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ORIGINAL ARTICLE

Autosomal dominant polycystic kidney disease: risk factor for nonmelanoma skin cancer following kidney transplantation

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Summary

Nonmelanoma skin cancers (NMSC) are the most common malignant tumors following solid organ transplantation. Risk factors for NMSC mainly include immunosuppression, age, sun exposure and patient phototype. Recent findings have suggested that autosomal dominant polycystic kidney disease (ADPKD) may increase the risk of developing NMSC. We performed a monocenter retrospective study including all kidney recipients between 1985 and 2006 ($n = 1019$). We studied the incidence of NMSC, solid cancers and post-transplantation lymphoproliferative disease (PTLD), and analyzed the following parameters: age, gender, phototype, time on dialysis, graft rank, immunosuppressive regimen, history of cancer and kidney disease (ADPKD versus others). Median follow-up was 5.5 years (range: 0.02–20.6; 79 838 patient-years). The cumulated incidence of NMSC 10 years after transplantation was 12.7% (9.3% for solid cancers and 3.5% for PTLD). Autosomal dominant polycystic kidney disease and age were risk factors for NMSC (HR 2.63; $P < 0.0001$ and HR 2.21; $P < 0.001$, respectively) using univariate analysis. The association between ADPKD and NMSC remained significant after adjustments for age, gender and phototype using multivariate analysis (HR 1.71; $P = 0.0145$) and for immunosuppressive regimens ($P < 0.0001$). Autosomal dominant polycystic kidney disease was not a risk factor for the occurrence of solid cancers after transplantation (HR 0.96; $P = 0.89$). Our findings suggest that ADPKD is an independent risk factor for developing NMSC after kidney transplantation.

Introduction

Renal transplantation is established as a reference treatment for end-stage renal failure. The systemic immunosuppressive treatment, which is needed to maintain allograft organ function, is also known to facilitate the occurrence of certain cancers, in particular nonmelanoma skin cancers (NMSC) [1]. The increased incidence of such tumors has been reported in renal graft recipients, with an incidence of 40–80% after 20 years post-transplantation, depending on the country [2]. Other known risk factors for NMSC include exposure to ultraviolet B and A radiation, older age, male gender, blue or hazel eyes, human papillomavirus (HPV) infection, duration of pre-transplant dialysis and smoking [3].

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease, which occurs in about one per 1000 people worldwide [4]. It is due to a mutation of the PKD 1 gene (on the short arm of chromosome 16) in about 85% of cases, or of the PKD 2 gene (on the long arm of chromosome 4) in the remaining 15%. PKD1 and PKD2 encode the membrane proteins polycystin 1 and

polycystin 2, the roles of which are complex. Their mutation may lead to various clinical conditions, not only renal failure but also extra-renal manifestations such as kidney or liver cysts, intracranial aneurysms, cardiac valve abnormalities and colon diverticula [4]. A greater incidence of new-onset diabetes after transplantation (NODAT) has been recently reported in renal graft recipients suffering from ADPKD compared with recipients who received a renal graft for other reasons [5]. A possible association between ADPKD and the occurrence of NMSC after kidney transplantation has been recently suggested in two retrospective cohort studies [6,7].

To evaluate the risk of renal graft recipients with ADPKD developing NMSC, we conducted a retrospective monocenter study including all kidney grafts at our institution from 1985 to 2006. We performed multivariate analysis with adjustment on risk factors for NMSC, including patient phototype.

Patients and methods

Study population

All renal graft recipients at our institution between January 1985 and December 2006 were analyzed for the study.

Nearly all patients had received induction therapy, either with antithymocyte globulins or (after 1999) interleukin-2-receptor antagonists (mainly basiliximab). Prednisone (1 mg/kg/day for the first 2 weeks) was progressively decreased and finally withdrawn within the first year after transplantation in patients with low immunological risk. Azathioprine (2 mg/kg/day) was added until 1998, thereafter replaced by mycophenolate mofetil (2 g/day). Cyclosporine, tacrolimus or, more recently, rapamycin were also given to most patients at 3–5 days after transplantation. Patients who experienced acute rejection episodes were treated with methylprednisolone for 5 days, followed by oral prednisone. In case of steroid-resistant rejection, polyclonal antibodies were prescribed.

