The Okinawa Screening Program

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Abstract. Predictors of ESRD were identified using independent registries of both ESRD patients and the general population in Okinawa, Japan. Besides male gender, we found that the significant predictors of ESRD to be proteinuria, hematuria, and hypertension, especially diastolic BP. Among the laboratory findings, a high serum creatinine level was shown to be a strong predictor of ESRD. The effects of age, obesity, and hypercholesterolemia were insignificant, but this needs to be confirmed in a larger cohort and other registries.

The number of ESRD patients requiring chronic dialysis is increasing worldwide. In Japan, a high incidence and prevalence of ESRD has been reported in Okinawa, the island prefecture in the southernmost part of the country (1,2). Since 1971, all chronic dialysis patients treated in Okinawa from the start of therapy have been entered into a registry, and the ESRD trends over the past 30 yr have recently been published (1). For geographic and cultural reasons, ESRD patients in Okinawa tend not to move away (3,4). Therefore, Okinawa provides a good population in which to study the outcomes of ESRD and cardiovascular disease (3,4). Understanding the process of disease progression is necessary in determining strategies for the prevention of ESRD.

We are fortunate to have access to independent registries for ESRD patients (5), the general population (6,7), and all hospital-based records of stroke and acute myocardial infarction (AMI) (3) in Okinawa. In this paper, we have identified predictors for ESRD using these registries.

Materials and Methods
Study Design
Data from three independent registries covering the entire area of Okinawa were accessed: the ESRD program (5), the screening program of the Okinawa General Health Maintenance Association (OGHMA) (6–11), and the hospital-based registry of stroke and AMI (3). The start date of chronic dialysis was used as the date of onset of ESRD in individual patients. The 1983 screening participants and the individuals who had become dialysis patients from April 1983 to March 1994 were identified by using the dialysis registry, which covers the entire geographic area. The identities of these dialysis patients were verified by reviewing their medical charts in the dialysis units.

ESRD Patient Registry
All chronic dialysis patients who survive at least 1 mo on scheduled dialysis are included in the Okinawa Dialysis Study (OKIDS) registry. Patients dying within 1 mo from the start of dialysis are not included in the registry because it cannot be determined whether renal function in these patients has been improving or deteriorating or whether other medical conditions accounted for their rapid demise. Pertinent clinical data were obtained for all new dialysis patients, and important medical events recorded in the files of chronic dialysis patients were noted. Data were obtained under collaboration with physicians in all dialysis units. In 1990, there were 27 dialysis units in Okinawa; by the end of 2000, there were 46: nine in the public sector, 17 in private hospitals, and 20 in clinics.

The OGHMA Screening Program
A large, community-based health examination is conducted annually by the OGHMA, a nonprofit organization founded in 1972. Once each year, the doctors, nurses, and staff of the association visit sites throughout Okinawa where people reside or are employed. They provide medical examinations, inform the participants of the results, and, when necessary, recommend further examination. The screening includes an interview regarding general health status, a physical examination, a urine test, and blood tests. A nurse or doctor measures BP using a standard mercury sphygmomanometer. Dipstick urinalysis is performed in spontaneously voided fresh urine. The results of the urine test are interpreted by the physicians or their associates and are recorded as (−), (±), (1+), (2+), (3+), and (4+). We defined results recorded as (−) and (±) as normal and the rest as abnormal. Computer-based data were available from April 1, 1983, through March 31, 1984, for the fiscal year of 1983. The total number of screening program participants was 107,192, approximately 13.7% of the population of all individuals over 18 yr of age in Okinawa. In a subgroup of screened subjects, data for serum creatinine (n = 14,609) and serum cholesterol (n = 38,053) were known. Data for BP at the screening were available in 104,331 screeneees (54,855 women and 49,476 men). Information regarding the use of antihypertensive medications, presence of chronic renal disease, family history of chronic renal disease, hypertension or diabetes mellitus, and the history of acute myocardial infarction or stroke were not available.

