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Mortality among solid organ transplant recipients with a pretransplant cancer diagnosis

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Abstract

Little is known about outcomes among solid organ transplant recipients with a pretransplant cancer diagnosis. We used linked data from the Scientific Registry of Transplant Recipients with 33 US cancer registries. Cox proportional hazards models assessed associations of pretransplant cancer with overall mortality, cancer-specific mortality, and development of a new posttransplant cancer. Among 311,677 recipients, the presence of a single pretransplant cancer was associated with increased overall mortality (adjusted hazard ratio [aHR] 1.19, 95%CI 1.15–1.23) and cancer-specific mortality (1.93, 1.76–2.12); results for 2+ pretransplant cancers were similar. Cancer-specific mortality was not significantly increased for uterine, prostate, or thyroid cancers (aHRs 0.83, 1.22, and 1.54, respectively) but strongly elevated for lung cancer and myeloma (aHRs 3.72 and 4.42). A pretransplant cancer diagnosis was also associated with increased risk of developing posttransplant cancer (aHR 1.32, 95%CI 1.23–1.40). Among 306 recipients

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whose cancer death was confirmed by cancer registry data, 158 deaths (51.6%) were from a *de novo* posttransplant cancer and 105 (34.3%) from the pretransplant cancer. Pretransplant cancer diagnoses are associated with increased mortality after transplantation, but some deaths are related to posttransplant cancers and other causes. Improved candidate selection and cancer screening and prevention may reduce mortality in this population.

1 INTRODUCTION

Solid organ transplantation is lifesaving for patients with end-stage organ disease, but the associated immunosuppression necessary to prevent allograft rejection increases the risk of cancer. The elevated incidence of posttransplant cancer has been well-described[1,2] and is associated with substantial posttransplant mortality.[3]

Less is known about posttransplant outcomes among patients with a pretransplant history of cancer.[4–10] Recurrence of cancer following transplantation is of concern, as transplant-related immunosuppression may facilitate cancer recurrence and worsen survival. Previous studies investigating the effect of pretransplant cancer diagnoses on posttransplant outcomes have been either small in size or lacked systematic data on relevant predictors of outcomes such as cancer type, stage, and the time interval between cancer diagnosis and transplantation.[4,11–14] In addition, the presence of a pretransplant cancer diagnosis is associated with elevated risk of developing a new cancer after transplantation,[4,15–20] but the relative contributions of pretransplant and posttransplant cancers to mortality in this population remain unclear.

Additional information on posttransplant outcomes among SOTRs can help inform transplant program decisions regarding waitlisting and transplantation. In this study, we used data from a large linkage of the United States transplant registry and multiple cancer registries to determine whether SOTRs with a pretransplant cancer diagnosis had higher mortality after transplantation compared to SOTRs without a pretransplant cancer. We also sought to identify predictors of posttransplant mortality related to the pretransplant cancers. Finally, we investigated whether the posttransplant cancer deaths among SOTRs with a pretransplant cancer were due to the pretransplant cancer or a *de novo* cancer arising after transplantation.

2 METHODS

This study used data from the Transplant Cancer Match (TCM) Study, a linkage of the Scientific Registry of Transplant Recipients (SRTR) with multiple state and regional cancer registries. SRTR includes data from every US transplant occurring since October 1987.[21] The current study utilized data from 33 cancer registries with varying calendar years of coverage for cancer diagnoses (see Table 1 note). This study is considered non-human subjects research by the National Institutes of Health and was approved by participating cancer registries.

From 591,780 US transplants identified in SRTR during 1995–2017, we restricted analysis to first transplants where the recipient resided in a participating cancer registry region

(N=419,167). We required at least 5 years of cancer registry coverage before the transplant date to ascertain pretransplant cancer diagnoses using the linked cancer data, excluding SOTRs for whom there was only 0.1–4.9 years of registry coverage available prior to transplantation to avoid missing pretransplant cancer diagnoses (N=331,468). We excluded SOTRs with colorectal or hepatobiliary cancers who received a liver transplant because the transplant may have been performed as treatment for their primary or metastatic cancer, leaving N=311,677 SOTRs (52.7% of all US transplants during 1995–2017). We collected only the month and year of cancer diagnoses and therefore assigned the 15th of the month as the diagnosis date. Cancers diagnosed up to 15 days after the transplant date were classified as pretransplant cancers, and those diagnosed more than 15 days post-transplant were classified as posttransplant cancers.

For each SOTR, follow-up began at transplantation and ended at the earliest of death, loss to follow up, or end of available cancer registry data. We used Cox proportional hazards models to estimate hazard ratios (HRs) for the associations of pretransplant cancer with overall and cancer-specific mortality (i.e., due to all types of cancer combined, including both pretransplant and posttransplant cancers). Cancer-specific mortality was ascertained using the primary cause of death provided by transplant centers in the SRTR database, including both deaths coded as due to cancer and those indicated in text fields.

We report adjusted HRs (aHRs) for mortality based on Cox models that included sex, age at transplant, race, ethnicity, transplanted organ, and calendar year of transplant. We evaluated mortality associated with the presence of either 1 or 2+ pretransplant cancers. In addition, we used similar Cox models to assess the association between pretransplant cancer and incidence of posttransplant cancer.

