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Risk of developing end-stage renal disease in a cohort of mass screening

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Risk of developing end-stage renal disease in a cohort of mass screening. The prognostic significance of abnormal findings has not been demonstrated in a setting of mass screening. To evaluate the relative risk of end-stage renal disease (ESRD) indicated by various results of community-based mass screening, we utilized the registries of both community mass screening and chronic dialysis programs. In 1983, a total of 107,192 subjects over 18 years of age (51,122 men and 56,070 women) participated in dipstick urinalysis and blood pressure measurement in Okinawa, Japan. During ten years of follow-up, we identified 193 dialysis patients (105 men and 88 women) among them. Logistic regression analysis of clinical predictors of ESRD over 10 years was done and the adjusted odds ratio and 95% confidence interval were calculated in each of the predictors with adjustment to others. In the clinical predictors such as sex, age at screening, proteinuria, hematuria, systolic and diastolic blood pressure, proteinuria was the most potent predictor of ESRD (adjusted odds ratio 14.9, 95% confidence interval 10.9 to 20.2), and the next most potent predictor was hematuria (adjusted odds ratio 2.30, 95% confidence interval 1.62 to 3.28). Being of male gender was a significant risk factor for ESRD (adjusted odds ratio 1.41, 95% confidence interval 1.04 to 1.92). Diastolic blood pressure was also a significant predictor of ESRD (adjusted odds ratio 1.39, 95% confidence interval 1.17 to 1.64), but systolic blood pressure was not. In a mass screening setting, positive urine test, high diastolic blood pressure, and male sex were identified as the significant predictors of ESRD. Effect of glycosuria and other possible predictors of ESRD remained to be determined.

The frequency of end-stage renal disease (ESRD) is increasing, yet the reasons are not clear [1, 2]. The social burden of ESRD is becoming heavier, and therefore it is an urgent matter to reduce the occurrence of ESRD or to retard the progression of renal failure. Mass urine screening using the dipstick test is widely used, and it often provides the first clue in the detection of renal disease. The natural course of the disease progression has been reported in specific groups of patients with renal diseases, such as biopsy proven glomerulonephritis [3] and insulin-dependent diabetes mellitus [4, 5], but the prognostic significance of abnormal mass urine screening test findings is largely unknown, and few studies in a large population [6] have been conducted. Other than those with proteinuria, it is still debatable whether all confirmed cases of occult hematuria should be fully investigated. Moreover, little or no relevant data have been acquired through prospective observational studies on the relationship of blood pressure with renal failure [7].

ESRD is not a specific disease entity, but rather provides a framework for the consideration of treatment options. In Okinawa, Japan, the criteria for acceptance for chronic dialysis have been quite open, and the proportion of the patients who transfer to other parts of Japan is quite small [2]. Therefore, Okinawa is an appropriate place to conduct an epidemiological study in terms of the heterogeneity and low mobility of chronic dialysis.

In this study, the incidence and the relative risk of ESRD were determined by using the community-based registries for both the mass urinalysis screening and the chronic dialysis patients. The public health implications of the results are discussed from the perspective of ESRD preventive strategies.

Methods

Study design

All individuals over 18 years of age who participated in the 1983 mass health screening examinations in Okinawa, Japan were eligible for the study. Okinawa is made up of 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 the data for birth date or the result of dipstick urinalysis were not available in the computer data file. Dialysis patients who had been among the 1983 mass screening participants who had become dialysis patients during the study period, up until March 31, 1994, were identified by using the Okinawa Dialysis Study (OKIDS) registry, which covers the same entire geographic area. Furthermore, their identity was verified by reviewing the medical records in the dialysis units. The cumulative incidence of ESRD and the relative risk of ESRD according to specific results of the mass screening were determined.

Mass screening registry

The large community-based health examination program is performed annually by the Okinawa General Health Maintenance Association, under the direction of Dr. Y. Ikemiya. The association is a non-profit organization 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 area of Okinawa, including 55 local residential areas such as villages, towns and cities and 864 sites organized around individual workplaces or units such as government offices, businesses, banks, worker's unions and so on. They provide the mass screening

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examinations and inform the participants as to the results and, when necessary, recommend further examination. The examination includes an interview regarding the health status, physical examinations, the urine test, and blood tests. Blood pressure is measured by a nurse or doctor using a standard mercury sphygmomanometer. Dipstick urinalysis (Ames dipstick) is performed using the spontaneously voided fresh urine, morning or afternoon. Screeners are instructed to provide a mid-stream urine sample. 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 as abnormal. Other abnormal urine test results were categorized into the three groups of hematuria only, proteinuria only, and combined hematuria and proteinuria. Data for glycosuria were incomplete; therefore, this analysis was not conducted in this study.

