Kidney International, Vol. 63 (2003), pp. 1468–1474

Proteinuria and the risk of developing end-stage renal disease

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Proteinuria and the risk of developing end-stage renal disease.

Background. Dipstick urinalysis for proteinuria and hematuria has been used to screen renal disease, but evidence of the clinical impact of this test on development of end-stage renal disease (ESRD) is lacking.

Methods. We assessed development of ESRD through 2000 in 106,177 screened patients (50,584 men and 55,593 women), 20 to 98 years old, in Okinawa, Japan, who participated in community-based mass screening between April 1983 and March 1984. We used data from the Okinawa Dialysis Study Registry to identify ESRD patients. Multivariate logistic analyses were performed to calculate adjusted odds ratio and 95% confidence interval (95% CI) for the significance of proteinuria and hematuria on the risk of developing ESRD with confounding variables such as age, gender, blood pressure, and body mass index. A similar analysis was repeated in a subgroup of screened patients in whom serum creatinine data existed.

Results. During 17 years of follow-up, 420 screened persons (246 men and 174 women) entered the ESRD program. We identified a strong, graded relationship between ESRD and dipstick urinalysis positive for proteinuria; adjusted odds ratio (95% CI) was 2.71 (2.51 to 2.92, $P < 0.001$). Similar trends were observed after adding serum creatinine data. Compared with dipstick-negative proteinuria, adjusted odds ratio (95% CI) of proteinuria (1+) was 1.93 (1.53 to 2.41, $P < 0.001$) in men and 2.42 (1.91 to 3.06, $P < 0.001$) in women.

Conclusion. Proteinuria was a strong, independent predictor of ESRD in a mass screening setting. Even a slight increase in proteinuria was an independent risk factor for ESRD. Therefore, asymptomatic proteinuria warrants further work-up and intervention.

The number of patients with end-stage renal disease (ESRD) requiring chronic dialysis is increasing worldwide [1, 2]. Therefore, it is necessary to detect early signs of renal disease and determine who is at high risk of developing ESRD. Proteinuria is a well-known marker of renal disease, and reduction of proteinuria is often associated with beneficial effect of treatment [3–5]. However, long-term renal survival based on the results of dipstick urinalysis for proteinuria is not known in the general population. Dipstick urinalysis is not usually recommended for the purpose of screening for renal disease because both evidence of the relationship between detection of proteinuria by dipstick urinalysis and long-term renal survival and financial benefit are lacking.

Natural courses of progressive renal disease are mostly unknown. Moreover, many patients come late to a nephrologist and begin chronic dialysis therapy with only a short duration of follow-up [6, 7]. In Japan, Okinawa has a high incidence and prevalence of dialysis patients [1, 8]. Since 1971, we have maintained a registry of all chronic dialysis patients treated in Okinawa [9, 10]. The Okinawa General Health Maintenance Association has run an independent, community-based mass screening program, and the collected data have been filed in a computer since 1983 [11]. We identified the individuals who developed ESRD among those participating in the 1983 screening, and we examined the clinical impact of the degree of proteinuria measured by dipstick urinalysis.

METHODS

Study design

All individuals over 20 years of age who participated in the 1983 mass health screening examinations in Okinawa, Japan, were eligible for the study. Okinawa includes a number of subtropical islands and is located in the southern-most part of Japan. The population is stable at around 1.2 million (1980 census). Screening participants were excluded from the study if birth date data or dipstick urinalysis results were not available in the computer file. Dialysis patients who had been among the 1983 screening participants and those individuals who had become dialysis patients during the study period through December 31, 2000, were identified by using the Okinawa Dialysis Study (OKIDS) Registry, which covers the entire geographic area. Furthermore, the identity of these dialysis patients was verified by reviewing their medical charts in the dialysis units. The cumulative incidence of ESRD and the relative risk of developing ESRD according to the urine test at screening were determined.

Key words: proteinuria, hematuria, end-stage renal disease, screening.