The OGHMA runs a 1-d “dry dock” clinic program. Participants in this program visit the OGHMA clinic. In 1997, there were 9,914 dry dock participants. Screenees responded to a questionnaire pertaining to lifestyle issues including smoking, alcohol consumption, and exercise habits. They also provided information regarding medical history and current medications (12–14). Body mass index (BMI) was calculated as body weight in kilograms divided by height squared in meters (kg/m2). Hypertension was defined as systolic BP (SBP) ≥140 mmHg, diastolic BP (DBP) ≥90 mmHg, or the use of anti-hypertensive drugs. Diabetes mellitus was diagnosed if the fasting blood
glucose level was $\geq 126$ mg/dl (7 mmol/L), the HbA1c was $\geq 7.0\%$, or the subjects were under diabetes mellitus therapy. All subjects fasted overnight before blood sampling. Questionnaire responses were discussed during the physical examination, and a physician further interviewed the subjects. Screenees who were already on chronic dialysis were excluded from the study.

**Hospital-Based Stroke and AMI Registry**

To determine the effect of previous stroke and AMI on the risk of developing ESRD, we retrospectively surveyed the hospital-based registry. This registry contains information regarding all patients who have suffered stroke and AMI in Okinawa (3). The Co-operative Study Group of Morbidity and Mortality of cardiovascular diseases in Okinawa (COSMO) registry recorded all hospital cases of stroke and AMI that occurred in Okinawa during the 3-yr period from April 1, 1988, through March 31, 1991. Whether the survivors of stroke or AMI entered a dialysis program was determined by checking both the COSMO registry and the OKIDS registry. Those already in an ESRD dialysis program at the time of their event were excluded. The study period was from April 1988 through December 1999. The COSMO registry listed 747 patients with AMI and 3809 patients with stroke who survived at least 28 d after onset of the event.

**Statistics**

The cumulative incidence of ESRD was calculated as the ratio of the number of dialysis patients to the number of screenees at risk for ESRD. All relative risks of ESRD were adjusted for age, SBP, DBP, proteinuria, and hematuria using the SAS model.

**Results**

**Participants in the 1983 Mass Screening**

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 yr, 13.3% in those aged 30 to 39 yr, 15.4% in those aged 40 to 49 yr, 16.8% in those aged 50 to 59 yr, 22.1% in those aged 60 to 69 yr, 22.2% in those aged 70 to 79 yr, and 14.2% in those aged 80 yr and older. In women, it was 5.7% in those aged 18 to 29 yr, 10.4% in those aged 30 to 39 yr, 15.1% in those aged 40 to 49 yr, 20.3% in those aged 50 to 59 yr, 25.5% in those aged 60 to 69 yr, 23.8% in those aged 70 to 79 yr, and 11.6% in those aged 80 yr and older. The incidence of hematuria increased linearly with age in men from 0.9% at age 18 to 29 yr to 8.2% at 80 yr and older. This trend was also observed in women; the incidence of hematuria increased with age from 7.3% at 18 to 29 yr to 15.3% at 80 yr and older. Similarly, the incidence of proteinuria increased linearly with age in men from 4% at 18 to 29 yr to 6% at 80 yr and older and women, from 3% incidence at 18 to 29 yr to 7% at 80 yr and older. The incidence of proteinuria and hematuria combined was less than 2% in all age groups for both genders (6). The prevalence of hypertension was 35.8% (7). The prevalence of elevated serum creatinine, $\geq 2.0$ mg/dl, for both genders remained at around 0.2% from 1983 to 1993, despite large changes in the sample number (Figure 1) (8). The incidence of obesity (defined as BMI $\geq 28.0$ kg/m$^2$) was 11.3% in men and 17.1% in women (9).

**Dry Dock Participants**

The prevalence of diabetes mellitus (DM) was 67.9 per 1000 screenees (84.4 for men and 40.8 for women). During the 2 yr of follow-up, the cumulative incidence of DM was 2.3% (2.9% in men and 1.3% in women) (15).

**Predictors of ESRD in the 1983 Mass Screening**

Predictors of ESRD examined in the Okinawa screening program are summarized in Table 1. From April 1983 to March 1994, there were 193 new ESRD patients (105 men and 88 women) from the fiscal year 1983 OGHEMA screenees (6). The 10-yr cumulative incidence of ESRD was 3% in the screenees with proteinuria and hematuria combined and 1.5% in screenees with proteinuria only. The adjusted odds ratio (95% CI) was 14.9 (10.9 to 20.2) for proteinuria and 2.30 (1.60 to 3.28) for hematuria. The dipstick reading (1+), (2+), (3+), and (4+) for proteinuria showed relative risk of ESRD of 1.0, 7.6, 16.1, and 19.5, respectively.

