

# Polycystic Kidney Disease and Cancer after Renal Transplantation

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## ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD), the most common form of polycystic kidney disease (PKD), is a disorder with characteristics of neoplasia. However, it is not known whether renal transplant recipients with PKD have an increased risk of cancer. Data from the Scientific Registry of Transplant Recipients, which contains information on all solid organ transplant recipients in the United States, were linked to 15 population-based cancer registries in the United States. For PKD recipients, we compared overall cancer risk with that in the general population. We also compared cancer incidence in PKD versus non-PKD renal transplant recipients using Poisson regression, and we determined incidence rate ratios (IRRs) adjusted for age, sex, race/ethnicity, dialysis duration, and time since transplantation. The study included 10,166 kidney recipients with PKD and 107,339 without PKD. Cancer incidence in PKD recipients was 1233.6 per 100,000 person-years, 48% higher than expected in the general population (standardized incidence ratio, 1.48; 95% confidence interval [95% CI], 1.37 to 1.60), whereas cancer incidence in non-PKD recipients was 1119.1 per 100,000 person-years. The unadjusted incidence was higher in PKD than in non-PKD recipients (IRR, 1.10; 95% CI, 1.01 to 1.20). However, PKD recipients were older (median age at transplantation, 51 years versus 45 years for non-PKD recipients), and after multivariable adjustment, cancer incidence was lower in PKD recipients than in others (IRR, 0.84; 95% CI, 0.77 to 0.91). The reason for the lower cancer risk in PKD recipients is not known but may relate to biologic characteristics of ADPKD or to cancer risk behaviors associated with ADPKD.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of inherited cystic renal disease and the fourth most common cause of ESRD in the United States.<sup>1–3</sup> There are currently >16,000 individuals with polycystic kidney disease (PKD, of which ADPKD is by far the most common type) living with a renal transplant in the United States.<sup>4</sup>

ADPKD is a result of mutations in one of two genes: *PKD1* and *PKD2*.<sup>1,5,6</sup> These genes are widely expressed in many tissues, consistent with the multiorgan pathology characterizing ADPKD. A key factor in cyst formation and enlargement in ADPKD is the abnormal proliferation of cyst epithelial cells in a cell-autonomous manner.<sup>7,8</sup> This

cyst formation is associated with cellular dedifferentiation and is considered a neoplastic process driven by upregulated proto-oncogenes.<sup>9–13</sup> While published case reports document the occurrence of renal cell carcinomas (RCCs) in ADPKD-affected kidneys,<sup>14,15</sup> these tumors may be partly due to

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acquired renal cystic disease resulting from long-term dialysis.<sup>16</sup> Because there do not appear to be widespread published reports of other cancers in patients with ADPKD, protective mechanisms might exist in ADPKD to prevent malignant transformation. Indeed, many oncogenes that promote cell proliferation also act as potent growth suppressors (e.g., *Ras*<sup>17</sup>) or inducers of apoptosis (e.g., *Myc*<sup>18,19</sup>). Thus, there is uncertainty whether ADPKD mutations are associated with increased rates of kidney cancer or cancer in general.

We therefore designed a study to compare cancer risk in kidney transplant recipients with PKD versus kidney recipients with other causes of ESRD. Organ transplant recipients are at increased risk of cancer, largely because of immunosuppressive therapy.<sup>20</sup> An increased risk of cancer in patients with PKD might be detectable in this high-risk cancer population. Alternatively, if there is no increased risk of cancer in ADPKD, the findings would suggest the need for further study to determine whether protective cellular mechanisms may be at work.

## RESULTS

Characteristics of the renal transplant recipients with and without PKD are shown in Table 1. Compared with non-PKD recipients, recipients with PKD were more likely to be female, non-Hispanic white, and older at time of transplant. PKD recipients were slightly more likely to receive a deceased-donor transplant and slightly more likely to receive a first kidney transplant. Furthermore, PKD recipients underwent transplant after a shorter duration on dialysis compared with non-PKD recipients. Initially prescribed maintenance calcineurin inhibitor immunosuppressive therapy did not differ. The median follow-up was 4.12 years after transplant for PKD recipients and 3.64 years for non-PKD recipients.

