Incident Renal Events and Risk Factors in Autosomal Dominant Polycystic Kidney Disease: A Population and Family-Based Cohort Followed for 22 Years

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For determination of the incidence of renal events in autosomal dominant polycystic kidney disease (ADPKD) all patients who had ADPKD and attended nephrology/urology clinics in Newfoundland in 1981 were identified, and members of 18 families who were at 50% risk for inheriting ADPKD were followed prospectively for 22 yr, including research clinics at 6-yr intervals. Time to hypertension treatment, stage 3 chronic kidney disease (CKD), ESRD, and death was measured, and the impact of genotype, gender, gender of parent who transmitted PKD, family, family history of essential hypertension, parity, and oral contraceptive pill was assessed. Nine (50%) families had PKD1, four (22%) had PKD2, and one had both PKD1 and PKD2. The number of family members with PKD1 was 136 and with PKD2 was 60. In PKD1 median age to hypertension treatment was 46 yr, to CKD stage 3 was 50 yr, to ESRD was 53 yr, and to death was 67 yr. In PKD2, median age to hypertension treatment was 51 yr, to CKD stage 3 was 66 yr, to death was 71 yr, and ESRD was infrequent. Although the incidence of CKD was later and ESRD occurred infrequently in PKD2 compared with PKD1, early onset of hypertension occurred and life expectancy was compromised. Genotype, family, and proteinuria were identified as risk factors for incident renal events. Gender, gender of parent who transmitted PKD, family history of essential hypertension, multiparity, and use of the oral contraceptive pill were not identified as risk factors for renal events in ADPKD.

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Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in two genes, *PKD1* and *PKD2*, which code for polycystin proteins that are involved in ciliary function of the renal epithelial cell (1). *PKD1* is associated with earlier age to ESRD/death than *PKD2* (2,3).

Few longitudinal studies that have investigated the clinical course of renal disease in ADPKD have been reported. Hypertension studies usually have been cross-sectional, providing data on prevalence but not on incidence (4–6). Studies of renal function have been influenced by referral and ascertainment bias, involved multiple probands and small family size (7,8), and provide few data on incidence of chronic kidney disease (CKD). Good information exists on age to dialysis/death, but, frequently, patients who were enrolled were not representative of the ADPKD population (5,8).

Information on other risk factors for incident renal events in ADPKD is limited. The impact of gender is uncertain (4–6,8–13), gender of the parent from whom the ADPKD was inherited has been reported to be a risk factor (10,13), phenotypic differences exist between families (5,10), and a family history of essential hypertension may influence clinical outcomes (13,14). Furthermore, parity may influence progression of CKD (15) and of ADPKD (7), and the use of the oral contraceptive pill (OCP) may be conducive to progression of CKD by increasing BP and filtration function and activating the renin angiotensin system (16).

Newfoundland, an island in the North Atlantic, is characterized by founder effects, large family size with family members settling near the core community, and little in- or out-migration since the founding migrations from Southeast Ireland and Southwest England in the late 18th and early 19th centuries. Investigation of large families with autosomal dominant disorders has occurred (17), facilitated by their eager participation in research and good access to the publicly funded Canadian health care system. In addition, exposure to a homogeneous environment diminishes the role of environmental factors as a potential confounder of clinical outcomes.

In 1981, we identified all patients who had ADPKD and attended nephrology/urology clinics in the province and ascertained family members who were at 50% risk for inheriting ADPKD. We subsequently reported the diagnostic utility of

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renal imaging and clinical outcomes in PKD1 and non-PKD1 (2,10), investigated the pathogenesis of hypertension (18), and collaborated to identify the genetic basis of cyst development in PKD2 (19,20). This cohort has little ascertainment bias and has been followed for 22 yr at serial research clinics. In this population-based and family-derived cohort, we report the probability of development of renal events (hypertension requiring treatment, stage 3 CKD, ESRD, and death) in PKD1 and PKD2 and assess factors that may have an impact on these risks.

Materials and Methods

Eighteen families, identified through the patients who attended nephrology/urology clinics across Newfoundland in 1981, were investigated. Family members who were at 50% risk for inheriting ADPKD had a clinical evaluation and renal ultrasound performed and DNA sample taken.