The cumulative incidence of ESRD per 100,000 screenees over the 10 yr was 450 in those with SBP of 150 to 159 mmHg and 200 in those with SBP of $\geq 160$ mmHg. Similarly, the cumulative incidence of ESRD per 100,000 subjects was 50 in those with DBP $\geq 69$ mmHg, and 1200 in those with DBP $\geq 110$ mmHg. The adjusted odds ratio (95% CI) was 1.10 (0.96 to 1.26) for SBP and 1.39 (1.17 to 1.64) for DBP for each for 10 mmHg increase (7). The risk of ESRD increased linearly when serum creatinine was $\geq 1.4$ mg/dl for men and $\geq 1.2$ mg/dl for women. The adjusted odds ratio (95% CI) was 5.31 (3.39 to 8.32) in men and 3.92 (2.88 to 5.34) in women (8) for each 0.2 mg/dl increment in serum creatinine. The mean time from the screening to the start of dialysis was 64.4 mo when serum creatinine was 2.0 mg/dl. The prevalence of elevated serum creatinine was relatively stable at around 0.2% in the general population in Okinawa (Figure 1).

The cumulative incidence of ESRD increased with each categorical unit increase in BMI, except in the range of 24.0 to 25.9 kg/m$^2$. However, the adjusted odds ratio (95% CI) was 0.99 (0.92 to 1.13) in men and 0.83 (0.72 to 0.96) in women per categorical unit increase in BMI. Therefore, BMI was a negative
Table 1. Summary of factors tested as predictors of end-stage renal disease (ESRD) in screened subjects in 1983 in Okinawa, Japan. Study period was from April 1983 through March 1994.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1: (Ref. 6)</td>
<td></td>
<td></td>
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<tr>
<td>men versus women</td>
<td>1.31 (0.99 to 1.74)</td>
<td>0.056</td>
<td>1.41 (1.04 to 1.92)</td>
<td>0.011</td>
</tr>
<tr>
<td>age (10-year increments)</td>
<td>1.25 (1.14 to 1.37)</td>
<td>&lt;0.001</td>
<td>1.11 (0.99 to 1.24)</td>
<td>0.313</td>
</tr>
<tr>
<td>proteinuria (versus normal)</td>
<td>22.9 (17.2 to 30.6)</td>
<td>&lt;0.001</td>
<td>14.9 (10.9 to 20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hematuria (versus normal)</td>
<td>2.30 (1.72 to 3.07)</td>
<td>&lt;0.001</td>
<td>2.30 (1.62 to 3.28)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Study 2: (Ref. 7)</strong></td>
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<tr>
<td>SBP (10 mmHg increments)</td>
<td>1.51 (1.39 to 1.65)</td>
<td>&lt;0.001</td>
<td>1.10 (0.96 to 1.26)</td>
<td>0.070</td>
</tr>
<tr>
<td>DBP (10 mmHg increments)</td>
<td>1.88 (1.68 to 2.11)</td>
<td>&lt;0.001</td>
<td>1.39 (1.17 to 1.64)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Study 3: (Ref. 8)</strong></td>
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<tr>
<td>SCR (0.2 mg/dl increments)</td>
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<tr>
<td>men</td>
<td>7.64 (4.97 to 11.75)</td>
<td>&lt;0.001</td>
<td>5.31 (3.39 to 8.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>woman</td>
<td>4.63 (3.54 to 6.07)</td>
<td>&lt;0.001</td>
<td>3.92 (2.88 to 5.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Study 4: (Ref. 9)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>men</td>
<td>1.09 (0.97 to 1.23)</td>
<td>0.086</td>
<td>0.99 (0.92 to 1.13)</td>
<td>0.776</td>
</tr>
<tr>
<td>woman</td>
<td>1.01 (0.88 to 1.15)</td>
<td>0.682</td>
<td>0.83 (0.72 to 0.96)</td>
<td>0.004</td>
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<tr>
<td><strong>Study 5: (Ref. 10)</strong></td>
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<tr>
<td>total cholesterol (mg/dl)</td>
<td>1.25 (1.04 to 1.49)</td>
<td>&lt;0.001</td>
<td>1.10 (0.91 to 1.33)</td>
<td>0.707</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; SCR, serum creatinine; BMI, body mass index. Subjects were categorized into six subgroups on BMI²: <20.0, 20.0 to 21.9, 22.0 to 23.9, 24.0 to 25.9, 26.0 to 27.9, and more than 28.0 kg/m², and into four subgroups on total cholesterol²: <168, 168 to 191, 192 to 217, and ≥ 218 mg/dl. The numbers of screenees were different among studies: study 1 (n = 107,192); study 2 (n = 104,331); study 3 (n = 14,509); study 4 (n = 101,516), and study 5 (n = 38,053), respectively. We adjusted for age, gender, proteinuria, hematuria, SBP, and DBP.