Received for publication August 26, 2002
and in revised form October 6, 2002
Accepted for publication November 14, 2002

Mass screening

The Okinawa General Health Maintenance Association (OGHMA) under the direction of Dr. Y. Ikemiya performs a large community-based health examination annually. The association is a nonprofit organization that was founded in 1972. Once each year, the staff of the association, doctors and nurses, visit sites where people reside or are employed throughout the entire Okinawa area. Those who are screened have participated voluntarily. They provide mass screening examinations, inform the participants of the results, and, when necessary, recommend further examination. The mass screening examination includes an interview regarding health status, a physical examination, a urine test, and blood tests. A nurse or doctor measures blood pressure with a standard mercury sphygmomanometer while the person being screened is in the sitting position. Dipstick urinalysis (Ames dipstick) is performed with spontaneously voided fresh urine. The results of the urine test are interpreted by the physicians or their assistants and are recorded as (−), (±), (1+), (2+), (3+), and (4+). We defined results recorded as (−) and (±) as normal, and the rest were defined as abnormal. Data for glycosuria and fasting blood glucose were incomplete and were, therefore, not analyzed in this study. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. The computer-based data included data acquired from April 1, 1983, through March 31, 1984. The present analysis was conducted on a total of 106,177 screened persons (50,584 men and 55,593 women), which was approximately 13.7% of the total adult population in Okinawa in 1983. In men, the estimated proportion of the general population in each age group who participated was as follows: 6.8% in those 20 to 29 years of age, 13.3% in those 30 to 39 years of age, 15.4% in those 40 to 49 years of age, 16.8% in those 50 to 59 years of age, 22.1% in those 60 to 69 years of age, 22.2% in those 70 to 79 years of age, and 14.2% in those 80 years old and older. In women, it was 5.3% in those 20 to 29 years of age, 10.4% in those 30 to 39 years of age, 15.1% in those 40 to 49 years of age, 20.3% in those 50 to 59 years of age, 25.5% in those 60 to 69 years of age, 23.8% in those 70 to 79 years of age, and 11.6% in those 80 years old and older. Because the cost for the blood test was not paid for by the public sector, it was not mandatory. Serum creatinine data were available for 14,609 screened persons [12]. Serum creatinine was measured using the modified method of Jaffe's reaction in an automated analyzer at OGHMA's laboratory. Screened persons who were already on chronic dialysis were excluded from the study. According to the 1980 census, the population in Okinawa over 15 years of age was 781,166 (377,479 men and 403,687 women).

Dialysis registry in Okinawa

All chronic dialysis patients residing in Okinawa, Japan, who survived at least 1 month on scheduled dialysis are registered in the OKIDS Registry [9, 10]. Patients dying within 1 month of the start of dialysis are not included in the registry because it is unknown whether their renal function was improving and whether other medical conditions accounted for their rapid demise. Pertinent clinical information for the new dialysis patients and medical events in the prevalent dialysis patients were collected almost perfectly by the collaboration of the physicians acknowledged herein. Records were updated at least twice a year for medical events such as death, renal transplantation, and patient transfer out of Okinawa. If needed, other information was obtained through nurses, medical clerks, and the patients themselves. All patients were followed up until a major medical event or until January 2001, whichever occurred first, and we verified outcomes. Because Okinawa includes subtropical islands that are separated from mainland Japan, there is little migration of patients. Several retrospective [9, 10] and prospective [13–15] studies based on the registry data have been reported.

Criteria for the differential diagnosis of ESRD were neither simple nor standardized. Therefore, the medical records were further reviewed, and patients were grouped into one of six disease categories. Chronic glomerulonephritis was diagnosed when proteinuria and/or hematuria was noted before the onset of hypertension and renal failure. Nephrosclerosis was diagnosed when hypertension or major vascular disease was documented before the onset of renal failure. Diabetes mellitus nephropathy was diagnosed clinically by a long history of diabetes mellitus, presence of diabetes mellitus retinopathy, and the use of insulin [16]. Systemic lupus erythematosus was diagnosed according to the criteria of the American Rheumatism Association [17]. Polycystic kidney disease was diagnosed, after chart review, by the presence of multiple cysts and a family history of the disease. A sixth category, "other" disease, was used for patients who did not fall into one of the aforementioned disease categories.

By the end of 2000, there were 46 dialysis units in Okinawa. Nine were in the public sector, 17 were in private hospitals, and 20 were in clinics.