All patients were seen monthly during the first year after transplantation and then annually. All events occurring during the year and current treatments were noted and, according to the current recommendations, patients were referred annually to a dermatologist for cutaneous examination.

Parameters studied

Data were extracted from our database and from the patients' files. This was a retrospective observational study, which was not previously submitted to an ethical committee. All patients were informed about the incorporation of data in the local transplant database. At the time of transplantation, donor characteristics (gender, age, cause of death) and recipient's gender, age, primary renal diagnosis, skin phototype, history of cancers, time on dialysis before transplantation, graft rank, degree of immunization and immunosuppressive induction regimen were recorded.

The immunosuppressive treatment at the 3-month consultation after transplantation was noted. Each acute rejection episode during the first year post-transplantation was recorded in the patient's file, as well as the occurrence of all types of histologically proven cancers following transplantation.

Diagnosis of ADPKD

The diagnosis of ADPKD was based on a personal history of progressive renal failure associated with a suggestive family history of ADPKD and typical ultrasonographic or tomodensitometric evidence of polycystic kidneys. No genetic studies were requested, and thus no formal distinction was made between ADPKD due to mutation of PKD1 and PKD2.

Definition of phototype

The phototype of each patient was determined by the dermatologist based on the Fitzpatrick classification [8], and recorded in the file. When this information was missing, two trained nephrologists who participated in the follow-up of the patient concerned independently reviewed the skin phototype and compared their results. In case of disagreement, the two physicians discussed their point of view and gave a final result.

Six stages were defined as follows:

1 Phototype I: skin color ivory white; easily sunburned; no tanning.

2 Phototype II: skin color white; easily sunburned; minimal tanning with difficulty;

3 Phototype III: skin color white; moderate sunburning; moderate and uniform tanning.

4 Phototype IV: skin color beige/olive, light tanning; minimal sunburning; moderate and easy tanning.

5 Phototype V: skin color light brown or tanned; rare sunburning; profuse tanning.

6 Phototype VI: skin color dark brown or black; no sunburning; profuse tanning.

In our cohort, nearly all patients lived in a temperate climate in the Loire valley.

Definition of NMSC

Only cases of biopsy-proven basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) were counted as NMSC. Cases of Bowen's disease were considered as

in situ SCC and therefore as NMSC. Melanomas, cutaneous Kaposi's sarcomas, primary cutaneous lymphomas and other rare types of skin tumor, including adnexal skin tumors, were not considered as NMSC.

Statistical analyses

The results are expressed as mean values, standard deviations and proportions. Cox models were used in univariate and multivariate analyses to assess the association between age, gender, time on dialysis before transplantation, polycystic kidney disease, immunosuppressive treatments, phototype, history of cancer before transplantation, graft rank and the development of solid cancers, post-transplantation lymphoproliferative diseases (PTLD) and NMSC after transplantation. The results were expressed as hazard ratios (HR), 95% confidence intervals (CI) and *P*-values. The parameters selected for the multivariate analyses included ADPKD, age, gender, and skin phototype. Moreover, we analyzed the risk of NMSC in patients with ADPKD after adjustment for immunosuppressive medication. Poisson regression was also used to assess whether ADPKD was associated with multiple skin cancers after transplantation. Analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA), and a *P*-value <0.05 was considered significant.

Results

Baseline characteristics

Mean duration of follow-up (±SD) was 6.5 ± 5.3 years (median 5.5 years; range 0.02–20.6 years; total observation period 79 838 patient-years). Our cohort comprised 1019 patients, including 53 pediatric patients (recipient age <18 years). Autosomal dominant polycystic kidney disease was the cause of renal failure in 156 patients (15.3%) (Table 1). Six patients were lost during follow-up in this cohort.

