.1)	50 (22.1)	0.1
Facility B	396 (53.2)	128 (56.6)	
Facility C	132 (17.7)	48 (21.2)	
Age (y)	31 (22-46)	34 (25-48)	0.001
Men	286 (38.4)	144 (63.7)	<0.001
Body mass index (kg/m^2)	22.2 ± 3.6	22.9 ± 3.5	0.005
SBP (mm Hg)	121 ± 17	124 ± 18	0.02
DBP (mm Hg)	74 ± 13	76 ± 14	0.2
Use of antihypertensives	119 (16.0)	51 (22.6)	0.02
Hypertension	211 (28.3)	87 (38.5)	0.004
SCr (mg/dL)	0.72 (0.60-0.90)	0.86 (0.70-1.00)	<0.001
eGFR (mL/min/1.73 m^2)	105 ± 34	96 ± 28	<0.001
CKD stage 1[a]	499 (67.0)	133 (58.9)	0.08
CKD stage 2[b]	189 (25.4)	71 (31.4)	
CKD stages 3-5[c]	57 (7.7)	22 (9.7)	
Urinary protein (g/d)	0.37 (0.16-0.79)	0.54 (0.23-1.21)	<0.001
Total cholesterol (mg/dL)	193 ± 42	202 ± 54	0.008
Uric acid (mg/dL)	5.4 ± 1.5	6.0 ± 1.6	<0.001
Therapeutic interventions within 1 year of kidney biopsy			
RAAS blockers	305 (40.9)	106 (46.9)	0.1
Immunosuppressants	201 (27.0)	65 (28.8)	0.6
Outcomes			
50% ↑ SCr	75 (10.1)	42 (18.6)	0.001
100% ↑ SCr or ESRD	51 (6.9)	30 (13.3)	0.002
ESRD	27 (3.6)	20 (8.9)	0.001
Death before ESRD	2 (0.3)	3 (1.3)	0.05
Observational period (y)	5.9 (2.8-10.3)	5.1 (1.8-9.1)	0.03

Note: Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical values are expressed as number (proportion). Conversion factors for units: SCr in mg/dL to μmol/L, ×88.4; GFR in mL/min/1.73 m^2 to mL/min/1.73 m^2, ×0.01667; total cholesterol in mg/dL to mmol/L, ×0.02586; uric acid in mg/dL to μmol/L, ×59.48.

Abbreviations: CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate[38]; ESRD, end-stage renal disease; IgA, immunoglobulin A; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SCr, serum creatinine.

[a]Stage 1 CKD is eGFR ≥90 mL/min/1.73 m^2.

[b]Stage 2 CKD is eGFR of 60-89 mL/min/1.73 m^2.

[c]Stages 3-5 CKD have eGFR <60 mL/min/1.73 m^2.

non-/past smokers, current smokers were significantly older, male predominant, and hypertensive; had lower eGFRs; and were more proteinuric, hypercholesterolemic, and hyperuricemic at kidney biopsy. For 209 current smokers (92.5%) who reported the number of cigarettes smoked per day at the time of diagnosis by kidney biopsy, 66 (31.6%) patients smoked 1-10 cigarettes daily; 93 (44.5%) patients, 11-20 cigarettes daily; 30 (14.4%) patients, 21-30 cigarettes daily; and 20 (9.6%) patients, 31 and more cigarettes daily.

During a median 5.8 years (interquartile range, 2.6-10.2) of an observational period, 117 patients (12.0%) developed a 50% increase in serum creatinine level before ESRD, 81 patients (8.3%) had a composite outcome of 100% increase in serum creatinine level (n = 80) or ESRD (n = 1), and 47 patients (4.8%) developed ESRD. No patient progressed to ESRD before developing a 50% increase in serum creatinine level. Five patients (0.5%) died before ESRD of acute coronary infarction, subarachnoid hemorrhage, sud-