Among the 10,166 renal transplant recipients with PKD, there were 622 cancers, for a rate of 1233.6 cancers per 100,000 person-years; among the 107,339 recipients without PKD, there were 5330 cancers, for a rate of 1119.1 per 100,000 person-years. Compared with the general population, overall cancer risk was increased 48% in PKD recipients (standardized incidence ratio, 1.48; 95% confidence interval [95% CI], 1.37 to 1.60;  $P<0.001$ ), while the overall cancer risk in non-PKD recipients was increased 86% (standardized incidence ratio, 1.86; 95% CI, 1.81 to 1.91;  $P<0.001$ ).

For individual cancers, unadjusted incidence rates are also shown in Table 2. The incidence of most cancers did not differ significantly between PKD and non-PKD recipients. In these analyses, cancers that occurred significantly more frequently in PKD recipients were soft tissue tumors, including those of the heart (incidence rate ratio [IRR], 2.36;  $P=0.05$ ), melanoma (IRR, 2.01;  $P<0.001$ ), and other nonepithelial skin cancers (IRR, 1.77;  $P=0.03$ ).

**Table 1.** Characteristics of the study sample

Characteristic	Kidney Transplant Recipients, n (%)	
	PKD (n=10,166)	No PKD (n=107,339)
Men	5656 (55.6)	64,327 (59.9)
Age at transplantation		
0–17 yr	265 (2.6)	6621 (6.2)
18–34 yr	435 (4.3)	23,758 (22.1)
35–49 yr	3672 (36.1)	34,707 (32.3)
50–64 yr	4896 (48.2)	32,515 (30.3)
≥ 65 yr	898 (8.8)	9738 (9.1)
Race/ethnicity		
Non-Hispanic white	7953 (78.2)	55,461 (51.7)
Non-Hispanic black	846 (8.3)	24,965 (23.3)
Hispanic	1049 (10.3)	19,381 (18.1)
Asian/Pacific Islander	318 (3.1)	7532 (7.0)
Donor type		
Deceased	6685 (65.8)	68,743 (64.0)
Living	3481 (34.2)	38,596 (36.0)
Kidney transplant number		
First	9541 (93.9)	97,237 (90.6)
Second	588 (5.8)	9342 (8.7)
Third or higher	37 (0.4)	760 (0.7)
Calendar year of transplant		
1987–1994	1812 (17.8)	20,541 (19.1)
1995–1999	2549 (25.1)	27,465 (25.6)
2000–2004	3341 (32.9)	34,218 (31.9)
2005–2009	2464 (24.2)	25,115 (23.4)
Initial dialysis duration		
0–5 mo	3043 (29.9)	20,113 (18.7)
6–11 mo	2918 (28.7)	33,587 (31.3)
12–23 mo	2047 (20.1)	24,903 (23.2)
≥24 mo	1453 (14.3)	21,863 (20.4)
Unknown	705 (6.9)	6873 (6.4)
Maintenance therapy with CNI		
Cyclosporine	4643 (45.7)	49,110 (45.8)
Tacrolimus	4417 (43.5)	46,178 (43.0)
Both	37 (0.4)	500 (0.5)
Neither	1069 (10.5)	11,551 (10.8)

CNI, calcineurin inhibitor.

For skin cancers, we assessed associations restricted to non-Hispanic whites in order to remove confounding by race. The unadjusted associations were attenuated in this subgroup and no longer significant (melanoma: IRR, 1.33 [95% CI, 0.95 to 1.81]; other nonepithelial skin cancers: IRR, 1.36 [95% CI, 0.84 to 2.19]). Furthermore, no association was apparent among whites, after adjustment for age, sex, dialysis duration, and time since transplant, for melanoma (IRR, 1.03 [95% CI, 0.73 to 1.41]) or other nonepithelial skin cancers (IRR, 1.02 [95% CI, 0.63 to 1.67]).

