

# Association between Smoking and Chronic Renal Failure in a Nationwide Population-Based Case-Control Study

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**Abstract.** For determining whether smoking is associated with an increased risk for chronic renal failure (CRF) overall and by type of renal disease, smoking data were analyzed from a nationwide population-based case-control study. Eligible as cases were native 18- to 74-yr-old Swedes whose serum creatinine for the first time and permanently exceeded 3.4 mg/dl (men) or 2.8 mg/dl (women). A total of 926 cases (78% of all eligible) and 998 control subjects (75% of 1330 randomly selected subjects from the source population), frequency matched to the cases by gender and age within 10 yr, were included. A face-to-face interview and a self-administered questionnaire provided information about smoking habits and other lifestyle factors. Logistic regression models estimated odds ratios (OR) as measures of relative risk for disease-

specific types of CRF among smokers compared with never-smokers. Despite a modest and nonsignificant overall association, the risk increased with high daily doses (OR among smokers of >20 cigarettes/d, 1.51; 95% confidence interval [CI], 1.06 to 2.15), long duration (OR among smokers for >40 yr, 1.45; 95% CI, 1.00 to 2.09), and a high cumulative dose (OR among smokers with >30 pack-years, 1.52; 95% CI, 1.08 to 2.14). Smoking increased risk most strongly for CRF classified as nephrosclerosis (OR among smokers with >20 pack-years, 2.2; 95% CI, 1.3 to 3.8), but significant positive associations were also noted with glomerulonephritis. This study thus suggests that heavy cigarette smoking increases the risk of CRF for both men and women, at least CRF classified as nephrosclerosis and glomerulonephritis.

Cigarette smoking is considered to be the most common identifiable cause of adult death in developed countries (1). Smoking may also increase the risk for renal disease. Among insulin- and non-insulin-dependent patients with diabetes, smoking seems to be an independent risk factor for nephropathy and accelerates the rate of progression of renal failure (2). In hypertensive patients, smoking independently increases the risk for albuminuria (3,4) and may cause decline of renal function (5). The role of smoking in primary renal diseases is less known, but studies have indicated a relation with the development of proteinuria in patients with polycystic kidney disease (6) and deterioration of renal function in patients with lupus nephritis, polycystic kidney disease, and glomerulonephritis (7–9). Other studies failed to find any relationship between smoking and renal disease (10–12). The purpose of

this report was to examine whether cigarette smoking or other tobacco use is associated with chronic renal failure (CRF) overall and with different types of CRF in a nationwide population-based case-control study of incident pre-uremic CRF.

## Materials and Methods

### Study Subjects

The study design has been described in detail elsewhere (13). Briefly, the Swedish Population Register (14) provided a well-defined source population of 5.3 million native Swedes who were aged 18 to 74 yr and lived in Sweden during the ascertainment period May 20, 1996, through May 31, 1998.

Medical laboratories covering virtually all inpatient and outpatient care in Sweden provided monthly lists of all serum creatinine measurements performed in this population. Eligible cases were men and women whose serum creatinine level for the first time and permanently exceeded 3.4 mg/dl (300  $\mu$ mol/L) and 2.8 mg/dl (250  $\mu$ mol/L), respectively. A second creatinine measurement, 3 mo after the first, was examined to ensure the chronicity of the renal failure. Patients with prerenal (*e.g.*, severe heart failure) or postrenal (*e.g.*, urinary outlet obstruction) causes of renal failure or with kidney transplants were ineligible. Local nephrologists determined final eligibility of cases. Diagnosis of the underlying disease causing CRF was based on routine clinical work-up. Of the eligible cases, 9% refused to participate, 7% were too severely disabled to participate, and 6% had died before being asked to participate, leaving 926 (78%) participants.

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Control subjects were randomly selected from the National Population Register and frequency matched with the cases according to age in 10-yr age groups and gender. Of 1330 selected control subjects, 998 (75%) participated, 17% refused, 4% could not be reached, and 4% were too sick to participate. All study subjects provided informed consent before enrollment. The regional ethics committees and the Swedish Data Inspection Board approved the study protocol.