To determine whether the families who were involved in this study were representative of the provincial population, we studied the cause of renal disease in all prevalent dialysis patients in 1987 and incident patients from 1987 to 1993 (21). Forty-six individuals had PKD as the cause of ESRD: 36 were already enrolled in our study, six did not have a family history of ADPKD, and the remaining four did not wish to participate in further studies (16). Subsequently, in 2003, we contacted all nephrologists and urologists who were practicing in the province to identify individuals who had received a diagnosis of ADPKD. Through the multiple referrals received, only one individual was unknown to the investigators, and upon review of the family pedigree, it was thought that this individual was a new mutation, because no other family history of ADPKD could be confirmed. From these two studies, we could conclude that although probands who entered the study were exposed to referral bias, the cohort enrolled in our study was representative of the population.

In 14 of 18 families, a disease-associated haplotype was identified at either the PKD1 or PKD2 locus. The remaining four (22%) families were small and uninformative from a genetic perspective. Family members were considered to have inherited ADPKD gene when (*1*) they had the PKD disease–associated haplotype or (*2*) they had renal cysts according to criteria of Ravine *et al.* (22). They were considered unaffected when (*1*) they did not carry the PKD-associated haplotype or (*2*) they did not have renal cysts and were older than 30 yr. In the 14 families, some going back seven generations, 613 individuals were at 50% risk for inheriting ADPKD in 147 sibships. To diminish ascertainment bias, we studied only members of well-ascertained sibships in whom at least 50% of siblings had known ADPKD disease status. This comprised 371 (61%) family members from 62 well-ascertained sibships who were at 50% risk for inheriting PKD. Within this group, 194 (52%) had ADPKD, 129 (35%) did not have ADPKD, nine (2%) were obligate carriers, nine (2%) had an equivocal diagnosis, and 43 (12%) had unknown status. It is unclear why there was an unequal distribution of affected and unaffected, but it is related to ascertainment in the PKD1 family (P17), in which 57 were affected and 16 were not (Table 1).

Four research clinics were held at 6-yr intervals (1982, 1988, 1994, and 2000), at which time family members were interviewed and examined; medical records were reviewed; and data were abstracted concerning smoking habits, body mass index (BMI), angiotensin-converting enzyme (ACE) inhibitor and statin use, hypertension diagnosis and treatment, serum creatinine levels, treatment of ESRD, and cause of death. BP and serum creatinine were measured. GFR was estimated using the Modification of Diet in Renal Disease formula (23). Age at hypertension diagnosis and treatment was determined; the prevalence and the incidence of stage 3 CKD were assessed; and age at ESRD, death, or last follow-up was recorded. Because age at hypertension diagnosis was followed closely by treatment, only the latter is discussed here.

The following risk factors for each renal event were studied: Genotype (PKD1 *versus* PKD2), gender, gender of parent who transmitted

Table 1. Genetic and clinical characteristics of families with PKD1 and PKD2[a]

Families	LOD Score		No. with Cysts	No. without Cysts	No. of Equivocal	No. of Obligate Carriers	No. of Unknowns
	PKD1	PKD2					
PKD1							
P1	2.41	−∞	6	7		0	0
P4	2.41	−∞	6	2		0	0
P6	6.04	−∞	11	6		1	0
P7	2.23	−∞	11	11		1	0
P8	1.7	−1.09	5	4		0	0
P9	—	—	8	8		0	0
P10	>3	—	14	10	3	0	6
P14	2.11	−∞	2	2		0	0
P17	0.86	−∞	55	16		2	10
P18	2.02	−∞	16	—	1	0	2
PKD2							
P3	−∞	2.54	10	11	—	3	0
P5	−∞	1.45	6	10	—	0	1
P10	—	>3	15	10	3	0	2
P13	−∞	1.65	11	7	1	0	2
P16	−∞	3.76	18	25	1	2	14

[a]LOD, logarithm of odds; PKD, polycystic kidney disease; −∞, shows no possibility of linkage to the other locus. P9 was linked to PKD1 in our original study (2), but no DNA was available for the current study. P10 had inheritance of both PKD1 and PKD2.