We derived curves for overall survival for SOTRs with 0, 1, or 2+ pretransplant cancers based on weighted Kaplan-Meier estimates, in which the curves for the groups with pretransplant cancer were weighted to resemble the group without pretransplant cancer in terms of sex, age at transplant, race/ethnicity, transplanted organ, and calendar year of transplant. Weights were calculated from multivariable polytomous logistic regression models with the number of pretransplant cancers (0, 1, 2+) as the outcome.

Using a dataset restricted to SOTRs with 0 or 1 pretransplant cancer, we performed additional Cox regression analyses to assess the associations with mortality for subgroups of SOTRs with cancer based on the characteristics of the pretransplant cancer: cancer type (for those cancer types where there were at least 200 cases), interval between cancer diagnosis and transplantation (0–1.99, 2–4.99, 5+ years), and cancer stage (local, regional, distant, unstaged/unknown). We then assessed multivariable models that included the combination of all three of these variables (cancer type, interval between cancer diagnosis and transplantation, cancer stage) to evaluate the independent associations of each of these characteristics with mortality. These models were restricted to SOTRs who had 1 pretransplant cancer, because multivariable assessment of tumor characteristics was not meaningful for individuals without cancer or with multiple cancers. These multivariable models used effect coding for cancer type,[22] so that aHRs for each cancer type compared that group of SOTRs to the overall average across all cancer types. We tested for

heterogeneity in the HR estimates across number of pretransplant cancers, cancer type, time from cancer diagnosis to transplant, and cancer stage using likelihood ratio tests.

We evaluated the proportional hazards assumption of the Cox regression models in two ways. First, to assess whether nonproportionality of variables other than pretransplant cancer affected our conclusions, we jointly stratified the models on these variables, rather than adjusting for them, and compared the HR estimates for pretransplant cancer in these models with those from the main analyses. Second, to assess whether the hazards for pretransplant cancer variables were proportional, we included an interaction term between pretransplant cancer and time since transplantation (1 degree of freedom for the trend across intervals of <2.5, 2.5–5.0, >5.0 years). When this interaction was significant, we used the interaction term to calculate separate HRs for pretransplant cancer for each time interval since transplantation.

The cause of death data in SRTR were not sufficiently detailed to determine whether a cancer death was due to the pretransplant cancer or a posttransplant cancer. However, cancer registries collect data for cancer patients on cause of death (including related to specific cancer diagnoses) from state and national death certificate databases. Therefore, for SOTRs with a pretransplant cancer diagnosis, we reviewed the cancer registry data on cause of death to determine whether the posttransplant cancer deaths specified in SRTR were due to the pretransplant cancer, a posttransplant cancer, or another cause.

3 RESULTS

3.1 Cohort description

Among 311,677 SOTRs in this study, 11,030 (3.5%) had 1 pretransplant cancer and 1,284 (0.4%) had 2 or more pretransplant cancers (Table 1). Compared to SOTRs without a pretransplant cancer, those with pretransplant cancer were slightly more likely to be male and were older (median age at transplantation 50, 60, and 62 years for SOTRs with 0, 1, or 2+ pretransplant cancers, respectively). SOTRs with a pretransplant cancer were also more likely to be non-Hispanic white and kidney recipients. The proportion of SOTRs with a pretransplant cancer increased over time from 2.04% in 1995–1999 to 5.58% in 2010–2017 (Table 1).

Among candidates with 1 pretransplant cancer, the median time from cancer to transplant was 5.7 years (interquartile range 2.7–9.4 years). The most common pretransplant cancers were cancers of the kidney (n=2567), prostate (n=2539), breast (n=1373), colorectum (n=802), thyroid (n=611), uterus (n=301), bladder (n=274), myeloma (n=251), and lung (n=226), as well as non-Hodgkin lymphoma (NHL, including chronic lymphocytic lymphoma; n=550) and melanoma (n=407).

3.2 Association between pretransplant cancer diagnoses and posttransplant mortality

SOTRs with 0, 1, or 2+ pretransplant cancers had a median follow-up of 5.0, 3.9, and 3.6 years after transplantation, respectively. The presence of 1 or 2+ pretransplant cancers was associated with increased overall mortality following transplantation (unadjusted HRs 1.45, 95%CI 1.40–1.50, and 1.46, 1.32–1.61, respectively). As shown in Table 2, these

associations were attenuated but persisted in adjusted analyses (aHRs 1.19, 95%CI 1.15–1.23, and 1.21, 1.10–1.34, respectively).

Figure 1 shows overall survival for SOTRs with 0, 1, or 2+ pretransplant cancers based on standardized Kaplan-Meier curves. At 5 years after transplantation, an estimated 81.7%, 76.4%, and 70.6% of SOTRs with 0, 1, or 2+ pretransplant cancers remained alive, while at 10 years after transplant, the corresponding proportions were 62.6%, 54.9%, and 53.5%. These estimates correspond to an absolute increase in mortality at 5 and 10 years of 5.3% (95%CI 4.0–6.9%) and 7.7% (5.6–9.7%), respectively, for SOTRs with 1 pretransplant cancer, and of 11.1% (4.0–18.2%) and 9.0% (0.5–17.5%), respectively, for those with 2+ pretransplant cancers, compared to SOTRs without a pretransplant cancer.

