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Cancer Risk Following HLA-Incompatible Living Donor Kidney Transplantation

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Background. Incompatible living donor kidney transplant recipients (ILDKTr) require desensitization to facilitate transplantation, and this substantial upfront immunosuppression may result in serious complications, including cancer. **Methods.** To characterize cancer risk in ILDKTr, we evaluated 858 ILDKTr and 12 239 compatible living donor kidney transplant recipients (CLDKTr) from a multicenter cohort with linkage to the US transplant registry and 33 cancer registries (1997–2016). Cancer incidence was compared using weighted Cox regression. **Results.** Among ILDKTr, the median follow-up time was 6.7 y (maximum 16.1 y) for invasive cancers (ascertained via cancer registry linkage) and 5.0 y (maximum 16.1 y) for basal and squamous cell carcinomas (ascertained via the transplant registry and censored for transplant center loss to follow-up). Invasive cancers occurred in 53 ILDKTr (6.2%) and 811 CLDKTr (6.6%; weighted hazard ratio [wHR] 1.01; 95% confidence interval [CI], 0.76-1.35). Basal and squamous cell carcinomas occurred in 41 ILDKTr (4.8%) and 737 CLDKTr (6.0%) (wHR 0.99; 95% CI, 0.69-1.40). Cancer risk did not vary according to donor-specific antibody strength, and in an exploratory analysis, was similar between CLDKTr and ILDKTr for most cancer types and according to cancer stage, except ILDKTr had a suggestively increased risk of colorectal cancer (wHR 3.27; 95% CI, 1.23-8.71); however, this elevation was not significant after correction for multiple comparisons. **Conclusions.** These findings indicate that the risk of cancer is not increased for ILDKTr compared with CLDKTr. The possible elevation in colorectal cancer risk is unexplained and might suggest a need for tailored screening or prevention.

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Kidney transplantation is the definitive treatment for end-stage renal disease, with improved survival and quality of life in comparison with dialysis.[1,2] However, successful transplantation requires potent immunosuppressive medications, which increase the risk for immunosuppression-related morbidity, including cancer. Type and intensity of antibody induction and maintenance immunosuppression have been associated with increased cancer risk.[3-5] Transplant recipients have a 2-fold increased risk of cancer compared with the general population, with risk especially heightened for cancers caused by viruses.[6]

Kidney recipients with preformed donor-specific antibodies (DSAs), including those directed at HLA proteins, require additional immunosuppression. Desensitization protocols, which remove or reduce preformed DSAs, facilitate incompatible living donor kidney transplantation (ILDKT) and confer a survival benefit for candidates who have a willing incompatible living donor in comparison with remaining on the waiting list for a potential compatible donor.[7] Classical desensitization regimens include plasmapheresis or immunoadsorption followed by low-dose or high-dose IVIG.[8] Allograft longevity for ILDKT recipients (ILDKTr) can be threatened by the post-desensitization resurgence of DSA, prompting use of adjunctive agents such as anti-CD20, anti-interleukin-6 receptor blockers, proteosome inhibitors, complement inhibitors, and the immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*.[8,9]

The upfront and maintenance immunosuppression administered to ILDKTr may predispose them to an increased risk for posttransplant complications. ILDKTr also have an elevated incidence of acute rejection, which necessitates further intensive immunosuppressive treatment.[10] A single-center study of 475 recipients found a higher incidence of infection in ILDKTr than among compatible living donor kidney transplantation recipients (CLDKTr), with 66.0% and 73.5% of ILDKTr with moderate and high crossmatch strength, respectively, developing an infection in the first post-transplant year.[11] Moreover, ILDKTr are at higher risk of developing recurrent infections.[11] In the setting of deficient immunosurveillance, infectious agents can induce a state of chronic inflammation, creating a potentially carcinogenic milieu, and viruses can directly induce malignant transformation of cells through the activity of viral oncogenes.[12,13] A prior national study of recipients who were transplanted across incompatibility at the ABO blood group locus did not observe an increased incidence of cancer.[14] However, use of the aforementioned adjunctive agents is less common in ABO-incompatible transplants, and thus the findings may not pertain to ILDKTr.[15,16]

A better understanding of cancer risk is necessary for counseling patients undergoing ILDKT and determining whether heightened or targeted cancer screening is warranted. In the present study, we analyzed data from a multicenter cohort of ILDKTr with novel linkage to transplant and cancer registry data to quantify cancer risk among ILDKTr, stratified by the strength of anti-HLA DSA, in comparison with CLDKTr.