Statistical analysis

The unpaired *t* test or the chi-square test was used to analyze differences in values or ratios between groups. The observation period was calculated from the date of screening until the start of dialysis. Multivariate logistic analysis was done to examine the correlates of proteinuria by variables such as age, gender, systolic blood pressure, diastolic blood pressure, and body mass index. In a subgroup of screened persons, analyses were repeated

Table 1. Clinical demographics of the screened subjects in 1983

	Total screened subjects	Screened subjects who developed end-stage renal disease
Number of screened subjects	106,177	420
Men	50,584 (47.6%)	246 (58.6%)[a]
Age *years*, mean *SD*	49.1 (16.2)	52.9 (13.0)[a]
Body mass index kg/m^2, mean *SD*	23.4 (3.3)[a]	24.4 (3.4)[a]
Systolic blood pressure *mm Hg*, mean *SD*	130.2 (19.4)	143.9 (22.0)[a]
Diastolic blood pressure *mm Hg*, mean *SD*	78.7 (11.4)	86.8 (12.7)[a]
Proteinuria %	5.3	44.3[a]
Hematuria %	9.0	18.1[a]

Screening was performed from April 1983 to March 1984. Proteinuria (hematuria) denotes 1+ and over by dipstick test.
[a] $P < 0.001$

Table 2. Clinical demographics of screenees in 1983 who eventually developed end-stage renal disease (ESRD) by the end of 2000

	Screened subjects who developed ESRD	Total ESRD population
Number of patients	420	4569
Men	246 (58.6%)	2564 (56.1%)
Age at start of dialysis *years*, mean *SD*	63.7 (13.5)	56.7 (16.4)[a]
Time to dialysis after screening *months*, mean *SD*	129.1 (53.8)	
Primary renal disease		
Chronic glomerulonephritis	205 (48.8%)	1955 (42.8%)
Diabetes mellitus	100 (23.8%)	1542 (33.7%)[a]
Polycystic kidney disease	12 (2.9%)	111 (2.4%)
Systemic lupus erythematosus	6 (1.4%)	100 (2.2%)
Nephrosclerosis	55 (13.1%)	490 (10.7%)
Other	42 (10.0%)	371 (8.1%)

Screening was performed from April 1983 to March 1984. Study period was from April 1983 to December 2000.
[a] $P < 0.001$

with addition of serum creatinine. Data are expressed as mean (SD). All analyses were done with SAS (Version 8.2, SAS Institute, Inc., Cary, NC, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The characteristics of the participants in this analysis are shown in Table 1. During the follow-up period, 420 subjects entered the dialysis program (Table 2). The mean time to dialysis after screening was 141.4 months in patients with proteinuria (−), and it decreased with the degree of proteinuria to 103.9 months with proteinuria (3+), $P < 0.01$. The cumulative incidence of ESRD increased sharply and linearly with the degree of proteinuria (Figs. 1 and 2) but did not increase much with that of hematuria (Fig. 3).

Risk of developing ESRD was evaluated by multivariate logistic analysis. Proteinuria was a strong, independent risk factor for developing ESRD. Overall, the nonadjusted odds ratio (95% CI) and adjusted odds ratio (95% CI) were 3.09 (2.89 to 3.31, $P < 0.001$) and 2.71 (2.51 to 2.92, $P < 0.001$) for proteinuria and 1.43 (1.30 to 1.57, $P < 0.001$) and 1.18 (1.06 to 1.32, $P = 0.002$) for hematuria in model 1 (Table 3). Hematuria was a significant risk factor for ESRD for men (odds ratio, 1.38; 95% CI, 1.19 to 1.61, $P < 0.001$), but not women (odds ratio, 1.02; 95% CI, 0.87 to 1.19, not significant). In a subgroup of screened subjects, similar analyses were repeated with adding data of serum creatinine in model 2. Overall, proteinuria remained significant (odds ratio, 2.53; 95% CI, 2.17 to 2.94, $P < 0.001$), but hematuria was not (odds ratio, 1.13; 95% CI, 0.95 to 1.36). In men, the odds ratios (95% CI) were 2.64 (2.04 to 3.42, $P < 0.001$) for proteinuria and 2.66 (1.41 to 5.01, $P = 0.003$) for hematuria. In women, the odds ratios (95% CI) were 2.32 (1.84 to 2.93, $P < 0.001$) for proteinuria and 1.05 (0.81 to 1.36, not significant) for hematuria.

Impacts of different degrees of proteinuria and hematuria on the risk of developing ESRD are summarized for both men and women (Table 4). Even a slight increase in the degree of proteinuria, such as proteinuria (±), caused a change in the adjusted odds ratios (95% CI), which were 1.77 (1.13 to 2.78, $P = 0.012$) in men and 1.34 (0.74 to 2.41, not significant) in women. The relation between the risk of ESRD and the degree of hematuria, however, was different from that of proteinuria (Table 5). Rates of ESRD adjusted for age and gender were shown by a combination of proteinuria and hematuria (Fig. 4).

