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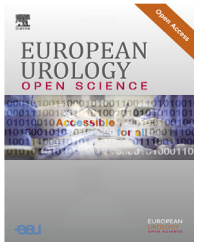

European Association of Urology

Brief Correspondence

Aggressive Prostate Cancer at Presentation Following Solid Organ Transplantation

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Abstract

Solid organ transplant (SOT) candidates and recipients are often subject to intense screening regimens that can potentially delay transplantation and cause unnecessary harm. Although initial studies suggested that SOT recipients had elevated risk of prostate cancer (PCa), contemporary studies have shown that transplant recipients with low- or intermediate-risk PCa have similar outcomes to their counterparts without a transplant. However, there are limited data on the relationship between prior transplant exposure and the risk of clinically significant aggressive PCa at presentation. To provide additional insight, we queried the Surveillance, Epidemiology and End Results-Medicare database to establish a cohort of prostate-specific antigen (PSA)-screened transplant patients who then went on to develop PCa. Procedure and diagnosis codes were then used to identify patients with a history of SOT. Aggressive PCa phenotype was defined as death from PCa or de novo metastasis, regional lymph node metastasis, PSA >20 ng/l, or Gleason score 8–10 at presentation. On univariable and multivariable (adjusted for age and race) analyses, transplant patients (n = 292) were not at significantly higher risk of an aggressive prostate cancer phenotype with odds ratios of 0.95 (95% confidence interval 0.72–1.25) and 1.18, (95% confidence interval 0.90–1.57), respectively. The results suggest that transplant recipients can have similar screening protocols to those for the general population.

Patient summary: Using database results for transplant recipients, we investigated their risk of developing aggressive prostate cancer after transplantation. We found that having a transplant did not increase the risk of aggressive prostate cancer. This work suggests that transplant recipients are unlikely to benefit from more rigorous screening protocols than those for the general population.

Cancer is becoming a leading cause of death among transplant recipients with improvements in surgical transplant techniques and the use of immunosuppressive regimens that prolong survival [1]. The connection between chronic immunosuppression in solid organ transplant (SOT) patients and overall cancer development is well defined, although the relationship with prostate cancer (PCa) specifically is less clear [2]. Initial studies suggested a higher risk

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of PCa for SOT recipients; however, these studies failed to account for detection bias whereby more frequent health encounters and more intense screening of transplant patients lead to higher rates of detection [3]. Recognizing this inherent bias, more recent population studies with rigorous methodology have found no relationship between immunosuppression or transplant exposure and the risk of PCa [4,5]. Despite these findings, owing to the perceived higher risk of PCa, SOT candidates and recipients are often subject to intense screening regimens that can potentially delay transplantation and cause unnecessary harm [6]. Although many studies have examined the overall risk of PCa for SOT recipients, there are limited data on clinically high-risk/aggressive disease at presentation. The aim of the present study was to define the risk of presenting with de novo aggressive, potentially lethal PCa at diagnosis for patients with a history of transplantation using a methodology to limit the effects of detection bias.

To evaluate the relationship between SOT and diagnosis of aggressive PCa, we queried the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database from 2004 to 2015 to identify men with PCa. To account for potential detection bias for SOT patients, we limited our analysis to a cohort of screened men. Screening was defined as a prostate-specific antigen (PSA) laboratory test or digital rectal examination in both the 12-mo period and the 13–36-mo period before PCa diagnosis. The SEER registry was used to extract demographic data (patient age, race) and tumor characteristics (de novo metastasis, nodal status, Gleason grade, tumor stage, PSA at diagnosis, and death from prostate cancer). Patients were excluded if data were missing for more than three of the following characteristics: metastasis (yes/no), lymph node metastasis (yes/no), PSA, or Gleason score. Supplementary Figure 1 shows the patient selection criteria used to build the study population.

SOT status was extracted from Medicare claims data using diagnosis or procedure codes for kidney, lung, liver, pancreas, and intestine transplants. Heart transplantation was excluded owing to potential coding errors limiting our ability to differentiate heart transplantation and heart valve transplantation. Patients were considered to have SOT if they had either a diagnosis of or procedure for SOT in the 3 yr before diagnosis of PCa. Supplementary Tables 1 and 2 list all the diagnosis and procedure codes included.

Patients were considered to have an aggressive PCa phenotype if they presented with de novo metastasis, regional lymph node metastasis, PSA >20 ng/ml, or Gleason score $\geq$8 at diagnosis or died from PCa within 1 yr from diagnosis.

