Cancer risk in dialyzed patients with and without diabetes

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*Highlights (for review)

Cancer risk in dialyzed patients with and without diabetes

Adélaïde Pladys[1], Gautier Defossez[2], Pierre Lemordant[3], Mathilde Lassalle[5], Pierre Ingrand[2], Christian Jacquelinet[5,6]*, Christine Riou[3], Guillaume Bouzillé[3], Pascal Van Hille[3], Cécile Vigneau[7,8], Marc Cuggia[3], Sahar Bayat[1].

[1]Univ Rennes, EHESP, REPERES (Recherche en pharmaco-épidémiologie et recours aux soins) – EA 7449, F-35000 Rennes, France; [2]Poitou-Charentes General Cancer Registry, Poitiers University Hospital, University of Poitiers, Poitiers, France; INSERM, CIC1402, Poitiers, France ; [3]Univ Rennes, CHU Rennes, Inserm, LTSI – UMR 1099, F-35000 Rennes, France; [5]Renal Epidemiology and Information Network (REIN), Biomedicine Agency, La Plaine Saint-Denis, France ; [6]CESP Centre for Research in Epidemiology and Population Health, Inserm UMRS 1018, Univ Versailles-Saint Quentin, Univ Paris-Saclay, Univ Paris Sud, Villejuif, France; [7]University of Rennes 1, INSERM U1085-IRSET, Rennes, France; [8]CHU Pontchaillou, Department of Nephrology, Rennes, France;

***Corresponding author and contact information:** Christian Jacquelinet (christian.jacquelinet@biomedecine.fr). Agence de la biomédecine, 1 avenue du Stade de France. 93212 SAINT DENIS LA PLAINE CEDEX. France

Declaration of interest

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AP, GD, PI, CJ, MC, SB contributed to the study conception and design, and provided general support to the study. GD, MS contributed to data acquisition. GD, PL, MS, GB, PVH controlled the data and algorithms qualities. PL performed the linkage procedure to merge data from the REIN and national Cancer registry. AP performed statistical analyses and AP, GD, PI, CJ, CR, MC, SB interpreted results. AP wrote the main body of this original article. BS and SG: contributed to data collection and provided general support to the study. And finally, all authors helped to revise the manuscript and approved the final manuscript for publication.

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Abstract

Background: The risk of cancer is higher in patients with renal diseases and diabetes compared with the general population. The aim of this study was to assess in dialyzed patients, the association between diabetes and the risk to develop a cancer after dialysis start.

Methods: All patients who started dialysis in the French region of Poitou-Charentes between 2008 and 2015 were included. Their baseline characteristics were extracted from the French Renal Epidemiology and Information Network and were linked to data relative to cancer occurrence from the Poitou-Charentes General Cancer Registry using a procedure developed by the INSHARE platform. The association between diabetes and the risk of cancer was assessed using the Fine & Gray model that takes into account the competing risk of death.

Results: Among the 1634 patients included, 591 (36.2%) had diabetes and 91 (5.6%) patients developed a cancer (n=24 before or at dialysis start, and n=67 after dialysis start). The risk to develop a cancer after dialysis initiation was lower in dialyzed patients with diabetes than without diabetes (SHR=0.54; 95%CI: 0.32-0.91). Moreover, compared with the general population, the cancer risk was higher in dialyzed patients without diabetes, but not in those with diabetes.

Conclusion: The risk of developing a cancer in the region of Poitou-Charentes is higher in dialyzed patients without diabetes than with diabetes.

Keywords: Cancer occurrence, Cancer registry, Diabetes, End Stage Renal Disease, INSHARE platform, REIN registry

1. Introduction

Type 2 diabetes is an important risk factor for End Stage Renal Disease (ESRD). In France, 47% of patients who started a Renal Replacement Therapy (RRT) in 2017 were diabetic, and diabetes was the second cause of ESRD (1). A recent French study showed that the current increase in the standardized incidence rate of RRT is mainly due to type 2 diabetes-related ESRD (2).

Beside diabetes, patients with ESRD often present comorbidities, particularly cardiovascular diseases, and are at higher risk to develop cancer compared with the general population (3-8). The higher incidence of cancer in patients with ESRD is explained by pro-tumor factors directly or indirectly associated with ESRD and the treatment regimens. In dialyzed patients, cancer concerns frequently the urinary system (4,5,7-10). For instance, Lin et al, recently reported that the risk of kidney (SHR=40.3; 95%CI: 13.4-121.8), bladder (SHR=41.95; 95%CI: 25.1-70.1) and upper urinary tract (SHR=61.3; 95%CI: 18.6-202.5) cancer is higher in dialyzed patients than in controls who never received dialysis (7). Indeed, urinary system organs are specifically affected by the nature of the disease that led to ESRD [primary kidney disease, acquired cystic kidney disease or associated urological abnormalities] and this could contribute to cancer development (3,5,10). In addition, altered DNA repair, impaired immune system function, chronic infection or inflammation, and also chronic immunosuppressive medication intake are factors associated with cancer development (3,6,10,11).

In the general population, diabetes increases the cancer risk (11-14). A Sweden study showed that type 2 diabetes is associated with higher standardized incidence rates of cancer in pancreas and liver [14], two organs affected by the metabolic alterations linked to diabetes (15). Hyperinsulinemia, increased oxidative stress and insulin resistance as well as stimulation of insulin-like growth factors, due to pancreas function alteration, have carcinogenic effects (12-15). Several factors common to both diseases could also explain the association between diabetes and cancer, such as obesity, hyperglycemia [14,15] and sedentary lifestyle (14). However, the association between anti-diabetic drugs and cancer is still debated. Indeed, it has been observed that insulin is associated with an

increased cancer risk, whereas metformin may reduce cancer incidence (14-17), by decreasing tumor cell proliferation.

Although ESRD and diabetes are independently associated with higher cancer risk, their combined presence does not further increase the overall risk of cancer in comparison to each disease on its own (11). On the other hand, in France, a large national cohort study observed that among dialyzed patients with ESRD, the risk of death by cancer was 30% lower in patients with diabetes than without diabetes (18). Consequently, a pilot study analyzed the medical records of dialyzed patients in Bretagne, a French region, during the 2002-2007 period to evaluate the potential association between diabetes and the incidence of specific malignancies in ESRD (19). Unfortunately, there were too few cancer events to detect a significant association between diabetes and cancer incidence among dialyzed patients. Therefore, the present study analyzed data from a larger population of dialyzed patients and followed for a longer period (data extracted from the French Renal Epidemiology and Information Network; REIN) after linkage to a regional cancer registry. The objective was to assess the association between diabetes and cancer incidence after dialysis start among patients with ESRD in the Poitou-Charentes region.

2. Material and Methods

2.1. Study population

For the present study, all ≥18-year-old incident patients who started dialysis (hemodialysis or peritoneal dialysis) in the French region of Poitou-Charentes between 2008 and 2015 were included. Poitou-Charentes is located in south-west France and had 1 783 991 inhabitants in 2012 (20). The patient data were extracted from two registries:

- The REIN registry was established in 2002 and since 2011 covers all French regions. REIN includes all patients with ESRD who start RRT (either dialysis or kidney transplantation) and live in France (21). Data on patients in the Poitou-Charentes region started to be included in REIN from 2007.

- The Poitou-Charentes General Cancer Registry was put in place at the beginning of 2008, and includes all incident cases of malignant tumor (hematological malignancies and solid tumors except for non-melanoma skin cancers) in subjects who reside regularly in the Poitou-Charentes region at the time of diagnosis, and in compliance with national and international guidelines (22).

To study cancer incidence among patients who initiated dialysis in the Poitou-Charentes region, data from the REIN registry for this region were linked to and integrated with data from the regional cancer registry. The matching procedure was automatically performed by a determinist algorithm using nominative variables that are common to both databases (family name, maiden name, name, sex, and birth date) using the INSHARE (INtegrating and Sharing Health dAta for Research) technologic platform which was developed during this project to facilitate access to health big data and foster collaborative research (23).

Ethical approval was granted by the French National Research Agency. Subjects involved in our study were extracted from the French REIN registry that received the agreement by the CNIL (Commission Nationale de l'Information et des Libertés) in 2010 (agreement number: 903188 Version 3). All involved subjects received an information leaflet before giving their verbal consent to participate. The ethics committee approved this procedure.