ADPKD, and family history of essential hypertension (presence of hypertension treated before the age of 60 in an unaffected first- or second-degree relative) (14). Outcomes in families with >10 affected individuals were compared. In women, parity (zero to two *versus* three or more children) and use of the OCP (≥1 *versus* no or <1 yr of use) were assessed.

Statistical Analyses

PKD1 and PKD2 family members were analyzed separately. In addition, PKD1 families P6, P7, P10, and P18 were compared with P17. The two PKD2 families with the same mutation were compared with PKD2 families with independent mutations. Time to each event was measured using Kaplan-Meier methods (29). The impact of each risk factor was assessed using Cox regression (30). Multivariate modeling was used where indicated.

For each outcome of interest as described, the Cox procedure was extended to test the independent role of variables with updated values over time (BMI, use of ACE inhibitors and statins, and smoking habits and proteinuria). In all cases, model specification and overall fit were checked by re-estimation; by formal tests based on Schoenfeld, Martingale, and Cox-Snell residuals; and testing the interaction with time of the variables in the model. Influence analysis was conducted on the basis of efficient score residuals. Within sensitivity analysis results, consistency was verified excluding and including in either group the two individuals who were found to be transheterozygous for both PKD1 and PKD2. All analyses were performed using STATA 9.1 SE (StataCorp, College Station, TX). Because of missing data, the members who were included in the analysis of each renal event are different.

Results

Genetic Epidemiology

Nine (64%) of 14 informative families had PKD1, four (29%) had PKD2, and one had bilineal inheritance of both PKD1 and PKD2, previously described by Pei *et al.* (24). The number of family members from well-ascertained PKD1 sibships in whom cysts were identified was 136 and from PKD2 sibships was 60. Table 1 describes each family by logarithm of odds score for disease associated haplotype, number with and without cysts, number with equivocal ultrasound results and obligate carriers.

Mutations

The largest family, P17, has a low logarithm of odds score (0.86) as a result of two independent recombinations. The *PKD1* mutation was 11587 del. 1 bp in the nonduplicated region of exon 40 (AA 3792 FS). This was not present in the other eight PKD1 families.

Two PKD2 families, P3 and P16, had the same disease haplotype and mutation (C→T1390, R464 X in exon 6). A third family (P13) from the same locality had the same disease haplotype but did not have the same mutation. The PKD2 mutation in P10 was 2152 del. A; L736 X in exon 11 (24).

Hypertension

The age to onset of hypertension treatment in those with and without cysts in PKD1 and PKD2 is presented in Table 2. The median age to hypertension treatment was 46 yr in PKD1 and 51 yr in PKD2. The youngest age at hypertension treatment was 18 yr in PKD1 and 20 yr in PKD2. In PKD1, the relative risk for hypertension treatment was 9.8 (95% confidence interval [CI] 3.5 to 27.8) in those with cysts compared with the unaffected family members. In PKD2, the relative risk was 4.1 (95% CI 1.6 to 10.8).

No difference in incidence of hypertension treatment was observed in PKD1 when analyzed by gender, parent who transmitted PKD, family history of essential hypertension, parity, and use of OCP (Table 3). In the five large PKD1 families with >10 affected family members, there was variability in the age to hypertension onset, with median ranging from 35 yr in P6 to 62 yr in P10 (Table 4). Age to onset of hypertension in P6 was significantly earlier compared with that in P17 (hazard ratio [HR] 4.08; 95% CI 1.53 to 10.8).

In the two PKD2 families with the known mutation, the median age to onset of hypertension treatment was 48 yr, and for the three combined PKD2 families with independent mutations, the median age was 53 yr. No risk factors were identified for the PKD2 group (Table 3).

CKD Stage 3

Serum creatinine was performed in 118 (87%) of 136 PKD1 cases at mean age of 27 ± 14.3 SD yr, and GFR was estimated (Figure 1A). The prevalence of stage 3 CKD at first measurement was 20% (n = 24). Seventeen of these cases had serial serum creatinine levels. The mean rate of progression of CKD was 3.0 ± 2.1 ml/min per yr. In 94 cases with estimated GFR >60 ml/min at baseline, the median age of *de novo* develop-

Table 2. Age to hypertension treatment in family members with PKD1 *versus* PKD2 and in unaffected family members[a]

Status	N	No. of Events	% Affected by Age					Median Age (Yr)	95% CI (Yr)	RR	95% CI
			30	40	50	60	70				
PKD1											
cysts	122	49	10	35	63	86	93	46	41 to 51	9.8	3.5 to 27.8
no cysts	63	5	—	2	5	23	38	—	—		
PKD2											
cysts	54	32	6	19	43	74	93	51	48 to 54	4.1	1.6 to 10.8
no cysts	59	5	—	3	9	27	45	72	57 to 87		

[a]CI, confidence interval; RR, relative risk.

