Original Article

Risk of Developing Low Glomerular Filtration Rate or Elevated Serum Creatinine in a Screened Cohort in Okinawa, Japan

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There are no known predictors of renal dysfunction, particularly for a community-based screening. We evaluated the changes in serum creatinine (SCr) and glomerular filtration rate (GFR) among screenees who participated in the screening program of the Okinawa General Health Maintenance Association both in 1983 and 1993. A total of 4,662 screenees at least 30 years of age at the 1983 screening were analyzed to examine whether they developed high SCr (≥1.4 mg/dl for men, ≥1.2 mg/dl for women) or low GFR (<60 ml/min/1.73 m^2). Overall, mean GFR (mean±SD) decreased slightly from 72.7±11.7 ml/min/1.73 m^2 to 70.8±15.0 ml/min/1.73 m^2. In 1983, the prevalences of high SCr and low GFR were 3.6% and 13.2%, respectively, and in 1993, they were 8.1% and 24.2%, respectively. Among the variables studied, dipstick proteinuria was the strongest predictor: the adjusted odds ratio (95% CI) was 1.282 (1.076–1.527, $p<0.01$) for high SCr and 1.215 (1.116–1.322, $p<0.01$) for low GFR. Dipstick proteinuria was best for detecting subjects who might develop low GFR in a screening setting. In subjects without proteinuria, systolic blood pressure was a significant predictor for low GFR (the adjusted odds ratio [95% CI] was 1.015 [1.009–1.020, $p<0.01$]) and for high SCr (the adjusted odds ratio [95% CI] was 1.028 [1.016–1.040, $p<0.01$]). In conclusion, the present study suggests that a dipstick urine test for proteinuria and both systolic and diastolic blood pressure are useful to identify those who are at risk of developing high SCr and low GFR and consequently end-stage renal disease. (*Hypertens Res* 2007; 30: 167–174)

***Key Words*: serum creatinine, chronic kidney disease, glomerular filtration rate, screening**

Introduction

The number of cases of end-stage renal disease (ESRD) requiring chronic dialysis therapy is increasing worldwide (*1–3*). Chronic kidney disease (CKD), namely low glomerular filtration rate (GFR), is not only the cause of ESRD, but also a risk factor for cardiovascular disease (*4*, *5*). Screening for CKD is therefore important for preventing ESRD and cardiovascular disease. Little is known, however, about the risk factors related to the development of CKD, and about low GFR in particular. A number of conventional risk factors of atherosclerosis are related to the development of CKD (*6*). Systolic hypertension, hyperuricemia, and elevated body mass index (BMI) were reported to be significant predictors for the development of decreased kidney function in a relatively young (35 to 55 years) cohort of Southeast Asians (*7*). However, the effect of aging on GFR in a large population is not known. People currently have a longer lifespan and the mean age at the start of dialysis is greater than 65 years old in Japan (*8*).

We have been studying the predictors of ESRD based on a

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Table 1. Characteristics of Participants in Both Screenings

Variables	1983 screening		1993 screening
	Re-visited in 10 years follow-up[#]	Total 1983 screened	
Number	4,662	13,713	4,662
Age (years)	53.1±10.8	53.2±13.2	63.0±10.8[$]
BMI (kg/m^2)	23.9±3.3	23.9±3.4	24.3±3.4
Systolic BP (mmHg)	130.1±19.1	131.9±20.1	131.1±17.1
Diastolic BP (mmHg)	79.3±11.1	80.1±11.5	77.5±10.1
S-creatinine (mg/dl)	0.98±0.17	1.00±0.24	0.99±0.38
GFR (ml/min/1.73 m^2)	72.7±11.7	72.0±13.1	70.8±15.0[$]
S-cholesterol (mg/dl)	196.1±37.7	196.0±38.4	209.9±34.3[$]
Hematocrit (%)	41.2±4.3	41.6±4.5	40.9±3.9
FPG (mg/dl)	91.9±17.4	92.7±22.8	97.7±19.2
Proteinuria (%)	16.1	19.4	8.1

All participants had serum creatinine data. Screening was performed from April 1 each year to March 31 the next year. BMI, body mass index (calculated by body weight in kg divided by the square of height in m); BP, blood pressure; S, serum; GFR, glomerular filtrarion rate; FPG, fasting plasma glucose. Data are mean±SD. [#]The characteristics were determined in the 1983 screening. [$]$p<0.05$ *vs*. participants in the 1983 screening. All participants were at least 30 years of age at the 1983 screening.