2.2. Data collection

For this study, patient-related data and cancer-related data were extracted from their respective databases.

Patient-related data were from the REIN registry. Three categories of variables were collected: i) sociodemographic data: sex and age; ii) clinical data at dialysis start: primary kidney disease, several comorbidities and biological parameters; and iii) ESRD management: dialysis regimen, vascular access, date of first dialysis, of renal transplantation, and of death.

Data on cancer in dialyzed patients were extracted from the regional cancer registry. For the study, the date of diagnosis, the anatomical site of origin, and the morphology (histology) of the cancer,

according to the International Classification of Diseases for Oncology (ICD-O) third edition, were collected.

2.3. Statistical analyses

Baseline characteristics were first described. Then, the characteristics of dialyzed patients with and without diabetes were compared using the Chi-square test.

Time to outcome (i.e., cancer occurrence after dialysis start) was assessed from dialysis start to the date of cancer diagnosis. The date of renal transplantation, date of death, or the endpoint (December 31, 2015) were used for patients without cancer occurrence. History of cancer was defined as a cancer that occurred before dialysis start, an active cancer at baseline (i.e., dialysis start), or a cancer as the origin of the primary renal disease. The data about cancers occurred before 2008 were issued from the REIN registry.

As death was considered a competing event, the association between patient-related data and the outcome of interest (i.e., cancer occurrence after dialysis start) was assessed by using univariate and multivariable Fine and Gray models that take into account the competing event of death. Missing data were handled using the Multiple Imputation by Chained Equations (MICE) approach with ten imputations and five cycles. To assess the association between diabetes and *de novo* cancer and to take into account the confounding effect of history of cancer, a second analysis was performed only among patients who did not have history of cancer.

Standardized Incidence Ratios (SIR) were used to compare the cancer incidence in the study population and in the French general population. SIR were calculated by dividing the observed number of cancer cases in the study population by the expected number of cases that would occur if the cancer incidence rate in the French general population (24) was applied to the study population, using person-years at risk for a given age and sex. Then, 95% Confidence Intervals (95%CI) were calculated. The SIR was calculated in function of the sex and diabetes status (yes/no).

Variables with a p-value <0.20 in univariate models were included in the multivariate models. A p-value <0.05 was considered statistically significant. Results were reported as Subdistribution Hazard Ratios (SHR) with 95% CI. All statistical analyses were performed with the STATA 13.1 software.

3. Results

3.1. Patients on dialysis

Between 2008 and 2015, 1648 patients initiated dialysis in the Poitou-Charentes region. After the exclusion of patients aged <18 years and patients with unknown diabetes status (n=14), 1634 patients were finally included in the study among whom 591 (36.2%) had diabetes (only 4.6% had type 1 diabetes) (Supporting Information Figure S1). The median follow up duration was 19,3 months (IQR: 7.7-36.3 months). During the follow up, 243 diabetic patients (41%) and 330 non-diabetic ones (32%) died. Forty-three diabetic (7%) and 253 non-diabetic patients (24%) were transplanted.

The patients' characteristics according to their diabetes status are summarized in Table 1. Compared with patients without diabetes (n=1043), patients with diabetes (n=591) were older (71.2 ± 11.2 vs 66.9 ± 16.2 years; p<0.001) and had more often comorbidities.

Table 1. Patients' characteristics at baseline by diabetes status

	With diabetes n=591	**Without diabetes n=1043**	
	n (%)	n (%)	p
Sex			0.883
Men	390 (66.3)	692 (66)	
Women	201 (33.7)	351 (34)	
Age (mean ± sd)	71.2 ± 11.2	66.9 ± 16.2	**<0.001**
Hemoglobin (g/dl)			**0.015**
<10	286 (48.4)	474 (45.4)	
10-12	236 (39.9)	389 (37.3)	
>12	45 (7.6)	132 (12.7)	
Missing	24 (4.1)	48 (4.6)	
Albumin (g/dl)			0.727
<30	115 (19.5)	192 (18.4)	
≥30	290 (49)	504 (48.3)	
Missing	186 (31.5)	347 (33.3)	
BMI (kg/m²)			**<0.001**
<18.5	6 (1.0)	53 (5.1)	
18.5-23	87 (14.7)	302 (29)	
23-25	69 (11.7)	165 (15.8)	
≥25	380 (64.3)	411 (39.4)	

Missing	49 (8.3)	112 (10.7)	
Tobacco			**<0.001**
Current/former smoker	257 (43.5)	483 (46.3)	
Non-smoker	257 (43.5)	484 (46.4)	
Missing	77 (13)	76 (7.3)	
Number of cardiovascular disease[1]			**<0.001**
0	142 (24)	504 (48.3)	
1	120 (20.3)	217 (20.8)	
≥2	329 (55.7)	322 (30.9)	
Respiratory insufficiency			**<0.001**
Yes	121 (20.5)	137 (13.1)	
No	465 (78.7)	901 (86.4)	
Missing	5 (0.8)	5 (0.5)	
Hepatic disease			0.198
Yes	14 (2.4)	15 (1.4)	
No	573 (97)	1025 (98.3)	
Missing	4 (0.6)	3 (0.3)	
History of cancer[2]			0.079
Yes	96 (16.2)	206 (19.8)	
No	495 (83.8)	837 (80.2)	
Physical impairment[3]			**<0.001**
Yes	103 (17.4)	103 (9.9)	
No	479 (81.1)	936 (89.7)	
Missing	9 (1.5)	4 (0.4)	
First dialysis modality			0.177
Peritoneal Dialysis	72 (12.2)	152 (14.6)	
Hemodialysis	519 (87.8)	891 (85.4)	
Vascular access			0.390
Catheter	219 (37.1)	385 (36.9)	
Arteriovenous fistula	236 (39.9)	411 (39.4)	
Other	64 (10.8)	94 (9.0)	
Missing	72 (12.2)	153 (14.7)	

[1]Cardiovascular diseases: coronary artery disease, peripheral vascular disease, congestive heart failure, arrhythmia, aortic aneurism, and cerebrovascular disease; [2]History of cancer: cancer occurred before dialysis start, active cancer at baseline, cancer as the cause of primary renal disease; [3]Physical impairment: physical impairment of ambulation, para- or hemi-plegia, blindness, member amputation and mental disability. BMI: Body Mass Index;

3.2. Cancer occurrence

Between 2008 and 2015, 245 patients included in the study had at least one cancer among which 154 were diagnosed before or at dialysis start. Among the 91 (5.6%) patients who developed an incident cancer after dialysis initiation (Supporting Information Fig. S1), 24 patients had another cancer before or at dialysis start and 67 were considered as having a *de novo* cancer. Among the 91 patients, only 30 had diabetes.

Overall, the most common cancer sites were lung and kidney (13.2%), followed by multiple myeloma and bladder (9.9%). The median interval between dialysis start and cancer diagnosis was 13.2 (IQR: 5.9-26.8) months. Cancer sites differed according to the patients' diabetes status (Table 2).

Table 2. Sites of cancers occurring after dialysis start.

	Entire n (%)	**Median interval between dialysis start and cancer (months)***	**With diabetes** n (%)	**Without diabetes** n (%)
Lung	12 (13.2)	17.5 (9.3-34.9)	4 (13.3)	8 (13.1)
Kidney	12 (13.2)	8.4 (2.1-22.8)	5 (16.7)	7 (11.5)
Multiple myeloma	9 (9.9)	9.6 (4.3-20.3)	0	9 (14.7)
Bladder	9 (9.9)	7.8 (4.2-9.4)	6 (20.0)	3 (4.9)
Colon	8 (8.8)	17.1 (11.4-25.8)	4 (13.3)	4 (6.6)
Prostate	6 (6.6)	11.7 (8.8-27.3)	1 (3.3)	5 (8.2)
Stomach	5 (5.5)	5.9 (2.9-6.3)	3 (10.0)	2 (3.3)
Thyroid	5 (5.5)	14.2 (10.5-17.5)	0	5 (8.2)
Rectum	4 (4.4)		1 (3.3)	3 (4.9)
Lymphomas	3 (3.3)		1 (3.3)	2 (3.3)
Breast	2 (2.2)		1 (3.3)	1 (1.6)
Esophagus	2 (2.2)		0	2 (3.3)
Pancreas	2 (2.2)		0	2 (3.3)
Others	12 (13.2)		4 (13.3)	8 (13.1)
Total	**91**	**13.2 (5.9-26.8)**	**10.5 (4.2-26.4)**	**16.5 (6.0-26.8)**

*median duration and interquartile ranges in months

Analysis of the SIR values by sex and diabetes status (Table 3) showed that the risk of cancer occurrence was significantly higher in non-diabetic men (SIR=1.48; 95%CI: 1.08-1.89) and non-diabetic women (SIR=1.81; 95%CI: 1.03-2.77) compared with men and women in the general population. Conversely, the risk of cancer was comparable in patients with diabetes and in the general population.