DISCUSSION

Our study confirmed the link between proteinuria or hematuria and ESRD. Compared to hematuria, proteinuria was a more potent predictor of ESRD than was hematuria in both men and women. Even a slight degree of proteinuria, such as proteinuria (±) for men and proteinuria (1+) for women, was a significant predictor of ESRD. Proteinuria is also a predictor of all-cause mortality [18, 19]. Those who had higher degrees of proteinuria may have died before reaching ESRD [20]. Therefore, our findings may underestimate the impact of the degree of proteinuria on development of ESRD.

The relation between microalbuminuria and cardiovascular disease is well established, and microalbuminuria, proteinuria, or both are predictors of cardiovascular disease in patients with diabetes, hypertension, or both. It is plausible that intrarenal vascular disease causes glomerular and tubular damage that, in turn, causes microalbuminuria. Therefore, screening for proteinuria could help identify patients who are at high risk for cardiovascular disease and ESRD.

Cumulative incidence of ESRD increased linearly with

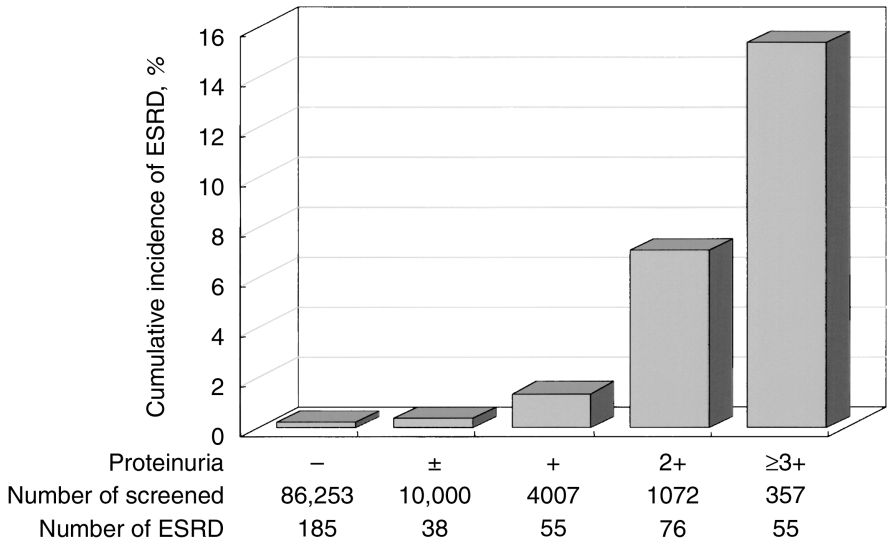

Fig. 1. Cumulative incidence of end-stage renal disease (ESRD) by the baseline results for proteinuria. There are some screened persons with no data for proteinuria. The study period was from April 1983 to December 2000.

