Complete Methods:

Study Design

The Transplant Cancer Match Study links 15 population-based cancer registries to the Scientific Registry of Transplant Recipients (SRTR), a registry of all US solid organ transplant candidates and recipients (including 517,686 kidney candidates or recipients).[1] The SRTR obtains information from the Organ Procurement and Transplantation Network, which requires reporting of kidney recipient outcomes, including graft failure and death, from all transplant hospitals, and supplements with data on dialysis from the Centers for Medicare and Medicaid Services End Stage Renal Disease Program. For this study, we included kidney candidates and recipients between 1987-2010 who resided in areas covered by participating cancer registries and who had follow-up time as described below (N=202,195, 39% of all kidney candidates/recipients).

Intervals of kidney non-function were defined as time from first kidney wait listing to transplant, or from failure of a kidney transplant to subsequent transplant, if one occurred. Intervals of kidney function were defined as any period after receipt of a kidney transplant and before kidney graft failure. As only a small number of people received more than two kidney transplants (N=559), intervals of kidney function corresponding to a second or later kidney transplant were combined. Similarly, all kidney non-function intervals corresponding to failure of second or later transplants were combined. This grouping yielded five intervals: wait list, first transplant, first graft failure, second or higher transplant, and second or higher graft failure. Each person could contribute to each interval, although some ESRD patients were preemptively transplanted without being on the wait list, and other patients had already received a kidney transplant by the time cancer registry coverage began.

We focused on infection-related cancers (i.e. cancers in which infections play a role in the etiology, though for some types infections may not be present in every case: Kaposi sarcoma [KS], lymphomas, and cervical, anal, vaginal/vulvar, penile, oropharyngeal, liver, and stomach cancers),[2] ESRD-related cancers (i.e., cancers increased in dialysis patients: kidney, urinary tract, and thyroid cancers),[3, 4] immune-related cancers (i.e., cancers unrelated to known infections but increased in immunosuppressed populations: melanoma and lung, lip, and non-epithelial skin cancers), and other common cancers with counts greater than 100 across all intervals (e.g., colorectal, breast, and prostate cancers).[5] Associations were considered with cancer groups (infection-related, ESRD-related, immune-related, and other) and individual cancers. Squamous cell and basal cell skin cancers were not included in any analyses as these diagnoses are not ascertained by cancer registries. For people with multiple cancer types, all primary cancer diagnoses were included. ESRD patients with a cancer diagnosis prior to wait list or transplant were included.

Statistical Analyses

At-risk time for each person started at the latest of: start of cancer registry coverage or entry onto the kidney transplant wait list (or kidney transplant, if it was performed pre-emptively). Follow-up ended at the earliest of: death, non-kidney transplant (including multi-organ kidney transplant), loss-to-follow-up by the SRTR, or end of cancer registry coverage. Non-kidney transplants were excluded because their immunosuppressant use may not clearly correspond with kidney function.

Incidence rates were calculated for each cancer within each of the five intervals. Cox regression models were used to estimate hazard ratios (HRs) comparing cancer risk in all kidney

function time to all non-function time, in order to provide a simple contrast of cancer risk during kidney transplant to risk during time on dialysis. In Cox regression, people were followed until the first diagnosis of the cancer type (or types) of interest, but follow-up for these outcomes was not censored when other cancer types were diagnosed. Kidney function status was considered a time-varying covariate, using age as the time scale. Multivariable regression models additionally adjusted for sex, race/ethnicity, and attained calendar year. To capture how risk changed over time, we also assessed models that compared each interval to the immediately preceding interval.

We hypothesized that cancers tightly related to immunosuppression (or kidney failure) would exhibit clear changes in incidence with each successive change in kidney function. For each cancer type, we used an alternating slopes test to evaluate this hypothesis in two steps. First, we required that all changes in incidence from a kidney function to a non-function interval had to be in the same direction, while all changes from a non-function to a function interval had to be in the opposite direction (even if individual changes were not statistically significant). Second, if this condition was met, we evaluated whether the combined relative changes from kidney function to non-function intervals were statistically significant[6] (i.e., that the pooled slope was different from 1.00 on the HR scale). The same test was done for the combined relative changes from kidney non-function to function intervals. For these tests we used a one-sided α of 0.05, because we tested for slopes in pre-specified directions. If both slope tests indicated statistical significance, then the cancer was considered tightly linked to immunosuppression or kidney failure.

We also calculated standardized incidence ratios (SIRs), which describe cancer incidence relative to the expected incidence, based on general population rates obtained from the cancer registries participating in the Transplant Cancer Match Study. SIRs were calculated by taking

the observed cancer counts in each interval in our study and dividing them by expected cancer counts. Expected cancer counts were derived by applying general population cancer rates stratified by age, sex, race/ethnicity, calendar year, and cancer registry area to the cohort's person-time within each stratum. Confidence intervals were calculated using the exact method.[7]

We expected that at least some time would need to occur before the effects of immunosuppression and kidney failure would manifest as more frequent cancer diagnoses, but that such effects could reasonably be expected to take place in less than 6 months in some instances. As such, all primary analyses were done with 3-month lags, in which incidence and association measures were calculated for cancers occurring 3 months after the time in each interval. In sensitivity analyses, we considered associations with no lag or a 6-month lag, but results were similar (not shown). We also examined incidence patterns separately for local and regional/distant stage cancers. If differences in incidence were limited to local stage cancers, this could indicate that differences are driven by changes in cancer screening across intervals. Alternatively, differences in incidence patterns by stage may reflect etiologic relationships that influence the aggressiveness of cancer.

References:

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Supplementary Table 1: Alternating slopes test results

Cancer Type	Changes in cancer risk consistently in opposite directions?	p-value for pooled slope from non-function to function intervals (Wait list →1st Tx, 1st Graft failure →2nd Tx)	p-value for pooled slope from function to non-function intervals (1st Tx →1st Graft failure, 2nd Tx →2nd Graft failure)	Were both pooled slopes statistically significant?
Infection-related				
Kaposi sarcoma	No	-	-	-
Non-Hodgkin lymphoma	Yes	<0.001	<0.001	Yes
Hodgkin lymphoma	No	-	-	-
Liver	No	-	-	-
Stomach	No	-	-	-
Oropharynx*	No	-	-	-
Anus	Yes	0.007	0.111	No
Cervix	No	-	-	-
Other genital†	No	-	-	-
Immune-related				
Lung	Yes	<0.001	0.042	Yes
Melanoma	Yes	<0.001	<0.001	Yes
Lip	No	-	-	-
Non-epithelial skin‡	Yes	<0.001	0.038	Yes
ESRD-related				
Kidney	Yes	<0.001	<0.001	Yes
Urinary Tract	No	-	-	-
Thyroid	Yes	0.003	<0.001	Yes
Other				
Colorectum	No	-	-	-
Prostate	No	-	-	-
Breast	No	-	-	-
Esophagus	No	-	-	-
Pancreas	Yes	0.004	0.041	Yes
Uterus	No	-	-	-
Myeloma	Yes	0.233	0.158	No
Leukemia	No	-	-	-

All p-values for the tests of pooled slopes are one-sided. A one-sided alpha of 0.05 was used to define statistical significance.

*Oropharynx cancer includes cancers of the base of tongue, tonsils, and other oropharynx sites.

†Other genital cancers include cancers of the vagina, vulva, and penis.

‡Non-epithelial skin is defined as skin cancers excluding melanoma, Kaposi sarcoma, squamous and basal cell carcinoma.

Tx=transplant, ESRD=end stage renal disease