Table 3. Standardized incidence ratios for all malignancies, stratified by sex and diabetes status.

	Person-years	O/E	SIR (95%CI)
Men			
All	2438.5	69/50.72	1.36 (1.06-6.22)
Diabetics	814.5	24/20.35	1.18 (0.76-1.60)
Non-diabetics	1524.0	45/30.37	1.48 (1.08-1.89)
Women			
All	1341.5	22/15.01	1.47 (0.92-6.86)
Diabetics	500.0	6/6.16	0.97 (0.36-1.69)
Non-diabetics	841.5	16/8.85	1.81 (1.03-2.77)

O: Observed number of cancer cases; E: expected number of cancer cases, based on the general population in France; SIR: Standardized Incidence Ratio (ratio of observed number of cancer cases in our study by the expected number of cases that would occur if the cancer incidence rate in the French general population)

3.3. Factors associated with the risk of cancer

Analysis of the association between patient-related data and cancer occurrence after dialysis initiation using univariate and multivariate Fine & Gray models showed that in the unadjusted model (Table 4, left panel), diabetes (SHR=0.79; 95%CI: 0.51-1.22) and history of cancer (SHR=1.51; 95%CI: 0.94-2.43) were not significantly associated with the risk to develop a cancer during RRT.

In the adjusted model (Table 4, right panel), diabetes, but not history of cancer was associated with a lower risk of cancer after dialysis start (SHR=0.54; 95%CI: 0.32-0.91). Conversely, the interaction between diabetes and history of cancer was associated with higher risk to develop a cancer (SHR= 3.29; 95%CI: 1.24-8.73).

Table 4. Association of patient-related data with cancer occurrence after dialysis start (univariate and multivariate Fine & Gray models).

	Univariate Fine & Gray model SHR (95%CI)	Multivariate Fine & Gray model SHR (95%CI)
Sex (vs Men)		
Women	0.61 (0.38-0.98)	0.78 (0.47-1.31)
Age (vs 40-59 years)		
18-39	0.69 (0.16-2.99)	0.63 (0.15-2.70)
60-79	1.37 (0.75-2.50)	1.46 (0.79-2.73)
≥80	0.76 (0.37-1.55)	0.88 (0.42-1.87)
Tobacco (vs Non-smoker)		
Current/former smoker	1.93 (1.22-3.05)	1.79 (1.07-3.0)
Hemoglobin (vs 10-12 g/dl)		
<10	1.24 (0.77-1.98)	n/a
>12	0.82 (0.37-1.80)	n/a
BMI (vs 23-25 kg/m²)		
<18.5	1.49 (0.59-3.73)	n/a
18.5-23	0.91 (0.47-1.75)	n/a
≥25	0.86 (0.48-1.53)	n/a
Diabetes (vs No)		
Yes	0.79 (0.51-1.22)	0.54 (0.32-0.91)
History of cancer[1] (vs No)		
Yes	1.51 (0.94-2.43)	0.98 (0.53-1.82)
Diabetes+History of cancer (vs No, No)		
Yes, yes	n/a	3.29 (1.24-8.73)
Hepatic disease (vs No)		
Yes	0.53 (0.07-3.80)	n/a
Respiratory insufficiency (vs No)		
Yes	1.41 (0.86-2.31)	n/a
Physical impairment (vs No)		
Yes	0.35 (0.14-0.86)	n/a
Cardiovascular disease (vs 0)		
1	1.03 (0.58-1.83)	n/a
≥2	1.19 (0.74-1.91)	n/a

[1]History of cancer: Cancer before or at dialysis start; BMI: Body Mass Index; SHR: Subdistribution Hazard Ratio; 95%CI: 95% Confidence Interval

3.4. Factors associated with the risk of de novo cancers

The association between patient-related factors and *de novo* cancer events after dialysis start (n=67) was assessed using univariate and multivariate Fine & Gray models in patients without history of cancer (n=1332; Supporting Information Table S1). After adjustment for sex, age and tobacco use, diabetes was associated with a lower risk of *de novo* cancer after dialysis start (SHR=0.52; 95%CI: 0.31-0.89).

4. Discussion

This study shows that among patients with ESRD who started dialysis in the French region of Poitou-Charentes between 2008 and 2015, cancer incidence after dialysis initiation was higher in patients without than with diabetes. This result was confirmed also when assessing the occurrence of *de novo* cancers in the subpopulation without history of cancer (i.e., tumors diagnosed before or at dialysis start). Moreover, compared with the general French population, cancer risk was higher in dialyzed patients without diabetes. Conversely, the risk to develop a cancer was similar in patients with ESRD and diabetes and in the general French population.

Our results are close to those by Wong et al, who showed that mild to moderate chronic kidney disease does not increase the risk of cancer in patients with type 2 diabetes (11). The authors suggested that renal disease and diabetes lead to common pro-tumor factors (chronic inflammation, DNA mutation…) that contribute to the association with cancer, but without additive effects. A previous study showed no significant association between diabetic nephropathy and cancer (6). Conversely, another work found that the incidence of any cancer is higher in patients with primary ESRD not caused by diabetes (25). A recent study in Taiwan also reported that the risk of new cancers after dialysis start is lower in patients with ESRD and diabetes (HR=0.74; 95%CI: 0.67-0.81) than in those without diabetes (26).

Our analysis also showed that the cancer site distribution differed according to the diabetes status. Indeed, cancers of the urinary system (kidney: 16.7%, and bladder: 20%) were more common in patients with diabetes, whereas multiple myeloma was more frequent in patients without diabetes. In our study, only one patient with diabetes (3.3%) developed prostate cancer (n=5, 8.2%, in the group without diabetes). A previous meta-analysis showed that the risk of developing prostate cancer is significantly lower in diabetic men (27), possibly due to hormonal changes (decreased insulin or testosterone levels) that may have growth inhibitory effects on prostate cancer cells. Moreover, as diabetic men are more likely to be screened for prostate-specific antigen, this cancer should be more easily diagnosed compared with non-diabetic men.

Previous studies showed that metformin therapy is associated with a reduced risk of cancer (17,28), including colon-rectal cancer, among patients without diabetes (29). Metformin activates the AMP-activated protein kinase (AMPK) signaling pathway that induces cell cycle arrest and apoptosis of myeloma cells (17,28,29). We could hypothesize that patients with diabetes in our study could have been treated with metformin before reaching stage 4 kidney disease, and this might have had a protective role against cancer cell proliferation/growth. As recent KDIGO guidelines recommend that metformin should not be used in patients on dialysis (30), dialyzed patients with diabetes are often treated with insulin that is associated with higher cancer risk (31,32). However, as renal function impairment leads to reduced insulin resistance and insulin clearance (33), patients with diabetes on dialysis need less insulin than patients with normal kidney function. Consequently, lower insulin doses might also contribute to reduce the cancer risk among dialyzed patients with diabetes.

Moreover, the French recommendations suggest that all patients with ESRD and hypertension or albuminuria should be treated with Angiotensin-Receptor Blockers (ARBs), particularly if they have diabetes (34). It has been shown that renin-angiotensin system inhibitors do not increase the risk of cancer development (35), or have a protective effect against cancer development (36-38). In our population, patients with diabetes also had frequently hypertension, therefore they might have been taking ARBs, with an additional anti-tumor effect. Nevertheless, as medications are not recorded in the REIN registry, we could not include them in our analysis.