As shown in Table 2, cancers of the kidney tended to occur less often in PKD recipients (IRR, 0.76;  $P=0.053$ ), although the difference was less apparent for RCC specifically (IRR, 0.84;  $P=0.26$ ). In regression models adjusted for age, sex, race/ethnicity, dialysis duration, and time since transplant,

**Table 2.** Unadjusted incidence rates and IRRs for cancer type, by PKD status

Cancer Type	PKD Recipients		Non-PKD Recipients		IRR (95% CI)
	Count (n)	Incidence Rate <sup>a</sup>	Count (n)	Incidence Rate <sup>a</sup>	
Lip	13	25.8	74	15.5	1.66 (0.88 to 2.89)
Salivary gland	7	13.9	30	6.3	2.20 (0.89 to 4.73)
Oropharynx	7	13.9	39	8.2	1.70 (0.69 to 3.56)
Other oral cavity and pharynx	5	9.9	75	15.7	0.63 (0.22 to 1.41)
Nasopharynx <sup>b</sup>	0	0	7	1.5	0
Esophagus	5	9.9	47	9.9	1.00 (0.35 to 2.29)
Stomach	8	15.9	91	19.1	0.83 (0.37 to 1.60)
Small intestine	2	4.0	19	4.0	0.99 (0.16 to 3.42)
Colon and rectum	25	49.6	328	68.9	0.72 (0.47 to 1.06)
Anus	3	5.9	51	10.7	0.56 (0.14 to 1.51)
Liver	4	7.9	51	10.7	0.74 (0.22 to 1.81)
Intrahepatic bile duct	2	4.0	3	0.6	6.30 (0.83 to 37.99)
Gallbladder <sup>b</sup>	0	0	7	1.5	0
Other biliary	4	7.9	11	2.3	3.43 (0.95 to 10.04)
Pancreas	14	27.8	84	17.6	1.57 (0.86 to 2.68)
Larynx	2	4.0	45	9.4	0.42 (0.07 to 1.36)
Lung	69	136.8	582	122.2	1.12 (0.86 to 1.43)
Bones and joints <sup>b</sup>	0	0	11	2.3	0
Soft tissue including heart	8	15.9	32	6.7	2.36 (1.01 to 4.87)
Melanoma	48	95.2	225	47.2	2.01 (1.46 to 2.72)
Other nonepithelial skin	20	39.7	107	22.5	1.77 (1.06 to 2.78)
Breast	37	73.4	299	62.8	1.17 (0.82 to 1.62)
Cervix <sup>b</sup>	0	0	27	13.9	0
Uterus	12	53.2	60	30.8	1.89 (0.97 to 3.38)
Ovary	4	17.7	26	13.3	1.45 (0.43 to 3.73)
Vagina <sup>b</sup>	0	0	8	4.1	0
Vulva	6	26.6	34	17.5	1.67 (0.63 to 3.69)
Prostate	74	265.6	555	197.2	1.26 (0.98 to 1.59)
Testis	5	17.9	26	9.2	1.82 (0.61 to 4.35)
Penis <sup>b</sup>	0	0	15	5.3	0
Bladder	13	25.8	142	29.8	0.86 (0.47 to 1.47)
Kidney	49	97.2	610	128.1	0.76 (0.56 to 1.00)
RCC <sup>c</sup>	45	89.2	505	106.0	0.84 (0.61 to 1.13)
Renal pelvis	1	2.0	15	3.1	0.63 (0.03 to 3.11)
Eye and orbit	4	7.9	12	2.5	3.15 (0.88 to 9.04)
Brain	5	9.9	29	6.1	1.63 (0.55 to 3.85)
Thyroid	16	31.7	168	35.3	0.90 (0.52 to 1.45)
Hodgkin lymphoma	5	9.9	49	10.3	0.96 (0.33 to 2.19)
Non-Hodgkin lymphoma	74	146.8	672	141.1	1.04 (0.81 to 1.31)
Plasma cell neoplasms	8	15.9	73	15.3	1.03 (0.46 to 2.02)
Acute lymphocytic leukemia	1	2.0	8	1.7	1.18 (0.06 to 6.44)
Chronic lymphocytic leukemia	1	2.0	14	2.9	0.67 (0.04 to 3.36)
Acute myeloid leukemia	7	13.9	36	7.6	1.84 (0.75 to 3.88)
Chronic myeloid leukemia	3	5.9	20	4.2	1.42 (0.33 to 4.13)
Acute monocytic leukemia <sup>b</sup>	0	0	1	0.2	0
Other acute leukemia <sup>b</sup>	0	0	4	0.8	0
Mesothelioma	1	2.0	12	2.5	0.79 (0.04 to 3.99)
Kaposi sarcoma	6	11.9	73	15.3	0.78 (0.30 to 1.64)
Miscellaneous	37	73.4	327	68.7	1.07 (0.75 to 1.48)
Tumors of poorly specified morphology	7	13.9	96	20.2	0.69 (0.29 to 1.38)
All cancers, combined	622	1233.6	5330	1119.1	1.10 (1.01 to 1.20)
All cancers excluding kidney, melanoma, and nonepithelial skin	505	1001.6	4388	921.3	1.09 (0.99 to 1.19)