MATERIALS AND METHODS

Data Sources and Study Population

The study used data from an ongoing observational cohort of ILDKTr at 25 US transplant centers.[10] ILDKTr were identified by transplant centers as individuals undergoing pretransplant desensitization therapy for DSA. We linked these data to the Transplant Cancer Match (TCM) Study,[6] a linkage between the Scientific Registry of Transplant Recipients (SRTR) and 33 state and regional cancer registries (see Table 1 note). The SRTR includes data on all US waitlist candidates and recipients of solid organs, including kidney recipients. The study was considered not human participants research by the National Institutes of Health. It was approved by the Johns Hopkins University Institutional Review Board and, as required, by participating sites.

We evaluated adult ILDKTr (age ≥18 y) from the multicenter study, who received a kidney-only transplant from HLA-incompatible living donors, from September 24, 1997, to December 15, 2016. Of 1400 such individuals, 858 (61%) resided in a state or region covered by a TCM cancer registry at the time of listing or transplantation and were included in this study. Participating centers classified ILDKTr as having low, moderate, or high levels of DSAs, corresponding, respectively, to positive Luminex, negative flow crossmatch (PLNF); positive flow, negative cytotoxic crossmatch (PFNC); or positive cytotoxic crossmatch (PCC). Some centers performed actual cell-based crossmatches, whereas others performed virtual crossmatches based on semi-quantitative DSA strength on solid-phase assays. In view of the minimal additional risk associated with ABO-incompatible transplantation, patients who required both HLA and ABO barriers to be crossed (6.1% of ILDKTr) were categorized on the basis of the strength of DSA directed against HLA.[7,15]

For comparison, we identified all adult CLDKTr who received kidney-only transplants at the same centers and time as their ILDKTr counterparts. Of 17 182 such individuals, 12 239 (71%) resided in a state/region covered by a TCM registry and were included in this study.

Ascertainment of Baseline Characteristics and Cancer Outcomes

From the linked SRTR data, we obtained information on recipient, donor, and transplant characteristics, including induction immunosuppression agents. For the purposes of this study, the constructs of race and ethnicity as collected by the Organ Procurement Transplantation Network were classified as Asian American/Pacific Islander, non-Hispanic Black, non-Hispanic White, Hispanic, and Other, which included missing race and ethnicity. Data on invasive cancer diagnoses (including cases prevalent at the time of transplantation and incident events during follow-up) were obtained from TCM cancer registries.

Our study had 2 primary outcomes: incident diagnosis of any invasive cancer and incident diagnosis of a skin cancer (ie, basal and squamous cell carcinomas [BCC and SCC]). Invasive cancers were classified using a modified version of the Surveillance, Epidemiology, and End Results recode. Cancer registries do not record diagnoses of cutaneous BCC and SCC. For these skin cancers, we used cases reported by

National Cancer Institute, SRTR, the US Government, cancer registries, or their contractors. The analyses described here are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

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TABLE 1.

Baseline characteristics of kidney recipients, according to compatibility status.