Table 3. Risk factors for hypertension treatment in PKD[a]

Risk Factor	PKD1					PKD2				
	N	No. of Events	Median Age	95% CI	RR (95% CI)	*N*	No. of Events	Median Age	95% CI	RR (95% CI)
Gender										
male	62	26	40	37 to 43		24	12	46	34 to 58	
female	60	23	46	42 to 50	1.4 (0.8 to 2.4)	29	20	44	43 to 45	0.7 (0.3 to 1.3)
Parent of origin										
mother	76	33	44	38 to 50		25	13	43	38 to 48	
father	44	15	38	35 to 41	0.9 (0.5 to 1.7)	29	19	51	44 to 58	1.5 (0.7 to 3.0)
Parity										
0 to 2	46	13	46	41 to 51		19	10	44	42 to 46	
≥3	15	10	47	26 to 68	1.2 (0.5 to 3.2)	9	8	44	22 to 66	2.7 (0.8 to 8.9)
OCP										
yes	33	12	47	42 to 52		7	5	46	33 to 58	
no	21	8	46	41 to 51	1.2 (0.5 to 3.0)	13	7	44	41 to 47	1.3 (0.4 to 4.0)
Family history of essential hypertension										
yes	14	9	40	35 to 45		18	13	46	41 to 51	
no	108	40	43	39 to 47	1.6 (0.8 to 3.3)	36	19	46	39 to 53	1.5 (0.7 to 3.0)

[a]OCP, oral contraceptive pill.

Table 4. Median age to onset of hypertension treatment by family in PKD1

Family	*N*	Events	Median Age	95% CI	HR (95% CI)
P17	50	18	47	45 to 49	—
P6	11	6	35	31 to 39	4.07 (1.53 to 10.84)
P7	9	2	50	—	1.23 (0.28 to 5.42)
P10	14	3	62	47 to 77	0.20 (0.04 to 0.86)
P18	16	5	40	38 to 42	1.84 (0.52 to 6.54)

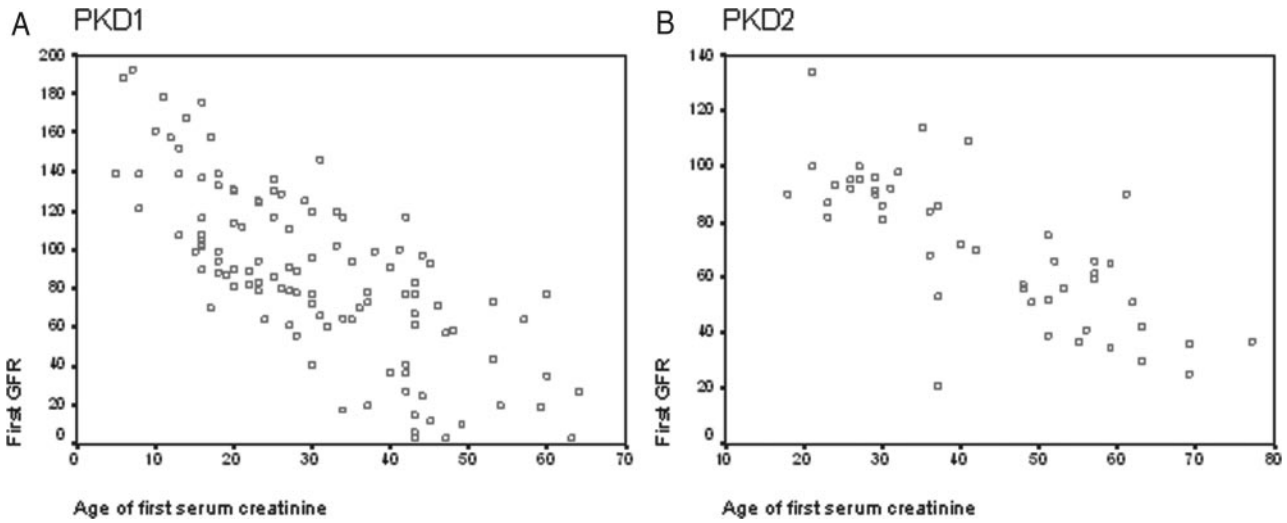

Figure 1. Estimated GFR by age at first serum creatinine in family members with PKD1 (A) and PKD2 (B).