Table 2. Mean (Median) Values of Serum Creatinine According to Sex and Age in All Screenees and in Those without Hypertension and Diabetes Mellitus at the 1983 and 1993 Screening

	1983		1993	
	All screenees	Screenees without hypertension/DM	All screenees	Screenees without hypertension/DM
Men (years)				
30–	1.12 (1.10)	1.10 (1.10)	1.08 (1.10)	1.07 (1.10)
40–	1.13 (1.10)	1.12 (1.10)	1.07 (1.10)	1.06 (1.00)
50–	1.13 (1.10)	1.11 (1.10)	1.08 (1.10)	1.07 (1.10)
60–	1.16 (1.10)	1.13 (1.10)	1.10 (1.10)	1.08 (1.10)
70–	1.19 (1.20)	1.16 (1.20)	1.15 (1.20)	1.13 (1.10)
80–	1.19 (1.20)	1.18 (1.20)	1.22 (1.20)	1.17 (1.20)
All	1.14 (1.10)	1.11 (1.10)	1.10 (1.10)	1.08 (1.10)
Women (years)				
30–	0.86 (0.90)	0.85 (0.90)	0.84 (0.80)	0.86 (0.80)
40–	0.88 (0.90)	0.87 (0.90)	0.84 (0.80)	0.83 (0.80)
50–	0.91 (0.90)	0.89 (0.90)	0.88 (0.90)	0.86 (0.90)
60–	0.95 (0.90)	0.94 80.90)	0.90 (0.90)	0.89 (0.90)
70–	0.99 (1.00)	0.93 (0.90)	0.95 (0.90)	0.93 (0.90)
80–	1.03 (1.00)	1.08 (0.95)	1.01 (1.00)	0.98 (1.00)
All	0.92 (0.90)	0.87 (0.90)	0.89 (0.90)	0.87 (0.90)

DM, diabetes mellitus. DM was defined as fasting plasma glucose ≥126 mg/dl. All participants were at least 30 years of age at the 1983 screening.

community-based screening program and dialysis registry (*9*, *10*). Dipstick proteinuria and elevated serum creatinine (SCr) are significant predictors of ESRD (*11*), but factors related to the development of CKD have not been evaluated extensively. It is well recognized that renal function decreases with aging. Aging *per se*, however, is not a risk factor for developing ESRD (*10*).

We have been conducting an ongoing investigation of the renal outcomes, such as high SCr and low GFR (<60 ml/min/1.73 m^2), of a screened population in Okinawa, Japan. For this purpose, we combined two registries from the 1983 and 1993 screening programs. The present study thus provides community-based data on renal outcomes, including the incidence and prevalence of CKD.

Methods

Screening Program

The Okinawa General Health Maintenance Association (OGHMA) conducts a large, annual community-based health examination. The OGHMA is a nonprofit organization founded in 1972 (*10*). Once each year, the staff, doctors, and nurses visit residences and work places throughout the prefecture to perform health examinations. All subjects voluntarily participated in the screening. The OGHMA personnel provided mass screening, informed the participants of the results, and, when necessary, recommended further evaluation or treatment. This process included an interview concerning health status, a physical examination, and urine and blood tests. A nurse or doctor measured blood pressure using a standard mercury sphygmomanometer with the subject in the sitting position. Dipstick testing for proteinuria, hematuria, and glucosuria (Ames Dipstick, Tokyo, Japan) was performed in spontaneously voided fresh urine. Proteinuria was assessed by a technician as negative, trace, 1+, 2+, 3+, or 4+. A blood sample was taken after overnight fast. The blood was analyzed at a central laboratory at the OGHMA. BMI was calculated as weight (kg) divided by the square of height (m).