### Data Collection

A mailed questionnaire was sent to the study subjects to obtain detailed information on tobacco use, including type of tobacco (cigarettes, cigars, pipes, and snuff), amounts used, starting and stopping dates, and changes in use over time. This questionnaire also included questions on alcohol consumption, anthropometric measures, dietary habits, and education. Specially trained interviewers from Statistics Sweden later interviewed the subjects face to face to obtain further information about medical history, use of analgesics, and occupations. The interviewers also examined the mailed questionnaire to ensure completeness and assisted the subjects in completing missing answers. On average, this interview lasted 80 min for case subjects and 70 min for control subjects. The time difference was mainly due to the usually more complicated medical history of the cases. Although blinding the interviewers to the case/control status of the subjects was impossible, the interviewers were instructed carefully to interact similarly with case subjects and control subjects in a standardized manner.

### Statistical Analyses

We defined regular tobacco use as either smoking at least one cigarette per day or at least one cigar or pipe per week, or using snuff at least once a week for a period of 6 mo or more. For reducing the possibility that symptoms of early CRF influenced tobacco use, the classification of former *versus* current tobacco use was based on smoking status 5 yr before the interview. To assess dose–effect relations, we analyzed lifetime average intensity, duration, and cumulative quantity (for cigarette smoking, we used average number of cigarettes per day, years, and pack-years, respectively). Never regular smokers of any tobacco type constituted the reference group.

As an estimate of the relative risk for CRF among tobacco users compared with nonusers, we computed odds ratios (OR) and 95% confidence intervals (95% CI), using unconditional logistic regression. We first estimated OR in simple age- and gender-adjusted models. Next, we explored the data for confounding and effect modification in stratified analyses. In our subsequent multivariate modeling, covariates were considered when they were known or suspected *a priori* to be confounding factors or when they were associated with both CRF and tobacco use in the data, assessed using the likelihood ratio test (15). The final model included gender, age in 10-yr age groups, education ( $\leq 9$  yr, 9 to 12 yr,  $> 12$  yr), alcohol consumption (grams per week), and regular use of salicylates and paracetamol (ever/never). Alcohol consumption in grams of pure alcohol, regardless of type of beverage, was grouped in quartiles according to the distribution among control subjects, whereas an indicator of regular use of aspirin and paracetamol was found to control sufficiently for possible confounding of nonnarcotic analgesic use. We also made mutual adjustments for cigarette smoking, cigar smoking, pipe smoking, and snuff use, when appropriate. We excluded other covariates such as body mass index, hypertension, and illicit drugs from the final model because their inclusion did not affect the risk estimates. We tested for interactions but did not include any interaction terms in the final models when they were statistically nonsignificant. We verified model fit with the Hosmer and Lemeshow test (16).

All analyses were carried out for CRF overall and by type of renal disease. In addition to these overall analyses, we stratified our multivariate models by gender to evaluate possible modification of smoking effects by this variable. Because of missing information on one or more covariates, we excluded 23 case subjects and 27 control subjects from our analyses of never *versus* regular use of cigarettes, pipes, or cigars and excluded 45 case subjects and 51 control subjects from our analyses of cumulative dose of cigarette smoking.

### Results

Sixty-five percent of case subjects and control subjects were men, and the mean age was 58 yr for men and 57 yr for women. Compared with control subjects, case subjects were less well-educated and more likely to be regular users of aspirin or paracetamol. The proportion of nonusers of alcohol was higher among case subjects, but case subjects had a higher mean consumption compared with control subjects (Table 1). The prevalence of self-reported hypertension was high among case subjects; 87% of men and 85% of women, compared with ~25% of male and female control subjects. Diabetes was reported in 35% of male case subjects, 37% of female case subjects, and 7% of control subjects in both genders. Thirty-one percent of case subjects were classified as having diabetic nephropathy, 24% glomerulonephritis, 15% nephrosclerosis, 11% hereditary renal diseases, 9% renal failure as a result of systemic diseases or vasculitis, and 11% “other” renal diseases (5% unknown causes, 3% interstitial nephropathy, and 3% miscellaneous). At ascertainment, the median serum creatinine was 3.8 mg/dl (336  $\mu$ mol/L) among men and 3.2 mg/dl (281  $\mu$ mol/L) among women. A majority of the patients were in the pre-uremic stage; 80% had a creatinine level  $< 4.5$  mg/dl (400  $\mu$ mol/L). The median value of the predicted GFR (calculated by Cockcroft-Gault formula) for men and women was 21 ml/min (interquartile range, 17 to 26 ml/min).

