

Prostate Cancer, Kidney Transplant Wait Time, and Mortality in Maintenance Dialysis Patients: A Cohort Study Using Linked United States Renal Data System Data



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Rationale & Objective: The impact of prostate cancer on mortality in patients with end-stage kidney disease may be different from the general population. Prostate cancer may also delay the kidney transplant but has not been studied in a population-based cohort. We examined how prostate cancer influenced time to kidney transplant and death in a dialysis population.

Study Design: Retrospective population-based, risk-set propensity score–matched cohort study.

Setting & Participants: Men, 40-79 years old, who were dialysis-dependent Medicare beneficiaries without prior documented prostate cancer, from the United States Renal Data System.

Exposures: Incident prostate cancer, identified using *International Classification of Disease, Ninth Revision, Clinical Modification* system diagnosis code 185.

Outcomes: Time to kidney transplant and death.

Analytical Approach: Propensity-based risk-set matching to reduce bias between cases and controls. Cox proportional hazards model for time to death, and Fine-Gray competing risk model for time to kidney transplant.

Results: Among a total of 588,478 male dialysis patients who met the eligibility criteria, 18,162 had claims for prostate cancer. After propensity-based risk-set matching, 15,554 pairs of prostate cancer cases and controls were identified. Among the matched pairs, survival rates were 76%, 48%, and 30% at 1, 3, and 5 years in the prostate cancer group, compared with 80%, 51%, and 33% in the control group, with relative mortality of 95%, 94%, and 91% respectively (log-rank test $P < 0.001$). Prostate cancer was associated with a 22% lower likelihood of kidney transplant (HR: 0.78; 95% CI: 0.72-0.85) and 11% higher likelihood of death (HR: 1.11; 95% CI: 1.08-1.14) compared with controls. Kidney transplant was associated with a 4-fold improvement in overall survival, both in patients with and without prostate cancer (HR: 0.20; 95% CI: 0.18-0.21).

Limitations: Retrospective registry study.

Conclusions: Prostate cancer is associated with a modest increase in the risk of death and time to transplant in patients with end-stage kidney disease. Kidney transplant is associated with the same degree of survival benefit among those with pretransplant prostate cancer as those without.

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Kidney Med. 3(6):1032-1040. Published online September 29, 2021.

doi: 10.1016/j.xkme.2021.07.008

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Similar to the general population, prostate cancer is the most common cancer, after skin cancer, in men with end-stage kidney disease (ESKD).¹ In the general population, prostate cancer is often a nonaggressive cancer, with a 5-year relative survival of 98% for all stages combined.²

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Patients with ESKD are remarkably different from the general population in terms of their mortality rates. Though the mortality rates for the ESKD population have decreased over time, patients with ESKD still have substantial excess mortality rates of 100-175 deaths per 1,000 person-years compared with age-, sex-, and race-adjusted US general population.³ Because of this higher overall mortality in ESKD, the relative risk of mortality among patients with ESKD with prostate cancer may be different from those without prostate cancer. However, limited literature exists that describes the relative risk of death due to prostate cancer in ESKD. Understanding how prostate cancer interacts with ESKD mortality is important for the appropriate management of these patients.

For patients with ESKD, compared with dialysis, kidney transplant is associated with a reduction in mortality, an improvement in the quality of life, and a reduction in cost.⁴⁻⁸ On the other hand, immunosuppression that is required after a kidney transplant is associated with increased risk of cancer among solid organ transplant recipients.⁹ Studies evaluating the degree of survival benefit kidney transplant offers for patients with ESKD with prostate cancer compared with those without prostate cancer have been limited. Quantifying this relative benefit is important in making decisions regarding the treatment of prostate cancer in patients with ESKD who are eligible for kidney transplant.

Formal evidence-based guidelines on the recommended waiting time after a diagnosis of prostate cancer also are limited. The largest series addressing the impact of waiting time before kidney transplant after prostate cancer is available from Israel Penn International Transplant Tumor Registry. In the most recent report from that registry, published in 2005, the investigators recommended that less than 2 years of waiting time for those with stage I prostate cancer was appropriate, although such patients

PLAIN LANGUAGE SUMMARY

A recent guideline from the American Society of Transplantation recommended no specified waiting time for kidney transplant in most patients with end-stage kidney disease diagnosed with prostate cancer. This is in contrast to previous guidelines, which recommended 2-5 years of waiting time. We studied the influence of a diagnosis of prostate cancer on time to kidney transplant and death among patients with end-stage kidney disease from the United States Renal Data System. We found that those with prostate cancer had an excellent relative survival and a delay in kidney transplant, although kidney transplant had a remarkable 4-fold improvement in survival. Our findings support the recent recommendations that kidney transplant may not need to be delayed in most patients with end-stage kidney disease with prostate cancer.