Table 2. Predictors of Progression of IgA Nephropathy

Outcomes	50% ↑ SCr	100% ↑ SCr or ESRD	ESRD
Baseline characteristics			
Age (/10 y)	1.40 (1.22-1.59)[a]	1.29 (1.11-1.51)[b]	1.26 (1.03-1.53)[c]
Male	1.60 (1.11-2.32)[c]	1.65 (1.06-2.57)[c]	1.48 (0.83-2.65)
Body mass index (/1 kg/m^2)	1.05 (1.01-1.11)[c]	1.06 (1.00-1.12)[c]	1.08 (1.01-1.16)[c]
Hypertension[d]	2.42 (1.68-3.49)[a]	2.92 (1.87-4.56)[a]	3.57 (1.96-6.50)[a]
SCr (/0.5 mg/dL)	2.74 (2.25-3.33)[a]	3.37 (2.59-4.37)[a]	4.46 (3.07-6.48)[a]
Urinary protein (/1 g/d)	1.53 (1.40-1.67)[a]	1.58 (1.44-1.75)[a]	1.62 (1.44-1.82)[a]
Total cholesterol (/20 mg/dL)	1.22 (1.14-1.30)[a]	1.23 (1.14-1.33)[a]	1.28 (1.17-1.39)[a]
Uric acid (/1 mg/dL)	1.46 (1.31-1.63)[a]	1.47 (1.29-1.67)[a]	1.62 (1.37-1.92)[a]
Current smokers[e]	2.25 (1.53-3.29)[a]	2.27 (1.44-3.57)[a]	2.77 (1.55-4.94)[b]
No. of cigarettes (/10/d)[e,f]	1.40 (1.25-1.59)[a]	1.47 (1.28-1.70)[a]	1.50 (1.26-1.78)[a]
Current smoking level			
1-20 cigarettes/d[e,f]	1.42 (0.86-2.33)	1.32 (0.72-2.44)	1.68 (0.79-3.58)
≥21 cigarettes/d[e,f]	4.65 (2.8-7.58)[a]	5.22 (3.00-9.10)[a]	6.04 (2.99-12.2)[a]
Therapeutic interventions within 1 year of kidney biopsy			
RAAS blockers	1.96 (1.35-2.86)[a]	1.93 (1.23-3.03)[b]	2.04 (1.12-3.69)[c]
Immunosuppressants	1.07 (0.70-1.61)	1.18 (0.72-1.93)	1.44 (0.78-2.65)

Note: Analysis based on univariate Cox proportional hazards models stratified on facilities; values shown are hazard ratio (95% confidence interval).

Abbreviations: ESRD, end-stage renal disease; IgA, immunoglobulin A; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

[a]$P < 0.001$.

[b]$P < 0.01$.

[c]$P < 0.05$.

[d]Defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or any antihypertensive medication.

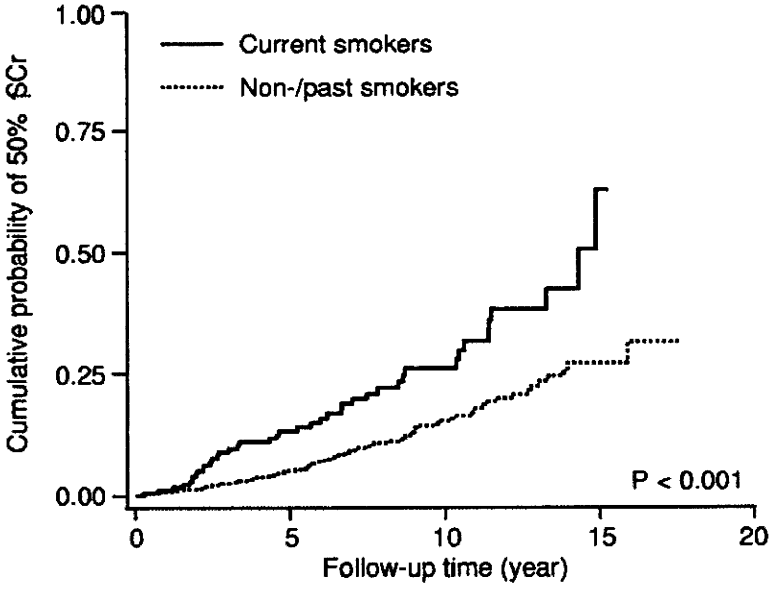
[e]Non-/past smokers were set as a reference.

[f]Based on the data from 954 patients because of missing number of cigarettes/day at kidney biopsy in 17 current smokers.

den death, lung cancer, and myelodysplastic syndrome.

In the entire cohort, cumulative probabilities of a 50% increase in serum creatinine level, the composite outcome of a 100% increase in serum creatinine level or ESRD, and ESRD were 0.07 (95% confidence interval [CI], 0.05-0.09), 0.05 (95% CI, 0.04-0.07), and 0.04 (95% CI, 0.03-0.06), respectively, at 5 years after kidney biopsy; 0.18 (95% CI, 0.14-0.21), 0.13 (95% CI, 0.10-0.16), and 0.08 (95% CI, 0.06-0.11), respectively, at 10 years; and 0.33 (95% CI, 0.27-0.41), 0.20 (95% CI, 0.15-0.26), and 0.10 (95% CI, 0.07-0.14), respectively, at 15 years. Log-rank test and univariate Cox proportional hazards model showed that current smokers were significantly associated with primary and secondary outcomes, along with age, body mass index, hypertension, serum creatinine level, urinary protein excretion, total cholesterol level, and uric acid level at kidney biopsy and use of RAAS blockers within 1 year of kidney biopsy (Table 2; Fig 1). Multivariate models identified current smoker as one of the significant predictors of outcomes, in addition to serum creatinine level, urinary protein excretion, and total cholesterol level at kidney biopsy (Table 3).