Characteristics	ILDKTr (N = 858)	CLDKTr (N = 12 239)	*P*
Recipient characteristics			
DSA strength, n (%)			–
PLNF	163 (19.0)	–	
PFNC	463 (54.0)		
PCC	232 (27.0)		
Age at transplantation, y, median (IQR)	45 (35–54)	50 (38–59)	<0.001
Female sex, n (%)	562 (65.5)	4717 (38.5)	<0.001
Race/ethnicity, n (%)			0.002
Asian American/Pacific Islander	37 (4.3)	861 (7.0)	
Black, non-Hispanic	162 (18.9)	1863 (15.2)	
Hispanic	112 (13.1)	1779 (14.5)	
Other	4 (0.5)	68 (0.6)	
White, non-Hispanic	543 (63.3)	7668 (62.7)	
High school education or greater, n (%)	432 (59.3)	6888 (61.0)	0.4
BMI, kg/m^2, median (IQR)	25.6 (22.4–30.4)	26.9 (23.4–31.2)	<0.001
ESRD diagnosis, n (%)			
Glomerular diseases	329 (38.3)	3767 (30.8)	<0.001
Diabetes	127 (14.8)	2961 (24.2)	<0.001
Polycystic kidney disease	73 (8.5)	1349 (11.0)	0.2
Tubular and interstitial diseases	38 (4.4)	575 (4.7)	0.7
Hypertensive nephrosclerosis	145 (16.9)	2545 (20.8)	0.006
Vascular disease	23 (2.7)	241 (2.0)	0.2
Congenital/rare familial/metabolic disorders	55 (6.4)	496 (4.1)	<0.001
History of invasive cancer, n (%)	47 (5.5)	740 (6.0)	0.5
Blood type, n (%)			0.007
O	426 (49.7)	5341 (43.6)	
A	286 (33.3)	4618 (37.7)	
B	115 (13.4)	1747 (14.3)	
AB	31 (3.6)	533 (4.4)	
CMV IgG positive, n (%)	575 (69.5)	6881 (58.5)	<0.001
EBV IgG positive, n (%)	632 (89.1)	8716 (88.5)	0.6
HBV IgG positive, n (%)	64 (7.7)	782 (6.6)	0.2
HCV IgG positive, n (%)	50 (6.2)	281 (2.5)	<0.001
Years on dialysis, median (IQR)	3.5 (0.8–11.0)	0.7 (0.0–2.2)	<0.001
c/PRA, n (%)			<0.001
Median (IQR)	64.0 (16.0–93.0)	0.0 (0.0–5.0)	
0	145 (16.9)	8215 (68.3)	
1–79	367 (42.8)	3237 (26.9)	
80–97	201 (23.4)	401 (3.3)	
98	26 (3.0)	42 (0.3)	
99	28 (3.3)	49 (0.4)	
100	91 (10.6)	91 (0.8)	
No. of previous transplants, n (%)			<0.001
0	486 (56.6)	10 708 (87.5)	
1	318 (37.1)	1306 (10.7)	
≥2	54 (6.3)	225 (1.8)	
Donor characteristics			
Age, y, median (IQR)	42 (32–50)	43 (33–52)	0.001
Female sex, n (%)	485 (56.5)	7398 (60.4)	0.02
Race/ethnicity, n (%)			0.04
Asian American/Pacific Islander	35 (4.1)	696 (5.7)	
Black, non-Hispanic	141 (16.4)	1651 (13.5)	
Hispanic	111 (12.9)	1763 (14.4)	
Other	8 (0.9)	105 (0.9)	
White, non-Hispanic	563 (65.6)	8023 (65.6)	
BMI, kg/m^2, median (IQR)	26.7 (23.7–29.8)	26.6 (23.7–29.8)	0.6
High school education or greater, n (%)	462 (53.8)	7604 (62.1)	<0.001
CMV IgG positive, n (%)	442 (55.9)	6130 (53.5)	0.2
EBV IgG positive, n (%)	622 (92.1)	8429 (90.6)	0.2
HBV IgG positive, n (%)	27 (3.5)	314 (2.8)	0.3
HCV IgG positive, n (%)	6 (0.8)	31 (0.3)	0.02
Living-related donor, n (%)	452 (52.7)	6606 (54.0)	0.5
HLA mismatches, n (%)			<0.001
0–1	46 (5.4)	1577 (13.0)	
2–3	407 (47.9)	4887 (40.3)	
4–6	397 (46.7)	5666 (46.7)	
Transplant characteristics			
Induction immunosuppression, n (%)			
Alemtuzumab	77 (9.0)	876 (7.2)	0.05
IL2-RA[b]	116 (13.5)	3267 (26.7)	<0.001
Polyclonal antibody[c]	544 (63.4)	6640 (54.3)	<0.001
Rituximab	96 (11.2)	103 (0.8)	<0.001
Steroids	489 (57.0)	9391 (76.1)	<0.001
Year of transplant, median (IQR)	2007 (2005–2010)	2010 (2006–2013)	<0.001

This study includes data on kidney recipients residing in geographic areas covered by 33 US cancer registries: Alaska, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Illinois, Iowa, Kentucky, Louisiana, Michigan, Nebraska, North Carolina, North Dakota, New Jersey, New Mexico, New York, Nevada, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, South Carolina, Seattle-Puget Sound area of Washington, Texas, Utah, and Virginia.

[a]Missing data were excluded.

[b]Daclizumab and basiliximab.

[c]ALG, ATGAM, and rabbit antithymocyte globulin (NRATG, NRATS, and ATG).