Baseline comorbidities and demographic characteristics for the transplant and nontransplant cohorts were compared using the Pearson χ^2 test, Fischer's exact test, or Student two-sided *t* test, as appropriate. Risk estimates of the likelihood of aggressive PCa at presentation for transplant versus nontransplant patients were calculated in univariable and multivariable logistic regression models adjusted for age (continuous) and race. Statistical significance was set at $\alpha < 0.05$. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

A total of 114 283 patients met our criteria for prior screening. Of these, 292 (0.26%) had a history of SOT and adequate clinical and pathological information necessary for analysis. The transplant cohort included 220 kidney, 27 lung, 57 liver, 13 pancreas, and six intestinal transplants, with some patients receiving multiple SOTs. Table 1 lists the

Table 1 – Baseline demographics for the transplant patients and the nontransplant control subjects in the comparative analysis cohort

Parameter	No transplant (*n* = 113 991)	Transplant (*n* = 292)	*p* value
Median age at diagnosis, yr (IQR)	74 (71–78)	72 (69–75)	<0.0001
Race, *n* (%)			<0.0001
White	91 214 (80.2)	200 (68.5)	
Hispanic	5695 (5.0)	28 (9.6)	
Black	10 218 (9.0)	42 (14.4)	
Other	6572 (5.8)	22 (7.5)	
De novo metastasis, *n* (%)			0.69
No	107 679 (94.7)	279 (95.5)	
Yes	4202 (3.7)	<11 (<3)[a]	
Unknown	1818 (1.6)	<11 (<2)[a]	
Regional lymph node status, *n* (%)			0.88
Clinical N0	95 856 (84.3)	249 (85.3)	
Pathologic N0	12 008 (10.7)	30 (10.3)	
Pathologic N1	1818 (1.6)	<11 (<1.0)[a]	
Unknown	4017 (3.5)	10 (3.4)	
Prostate-specific antigen category, *n* (%)			0.39
0.1–10.0 ng/ml	69 439 (61.1)	186 (63.7)	
10.1–20.0 ng/ml	16 332 (14.4)	45 (15.4)	
>20.1 ng/ml	9698 (8.5)	25 (8.6)	
Unknown	18 230 (16.0)	36 (12.3)	
Gleason score, *n* (%)			0.07
2–6	35 755 (31.5)	90 (30.8)	
7	35 348 (31.1)	109 (37.3)	
8–10	18 845 (16.6)	46 (15.8)	
Unknown	23 751 (20.9)	47 (16.1)	
Death from prostate cancer, *n* (%)	1507 (1.3)	<11 (<2)[a]	0.56
Aggressive disease, *n* (%)	26 361 (23.2)	65 (22.2)	0.71

IQR = interquartile range.
[a] All results for which *n* < 10 and the associated percentage are suppressed according to the Surveillance, Epidemiology and End Results cell suppression guidelines.

Table 2 – Univariable and multivariable odds of aggressive prostate cancer phenotype at diagnosis

Variable	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Transplant receipt	0.95 (0.72–1.25)	0.71	1.19 (0.90–1.57)	0.23
Age	1.11 (1.11–1.12)	<0.0001	1.10 (1.09–1.10)	<0.0001
Black race	1.28 (1.21–1.35)	<0.0001	1.26 (1.20–1.32)	<0.0001

CI = confidence interval; OR = odds ratio.

demographic data for the two cohorts. There was a significant difference in median age at diagnosis ($p < 0.001$) and race composition ($p < 0.001$) between the transplant and nontransplant cohorts. There were no differences for any of the other clinical or pathological characteristics, including screening intensity ($p = 0.34$; Supplementary Table 3).

The rates of aggressive disease at presentation were similar between the nontransplant (23.2%) and transplant (22.2%) cohorts ($p = 0.71$). On both univariable and multivariable (adjusted for age and race) analyses there was no significant difference in the risk of aggressive PCa between the SOT and nontransplant groups (univariable OR 0.95, 95% confidence interval 0.72–1.25; adjusted OR 1.18, 95% confidence interval 0.90–1.57; Table 2).

Our findings are in-line with other contemporary studies that showed that prior transplantation does not seem to influence the natural progression of PCa. In a large retrospective cohort study of nearly 180,000 transplant recipients using the Scientific Registry of Transplant Recipients, Engels et al. [7] found that transplant exposure did not increase the risk of PCa. A recently published systematic review examined recurrence rates and overall survival for men who underwent treatment for urologic malignancy before renal transplantation and found that men treated for low- or intermediate-risk PCa did not have a higher risk of PCa recurrence after their transplant [8]. Using SEER-Medicare data, Liauw et al. [9] observed no difference in PCa-specific mortality between transplant and nontransplant cohorts. Our findings indicate that SOT recipients are not at higher risk of developing aggressive PCa, even after adjusting for multiple confounders. Collectively, these studies suggest that SOT recipients can be managed using PCa screening protocols and management strategies similar to those for the general population. This not only decreases the likelihood of unnecessary treatment in this cohort but also mitigates costs associated with increased surveillance.

Despite attempts to limit the effects of detection bias and accounting for potential confounders, potentially unknown confounders may still have influenced our results because of the retrospective nature of the study design. For example, owing to racial differences, our SOT patients may have higher rates of certain comorbidities (eg, diabetes, hypertension). However, addition of these variables had a negligible effect on the risk estimates in the multivariable model and are thus unlikely to have biased the association observed. In addition, the cohort is restricted to those aged >68 yr and did not include heart transplant recipients, who require higher immunosuppressive doses, limiting the generalizability of the findings [10].

Author contributions: George R. Schade had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Holt, Schade, Singh.
Acquisition of data: Holt.
Analysis and interpretation of data: Schade, Holt, Singh.
Drafting of the manuscript: Singh, Schade, Holt.
Critical revision of the manuscript for important intellectual content: Gore, Wright, Nyame, Schade, Holt, Singh.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.03.001.

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