To control for significant differences in clinical characteristics of non-/past smokers and current smokers (Table 1), we computed propensity score using the logistic regression model with current smoker as the dependent variable. The model was well calibrated (Hosmer-Lemeshow goodness-of-fit test, $P = 0.3$) and had moderate discrimination in determining smoking status (area under the receiver operating characteristic curve = 0.676). In each quartile of propensity score, clinical characteristics were well balanced, except for baseline total cholesterol level in the fourth quartile (non-/past smokers, median



Current smokers (n = 226)

Cumulative probability	0.13	0.26	0.63
95% CI	0.09-0.20	0.19-0.35	0.39-0.86
No. at risk	108	45	4

Non-/past smokers (n = 745)

Cumulative probability	0.05	0.15	0.27
95% CI	0.04-0.07	0.12-0.19	0.21-0.34
No. at risk	410	182	32

Figure 1. Cumulative probability of primary outcome (50% increase in serum creatinine level) for non-/past and current smokers. Death before end-stage renal disease (n = 5) was regarded as censored. Abbreviation: CI, confidence interval.

201 mg/dL [interquartile range, 179-225] vs current smokers, median 211 mg/dL [interquartile range, 185-245]: $P = 0.01$). Multivariate Cox proportional hazards models adjusted for propensity score and stratified on quartiles of propensity score verified that current smokers were significantly associated with primary outcomes (HR, 2.02 [95% CI, 1.32-3.09], $P = 0.001$ in the adjustment model and HR, 2.13 [95% CI, 1.39-3.25], $P < 0.001$ in the stratification model) and also secondary outcomes (Table 4). Even after each current smoker was matched to the non-/past smoker with the closest propensity score, leading to 220 matched pairs with well-balanced clinical characteristics (Table 5), current smokers also were identified as the significant predictor of primary outcomes (HR, 2.18 [95% CI, 1.67-11.6]; $P = 0.003$) and secondary outcomes. All propensity score models confirmed a significant association between current smokers and outcomes.

After identifying smoking status as the significant predictor of outcomes, we further assessed a dose-dependent association between cigarette smoking and outcomes. Number of cigarettes per day as recorded at the time of kidney biopsy was associated significantly with primary and secondary outcomes in univariate models (Table 2) and also multivariate models (HR, 1.21 [95% CI, 1.06-1.39]; $P = 0.005$ for primary outcome; Table 6, multivariate model 1). Individuals smoking more than 20 cigarettes per day at kidney biopsy were significantly associated with outcomes, whereas current smokers reporting 20 or fewer cigarettes smoked per day were not, compared with non-/past smokers (Table 6, multivariate model 2). These results suggested that heavier smokers, especially with more than 20 cigarettes smoked per day, were at increased risk of progression of IgA nephropathy.

To assess whether smoking status was associated with progression in patients at early and advanced stages of IgA nephropathy, effect modification between smoking status and kidney function was examined. Facility-stratified multivariate models adjusted for baseline covariates (age,

Table 3. Predictors of Progression of IgA Nephropathy

Outcomes	50% ↑ SCr	100% ↑ SCr or ESRD	ESRD
Baseline characteristics			
Age (/10 y)	1.05 (0.89-1.24)	0.85 (0.69-1.04)	0.73 (0.56-0.96)[a]
Male	0.73 (0.46-1.18)	0.80 (0.46-1.40)	0.60 (0.29-1.27)
Body mass index (/1 kg/m^2)	0.99 (0.93-1.05)	1.03 (0.96-1.11)	1.06 (0.98-1.15)
Hypertension[b]	1.42 (0.93-2.17)	1.89 (1.13-3.18)[a]	1.93 (0.93-4.01)
SCr (/0.5 mg/dL)	2.07 (1.68-2.56)[c]	2.74 (2.03-3.71)[c]	3.72 (2.45-5.65)[c]
Urinary protein (/1 g/d)	1.36 (1.21-1.52)[c]	1.38 (1.21-1.57)[c]	1.29 (1.09-1.54)[d]
Total cholesterol (/20 mg/dL)	1.08 (1.00-1.17)[a]	1.13 (1.03-1.24)[d]	1.15 (1.03-1.29)[a]
Uric acid (/1 mg/dL)	1.14 (0.98-1.33)	1.02 (0.84-1.23)	1.07 (0.83-1.37)
Current smokers[e]	2.03 (1.33-3.10)[d]	2.06 (1.24-3.43)[d]	2.73 (1.40-5.34)[d]
Therapeutic interventions within 1 year of kidney biopsy			
RAAS blockers	1.10 (0.72-1.67)	1.07 (0.64-1.79)	1.06 (0.52-2.17)
Immunosuppressants	0.59 (0.37-0.96)[a]	0.55 (0.30-1.00)[a]	0.65 (0.30-1.42)

Note: Analysis based on multivariate Cox proportional hazards models stratified on facilities; values shown are hazard ratio (95% confidence interval).