ALG, antilymphocyte globulin; ATG, antithymocyte globulin; ATGAM, equine antithymocyte globulin; BMI, body mass index; CMV, cytomegalovirus; CLDKTr, compatible live donor kidney transplant recipients; c/PRA, calculated/panel-reactive antibody; DSA, donor-specific antibody; EBV, Epstein-Barr virus; ESRD, end-stage renal disease; IgG, immunoglobulin G; IL2-RA, interleukin-2 receptor antagonist; ILDKTr, incompatible living donor kidney transplant recipient; IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus; PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch; NRATS, Nashville rabbit antithymocyte serum.

transplant centers and recorded in the SRTR. A prior study demonstrated that 14% of BCC cases and 22% of SCC cases ascertained using Medicare claims were captured by the SRTR, indicating low sensitivity.[17] However, 71% of BCCs and 73% of SCCs captured by the SRTR were confirmed by Medicare claims, indicating a high positive predictive value.[17]

Statistical Analyses

Cancer incidence was assessed starting at transplantation and continued until the earliest of a first cancer diagnosis, death, retransplantation, or end of registry coverage. We conducted analyses separately for cancer registry diagnoses of invasive cancers and SRTR diagnoses of BCC and SCC because these had different censoring dates related to the end of registry coverage. For skin cancers, we additionally censored at the time of graft failure or loss to follow-up by

the transplant center because skin cancer reports came from transplant centers. In a sensitivity analysis, we additionally censored for graft failure; these results were consistent with our main analysis (data not shown).

We compared cancer risk in ILDKTr and CLDKTr using weighted Cox regression. Specifically, we first used logistic regression to obtain a propensity score that estimated the probability of receiving an ILDKT, incorporating variables for age, sex, race, cause of end-stage renal disease, and calendar year of transplantation. For the CLDKTr population, we calculated weights from the propensity score converted to the odds scale; ILDKTr were given a weight of 1. This method allows for CLDKTr who most closely match their ILDKT counterparts to be upweighted. We quantified the standardized mean differences in measured covariates to compare the balance between ILDKTr and CLDKTr; balance was achieved for all measured covariates (data not shown). Finally, the weighted Cox models incorporated a robust sandwich estimator to account for the within-center clustering of outcomes. In a sensitivity analysis, we included additional adjustments for differences between ILDKTr and CLDKTr, including education, blood type, calculated and panel-reactive antibody (c/PRA), previous history of transplant, and years on dialysis (**Table S1, SDC,** http://links.lww.com/TXD/A547). Using the propensity weights, we also estimated the standardized cumulative incidence of invasive cancer overall and cutaneous BCC/SCC combined, treating death as a competing risk.

We first compared risk for both invasive cancers overall and cutaneous BCC/SCC combined, and then compared them according to DSA level. Additionally, in exploratory analyses, we analyzed results for individual cancer sites when there were at least 20 events in total, under the assumption that we would expect to see at least 1 cancer among ILDKTr. Specifically, given the null hypothesis of comparable cancer risk in both groups, the expected number of cancers among ILDKTr would be 20 × (total number of ILDKTr)/(total number of ILDKTr and CLDKTr combined) = 1.3. We grouped cancer sites into systems when they were too rare to analyze individually. Furthermore, we analyzed grouped invasive cancers according to the stage at the time of diagnosis; non-melanoma skin and hematologic cancers were excluded from this analysis. We report 95% confidence intervals (CIs) and used the false discovery rate method to correct for multiple comparisons.[18]

To compare the characteristics of ILDKTr and CLDKTr, we used Kruskal-Wallis tests for continuous variables, and Pearson's chi-square tests or Fisher exact tests for categorical variables. All analyses were performed using Stata version 17.0/MP for Linux (College Station, TX).

RESULTS

Study Population

We included 858 ILDKTr and 12 239 CLDKTr transplanted in states/regions covered by TCM cancer registries. Among ILDKTr, 163 (19.0%) were PLNF, 463 (54.0%) were PFNC, and 232 (27.0%) were PCC transplants (Table 1). Compared to CLDKTr, ILDKTr were younger (median age at transplantation: 45.0 versus 50.0 y; $P < 0.001$) and more likely to be female (65.5% versus 38.5%; $P < 0.001$) and non-Hispanic Black (18.9% versus 15.2%; $P = 0.002$). As shown in Table 1, there were additional notable differences ($P < 0.001$ for all comparisons), including that ILDKTr were more likely to have glomerular diseases as the cause of their end-stage renal disease (38.3% versus 30.8%) and to have undergone ≥1 previous transplants (43.4% versus 12.5%). ILDKTr also had spent longer time on dialysis (median 3.5 versus 0.7 y), had higher c/PRA (median 64.0% versus 0.0%), and were more likely to receive a transplant from a donor who had ≥2 HLA mismatches (94.6% versus 87.0%). Finally, ILDKTr were more likely to receive rituximab induction immunosuppression (11.2% versus 0.8%, $P < 0.001$).