A pretransplant cancer diagnosis was strongly associated with increased cancer-specific mortality (unadjusted HR for cancer-specific mortality 2.73, 95%CI 2.49–2.99, for 1 pretransplant cancer, and 3.53, 2.78–4.49, for 2+ pretransplant cancers, versus 0 pretransplant cancers). These associations for cancer-specific mortality persisted in adjusted analyses (aHRs 1.93, 95%CI 1.76–2.12, and 2.57, 2.02–3.26, for 1 and 2+ pretransplant cancers, respectively; Table 3).

In analyses restricted to SOTRs with 0 or 1 pretransplant cancer (Table 3), those with progressively advanced stage pretransplant cancers exhibited increasing cancer-specific mortality relative to SOTRs without a pretransplant cancer (local stage: aHR 1.65, 95%CI 1.47–1.86; regional stage: 2.52, 1.99–3.18; distant stage: 5.54, 3.71–8.28). While time from cancer diagnosis to transplant was not significantly predictive, there was a trend toward worse outcomes for patients transplanted within 2 years. Cancer-specific mortality also differed by cancer type. Specifically, pretransplant diagnoses of thyroid, prostate, and uterine cancers were not associated with significantly increased cancer-specific mortality (thyroid cancer: aHR 1.54, 95%CI 0.91–2.60; prostate cancer: 1.22, 0.99–1.51; uterine cancer: 0.83, 0.34–1.99). In contrast, myeloma and lung cancer conferred the greatest cancer-specific mortality risk (myeloma: aHR 4.42, 95%CI 2.70–7.22; lung cancer: 3.72, 2.40–5.77), while cancer-specific mortality was increased approximately 2-fold for cancers of the breast, bladder, colorectum, and melanoma (Table 3). Some findings were similar for overall mortality (e.g., significantly elevated risks associated with pretransplant cancers that were distant stage [aHR 1.56, 95%CI 1.27–1.91] or lung cancer [1.80, 1.49–2.18]) (Table 2).

We also assessed time between cancer diagnosis and transplantation, cancer stage, and cancer type together as independent predictors of cancer-specific mortality (Table 4). Time intervals of at least 2 years between cancer diagnosis and transplantation tended to be associated with decreased risk of cancer-specific mortality, although these associations were not statistically significant. Regional and distant stage cancers were associated with higher cancer-specific mortality compared to local stage cancers (aHRs 1.42, 95%CI 1.08–1.86, and 2.04, 1.29–3.20, respectively), and myeloma and lung cancer were associated with elevated cancer-specific mortality compared to the average for all cancers (aHRs 2.17, 95%CI 1.29–3.65, and 1.82, 1.19–2.81, respectively). In contrast, uterine and prostate cancers were associated with below-average cancer-specific mortality (aHRs 0.38, 95%CI 0.17–0.86, and 0.73, 0.56–0.95, respectively).

Stratifying the Cox models on the covariates other than pretransplant cancer, rather than adjusting for them, yielded similar aHRs for pretransplant cancer compared to the fully adjusted models, indicating that any nonproportionality in these covariates did not bias the estimated aHRs for pretransplant cancer. However, the aHRs for pretransplant cancer were nonproportional for some analyses, so that the association with cancer-specific mortality (Table 3) or overall mortality (Table 2) changed with greater time since transplantation. In general, when nonproportionality was present, aHRs for cancer-specific mortality were highest in the early posttransplant period and decreased over time. For example, distant stage cancer was associated with nearly 10-fold increased cancer-specific mortality in the first 2.5 years posttransplant (aHR 9.69, 95%CI 5.60–16.8) but only 6-fold and 3-fold increases at 2.5–5 years and >5 years posttransplant (5.54, 3.67–8.38, and 3.17, 1.56–6.36, respectively) (Table 3). Similarly, a pretransplant lung cancer diagnosis was associated with 6-fold increased cancer-specific mortality in the first 2.5 years posttransplant (aHR 5.99, 95%CI 3.42–10.5) but only 3-fold and 2-fold increases at 2.5–5 years and >5 years posttransplant (3.28, 2.00–5.39, and 1.80, 0.72–4.51, respectively) (Table 3).

For overall mortality, in contrast, when nonproportionality was present, aHRs typically increased with greater time since transplantation (Table 2). For example, time between cancer diagnosis and transplant of 2–5 and >5 years was not associated with overall mortality during the period <2.5 years after transplantation (aHRs 1.04, 95%CI 0.94–1.14, and 1.08, 1.00–1.15, respectively) but was associated with a 29–41% increased risk 2.5 years or more from transplant (1.29, 1.18–1.40, and 1.41,1.32–1.51, respectively) (Table 2). An exception to this pattern was seen for distant stage pretransplant cancers, for which the aHR was highest during the period <2.5 years after transplantation.