ment of stage 3 CKD was 50 yr (Table 5). The youngest age of diagnosis of CKD stage 3 was 35 yr.

Serum creatinine was performed in 48 (80%) of 60 PKD2 cases at a median age of 40 ± 15 SD yr (Figure 1B). The prevalence of stage 3 CKD was 38% (n = 18). The mean rate of progression in this group (n = 15) was 3.5 ± 2.1 ml/min per yr. In 30 cases with estimated GFR >60 ml/min, the median age to development of CKD stage 3 was 66 yr (Table 5). The youngest age at diagnosis of CKD stage 3 was 48 yr. The median age to diagnosis of CKD stage 3 in the incident cohort in PKD2 families with the same mutation was 66 yr and for the three combined PKD2 families with unknown mutations was 65 yr.

Table 5. Age to onset of CKD stage 3 and ESRD in PKD1 *versus* PKD2

Status	*N*	No. of Events	% Affected by Age					Median Age (Yr)	95% CI
			30	40	50	60	70		
CKD stage 3[a]									
PKD1	94	21	1	15	49	74	87	50	45 to 55
PKD2	30	5	—	4	15	15	72	66	64 to 68
ESRD									
PKD1	136	30	—	6	36	54	79	53	47 to 59
PKD2	60	6	—	—	2	6	21	—	—

[a]Only patients who had estimated GFR >60 ml/min at baseline were included in this analysis.

ESRD

The median age to onset of ESRD for PKD1 was 53 yr (Table 5). In PKD2, only 21% ($n = 6$) developed ESRD by age 70 yr. The youngest age at ESRD in PKD1 was 30 yr and in PKD2 was 42 yr.

There was no difference in the incidence of ESRD in PKD1 when analyzed by gender, parent who transmitted PKD1, family history of essential hypertension, parity, or taking the OCP (Table 6). In the families with >10 affected members, P18 had a lower median age to onset of ESRD than the other large families (Table 6), which was significantly earlier then in P17 (HR 13.42; 95% CI 3.77 to 47.81).

In family P10, in which inheritance of both PKD1 and PKD2 occurred, two members inherited both PKD1 and PKD2. Both developed ESRD at ages 48 and 52 yr (24).

Mortality

In PKD1, median age to death in those with cysts was 67 yr and in PKD2 was 71 yr (Table 7). In PKD1, cause of death was known in 11 of 14 cases: Uremia in four (36%), cerebral hemorrhage in two (18%), ruptured cerebral aneurysm in two (18%), cancer in two (18%), and other causes in one (10%). In PKD2, cause of death was known in 16 of 17 cases: Uremia in two (13%), cerebral hemorrhage in four (25%), ruptured cerebral aneurysm in two (13%), cardiac disease in one (6%), cancer in four (25%), and other causes in three (19%).

Impact of ESRD Therapy

In PKD1, 24 patients received dialysis or transplantation, seven of whom died. The mean survival from time of initiation of therapy after ESRD to death was 15.2 yr.