Computer-based data were available from April 1, 1983 through March 31, 1984 ($n=106,171$) for the 1983 screening, and from April 1, 1993 through March 31, 1994 ($n=143,948$) for the 1993 screening. Participants who were screened during both screenings were identified using ID number, birthdate, and other identifiers. In addition to formulaic matching, all matches were visually inspected to confirm their accuracy. SCr was measured using a modified Jaffe's reaction in an auto-analyzer at the OGHMA laboratory. The estimated GFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula (*12*). Low GFR was defined as a GFR of less than 60 ml/min/1.73 m^2 (*13*). High SCr was defined as ≥1.4 mg/dl in men and ≥1.2 mg/dl in women (*11*). Subjects who were already on chronic dialysis were excluded from the 1983 screening registry. GFR was considered zero in screenees who entered the dialysis program by the 1993 screening. The ethics committee of the OGHMA approved the study protocol. Only coded data were used for this study.

Statistical Analysis

The statistical significance of differences in the characteristics across participants was examined using the paired *t*-test, and the Wald χ^2 test (categorical variables). Multivariate logistic analyses were performed using SAS (Version 8.2; SAS Institute Inc, Cary, USA). A *p* value of less than 0.05 was considered statistically significant.

Table 3. Changes in Renal Function in the Participants of the 1983 Screening That Were Re-Screened in 1993 ($n=4,662$)

Variables	1983 screening	1993 screening
High SCr (mg/dl)		
Men (≥1.4)	100 (6.3%)	167 (10.4%)
Women (≥1.2)	70 (2.3%)	212 (6.9%)
Total	170 (3.6%)	379 (8.1%)
Low GFR, <60 ml/min/1.73 m^2		
Total	617 (13.2%)	1,129 (24.2%)

Renal function was evaluated by either SCr or GFR. SCr, serum creatinine; GFR, glomerular filtrarion rate. GFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula.

Results

We identified 30,724 subjects (13,541 men and 17,183 women) among the 92,666 screenees in the 1983 screening who were at least 30 years of age and participated in the 1993 screenings (33.2% of the total). There were no differences in the percentage of subjects who participated in both screenings between the total screenees and those with SCr data for either men or women. Characteristics at the 1983 screening were similar between those who participated in the 1993 screening and those who did not. Of the 13,713 screenees that had SCr data and were at least 30 years of age at the 1983 screening, 4,662 (34.0%) were also screened and tested for SCr at the 1993 screening (Table 1) and were the subjects of this study. The mean decrease in GFR was −1.9 ml/min/1.73 m^2 from the 1983 screening to the 1993 screening. The most frequent change in GFR was in the range of −10.0 to 0 ml/min/1.73 m^2, which represented 39.1% of the total subjects.

Changes in SCr measurements were examined in the total subjects and in those without hypertension and diabetes mellitus (DM; Table 2). Both mean and median levels of SCr were compared between the two screenings. There were no appreciable changes in these values in either total subjects or in those without hypertension and DM (Table 2).

Changes in kidney function were evaluated by a change either in the prevalence of high SCr or the prevalence of low GFR (Table 3). The prevalence of low GFR (less than 60 ml/min/1.73 m^2) increased from 13.2% in the 1983 screening to 24.2% in the 1993 screening. Figure 1 shows the incidence of high SCr according to age and sex. The prevalence was significantly greater in men older than 60 years of age. This was also true for the change in GFR.

Risk factors related to the future development of high SCr and low GFR are summarized in Tables 4 and 5, respectively. As expected, proteinuria was a strong predictor of developing both high SCr and low GFR. However, there were numerous