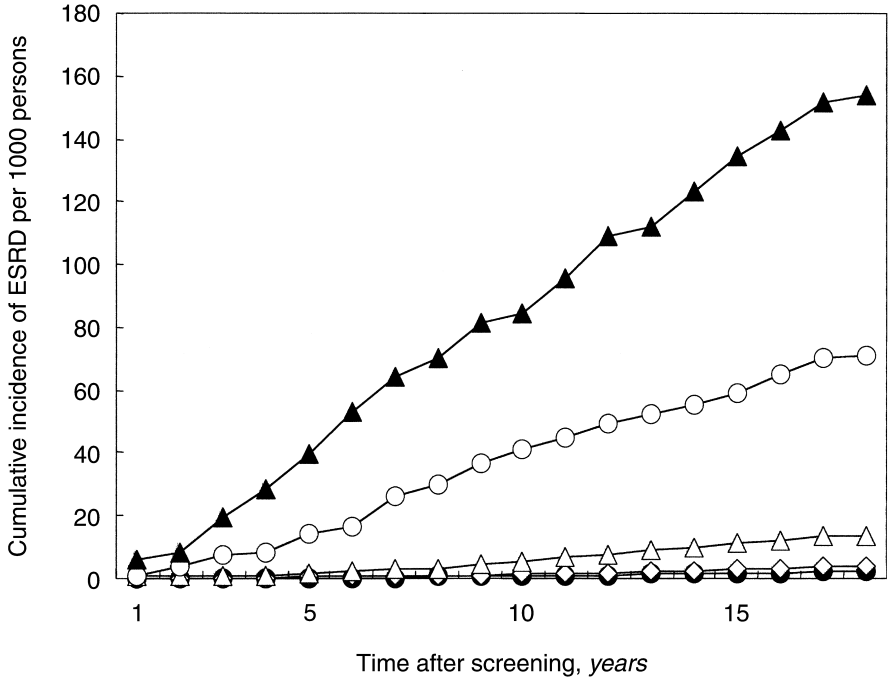

Fig. 2. Cumulative incidence of end-stage renal disease (ESRD) by the time after screening in each degree of proteinuria. Study period was from April 1983 to December 2000. Symbols are: (▲), proteinuria ≥3+; (○), proteinuria 2+; (△), proteinuria +; (◇), proteinuria ±; and (●), proteinuria −.

the degree of proteinuria (Fig. 1). The cumulative incidence of ESRD was 1.4% in the screened persons with proteinuria (1+) and 7.1% in the screened persons with proteinuria (2+) for the 17-year follow-up period. Screened persons with proteinuria (2+) or more are at high risk of ESRD; therefore, they are candidates for further workups. However, for those with proteinuria (1+) and (±), the absolute risk of ESRD was not as high, meaning further workups may not be necessary, unless otherwise indicated.

Proteinuria is relatively common in obese subjects. Body mass index was significantly correlated with microalbuminuria in a cross-sectional population-based study [21, 22]. In the present study, proteinuria was a significant, independent predictor of ESRD, even after adjustment for body mass index (Table 3). Smoking is a significant risk factor for proteinuria in various clinical settings [23, 24]. Unfortunately, lifestyle-related variables such as smoking, drinking, and exercise were not included in this study. Incidence of hematuria was higher in women than in men. However, hematuria was not helpful to predict for ESRD in women. Risk of developing ESRD with isolated hematuria in women was similar to that of normal urinalysis.

There are several limitations in the present study. Dip-

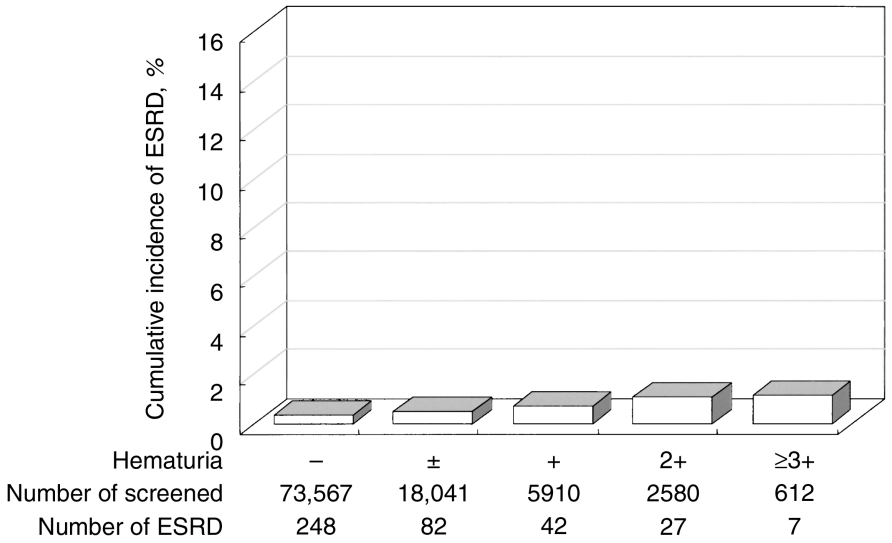

Fig. 3. Cumulative incidence of end-stage renal disease (ESRD) by the baseline results for hematuria. There are some screened persons with no data for hematuria. The study period was from April 1983 to December 2000.