Potential Confounding Factors

Considering the variable with updating values over time, information on proteinuria was available for 144 patients, on statin use for 155, on ACE inhibitor use for 156, on smoking habit for 117, and on BMI for 143. Neither updating nor baseline values of all except proteinuria were associated with any sig-

Table 6. Risk factors for ESRD in PKD1

Risk Factor	No. at Risk	No. of Events	Median Age to ESRD	95% CI	RR (95% CI)
Gender					
male	68	15	53	46 to 60	1.2 (0.63 to 2.7)
female	65	15	53	47 to 59	
Parent of origin					
mother	84	19	56	47 to 65	0.53 (0.25 to 1.12)
father	47	11	53	44 to 62	
Family					HR (95% CI)
P17	53	11	56	47 to 65	—
P6	11	3	47	—	1.78 (0.47 to 6.72)
P7	11	2	53	40 to 66	1.64 (0.35 to 7.77)
P10	14	—	—	—	—
P18	15	5	40	38 to 42	13.42 (3.77 to 47.8)
Parity					
0 to 2	47	4	—	—	
≥3	18	11	49	45 to 53	2.1 (0.65 to 6.8)
OCP					
yes	33	7	52	39 to 65	1.05 (0.31 to 3.62)
no	21	4	—	—	

Table 7. Age to death in PKD1 *versus* PKD2 in cyst-positive *versus* cyst-negative family members

Status	*N*	No. of Events	% Affected by Age					Median Age (Yr)	95% CI (Yr)
			30	40	50	60	70		
PKD1									
cysts	138	16	1	3	7	22	61	67	61 to 73
no cysts	66	2	—	—	—	—	—	77	67 to 87
PKD2									
cysts	61	18	—	2	8	21	46	71	66 to 76
no cysts	63	4	2	—	2	21	21	—	—

nificant effect on outcomes. Patients with baseline proteinuria >1 g/d had a four-fold higher risk for reaching ESRD (HR 4; 95% CI 1.17 to 14). However, results did not change when proteinuria was accounted for in the regression model of time to ESRD.

Discussion

PKD1 occurs more frequently than PKD2 (25). The identification of PKD1 and PKD2 in the same family (P10), although a novel observation, would be expected in 1:250,000 to 1000,000 marriages in the general population (24). The observation that three PKD2 families from the same region had the same disease-associated haplotype but two different mutations was unexpected. This suggests that the disease-associated haplotype occurred frequently in the founder population and that two separate mutations occurred, each linked to the same haplotype. In Bardet-Biedl syndrome, we have made a similar observation in that the BBS1 mutation M390R arose in a haplotype that occurred frequently in the founder population and that both the same ancestral wild-type and disease-associated haplotype were introduced to Newfoundland in founder groups (26).

Figure 2 summarizes the important prognostic data identified in this longitudinal study of PKD1 and PKD2 cases. For screening and genetic counseling purposes, the most useful information is the youngest age at which the clinical event of interest occurred and the median age to the event. Although the incidence of hypertension that required treatment was frequent in both PKD1 and PKD2, ESRD occurred less frequently and at a later age in PKD2 compared with PKD1. Nonetheless, life expectancy in PKD2 was compromised, an observation also made by Hateboer *et al.* (3). In the PKD1 group, life expectancy was extended by renal replacement therapy, and median life expectancy was almost similar to that in PKD2 (67 *versus* 71 yr). This observation is consistent with the fact that a lower mortality rate has been found in patients with ADPKD and ESRD compared with nondiabetic control patients with ESRD (27). The observation that ESRD occurred earlier in PKD1 compared with PKD2 is not novel (2,3), but the lifetime probabilities of developing hypertension that requires treatment and of development of stage 3 CKD are new and of clinical importance.

Several potential predictors of adverse outcome were assessed. In PKD1, variability in time to hypertension treatment and ESRD was observed between families. This was not attrib-