Mean age of kidney recipients at transplantation was 44.3 ± 15.1 years. Most were phototype II or III as they were of Caucasian origin. A history of cancer before transplantation was reported in 3.7% of all the transplant recipients, and 0.7% of them suffered from NMSC before grafting.

Immunosuppressive induction treatment was based on antithymocyte antibodies for 69.6% of the patients, mainly those grafted between 1985 and 1999, and on interleukin-2 receptor antagonists for 24% of the patients, mainly those grafted after 1999. Three months after transplantation, 75.1% of the patients were treated with cyclosporine, 21% with tacrolimus and 3.7% with sirolimus. Fifty-eight percent of them were also receiving mycophenolate mofetil, whereas 37.4% were treated with azathioprine, mainly until 1998. Nearly all patients (94.4%) were still treated with corticosteroids at 3 months after grafting.

Table 1. Study population characteristics.

	ADPKD (n = 156)	Other kidney disease (n = 863)
Donor characteristics		
Donor age (years)	44.2 ± 15.7	38.1 ± 15.8
Male *n* (%)	104 (66.7)	550 (63.7)
Cause of death (vascular) *n* (%)	82 (53.2)	439 (51.4)
Deceased donor *n* (%)	153 (98.0)	845 (97.9)
Recipient characteristics at time of transplantation		
Male *n* (%)	81 (51.9)	547 (63.4)
Age (years)	52.7 ± 15.0	42.8 ± 12.0
Phototype *n* (%)		
I	1 (0.5)	6 (0.6)
II	40 (25.9)	216 (26.2)
III	97 (62.9)	433 (52.6)
IV	13 (8.3)	138 (16.7)
V	2 (1.3)	21 (2.5)
VI	1 (0.5)	12 (1.4)
History of cancer *n* (%)	9 (5.8)	31 (3.5)
History of NMSC *n* (%)	2 (1.3)	5 (0.5)
Time on dialysis before graft (years)	2.3 ± 3.7	3.2 ± 3.7
Immunosuppressive status		
Graft rank *n* (%)		
Second	8 (5.1)	99 (11.5)
Third	0 (0)	19 (1)
Total HLA mismatches (mean ± SD)	3.9 ± 1.2	4.1 ± 1.1
Panel reactive antibodies >75% *n* (%)	8 (5.1)	54 (6.2)
Acute rejection at 1 year *n* (%)	44 (28.2)	213 (24.7)
Induction treatment *n* (%)		
No induction	17 (10.9)	55 (6.4)
IL-2 receptor antagonists	51 (31.4)	193 (22.4)
Antithymocyte antibodies	91 (59.6)	617 (71.8)
Immunosuppressive drugs at 3 months *n* (%)		
Cyclosporine	111 (74.4)	597 (75.1)
Tacrolimus	32 (21.4)	166 (20.9)
Sirolimus	7 (4.6)	28 (3.5)
Mycophenolate mofetil	95 (63.7)	453 (56.9)
Azathioprine	46 (30.9)	307 (38.6)
Corticosteroids	137 (91.9)	754 (94.8)

ADPKD, autosomic dominant polycystic kidney disease; IL2, interleukin-2; NMSC, nonmelanoma skin cancer.

Mean age at transplantation for patients with ADPKD was 52.7 ± 15.0 years, higher than for patients without ADPKD. Nearly 6% of the patients with ADPKD had a history of cancer and 1.3% reported at least one NMSC prior to transplantation.