Finally, patients with diabetes, which is often characterized by the presence of several comorbidities (i.e., cardiovascular diseases, respiratory insufficiency, obesity…), might have had a closer medical follow-up than patients with fewer comorbidities, and consequently more targeted preventive treatments and medical examinations. Otherwise, diabetic patients with chronic kidney disease could develop cancer and die before the terminal stage of the kidney disease; or the association of cancer and diabetes could be considered as a barrier to dialysis initiation. This may explain the lower rate of cancer in patients with diabetes than in those without diabetes at the moment of their inclusion in the REIN registry.

This study has several strengths. We studied cancer incidence by taking into account the competing risk of death to avoid over-evaluating the risk of death for patients with diabetes before cancer development. From a technical point of view, this study provided one of the use cases to develop the INSHARE platform. This platform is the first authorized in France to securely integrate and share multisource and multiscale health data for research purposes. In our study, INSHARE facilitated the linkage procedure to merge REIN data to data relative to cancer occurrence and characteristics and made easier the data integration for statistics analysis. In terms of perspectives, the platform can be used to perform similar studies in other regions or to enrich the study with supplementary information such as individual drug consumptions or reimbursed claims coming from the French National Health Data System (39).

Our study has also limitations. As the cancer registry of the Poitou-Charentes region started only in 2008, we could not assess the cancer history of patients with the same method before and after 2008. Because our study was conducted on a specific French region and relatively low numbers of patients during a limited time period, our results can't be generalized to the entire population. Further studied are needed in order to confirm our results. Moreover, unmeasured confounding variables might influence the results. For example, we did not have data on treatments and therefore we could not study the association between drugs and cancer development. Finally, the results of the Fine and Gray model might be influenced by unmeasured confounders of the effect of the diabetes on cancer and on death.

5. Conclusions

Our study showed that the risk of developing a cancer, including *de novo* cancer, is higher in dialyzed patients without diabetes than with diabetes. ~~Similarly~~, Moreover, in comparison to the general population, the risk of developing a cancer was higher in non-diabetic than in diabetic dialyzed patients.

6. References

1. REIN annual report 2017.

https://www.agence-biomedecine.fr/IMG/pdf/rapport_rein_2017_v3.pdf

2. Vigneau C, Kolko A, Stengel B, et al. Ten-years trends in renal replacement therapy for end-stage renal disease in mainland France: Lessons from the French Renal Epidemiology and Information Network (REIN) registry. Nephrol Ther 2017; 13: 228–235
3. Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999; 354: 93–99
4. Stewart JH, Buccianti G, Agodoa L, et al. Cancers of the Kidney and Urinary Tract in Patients on Dialysis for End-Stage Renal Disease: Analysis of Data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol 2003; 14: 197–207
5. Stewart JH, Vajdic CM, Van Leeuwen LT, et al. The pattern of excess cancer in dialysis and transplantation. Nephrol Dial Transplant 2009; 24: 3225–3231
6. Cheung CYC, Chan GCW, Chan SK, et al. Cancer Incidence and Mortality in Chronic Dialysis Population: A Multicenter Cohort Study. Am J Nephrol 2016;43:153–159
7. Lin MY, Kuo MC, Hung CC, et al. Association of Dialysis with the Risks of Cancers. PLoS ONE 2015; 10(4): e0122856.
8. Lin HF, Li YH, Wang CH, Chou CL, Kuo DJ, Fang TC. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. Nephrol Dial Transplant 2012; 27: 1585–1590
9. Lee YC, Hung SY, Wang HK, et al. Is there different risk of cancer among end-stage renal disease patients undergoing hemodialysis and peritoneal dialysis? Cancer Medicine 2018; 7(2):485–498
10. Vamvakas S, Bahnerb U, Heidland A. Cancer in End-Stage Renal Disease: Potential Factors Involved. Am J Nephrol 1998; 18:89–95

11. Wong G, Zoungas S, Lo S, et al. The risk of cancer in people with diabetes and chronic kidney disease. Nephrol Dial Transplant 2012; 27: 3337–3344
12. Donadon V, Balbi M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: Potential role of insulin. World J Gastroenterol 2008;14(37): 5695-5700
13. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004; 159:1160–7.
14. Liu X, Hemminki K, Försti A, Sundquist K, Sundquist J, Ji J. Cancer risk in patients with type 2 diabetes mellitus and their relatives. Int J Cancer 2015; 137: 903-910
15. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009 ; 16 : 1103-1123
16. Shlomai G, Neel B, Le Roith D, Gallagher EJ. Type 2 Diabetes Mellitus and Cancer: The Role of Pharmacotherapy. J Clin Oncol 2016; 34:4261-4269.
17. Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009; 52:1766–1777
18. Pladys A, Couchoud C, LeGuillou A, Siebert M, Vigneau C, Bayat S. Type 1 and Type 2 Diabetes and Cancer Mortality in the 2002-2009 Cohort of 39 811 French Dialyzed Patients. Plos One 2015; 10(5): e0125089.
19. Le Guillou A, Pladys A, Kihal W, et al. Is cancer incidence different between type 2 diabetes patients compared to nondiabetics in hemodialysis? A study from the REIN registry? Nephrologie & Therapeutique 2018; 14: 142–147
20. Institut national de la statistique et des études économiques (Insee). Insee Analyses Poitou-Charentes 2014, n°08. www.insee.fr
21. Couchoud C, Stengel B, Landais P, et al. The renal epidemiology and information network (REIN): new registry for endstage renal disease in France. Nephrol Dial Transplant 2006; 21: 411.

22. Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG. Cancer Registration: Principles and Methods. Lyon: IARC; 1991
23. Bouzillé G, Westerlynck R, Defossez G, et al. Sharing Health Big Data for Research - A Design by Use Cases: The INSHARE Platform Approach. Stud Health Technol Inform 2017; 245:303-307.
24. Binder-Foucard F, Belot A, Delafosse P, Remontet L, Woronoff AS, Bossard N. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Partie 1 – Tumeurs solides. Saint-Maurice (Fra) : Institut de veille sanitaire, 2013. 122 p.
25. Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer Incidence Among US Medicare ESRD Patients Receiving Hemodialysis, 1996-2009. Am J Kidney Dis 2015; 65(5):763-72
26. Chien CC, Han MM, Chiu YH, et al. Epidemiology of cancer in end-stage renal disease dialysis patients: a national cohort study in Taiwan. J Cancer 2017; 8(1): 9–18.
27. Kasper JS, Giovannucci E. A Meta-analysis of Diabetes Mellitus and the Risk of Prostate Cancer. Cancer Epidemiol Biomarkers Prev 2006;15(11):2056-2062.
28. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 2009; 32(9):1620-1625
29. Hosono K, Endo H, Takahashi H, et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. Cancer Prev Res (Phila) 2010; 3(9):1077-1083
30. KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013. 2012; 3(1):1–163
31. Donadon V, Balb M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: Potential role of insulin. World J Gastroenterol 2008; 14(37): 5695–5700.
32. Coughlin SS, Calle EE, Teras LR, Jennifer Petrelli J, Thun MJ. Diabetes Mellitus as a Predictor of Cancer Mortality in a Large Cohort of US Adults. Am J of Epidemiol 2004; 159: 1160–1167

33. Rhee CM, Leung AM, Kovesdy CP, Lynch KE, Brent GA, Kalantar-Zadeh K. Updates on the management of diabetes in dialysis patients. Semin Dial 2014; 27(2):135-45
34. Haute Autorité de Santé. Guide du parcours de soins – Maladie Rénale Chronique de l'adulte. Saint-Denis La Plaine: HAS; 2012. https://www.has-sante.fr/portail/upload/docs/application/pdf/2012-04/guide_parcours_de_soins_mrc_web.pdf
35. Datzmann T, Fuchs S, Andree D, Hohensteinc B, Schmitte J, Schindler C. Systematic review and meta-analysis of randomised controlled clinical trial evidence refutes relationship between pharmacotherapy with angiotensin receptor blockers and an increased risk of cancer. European Journal of Internal Medicine 2019; https://doi.org/10.1016/j.ejim.2019.04.019
36. Huang CC, Chan WL, Chen YC, et al. Angiotensin II receptor blockers and risk of cancer in patients with systemic hypertension. Am J Cardiol 2011; 107(7):1028–33.
37. Chang CH, Lin JW, Wu LC, Lai MS. Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. J Clin Oncol 2011;29(22):3001–7.
38. Verhoest G, Dolley-Hitze T, Jouan F, et al. Sunitinib Combined with Angiotensin-2 Type-1 Receptor Antagonists Induces More Necrosis: A Murine Xenograft Model of Renal Cell Carcinoma. BioMed Research International 2014; http://dx.doi.org/10.1155/2014/901371
39. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, et al. Value of a National Administrative Database to Guide Public Decisions: From the Système National d'information Interrégimes de l'Assurance Maladie (SNIIRAM) to the Système National Des Données de Santé (SNDS) in France. Revue D'Epidemiologie Et De Sante Publique 2017; 65 Suppl 4: S149–67. https://doi.org/10.1016/j.respe.2017.05.004.