Table 3. Results of multivariate logistic analysis on the risk of end-stage renal disease (ESRD)

Variables	OR	95% CI	*P* value
Proteinuria			
Model 1			
Overall	2.71	2.51–2.92	<0.001
Men	2.62	2.36–2.90	<0.001
Women	2.81	2.50–3.15	<0.001
Model 2			
Overall	2.53	2.17–2.94	<0.001
Men	2.64	2.04–3.42	<0.001
Women	2.32	1.84–2.93	<0.001
Hematuria			
Model 1			
Overall	1.18	1.06–1.32	0.002
Men	1.38	1.19–1.61	<0.001
Women	1.02	0.87–1.19	NS
Model 2			
Overall	1.13	0.95–1.36	NS
Men	2.66	1.41–5.01	0.003
Women	1.05	0.81–1.36	NS

NS is not significant. Proteinuria and hematuria are grouped into six groups by the results of dipstick urinalysis as (−), (±), (1+), (2+), (3+), and (4+). Variables in model 1 were age, gender, systolic and diastolic blood pressure, and body mass index and variables in model 2 were the variables in model 1 plus serum creatinine. The study period was from April 1983 to December 2000.

Table 4. Results of multivariate analysis on the risk of developing end-stage renal disease (ESRD) based on the degree of proteinuria by dipstick urinalysis

Variables	OR	95% CI	*P* value
Men			
Proteinuria (−)	1.00		
Proteinuria (±)	1.77	1.13–2.78	0.012
Proteinuria (1+)	1.93	1.53–2.41	<0.001
Proteinuria (2+)	2.95	2.59–3.37	<0.001
Proteinuria (3+)	2.60	2.28–2.96	<0.001
Proteinuria (4+)	2.56	1.51–4.34	0.001
Women			
Proteinuria (−)	1.00		
Proteinuria (±)	1.34	0.74–2.41	NS
Proteinuria (1+)	2.42	1.91–3.06	<0.001
Proteinuria (2+)	2.66	2.26–3.14	<0.001
Proteinuria (3+)	2.81	2.45–3.22	<0.001
Proteinuria (4+)	3.43	2.21–5.31	<0.001

NS is not significant. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated with adjustment for age, hematuria, systolic blood pressure, diastolic blood pressure, and body mass index. The study period was from April 1983 to December 2000.

stick urinalysis was measured on only one occasion, resulting in an underestimation of the strength of the association of ESRD with proteinuria and hematuria. An average value, determined from measurements taken on multiple occasions, would yield greater differences in the incidence of ESRD associated with abnormal urinalysis. We were not certain of the causes of proteinuria in this study. Even in patients with benign nephrosclerosis, significant rates of proteinuria were observed. Transient proteinuria was reported to be 4% in men and 8% in women, with resolution on subsequent examination [25]. Renal function was not measured at baseline, except in the serum creatinine subgroup. Serum creatinine was measured in about 14% of the screened population. The reasons for serum creatinine measurement in this screening are not known. The test may have possibly been ordered by physicians, or the subjects requested it because of concerns about abnormal kidney function. However, the percentage of abnormally high serum creatinine of ≥2.0 mg/dL have been as low as 0.28% in 1983 (N = 14,609) and 0.15% in 1992 (N = 91,033) in this screening program. The type of primary renal disease in the ESRD of the screened individuals was slightly different from that of the entire ESRD population in Okinawa during the study period. Of the screened individuals, 23.8% had ESRD caused by diabetes mellitus, whereas the rate of ESRD caused by diabetes mellitus in the entire popula-

Table 5. Results of multivariate analysis on the risk of developing end-stage renal disease (ESRD) based on the degree of hematuria by dipstick urinalysis

Variables	OR	95% CI	*P* value
Men			
Hematuria (−)	1.00		
Hematuria (±)	1.38	0.96–1.96	NS
Hematuria (1+)	1.73	1.39–2.15	<0.001
Hematuria (2+)	1.45	1.14–1.84	0.002
Hematuria (3+)	1.02	0.70–1.48	NS
Hematuria (4+)	NA		
Women			
Hematuria (−)	1.00		
Hematuria (±)	0.67	0.45–1.00	NS
Hematuria (1+)	0.76	0.56–1.04	NS
Hematuria (2+)	1.16	0.97–1.40	NS
Hematuria (3+)	1.04	0.79–1.35	NS
Hematuria (4+)	2.66	1.51–4.67	0.001

NS is not significant. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated with adjustment for age, urinalysis, systolic blood pressure, diastolic blood pressure, and body mass index. NA was not assessed because no men tested for hematuria (4+). The study period was from April 1983 to December 2000.