TABLE 2.

Overall cancer risk in HLA-incompatible kidney transplant recipients, according to strength of desensitization.

Category of kidney transplant recipient	Invasive cancers wHR (95% CI)	Cutaneous BCC and SCC wHR (95% CI)
CLDKT	Reference	Reference
ILDKT	1.01 (0.76-1.35)	0.99 (0.69-1.40)
PLNF	0.98 (0.57-1.68)	0.74 (0.38-1.45)
PFNC	1.06 (0.74-1.50)	1.07 (0.62-1.84)
PCC	0.96 (0.61-1.52)	0.99 (0.49-2.00)

BCC, basal cell carcinoma; CI, confidence interval; CLDKT, compatible living donor kidney transplantation; ILDKT, incompatible living donor kidney transplantation; PCC, positive cytotoxic crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PLNF, positive Luminex, negative flow crossmatch; SCC, squamous cell carcinoma; wHR, weighted hazard ratio.

Cancer Incidence in ILDKTr

ILDKTr and CLDKTr were followed for invasive cancers for a total of 5683 person-years (median 6.7 y; interquartile range [IQR], 3.7–9.5 y; maximum: 16.1 y) and 70 296 person-years (median 5.3 y; IQR, 2.7–8.3 y; maximum: 19.3 y), respectively. Over this period, invasive cancers were diagnosed in 53 ILDKTr (6.2%; 9 PLNF, 28 PFNC, 16 PCC) and 811 CLDKTr (6.6%; Table 2). There was no significant difference in invasive cancer incidence between ILDKTr and CLDKTr, overall (weighted hazard ratio [wHR] 1.01; 95% CI, 0.76-1.35; $P = 0.9$) or according to DSA level. Fifteen-y standardized cumulative incidence of invasive cancer was 12.1% in ILDKTr and 14.6% in CLDKTr (Figure 1A).

ILDKTr and CLDKTr were followed for cutaneous BCC and SCC for a total of 4928 person-years (median 5.0 y; IQR, 2.9–8.8 y; maximum: 16.1 y) and 67 685 person-years (median 5.0 y; IQR, 2.9–7.9 y; maximum: 19.9 y), respectively. These cancers were observed in 41 ILDKTr (4.8%; 6 PLNF, 24 PFNC, and 11 PCC) and 737 CLDKTr (6.0%), which did not translate into a significant difference in incidence (wHR 0.99; 95% CI, 0.69-1.40; $P = 0.9$; Table 2). Fifteen-y standardized cumulative incidence of BCC and SCC was 8.1% in ILDKTr and 9.9% in CLDKTr (Figure 1B).

As shown in Table 3, the most frequently diagnosed invasive cancers were breast cancer in women (9 in ILDKTr versus 49 in CLDKTr), urological cancers (8 versus 130), gastrointestinal cancers (7 versus 67), and hematologic malignancies (6 versus 131). We examined the incidence of individual cancer types in an exploratory analysis. Although similar risk was observed between ILDKTr and CLDKTr across most individual and grouped cancer sites, ILDKTr had higher incidence of colorectal cancer (wHR 3.27; 95% CI, 1.23-8.71; $P = 0.02$). However, this association did not meet the definition of statistical significance after correction with the false discovery rate method for multiple comparisons. Similarly, risk did not