Tobacco products other than cigarettes were used almost exclusively by men. Regular pipe smoking was reported by 21 and 20% of male case subjects and control subjects, respectively. Seventeen percent of male case subjects compared with 18% of male control subjects had used oral snuff regularly. After adjustment for other tobacco products, no significant association was found between CRF (overall or by subtype) and regular pipe smoking (OR among ever pipe smokers of any intensity or duration relative to never-smokers of any tobacco, 1.0; 95% CI, 0.5 to 2.1), cigar smoking (OR, 0.7; 95% CI, 0.2 to 2.4), or regular use of oral snuff (OR, 0.8; 95% CI, 0.6 to 1.1). These negative findings pertained to all measures of dose–effect relations (duration, average daily consumption, and cumulative dose). Thirty-two case subjects and 45 control subjects were never-smokers but regular users of snuff. OR in this group with  $> 10$  yr of snuff use was 0.7 (95% CI, 0.3 to 1.3).

The association between cigarette smoking and CRF is shown in Table 2. Slightly more case subjects (31%) than control subjects (29%) were current smokers 5 yr before interview, but the proportion of former smokers was similar in both groups. At time of interview, somewhat fewer case subjects (19%) than control subjects (20%) were current smokers,

Table 1. Characteristics of case and control subjects

Characteristic	Cases ( <i>n</i> = 926)		Controls ( <i>n</i> = 998)	
	<i>n</i>	%	<i>n</i>	%
Gender				
male	597	64	653	65
female	329	36	345	35
Age (yr)				
18–24	11	1	20	2
25–34	63	7	58	6
35–44	95	10	97	10
45–54	193	21	186	19
55–64	186	21	204	20
65–74	378	41	433	43
Years of education				
≤9 (compulsory school)	537	58	525	53
10–12 (secondary school)	209	23	246	25
>12 (university)	168	18	220	22
Aspirin and/or paracetamol use				
nonregular user	575	62	789	79
regular user <sup>a</sup>	343	37	191	19
Weekly alcohol intake				
nonuser	234	25	202	20
1–17.6 g	217	23	258	26
17.7–33 g	116	13	135	14
33.1–66 g	143	15	190	19
>66 g	206	22	209	21

<sup>a</sup> At least two tablets per week for 2 mo or longer.

whereas more case subjects (39%) than control subjects (36%) were former smokers, suggesting some influence of current disease status on smoking habits. Among regular smokers, case subjects were more often heavier smokers than control subjects: The mean ( $\pm$ SD) lifetime consumption (pack-years) of cigarettes differed significantly between male case subjects ( $23.0 \pm 17.5$ ) and male control subjects ( $19.7 \pm 14.3$ ;  $P = 0.004$ ) and between female case subjects ( $19.1 \pm 11.0$ ) and female control subjects ( $15.4 \pm 11.4$ ;  $P = 0.003$ ). Although slight excess risks among all previous and current smokers failed to attain statistical significance (OR, 1.18; 95% CI, 0.90 to 1.55 and OR, 1.14; 95% CI, 0.89 to 1.47, respectively), the risk increased with intensity (number of cigarettes), duration (years smoked), and cumulative dose (pack-years). Smoking >20 cigarettes daily increased risk for CRF by 51% compared with never-smokers (OR, 1.51; 95% CI, 1.06 to 2.15). Those who had smoked for >40 yr had a 45% increased risk (OR, 1.45; 95% CI, 1.00 to 2.09) in relation to never-smokers. Similarly, a cumulative dose of >30 pack-years yielded a 52% increased risk (OR, 1.52; 95% CI, 1.08 to 2.14).