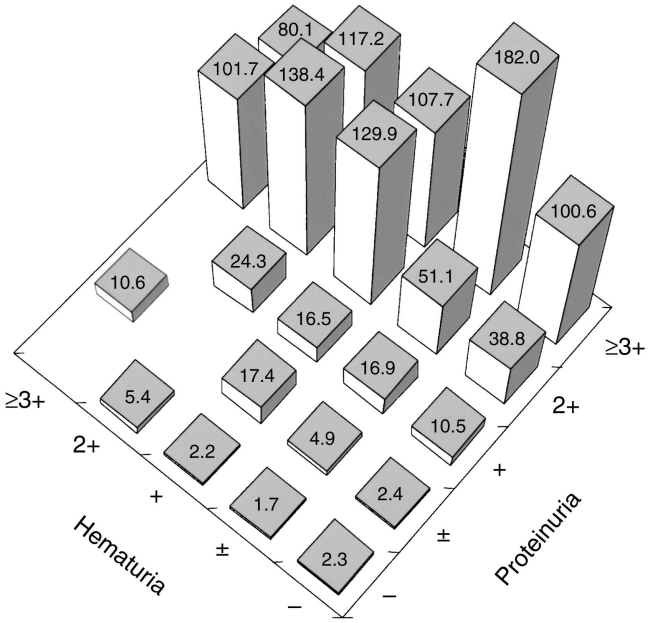

Fig. 4. Rate of end-stage renal disease (ESRD), per 1000 in 17 years of follow-up, adjusted for age and gender by the results of dipstick measurement for proteinuria and hematuria. The study period was from April 1983 to December 2000.

tion was 33.7% during this study period. Unfortunately, data for glycosuria and fasting blood glucose were not available in the 1983 screening. We also have no information regarding the onset of urinary tract malignancies and kidney stone disease in this cohort. The incidence and prevalence of ESRD are high in Okinawa, yet the reasons for this are not clear. Regional variations in the incidence and prevalence of ESRD are increasingly recognized; therefore, our results may need to be confirmed in other regions or countries.

Economic and social burdens of ESRD are increasing as patient age or become ill. Identification of modifiable risk factors such as hypertension and proteinuria may alert subjects at risk of developing ESRD to appropriately modify their lifestyles or seek treatment to prevent ESRD. The present study showed epidemiologic evidence supporting the significance of dipstick urinalysis for proteinuria as a way to predict ESRD. However, the costs and benefits to those with proteinuria of (±) or (1+) need to be examined by further analysis.

ACKNOWLEDGMENTS

Parts of this study were supported by grants from the Ministry of Health and Welfare of Japan. We are indebted to the staff of the Okinawa General Health Maintenance Association, in particular to Mr. M. Itokazu and Mr. K. Shiroma for retrieving data files from the 1983 health check. The authors are grateful for the collaboration of the physicians and co-medical staff of all the dialysis units in Okinawa. The following doctors gave us invaluable advice, support, and encouragement: Drs. T. Minei, T. Kowatari, K. Nishime, H. Ogimi, T. Yonaha, C. Mekaru, K. Kinjo, M. Nakayama, H. Uehara, H. Sunagawa, S. Nakasato, Y. Oshiro, N. Kuwae, T. Wake, M. Arakaki, S. Yoshi, S. Miyagi, K. Tokuyama, I. Kyan, Y. Uezu, T. Hokama, S. Kiyuna, H. Henzan, T. Asato, Y. Nakasone, Y. Shiohira, K. Higa, T. Miyagi, H. Afuso, F. Miyasato, S. Maeshiro, T. Sakuda, H. Momozono, T. Asato, M. Ikemura, T. Taminato, Y. Oshiro, M. Yamasato, T. Izumi, T. Oura, S. Toma, T. Sunagawa, T. Funakoshi, S. Terukina, T. Oyama, Y. Chinen, Y. Oshiro, K. Nakama, K. Nakao, O. Shiranezawa, K. Nagasawa, H. Uchima, T. Higa, A. Higa, K. Yoshihara, M. Maeshiro, S. Miyagi, T. Kinjo, M. Ishu, H. Yoshimura, Y. Arakaki, N. Nakamura, H. Kinjo, O. Shinjo, T. Nakanishi, I. Shiroma, S. Shiroma, K. Ishikawa, K. Nagata, K. Akamine, T. Tana, S. Oshiro, N. Tomiyama, K. Kohagura, H. Muratani, Professor Y. Ogawa, ex-Prof. A. Osawa, and ex-Prof. K. Fukiyama. The authors are grateful to Dr. O. Morita for helping with data processing and statistical analysis.

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