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Cancer risk in dialyzed patients with and without diabetes

Abstract

Background: The risk of cancer is higher in patients with renal diseases and diabetes compared with the general population. The aim of this study was to assess in dialyzed patients, the association between diabetes and the risk to develop a cancer after dialysis start.

Methods: All patients who started dialysis in the French region of Poitou-Charentes between 2008 and 2015 were included. Their baseline characteristics were extracted from the French Renal Epidemiology and Information Network and were linked to data relative to cancer occurrence from the Poitou-Charentes General Cancer Registry using a procedure developed by the INSHARE platform. The association between diabetes and the risk of cancer was assessed using the Fine & Gray model that takes into account the competing risk of death.

Results: Among the 1634 patients included, 591 (36.2%) had diabetes and 91 (5.6%) patients developed a cancer (n=24 before or at dialysis start, and n=67 after dialysis start). The risk to develop a cancer after dialysis initiation was lower in dialyzed patients with diabetes than without diabetes (SHR=0.54; 95%CI: 0.32-0.91). Moreover, compared with the general population, the cancer risk was higher in dialyzed patients without diabetes, but not in those with diabetes.

Conclusion: The risk of developing a cancer in the region of Poitou-Charentes is higher in dialyzed patients without diabetes than with diabetes.

Keywords: Cancer occurrence, Cancer registry, Diabetes, End Stage Renal Disease, INSHARE platform, REIN registry

1. Introduction

Type 2 diabetes is an important risk factor for End Stage Renal Disease (ESRD). In France, 47% of patients who started a Renal Replacement Therapy (RRT) in 2017 were diabetic, and diabetes was the second cause of ESRD (1). A recent French study showed that the current increase in the standardized incidence rate of RRT is mainly due to type 2 diabetes-related ESRD (2).

Beside diabetes, patients with ESRD often present comorbidities, particularly cardiovascular diseases, and are at higher risk to develop cancer compared with the general population (3-8). The higher incidence of cancer in patients with ESRD is explained by pro-tumor factors directly or indirectly associated with ESRD and the treatment regimens. In dialyzed patients, cancer concerns frequently the urinary system (4,5,7-10). For instance, Lin et al, recently reported that the risk of kidney (SHR=40.3; 95%CI: 13.4-121.8), bladder (SHR=41.95; 95%CI: 25.1-70.1) and upper urinary tract (SHR=61.3; 95%CI: 18.6-202.5) cancer is higher in dialyzed patients than in controls who never received dialysis (7). Indeed, urinary system organs are specifically affected by the nature of the disease that led to ESRD [primary kidney disease, acquired cystic kidney disease or associated urological abnormalities] and this could contribute to cancer development (3,5,10). In addition, altered DNA repair, impaired immune system function, chronic infection or inflammation, and also chronic immunosuppressive medication intake are factors associated with cancer development (3,6,10,11).

In the general population, diabetes increases the cancer risk (11-14). A Sweden study showed that type 2 diabetes is associated with higher standardized incidence rates of cancer in pancreas and liver [14], two organs affected by the metabolic alterations linked to diabetes (15). Hyperinsulinemia, increased oxidative stress and insulin resistance as well as stimulation of insulin-like growth factors, due to pancreas function alteration, have carcinogenic effects (12-15). Several factors common to both diseases could also explain the association between diabetes and cancer, such as obesity, hyperglycemia [14,15] and sedentary lifestyle (14). However, the association between anti-diabetic drugs and cancer is still debated. Indeed, it has been observed that insulin is associated with an

increased cancer risk, whereas metformin may reduce cancer incidence (14-17), by decreasing tumor cell proliferation.

Although ESRD and diabetes are independently associated with higher cancer risk, their combined presence does not further increase the overall risk of cancer in comparison to each disease on its own (11). On the other hand, in France, a large national cohort study observed that among dialyzed patients with ESRD, the risk of death by cancer was 30% lower in patients with diabetes than without diabetes (18). Consequently, a pilot study analyzed the medical records of dialyzed patients in Bretagne, a French region, during the 2002-2007 period to evaluate the potential association between diabetes and the incidence of specific malignancies in ESRD (19). Unfortunately, there were too few cancer events to detect a significant association between diabetes and cancer incidence among dialyzed patients. Therefore, the present study analyzed data from a larger population of dialyzed patients and followed for a longer period (data extracted from the French Renal Epidemiology and Information Network; REIN) after linkage to a regional cancer registry. The objective was to assess the association between diabetes and cancer incidence after dialysis start among patients with ESRD in the Poitou-Charentes region.

2. Material and Methods

2.1. Study population

For the present study, all ≥18-year-old incident patients who started dialysis (hemodialysis or peritoneal dialysis) in the French region of Poitou-Charentes between 2008 and 2015 were included. Poitou-Charentes is located in south-west France and had 1 783 991 inhabitants in 2012 (20). The patient data were extracted from two registries:

- The REIN registry was established in 2002 and since 2011 covers all French regions. REIN includes all patients with ESRD who start RRT (either dialysis or kidney transplantation) and live in France (21). Data on patients in the Poitou-Charentes region started to be included in REIN from 2007.

- The Poitou-Charentes General Cancer Registry was put in place at the beginning of 2008, and includes all incident cases of malignant tumor (hematological malignancies and solid tumors except for non-melanoma skin cancers) in subjects who reside regularly in the Poitou-Charentes region at the time of diagnosis, and in compliance with national and international guidelines (22).

To study cancer incidence among patients who initiated dialysis in the Poitou-Charentes region, data from the REIN registry for this region were linked to and integrated with data from the regional cancer registry. The matching procedure was automatically performed by a determinist algorithm using nominative variables that are common to both databases (family name, maiden name, name, sex, and birth date) using the INSHARE (INtegrating and Sharing Health dAta for Research) technologic platform which was developed during this project to facilitate access to health big data and foster collaborative research (23).

Ethical approval was granted by the French National Research Agency. Subjects involved in our study were extracted from the French REIN registry that received the agreement by the CNIL (Commission Nationale de l'Information et des Libertés) in 2010 (agreement number: 903188 Version 3). All involved subjects received an information leaflet before giving their verbal consent to participate. The ethics committee approved this procedure.

2.2. Data collection

For this study, patient-related data and cancer-related data were extracted from their respective databases.

Patient-related data were from the REIN registry. Three categories of variables were collected: i) sociodemographic data: sex and age; ii) clinical data at dialysis start: primary kidney disease, several comorbidities and biological parameters; and iii) ESRD management: dialysis regimen, vascular access, date of first dialysis, of renal transplantation, and of death.

Data on cancer in dialyzed patients were extracted from the regional cancer registry. For the study, the date of diagnosis, the anatomical site of origin, and the morphology (histology) of the cancer,

according to the International Classification of Diseases for Oncology (ICD-O) third edition, were collected.

2.3. Statistical analyses

Baseline characteristics were first described. Then, the characteristics of dialyzed patients with and without diabetes were compared using the Chi-square test.

Time to outcome (i.e., cancer occurrence after dialysis start) was assessed from dialysis start to the date of cancer diagnosis. The date of renal transplantation, date of death, or the endpoint (December 31, 2015) were used for patients without cancer occurrence. History of cancer was defined as a cancer that occurred before dialysis start, an active cancer at baseline (i.e., dialysis start), or a cancer as the origin of the primary renal disease. The data about cancers occurred before 2008 were issued from the REIN registry.