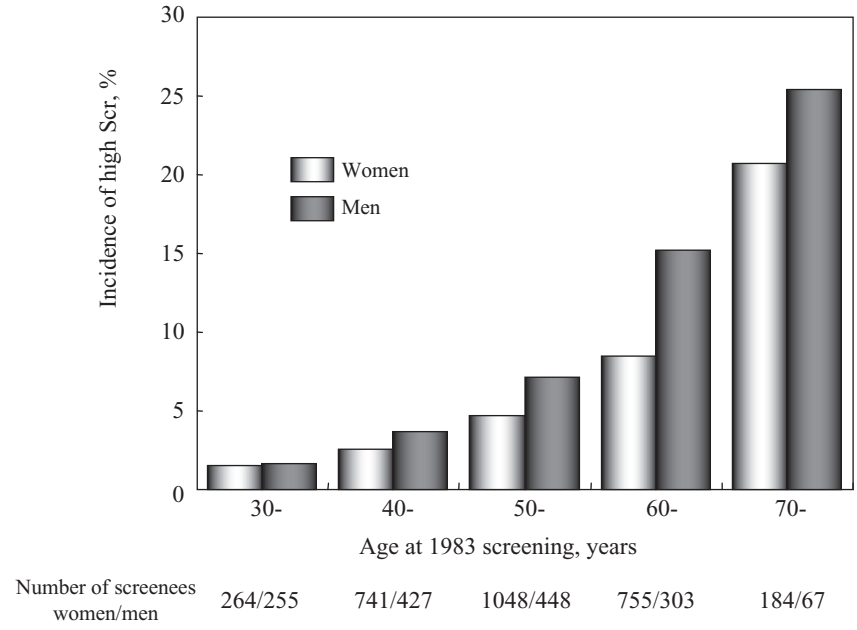

Fig. 1. *Incidence of developing high serum creatinine (SCr; women ≥1.2 mg/dl, men ≥1.4 mg/dl) from the 1983 screening to the 1993 screening (10 years) according to age and sex.*

Table 4. Factors Associated with Future Development of High Serum Creatinine (from the 1993 Screening)[#]

Input variable	Odds ratio (95% CI)	
	Unadjusted	Adjusted
All (n=4,492)		
Systolic BP (mmHg)	1.026 (1.021–1.032)**	1.024 (1.015–1.033)**
Diastolic BP (mmHg)	1.035 (1.024–1.046)**	1.049 (1.032–1.067)**
BMI (kg/m^2)	0.993 (0.957–1.030)	0.909 (0.855–0.967)*
Proteinuria	1.495 (1.342–1.665)**	1.282 (1.076–1.527)**
No proteinuria (n=3,335)		
Systolic BP (mmHg)	1.024 (1.016–1.032)**	1.028 (1.016–1.040)**
Diastolic BP (mmHg)	1.032 (1.017–1.046)**	1.055 (1.031–1.080)**
BMI (kg/m^2)	0.953 (0.905–1.004)	0.895 (0.821–0.976)*

[#]The input variables were obtained from the 1983 screening. High serum creatinine: men ≥1.4 mg/dl and women ≥ 1.2 mg/dl. CI, confidence interval; BP, blood pressure; BMI, body mass index. Proteinuria was categorized into five subgroups: (–), (±), (1+), (2+), and (≥3+). No proteinuria denotes dipstick (–) proteinuria. For the multivariate analysis, input variables were BMI and proteinuria for systolic BP, BMI and proteinuria for diastolic BP, systolic BP and proteinuria for BMI, and systolic BP and diastolic BP for proteinuria. In cases of no proteinuria, input variables were BMI for systolic BP and diastolic BP, and systolic BP for BMI. *p<0.05, **p<0.01.

patients who developed renal failure without proteinuria. Therefore, we did similar analyses in the subjects without proteinuria and found that increased systolic blood pressure (SBP) was a significant predictor of both high SCr and low GFR. There was a significant increase in the adjusted odds ratios as the SBP values increased. Using a forward stepwise procedure, age, proteinuria, and sex were the first three determinants of developing low GFR. The partial r^2 was 0.1358 (p<0.0001) for age (in years), 0.0067 (p<0.0018) for proteinuria, and 0.0040 (p<0.0157) for sex (*vs*. women). However, the presence of hypertension, DM, and obesity were not significant (r^2<0.0005).

Incidence of high SCr increased with the degree of proteinuria (Fig. 2), SBP (Fig. 3), and diastolic blood pressure (DBP) (Fig. 4). Similar results were obtained for the degrees of change in GFR, except with respect to DBP. We further analyzed the isolated effect of SBP or DBP on the development of low GFR after adjusting for age, sex, BMI, and proteinuria. The adjusted odds ratio (95% CI) was 1.016 (1.009–1.022, p<0.0001) for SBP and 1.032 (1.020–1.044,

Table 5. Factors Associated with the Future Development of Low GFR (from the 1993 Screening)[#]