3.3 Associations of pretransplant and posttransplant cancer diagnoses with cancer-specific mortality

During follow-up after transplantation, at least one posttransplant cancer diagnosis was observed in 1047 (9.5%) SOTRs with 1 pretransplant cancer (Table S1 and 20,236 (6.8%) SOTRs without a pretransplant cancer (unadjusted HR for posttransplant cancer 1.82, 95%CI 1.71–1.94; aHR 1.32, 95%CI 1.23–1.40). Among the 489 cancer-specific deaths identified in the SRTR database among SOTRs with a pretransplant cancer, the cancer registry confirmed cancer as the cause of death in 306 (62.6%) (Table 5). Among the 306 SOTRs for whom a cancer-specific death was confirmed, 105 deaths (34.3%) were due to the pretransplant cancer, 158 (51.6%) were due to a posttransplant cancer, and 43 deaths (14.1%) were from cancers of uncertain timing.

A large fraction of deaths were due to the pretransplant cancer when the tests of nonproportionality indicated that the strongest aHR for cancer-specific mortality was in the period <2.5 years after transplant (Table 3). Notable examples included pretransplant cancers that were distant stage (58% of cancer-specific deaths were due to the pretransplant cancer) or lung cancer (77%; Table S2). Among the 158 posttransplant cancers that led to death (Table 4), 67 (42%) were potentially “screen-detectable,” including deaths due to lung cancer (N=43), skin cancer (including melanoma, N=13), colorectal cancer (N=10), and breast cancer (N=1).

4 DISCUSSION

In our analysis of linked data on SOTRs from the US transplant registry and 33 cancer registries, the presence of a pretransplant cancer diagnosis was associated with an increased risk of both overall and cancer-specific mortality. Certain adverse features of these pretransplant cancers were associated with increased mortality after transplantation. Notably, however, close examination of the cause of death information indicated that a substantial fraction of cancer deaths in these individuals were due to *de novo* cancers arising after transplantation, rather than from recurrence of their pretransplant cancer.

It has long been recognized that solid organ transplantation can greatly increase the risk of recurrence in cancer patients when treatment has been inadequate or when insufficient time has elapsed since the completion of cancer therapy, due to the immunosuppression to prevent graft rejection.[23,24] These observations led to the development of guidelines to screen for cancer in waitlist candidates, and to wait 2–5 years after completion of cancer treatment prior to listing.[23,25,26] For decades, the Israel Penn International Transplant Tumor Registry has been a source of guidance to clinicians with regards to waiting periods for different cancers,[23] but this registry only collects data voluntarily provided by participating hospitals.

In the absence of systematic data on SOTRs with a pretransplant cancer, recommendations regarding transplantation in this setting have been based largely on expert opinion.[27,28] In the meantime, the proportion of SOTRs with a prior history of cancer is increasing.[13] In our cohort, this proportion rose from 2% in 1995–1999 to more than 5% in 2010–2017. Other aspects of our data similarly reflect accepted clinical practice. For example, we observed that relatively few patients with a previous history of lung cancer underwent transplant compared to the typically less aggressive prostate and thyroid cancers, and the median time interval between cancer diagnosis and transplantation was more than 5 years.

Previous epidemiologic studies have evaluated outcomes among SOTRs with a pretransplant cancer but lacked data on important predictors that are needed to inform patient-level decisions about listing. In a 2017 meta-analysis by Acuna et. al.,[4] SOTRs with a pretransplant cancer had 1.5-fold and 3-fold elevations in overall and cancer-specific mortality, respectively, compared to SOTRs without a pretransplant cancer, and they had nearly twice the risk of developing a *de novo* cancer. We found similar associations in our unadjusted analyses, but the associations for overall mortality and posttransplant cancer were more modest after adjustments. Our study with 311,677 SOTRs is much larger than the combined studies in the meta-analysis, which analyzed 78,041 and 193,629 SOTRs for overall and cancer-specific mortality, respectively.[4] More recent studies have been similarly small and limited to kidney recipients,[11,12] lacked specifics about cancer type, cancer stage, or the cancer leading to death,[11,14] or were largely restricted to White SOTRs.[11,12,14]

Importantly, our analysis of SOTRs with pretransplant cancer found several characteristics associated with increased cancer-specific mortality after transplantation, including the presence of certain cancer types with poor prognosis (e.g., lung cancer and myeloma) and advanced cancer stage at diagnosis. Similar to previous studies,[11,12,14] time between cancer

diagnosis and transplantation was not significantly associated with increased cancer-specific mortality in our cohort, although there appeared to be a trend toward increased mortality when the interval was only 0–1.99 years. The lack of a strong difference in cancer-specific mortality related across these time intervals between cancer diagnosis and transplantation could reflect the way in which providers use other factors, such as cancer type and stage, to determine how long to wait before offering transplantation.

For pretransplant cancers that were distant stage cancers or lung cancers, the HRs for cancer-specific mortality showed nonproportionality, with the strongest associations in the first 2.5 years after transplantation. Such cancers are typically aggressive, and the nonproportionality is in line with a high risk of recurrence immediately following transplantation. Consistent with this observation, our review of additional data provided by cancer registries indicated that a large fraction of the cancer-specific deaths in these SOTRs was due to the pretransplant cancer, rather than a *de novo* cancer.

