

# Family History of End-Stage Renal Disease among Incident Dialysis Patients

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**Abstract.** As part of a larger study of genetic risk factors for the occurrence of renal failure, the prevalence of a family history of end-stage renal disease (ESRD) in first- and second-degree relatives of all incident dialysis patients treated in Georgia, North Carolina, and South Carolina (ESRD Network 6) in 1994 was ascertained. Family histories were obtained from 4365 dialysis patients (83% of those eligible), and 856 (20%) reported having a family history of ESRD. Among race-sex groups, 14.1% of Caucasian men, 14.6% of Caucasian women, 22.9% of African-American men, and 23.9% of African-American women reported a first- or second-degree relative with ESRD ( $P = 0.001$ ). The prevalence of relatives with ESRD

varied by the reported etiology: 22.2% in diabetes mellitus; 18.9% in hypertension, 22.7% in glomerulonephritis; and 13.0% of other etiologies ( $P = 0.001$ ). Patient characteristics independently associated with family history of ESRD included race, younger age, higher levels of education, and etiology of ESRD. In this report, it is concluded that a large proportion of incident ESRD cases have close relatives with ESRD in whom preventive actions might be directed. Genetic analyses in multiply affected families may identify the inherited factors contributing to progressive renal failure. (*J Am Soc Nephrol* 8: 1942–1945, 1997)

The incidence rate of end-stage renal disease (ESRD) is markedly higher in African-Americans compared with Caucasians in the United States (1). The elevated risk of ESRD in African-Americans is independent of differences in socioeconomic status and prevalence of hypertension and diabetes mellitus (2–4). Several studies (5–8) have demonstrated a consistent familial aggregation of ESRD in African-American, and, to a lesser extent, Caucasian families (9). However, no study has assessed the familial clustering of ESRD in a large cohort of new patients from a wide geographic area. The purpose of this study was to determine how often incident dialysis patients reported first- or second-degree relatives with ESRD and to identify risk factors associated with the familial clustering.

## Materials and Methods

The study population comprised all patients who initiated Medicare-supported renal replacement therapy in ESRD Network 6 dialysis facilities (North Carolina, South Carolina, and Georgia) during 1994 (10). Eligible patients had ESRD attributed to diabetes mellitus, hypertension, primary or systemic diseases with glomerular involvement, or other etiologies by the treating nephrologist. We excluded

from the analyses patients with ESRD attributed to adult polycystic kidney disease, Alport's syndrome, or urologic disease (surgical nephrectomy, reflux nephropathy, etc.).

A standardized data collection instrument was used to record the number of siblings and children of each incident dialysis patient, the names, vital status, and addresses of relatives with ESRD, and the name, address, and phone number of a relative without ESRD to serve as a family contact. Facility staff members, primarily social workers or nurses, collected this information during the patient's initial visit to a facility. Data were entered into a computer data base by network staff.

## Statistical Analyses

The family history was considered positive if an incident ESRD patient (index case) reported having either a first-degree (parent, sibling, or child) or second-degree (grandparent, aunt, uncle, grandchild, or half sibling) relative with ESRD. The ratios of the proportion of patients with a positive family history (prevalence ratio) were used to estimate the crude relative risk for levels of demographic and clinical characteristics (11). Adjustment for the simultaneous influence of characteristics associated with risk for ESRD (age, race, sex, state of residence, and cause of ESRD) was performed using logistic regression analysis with family history of ESRD (yes or no) as the outcome variable (12). White men served as the index group for the race-gender analyses because they had the fewest relatives with ESRD. For the same reason, etiologies of ESRD other than hypertension, diabetes, and glomerular disease served as the index group for the cause of ESRD analyses. Residence in Georgia, a younger age at onset of ESRD (<45 yr), and fewer years of formal education (0 to 8 yr) were randomly selected as index criteria for their respective analyses.

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## Results

A total of 5236 patients initiated renal replacement therapy for ESRD in Network 6 facilities during 1994 and were eligible for inclusion in the study. Family history data were collected for 4365 (83%) of these patients. After the exclusion of 76 patients who self-reported their race as other than African-American or Caucasian, 4289 patients remained in the study group.