<sup>a</sup>Incidence rate is per 100,000 person-years.<sup>b</sup>Because there were no cases among PKD recipients, the Poisson regression model did not converge.<sup>c</sup>RCCs are shown separately in the table, but because all were located in the kidney, they do not contribute to the total.

risk of kidney cancer in PKD recipients was significantly decreased (adjusted IRR, 0.70; 95% CI, 0.51 to 0.93;  $P=0.013$ ), but the association remained nonsignificant for RCC (IRR, 0.78; 95% CI, 0.56 to 1.05;  $P=0.11$ ).

In unadjusted analyses, PKD was associated with an increased risk of cancer overall (IRR, 1.10; 95% CI, 1.01 to 1.20;  $P=0.024$ ) (Table 2). After exclusion of kidney cancers (and therefore RCCs, since all RCCs were in the kidney), melanomas, and nonepithelial skin cell cancers, PKD recipients still tended toward having an increased cancer risk (IRR, 1.09; 95% CI, 0.99 to 1.19;  $P=0.08$ ).

However, after adjustment for potential confounders, the direction of the association was reversed: the adjusted IRR was 0.84 (95% CI, 0.77 to 0.91;  $P<0.001$ ) for all cancers combined and 0.83 (95% CI, 0.75 to 0.91;  $P<0.001$ ) for all cancers excluding kidney cancers, melanomas, and nonepithelial skin cancers (Table 3). The point estimates of these IRRs and the associated 95% CIs are shown graphically in Figure 1. Adjustment for age alone accounted for most of the effect of adjustment for the combined cancer outcomes (age-adjusted IRR, 0.88 [95% CI, 0.81 to 0.96;  $P=0.003$ ] for all cancers; IRR, 0.87 [95% CI, 0.80 to 0.96;  $P=0.004$ ] for all cancers excluding kidney cancers, melanomas, and nonepithelial skin cancers).

## DISCUSSION

In this study, we sought to determine whether cancer risk following renal transplantation differed between individuals with ADPKD and those without. Although unadjusted analyses suggested a small excess risk of cancer overall, PKD recipients were older than other kidney recipients, and when we adjusted for age and other factors, PKD recipients were actually 16% less likely to develop cancer. This decrement remained apparent after we excluded renal and skin cancers.