Nonetheless, a critical finding of our review of cancer-related deaths is that not all cancer deaths were due to the pretransplant cancer. Of the 263 SOTRs with a pretransplant cancer who died from cancer and for whom the cancer leading to death could be ascertained, the majority (n=158, 60.0%) were due to a new posttransplant cancer. Indeed, we found that a pretransplant cancer diagnosis was associated with 1.8-fold increased risk of developing a new posttransplant cancer, which mirrors the findings of Acuna et. al.[4] as well as the increased risk for new cancer diagnoses observed among cancer survivors in the general population.[29] Our estimate of the fraction of cancer deaths due to posttransplant cancer diagnoses is higher than the estimate from a small Swedish registry study of SOTRs, in which 27 of 66 cancer-related deaths (41%) were from a posttransplant cancer.[9]

We also identified an increase in overall mortality associated with a pretransplant cancer. These deaths include those from non-cancer conditions, such as cardiovascular disease and infections, which may be made more likely by prolonged time on the waitlist. For example, longer time on dialysis prior to kidney transplantation confers worse outcomes after transplant, probably due to increased cardiovascular mortality.[30] There is thus an important trade-off in delaying transplantation to ensure cancer remission, and it may take extended follow-up for the adverse effects to become apparent. This tradeoff appears supported by our finding that some associations between pretransplant cancer and overall mortality became stronger with longer time since transplant, including in SOTRs with 5+ years between cancer diagnosis and transplant (Table 2). This suggests that the adverse biological effects of prolonged waiting time become progressively more apparent over time following transplantation.

This study is the largest population-based study to date with granular detail regarding the cancer characteristics as well as detail on whether posttransplant deaths are due to pretransplant vs. de novo cancers. SRTR captures data on all US SOTRs, most of whom were also covered in participating cancer registries. Our study thus had a large sample size representative of the US SOTR population, including all solid organ transplant types and a racially and ethnically diverse population. Because of the lack of specificity in cause of death information in SRTR, we obtained additional data from cancer registries for SOTRs

who had a pretransplant cancer, which provided a more complete picture of posttransplant outcomes. Our assessment of overall mortality did not depend on assignment of cause of death, although the analyses of overall mortality may have been confounded by some factors related to both cancer and mortality that we could not adjust for (e.g., smoking). In addition, cancer registries lacked data on some cancer characteristics that are prognostic, including tumor markers and genomics.

Our results provide insights into the clinical implications of a pretransplant cancer diagnosis and suggest areas for additional research. The mortality that we demonstrate due to the pretransplant cancers themselves indicates a need for continued study to better discern which cancers are likely to recur after transplantation. The probability that a given cancer is cured can be modeled over time accounting for factors such as cancer type, stage, and other patient characteristics.[31] Such models can indicate when a given patient's probability of being cured exceeds a threshold deemed acceptable by the transplant team and may aid in determining which patients could reasonably undergo transplant sooner. Cancer recurrence risk then needs to be balanced against mortality that patients experience while awaiting transplant eligibility, as well as the increased posttransplant mortality conferred by longer waitlist time.

Our finding that a substantial proportion of posttransplant cancer deaths were from cancers arising after transplantation prompts important considerations for cancer prevention and screening in SOTRs. One implication is that a pretransplant cancer diagnosis should be considered a marker of susceptibility to developing a posttransplant cancer. Importantly, many of the *de novo* posttransplant cancers that led to death in this study were screen-detectable. Some enhanced cancer screening, such as regular skin cancer screening, is already recommended for SOTRs.[25] However, the large number of posttransplant lung cancers that caused death among SOTRs with a pretransplant cancer indicates that smoking cessation should be especially emphasized. The potential for lung cancer screening with low-dose computed tomography among smokers, which is recommended in the general population,[32] should be evaluated. Research should also be directed to understand the reasons for the deaths from breast and colorectal cancers, as screening for these cancers is recommended for SOTRs following general population guidelines, as well as the use of novel biomarkers for cancer screening and surveillance, such as circulating tumor DNA.[25,33,34] Finally, additional research on the use of mTOR inhibitors, a class of immunosuppressant medications with anticancer properties, as well as minimizing medications known to increase the risk of cancer, may be warranted as a possible route to decreasing the risk of recurrent or *de novo* cancer.

In conclusion, our study demonstrated increased mortality among SOTRs with a pretransplant cancer diagnosis. To facilitate decisions regarding whether and when to offer a transplant to individuals with a prior cancer diagnosis, additional studies are needed to determine how the magnitude of this increase should be balanced against waitlist mortality, as well as the worse posttransplant outcomes conferred by longer waiting time prior to transplantation. In addition, the finding of a large proportion of deaths related to cancers that developed after transplantation indicates a need to evaluate cancer prevention and screening guidelines for this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

The Transplant Cancer Match Study principal investigator is the custodian for the data. Agreements between the National Cancer Institute, the Health Resources and Services Administration, and participating registries do not allow the investigators to share the data with outside researchers. Interested collaborators can use the study data at the National Cancer Institute under supervision by the principal investigator, or can participate in analyses through review of tabulated data.