ESRD Development in the Hospital-Based Stroke and AMI Registry

The 10-yr cumulative incidence of ESRD was approximately 2.0% in those who survived stroke or AMI. Among subjects aged 30 to 59 yr, the observed-expected ratio was 4.1 in men (P < 0.01) and 5.8 in women (P < 0.01). Among subjects 60 yr and older, the observed-expected ratio was 0.8 in men and 0.4 in women, and was NS (16).

Discussion

Okinawa is a prefecture located in Japan’s southernmost part (127E by 26N). In 2000, the population was 1.32 million. After the Second World War, Okinawa was occupied and governed by the United States until it was returned to Japan in 1972. Despite rapid changes in lifestyle and regional politics, Okinawa’s people maintain cultural respect of their ancestry and the elderly (17).

ESRD affects more men than women (18). However, the reasons for this phenomenon are unclear. The incidence of smoking is higher in men than women, as is the incidence and prevalence of DM (15). Besides male gender, we found that the significant predictors of ESRD to be proteinuria, hematuria, and hypertension, especially DBP. Among the laboratory findings, a high serum creatinine level was shown to be a strong predictor of ESRD. In the 1983 screening, the cost for this blood test was not paid for by the public sector as it was not mandatory. As such, the cost saving of the blood test for serum creatinine for ESRD prevention remains to be shown.

In Okinawa, public concern regarding the prevalence of chronic renal disease as well as risk factors of ESRD is lacking. We recently studied the referral pattern to nephrology screenees in our population (19). Late referral (LR), which was defined as the start of dialysis therapy within 1 mo after the start of nephrological care, was as common in our district as in others. The frequency of LR was 23.1% in men and 19.7% in women. Similarly, more than 50% of patients diagnosed with type 2 DM had evidence of proteinuria, hypertension, or a major vascular disease (20). This is consistent with our previous assumption that only 20% of subjects were informed about the results of their urine test at the time of screening (17). We believe this trend is not due to a lack of nephrologists (19). Lack of awareness on the part of patients, their family members, and their physicians (including general practitioners, cardiologists, and diabetologists) about the benefits of regular nephrological care may explain this trend (21). Most members...
of the high-risk group did not visit medical facilities and remained untreated until they became symptomatic.

Our study has several limitations. During the follow-up period, all of the new ESRD patients were detected, however, information for subjects who died were not available, and those subjects were not excluded from the logistic analysis. Therefore, we underestimate the risk of BP, obesity, and other possible predictors of ESRD. BP was measured on only one occasion. This also underestimated the strength of the association of ESRD with BP. Against these limitations, we recently analyzed the effect of the degree of proteinuria on the risk of developing ESRD by extending the follow-up to 2000 (22) We are also analyzing the effects of age, BMI (obesity), and hypercholesterolemia, which were insignificant in the relatively short follow-up study (10 yr). Relationship between BMI and the cumulative incidence of ESRD was not simply linear (9). We recently showed that triglyceride, but not total cholesterol or LDL cholesterol, levels predict development of proteinuria (23).

We have no data regarding the treatment regimen for hypertension and chronic renal disease. Angiotensin-converting enzyme inhibitor has been available since 1983, and angiotensin receptor blockade has been available since 1998 in Japan. These drugs have been shown to retard proteinuria and the flow-on effects of renal failure and cardiovascular disease. Early detection of renal dysfunction and identification of risk factors for ESRD may encourage otherwise healthy individuals to modify their lifestyle and improve treatment follow-through. There are substantial regional differences in the incidence and prevalence of ESRD between Japan and the United States; therefore, our results may not be applicable in other regions and countries. Mortality rates from stroke and AMI have decreased tremendously over the past 30 yr (24). Life expectancy at birth in Japan is longer than that in any other country. Therefore, the population at risk for ESRD is ever increasing. More public education regarding the risks for ESRD is needed to reduce the number of ESRD patients.

Acknowledgments

I am indebted to the staff of all dialysis units in Okinawa and to the staff of OGHMA. I am also grateful to Dr. O. Morita, Department of Physics, Kyushu University, Fukuoka, Japan.

References