The computer-based data include data acquired since 1983, for the fiscal year from April 1, 1983 through March 31, 1984. Included are the name of the screenee, birth date, sex, zip code, employment group code, residential code, and the results of clinical and laboratory tests. A total of 116,283 inhabitants over 18 years of age received the urine screening test in 1983. Among them, 5,137 participants (4.4% of the total) had data for the birth dates which were missing or incomplete. A total of 3,954 participants (3,283 men and 671 women) had received the urine test more than twice in 1983. In these cases, we used only the first data set. Thus, 3,600 men and 5,491 women were excluded. Therefore, the present analysis was conducted in a total of 107,192 participants (51,122 men and 56,070 women; Table 1). According to the 1980 Census, the total population of Okinawa over 15 years of age was 781,166 (377,479 men and 403,687 women). Therefore, the estimated proportion of the adult population over 18 years of age in 1983 who participated in the mass screening was about 13.7% (13.6% in men and 13.9% in women). In men, the estimated proportion of the general population in each age group who participated was as follows: 7.2% in those aged 18 to 29 years, 13.3% in those aged 30 to 39 years, 15.4% in those aged 40 to 49 years, 16.8% in those aged 50 to 59 years, 22.1% in those aged 60 to 69 years, 22.2% in those aged 70 to 79 years, and 14.2% in those aged 80 years and over. In women, it was 5.7% in those aged 18 to 29 years, 10.4% in those aged 30 to 39 years, 15.1% in those aged 40 to 49 years, 20.3% in those aged 50 to 59 years, 25.5% in those aged 60 to 69 years, 23.8% in those aged 70 to 79 years, and 11.6% in those aged 80 years and over.

Data for blood pressure at the screening were available in 104,331 screenees (54,855 women and 49,476 men). Table 1 shows the frequency distribution of the screenees at each blood pressure level. Information regarding the use of antihypertensives was not available.

Dialysis registry

In an independent program, all chronic dialysis patients in Okinawa have been registered since 1971. The acceptance policy for chronic dialysis has been quite open and does not exclude patients with diabetes mellitus and the elderly. The number of dialysis patients is steadily increasing, and the annual acceptance rate has been more than 160 per million population since 1988. Only patients with end-stage renal disease and those who have survived at least one month on scheduled dialysis were registered for the study. The characteristics and other epidemiological features of the patients enrolled in this registry have been reported previously [2, 8, 9].

Table 1. Demographics of the 1983 mass screening participants

	Number of screeners %	
	Men (N = 51,122)	Women (N = 56,070)
Age at screening *years*		
18–29	7,832 (15.3)	6,038 (10.8)
30–39	11,714 (22.9)	8,555 (15.3)
40–49	11,212 (21.9)	10,633 (19.0)
50–59	8,605 (16.9)	11,572 (20.5)
60–69	6,589 (12.9)	10,461 (18.7)
70–79	3,949 (7.7)	6,605 (11.8)
80+	1,221 (2.4)	2,206 (3.9)
Results of urine test		
Normal	45,719 (89.4)	46,800 (83.5)
Abnormal	5,403 (10.6)	9,270 (16.5)
Proteinuria only	2,421 (4.7)	1,965 (3.5)
Hematuria only	1,444 (2.8)	6,166 (11.0)
Proteinuria and hematuria	339 (0.7)	753 (1.3)
Other combinations	1,199 (2.3)	396 (0.7)
Systolic blood pressure *mm Hg*		
No data	1,646 (3.2)	1,215 (2.2)
≤119	10,254 (20.1)	17,700 (31.6)
120–129	12,618 (24.7)	11,409 (20.3)
130–139	10,872 (21.3)	8,773 (15.6)
140–149	7,396 (14.5)	7,071 (12.6)
150–159	3,930 (7.7)	4,478 (8.0)
160+	4,406 (8.6)	5,424 (9.7)
Diastolic blood pressure		
No data	1,653 (3.2)	1,220 (2.2)
≤69	5,325 (10.4)	10,490 (18.7)
70–79	14,862 (29.1)	17,951 (32.0)
80–89	17,497 (34.2)	16,420 (29.3)
90–99	8,685 (17.0)	7,522 (13.4)
100–109	2,361 (4.6)	1,893 (3.4)
110+	739 (1.4)	574 (1.0)