had a recurrence rate of 14%.¹⁰ This recommendation was contradictory to an older recommendation of at least 2 years waiting time, based on information from the same registry.¹¹ In more recent years, it is evident from the literature that centers are not mandating any waiting period after a diagnosis of localized prostate cancer.¹² A very recent expert opinion recommendation by a panel of experts from the American Society of Transplantation suggested a waiting time of 2 years only in metastatic, castration-sensitive prostate cancer.¹³ This recommendation was based on the extrapolations from the general population to patients with ESKD suggesting that the rates of prostate cancer-specific deaths are low. Understanding the impact of prostate cancer on death in patients with ESKD will help develop future evidence-based guidelines.

In this study of patients with ESKD, our primary objective was to examine how mortality is influenced by a diagnosis of prostate cancer and a subsequent kidney transplant. Our secondary objective was to examine the influence of prostate cancer diagnosis on time to kidney transplant.

METHODS

This was a retrospective cohort study using the 1999-2015 United States Renal Data System (USRDS) data with linked Medicare claims. The University Hospitals Cleveland Medical Center institutional review board approved the study protocol for the protection of human participants, and informed consent was waived because data were deidentified (IRB # EM-16-58).

The USRDS is a national data system for ESKD in the United States.¹⁴ As all patients requiring dialysis are required to be reported to Medicare with the CMS-2728 Medical Evidence Form, the USRDS contains nearly all patients diagnosed and treated for ESKD in the United States. The Medicare standard analytic files claims data are

available for all Medicare-enrolled patients with ESKD in the USRDS. Medicare claims contain information on the *International Classification of Diseases Ninth Revision, Clinical Modification* diagnosis codes and dates of service.

Study Population

The study population consisted of men, aged 40 to 79 years, with ESKD, who were enrolled in Medicare Part A and B. We chose 40 years as the lower limit because it is rare to have prostate cancer before the age of 40, and we chose 79 years as the upper limit because it is rare to have a kidney transplant after the age of 79. Because patients with ESKD are eligible for Medicare enrollment, our study population represented the general ESKD population in the United States. Patients were excluded if their mortality date or kidney transplant date occurred within 90 days after the first recorded date of ESKD service or if they had any cancer at baseline.

Main Exposure

The key study variable was incident prostate cancer that occurred after the initiation of dialysis and before the kidney transplant, as defined by the presence of *International Classification of Diseases Ninth Version, Clinical Modification* diagnosis code 185 in Medicare claims data.

Outcomes

The outcome measures for this study were time to death and time to kidney transplant, both measured starting from 90 days after the first ESKD index date to account for the Medicare waiting period. Time to death and time to kidney transplant were right censored at the end of the study follow-up period (December 31, 2015). We also studied the primary cause of death as recorded on the Center for Medicare Services-2746 death notification form. The primary cause of death was categorized into cardiovascular, infection, malignancy, withdrawal of dialysis, other, and unknown. Malignancy was a composite cause of death from any malignancy, including prostate cancer, because USRDS lacked granularity on the type of malignancy.

Other Covariates

Other variables included in our analysis were age (categorized into 3 groups based on American Urologic Association risk groups), race (Black, White, or other), Hispanic ethnicity, dialysis type (continuous ambulatory peritoneal dialysis, continuous cycler peritoneal dialysis, and hemodialysis), access type (arteriovenous fistula, graft, catheter, and other), inability to ambulate, inability to transfer, employment status (employed, retired, unemployed, or other), health insurance coverage at baseline (ie, the health insurance coverage of the patient immediately before the ESKD index date) (employer group plan, Medicaid, Medicare, uninsured, and other), body mass index, and comorbid conditions. Comorbid conditions included atherosclerotic heart disease, alcohol dependence, cancer, congestive heart failure, chronic

obstructive pulmonary disease, diabetes, hypertension, needing assistance with the activities of daily living, peripheral vascular disease, and current tobacco use. Patients could have multiple health insurance plans at baseline (eg, dual Medicare-Medicaid enrollees). The only variables that had missing data were body mass index and access type. This was managed using mean substitution and creating a missing indicator dummy variable. A “missing” category was created for access type. These variables were derived from data collected on the CMS 2728 Medical Evidence Form.