Abbreviations: ESRD, end-stage renal disease; IgA, immunoglobulin A; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

[a]$P < 0.05$.

[b]Defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or any antihypertensive medication.

[c]$P < 0.001$.

[d]$P < 0.01$.

[e]Non-/past smokers were set as a reference.

sex, body mass index, hypertension, serum creatinine level, urinary protein excretion, serum total cholesterol level, and serum uric acid level) and therapeutic interventions (use of RAAS blockers and immunosuppressants) showed significant interactions between serum creatinine level and current smokers regarding primary and secondary outcomes (P values for interaction in 50% increase in serum creatinine level, a composite outcome of 100% increase in serum creatinine level and ESRD, and ESRD were <0.001, <0.001, and 0.002, respectively). We therefore classified patients into 6 categories: non-/past smokers with CKD stages 1, 2, and 3-5 and

Table 4. Association Between Current Smokers and Outcomes

Outcomes	50% ↑ SCr	100% ↑ SCr or ESRD	ESRD
Adjustment for propensity score (n = 971)[a,b]	2.02 (1.32-3.09)[c]	2.10 (1.26-3.49)[c]	2.80 (1.43-5.48)[c]
Stratification on quartiles of propensity score (n = 971)[a]	2.13 (1.39-3.25)[d]	2.16 (1.30-3.58)[c]	2.61 (1.33-5.12)[c]
Matching by propensity score (n = 440)	2.18 (1.67-11.6)[c]	2.74 (1.71-14.6)[c]	7.00 (1.59-30.8)[e]

Note: Values shown are hazard ratio (95% confidence interval) for current smokers, with non-/past smokers set as the reference group. Analysis based on propensity score–based multivariate Cox proportional hazards models.

Abbreviations: ESRD, end-stage renal disease; SCr, serum creatinine.

[a]Adjusted for baseline characteristics (age, sex, body mass index, hypertension, SCr level, urinary protein excretion, total cholesterol level, and uric acid level) and therapeutic interventions within 1 year of kidney biopsy (renin-angiotensin-aldosterone system blockers and immunosuppressants).

[b]Stratified on facilities.

[c]$P < 0.01$.

[d]$P < 0.001$.

[e]$P < 0.05$.

Table 5. Clinical Characteristics of 220 Pairs of Non-/Past and Current Smokers Matched by Propensity Score

Smoking Status	Non-/Past Smokers (n = 220)	Current Smokers (n = 220)	P
Baseline characteristics			
Facility A	49 (22.3)	50 (22.7)	0.7
Facility B	129 (58.6)	123 (55.9)	
Facility C	42 (19.1)	47 (21.4)	
Age (y)	37 (23-50)	33 (25-48)	0.7
Men	137 (62.3)	138 (62.7)	0.8
Body mass index (kg/m^2)	22.9 ± 3.3	22.9 ± 3.6	0.9
Hypertension	88 (40.0)	83 (37.7)	0.6
SCr (mg/dL)	0.84 (0.69-1.00)	0.84 (0.70-1.00)	0.4
Urinary protein (g/d)	0.45 (0.21-0.94)	0.51 (0.22-1.14)	0.2
Total cholesterol (mg/dL)	197 ± 38	199 ± 50	0.7
Uric acid (mg/dL)	6.0 ± 1.5	5.9 ± 1.6	0.8
Therapeutic interventions within 1 year of kidney biopsy			
Use of RAAS blockers	101 (45.9)	101 (45.9)	0.9
Use of immunosuppressants	64 (29.1)	62 (28.2)	0.8
Outcomes			
50% ↑ SCr	19 (8.6)	40 (18.2)	0.002
100% ↑ SCr or ESRD	11 (5.0)	28 (12.7)	0.002
ESRD	6 (2.7)	19 (8.6)	0.002
Observational period (y)	6.2 (3.2-10.7)	5.1 (1.7-9.1)	0.02

Note: Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as number (proportion). Conversion factors for units: SCr in mg/dL to μmol/L, ×88.4; total cholesterol in mg/dL to mmol/L, ×0.02586; uric acid in mg/dL to μmol/L, ×59.48.