Analyses were conducted separately for subjects with and without diabetes; among nondiabetics, a cumulative dose of >20 pack-years of cigarettes was associated with a 35% increased risk for CRF (OR, 1.3; 95% CI, 1.0 to 1.9). Among subjects with diabetes, there was no excess in risk, but because

only 68 control subjects had diabetes, the CI was wide (OR, 1.0; 95% CI, 0.4 to 2.1).

The positive smoking–CRF relationship was not observable among users of angiotensin-converting enzyme (ACE) inhibitors. In fact, we saw a tendency toward an inverse relationship; OR for heavy smokers, relative to never smokers, was 0.7 (95% CI, 0.3 to 2.0) in this stratum. The corresponding OR in the stratum of never-users of ACE inhibitors was 1.7 (95% CI, 1.1 to 2.5). This difference, however, was not statistically significant; neither was the interaction between smoking and ACE use. Adjustment for hypertension in this analysis did not change the risk estimates.

Table 3 presents OR for different types of CRF in relation to cigarette smoking status 5 yr before interview. The results are presented for both genders combined as well as stratified for gender. Among current smokers, the strongest association was found for CRF classified as nephrosclerosis (OR, 1.9; 95% CI, 1.1 to 3.2, relative to never-smokers). If anything, the association was slightly stronger among women. There was a weaker and statistically nonsignificant association with risk of CRF caused by glomerulonephritis, similarly in men and women. This association was stronger and close to significant among former smokers. Overall, there was no statistical link between smoking and diabetic nephropathy. However, a trend toward positive association was evident among women but not among

Table 2. OR and 95% CI for chronic renal failure among smokers<sup>a</sup>

	Cases		Controls		OR <sup>b</sup> (95% CI)
	<i>n</i>	%	<i>n</i>	%	
Ever regular use of cigarettes, <sup>c</sup> cigars, or pipe <sup>d</sup>					
no <sup>e</sup>	348	38	420	42	1.00 (Referent)
yes	567	61	574	58	1.17 (0.95–1.44)
Regular use of cigarettes <sup>c</sup>					
former	252	27	268	27	1.18 (0.90–1.55)
current	291	31	285	29	1.14 (0.89–1.47)
Average no. of cigarettes/d					
1–10	128	14	171	17	0.89 (0.66–2.11)
11–20	298	32	286	29	1.24 (0.96–1.60)
>20	117	13	96	10	1.51 (1.06–2.15)
Duration of cigarette smoking (yr)					
1–20	180	19	225	23	0.99 (0.74–1.31)
21–40	259	28	238	24	1.23 (0.94–1.60)
>40	104	11	90	9	1.45 (1.00–2.09)
No. of pack-years, cigarettes					
1–15	202	22	263	26	0.95 (0.73–1.24)
16–30	207	22	184	18	1.32 (1.00–1.75)
>30	134	15	106	11	1.52 (1.08–2.14)

<sup>a</sup> Smoking status 5 yr before interview. OR, odds ratio; CI, confidence interval.

<sup>b</sup> Adjusted for age, gender, education, alcohol, and use of paracetamol and salicylates. Analyses of cigarette smoking also adjusted for pipe smoking, cigar smoking, and snuff use.

<sup>c</sup> Regular use: daily cigarette smoking for 6 mo or more 5 yr before interview.

<sup>d</sup> Regular use: cigar smoking or pipe smoking at least once a week for 6 mo or more 5 yr before interview.

<sup>e</sup> Never regular smokers of any tobacco type was the reference group for all comparisons.