Statistical Analysis and Propensity Score Matching

Patients with prostate cancer had clinical characteristics that differed from those without prostate cancer. To control for confounding variables, we used propensity score matching.¹⁵ The matching algorithm was a 1:1 greedy match of prostate cancer patients to controls using a caliper of 0.1 standard deviations of the linear propensity score. Controls were persons with ESKD who did not have prostate cancer. All of the aforementioned covariates were included as independent variables in the propensity score model, and the log-transformed predicted probability of developing prostate cancer was used as the propensity score. Additionally, to account for that prostate cancer could develop at different time points in the study period, we used risk-set propensity score matching.¹⁶ In risk-set matching, a patient diagnosed with prostate cancer at time *t* is matched to a “control,” who has not yet been diagnosed with prostate cancer as of time *t* (but may in the future), based only on the (potentially time-varying) characteristics up to time *t*. That time point *t* then becomes the index date, and the matched case-control patients are followed forward from there. An advantage of this method is that it accounts for the possibility that controls are just patients who have not been diagnosed with prostate cancer yet but may be diagnosed at some later time point. We assessed covariate balance by calculating the standardized mean difference before and after matching. Covariates with <20% difference in standardized mean difference were considered balanced between groups.

We tabulated the relevant descriptive statistics for all study variables. Statistical tests were used to compare distributions of covariates across prostate cancer. We calculated the standardized mean difference for each variable both before and after matching. We used the Kaplan-Meier method to generate survival curves for time to death and cumulative incidence curves for time to kidney transplant and the log-rank test to test for significant differences between groups. For each outcome, we stratified by prostate cancer. For time to death, we also generated curves stratifying by kidney transplant status along with prostate cancer. These analyses were conducted both before and after propensity score matching. In addition, we calculated the relative mortality of patients with ESKD with prostate cancer compared with those with ESKD

without prostate cancer by dividing the survival rates of those with prostate cancer by those without prostate cancer at 1, 3, and 5 years of follow-up. We used Cox proportional hazards model to calculate hazard ratios (HR) and 95% confidence intervals (CI) for time to death. We ran 2 different models with time to death as the outcome, with prostate cancer or prostate cancer and kidney transplant status as the independent variables. We also ran another model, Fine and Gray competing risk model, with time to kidney transplant as the event of interest, death as the competing event, and prostate cancer as the independent variable. Prostate cancer and kidney transplant status variables were modeled as time-varying. We also ran an interaction model between prostate cancer and kidney transplant status. The analysis was conducted using Statistical Analysis System version 9.4.

RESULTS

Baseline Characteristics of the Entire Cohort

A total of 588,478 male patients with ESKD met our eligibility criteria. Among these, 18,162 (3.1%) had claims for prostate cancer (Fig 1). Table 1 illustrates the baseline characteristics of patients with ESKD stratified by prostate cancer. Compared with those without prostate cancer, those with prostate cancer were older (48% over 70 years compared with only 28% in the controls), were more likely to be of Black and less likely to be of Hispanic ethnicity, had lesser body mass index, were less likely to start hemodialysis with a catheter as access, and were less likely to have diabetes. More patients in the prostate cancer group had Medicare insurance at baseline and were more often retired compared with the control group (Table 1).

Assessing Balance After Matching

We were able to match 15,554 patients with prostate cancer to the same number of controls. After matching, we assessed the balance of these baseline variables. The balance of most covariates across exposure groups significantly improved after matching. The standardized mean difference between the groups was <0.2, indicating adequate match (Table 2 and Fig S1).¹⁷

Impact of Prostate Cancer and Subsequent Kidney Transplant on Mortality

In the matched groups, 12,067 (77.6%) patients with prostate cancer died, compared with 11,978 (77.1%) of the controls during a mean follow-up of 3.1 years for prostate cancer group and 3.5 years for the matched controls. Figure 2 illustrates Kaplan-Meier curves for survival of patients with prostate cancer, compared with matched controls. Patient survival was 76%, 48%, and 30% at 1, 3, and 5 years among the prostate cancer group, compared with 80%, 51%, and 33% among the control group, with a relative mortality of 95%, 94%, and 91%, respectively (log-rank test $P < 0.001$). At any given point in time, prostate cancer was associated with 11% higher