Abbreviations:

aHR	adjusted hazard ratio

HR	hazard ratio
NHL	non-Hodgkin lymphoma
SOTR	solid organ transplant recipients
SRTR	Scientific Registry of Transplant Recipients
TCM	Transplant Cancer Match

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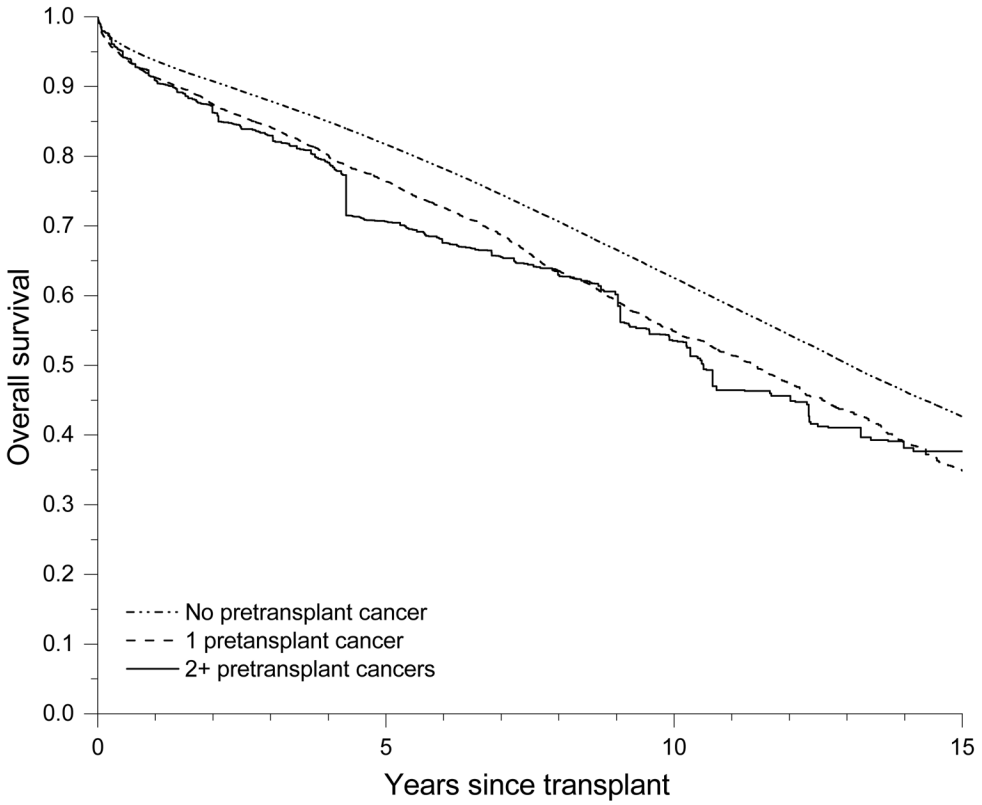

No pretransplant cancer	299363	150928	60904	14402
1 pretransplant cancer	11030	4444	1226	204
2+ pretransplant cancers	1284	469	121	22

Figure 1.

Overall survival in solid organ transplant recipients with 0, 1, or 2+ pretransplant cancers. Kaplan-Meier curves for the latter two groups were weighted to the group without a pretransplant cancer diagnosis.

Table 1.

Characteristics of solid organ transplant recipients with and without a pretransplant cancer diagnosis

Characteristic	No pretransplant cancer, N (%)	1 pretransplant cancer, N (%)	2+ pretransplant cancers, N (%)
Total	299,363 (100)	11,030 (100)	1,284 (100)
Sex			
Female	116,099 (38.78)	4,021 (36.46)	462 (35.98)
Male	183,264 (61.22)	7,009 (63.54)	822 (64.02)
Age at transplant, years			
0–17	21,570 (7.21)	230 (2.09)	6 (0.47)
18–34	39,732 (13.27)	380 (3.45)	38 (2.96)
35–49	82,168 (27.45)	1,638 (14.85)	174 (13.55)
50–64	119,049 (39.77)	5,156 (46.75)	570 (44.39)
65–96	36,844 (12.31)	3,626 (32.87)	496 (38.63)
Race/ethnicity			
White, Non-Hispanic	172,134 (57.50)	7,028 (63.72)	824 (64.17)
Black, Non-Hispanic	57,691 (19.27)	2,252 (20.42)	321 (25.00)
Hispanic	49,027 (16.38)	1,147 (10.40)	84 (6.54)
Asian/Pacific Islander	17,404 (5.81)	513 (4.65)	46 (3.58)
Other/unknown	3,107 (1.04)	90 (0.82)	9 (0.70)
Transplanted organ			
Kidney	181,448 (60.61)	7,629 (69.17)	1,035 (80.61)
Liver	52,314 (17.48)	1,289 (11.69)	79 (6.15)
Heart and/or lung	47,843 (15.98)	1,778 (16.12)	133 (10.36)
Other or multiple	17,758 (5.93)	334 (3.03)	37 (2.88)
Year of transplant			
1995–1999	34,651 (11.57)	667 (6.05)	54 (4.21)
2000–2004	75,866 (25.34)	1,714 (15.54)	162 (12.62)
2005–2009	83,466 (27.88)	3,130 (28.38)	358 (27.88)
2010–2017	105,380 (35.20)	5,519 (50.04)	710 (55.30)