Abbreviations: ESRD, end-stage renal disease; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

current smokers with CKD stages 1, 2 and 3-5, and calculated their multivariate adjusted HRs for primary outcome (Fig 2). When non-/past smokers with CKD stage 1 served as reference, those with CKD stage 2 did not have a significantly increased risk (HR, 0.95 [95% CI, 0.51-1.77]; $P = 0.9$), but those with CKD stage 3 (HR, 3.32 [95% CI, 1.66-6.62]; $P = 0.001$; Fig

Table 6. Dose-Dependent Associations Between Number of Cigarettes Smoked Per Day at Time of Kidney Biopsy and Outcomes

Outcomes	50% ↑ SCr	100% ↑ SCr or ESRD	ESRD
Multivariate model 1			
No. of cigarettes (/10/d)[a]	1.21 (1.06-1.39)[b]	1.29 (1.09-1.53)[b]	1.37 (1.10-1.70)[b]
Multivariate model 2			
Current smoking level			
1-20 cigarettes/d[a]	1.55 (0.91-2.62)	1.41 (0.73-2.71)	1.83 (0.79-4.21)
≥21 cigarettes/d[a]	3.00 (1.68-5.35)[c]	3.89 (1.96-7.73)[c]	5.50 (2.20-13.7)[c]

Note: Analysis based on multivariate Cox proportional hazards models; values shown are hazard ratio (95% confidence interval). Model 1 and 2 are based on data from 954 patients because of the missing number of cigarettes per day at kidney biopsy in 17 current smokers, adjusted for baseline characteristics (age, sex, body mass index, hypertension, SCr level, urinary protein excretion, total cholesterol level, and uric acid level) and therapeutic interventions within 1 year of kidney biopsy (renin-angiotensin-aldosterone system blockers and immunosuppressants) and stratified on facilities.

Abbreviations: ESRD, end-stage renal disease; SCr, serum creatinine.

[a]Non-/past smokers were set as the reference group.

[b]$P < 0.01$.

[c]$P < 0.001$.

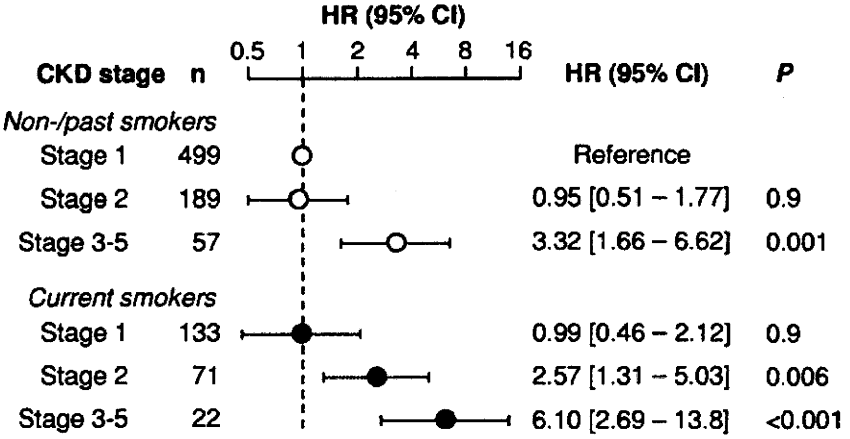


Figure 2. Effect modification between smoking status and chronic kidney disease (CKD) stages at kidney biopsy. Hazard ratio (HR) for each category for primary outcome was calculated in a facility-stratified multivariate Cox proportional hazards model adjusted for baseline clinical characteristics (age, sex, body mass index, hypertension, urinary protein excretion, total cholesterol level, and uric acid level) and therapeutic interventions (renin-angiotensin-aldosterone system blockers and immunosuppressants). Abbreviation: CI, confidence interval.

2) did. On the contrary, current smokers even with CKD stage 2 were significantly vulnerable to progression (HR, 2.57 [95% CI, 1.31-5.03]; $P = 0.006$), along with those with CKD stages 3-5 (HR, 6.10 [95% CI, 2.69-13.8]; $P < 0.001$).

DISCUSSION

We found that cigarette smoking was a dose-dependent predictor of progression of IgA nephropathy, even after adjusting for conventional risk factors (impaired kidney function, proteinuria, and hypertension) and metabolic atherosclerotic factors (hypercholesterolemia and hyperuricemia) using different propensity score–based methods. Significant effect modification between serum creatinine level and smoking status at kidney biopsy interestingly showed that patients with decreased kidney function at kidney biopsy were more vulnerable to cigarette smoking. Advantages of the present study are an etiologically homogenous cohort with substantially younger age and higher proportion of patients with impaired kidney function in contrast to previous community-based studies,[24-33] larger sample size than those in previous cohort studies of IgA nephropathy,[4-19] and robust results based on multiple kidney outcomes (50% increase in serum creatinine level, a composite outcome of 100% increase in serum creatinine level or ESRD, and ESRD) in different propensity score–based models controlling for significant differences in clinical characteristics between non-/past smokers and current smokers (Table 4).