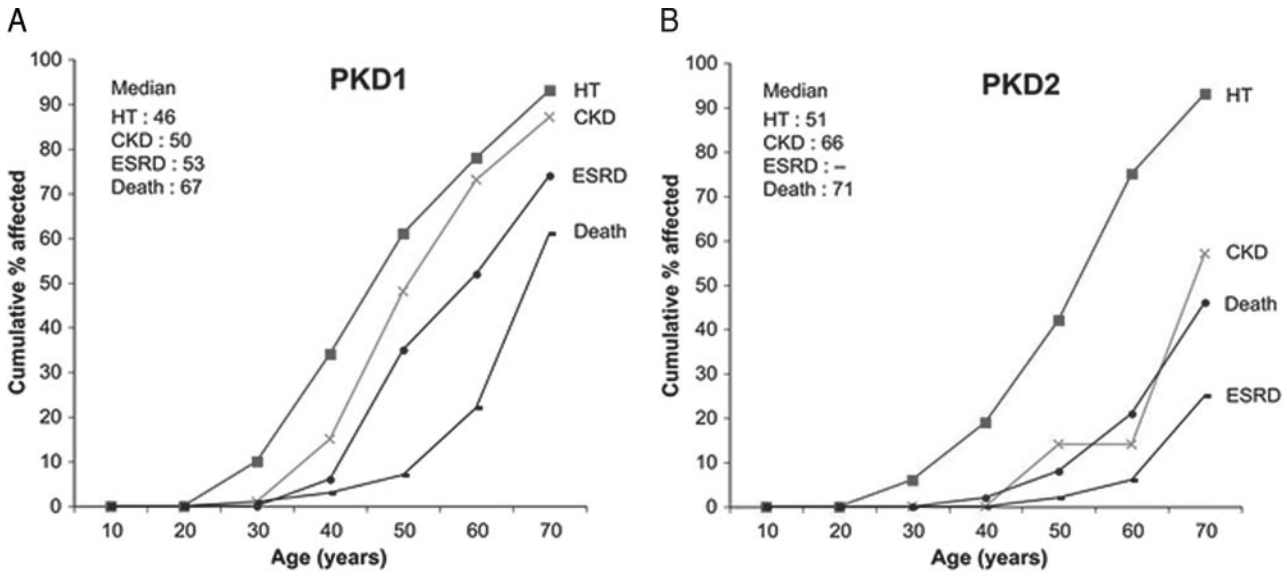

Figure 2. Summary of age to onset of renal events in PKD1 (A) and PKD2 (B). HT, hypertension; CKD, stage 3 chronic kidney disease.

utable to a family history of essential hypertension. It suggests that different mutations or modifier genes influence the progression of renal disease in ADPKD. In PKD1, the position of the mutation correlates with the severity of renal disease (28), and in PKD2, patients with splice-site mutations seem to have milder renal disease compared with patients with other mutation types (8).

A gender effect on renal survival that favors female patients has been reported in PKD2 but not in PKD1 (3), and we have suggested that the gender of the parent who transmits PKD might be a risk factor (10). However, this study did not identify gender, gender of that parent who transmitted PKD, parity, or use of the OCP as risk factors for renal events in PKD1 or PKD2. Some of these conclusions are limited by the relatively small numbers of cases studied, particularly of women with PKD1 and PKD2.

This study has others limitations besides sample size. The incidence rates of stage 3 CKD are influenced by the fact that, at first serum creatinine measurement, CKD was already prevalent in 20% of PKD1 and in 38% of PKD2 (Figure 1). It is likely that median age to onset of stage 3 CKD is earlier than the incidence rates observed in our groups, particularly for PKD2. Nine individuals with PKD1 and 16 with PKD2 had estimated GFR between 30 and 60 ml/min at first measurement and were excluded from the assessment of age to onset of CKD. A third limitation is that the 18 probands, although representative of the population, were subject to referral bias, because they were identified through the province's nephrology/urology clinics.

Another limitation concerns study design. Family members were enrolled at different ages and phases of their disease. Accurate data on age to onset of each renal event was feasible, and potential risk factors that were present before the event happened were analyzed. Potential confounding factors such as proteinuria, smoking, BMI, and therapy with ACE inhibitors or statins were assessed and did not alter the conclusions. However, the presence of proteinuria of >1 g/d was an adverse risk factor for ESRD, which is consistent with current knowledge (31). Despite these limitations, the study has several advantages. It is population based, little ascertainment bias has occurred in family members studied, families were large, follow-up was prospective and long (22 yr), and relative risks that were observed for most risk factors studied were relatively small.

Conclusion

Hypertension that required treatment was frequent and occurred at an early age in both PKD1 and PKD2. CKD occurred later, and ESRD was infrequent in PKD2. Longevity was enhanced substantially by dialysis and transplantation in PKD1, such that life expectancy was almost as long as that in PKD2. Besides genotype, variability in outcomes was observed between families, and proteinuria was an adverse risk factor for ESRD. However, gender, gender of parent who transmitted PKD1, family history of essential hypertension, multiparity, and use of the OCP were not identified as risk factors for renal events in PKD.

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