Incidence of NMSC, cancer and PTLD during period of follow-up

Ten years after transplantation, 12.7% of all patients had at least one NMSC, and 9.3% of them at least a solid

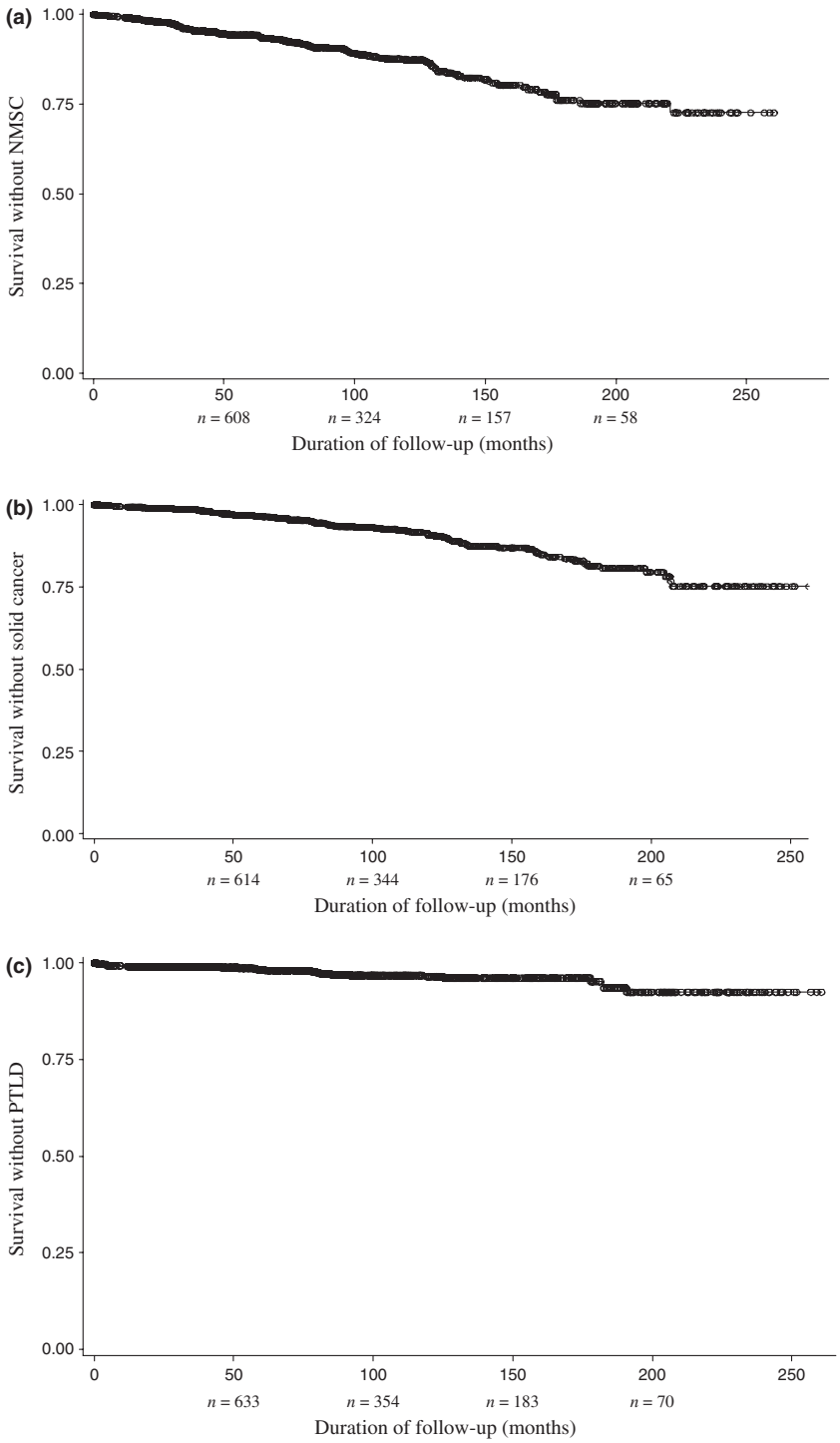

Figure 1 Incidence of nonmelanoma skin cancer (NMSC), solid cancers and post-transplant lymphoproliferative disease (PTLD) during follow-up in 1019 renal graft recipients. (a) Incidence of NMSC during follow-up. (b) Incidence of solid cancers during follow-up. (c) Incidence of PTLD during follow-up.

cancer. The incidence of NMSC at 20 years was 27.4% (Fig. 1).