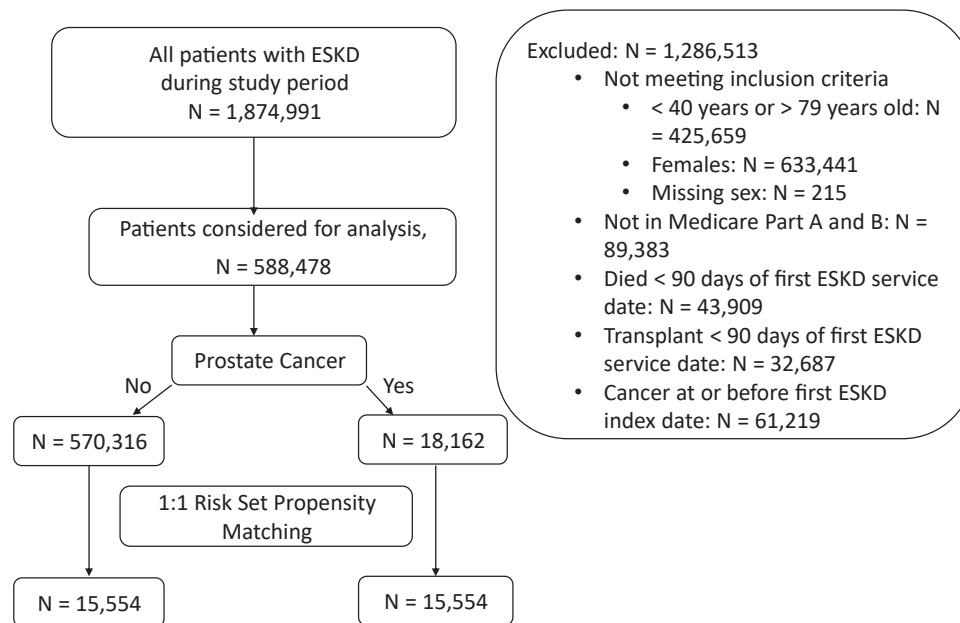


Figure 1. Flow chart of study population.

likelihood of death (HR: 1.11; 95% CI: 1.08-1.14) than matched controls (Table 3). On further stratification by kidney transplant status, Figure 3 illustrates the Kaplan-Meier estimates of time to death. The mean duration of survival among patients who did not have prostate cancer and who did not get a kidney transplant was 2.9 years, compared with 2.7 years for patients who had prostate cancer and did not receive kidney transplant, 7.3 years for patients who did not have prostate cancer but received kidney transplant, and 7.1 years for patients who had prostate cancer and received a transplant (Fig 3). Transplantation was associated with improvement in survival by approximately 80%, both in patients with prostate cancer and matched controls (Table 3). Lastly, there was no significant interaction between prostate cancer and transplant status ($\beta = -0.085$, 95%CI: -0.204 , 0.035 , $P = 0.16$). On further assessment of the causes of death, any malignancy accounted for 3.5% in the patients who did not have prostate cancer and who did not get a kidney transplant group and 8.2% in the patients who had prostate cancer and did not receive kidney transplant group. However, there was no difference in the rates of causes of death from any malignancy between patients who did not have prostate cancer but received kidney transplant and patients who had prostate cancer and received a transplant (6.3% and 6.6%) (Table S1).

Prostate Cancer and Kidney Transplantation

Of the 15,544 patients with prostate cancer, 961 (6.2%) patients received a kidney transplant, compared with 1,220 (7.8%) matched controls during the study period. Figure 4 illustrates the cumulative incidence curves for time to transplant among the propensity-based matched controls. The transplant rates were 2%, 7%, and 11% at 1,

3, and 5 years for the prostate cancer group, respectively, compared with 3%, 8%, and 13% for the control group (log-rank test $P < 0.001$). The median time to kidney transplant among those who had prostate cancer was 3.9 years (interquartile range: 1-6.4 years). At any given time during the follow-up, prostate cancer was associated with 16% less likelihood of transplant (HR:0.84; 95% CI: 0.77-0.91) (Table 3). Although the rates of living donor kidney transplants were identical among those with and without prostate cancer (18%), donation after cardiac death was more prevalent among those with prostate cancer (17% vs 13%), which also probably accounted for higher delayed graft function among those with prostate cancer (33% vs 27%) (Table S2).

DISCUSSION

In this retrospective study of US national registry of patients with ESKD, in which we examined the associations of incident prostate cancer with mortality and time to kidney transplant, we observed the following findings. First, prostate cancer was associated with a modest but statistically significant increase in mortality. Second, prostate cancer was associated with a modest but statistically significant delay in kidney transplant. Third, the reduction in mortality associated with kidney transplant was comparable in those with prostate cancer to those without prostate cancer.