Table 3. OR and 95% CI for chronic renal failure by type of renal disease among regular smokers of cigarettes<sup>a</sup>

	Diabetic Nephropathy ( <i>n</i> = 286)	Glomerulonephritis ( <i>n</i> = 222)	Nephrosclerosis ( <i>n</i> = 139)	Hereditary Disease ( <i>n</i> = 98)	Systemic Disease/Vasculitis ( <i>n</i> = 82)	Other ( <i>n</i> = 99)
All						
ever regular use <sup>b</sup>	1.1 (0.8–1.5)	1.4 (1.0–2.0)	1.7 (1.0–2.7)	1.2 (0.7–2.0)	0.5 (0.3–0.9)	1.0 (0.6–1.7)
former	1.1 (0.7–1.7)	1.5 (1.0–2.4)	1.4 (0.8–2.5)	1.5 (0.9–2.8)	0.5 (0.2–1.0)	0.9 (0.5–1.7)
current	1.0 (0.7–1.5)	1.3 (0.9–2.0)	1.9 (1.1–3.2)	1.0 (0.6–1.8)	0.5 (0.2–1.0)	1.1 (0.6–2.0)
Men						
ever regular use <sup>b</sup>	0.9 (0.6–1.4)	1.4 (0.9–2.2)	1.5 (0.8–2.8)	1.3 (0.6–2.6)	0.5 (0.2–1.3)	0.4 (0.2–1.0)
former	1.0 (0.6–1.7)	1.6 (0.9–2.7)	1.4 (0.7–2.8)	1.7 (0.7–3.8)	0.6 (0.2–1.7)	0.4 (0.1–1.0)
current	0.8 (0.4–1.3)	1.3 (0.8–2.1)	1.6 (0.8–3.3)	1.1 (0.5–2.3)	0.4 (0.2–1.2)	0.4 (0.2–1.1)
Women						
regular use <sup>b</sup>	1.4 (0.8–2.4)	1.4 (0.7–2.7)	2.1 (1.0–4.7)	1.2 (0.6–2.6)	0.4 (0.2–1.0)	1.9 (0.9–3.8)
former	1.1 (0.5–2.2)	1.4 (0.6–3.4)	1.6 (0.6–4.3)	1.6 (0.6–3.9)	0.3 (0.1–1.2)	1.6 (0.7–3.9)
current	1.6 (0.9–3.0)	1.3 (0.6–2.9)	2.7 (1.1–6.7)	0.9 (0.4–2.4)	0.5 (0.2–1.3)	2.1 (0.9–4.6)

<sup>a</sup> Smoking status 5 yr before interview. Adjusted for gender, age, education, alcohol, use of paracetamol and salicylates, pipe smoking, cigar smoking, and snuff use. Never regular smokers of any tobacco type was the reference group for all comparisons.

<sup>b</sup> Regular use: daily smoking for 6 mo or more 5 yr before interview.

men. Current smoking was unrelated to CRF caused by hereditary disease and “other causes,” but the association with the latter disease group was not consistent between genders. We observed a significant *inverse* relation with CRF caused by systemic disease/vasculitis. Table 4 displays dose–effect anal-

yses for the different types of CRF, stratified by gender. A clearer pattern of association emerged for glomerulonephritis-related CRF; relative to never-users, OR among smokers of >15 cigarettes per day on average was 1.7 (95% CI, 1.1 to 2.6). Similar relationships were noted for both men and women. A more than

Table 4. OR and 95% CI for chronic renal failure by type of renal disease among cigarette smokers, dose-effect analyses<sup>a</sup>