Percents may not add up to 100 because of rounding. Screening was performed from April 1, 1983 to March 31, 1984.

Statistical analysis

Two methods (the unpaired t-test and the equivalent nonparametric test, the Wilcoxon rank-sum test) were used to compare continuous variables, and Fisher's exact test was used for comparison between the groups of discrete variables. Screenees of the 1983 mass health examination were categorized according to the results of the urine test and the levels of blood pressure. The cumulative incidence was calculated as the ratio of the number of dialysis patients to the number of screenees at risk and expressed per 100,000 persons. The relative risk was calculated by dividing the incidence rate by the corresponding rate in the reference category. Age-adjusted rates were calculated for age and other variables simultaneously with proportional-hazard analysis using the SAS model [10, 11]. The dependent variable in this model was binary, that is, dialysis or non-dialysis status as of the end of the observation period. For all relative risks we calculated 95% confidence limits. Pearson correlation coefficients were calculated to examine the linear trends. Data are expressed as mean ± SD.

Results

Screening registry

The relationship between the age at urine test and the incidence of abnormal urine findings is shown in Figure 1 (men) and in

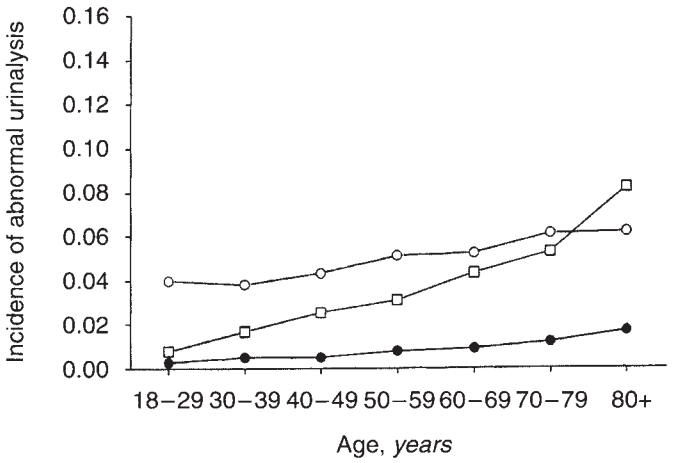

Fig. 1. *Relationship between age and the incidence of urinary abnormality in men.* The incidence of each of hematuria (–□–), proteinuria (–○–), and combined hematuria and proteinuria (–●–) increased significantly with age.

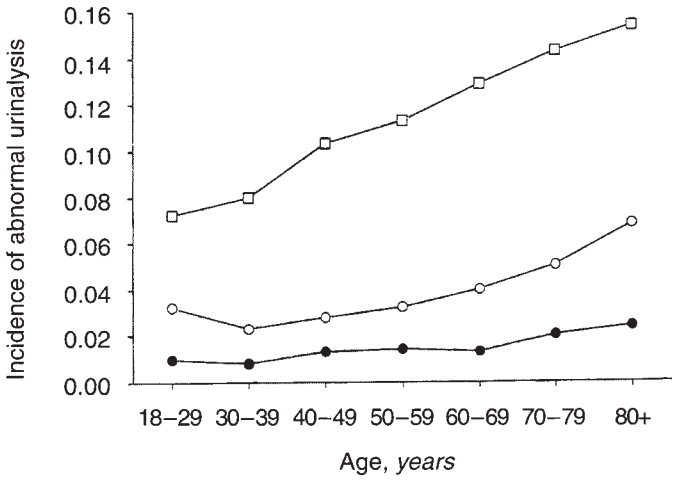

Fig. 2. *Relationship between age and the incidence of urinary abnormality in women.* The incidence of hematuria (–□–) was higher than that in men and increased sharply with age. The incidence of both proteinuria (–○–) and combined hematuria and proteinuria (–●–) increased significantly with age.