One hundred and seventy-two cancers were diagnosed during the follow-up period, of which 101 (58.7%) were skin cancers. Forty-seven cases of NMSC (46.9%) were BCC and 42 (41.6%) SCC, giving a BCC/SCC ratio of 1:12. Nearly half of the patients suffering from NMSC (45.5%) developed more than one NMSC during follow-up and 2.4% of the patients had both NMSC and a solid cancer.

ADPKD and NMSC

Patients suffering from ADPKD had a significantly higher risk of developing NMSC after transplantation (Table 2),

Table 2. Risk factors for nonmelanoma skin cancer during follow-up: univariate analysis.

	NMSC		
	HR	95% CI	*P*-value
Clinical parameters			
ADPKD (yes/no)	2.63	1.71–4.02	<0.0001
Age (per 10 years)	2.21	1.84–2.65	<0.0001
Gender (male versus female)	1.39	0.92–2.11	0.12
Skin phototype ≤3	2.25	1.14–4.47	0.0202
Time on dialysis (per year of dialysis)	1.02	0.98–1.08	0.33
History of cancer prior to transplantation (yes/no)	2.32	0.94–5.72	0.07
Graft rank (per graft)	1.10	0.62–1.96	0.75
Immunosuppressive medications			
Antithymocyte antibodies (yes/no)	0.74	0.45–1.21	0.23
IL-2 receptor antagonists (yes/no)	1.06	0.55–2.04	0.86
MMF versus Aza	1.11	0.68–1.82	0.67
FK versus CsA	1.20	0.64–2.25	0.56

NMSC, nonmelanoma skin cancer; ADPKD, autosomal dominant polycystic kidney disease; IL-2, interleukin-2; MMF, mycophenolate mofetil; Aza, azathioprine; FK, tacrolimus; CsA, cyclosporine; HR, hazard ratio; CI, confidence interval.

whether it was BCC or SCC (HR 2.57; $P = 0.003$ and HR 2.68; $P = 0.004$, respectively). Age and a skin phototype ≤3 were also significantly associated with an increased risk of NMSC in the univariate analysis. Gender, time on dialysis before grafting and graft rank did not significantly affect the risk of NMSC.

After multivariate analysis including age at transplantation, gender and skin phototype, ADPKD still remained significantly associated with the occurrence of NMSC (Table 3).

Finally, we analyzed the impact of ADPKD on NMSC with relation to the immunosuppressive treatment. After adjustments for each immunosuppressive medication used (for induction or as maintenance treatment at the third month after transplantation), the presence of ADPKD remained significantly associated with the risk of NMSC (Table 4).

Table 3. Autosomal dominant polycystic kidney disease as risk factor for nonmelanoma skin cancer after kidney transplantation: multivariate analysis.

	ADPKD		
	HR	95% CI	*P*-value
Model 1	1.74	1.14–2.67	0.01
Model 2	1.74	1.14–2.67	0.01
Model 3	1.71	1.11–2.63	0.01

ADPKD, autosomal dominant polycystic kidney disease; HR, hazard ratio; CI, confidence interval.
Model 1: adjustment on age.
Model 2: Model 1 + adjustment on gender.
Model 3: Model 2 + adjustment on skin phototype.

Table 4. Autosomal dominant polycystic kidney disease as a risk factor for nonmelanoma skin cancer after adjustment on immunosuppressive regimen.

	HR	95% CI	*P*-value
Induction treatment			
Adjustment on use of antithymocyte antibodies	2.57	1.67–3.95	<0.0001
Adjustment on use of IL-2 receptors antagonists	2.62	1.70–4.01	<0.0001
Treatment at 3 months			
Adjustment on use of tacrolimus	2.60	1.67–4.04	<0.0001
Adjustment on use of cyclosporine	2.60	1.67–4.04	<0.0001
Adjustment on use of corticosteroids	2.67	1.72–4.17	<0.0001
Adjustment on use of azathioprine	2.60	1.67–4.05	<0.0001
Adjustment on use of mycophenolate mofetil	2.60	1.67–4.04	<0.0001
Adjustment on use of rapamycin	2.62	1.69–4.08	<0.0001

HR, hazard ratio; CI, confidence interval; IL-2, interleukin-2; ADPKD, autosomal dominant polycystic kidney disease; NMSC, nonmelanoma skin cancer.