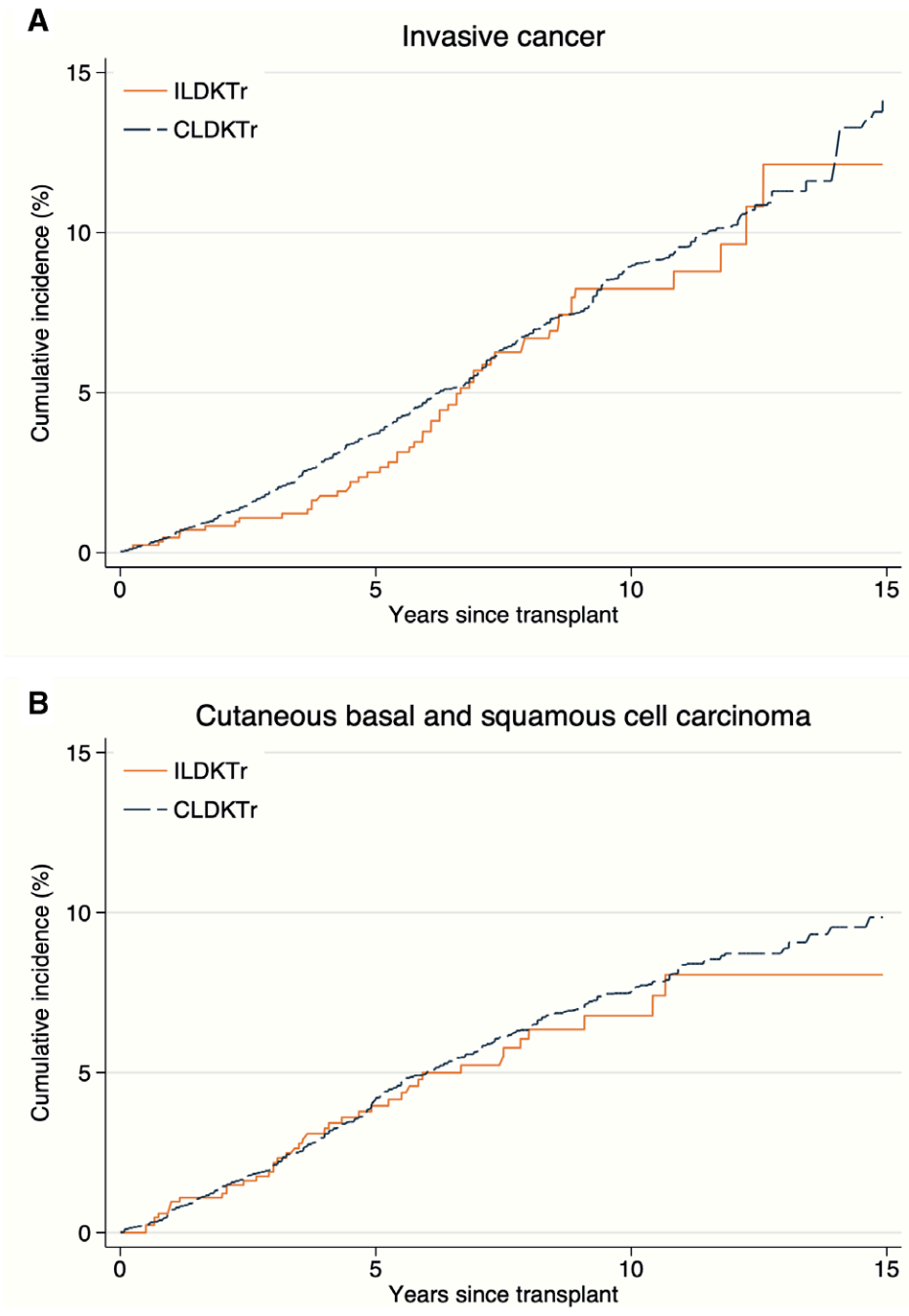

FIGURE 1. Standardized cumulative incidence of invasive cancers and skin cancers in ILDKT and CLDKT recipients. Fifteen-y standardized cumulative incidence for invasive cancers (A) and cutaneous BCC and SCC (B). Estimates for ILDKTr and CLDKTr were standardized using propensity weights (see Materials and Methods section). BCC, basal cell carcinoma; CLDKTr, compatible living donor kidney transplant recipient; ILDKTr, incompatible living donor kidney transplant recipient; SCC, squamous cell carcinoma.

differ between ILDKTr and CLDKTr for cancers diagnosed at localized, regional, or distant stage (Table 3).

In a sensitivity analysis adjusting for education, blood type, c/PRA, previous history of transplant, and years on dialysis, inferences were consistent with our main findings (**Table S1, SDC,** http://links.lww.com/TXD/A547).

DISCUSSION

In this multicenter study of 858 ILDKTr and 12 239 CLDKTr, we found that ILDKTr were not at increased risk of developing cancer compared with their CLDKT counterparts, despite undergoing desensitization before transplant. The 15-y risks of invasive and skin cancers in ILDKTr were 12.1% and 8.1%, respectively, which were similar to the risks observed in CLDKTr. Notably, cancer risk did not vary by DSA level. These trends were consistent across most cancer sites and systems and according to cancer stage. In an exploratory analysis, there was a suggestion of a 3-fold higher risk of colorectal cancer associated with ILDKT, which we discuss further below, but this finding was not statistically significant following correction for multiple comparisons. Overall, these

TABLE 3.