Figure 2 (women). In men, the incidence of hematuria increased linearly with age, from 0.9% in the 18 to 29-year age group to 8.2% in those 80 years and over ($r = 0.890$, $P < 0.01$). The incidence of both proteinuria and combined hematuria and proteinuria also increased linearly with age ($r = 0.790$, $P < 0.01$ and $r = 0.790$, $P < 0.02$, respectively). In women, the incidence of hematuria was higher than that in men in every age class ($P < 0.001$). It increased linearly from 7.3% in those 18 to 29 years old to 15.3% in those aged 80 years or more ($r = 0.899$, $P < 0.001$). The incidence of both proteinuria and combined proteinuria and hematuria increased significantly with age ($r = 0.890$, $P < 0.01$ and $r = 0.888$, $P < 0.01$, respectively), and the incidence of proteinuria in men was significantly higher than that in women ($P < 0.01$).

In men, the mean systolic and diastolic blood pressures were distributed as follows: 123.8 mm Hg and 75.0 mm Hg (aged 18 to 29); 125.5 mm Hg and 78.9 mm Hg (aged 30 to 39); 130.3 mm Hg and 82.8 mm Hg (aged 40 to 49); 135.6 mm Hg and 83.0 mm Hg (aged 50 to 59); 138.8 mm Hg and 81.1 mm Hg (aged 60 to 69); 141.6 mm Hg and 79.7 mm Hg (aged 70 to 79); and 140.4 mm Hg and 77.8 mm Hg (aged 80 and over). In women, the mean systolic and diastolic blood pressure were distributed as follows: 113.0 mm Hg and 68.8 mm Hg (aged 18 to 29); 115.9 mm Hg and 72.2 mm Hg (aged 30 to 39); 124.5 mm Hg and 77.4 mm Hg (aged 40 to 49); 132.0 mm Hg and 80.2 mm Hg (aged 50 to 59); 136.9 mm Hg and 80.0 mm Hg (aged 60 to 69); 142.1 mm Hg and 80.1 mm Hg (aged 70 to 79); and 144.6 mm Hg and 79.6 mm Hg (aged 80 and over).

Dialysis patients

A total of 2,009 patients who were over 18 years of age in 1983 (1,126 men and 883 women) started chronic dialysis between April 1, 1984 and March 31, 1994 (Table 2). The distribution of primary renal disease in total was as follows: chronic glomerulonephritis 51%; diabetes mellitus 28.5%; polycystic kidney disease 2.0%; systemic lupus erythematosus 1.9%; nephrosclerosis 8.2%; and others 8.4%. Among them, a total of 193 dialysis patients, 105 men and 88 women, were identified through the screening registry by the 10-year follow-up (Table 2). The 22 case dialysis patients with other renal diseases had chronic interstitial nephritis ($N = 5$), rheumatoid arthritis ($N = 6$), hydronephrosis and urological abnormalities ($N = 8$), and other unknown renal disease ($N = 3$).

Risk of ESRD

Table 3 shows the result of the logistic regression analysis on the risk of development of ESRD according to sex, age, urine test result, and blood pressure. The adjusted odds ratio (95% confidence interval) in men was 1.41 (1.04 to 1.92) compared to women. The strong predictive power of ESRD was shown in both proteinuria (the odds ratio 14.9 and 95% confidence interval 10.9 to 20.2) and hematuria (the odds ratio 2.30 and 95% confidence interval 1.62 to 3.28). Risk profile of ESRD by dipstick reading was 1.0 (1+), 7.6 (2+), 16.1 (3+), and 19.5 (4+), respectively. Risk of ESRD increased with both the systolic and diastolic blood pressure level, even though most of the screenees showed blood pressure in the normal range. Compared to the risk when the diastolic blood pressure was less than 69 mm Hg, the odds ratio (95% confidence interval) was 1.39 (1.17 to 1.64) in 10 mm Hg increments.

The relationship between the cumulative incidence of ESRD and the duration after the screening for each of the risk factors of gender, dipstick urinalysis result, and diastolic blood pressure is shown in Figures 3, 4, and 5, respectively.