Along with smoking status at kidney biopsy, the present study clarified that number of cigarettes smoked at the time of diagnosis using kidney biopsy was a significant predictor of progression of IgA nephropathy. Few studies of primary kidney diseases have found a dose-dependent association between progression and cigarette smoking in a multivariate model. Even in community-based large-scale cohort studies, their dose-dependent association was identified in only 2 studies based on the cohorts of the Cardiovascular Health Study, which enrolled elderly participants aged at least 65 years,[24] and the Second National Health and Nutrition Examination Survey (NHANES II), including entirely middle-aged participants (aged 49.3 ± 13.3 years).[27] Results of the present study were compatible with those of NHANES II, which showed that current smokers reporting more than 20 cigarettes per day were at significantly higher risk of ESRD or CKD-associated death compared with non-smokers. Our findings extend the dose-dependent nephrotoxic effect of cigarette smoking, especially more than 20 cigarettes per day, to younger patients with IgA nephropathy. Smoking cessation should be recognized as one of

the potential treatment modalities of IgA nephropathy.

The present study also showed an interesting interaction between baseline serum creatinine level and current smokers, suggesting that the nephrotoxic effect of cigarette smoking was enhanced in patients with decreased kidney function. Although the precise mechanism of a nephrotoxic effect of cigarette smoking is unsolved, one of the biologically plausible hypotheses is oxidative stress, which may be the reason that patients with IgA nephropathy with impaired kidney function were substantially vulnerable to cigarette smoking. Oxidative stress is already increased at early stages of CKD because of enhanced production of oxidants and a compromise in the antioxidant mechanism,[44] and oxidative stress may have an important role in the progression of CKD. A French cohort study of 120 patients with IgA nephropathy showed that increased serum levels of advanced oxidation protein products, a relevant marker of oxidative stress, proved a potential renal prognostic factor.[45] Long-term smoking can result in depletion of antioxidants, leading to a systemic imbalance between oxidants and antioxidants.[46] Consequently, current smokers with impaired kidney function might easily expose themselves to endogenous and exogenous (smoke-derived) oxidants and induce a remarkably increased risk of progression of IgA nephropathy in a dose-dependent manner.

Our study has several limitations. First, smoking status only at diagnosis was assessed. It was uncertain whether current smokers at diagnosis kept smoking during the entire follow-up period. Second, smoking status was based on a questionnaire filled in at admission for kidney biopsy. Smoking status was not validated using biochemical tests, such as measurements of cotinine and carbon monoxide. Self-reported smoking status might be biased. Third, lack of calibration of serum creatinine levels between facilities might lead to biased results. Fourth, although all patients were given a diagnosis of IgA nephropathy using kidney biopsy, histologic findings were not included as covariates of interest in the present study, partly because each facility used a different histologic grading system and changed its grading system during 14 years of the entry period between 1992 and 2005. Another critical reason was that a large number of specimens stained with periodic acid–Schiff or other methods became too pale for histopathologic reevaluation. Fifth, eGFR was relatively inaccurate in the present study because most patients had CKD stages 1 and 2, based on eGFR. Because a recent study of 255 kidney donors with mainly CKD stages 1 and 2 showed a moderately positive correlation between iohexol-measured GFR and eGFR ($R^2 = 0.41$),[47] distribution of "real" GFR of patients with eGFR-based CKD stage decreased as eGFR-based CKD stage advanced, even CKD stages 1 and 2.

In conclusion, our long-term retrospective cohort study of approximately 1,000 patients with IgA nephropathy showed that cigarette smoking was one of the key predictors of progression of IgA nephropathy in a dose-dependent manner. The deleterious impact of cigarette smoking was likely to be enhanced as IgA nephropathy progressed. Thus, smoking cessation should be considered as one of the potential treatment modalities to suppress further progression at an advanced stage of IgA nephropathy and also prevent future progression at an earlier stage.

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Presenteeism in college students: reliability and validity of the Presenteeism Scale for Students

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Abstract
Objective Presenteeism is the impaired work performance due to health problems. We aimed to develop a Presenteeism Scale for Students (PSS), and to reveal the existence of presenteeism among students.
Methods Students ($n = 5{,}701$) in 4 national universities in Japan were recruited via the school-based health examination. Moreover, 122 students participated in a 2-week interval test–retest to examine the reliability and criterion-related validity of the PSS.
Results Of the students, 59.2% indicated some health problems. Allergy was most prevalent health problems, affecting 35.7% of the whole students. Students with emotional problems had higher degree of presenteeism than those with the other problems. The Cronbach's α of the work impairment score of the PSS was 0.90. The Spearman's coefficient for the test–retest score was 0.80 ($P < 0.001$). Regarding criterion-related validity, Spearman's coefficient between the work impairment score of the PSS and summary score of the SF-36 was −0.60 ($P < 0.001$).
Conclusions These findings suggest that the PSS can be expected to be useful for assessment of students with presenteeism. Furthermore, we found that the majority of students have some health problems, and proposed that the issue of presenteeism on campus should be addressed.