As some patients had more than one skin cancer, Poisson regression was also used: ADPKD was a predictor of multiple skin cancer after transplantation [OR for each additional skin cancer: 2.59 (1.33–4.53), $P < 0.0001$] even after adjustment for age, mycophenolate mofetil use, duration of follow-up, induction with thymoglobulin and phototype [OR for each additional skin cancer: 1.77 (1.17–2.65), $P = 0.0064$].

ADPKD, solid cancers and PTLD

Patients suffering from ADPKD were not at increased risk of developing a solid cancer (HR 0.96; $P = 0.89$) or PTLD (HR 0.98; $P = 0.97$) after transplantation (Table 5).

Both history of cancer and higher age at transplantation were significantly associated with the occurrence of a solid cancer post-transplantation using univariate analysis. None of the other parameters studied, including immunosuppressive regimen, were associated with the occurence of solid cancers.

It is of note that patients who developed NMSC after transplantation were also at higher risk of developing a solid cancer thereafter (HR 4.97; $P < 0.0001$).

ADPKD and the incidence of NMSC and solid cancers during follow-up

The incidence of NMSC during follow-up was significantly higher for patients suffering from ADPKD

Table 5. Risk factors for solid cancer and post-transplantation lymphoproliferative disease (PTLD): univariate analysis.

	Solid cancer			PTLD		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Clinical parameters						
ADPKD (yes/no)	0.96	0.5–1.8	0.89	0.98	0.3–2.8	0.97
Age (per 10 years)	1.69	1.4–2.0	<0.05	0.86	0.7–1.1	0.21
Gender (male/female)	0.93	0.6–1.5	0.75	0.38	0.2–0.8	0.01
Time on dialysis (per year of dialysis)	1.03	0.9–1.1	0.79	0.94	0.8–1.1	0.43
History of cancer (yes/no)	3.92	1.6–9.8	0.004	–	–	–
Graft rank (per graft)	1.11	0.6–2.2	0.77	0.34	0.1–2.4	0.28
Immunosuppressive regimens						
Antithymocyte antibodies (yes/no)	2.03	0.9–4.8	0.10	1.63	0.4–5.6	0.44
IL-2 receptor antagonists (yes/no)	1.06	0.5–2.0	0.86	0.30	0.1–2.2	0.24
MMF versus Aza	0.94	0.5–1.7	0.83	0.44	0.1–1.4	0.16
FK versus CsA	1.07	0.5–2.4	0.87	0.33	0.1–2.5	0.28

PTLD, post-transplantation lymphoproliferative disease; ADPKD, autosomal dominant polycystic kidney disease; IL-2, interleukin-2; MMF, mycophenolate mofetil; Aza, azathioprine; FK, tacrolimus; CsA, cyclosporine; HR, hazard ratio; CI, confidence interval.

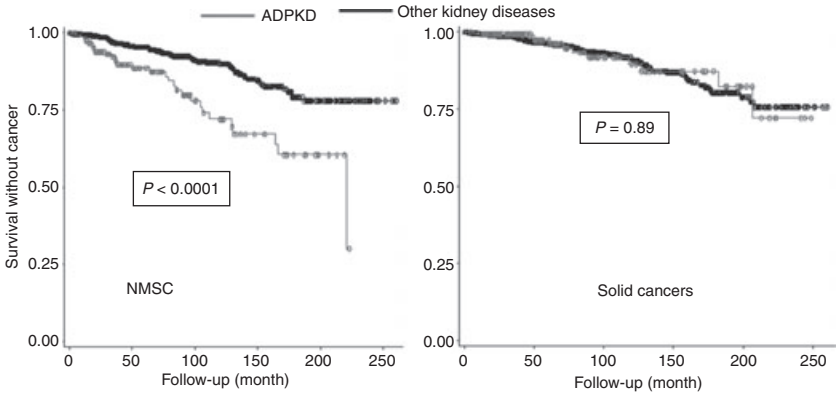

Figure 2 Incidence of nonmelanoma skin cancer (NMSC) and solid cancers during post-transplantation follow-up in patients with and without autosomal dominant polycystic kidney disease (ADPKD).