Discussion

The cumulative incidence of ESRD was 180 per 100,000 persons in the 1983 screening participants. During the follow-up period, a total of 2,009 patients began chronic dialysis therapy, and the estimated incidence of ESRD was 257 per 100,000 persons in the general population in Okinawa. This difference in the incidence could be explained either by expressing rates of ESRD based on the original screening participants rather than person years or in terms of the nature of the screening test. Those who had hypertension, proteinuria, and older aged participants may have died before reaching ESRD. Those individuals with morbid conditions, who were hospitalized, or were regularly

Table 2. Demographics of the dialysis patients who began chronic dialysis between April 1, 1984 and March 31, 1994 and the case dialysis patients who had participated in the screening in 1983

	Total ESRD patients		Case dialysis patients	
	Number of patients %			
	Men	Women	Men	Women
	1,126 (56.0)	883 (44.0)	105 (54.4)	88 (45.6)
Age at start of dialysis *years*				
18–29	74 (6.6)	49 (5.5)	3 (2.9)	1 (1.1)
30–39	175 (15.5)	99 (11.2)	15 (14.3)	1 (1.1)
40–49	204 (18.0)	121 (13.7)	14 (13.3)	11 (12.5)
50–59	270 (24.0)	175 (19.8)	19 (18.1)	13 (14.8)
60–69	241 (21.4)	218 (24.7)	24 (22.8)	27 (30.7)
70+	162 (14.5)	221 (25.1)	30 (28.6)	35 (39.8)
Primary renal disease				
Chronic glomerulonephritis	606 (53.8)	418 (47.3)	60 (57.1)	50 (56.8)
Diabetes mellitus	310 (27.5)	263 (29.8)	17 (16.2)	19 (21.6)
Polycystic kidney disease	23 (2.0)	17 (1.9)	3 (2.9)	1 (1.1)
Systemic lupus erythematosus	11 (1.0)	27 (3.1)	1 (1.0)	1 (1.1)
Nephrosclerosis	94 (8.3)	71 (8.0)	12 (11.4)	7 (8.0)
Other renal disease	82 (7.3)	87 (9.9)	12 (11.4)	10 (11.4)

Table 3. Logistic regression analysis of clinical predictors of end-stage renal disease over 10 years among the participants of the mass screening on 1983 in Okinawa, Japan

Prognostic factor	Odds ratio (95% confidence interval)	
	Not adjusted	Adjusted[a]
Male (vs. female)	1.31 (0.99–1.74)	1.41 (1.04–1.92)
Age (vs. 18–39 years) 10 year increments	1.25 (1.14–1.37)	1.11 (0.99–1.24)
Proteinuria (vs. normal)	22.9 (17.2–30.6)	14.9 (10.9–20.2)
Hematuria (vs. normal)	2.30 (1.72–3.07)	2.30 (1.62–3.28)
Systolic blood pressure (vs. less than 119 mm Hg) 10 mm Hg increments	1.51 (1.39–1.65)	1.10 (0.96–1.26)
Diastolic blood pressure (vs. less than 69 mm Hg) 10 mm Hg increments	1.88 (1.68–2.11)	1.39 (1.17–1.64)

[a] Adjusted for other prognostic factors.

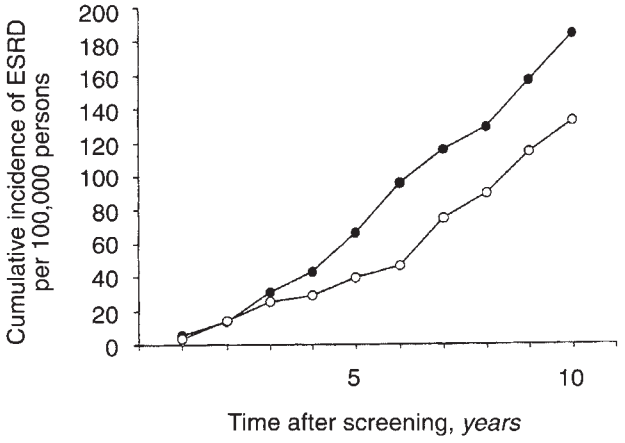

Fig. 3. *Relationship between the cumulative incidence of ESRD and the duration from the mass screening, in years, is shown in each sex.* Symbols are: (–●–) men; (–○–) women.