As death was considered a competing event, the association between patient-related data and the outcome of interest (i.e., cancer occurrence after dialysis start) was assessed by using univariate and multivariable Fine and Gray models that take into account the competing event of death. Missing data were handled using the Multiple Imputation by Chained Equations (MICE) approach with ten imputations and five cycles. To assess the association between diabetes and *de novo* cancer and to take into account the confounding effect of history of cancer, a second analysis was performed only among patients who did not have history of cancer.

Standardized Incidence Ratios (SIR) were used to compare the cancer incidence in the study population and in the French general population. SIR were calculated by dividing the observed number of cancer cases in the study population by the expected number of cases that would occur if the cancer incidence rate in the French general population (24) was applied to the study population, using person-years at risk for a given age and sex. Then, 95% Confidence Intervals (95%CI) were calculated. The SIR was calculated in function of the sex and diabetes status (yes/no).

Variables with a p-value <0.20 in univariate models were included in the multivariate models. A p-value <0.05 was considered statistically significant. Results were reported as Subdistribution Hazard Ratios (SHR) with 95% CI. All statistical analyses were performed with the STATA 13.1 software.

3. Results

3.1. Patients on dialysis

Between 2008 and 2015, 1648 patients initiated dialysis in the Poitou-Charentes region. After the exclusion of patients aged <18 years and patients with unknown diabetes status (n=14), 1634 patients were finally included in the study among whom 591 (36.2%) had diabetes (only 4.6% had type 1 diabetes) (Supporting Information Figure S1). The median follow up duration was 19,3 months (IQR: 7.7-36.3 months). During the follow up, 243 diabetic patients (41%) and 330 non-diabetic ones (32%) died. Forty-three diabetic (7%) and 253 non-diabetic patients (24%) were transplanted.

The patients' characteristics according to their diabetes status are summarized in Table 1. Compared with patients without diabetes (n=1043), patients with diabetes (n=591) were older (71.2 ± 11.2 vs 66.9 ± 16.2 years; p<0.001) and had more often comorbidities.

Table 1. Patients' characteristics at baseline by diabetes status

	With diabetes n=591	**Without diabetes n=1043**	
	n (%)	n (%)	p
Sex			0.883
Men	390 (66.3)	692 (66)	
Women	201 (33.7)	351 (34)	
Age (mean ± sd)	71.2 ± 11.2	66.9 ± 16.2	**<0.001**
Hemoglobin (g/dl)			**0.015**
<10	286 (48.4)	474 (45.4)	
10-12	236 (39.9)	389 (37.3)	
>12	45 (7.6)	132 (12.7)	
Missing	24 (4.1)	48 (4.6)	
Albumin (g/dl)			0.727
<30	115 (19.5)	192 (18.4)	
≥30	290 (49)	504 (48.3)	
Missing	186 (31.5)	347 (33.3)	
BMI (kg/m²)			**<0.001**
<18.5	6 (1.0)	53 (5.1)	
18.5-23	87 (14.7)	302 (29)	
23-25	69 (11.7)	165 (15.8)	
≥25	380 (64.3)	411 (39.4)	

Missing	49 (8.3)	112 (10.7)	
Tobacco			**<0.001**
Current/former smoker	257 (43.5)	483 (46.3)	
Non-smoker	257 (43.5)	484 (46.4)	
Missing	77 (13)	76 (7.3)	
Number of cardiovascular disease[1]			**<0.001**
0	142 (24)	504 (48.3)	
1	120 (20.3)	217 (20.8)	
≥2	329 (55.7)	322 (30.9)	
Respiratory insufficiency			**<0.001**
Yes	121 (20.5)	137 (13.1)	
No	465 (78.7)	901 (86.4)	
Missing	5 (0.8)	5 (0.5)	
Hepatic disease			0.198
Yes	14 (2.4)	15 (1.4)	
No	573 (97)	1025 (98.3)	
Missing	4 (0.6)	3 (0.3)	
History of cancer[2]			0.079
Yes	96 (16.2)	206 (19.8)	
No	495 (83.8)	837 (80.2)	
Physical impairment[3]			**<0.001**
Yes	103 (17.4)	103 (9.9)	
No	479 (81.1)	936 (89.7)	
Missing	9 (1.5)	4 (0.4)	
First dialysis modality			0.177
Peritoneal Dialysis	72 (12.2)	152 (14.6)	
Hemodialysis	519 (87.8)	891 (85.4)	
Vascular access			0.390
Catheter	219 (37.1)	385 (36.9)	
Arteriovenous fistula	236 (39.9)	411 (39.4)	
Other	64 (10.8)	94 (9.0)	
Missing	72 (12.2)	153 (14.7)	

[1]Cardiovascular diseases: coronary artery disease, peripheral vascular disease, congestive heart failure, arrhythmia, aortic aneurism, and cerebrovascular disease; [2]History of cancer: cancer occurred before dialysis start, active cancer at baseline, cancer as the cause of primary renal disease; [3]Physical impairment: physical impairment of ambulation, para- or hemi-plegia, blindness, member amputation and mental disability. BMI: Body Mass Index;

3.2. Cancer occurrence

Between 2008 and 2015, 245 patients included in the study had at least one cancer among which 154 were diagnosed before or at dialysis start. Among the 91 (5.6%) patients who developed an incident cancer after dialysis initiation (Supporting Information Fig. S1), 24 patients had another cancer before or at dialysis start and 67 were considered as having a *de novo* cancer. Among the 91 patients, only 30 had diabetes.

Overall, the most common cancer sites were lung and kidney (13.2%), followed by multiple myeloma and bladder (9.9%). The median interval between dialysis start and cancer diagnosis was 13.2 (IQR: 5.9-26.8) months. Cancer sites differed according to the patients' diabetes status (Table 2).

Table 2. Sites of cancers occurring after dialysis start.

	Entire n (%)	**Median interval between dialysis start and cancer (months)***	**With diabetes** n (%)	**Without diabetes** n (%)
Lung	12 (13.2)	17.5 (9.3-34.9)	4 (13.3)	8 (13.1)
Kidney	12 (13.2)	8.4 (2.1-22.8)	5 (16.7)	7 (11.5)
Multiple myeloma	9 (9.9)	9.6 (4.3-20.3)	0	9 (14.7)
Bladder	9 (9.9)	7.8 (4.2-9.4)	6 (20.0)	3 (4.9)
Colon	8 (8.8)	17.1 (11.4-25.8)	4 (13.3)	4 (6.6)
Prostate	6 (6.6)	11.7 (8.8-27.3)	1 (3.3)	5 (8.2)
Stomach	5 (5.5)	5.9 (2.9-6.3)	3 (10.0)	2 (3.3)
Thyroid	5 (5.5)	14.2 (10.5-17.5)	0	5 (8.2)
Rectum	4 (4.4)		1 (3.3)	3 (4.9)
Lymphomas	3 (3.3)		1 (3.3)	2 (3.3)
Breast	2 (2.2)		1 (3.3)	1 (1.6)
Esophagus	2 (2.2)		0	2 (3.3)
Pancreas	2 (2.2)		0	2 (3.3)
Others	12 (13.2)		4 (13.3)	8 (13.1)
Total	**91**	**13.2 (5.9-26.8)**	**10.5 (4.2-26.4)**	**16.5 (6.0-26.8)**

*median duration and interquartile ranges in months

Analysis of the SIR values by sex and diabetes status (Table 3) showed that the risk of cancer occurrence was significantly higher in non-diabetic men (SIR=1.48; 95%CI: 1.08-1.89) and non-diabetic women (SIR=1.81; 95%CI: 1.03-2.77) compared with men and women in the general population. Conversely, the risk of cancer was comparable in patients with diabetes and in the general population.

Table 3. Standardized incidence ratios for all malignancies, stratified by sex and diabetes status.

	Person-years	O/E	SIR (95%CI)
Men			
All	2438.5	69/50.72	1.36 (1.06-6.22)
Diabetics	814.5	24/20.35	1.18 (0.76-1.60)
Non-diabetics	1524.0	45/30.37	1.48 (1.08-1.89)
Women			
All	1341.5	22/15.01	1.47 (0.92-6.86)
Diabetics	500.0	6/6.16	0.97 (0.36-1.69)
Non-diabetics	841.5	16/8.85	1.81 (1.03-2.77)

O: Observed number of cancer cases; E: expected number of cancer cases, based on the general population in France; SIR: Standardized Incidence Ratio (ratio of observed number of cancer cases in our study by the expected number of cases that would occur if the cancer incidence rate in the French general population)

3.3. Factors associated with the risk of cancer

Analysis of the association between patient-related data and cancer occurrence after dialysis initiation using univariate and multivariate Fine & Gray models showed that in the unadjusted model (Table 4, left panel), diabetes (SHR=0.79; 95%CI: 0.51-1.22) and history of cancer (SHR=1.51; 95%CI: 0.94-2.43) were not significantly associated with the risk to develop a cancer during RRT.