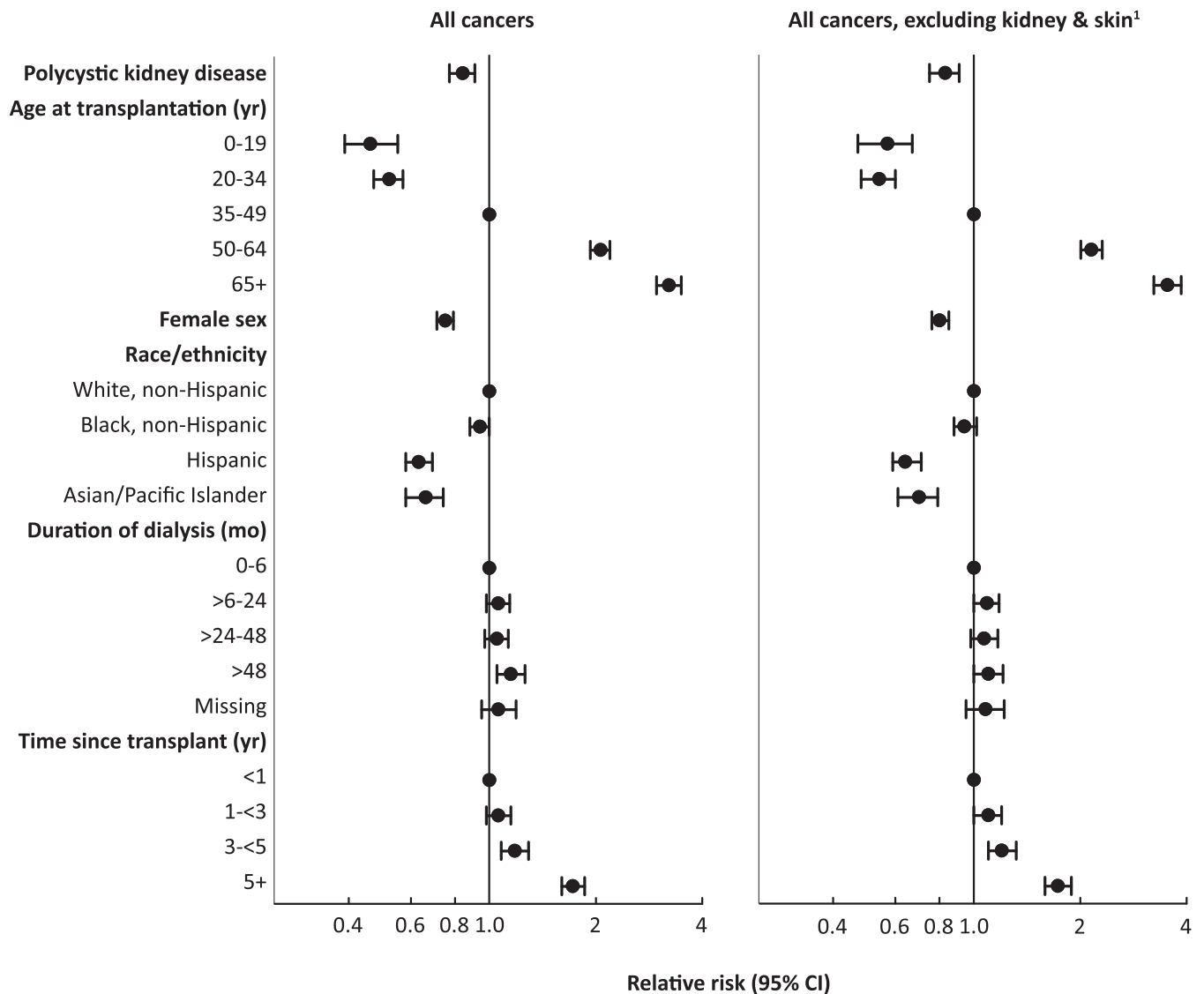
Although kidney transplant recipients have an elevated risk of cancer relative to the general population, cancer risk is lower for patients with PKD than for other kidney recipients. This finding was unexpected given that ADPKD is a multiorgan disease process with characteristics of neoplasia.<sup>9,21,22</sup> Nonetheless, no published studies that we are aware of indicate that ADPKD is associated with increased rates of cancer. Although PKD mutations clearly cause cyst formation, it is also possible that these mutations somehow trigger protective cellular mechanisms that prevent cells from undergoing malignant transformation. Potential support for this comes from a recently reported population study by Ward *et al.*<sup>23</sup> in which germline mutations in *PKHD1* (the gene responsible for autosomal recessive PKD) were protective against colorectal cancer. This group speculated