compared with patients with other primary kidney diseases ($P < 0.0001$) and this difference increased with time (Fig. 2). On the other hand, the incidence of solid cancers was not significantly different between patients with and without ADPKD ($P = 0.89$).

Discussion

Our results indicate an increased risk of developing NMSC in a specific population of renal graft recipients, i.e. patients suffering from ADPKD. Indeed, ADPKD remained a risk factor for developing both BCC and SCC after kidney transplantation, even after adjustments for age, gender and skin phototype, but not for developing solid cancers or PTLD.

Nonmelanoma skin cancers are the most common cancers following transplantation [3]. Not only do they have a deleterious impact on patients' quality of life, but they also may be life-threatening. One retrospective multicenter study found a 3-year disease-specific survival rate of 56% for organ transplant recipients with metastatic skin cancers, mainly NMSC (85%) [9]. Moreover, NMSC, and in particular SCC, may be associated with more frequent occurrence of other solid cancers [10]. This has also been reported in a recent Canadian study where the authors describe a higher incidence of death caused by malignancy in renal graft recipients who had developed NMSC [11]. Our results are in accordance with these findings.

Many risk factors for NMSC have been reported in previous studies, either linked to individual factors, such as sun exposure, age, gender, skin phototype, HPV infection and tobacco consumption, or linked to immunosuppression [3,11,12]. Immunosuppressive treatments seem

to act as a catalyst for skin carcinogenesis as they increase the frequency, number and aggressiveness of such tumors [3]. North American kidney graft recipients were reported to have an approximately 90-fold increased risk of NMSC 3 years after transplantation than the general American population [7], and in German kidney graft recipients, there was an approximately 52-fold risk 10 years after transplantation than in an age and sex-adjusted general population [13].

Two large retrospective cohort studies recently reported a relationship between ADPKD and the occurrence of NMSC in renal graft recipients. The first was based on the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) database [6], and included 46 355 renal graft recipients. The authors evaluated the effects of the primary renal disease on the incidence of skin cancer. In this study, the relative risk of developing skin cancer was reported to be 1.65 times higher in renal recipients with ADPKD than in patients with glomerular disease. No other disease in native kidneys was associated with such an increased risk. The second study, based on the United States Renal Data System (USRDS), reported the occurrence of cancer after kidney transplantation in the United States, and the association between cancer and outcome [7]. In this cohort (35 765 graft recipients), an incidence of NMSC of 7.4% was reported within the first 3 years post-transplantation. Patients with cystic kidney disease (ADPKD was not clearly identified) were shown to have a higher relative risk of developing NMSC after grafting compared with patients with glomerulonephritis. However, both studies had a brief follow-up period (3 years), whereas a recent prospective study showed a relatively low rate of annual incidence of NMSC during the first 5 years after transplantation [14]. Moreover, none of these studies reported the skin phototype and they both involved North American populations. In our study, the HR for developing NMSC during the follow-up period was 2.63 times higher for patients suffering from ADPKD than for patients with other kidney diseases. We expected initially that more patients with ADPKD would develop NMSC because they were older at transplantation, with end-stage renal failure occurring at a higher age in these patients. However, our results remained significant even after adjustment for age. Our results were also not influenced by other known risk factors for NMSC such as gender, phototype, or immunosuppressive medications. No increased risk of developing NMSC has been reported in patients suffering from ADPKD but not yet transplanted, and we did not observe an increased risk of other solid cancers post-transplantation in patients with ADPKD.