In the adjusted model (Table 4, right panel), diabetes, but not history of cancer was associated with a lower risk of cancer after dialysis start (SHR=0.54; 95%CI: 0.32-0.91). Conversely, the interaction between diabetes and history of cancer was associated with higher risk to develop a cancer (SHR= 3.29; 95%CI: 1.24-8.73).

Table 4. Association of patient-related data with cancer occurrence after dialysis start (univariate and multivariate Fine & Gray models).

	Univariate Fine & Gray model SHR (95%CI)	Multivariate Fine & Gray model SHR (95%CI)
Sex (vs Men)		
Women	0.61 (0.38-0.98)	0.78 (0.47-1.31)
Age (vs 40-59 years)		
18-39	0.69 (0.16-2.99)	0.63 (0.15-2.70)
60-79	1.37 (0.75-2.50)	1.46 (0.79-2.73)
≥80	0.76 (0.37-1.55)	0.88 (0.42-1.87)
Tobacco (vs Non-smoker)		
Current/former smoker	1.93 (1.22-3.05)	1.79 (1.07-3.0)
Hemoglobin (vs 10-12 g/dl)		
<10	1.24 (0.77-1.98)	n/a
>12	0.82 (0.37-1.80)	n/a
BMI (vs 23-25 kg/m²)		
<18.5	1.49 (0.59-3.73)	n/a
18.5-23	0.91 (0.47-1.75)	n/a
≥25	0.86 (0.48-1.53)	n/a
Diabetes (vs No)		
Yes	0.79 (0.51-1.22)	0.54 (0.32-0.91)
History of cancer[1] (vs No)		
Yes	1.51 (0.94-2.43)	0.98 (0.53-1.82)
Diabetes+History of cancer (vs No, No)		
Yes, yes	n/a	3.29 (1.24-8.73)
Hepatic disease (vs No)		
Yes	0.53 (0.07-3.80)	n/a
Respiratory insufficiency (vs No)		
Yes	1.41 (0.86-2.31)	n/a
Physical impairment (vs No)		
Yes	0.35 (0.14-0.86)	n/a
Cardiovascular disease (vs 0)		
1	1.03 (0.58-1.83)	n/a
≥2	1.19 (0.74-1.91)	n/a

[1]History of cancer: Cancer before or at dialysis start; BMI: Body Mass Index; SHR: Subdistribution Hazard Ratio; 95%CI: 95% Confidence Interval

3.4. Factors associated with the risk of de novo cancers

The association between patient-related factors and *de novo* cancer events after dialysis start (n=67) was assessed using univariate and multivariate Fine & Gray models in patients without history of cancer (n=1332; Supporting Information Table S1). After adjustment for sex, age and tobacco use, diabetes was associated with a lower risk of *de novo* cancer after dialysis start (SHR=0.52; 95%CI: 0.31-0.89).

4. Discussion

This study shows that among patients with ESRD who started dialysis in the French region of Poitou-Charentes between 2008 and 2015, cancer incidence after dialysis initiation was higher in patients without than with diabetes. This result was confirmed also when assessing the occurrence of *de novo* cancers in the subpopulation without history of cancer (i.e., tumors diagnosed before or at dialysis start). Moreover, compared with the general French population, cancer risk was higher in dialyzed patients without diabetes. Conversely, the risk to develop a cancer was similar in patients with ESRD and diabetes and in the general French population.

Our results are close to those by Wong et al, who showed that mild to moderate chronic kidney disease does not increase the risk of cancer in patients with type 2 diabetes (11). The authors suggested that renal disease and diabetes lead to common pro-tumor factors (chronic inflammation, DNA mutation…) that contribute to the association with cancer, but without additive effects. A previous study showed no significant association between diabetic nephropathy and cancer (6). Conversely, another work found that the incidence of any cancer is higher in patients with primary ESRD not caused by diabetes (25). A recent study in Taiwan also reported that the risk of new cancers after dialysis start is lower in patients with ESRD and diabetes (HR=0.74; 95%CI: 0.67-0.81) than in those without diabetes (26).

Our analysis also showed that the cancer site distribution differed according to the diabetes status. Indeed, cancers of the urinary system (kidney: 16.7%, and bladder: 20%) were more common in patients with diabetes, whereas multiple myeloma was more frequent in patients without diabetes. In our study, only one patient with diabetes (3.3%) developed prostate cancer (n=5, 8.2%, in the group without diabetes). A previous meta-analysis showed that the risk of developing prostate cancer is significantly lower in diabetic men (27), possibly due to hormonal changes (decreased insulin or testosterone levels) that may have growth inhibitory effects on prostate cancer cells. Moreover, as diabetic men are more likely to be screened for prostate-specific antigen, this cancer should be more easily diagnosed compared with non-diabetic men.

Previous studies showed that metformin therapy is associated with a reduced risk of cancer (17,28), including colon-rectal cancer, among patients without diabetes (29). Metformin activates the AMP-activated protein kinase (AMPK) signaling pathway that induces cell cycle arrest and apoptosis of myeloma cells (17,28,29). We could hypothesize that patients with diabetes in our study could have been treated with metformin before reaching stage 4 kidney disease, and this might have had a protective role against cancer cell proliferation/growth. As recent KDIGO guidelines recommend that metformin should not be used in patients on dialysis (30), dialyzed patients with diabetes are often treated with insulin that is associated with higher cancer risk (31,32). However, as renal function impairment leads to reduced insulin resistance and insulin clearance (33), patients with diabetes on dialysis need less insulin than patients with normal kidney function. Consequently, lower insulin doses might also contribute to reduce the cancer risk among dialyzed patients with diabetes.

Moreover, the French recommendations suggest that all patients with ESRD and hypertension or albuminuria should be treated with Angiotensin-Receptor Blockers (ARBs), particularly if they have diabetes (34). It has been shown that renin-angiotensin system inhibitors do not increase the risk of cancer development (35), or have a protective effect against cancer development (36-38). In our population, patients with diabetes also had frequently hypertension, therefore they might have been taking ARBs, with an additional anti-tumor effect. Nevertheless, as medications are not recorded in the REIN registry, we could not include them in our analysis.

Finally, patients with diabetes, which is often characterized by the presence of several comorbidities (i.e., cardiovascular diseases, respiratory insufficiency, obesity…), might have had a closer medical follow-up than patients with fewer comorbidities, and consequently more targeted preventive treatments and medical examinations. Otherwise, diabetic patients with chronic kidney disease could develop cancer and die before the terminal stage of the kidney disease; or the association of cancer and diabetes could be considered as a barrier to dialysis initiation. This may explain the lower rate of cancer in patients with diabetes than in those without diabetes at the moment of their inclusion in the REIN registry.

This study has several strengths. We studied cancer incidence by taking into account the competing risk of death to avoid over-evaluating the risk of death for patients with diabetes before cancer development. From a technical point of view, this study provided one of the use cases to develop the INSHARE platform. This platform is the first authorized in France to securely integrate and share multisource and multiscale health data for research purposes. In our study, INSHARE facilitated the linkage procedure to merge REIN data to data relative to cancer occurrence and characteristics and made easier the data integration for statistics analysis. In terms of perspectives, the platform can be used to perform similar studies in other regions or to enrich the study with supplementary information such as individual drug consumptions or reimbursed claims coming from the French National Health Data System (39).

Our study has also limitations. As the cancer registry of the Poitou-Charentes region started only in 2008, we could not assess the cancer history of patients with the same method before and after 2008. Because our study was conducted on a specific French region and relatively low numbers of patients during a limited time period, our results can't be generalized to the entire population. Further studied are needed in order to confirm our results. Moreover, unmeasured confounding variables might influence the results. For example, we did not have data on treatments and therefore we could not study the association between drugs and cancer development. Finally, the results of the Fine and Gray model might be influenced by unmeasured confounders of the effect of the diabetes on cancer and on death.