**Table 3.** Adjusted IRRs for combined cancer outcomes in PKD versus non-PKD kidney transplant recipients

Characteristic	All Cancers		All Cancers, Excluding Kidney and Skin <sup>a</sup>	
	Multivariate IRR (95% CI) <sup>b</sup>	P Value	Multivariate IRR (95% CI) <sup>b</sup>	P Value
PKD	0.84 (0.77 to 0.91)	<0.001	0.83 (0.75 to 0.91)	<0.001
Age at transplantation		<0.001		<0.001
0–19 yr	0.46 (0.39 to 0.55)		0.57 (0.47 to 0.67)	
20–34 yr	0.52 (0.47 to 0.57)		0.54 (0.48 to 0.60)	
35–49 yr	Reference		Reference	
50–64 yr	2.06 (1.93 to 2.19)		2.15 (2.01 to 2.31)	
≥65 yr	3.22 (2.97 to 3.49)		3.53 (3.23 to 3.86)	
Female sex	0.75 (0.71 to 0.79)	<0.001	0.80 (0.76 to 0.85)	<0.001
Race/ethnicity		<0.001		<0.001
White, non-Hispanic	Reference		Reference	
Black, non-Hispanic	0.94 (0.88 to 1.00)		0.94 (0.88 to 1.02)	
Hispanic	0.63 (0.58 to 0.69)		0.64 (0.59 to 0.71)	
Asian/Pacific Islander	0.66 (0.58 to 0.74)		0.70 (0.61 to 0.79)	
Duration of dialysis		0.037		0.27
0–6 mo	Reference		Reference	
>6–24 mo	1.06 (0.98 to 1.14)		1.09 (1.00 to 1.18)	
>24–48 mo	1.05 (0.97 to 1.13)		1.07 (0.98 to 1.17)	
>48 mo	1.15 (1.05 to 1.26)		1.10 (1.00 to 1.21)	
Missing mo	1.06 (0.95 to 1.19)		1.08 (0.95 to 1.22)	
Time since transplant		<0.001		<0.001
<1 yr	Reference		Reference	
1 to <3 yr	1.06 (0.98 to 1.15)		1.10 (1.00 to 1.20)	
3 to <5 yr	1.18 (1.08 to 1.29)		1.20 (1.10 to 1.32)	
>5 yr	1.72 (1.60 to 1.86)		1.73 (1.59 to 1.89)	

<sup>a</sup>These analyses exclude kidney cancers, RCCs, melanomas, and nonepithelial skin cancers.

<sup>b</sup>Adjusted for factors in this table.



<sup>1</sup>These analyses exclude kidney cancers, renal cell carcinomas, melanomas, and non-epithelial skin cancers.

**Figure 1.** The incidence of cancer overall, and of all cancers excluding kidney and skin, is lower in PKD renal transplant recipients compared with non-PKD recipients after statistical adjustment.

that a reduction of fibrocystin activity might increase mitotic instability, “paradoxically” inhibiting carcinogenesis.

Alternatively, another possibility for our observation of an inverse association between PKD and cancer invokes patterns of healthy behaviors or medical care that may distinguish patients with ADPKD from others with CKD. Those with ADPKD frequently know at a relatively early age that they have a progressive genetic condition. This might prompt them to adopt healthy behaviors, encouraged by providers who see them on a regular long-term basis.

Notably, we found a significantly lower risk of kidney cancer in PKD recipients. We believe this association arises because ADPKD recipients are more likely to have nephrectomies than their non-PKD counterparts. The Scientific Registry of

Transplant Recipients (SRTR) does not include data on nephrectomies, so we could not directly examine this possibility. Small case series suggest that the lifetime nephrectomy rate (of at least one kidney) is approximately 20%–30% for patients with ADPKD.<sup>24,25</sup> We therefore reviewed nephrectomy data from the University of Kansas Medical Center. Of 90 ADPKD recipients who underwent transplantation there during 2004–2012, 21 (23%) had a nephrectomy before or at the time of kidney transplantation (presumably, this total would be increased slightly in the post-transplant environment). In contrast, almost no pretransplant nephrectomies occurred in non-ADPKD recipients. Nephrectomy rates of 20%–30% could lead to a deficit of RCCs among ADPKD recipients. Although RCCs have been found at higher-than-expected rates in two recent large case

series of patients with PKD,<sup>14,15</sup> our data do not support a greatly increased risk of RCC associated with PKD following kidney transplantation.