	Diabetic Nephropathy (n = 286)	Glomerulonephritis (n = 222)	Nephrosclerosis (n = 139)	Hereditary Disease (n = 98)	Systemic Disease/Vasculitis (n = 82)	Other (n = 99)
Average number/day						
all						
1–15	0.8 (0.6–1.2)	1.2 (0.8–1.8)	1.8 (1.1–3.0)	1.3 (0.8–2.3)	0.5 (0.2–0.9)	1.2 (0.7–2.0)
>15	1.4 (1.0–2.1)	1.7 (1.1–2.6)	1.4 (0.8–2.6)	1.0 (0.5–1.9)	0.5 (0.2–1.0)	0.8 (0.4–1.5)
men						
1–15	0.7 (0.4–1.2)	1.2 (0.7–2.0)	1.6 (0.8–3.2)	1.3 (0.6–2.7)	0.6 (0.2–1.7)	0.4 (0.2–1.0)
>15	1.1 (0.7–1.9)	1.7 (1.0–2.8)	1.4 (0.7–2.8)	1.3 (0.6–3.0)	0.4 (0.1–1.2)	0.4 (0.2–1.1)
women						
1–15	1.1 (0.6–2.0)	1.1 (0.5–2.4)	2.3 (1.0–5.2)	1.4 (0.6–3.1)	0.3 (0.1–0.9)	2.4 (1.2–5.0)
>15	2.0 (1.0–4.1)	1.9 (0.8–4.7)	1.5 (0.4–5.5)	0.6 (0.2–2.5)	0.6 (0.2–1.8)	0.8 (0.2–2.6)
No. of pack-years						
all						
1–20	0.9 (0.6–1.3)	1.3 (0.9–2.0)	1.3 (0.8–2.3)	1.4 (0.8–2.3)	0.3 (0.2–0.7)	1.1 (0.6–1.9)
>20	1.4 (0.9–2.1)	1.6 (1.0–2.5)	2.2 (1.3–3.8)	0.9 (0.4–1.8)	0.7 (0.4–1.5)	0.9 (0.5–1.7)
men						
1–20	0.7 (0.4–1.2)	1.3 (0.8–2.1)	1.2 (0.6–2.5)	1.3 (0.6–2.7)	0.5 (0.2–1.3)	0.4 (0.2–1.0)
>20	1.1 (0.6–1.8)	1.6 (0.9–2.7)	1.8 (0.9–3.5)	1.3 (0.5–3.0)	0.6 (0.2–1.7)	0.4 (0.2–1.1)
women						
1–20	1.1 (1.0–4.5)	1.2 (0.6–2.6)	1.4 (0.5–3.4)	1.5 (0.7–3.3)	0.1 (0.0–0.5)	2.2 (1.0–4.8)
>20	2.1 (1.0–4.5)	1.7 (0.6–4.5)	4.9 (1.8–13.5)	0.5 (0.1–2.2)	1.2 (0.4–3.5)	1.2 (0.4–3.3)

<sup>a</sup> Never regular smokers of any tobacco type was the reference group for all comparisons. Adjusted for gender (when appropriate), age, education, alcohol, use of paracetamol and salicylates, pipe smoking, cigar smoking, and snuff use.

twofold overall excess was observed for CRF classified as nephrosclerosis among subjects with a cumulative dose of >20 pack-years. The point estimates were considerably higher among women than among men. Dose–risk trends also emerged for diabetic nephropathy among women. No clear dose–effect relationship was observed for the unexpected inverse association with CRF linked to systemic disease/vasculitis. A weak inverse dose–risk trend was suggested for CRF from “other causes,” but the levels of risk relative to never-users of tobacco varied widely between genders.

## Discussion

We observed a moderate dose-dependent increased risk for CRF among cigarette smokers not explained by age; gender; body mass; hypertension; education; or use of analgesics, alcohol, or illicit drugs. On the whole, risk elevations were at least as evident in women as in men. Increases in risk seemed to be limited to nephrosclerosis and glomerulonephritis, but the precision of the relative risk estimates for other kinds of CRF was lacking. A positive association with diabetic nephropathy risk seemed to be confined to women, but comparisons between genders were somewhat hampered by small numbers. We found no link between CRF and pipe smoking, cigar smoking, or use of oral snuff.

A major strength of our study is its population-based design and large sample size. Our comprehensive nationwide protocol for case ascertainment and the open and universal access to health care in Sweden ensured identification of virtually all

eligible cases in the study base. The continuously updated, computerized Swedish Population Registry permitted random selection of frequency-matched population control subjects.