The mean (SD) age was 58.4 (15.6) yr, and 79% were aged 45 or older (Table 1). African-American women comprised the largest race-sex group, and 62% of all patients were African-American. Forty percent of cases reportedly had ESRD associated with diabetes mellitus, 39% with hypertension, 10% with chronic glomerular diseases (primary or systemic disease combined), and 11% with other etiologies. Nearly half of patients had 8 yr of formal education or less.

A positive family history of ESRD was reported by 856 (20%) of the 4289 incident dialysis patients. Family members reported as having ESRD included parents of 258 (30%) patients, children of 54 (6%), siblings of 351 (41%), half-siblings of 20 (2%), uncles or aunts of 128 (15%), grandparents of 43 (5%), and grandchildren of two patients.

The prevalence of a positive family history varied according to the level of demographic and clinical characteristics of the case patients (Table 1). The prevalence decreased with age, was higher among African-Americans than Caucasians, and was higher among people with some high school compared to

those with either less or more formal education. Compared to patients with other causes of ESRD, the prevalence of a positive family history was 50% higher for patients with ESRD from hypertension and nearly twice as high for patients with glomerulonephritis or diabetes as the cause of ESRD. No differences in the prevalence of a family history of ESRD were detected between the three states comprising ESRD Network 6. These associations between demographic and clinical characteristics and family history of ESRD persisted when the simultaneous influence of these factors was examined using a multivariate model (Table 2).

## Discussion

This study reports on the familial clustering of ESRD in a large incident cohort of dialysis patients. Our findings strongly support earlier reports of familial aggregation of ESRD and are relevant for several reasons. First, the incidence rates of ESRD are highest in the Southeast region of the United States (10). If 20% of incident patients have additional family members at risk for ESRD, then our findings may help identify these individuals so that they may be targeted for interventions aimed at delaying or preventing renal failure. For example, a family history of nephropathy is a reliable predictor of whether diabetic individuals will develop future renal failure (7,13,14). Increased screening among at-risk family members and early institution of angiotensin-converting enzyme inhibitors at the

*Table 1.* Demographic and clinical characteristics and associations with family history of ESRD among 4289 incident dialysis patients, ESRD Network 6, 1994<sup>a</sup>

Factor	n (%)	Family History n (%)	Prevalence Ratio (95% CI)
<b>Age level</b>			
<45	906 (21)	220 (24.3)	
45 to 64	1688 (39)	362 (21.4)	0.9 (0.8to1.0)
65+	1695 (40)	274 (16.2)	0.7 (0.6to0.8)
<b>Race-sex group</b>			
Caucasian men	915 (21)	129 (14.1)	
Caucasian women	725 (17)	106 (14.6)	1.0 (0.8to1.3)
African-American men	1172 (27)	268 (22.9)	1.6 (1.3to2.0)
African-American women	1477 (35)	353 (23.9)	1.7 (1.4to2.0)
<b>State of residence</b>			
Georgia	1525 (36)	313 (20.5)	
North Carolina	1775 (41)	343 (19.3)	0.9 (0.8to1.1)
South Carolina	989 (23)	200 (20.2)	1.0 (0.9to1.3)
<b>Education level</b>			
0 to 8 yr	1989 (46)	354 (17.8)	
9 to 12 yr	1707 (40)	385 (22.6)	1.3 (1.1to1.4)
>12 yr	593 (14)	117 (19.7)	1.1 (0.9to1.3)
<b>Cause of ESRD</b>			
other	461 (11)	60 (13.0)	
hypertension	1658 (39)	313 (18.9)	1.5 (1.1to1.9)
glomerulonephritis	450 (10)	102 (22.7)	1.7 (1.3to2.3)
diabetes mellitus	1720 (40)	381 (22.2)	1.7 (1.3to2.2)

<sup>a</sup> ESRD, end-stage renal disease; CI, confidence interval.