Cancer incidence in ILDKTr and CLDKTr.

Cancer outcome[a]	No. of cancer diagnoses (% of recipients)		ILDKTr versus CLDKTr wHR (95% CI)	P
	ILDKTr	CLDKTr		
Cancer system and site				
Nonmelanoma skin[b]				
BCC	23 (2.7)	367 (3.0)	1.29 (0.74-2.28)	0.4
SCC	22 (2.6)	488 (4.0)	0.76 (0.46-1.26)	0.3
Other	1 (0.1)	22 (0.2)	0.76 (0.13-4.34)	0.8
Melanoma	1 (0.1)	39 (0.3)	0.36 (0.07-1.91)	0.2
Head and neck	3 (0.3)	21 (0.2)	2.60 (0.64-10.47)	0.2
Breast, female	9 (1.0)	49 (0.4)	1.73 (0.65-4.55)	0.3
Respiratory tract	1 (0.1)	108 (0.9)	0.15 (0.02-1.09)	0.06
Lung	1 (0.1)	103 (0.8)	0.16 (0.02-1.13)	0.07
Hepatobiliary tract and pancreas	0 (0.0)	32 (0.3)	–	–
Gastrointestinal tract	7 (0.8)	67 (0.5)	1.98 (0.93-4.22)	0.08
Colorectum	5 (0.6)	34 (0.3)	3.27 (1.23-8.71)	0.02[c]
Female genitourinary tract	4 (0.5)	29 (0.2)	1.22 (0.60-2.47)	0.6
Male genitourinary tract	4 (0.5)	91 (0.7)	0.95 (0.48-1.92)	0.9
Prostate	4 (0.5)	85 (0.7)	1.02 (0.49-2.10)	>0.9
Urological sites	8 (0.9)	130 (1.1)	0.97 (0.49-1.90)	0.9
Kidney	5 (0.6)	99 (0.8)	0.85 (0.32-2.28)	0.8
Urinary bladder	2 (0.2)	27 (0.2)	0.96 (0.23-3.91)	>0.9
Endocrine sites	5 (0.6)	35 (0.3)	1.39 (0.59-3.29)	0.4
Thyroid	5 (0.6)	34 (0.3)	1.42 (0.61-3.32)	0.4
Hematologic malignancies	6 (0.7)	131 (1.1)	0.70 (0.38-1.29)	0.3
Diffuse large B-cell lymphoma	3 (0.3)	46 (0.4)	0.92 (0.31-2.75)	0.9
Other/unspecified lymphomas	2 (0.2)	54 (0.4)	0.63 (0.19-2.12)	0.5
Other	4 (0.5)	57 (0.5)	1.36 (0.42-4.38)	0.6
Cancer stage at diagnosis[d]				
Localized	28 (3.3)	353 (2.9)	1.21 (0.71-2.08)	0.5
Regional	8 (0.9)	131 (1.1)	0.88 (0.44-1.75)	0.7
Distant	6 (0.7)	117 (1.0)	0.87 (0.41-1.83)	0.7

[a]Recipients may have been diagnosed with >1 cancer type (eg, 4 ILDKTr and 118 CLDKTr were diagnosed with both BCC and SCC post-transplant).
[b]Basal cell and squamous cell carcinomas were ascertained using data from the SRTR, whereas other nonmelanoma skin cancers were ascertained using data from cancer registries.
[c]Not statistically significant after correction for multiple comparisons.
[d]Hematologic malignancies, cutaneous basal cell and squamous cell carcinomas, and unstaged cancers were excluded.
BCC, basal cell carcinoma; CI, confidence interval; CLDKT, compatible living donor kidney transplant recipient; ILDKTr, incompatible living donor kidney transplant recipient; SCC, squamous cell carcinoma; SRTR, Scientific Registry of Transplant Recipients; wHR, weighted hazard ratio.

findings are reassuring regarding the safety of ILDKT for carefully selected candidates.