Compared with the general population, in which the 5-year relative survival of those with prostate cancer to those without prostate cancer is 98%, our finding of 91% for patients with ESKD with prostate cancer to matched controls is lower.² There are multiple potential explanations for this difference. First, as shown by Taneja et al,¹⁸ the

Table 1. Baseline Characteristics of Dialysis Patients With and Without an Incident Diagnosis of Prostate Cancer From the United States Renal Data System (1999-2015)

Overall population	No Prostate Cancer		Prostate Cancer		SMD
	N = 570,316		N = 18,162		
Age (y)					
40-54	156,046	27%	1,479	8%	-0.52
55-69	257,143	45%	7,920	44%	-0.03
70-79	157,127	28%	8,763	48%	0.44
Race					
Black	152,117	27%	7,139	39%	0.27
White	384,323	67%	10,389	57%	-0.21
Other	33,876	6%	634	3%	-0.12
Hispanic ethnicity	87,600	15%	1,796	10%	-0.17
Dialysis type					
CAPD	28,244	5%	838	5%	-0.02
CCPD	17,442	3%	457	3%	-0.03
Hemo	523,362	92%	16,817	93%	0.03
Other	1,268	0%	50	0%	0.01
Access type					
AVF	68,296	12%	2,125	12%	-0.01
Graft	9,455	2%	385	2%	0.03
Catheter	275,272	48%	7,554	42%	-0.13
Other	2,600	0%	104	1%	0.02
Missing data	214,693	38%	7,994	44%	0.13
Inability to ambulate	26,738	5%	537	3%	-0.09
Inability to transfer	11,473	2%	236	1%	-0.06
Comorbid conditions					
Atherosclerotic heart disease	79,907	14%	2,245	12%	-0.05
Alcohol dependence	12,551	2%	252	1%	-0.06
Congestive heart failure	180,472	32%	5,138	28%	-0.07
COPD	50,754	9%	1,479	8%	-0.03
Cerebrovascular disease	54,237	10%	1,542	8%	-0.04
Diabetes	284,210	50%	6,624	36%	-0.27
Hypertension	493,655	87%	15,681	86%	-0.01
Needs assistance with ADL	36,519	6%	777	4%	-0.09
Peripheral vascular disease	89,013	16%	2,217	12%	-0.10
Current tobacco user	42,794	8%	971	5%	-0.09
Employment status					
Employed	91,913	16%	2,051	11%	-0.14
Retired	361,650	63%	13,456	74%	0.23
Unemployed	108,273	19%	2,343	13%	-0.17
Other	8,480	1%	312	2%	0.02
Insurance at first ESKD date ^a					
Employer group plan	144,117	25%	4,340	24%	-0.03
Medicaid	114,173	20%	2,874	16%	-0.11
Medicare	334,191	59%	13,220	73%	0.30
None	43,437	8%	941	5%	-0.10
Other	147,489	26%	5,741	32%	0.13
	Mean	SD	Mean	SD	
Body mass index	28.4	7.1	27.7	6.3	-0.13

Note: All cells reflect counts except for body mass index. All counts are column percentages.

Abbreviations: ADL, Activities of daily living; AVF, arteriovenous fistula; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; COPD, chronic obstructive pulmonary disease; ESKD, end-stage kidney disease SD, standard deviation; SMD, standardized mean difference.

^aPercentages for insurance at first ESKD do not add up to 100% because a given patient could have more than 1 type of insurance.

proportion of patients presenting with advanced stages of prostate cancer is higher in the ESKD population than in the general population. Second, the multiple comorbid

conditions characteristic of the ESKD population could result in a less aggressive treatment of prostate cancer and, in some cases, may actually lead to the discontinuation of

Table 2. Baseline Characteristics of Propensity Matched Dialysis Patients With and Without Incident Prostate Cancer From the United States Renal Data System (1999-2015)