Input variable	Odds ratio (95% CI)	
	Unadjusted	Adjusted
All (n=4,045)		
Systolic BP (mmHg)	1.015 (1.011–1.019)**	1.014 (1.010–1.019)**
Diastolic BP (mmHg)	1.011 (1.004–1.018)**	1.008 (1.000–1.016)*
BMI (kg/m^2)	1.007 (0.982–1.032)	0.979 (0.954–1.005)
Proteinuria	1.268 (1.168–1.377)**	1.215 (1.116–1.322)**
No proteinuria (n=3,005)		
Systolic BP (mmHg)	1.014 (1.009–1.019)*	1.015 (1.009–1.020)**
Diastolic BP (mmHg)	1.006 (0.997–1.015)	1.006 (0.996–1.015)
BMI (kg/m^2)	1.010 (0.979–1.041)	0.988 (0.957–1.021)

[#]The input variables were obtained from the 1983 screening. CI, confidence interval; BP, blood pressure; BMI, body mass index. Proteinuria was categorized into five subgroups: (–), (±), (1+), (2+), and (≥3+). No proteinuria denotes dipstick (–) proteinuria. For the multivariate analysis, input variables were BMI and proteinuria for systolic BP, BMI and proteinuria for diastolic BP, systolic BP and proteinuria for BMI, and systolic BP and diastolic BP for proteinuria. In cases of no proteinuria, input variables were BMI for systolic BP and diastolic BP, and systolic BP for BMI. *p<0.05, **p<0.01.

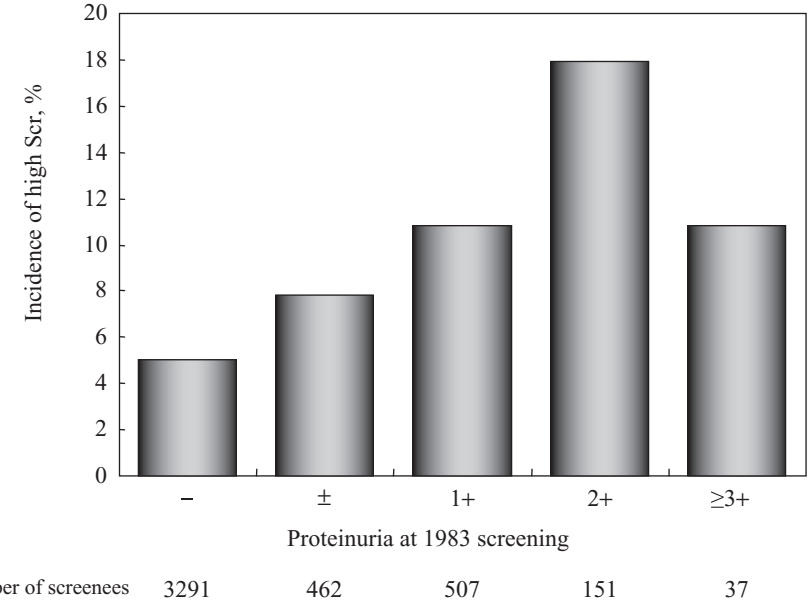

Fig. 2. *Incidence of developing high serum creatinine (SCr; women ≥1.2 mg/dl, men ≥1.4 mg/dl) from the 1983 screening to the 1993 screening (10 years) according to the degree of proteinuria. Proteinuria was tested using a dipstick.*

p<0.0001) for DBP, suggesting that the risk of developing low GFR increases with either higher SBP or DBP.

Discussion

Changes in kidney function over 10 years were examined on the basis of two screenings conducted in 1983 and 1993. The present study identified proteinuria and SBP as independent predictors of the development of low GFR. GFR decreased more in the older population (>60 years). Age was also a significant risk factor for developing high SCr. It is uncertain whether increasing age of the subjects or an increase in age-related risk factors was the cause of the increased prevalence of CKD. A number of conventional risk factors for atherosclerosis are associated with the development of CKD (*6*).