The differences that we observed between ILDKTr and CLDKTr reflect factors that are related to sensitization and selection for kidney transplantation. For example, compared with CLDKTr, a higher proportion of ILDKTr were female and previously transplanted, reflecting some of the known risk factors for sensitization, including pregnancy and prior solid organ transplantation.[8,19] Given that sensitization has historically been a barrier to successful transplantation, ILDKTr had accrued longer dialysis compared with CLDKTr.[19-21]

Desensitization and management of DSAs post-transplant require increased immunosuppression, which might lead one to expect relatively high cancer risk among ILDKTr.[9] Also, dialysis vintage has been associated with increased cancer risk in other settings.[22] However, our results suggest that these factors do not result in ILDKTr having a higher risk of cancer than CLDKTr, even after substantial follow-up time. Our findings for ILDKTr are consistent with those from several studies demonstrating comparable risk between recipients with ABO blood group sensitization and other transplant recipients.[14,23,24] Moreover, we did not find any evidence that cancer risk varied by DSA strength, which extends findings from a prior single-center report on outcomes in ILDKTr who had high-level sensitization (PCC).[25]

We observed a borderline increased risk of colorectal cancer for ILDKTr in an exploratory analysis, although it was not statistically significant after we corrected for multiple comparisons. Other studies have reported inconsistent findings regarding colorectal cancer risk among kidney transplant recipients overall, with relative risks ranging from 0.99 to 3.94 compared with the general population.[26,27] Although statistical uncertainty precludes a firm conclusion, it is possible that an increase in colorectal cancer risk in ILDKTr may result from breakdown in the intestinal barrier and an altered composition of the gut microbiota.[28-30] In fact, previous studies have noted major post-transplant changes to the intestinal microbiota, with the most substantial changes occurring in the first month owing to induction immunosuppression.[28,31] Various aspects of the gut microbiome have been associated with increased colorectal cancer risk.[30]

Several limitations of our study should be noted. First, the median follow-up time was between 5.0 and 6.7 y, which may not be long enough to observe the development of some cancers. Nonetheless, a quarter of our population was followed for 7.9 to 19.9 y, and our cumulative incidence curves do not illustrate any divergence between ILDKTr and CLDKTr over this long interval. Second, ILDKTr and CLDKTr differed in several ways that we could assess, and they may also have differed in other unmeasured ways. Given the known risks associated with ILDKT, it is possible that these recipients may be more intensely surveilled for the development of adverse outcomes, such as cancer. These factors may have affected the comparison of cancer incidence between ILDKTr and CLDKTr such that they would likely have biased our findings away from the null. Despite this, we observed no overall increase in cancer incidence among ILDKTr. Third, desensitization protocols and post-transplant management of DSA vary across centers, but our study was not designed to address these differences. Finally, because the cancer registries do not capture BCC and SCC, we were forced to analyze these cancers using data in the SRTR, despite very low sensitivity as demonstrated in a prior study.[17] Our study should not be interpreted as making authoritative claims of absolute risk in ILDKTr and CLDKTr with respect to BCC and SCC incidence. However, we have no reason to believe that the low sensitivity captured by the SRTR would differentially impact ILDKTr as compared with CLDKTr. Therefore, we do not believe that our estimates of relative risk are biased.

Strengths of our study include our inclusion of a multicenter sample study of ILDKTr and appropriate controls with linkage to population-based cancer registries, which assured nearly complete case ascertainment. Our robust study design facilitates generalization of our findings, such that they apply to other centers that perform ILDKT across the United States. To our knowledge, this is the first multicenter study to comprehensively evaluate cancer risk among ILDKTr.

The present study can help inform discussions regarding the safety of ILDKT. All transplant recipients are recommended

to receive cancer screening.[32] Although overall cancer risk was similar between ILDKTr and CLDKTr, the suggestive increase in colorectal cancer points to a need for strict adherence to screening guidelines for this cancer. It is also important to interpret our findings within the context of the broader literature on ILDKT. Despite the significant survival benefit provided by ILDKT, enthusiasm has waned due in part to the cost of desensitization treatments and post-transplant complications.[33,34] Concomitantly, the ecosystem of transplant modalities for candidates with DSA has changed as a result of increased prioritization of highly sensitized candidates in the Kidney Allocation System and the expansion of kidney paired donation programs.[20] Nonetheless, desensitization remains an important option to reduce long wait times and facilitate a compatible match, especially for centers that have combined kidney paired donation with ILDKT.[20]

In conclusion, the absence of an overall increased cancer risk associated with ILDKT is reassuring, and our results can help facilitate patient counseling and management. We believe that most cancer guidelines developed for CLDKTr can be applied to ILDKTr, although there may be a need for tailored screening or prevention for colorectal cancer.

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