Case definition in epidemiologic studies of slowly progressing diseases such as CRF requires careful consideration. In most cases of CRF, there is no distinct disease onset but rather an insidious and continuous transition from full health to incapacitating disease. If the cut point is placed too far into the disease trajectory, then selective losses of cases caused by general deterioration or death, biased recall of etiologically relevant exposures in the distant past, and reversed causation as a result of changes in habits prompted by the CRF itself (or its treatment) will threaten the internal validity of the study. If, however, the cut point is placed too early, when the disease has not yet manifested itself clinically, then there is an imminent risk of ascertainment bias, because smoking and smoking-related comorbidity will increase the probability of serum creatinine testing and hence of CRF detection. Moreover, with a cut point that is close to the upper limit of the normal range, it will be difficult to single out the truly chronic cases. The cut points used in this study reflect our balancing between the above-mentioned risks. Practically all of our cases had clinically evident disease, but their general condition was normally good and did not importantly affect the activities of daily life. Losses as a result of death or poor clinical condition were noted in 13% of our eligible case subjects, but this was typically due to delayed interviews in combination with rapidly progressing disease. We cannot exclude the possibility that some of our

case subjects had been counseled to quit smoking (which would lead to a spuriously weak association) or to otherwise importantly change their lifestyle. To diminish the possible impact of reversed causation, we did not consider smoking data at time of interview but analyzed self-reports of smoking status 5 yr earlier. Then, the proportion of ex-smokers was identical among case subjects and control subjects, indicating that the disease had not brought about any smoking cessation. At time of interview, however, slightly more case subjects than control subjects were former cigarette smokers. This shift led to an attenuation of the relative risk estimates among current smokers and a corresponding inflation of the estimates among former smokers in supplementary analyses based on smoking status at interview (data not shown). Our choice of cut point well into the course of the disease might have entailed that the etiologically critical exposures occurred decades before the interview in some cases with very slow progression. This may have increased exposure misclassification. The likely consequence is underestimation of the studied associations.

We deem recall bias unlikely. Self-reported smoking data are relatively robust (17), and the public is unlikely to have preconceptions about a possible link between smoking and CRF. Moreover, the professional interviewers were trained to interview case subjects and control subjects in the same standardized way.

We did not estimate serum creatinine levels among control subjects; hence, we cannot completely exclude the presence of control individuals with a moderate renal insufficiency. If this potential misclassification of case subjects and control subjects is unrelated to smoking habits, then the positive association between smoking and CRF in our study is partly masked. However, because pre-uremic CRF is a rare disease (in our population-based study, the incidence rate was 115 patients per million person-years), it is not likely that an appreciable number of control subjects had significant, clinically silent renal disease.

Our results are consistent with those of two previous cohort studies in which relative risks for serum creatinine elevations and ESRD among male smokers were 2.1- and 1.7-fold, respectively (18,19). Furthermore, a previous, hospital-based case-control study (9) found a threefold increased risk for glomerulonephritis associated with CRF among heavy smokers. In contrast, two case-control studies failed to find any significant association of smoking with CRF (11) or ESRD (12). Smokers with ESRD may have higher mortality compared with nonsmokers (20); therefore, selection bias as a result of high mortality among the cases may explain the null finding in the latter study (12). Although not directly comparable with our investigation, studies of the progression of renal failure among patients with specific renal diseases support the role of smoking. A cumulative dose of >15 pack-years relative to <5 pack-years increased risk for ESRD 5.8 times among patients with IgA glomerulonephritis or autosomal dominant polycystic disease (8). Moreover, smoking seemed to promote proteinuria in polycystic kidney disease (6). Most studies in patients with diabetes show a two- to threefold increased risk of diabetic nephropathy among smokers (2), although the

World Health Organization Multinational Study of Vascular Disease in Diabetes after an average 8.4 yr follow-up did not find any association between smoking and CRF (21).

The strongest association in our study was between smoking and CRF caused by nephrosclerosis. Ninety-six percent of these cases were diagnosed as nephrosclerosis after benign or malignant hypertension. Several studies have found a relationship between smoking and renal disease among hypertensive subjects (3,4). However, because hypertension accompanies virtually all renal diseases, the entity nephrosclerosis may be a mixture of renal diagnoses in which atherosclerotic nephropathy (renal artery stenosis and “ischemic renal disease”) is likely to contribute to a substantial proportion of the cases. In one study of 56 patients who had a clinical diagnosis of hypertensive nephrosclerosis, only 26 had in fact true hypertensive nephrosclerosis and 19 patients had atheromatous vascular disease (22). It seems that the atherosclerotic process in the kidney is enhanced by common cardiovascular risk factors, including smoking (23).