The study included data from the following cancer registries (years of cancer registry data): Alaska (2001–2017), California (1995–2017), Colorado (1995–2016), Connecticut (1995–2017), Florida (1995–2009), Georgia (2000–2017), Hawaii (2000–2017), Idaho (1995–2017), Iowa (1995–2017), Illinois (1995–2013), Kentucky (2000–2017), Louisiana (2000–2017), Michigan (1995–2009), Montana (1995–2017), North Carolina (1995–2010), North Dakota (2002–2016), Nebraska (1995–2017), Nevada (2000–2015), New Jersey (1995–2016), New Mexico (1995–2016), New York (2000–2017), Ohio (2001–2015), Oklahoma (2002–2017), Oregon (2001–2016), Pennsylvania (2000–2017), Puerto Rico (1995–2016), Rhode Island (2000–2015), South Carolina (2001–2016), Seattle (1995–2017), Texas (2000–2016), Utah (1995–2017), and Virginia (2000–2016).

Table 2.

Associations of pretransplant cancer diagnoses with overall mortality

Characteristics of pretransplant cancer	Adjusted HR (95%CI)*	*P* value for heterogeneity	*P* value for test of nonproportionality***	Adjusted HR (95%CI), according to time period since transplantation		
				< 2.5 years	2.5 – 5 years	> 5 years
Number of cancers prior to transplant						
None	ref					
1	1.19 (1.15, 1.23)	0.75	<0.01	1.07 (1.02–1.13)	1.19 (1.15–1.23)	1.32 (1.26–1.39)
2+	1.21 (1.10, 1.34)		0.38			
Years between cancer and transplant**						
No cancer	ref					
0 – 1.99	1.14 (1.06, 1.23)	0.20	0.85			
2 – 4.99	1.16 (1.09, 1.24)		<0.01	1.04 (0.94–1.14)	1.16 (1.09–1.23)	1.29 (1.18–1.40)
5+	1.22 (1.17, 1.28)		<0.01	1.08 (1.00–1.15)	1.23 (1.18–1.29)	1.41 (1.32–1.51)
Stage at diagnosis**						
No cancer	ref					
Local	1.12 (1.08, 1,17)		<0.01	0.94 (0.88–1.00)	1.12 (1.07–1.17)	1.34 (1.26–1.42)
Regional	1.25 (1.14, 1.38)	<0.01	0.03	1.12 (0.97–1.29)	1.26 (1.14–1.38)	1.41 (1.23–1.63)
Distant	1.56 (1.27, 1.91)		<0.01	2.11 (1.61–2.78)	1.52 (1.23–1.88)	1.09 (0.77–1.54)
Unstaged/unknown	1.36 (1.26, 1.46)		0.02	1.48 (1.34–1.64)	1.35 (1.26–1.45)	1.23 (1.10–1.38)
Pretransplant cancer type**						
No cancer	ref					
Colorectum	1.35 (1.20, 1.51)		<0.01	1.05 (0.88–1.27)	1.34 (1.19–1.50)	1.69 (1.44–1.99)
Lung	1.80 (1.49, 2.18)		0.47			
Melanoma	1.08 (0.91, 1.29)	<0.01	0.54			
Breast	1.06 (0.96, 1.18)		0.89			
Uterus	1.20 (0.98, 1.47)		0.23			
Prostate	1.01 (0.94, 1.08)		<0.01	0.82 (0.74–0.92)	1.01 (0.94–1.08)	1.23 (1.11–1.37)
Kidney	1.07 (0.99, 1.17)		<0.01	0.77 (0.67–0.88)	1.05 (0.96–1.14)	1.43 (1.28–1.60)

Characteristics of pretransplant cancer	Adjusted HR (95%CI)*	*P* value for heterogeneity	*P* value for test of nonproportionality***	Adjusted HR (95%CI), according to time period since transplantation		
				< 2.5 years	2.5 – 5 years	> 5 years
Bladder	1.54 (1.28, 1.85)		0.92			
Thyroid	0.91 (0.76, 1.10)		<0.01	0.65 (0.48–0.88)	0.90 (0.74–1.09)	1.25 (0.97–1.61)
NHL	1.32 (1.14, 1.53)		0.08			
Myeloma	1.62 (1.29, 2.03)		<0.01	1.06 (0.73–1.54)	1.66 (1.32–2.09)	2.60 (1.88–3.61)

*All HRs are adjusted for sex, age at transplant, race/ethnicity, organ type, and year of transplant. *P* value for heterogeneity tests whether HR differs across subgroups.

**Analysis is restricted to patients with 0 or 1 pretransplant cancer.

***Test for interaction with ordinal variable reflecting time since transplantation (<2.5, 2.5–5.0, >5.0 years)

Abbreviations: HR, hazard ratio; NHL, non-Hodgkin lymphoma; ref, referent group

Table 3.