Keywords Presenteeism Scale for Students (PSS) · Presenteeism · Absenteeism · Campus health · Health problems

Abbreviations

PSS	Presenteeism Scale for Students
SF-36	Medical Outcomes Study 36-Item Health Survey
PHC	Primary health condition
WIS	Work impairment score
WOS	Work output score
HA	Hours of absenteeism

Introduction

Presenteeism, defined as a self-rated measurable loss of work performance due to health problems in the workplace,

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contributes to economic costs through loss in productivity [1, 2]. Presenteeism is coinage contrary to absenteeism, and the impact of presenteeism in the field of occupational health has been discussed. Presenteeism among workers has been associated not only with the economic cost of lost productivity in an enterprise but also with an individual's health, deterioration of quality of life (attention-concentration problems, mood disturbances, or fatigue), and increased medical costs [3–5].

The number of college students who visit academic healthcare centers because of both physical and psychiatric illness has increased recently. It can be considered that many of these students have been frustrated with academic life. This behavior can be interpreted as presenteeism in school. Although the negative impact of absenteeism from the classroom on academic achievement can be easily understood, no study has been done to reveal the effect of presenteeism on academic performance. If students' mental and physical illnesses are left untreated in the early stage, these conditions will become aggravated, leading to the need for long-term medical treatment [6]. Recognition of a student's health condition in the early stage might be crucial to decrease the risk of further morbidity. Hence, more attention should be given to the issue of presenteeism in school and a credible measurement of presenteeism for students should be developed.

Assessment of presenteeism has been made by means of self-reported scales, the most often used being the Work Limitations Questionnaire developed by Lerner et al. [7], Work Productivity and Activity Impairment questionnaire, general health version, constructed by Reilly et al. [8], and the Stanford Presenteeism Scale (SPS) established by Koopman et al. in the United States [9, 10]. In Japan, only one document has examined the applicability of the SPS translated into Japanese, reporting good reliability and validity in workers [11]. However, a questionnaire on presenteeism for students has not been developed even though the generalizability of the issue of presenteeism among non-workers is important.

In this study, we aimed to develop a Presenteeism Scale for Students (PSS) and to examine its reliability and criterion-related validity. In addition to assessing the PSS, we examined the extent of presenteeism among students.

Methods

Procedure

This study was carried out at 4 universities that cooperated within the framework of the National University Council of Health Administration Facilities. These universities had different characteristics. Geographically, Akita University is located in the northeast area of Japan and is hit by heavy snowfall during the winter. Osaka University is located in the metropolitan area of Japan, and has the largest number of students among Japanese national universities. Fukuoka University of Education had been founded as a teacher-training institution, which is located in Kyushu Island. Finally, Nara Woman's University is located in Nara Prefecture, and had taken on a historic role of fostering women teachers.

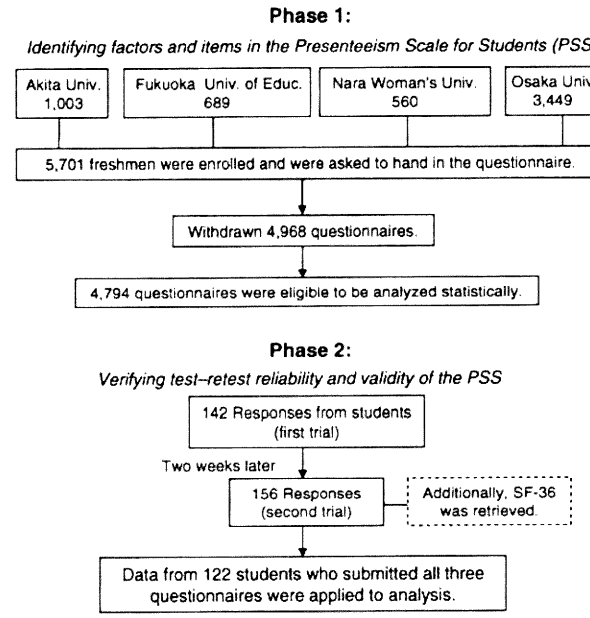

Fig. 1 Flowchart of the two phases in the present study

This study consisted of two phases (Fig. 1). For the first phase, in April 2008, staff of 4 health administration centers distributed the packaged questionnaire to all first-year students in each of the 4 universities. This package, which was collected at the school-based health examination, not only included a survey on presenteeism, but also a questionnaire on mental health and eating behavior. Findings on the latter issues will be reported separately. The rate of data collection was 87.1%.