The underlying mechanisms linking ADPKD and NMSC are not clear. However, a genetic susceptibility to the development of NMSC, accelerated by the immunosuppressive treatment, may be suspected in patients with PKD1 or PKD2 mutations. Genetic susceptibility to developing NMSC after transplantation has already been reported. Polymorphisms of the interleukin-10 gene (IL-10), the glutathione-S-transferase gene (GST), the gene encoding for p-53 (TP53) and the methylenetetrahydrofolate reductase gene (MTHFR) have in particular been reported to be associated with the occurrence of NMSC after transplantation [15].

Moreover, polycystin-1, the protein encoded by PKD1, has a role in cation transport, mechanosensitivity and cell–cell/matrix interactions and also in the regulation of the cell cycle. Zheng *et al.* [16] have hypothesized that polycystin-1 may act as a potential tumor suppressor. They recently reported that *in vitro* overexpression of polycystin-1 induced apoptosis and cell cycle arrest in the Go/G_1 phase in cancer cells. Polycystin-1 is expressed in many tissues, in particular the skin [17], and has been shown to interact with polycystin-2 [16]. Whether the association of ADPKD is linked more specifically to one of the two genes (PKD1 or PKD2) of ADPKD remains to be elucidated.

The presence of ADPKD in renal graft recipients has also been shown to increase the risk of NODAT [8,18]. De Mattos *et al.* [18] found an association between ADPKD and NODAT and suggested the role of unidentified co-inherited gene(s) associated with insulin resistance in patients with ADPKD gene mutations. However, physiopathological explanations remain to be demonstrated.

Immunosuppressive treatment may need to be modified as the risk of developing NMSC is greater in patients with ADPKD. An association between the occurrence of NMSC and the level of immunosuppressive treatment has been reported [10]. We did not demonstrate an increased risk of NMSC in patients treated with tacrolimus (versus cyclosporine), or azathioprine (versus mycophenolate mofetil) at 3 months. The number of patients taking sirolimus at 3 months in our cohort was too small to be analyzed.

Nevertheless, m-TOR inhibitors (sirolimus and everolimus) may be of particular value in long-term immunosuppressive treatment for patients with ADPKD. First, m-TOR inhibitors have been demonstrated to have antineoplasic properties [19]. A recent study reported a decrease in the incidence and progression of ultraviolet B radiation-induced skin cancers in SKH mice treated with sirolimus alone or in combination with cyclosporine, whereas cyclosporine-treated mice had increased tumor size and progression [20]. Campistol *et al.* [21] showed that sirolimus-based, calcineurin inhibitor-free therapy after cyclosporine withdrawal at month 3 significantly reduced the risk of skin cancer at 5 years after renal trans-

plantation. Second, recent studies have shown inappropriate activity of m-TOR in patients suffering from ADPKD [22]. Experimental studies on animal models of ADPKD [23] and retrospective studies on rapamycin-treated ADPKD transplant patients [22] have reported delayed kidney cyst development and reduced renal volume, respectively. A clinical trial is in progress to evaluate the effectiveness and safety of sirolimus in young patients with early signs of ADPKD and intact renal function [24].

It should be borne in mind that this study was a retrospective analysis, and thus some information may not have been available. Furthermore, the duration of follow-up may not have been long enough to appreciate fully the occurrence of NMSC. Finally, sun exposure, which is a major risk factor for NMSC, was difficult to evaluate, particularly in this retrospective study, but nearly all the patients lived in the center of France.

Nevertheless, our study supports the view that ADPKD is an independent risk factor for NMSC after kidney transplantation. These results will need to be confirmed by prospective studies including evaluation of professional and recreational sun exposure, and if they are, the genetic mechanisms underlying this tendency would need to be investigated.

Authorship

MB, AB, LM, YL: design of the study; AB, JMH, YL, MB: writing of the paper; AAN, JB, CB, MR, AB: collected data; JMH, HN, YL, AB, MB: analyzed data; AB, JMH, MR, MB: performed research.

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