Overall population	No Prostate Cancer		Prostate Cancer		SMD
	N = 15,544		N = 15,544		
Age (y) ^a					
40-54	1,720	11%	1,095	7%	-0.14
55-69	6,530	42%	6,755	43%	0.03
70-79	7,294	47%	7,694	49%	0.05
Race					
Black	6,455	42%	6,002	39%	-0.06
White	8,534	55%	9,004	58%	0.06
Other	555	4%	538	3%	-0.01
Hispanic ethnicity	1,616	10%	1,511	10%	0.01
Dialysis type					
CAPD	743	5%	727	5%	0.00
CCPD	388	2%	403	3%	0.01
Hemo	14,373	92%	14,370	92%	0.00
Other	40	<1%	44	<1%	0.01
Access type					
AVF	1,768	11%	1,940	12%	0.03
Graft	252	2%	349	2%	0.05
Catheter	6,061	39%	6,890	44%	0.11
Other	77	0%	91	1%	0.01
Missing data	7,386	48%	6,274	40%	-0.14
Inability to ambulate	340	2%	491	3%	0.06
Inability to transfer	136	1%	211	1%	0.05
Comorbid conditions					
Atherosclerotic heart disease	1,830	12%	2,075	13%	0.05
Alcohol dependence	205	1%	215	1%	0.01
Congestive heart failure	4,274	27%	4,573	29%	0.04
COPD	1,211	8%	1,338	9%	0.03
Cerebrovascular disease	1,337	9%	1,384	9%	0.01
Diabetes	5,658	36%	5,988	39%	0.04
Hypertension	14,004	90%	13,885	89%	-0.03
Needs assistance with ADL	551	4%	713	5%	0.05
Peripheral vascular disease	1,839	12%	2,005	13%	0.03
Current tobacco user	861	6%	852	5%	0.00
Employment status					
Employed	1,969	13%	1,668	11%	-0.06
Retired	11,250	72%	11,701	75%	0.07
Unemployed	2,083	13%	1,960	13%	-0.02
Other	242	2%	215	1%	-0.01
Insurance at first ESKD date ^b					
Employer group plan	3,883	25%	3,677	24%	-0.03
Medicaid	2,437	16%	2,469	16%	0.01
Medicare	10,729	69%	11,580	74%	0.12
None	746	5%	763	5%	0.01
Other	4,643	30%	4,866	31%	0.00
Dead at end of study period	11,978	77%	12,067	78%	0.01
Received a transplant	1,220	8%	961	6%	-0.07
	Mean	SD	Mean	SD	SMD
Body mass index	28.2	6.6	28.0	6.4	-0.03

Note: All cells reflect counts except for body mass index. All counts are column percentages.

Abbreviations: ADL, Activities of daily living; AVF, arteriovenous fistula; CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycling peritoneal dialysis; COPD, chronic obstructive pulmonary disease; ESKD, end-stage kidney disease SD, standard deviation; SMD, standardized mean difference.

^aAge was a continuous variable in the propensity score model.

^bPercentages for insurance at first ESKD do not add up to 100% because a given patient could have more than 1 type of insurance.

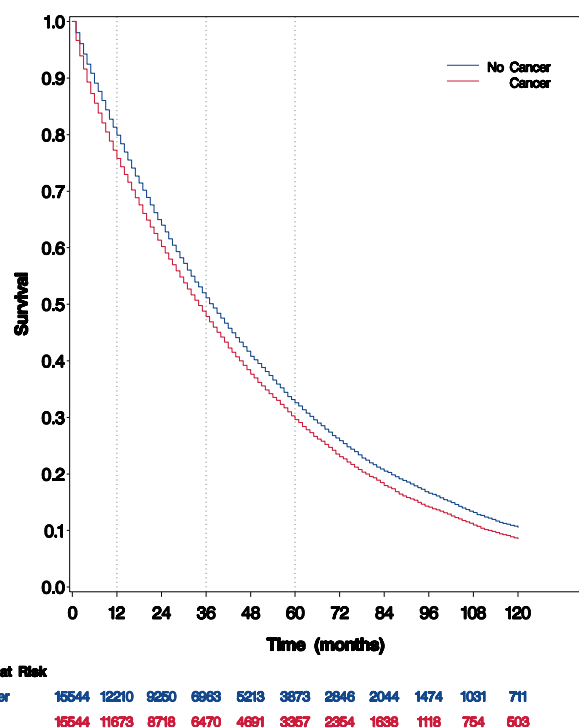


Figure 2. Kaplan-Meier curve comparing survival time in months between those with prostate cancer (red) and those without prostate cancer (blue). Time zero is the timepoint when a prostate cancer case is matched to a control. For example, if a man was diagnosed with prostate cancer 9 months after end-stage kidney disease (ESKD), then he would be matched to a control that was also at 9 months after ESKD.

dialysis. Third, the complications of treatments for prostate cancer may be worse among patients with ESKD than general population. Finally, a delay in kidney transplant because of a diagnosis of prostate cancer may contribute to an increase in relative mortality.

The finding that prostate cancer was associated with delay and less likelihood of kidney transplant is not surprising. Older reports recommended waiting times of 2-5 years after the diagnosis of prostate cancer.¹¹ However, those older recommendations are now being challenged because of the higher mortality associated with dialysis, compared with a kidney transplant. A very recent report by a panel of experts from the American Society of

Transplantation made recommendations that for low- and intermediate-risk prostate cancer, no waiting time is necessary with or without treatment for prostate cancer.¹³ These recommendations were made based on the extrapolation of data from the general population that indicated that prostate cancer-specific death is low. Our study provides evidence that death from any cancer in ESKD with prostate cancer is low, at 8.2% for dialysis patients who never received a kidney transplant, and the relative mortality of patients with ESKD with prostate cancer is over 90% compared with those with ESKD without prostate cancer. These data will enable policy makers to develop future evidence-based guidelines.