visiting medical facilities would not participate in the mass screening. This could also be a reason that the frequency of participation by individuals aged 80 years and over was low. Younger individuals may be relatively less concerned about their health status or may be too busy with activities to come to the mass screening. In contrast to the observations of Simon et al [12] the patients in our dialysis registry had a low incidence of renal biopsy, therefore the diagnosis of renal disease may not have been accurate. In a reported population-based study, among patients with non-insulin dependent diabetes mellitus (DM) who did not have persistent proteinuria when DM was diagnosed, 0.3% had developed chronic renal failure within 10 years [13]. This incidence is five times higher than that in the screening participants in our study who had negative urinalysis results. The annual incidence of systemic lupus erythematosus in Okinawa [14] has been stable for the past 20 years at around 30 new cases each year per million population. Similarly, the frequency of systemic lupus erythematosus was about 1.0% in both the total dialysis and the case dialysis patients.

Dipstick urinalysis is probably the most commonly performed screening test [15, 16]. To our knowledge, this is the first study which attempted to address the issue of the relationship between the dipstick urinalysis result and the subsequent incidence of ESRD. The results strongly support the concept that proteinuria and hematuria have prognostic significance. In this study, we used only one dipstick urinalysis for each participant, and the exact rates of false-positive or false-negative results were not known. However, the risk profile of ESRD was dependent on the result of dipstick urinalysis and it increased sharply from dipstick (2+). Those who had dipstick (1+) or (±) have a slightly higher, but significant, risk of ESRD compared to those with dipstick (−). Therefore, confirmation of the clinical proteinuria [17] should be obtained by multiple dipstick urinalysis. Microalbuminuria is a predictor of nephropathy in insulin-dependent diabetes mellitus and essential hypertension. Obviously, dipstick positive result indicates a level of proteinuria which is an even higher concentration than the level of microalbuminuria. Proteinuria could be a marker of organ damage of the kidney. It has been suggested that the magnitude of proteinuria itself may be associated with the rate of progression of kidney damage [18].

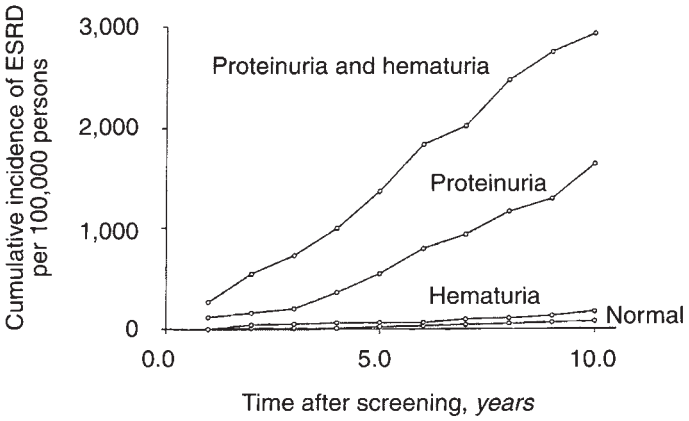

Fig. 4. *Relationship between the cumulative incidence of ESRD and the duration from the mass screening, in years, is shown according to the results of the mass screening urinalysis.*

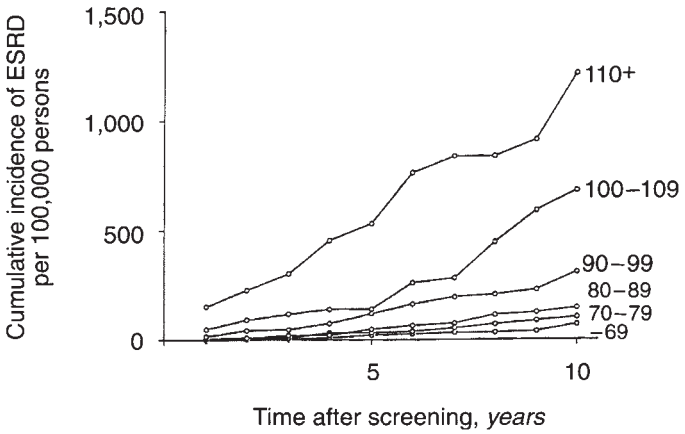

Fig. 5. *Relationship between the cumulative incidence of ESRD and the duration after the mass screening is shown according to the diastolic blood pressure level.* Diastolic blood pressure levels (mm Hg) are indicated at the far right of the figure.