The present study confirmed the importance of dipstick proteinuria for identifying subjects that are likely to develop low GFR as well as ESRD (*14*). The prevalence of proteinuria was higher in the study population (19.4%) than in the whole screening population (3.5%). Therefore, those that were tested for SCr were at higher risk for low GFR. Unfortunately, we do not have further information to determine the

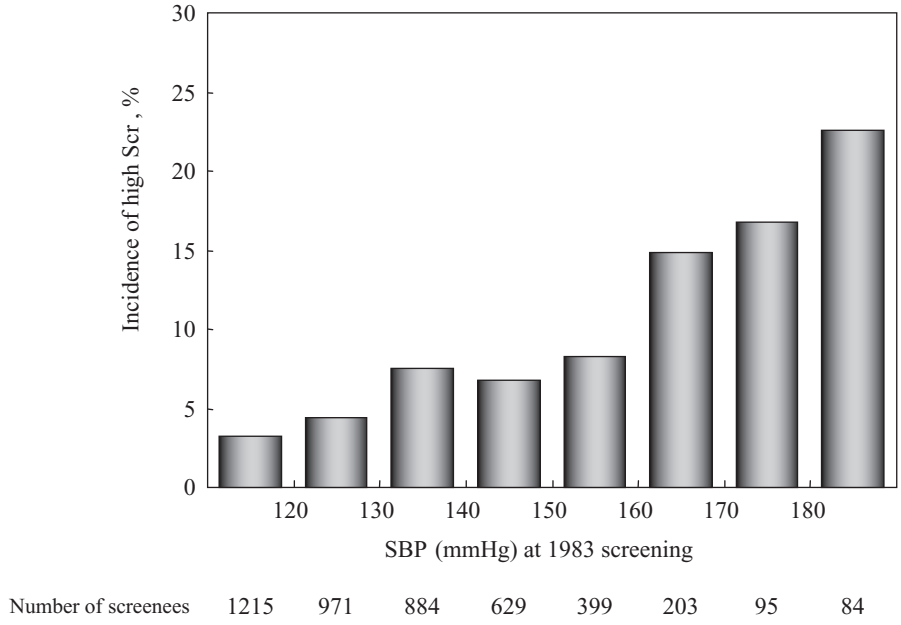

Fig. 3. *Incidence of developing high serum creatinine (SCr; women ≥1.2 mg/dl, men ≥1.4 mg/dl) from the 1983 screening to the 1993 screening (10 years) according to the baseline systolic blood pressure (SBP).*

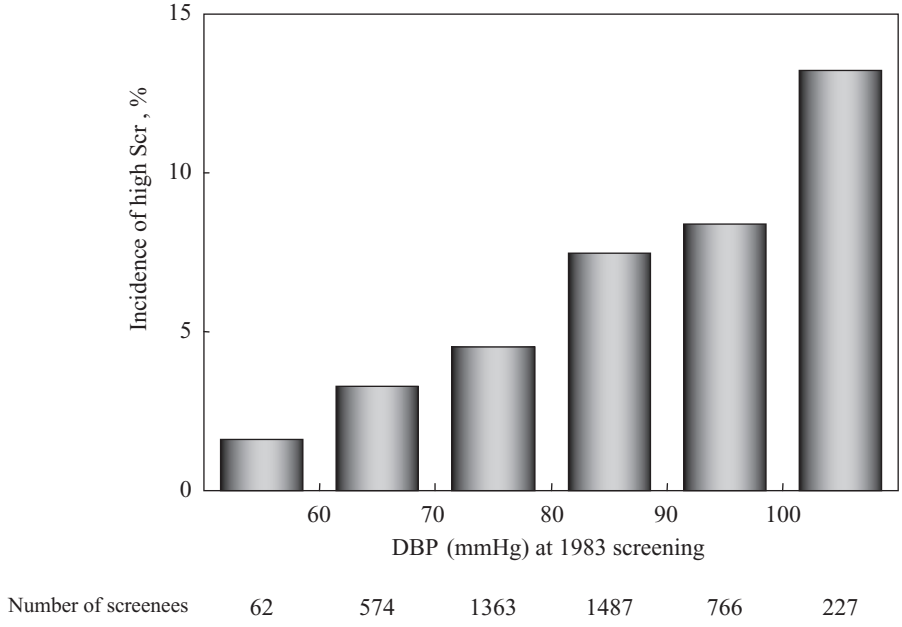

Fig. 4. *Incidence of developing high serum creatinine (SCr; women ≥1.2 mg/dl, men ≥1.4 mg/dl) from the 1983 screening to the 1993 screening (10 years) according to the baseline diastolic blood pressure (DBP).*

causes of proteinuria. The prevalence of low GFR was higher in our cohort than in the general US population (*6*).