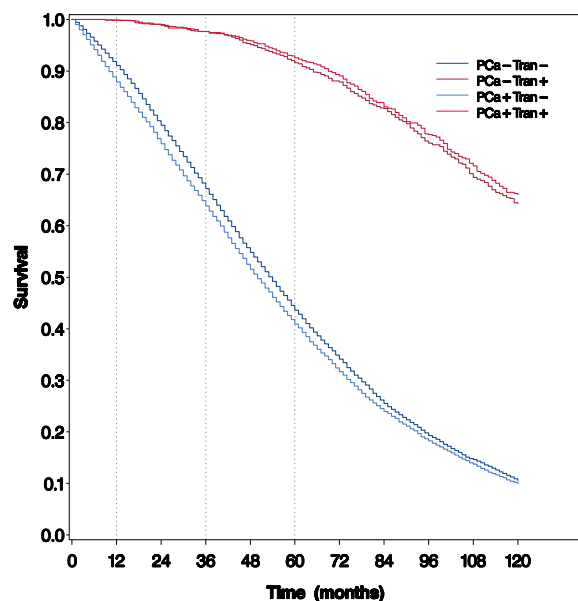
In our study, the association of reduced mortality because of kidney transplant was exactly the same among those with prostate cancer and those without prostate cancer. This finding implies that a history of prostate cancer has no negative effect on the posttransplant mortality, which is probably not surprising because of the well-known beneficial effect of kidney transplant in ESKD. Contrary to the general notion that the risk of prostate cancer, like any other cancer, may be increased because of immunosuppression burden after kidney transplant, a few large studies have shown that prostate cancer risk is not increased after solid organ transplant.^{19,20} Liauw et al²⁰ studied 620 men with kidney, heart, lung, liver, pancreas, or intestine transplants and matched them with those without any transplant. They found no difference in prostate cancer-specific death between both groups.²⁰ A study that analyzed both transplant and cancer registries found that prostate cancer incidence is low at 1,544 (0.8%) among 187,384 solid organ transplant recipients.¹⁹ Another study that linked transplant patients from the Scientific Registry of Transplant Recipients and cancer registry found that interestingly, while excess absolute risk for lung, colon, and kidney cancers were higher for organ transplant recipients, excess absolute risk was lower for prostate cancer.²¹

Our study has several limitations. Our statistical models comparing time to death and time to transplant between those with prostate cancer and those without prostate cancer have the limitation of residual selection bias because of unmeasured confounders. The USRDS database relies on administrative data submitted by dialysis providers. As such, it is dependent on the accuracy and completeness of

Table 3. Unadjusted and Propensity Score-adjusted Associations of Incident Prostate Cancer With Time to Death and Time to Kidney Transplant Among Dialysis Patients from the United States Renal Data System (1999-2015)

Model	Outcome	Explanatory Variable	Unadjusted HR (95% CI)	Propensity Score-matched HR
1	Time to death	Prostate cancer	1.44 (1.42-1.47)	1.11 (1.08-1.14)
2	Time to transplant	Prostate cancer	0.72 (0.67-0.76)	0.78 (0.72-0.85)
3	Time to death	Prostate cancer, Transplant	0.17 (0.15-0.19)	0.20 (0.18-0.21)
		Prostate cancer, No transplant	0.75 (0.74-0.76)	1.08 (1.06-1.11)
		No prostate cancer, Transplant	0.16 (0.16-0.16)	0.20 (0.18-0.21)
		No prostate cancer, No transplant	Reference	Reference

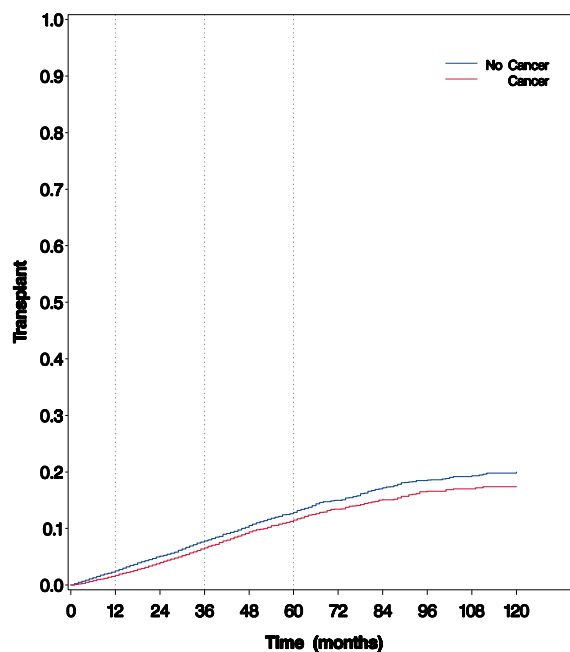
Abbreviations: CI, Confidence interval; HR, hazard ratio.