The prognostic value of hematuria was smaller than that of the proteinuria, although it was significant. The test result for women of menstrual age may be false-positive because of contamination of the urine by menstrual blood. The incidence of hematuria increased with age in both men and women. A result indicating hematuria can be caused by the presence of oxidizing agents or myoglobin, contamination of the specimen, or hemolysis in hypotonic urine. The sensitivity of the dipstick urinalysis for hematuria is 75.3% and the specificity is 88.6% when microscopic hematuria is used as the gold standard [19].

The predictive value of glycosuria was not examined in this study. The fraction of ESRD due to DM was lower than that of the general population (Table 2). This could be due to the selection bias in this cohort or the rapid change in acceptance rate for chronic dialysis. The annual acceptance rate of DM dialysis patients was 21.7 per million population in 1984, and it increased to 76.0 per million population in 1994.

ESRD showed higher risk and earlier development in men compared to women. This was not due to the difference in the incidence of the urinary abnormalities and the levels of blood pressure. Such gender difference in disease progression was also observed in a more focused renal biopsy study [20, 21] and has been noted in autosomal dominant polycystic kidney disease [22]. Primary glomerular disease occurs more frequently in men than women. We have also noted that among patients with lupus nephritis the renal survival in men is poorer than that in women [14]. In an animal study, testosterone and other sex-related hormones were found to be involved in the sex-related differences in proteinuria and glomerulosclerosis [23]. A preponderance of men in renal replacement therapy has been noted worldwide, and sex discrimination in acceptance for dialysis, if present, would not be marked enough to explain the difference. Recently, it was estimated that acquired obstruction is responsible for 3 to 5% of all new cases of ESRD in patients over the age of 65 years, due most often to prostatic disease in men [24].

We noted that the incidence of ESRD increased sharply with age in both sexes. It is well-known that the average age of new dialysis patients is increasing [2]. Although the incidence of urinary abnormalities showed a linear increase with age, it did not seem high enough to account for the increased risk of ESRD. In fact, age *per se* was not identified as a significant predictor of ESRD. Such results support the concept of the importance of other risk factors such as dehydration, drugs [25], infection, and nutrition. In the long-term prognosis of IgA nephropathy, for instance, immunologic factors have been found to have little influence, and hypertension, arteriosclerosis, and aging were found to be more important [26]. Both cross-sectional [27] and longitudinal studies [28] clarified that the systolic blood pressure rises progressively throughout the course of life and that the diastolic blood pressure shows a decline after age 50 to 60 in the general population in Westernized cultures. Little or no relevant data are available from prospective observational studies of the relationship of blood pressure with renal failure [29, 30]. In the Modification of Diet in Renal Disease (MDRD) Study [31], a benefit of low blood pressure in patients with urinary excretion exceeding 1 g per day was shown, but not in patients with 1 g or less per day. Our results clearly revealed that high diastolic blood pressure is an independent predictor of ESRD.

Information regarding the medical response to the detection of positive urine tests and/or high blood pressure at the screening was limited. However, judging from the records for the case dialysis patients, we think that most of them were left untreated or were not regularly followed by a nephrologist. Whether closer follow-up would have been beneficial in these patients remains unknown. However, Bergstrom et al [32] found that more frequent and better quality of the clinical management of the patients seems to slow the progression of renal failure. In diabetic nephropathy, Lewis et al [33] reported the beneficial effect of converting enzyme inhibitor to retard the progression of renal failure. In contrast, most specific therapeutic regimens for glomerulonephritis except fish oil [34] have not been demonstrated to be effective in controlled trials.

In summary, the independent predictive factors for the development of ESRD in the setting of the mass screening tests identified in this study were positive dipstick urinalysis test result, proteinuria or hematuria, and high diastolic blood pressure. Men are at higher risk of ESRD, regardless of the result of the dipstick urinalysis or blood pressure. The public health implications and

the effects of other possible predictors of ESRD such as glycosuria, smoking, alcohol intake, hypercholesterolemia, and hyperuricemia, deserve further investigation.

Acknowledgments

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