Association between pretransplant cancer diagnoses and posttransplant cancer-specific mortality

Characteristics of pretransplant cancer	Adjusted HR (95%CI)	*P* value for heterogeneity	*P* value for test of nonproportionality***	Adjusted HR (95%CI), according to time period since transplantation		
				< 2.5 years	2.5 – 5 years	> 5 years
Number of cancers prior to transplant						
None	ref					
1	1.93 (1.76, 2.12)	0.03	0.57			
2+	2.57 (2.02, 3.26)		<0.01	3.92 (2.84–5.42)	2.43 (1.89–3.13)	1.51 (0.96–2.36)
Years between cancer and transplant **						
No cancer	ref					
0 – 1.99	2.37 (1.96, 2.86)	0.06	0.32			
2 – 4.99	1.79 (1.51, 2.13)		0.33			
5+	1.85 (1.62, 2.10)		0.65			
Stage at diagnosis **						
No cancer	ref					
Local	1.65 (1.47, 1.86)		0.15			
Regional	2.52 (1.99, 3.18)	<0.01	0.78			
Distant	5.54 (3.71, 8.28)		0.02	9.69 (5.60–16.8)	5.54 (3.67–8.38)	3.17 (1.58–6.36)
Unstaged/unknown	2.26 (1.86, 2.75)		<0.01	3.19 (2.40–4.24)	2.26 (1.86–2.76)	1.60 (1.16–2.22)
Pretransplant cancer type **						
No cancer	ref					
Colorectum	1.98 (1.44, 2.73)		0.85			
Lung	3.72 (2.40, 5.77)		0.04	5.99 (3.42–10.5)	3.28 (2.00–5.39)	1.80 (0.72–4.51)
Melanoma	1.98 (1.30, 3.00)		0.87			
Breast	2.09 (1.61, 2.71)		0.44			
Uterus	0.83 (0.34, 1.99)	<0.01	0.59			
Prostate	1.22 (0.99, 1.51)		0.20			
Kidney	1.72 (1.36, 2.17)		0.08			
Bladder	2.47 (1.53, 3.98)		0.84			
Thyroid	1.54 (0.91, 2.60)		0.29			

Characteristics of pretransplant cancer	Adjusted HR (95%CI)	*P* value for heterogeneity	*P* value for test of nonproportionality***	Adjusted HR (95%CI), according to time period since transplantation		
				< 2.5 years	2.5 – 5 years	> 5 years
NHL	1.93 (1.27, 2.93)		0.23			
Myeloma	4.42 (2.70, 7.22)		0.92			

* All HRs are adjusted for sex, age at transplant, race/ethnicity, organ type, and year of transplant.

** Analysis is restricted to patients with 0 or 1 pretransplant cancer.

*** Test for interaction with ordinal variable reflecting time since transplantation (<2.5, 2.5–5.0, >5.0 years)

Abbreviations: HR, hazard ratio; NHL, non-Hodgkin lymphoma; ref, referent group

Table 4.

Independent associations of interval between cancer diagnosis and transplant, cancer stage, and cancer type with posttransplant cancer-specific mortality among patients with 1 pretransplant cancer.

	Cancer Deaths(N)	Adjusted HR*	95% Confidence Interval	*P* value for heterogeneity
Years cancer prior to transplant				
0 – 1.99	111	ref		
2 – 4.99	136	0.78	(0.60, 1.01)	0.10
5+	242	0.79	(0.63, 1.01)	
Summary stage				
Local	291	ref		
Regional	72	1.42	(1.08, 1.86)	
Distant	24	2.04	(1.29, 3.20)	0.001
Unstaged/unknown	102	0.94	(0.70, 1.28)	
Pretransplant cancer type **				
Colorectum	38	0.99	(0.71, 1.37)	
Lung	20	1.82	(1.19, 2.81)	
Melanoma	22	1.04	(0.69, 1.57)	
Breast	58	1.02	(0.74, 1.40)	
Uterus	5	0.38	(0.17, 0.86)	
Prostate	89	0.73	(0.56, 0.95)	0.0004
Kidney	72	0.83	(0.64, 1.08)	
Bladder	17	1.36	(0.86, 2.16)	
Thyroid	14	0.61	(0.37, 1.01)	
NHL	22	1.04	(0.66, 1.66)	
Myeloma	16	2.17	(1.29, 3.65)	

Abbreviations: HR, hazard ratio; NHL, non-Hodgkin lymphoma; ref, referent group

*All HRs are adjusted for sex, age at transplant (0–17, 18–34, 35–49, 50–64, 65+), race/ethnicity (non-Hispanic Black, non-Hispanic White, Hispanic/other/unknown), transplanted organ, and calendar year of transplant (1995–1999, 2000–2004, 2005–2009), and also mutually adjusted for the other factors in the table.

**The estimates for pretransplant cancer type are based on effect coding, so that the HR compares the risk for each cancer type versus the overall average *across all cancers*.

Table 5.

Cancer registry cause of death in 489 recipients with one pretransplant cancer diagnosis and cancer death specified in SRTR

Cancer registry cause of death	N	Proportion of total deaths specified as due to cancer in SRTR	Proportion of deaths confirmed as due to cancer by cancer registry
Cancer	306	62.6%	100%
Pretransplant cancer	105	21.5%	34.3%
Posttransplant cancer	158	32.3%	51.6%
Uncertain*	43	8.8%	14.1%
Noncancer	44	9.0%	-
Missing/unknown	139	28.4%	-
Total	489	100%	

* Information was insufficient to determine whether the cancer death was due to the pretransplant cancer or posttransplant cancer.

Abbreviation: SRTR; Scientific Registry of Transplant Recipients