Number at Risk											
Pca-Tran-	14324	13030	11119	9106	7065	5348	3911	2715	1892	1285	839
Pca-Tran+	1220	1216	1198	1170	1118	1043	949	840	707	576	467
Pca+Tran-	14683	12842	10813	8785	6783	5072	3654	2510	1724	1147	733
Pca+Tran+	961	959	946	912	872	805	719	609	508	412	319

Figure 3. Kaplan-Meier curve comparing survival time in months between those with prostate cancer and no kidney transplant (dark blue), prostate cancer and transplant (light red), no prostate cancer and no transplant (light blue), and no prostate cancer and transplant (dark red). Time zero is the timepoint when a prostate cancer case is matched to a control. For example, if a man was diagnosed with prostate cancer 9 months after ESKD, then he would be matched to a control that was also at 9 months after ESKD. Abbreviations: ESKD, End-stage kidney disease; Pca, prostate cancer; Tran, kidney transplant.

data submitted by the dialysis community. In addition, the use of the International Classification of Diseases Ninth Revision diagnosis code for prostate cancer in Medicare data was shown to be 70%-73% concordant, for capturing true incidence of prostate cancer, with a cancer registry in one study, and there are no chart review validation studies to our knowledge.²² We were unable to ascertain the degree of prostate-specific antigen elevation, Gleason score, or stage (localized, regional, or metastatic) of prostate cancer, because the USRDS lacks reliable granularity on these issues. We did not evaluate for the effect of treatment modality (surgery or radiation, hormonal therapy, and/or watchful waiting) on time to transplant or time to death. We lacked information on the time of referral to the transplant centers, and hence we calculated time to transplant from the date of ESKD onset. Because we dealt with the occurrence of prostate cancer as a time-dependent covariate, we were able to overcome this weakness partially. We could not identify exactly how many deaths were directly related to prostate cancer. Instead, we were able to ascertain deaths from any cancer and hence deaths from prostate cancer alone are probably even lower than



Number at Risk											
No Cancer	15544	11781	8577	6170	4379	3086	2086	1377	912	581	357
Cancer	15544	11318	8212	5857	4033	2729	1801	1180	747	473	281

Figure 4. Cumulative incidence curve comparing the receipt of transplant over time in months between those with prostate cancer (red) and those without prostate cancer (blue). Time zero is the timepoint when a prostate cancer case is matched to a control. For example, if a man was diagnosed with prostate cancer 9 months after end-stage kidney disease (ESKD), then he would be matched to a control that was also at 9 months after ESKD.

overall deaths from any cancer. Lastly, we did not assess for the effect of prostate cancer that occurred after kidney transplant because it was beyond the scope of our study question. Because of these limitations, our findings are not generalizable to all patients with prostate cancer, and the benefits of kidney transplantation will still need to be evaluated on an individual basis.

In conclusion, prostate cancer in ESKD is associated with only a modest increase in mortality and a delay in kidney transplant. Kidney transplant is associated with similar survival benefit irrespective of if the patient had prostate cancer before kidney transplant. Very few prostate cancer patients die of cancer. Future studies should investigate the underpinnings of increased mortality and the impact of delay in transplant in balancing the risks of increased mortality associated with remaining on dialysis and the benefits of avoiding progression of the cancer because of immunosuppression.

SUPPLEMENTARY MATERIAL

Supplementary File 1 (PDF)

Figure S1: Standardized mean differences for prevalent dialysis patients from the United States Renal Data System (1999-2015) diagnosed with incident prostate cancer, before and after propensity score matching.

Table S1: Causes of death for prevalent dialysis patients from the United States Renal Data System (1999-2015), stratified by subsequent prostate cancer and kidney transplant incidence.

Table S2: Key transplant-related variables for those who received kidney transplant among prevalent dialysis patients from the United States Renal Data System (1999-2015), stratified by prostate cancer incidence.

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Support: This study was funded by Team Science intramural grant by the Department of Medicine at University Hospitals Cleveland Medical Center. Funders had no role in the design and conduct of the study. Authors of this study take complete responsibility for the findings and report of this study.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Disclaimer: The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

Peer Review: Received February 25, 2021. Evaluated by 2 external peer reviewers, with direct editorial input by the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form July 25, 2021.

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