**Table 2.** Independent associations between demographic and clinical characteristics and family history of ESRD among 4289 incident dialysis patients, ESRD Network 6, 1994<sup>a</sup>

Factor	Level	Odds Ratio (95% CI)
Age	45 to 64	0.8 (0.7to1.0)
	65+	0.7 (0.5to0.8)
Race-sex group	Caucasian women	1.1 (0.8to1.4)
	African-American men	1.8 (1.4to2.3)
	African-American women	1.9 (1.5to2.4)
Education (yr)	9 to 12	1.3 (1.1to1.5)
	>12	1.1 (0.9to1.5)
Cause of ESRD	Hypertension	1.5 (1.1to2.1)
	Diabetes mellitus	1.9 (1.4to2.6)
	Glomerulonephritis	2.1 (1.5to3.0)

<sup>a</sup> Abbreviations as in Table 1.

onset of microalbuminuria may prevent subsequent overt proteinuria and deterioration in renal function (15,16).

Second, a potentially cost-effective method for combating the current epidemic of ESRD might be to make available to first- and second-degree relatives of ESRD patients annual blood pressure screening, urinalysis (including microalbuminuria measurement in diabetic patients), serum creatinine determination, and counseling for avoidance of nephrotoxins. Because the vast majority of hypertensive subjects in the general population (17) and approximately 70% of diabetic patients (18) will never develop renal disease, such a targeted screening strategy might identify a greater proportion of hypertensive and diabetic patients who are at risk for ESRD (19).

Third, our observations extend previous studies that used strict entry criteria and limited the analyses to cases of ESRD with a predominantly hypertensive or diabetic etiology (5–9). Approximately 35 to 40% of African-American ESRD patients from Winston-Salem, NC, with carefully defined hypertension- (6) or type II diabetes mellitus-associated ESRD (7) had first-, second-, or third-degree relatives with ESRD. Twenty-six percent of whites with type II diabetes mellitus-associated ESRD from Winston-Salem reported close relatives with ESRD as well (9). Bergman *et al.* reported that 18 of 75 African-American index cases with hypertension-associated ESRD living in Birmingham, AL, had first-degree relatives with ESRD, and evidence for renal disease was present in 47% (35 of 75) of families (8). The investigators in North Carolina demonstrated that multiple etiologies of ESRD were frequently present in families (6). This was confirmed by the Alabama investigators (8). The initial family analyses used prevalent populations of ESRD patients. Prevalent study populations could bias the results if patient survival in familiarly clustered cases of ESRD was different from those in sporadically occurring cases. Therefore, although important, the results of these initial studies may not be applicable to general populations of dialysis patients in whom the etiologies of ESRD are more

variable. The results of this analysis are more general because we analyzed all incident cases regardless of their eventual dialysis modality, and used the etiology of ESRD reported by the referring nephrologist; however, we recognize that the diagnosis in an individual case may not always be correct (20).

Our findings rely on the ability of patients to correctly identify a positive family history. In an attempt to collect DNA for genetic analysis from African-American sibling pairs concordant for ESRD, we contacted all 113 living siblings reportedly having ESRD from the 2649 African-American index cases in this data base. The family history was correct in 88% of these cases. Therefore, the prevalence of a family history in this group may have been slightly overestimated. We have no comparable data for Caucasian index patients; however, we consider it unlikely that the large racial differences in prevalence of family history that we observed can be accounted for solely by these kinds of misclassification errors.

Another application of the family history of ESRD data base includes identification of multiply affected families for genetic linkage analysis. Inherited, not environmental, risk factors appear to contribute strongly to the familial clustering of ESRD in African-Americans (17,21). Lei *et al.* recently demonstrated that the familial clustering of ESRD in African-Americans is in excess of what is expected based on the familial clustering of hypertension and diabetes mellitus in families (21). They suggested that genetic susceptibility increased the risk of developing the commonly reported etiologies of ESRD. We now have the potential to perform an efficient search for the genetic determinants of progressive renal failure (22–24). This may lead to the discovery of genetic markers for the early detection of individuals at risk. It is also possible that shared environmental influences may be responsible for some of the familial aggregation we have reported, and this possibility should be explored further (25).

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