Smoking did not clearly affect risk for CRF among case subjects with polycystic disease (85% of the patients with “hereditary disease” in our study); however, the sample size was limited. Smoking seemed to reduce risk for CRF caused by systemic disease or vasculitis. In the absence of a clear dose-response trend, this could be a chance finding. Previous studies have yielded disparate results; in a cohort of patients with systemic lupus erythematosus, smoking was associated with a much more rapid progression to ESRD (7), whereas another study found no association between smoking and lupus nephritis (24). If there is a detrimental effect of smoking in systemic diseases, then it is likely to be small.

Several previous studies have noted that the risk of renal impairment associated with smoking was restricted to men, whereas there was no increased risk at all in women (8,9,25). The consistency across several studies has prompted speculations about the biologic background (26). The gender difference is not implausible, because men are generally more likely than women to progress to renal disease and ESRD (27). The results of our study, however, strongly contradict the hypothesis that all women are intrinsically insensitive to renal effects of smoking. The most plausible explanation for the negative findings in several previous studies is lack of power, as a result of small sample sizes of women. Methodologic issues such as possible selection bias of prevalent hospital cases and uncertain appropriateness of hospital controls are other potential explanations for the findings in some studies. A recent published American prospective study supports our result; the relative risk of chronic kidney disease associated with smoking was 2.4 in men and 2.9 in women after 20 yr of follow-up (28).

A past study suggested that ACE inhibitors may modify the effect of smoking, as smoking increased CRF risk only 1.4-fold among users of ACE inhibitors compared with 10-fold among nonusers (8). The difference in risk for CRF among nonusers and users of ACE inhibitors was substantially less marked and not statistically significant in our study (independent of hypertension). This result must be interpreted cautiously, however, because only 5% of control subjects used ACE inhibitors.

This is the first study to investigate the relation between tobacco products other than cigarettes and CRF. We did not observe any association of CRF with pipe smoking, cigar smoking, or use of oral snuff. The results must be interpreted cautiously because our power to detect increases was limited. There is no obvious explanation for the discrepancy in effects of cigarette smoking on the one hand and pipe and cigar smoking on the other. The most likely explanation is that the absence of effect in the last categories was due to chance. One can further speculate about negative confounding by other lifestyle factors that also affect the baseline risk of CRF. The absence of effects of snuff use could potentially give rise to speculations about the importance of peak levels of nicotine; whereas smokers have short-lived but very high peaks, users of snuff have considerably lower levels of nicotine, albeit steady and long lasting. Chance and/or negative confounding by unmeasured lifestyle factors remain a viable alternative explanation, though.

Smoking might theoretically initiate renal disease because it adversely affects renal function in healthy subjects (29,30). However, there is a growing consensus that vascular risk factors such as smoking, hypertension, and hyperlipidemia act as promoters of preexisting renal disease regardless of the underlying cause (31). In light of the various ways that smoking might injure the kidneys, the effects of smoking are probably not uniform and may also depend on underlying renal disease. Smoking induces both systemic and intrarenal hemodynamic alterations that can be significant for renal disease progression. Smoking may also injure the kidneys by damaging the renal microvasculature through oxidative stress, reduced nitric oxide generation, and increased endothelin plasma concentration. Smoking-induced tubular cell dysfunction may further contribute to tubulointerstitial injury and progression of CRF (2).

In conclusion, our study supports the hypothesis that smoking, particularly heavy smoking, contributes to the development of CRF. The association was strongest for CRF classified as nephrosclerosis and glomerulonephritis. Assuming that the OR of 1.17 among regular smokers reflects a true excess risk, the proportion of all Swedish CRF cases that can be attributable to smoking is 8.9%. Although the population attributable risk is modest, smoking is a preventable risk factor. Identifying risk factors for CRF and preventing ESRD are critical because the global dialysis population (>1.1 million patients in 2001) is expanding at a rate of 7% per year (32). Therefore, patients who are at risk of CRF should be advised to stop smoking.

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