We found a roughly 2-fold increase in melanomas and other nonepithelial skin cancers among ADPKD recipients, but this excess was the result of confounding by race because ADPKD recipients were more likely to be white. Restricting analysis to non-Hispanic whites demonstrated this to be the case, even before subsequent statistical adjustments. These findings are concordant with far higher rates of skin cancers in whites. We cannot draw conclusions about the association of ADPKD with the most common types of skin cancers that arise after transplantation, namely squamous and basal cell carcinomas, because cancer registries do not collect data on these cancers.

Several important study limitations must be considered. First, we only studied individuals following renal transplantation. As such, our analysis is unable to answer the question of whether the natural history for cancer varies between patients with and without PKD who have not received a transplant. Second, many low-frequency cancers occurred infrequently in PKD recipients, rendering some estimates unstable. Third, we made many statistical comparisons, which could have led to some chance associations. Indeed, we believe that the borderline-significant association between PKD and soft tissue tumors was a chance finding.

In conclusion, this was the first large-scale study of cancer in kidney recipients with PKD patients. We found a significantly lower rate compared with non-PKD recipients after adjustment for important potential confounders. The reason for this decreased risk is uncertain, and further study is required to determine how ADPKD mutations might influence development of cancer.

## CONCISE METHODS

The Transplant Cancer Match Study has been described elsewhere in detail (<http://www.transplantmatch.cancer.gov>).<sup>26</sup> Briefly, we used data from the SRTR, which contains information on all solid organ transplant recipients in the United States since 1987. This includes information on demographic characteristics, reason for transplantation, and characteristics of transplanted organs.

The SRTR has been linked to 15 population-based United States cancer registries, covering California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Michigan, New Jersey, New York, North Carolina, Texas, Utah, and the Seattle–Puget Sound area of Washington. Database linkages between the SRTR and these cancer registries used a computer-matching algorithm incorporating name, sex, date of birth, and Social Security number. This was followed by manual review of potential matches in cases of ambiguity. The linkage was approved by the human subjects committees of the National Cancer Institute and, as required, participating cancer registries.

Our study population consisted of renal transplant recipients who resided in the geographic areas covered by the 15 cancer registries (1987–2009); we excluded multiorgan recipients. Transplant recipients were considered at risk for cancer beginning with transplantation

or start of cancer registry coverage, whichever came last. Follow-up ended at death, failure of the transplanted kidney, subsequent transplant, loss to follow-up, or last date of cancer registry coverage (whichever came first). We restricted analysis to non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asian/Pacific Islanders.

Invasive cancers were identified using the linked cancer registry data and classified using the Surveillance, Epidemiology, and End Results program “site recode with Kaposi sarcoma and mesothelioma” with minor modifications.<sup>26</sup> Cancer registries do not capture basal cell and squamous cell skin cancers, but they record the occurrence of other rare nonmelanoma skin cancers (*i.e.*, nonepithelial skin cancers). Additionally, RCCs were defined by International Classification of Diseases for Oncology (version 3) morphology codes 8260 or 8310 so long as the site was in the kidney (topography code C64.9) or morphology codes 8312, 8316, 8317, or 8318 occurring at any site (although we observed all of these to arise in the kidney). Individuals could develop multiple cancers (*i.e.*, they were not censored at first cancer).

The SRTR records the presence of PKD (most cases of which are ADPKD) as an indication for transplantation. We divided renal transplant recipients into those with PKD and those without. We first compared overall cancer rates in recipients with PKD to those in the general population, using expected rates stratified by sex, age, race/ethnicity, calendar year, and registry, to generate standardized incidence ratios. We then compared the incidence of each cancer type in PKD versus non-PKD renal transplant recipients using Poisson regression. We report unadjusted IRRs. For cancer outcomes where risk differed significantly, we adjusted the IRRs for age, sex, race/ethnicity, dialysis duration, and time since transplantation. For melanoma and the included nonmelanoma skin cancers, we also evaluated Poisson models restricted to non-Hispanic whites.

All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

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## DISCLOSURES

None.

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