In phase 2, test–retest reliability of the PSS was determined in students of Osaka University in 2008 November at a 2-week interval. The questionnaire in the second survey (retest) also included the Medical Outcomes Study 36-Item Health Survey (SF-36) to test criterion-related validity of the PSS.

Informed consent was obtained from participants after we provided them with a written explanation of the aims of this study. This study protocol was approved by the Ethics Committee of the Osaka University Health Care Center.

Participants

We recovered 4,968 questionnaires from the 4 universities. Eligible for data analysis were 4,794 college students (valid response rate: 96.5%). The average age of responders was 18.56 years (SD = 1.82), and 2,774 students (58.2%) were male (female, 1,990; unknown, 30). The participants in phase 2 were those who attended a class that was part of a university course and were recruited through an announcement. Participating in the test of reliability and validity of the PSS were 122 students.

Measures

Presenteeism

The 13-item Stanford Presenteeism Scale (SPS) was designed as a measure of lost productivity derived from being at work with a specific health condition over the previous 4 weeks [10]. Based on the established SPS, Yamashita and Arakida developed a Japanese version of the SPS [11]. In the present study, amending the instrument for the intended subjects was taken into consideration. Therefore, we modified two points in the Japanese version of the SPS to adapt this questionnaire to our purpose. Firstly, the word "work" in the Japanese version of the SPS was changed to "academic" to apply to the health of students. Secondly, we added three health problems that had been observed characteristically in the Osaka University Health Care Center to the list of health conditions in the Japanese version of the SPS to make this list more specific to students. These problems were "menstrual pain or irregular menstruation", "injury of limb" and "eating disorder". With respect to modifying the SPS, we obtained permission from Merck & Co., Inc., which holds the copyright of the original SPS.

The PSS is composed of the following 4 modules: (1) list of health conditions with yes/no responses as to whether the student has or has had a particular condition within the past month and the request to select a single primary health condition (PHC) from that list that most influenced the student's functioning; (2) degree of presenteeism due to the PHC [work impairment score (WIS)]; (3) effect of the PHC on work output [work output score (WOS)]; and (4) hours of absenteeism (HA) due to the PHC.

(1) The list of health conditions includes 16 conditions that might have affected the student's health/disability status in the past 1 month (allergies, arthritis or joint pain/stiffness, injury of limb, asthma, back or neck pain, breathing disorder (bronchitis, emphysema), depression/anxiety or emotional disorder, insomnia, diabetes, menstrual pain or irregular menstruation, disturbance of liver function, heart or circulatory problem (artery disease, high blood pressure, angina), migraines/chronic headaches, stomach or bowel disorder, eating disorder, and other). The respondent indicates whether these conditions occurred by "yes" or "no." Then, the respondent is asked to choose from the list the one condition (PHC) that most affected him or her. Respondents who did not indicate the presence of any of these health conditions did not have to complete the other 3 modules comprising the PSS.

(2) The WIS is assessed with the question: "In the past 4 weeks, how often has your primary health condition (PHC) affected your academic work?" and 10 items that determine the degree of presenteeism due to the PHC. Responses are on a 5-point Likert scale (from 'always' to 'never'), which are shown in Table 2. The raw score of the WIS is converted to a 100-point scale; the higher the score, the more serious is the degree of presenteeism. Factor analysis of the original [10] and Japanese versions of the SPS [11] found two underlying factors, which were designated as 'completing work' and 'avoiding distraction.'

(3) The WOS, which is a single visual analog scale, is an index of the magnitude of the effect of the PHC on performance. We asked the following question: "Given your primary health condition, what percentage of your usual productivity level were you able to achieve academically over the last 4 weeks?" The respondents were required to indicate what point on the scale best described their feelings. This item is scored ranging from 0% (incapable) to 100% (capable) scale.

(4) To determine the HA, respondents were asked "Because of your primary condition, how many academic hours (and/or work hours) did you miss in the past 4 weeks?" Subjects selected the number of hours from 0 to 40 on a straight line with reference anchors of '0 h' on the left side and 'over 40 h' on the right. Each unit on the scale represents 1 h.

Quality of life

The Japanese language version of the Medical Outcomes Study 36-Item Health Survey (SF-36) [12, 13] was used to address the relationships between presenteeism and the quality of life. The SF-36 is a self-report scale about the quality of life and is composed of the following 8 subscales: Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, Role Emotional, and Mental Health. The Japanese language version asks additional questions for comparisons of