In subjects without proteinuria, SBP was a significant predictor for developing low GFR. An increase in SBP is an important component of metabolic syndrome (*15*). We (*16*) and others (*15*) have reported that metabolic syndrome is associated with CKD. We have also shown that proteinuria developed more often in obese individuals with higher triglyceride levels (*17*, *18*). Moreover, BMI was a significant predictor of ESRD, particularly in men (*19*). In the present

study, however, the follow-up duration of 10 years may have been too short to observe the effect of obesity on the incidence of CKD.

Identification of CKD is important, since it is also a risk factor for cardiovascular disease and death (*4*, *5*). Ninomiya *et al*. demonstrated that CKD is a significant predictor of cardiovascular disease in Japanese (*20*). Therefore, early detection and intervention might prevent the morbidity and mortality related to CKD. A recent study, however, demonstrated that the most cost effective frequency for general screening is once every 10 years in asymptomatic individuals (*21*). Currently, annual health checks are mandatory for employees age 40 years and over in Japan (*22*).

The prevalence of non-conventional risk factors for cardiovascular disease has increased in relation to the degree of GFR. Low GFR is often associated with anemia. Correction of anemia effectively prevents the progression of renal failure (*23*) and improves the prognosis of patients with congestive heart failure (*24*). Vascular calcification including the coronary arteries is common in patients with CKD (*25*).

There are several limitations to our study. We used the abbreviated MDRD formula to estimate GFR and did not use the racial factor. Several reports suggest that the Japanese might have a lower GFR than others (*26*, *27*). The baseline GFR and BMI levels were lower in our cohort than in the general US population. The study subjects were relatively healthy individuals that were concerned about their general health, and should therefore be considered a self-selected population. As in other large-cohort studies, the follow-up was passive.

Some of the individuals who participated in the screening may already have been diagnosed with CKD. Long-term follow-up studies of subjects with low GFR are not available for the Japanese. Twenty-two ESRD patients were diagnosed during the study period: the calculated incidence was 47 per 10,000 subjects in the cohort whereas it was 22 per 10,000 people in the whole Okinawa area (*10*). It is possible that those with low GFR died before entering an ESRD program; therefore our results might underestimate the incidence of ESRD. In addition, a survival bias was present, because study participants had to attend both screenings.

The proteinuria and SCr measurements were performed only once. This may have resulted in an underestimation of the strength of the association between the variables studied and the incidence of CKD. The dipstick urine test for proteinuria has low sensitivity, but is convenient to use and is inexpensive (*14*). We are not certain about the causes of low GFR and proteinuria, which might be associated with DM nephropathy and other types of renal disease. Unfortunately, the serum uric acid data were not sufficient from the 1983 screening. Recently, the role of hyperuricemia was reappraised (*28*). We subsequently reported a role for hyperuricemia in the risk of developing CKD in a screening cohort (*29*).

Significant changes in risk factors and treatments have occurred during the study period. The introduction of new antihypertensive drugs such as angiotensin converting enzyme inhibitors, available since 1983, might slow the progression of renal failure. Angiotensin II receptor blockers have been available since 1998 in Japan. Finally, although we adjusted our analyses for age, gender, and other confounding variables, additional factors might be associated with the development of CKD. Among them, DM is a strong risk factor for the development of CKD and ESRD (*6*, *30*). In our study, however, the duration of 10 years might be sufficient to exclude those who already had significant DM nephropathy at the 1983 screening, because the screenees might have died or developed significant disability and therefore could not attend the 1993 screening. The relative homogeneity of the Okinawa population enhanced the internal validity of our results. Our findings remain to be confirmed, however, in other parts of Japan and among other races.

In conclusion, the present study indicated changes in SCr and estimated GFR in the same screenees using a community-based screening of over 10 years' duration. The prevalence of high SCr and low GFR increased significantly, particularly in aged men. In the whole screened population, however, GFR decreased only 1.9 ml/min/1.73 m^2 in 10 years. Dipstick proteinuria was useful to detect individuals at high risk for developing low GFR among otherwise healthy screenees. In screenees without proteinuria, a slight increase in SBP was associated with an increased risk of developing low GFR. It remains unknown whether intervention for proteinuria or early identification of risk factors for CKD is effective for reducing the risk of cardiovascular disease and CKD.

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