5. Conclusions

Our study showed that the risk of developing a cancer, including *de novo* cancer, is higher in dialyzed patients without diabetes than with diabetes. Moreover, in comparison to the general population, the risk of developing a cancer was higher in non-diabetic than in diabetic dialyzed patients.

6. References

1. REIN annual report 2017.

https://www.agence-biomedecine.fr/IMG/pdf/rapport_rein_2017_v3.pdf

2. Vigneau C, Kolko A, Stengel B, et al. Ten-years trends in renal replacement therapy for end-stage renal disease in mainland France: Lessons from the French Renal Epidemiology and Information Network (REIN) registry. Nephrol Ther 2017; 13: 228–235
3. Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999; 354: 93–99
4. Stewart JH, Buccianti G, Agodoa L, et al. Cancers of the Kidney and Urinary Tract in Patients on Dialysis for End-Stage Renal Disease: Analysis of Data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol 2003; 14: 197–207
5. Stewart JH, Vajdic CM, Van Leeuwen LT, et al. The pattern of excess cancer in dialysis and transplantation. Nephrol Dial Transplant 2009; 24: 3225–3231
6. Cheung CYC, Chan GCW, Chan SK, et al. Cancer Incidence and Mortality in Chronic Dialysis Population: A Multicenter Cohort Study. Am J Nephrol 2016;43:153–159
7. Lin MY, Kuo MC, Hung CC, et al. Association of Dialysis with the Risks of Cancers. PLoS ONE 2015; 10(4): e0122856.
8. Lin HF, Li YH, Wang CH, Chou CL, Kuo DJ, Fang TC. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. Nephrol Dial Transplant 2012; 27: 1585–1590
9. Lee YC, Hung SY, Wang HK, et al. Is there different risk of cancer among end-stage renal disease patients undergoing hemodialysis and peritoneal dialysis? Cancer Medicine 2018; 7(2):485–498
10. Vamvakas S, Bahnerb U, Heidland A. Cancer in End-Stage Renal Disease: Potential Factors Involved. Am J Nephrol 1998; 18:89–95

11. Wong G, Zoungas S, Lo S, et al. The risk of cancer in people with diabetes and chronic kidney disease. Nephrol Dial Transplant 2012; 27: 3337–3344
12. Donadon V, Balbi M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: Potential role of insulin. World J Gastroenterol 2008;14(37): 5695-5700
13. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004; 159:1160–7.
14. Liu X, Hemminki K, Försti A, Sundquist K, Sundquist J, Ji J. Cancer risk in patients with type 2 diabetes mellitus and their relatives. Int J Cancer 2015; 137: 903-910
15. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009 ; 16 : 1103-1123
16. Shlomai G, Neel B, Le Roith D, Gallagher EJ. Type 2 Diabetes Mellitus and Cancer: The Role of Pharmacotherapy. J Clin Oncol 2016; 34:4261-4269.
17. Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009; 52:1766–1777
18. Pladys A, Couchoud C, LeGuillou A, Siebert M, Vigneau C, Bayat S. Type 1 and Type 2 Diabetes and Cancer Mortality in the 2002-2009 Cohort of 39 811 French Dialyzed Patients. Plos One 2015; 10(5): e0125089.
19. Le Guillou A, Pladys A, Kihal W, et al. Is cancer incidence different between type 2 diabetes patients compared to nondiabetics in hemodialysis? A study from the REIN registry? Nephrologie & Therapeutique 2018; 14: 142–147
20. Institut national de la statistique et des études économiques (Insee). Insee Analyses Poitou-Charentes 2014, n°08. www.insee.fr
21. Couchoud C, Stengel B, Landais P, et al. The renal epidemiology and information network (REIN): new registry for endstage renal disease in France. Nephrol Dial Transplant 2006; 21: 411.

22. Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG. Cancer Registration: Principles and Methods. Lyon: IARC; 1991
23. Bouzillé G, Westerlynck R, Defossez G, et al. Sharing Health Big Data for Research - A Design by Use Cases: The INSHARE Platform Approach. Stud Health Technol Inform 2017; 245:303-307.
24. Binder-Foucard F, Belot A, Delafosse P, Remontet L, Woronoff AS, Bossard N. Estimation nationale de l'incidence et de la mortalité par cancer en France entre 1980 et 2012. Partie 1 – Tumeurs solides. Saint-Maurice (Fra) : Institut de veille sanitaire, 2013. 122 p.
25. Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer Incidence Among US Medicare ESRD Patients Receiving Hemodialysis, 1996-2009. Am J Kidney Dis 2015; 65(5):763-72
26. Chien CC, Han MM, Chiu YH, et al. Epidemiology of cancer in end-stage renal disease dialysis patients: a national cohort study in Taiwan. J Cancer 2017; 8(1): 9–18.
27. Kasper JS, Giovannucci E. A Meta-analysis of Diabetes Mellitus and the Risk of Prostate Cancer. Cancer Epidemiol Biomarkers Prev 2006;15(11):2056-2062.
28. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 2009; 32(9):1620-1625
29. Hosono K, Endo H, Takahashi H, et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. Cancer Prev Res (Phila) 2010; 3(9):1077-1083
30. KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013. 2012; 3(1):1–163
31. Donadon V, Balb M, Casarin P, Vario A, Alberti A. Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: Potential role of insulin. World J Gastroenterol 2008; 14(37): 5695–5700.
32. Coughlin SS, Calle EE, Teras LR, Jennifer Petrelli J, Thun MJ. Diabetes Mellitus as a Predictor of Cancer Mortality in a Large Cohort of US Adults. Am J of Epidemiol 2004; 159: 1160–1167

33. Rhee CM, Leung AM, Kovesdy CP, Lynch KE, Brent GA, Kalantar-Zadeh K. Updates on the management of diabetes in dialysis patients. Semin Dial 2014; 27(2):135-45
34. Haute Autorité de Santé. Guide du parcours de soins – Maladie Rénale Chronique de l'adulte. Saint-Denis La Plaine: HAS; 2012. https://www.has-sante.fr/portail/upload/docs/application/pdf/2012-04/guide_parcours_de_soins_mrc_web.pdf
35. Datzmann T, Fuchs S, Andree D, Hohensteinc B, Schmitte J, Schindler C. Systematic review and meta-analysis of randomised controlled clinical trial evidence refutes relationship between pharmacotherapy with angiotensin receptor blockers and an increased risk of cancer. European Journal of Internal Medicine 2019; https://doi.org/10.1016/j.ejim.2019.04.019
36. Huang CC, Chan WL, Chen YC, et al. Angiotensin II receptor blockers and risk of cancer in patients with systemic hypertension. Am J Cardiol 2011; 107(7):1028–33.
37. Chang CH, Lin JW, Wu LC, Lai MS. Angiotensin receptor blockade and risk of cancer in type 2 diabetes mellitus: a nationwide case-control study. J Clin Oncol 2011;29(22):3001–7.
38. Verhoest G, Dolley-Hitze T, Jouan F, et al. Sunitinib Combined with Angiotensin-2 Type-1 Receptor Antagonists Induces More Necrosis: A Murine Xenograft Model of Renal Cell Carcinoma. BioMed Research International 2014; http://dx.doi.org/10.1155/2014/901371
39. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, et al. Value of a National Administrative Database to Guide Public Decisions: From the Système National d'information Interrégimes de l'Assurance Maladie (SNIIRAM) to the Système National Des Données de Santé (SNDS) in France. Revue D'Epidemiologie Et De Sante Publique 2017; 65 Suppl 4: S149–67. https://doi.org/10.1016/j.respe.2017.05.004.

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Credit role

Pladys, Defossez, Ingrand, Jacquelinet, Riou, Cuggia, Bayat: Conceptualization, Project administration; Defossez, Lemordant, Lassalle, Bouzillé, Van Hille: Data curation; Lemordant: Software; Pladys: Formal analysis; Pladys, Defossez, Ingrand, Jacquelinet, Riou, Cuggia, Bayat: Supervision, Validation, Resources; Cuggia, Defossez, Bayat: Funding acquisition; Pladys, Defossez, Ingrand, Vigneau, Bayat: Writing –original draft; Pladys, Defossez, Ingrand, Vigneau, Bayat: Writing –review and editing.