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Survival after cancer diagnosis among solid organ transplant recipients in the United States

Monica E. D'Arcy, PhD[1], **Anna E. Coghill, PhD**[1], **Charles F. Lynch, MD**[2], **Lori Koch, PhD**[3], **Jie Li, PhD**[4], **Karen S. Pawlish, PhD**[4], **Cyllene R. Morris, BA**[5], **Chandrika Rao, PhD**[6], and **Eric A. Engels, MD, MPH**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD

[2]Department of Epidemiology, University of Iowa, Iowa City

[3]Illinois State Cancer Registry, Illinois Department of Public Health, Springfield, Illinois

[4]Cancer Epidemiology Services, New Jersey Department of Health, Trenton, New Jersey

[5]California Cancer Reporting and Epidemiologic Surveillance Program, Institute for Population Health Improvement, University of California Davis Health System, Sacramento, California

[6]North Carolina Central Cancer Registry, Raleigh, NC

Abstract

Purpose: Transplant recipients have an elevated risk of cancer because of organ rejection immunosuppressive medications, but no study has comprehensively examined associations between transplant status and mortality following a cancer diagnosis.

Methods: For 16 different cancer types, we assessed cases in the US general population (N=7,147,476) ascertained from 11 cancer registries. Presence of a solid organ transplant prior to diagnosis (N=11,416 cancer cases) was identified through linkage with the national transplant registry (1987–2014). We used Cox models to examine the association between transplant status and cancer-specific mortality, adjusting for demographic characteristics and cancer stage.

Results: For most cancers, cancer-specific mortality was higher in transplant recipients than for other cancer patients. The increase was particularly pronounced for melanoma (adjusted hazard ratio (aHR)=2.59, 95%CI 2.18–3.00) and cancers of the breast (1.88, 1.61–2.19), bladder (1.85, 1.58–2.17), and colorectum (1.77, 1.60–1.96), but it was also increased for cancers of the oral cavity/pharynx, stomach, pancreas, kidney, and lung, and diffuse large B-cell lymphoma (aHRs ranging from 1.21 to 1.47). Associations remained significant after adjustment for first-course cancer treatment and were generally stronger among local stage cancers for which potentially

Corresponding Author: Monica E. D'Arcy, PhD, 9609 Medical Center Drive, Room 6E228, Rockville, MD, 20850; Monica.d'arcy@nih.gov; Telephone: 240-276-5757.

Author contributions: Monica E. D'Arcy: Conceptualization, formal analysis, writing-original draft, writing-review and editing. Anna E. Coghill: Conceptualization, writing-review and editing. Charles F. Lynch: Conceptualization, data curation, writing-review and editing. Lori Koch: Conceptualization, data curation, writing - review and editing. Jie Li: Conceptualization, data curation, writing-review and editing. Karen S. Pawlish: Conceptualization, data curation, writing - review and editing. Cyllene R. Morris: Conceptualization, data curation, writing-review and editing. Chandrika Rao: Conceptualization, data curation, writing-review and editing. Eric A. Engels: Conceptualization, formal analysis, writing-review and editing, project administration, supervision.

Conflicts of Interest: None

curative treatment was provided, e.g., for melanoma (aHR=3.82, 95%CI 2.94–4.97), and cancers of the colorectum (2.77, 2.07–3.70), breast (2.08, 1.50–2.88), and prostate (1.60, 1.12–2.29), despite lack of association for prostate cancer overall.

Conclusion: For multiple cancer types, transplant recipients with cancer have an elevated risk of dying from their cancer, even after adjustment for stage and treatment, which may be due to impaired immunity.

Precis:

For multiple cancer types, transplant recipients with cancer have an elevated risk of dying from their cancer, even after adjustment for stage and treatment, which may be due to impaired immunity.

Keywords

Population Based; Solid Organ Transplant Recipient; Immunosuppression; Melanoma Breast Colorectal Bladder; Neoplasms Survival

Background

The number of solid organ recipients has increased in the last decade with almost 35,000 transplants occurring in the United States in 2017[1]. Although solid organ transplant is life-saving, recipients have elevated risk for many cancer types[2–4]. Immunosuppression attributable to medications used to prevent organ rejection plays a large role in the increased risk, especially for cancers caused by viruses. Additionally, some medications given post-transplant may be inherently carcinogenic or promote tumor growth[5–7].

If immunosuppression contributes to cancer outcomes, it could be reasoned that transplant recipients with cancer would also have higher cancer-specific mortality than cancer patients without a transplant, although the evidence to date is limited[8,9]. Several factors may contribute to mortality differences between transplant recipients and others who develop cancer. Because of frequent interaction with the medical system, transplant recipients may tend to be diagnosed at an early stage of cancer, which could favorably impact prognosis. Transplant recipients also have an elevated risk of dying from other transplant-related complications (e.g., organ failure, infections), so it is critical to accurately identify deaths attributable to cancer. Recipients of different organs can also have variable mortality. For example, differences for kidney recipients may result from a propensity for tumors to develop in native organs left in place at the time of transplantation

Because transplant recipients continue to live longer and the number of people living with a transplant has increased over time, characterizing outcomes following a cancer diagnosis in this population is important. The goal of this population-based study was to comprehensively examine the association between transplant status and mortality following a cancer diagnosis, focusing on cancer-specific mortality.

Methods

We used data from the Transplant Cancer Match (TCM) Study, which links the Scientific Registry of Transplant Recipients (SRTR) and 17 US regional and state cancer registries[3]. The SRTR contains information on recipient demographic and transplant characteristics. We used data from 11 participating cancer registries that provided vital status and cause of death (COD) information (Table 1). The TCM Study was approved by human subjects research review committees at the National Cancer Institute (NCI) and, as required, at participating cancer registries.

We selected cancer cases using cancer registry data and identified which cases were in individuals with a prior transplant through SRTR-linkage. We examined cancer types with at least 150 cases among transplant recipients in a preliminary tabulation (we included esophageal cancer in the study even though the final number of cases was 140). Using a modified version of the Surveillance, Epidemiology, and End Results (SEER) site recode[10], we assessed cases of the following cancers: oral cavity/pharynx, colorectum (CRC), esophagus, stomach, liver, pancreas, larynx, lung, melanoma, breast, prostate, bladder, kidney, thyroid, and myeloma. We additionally included diffuse large B-cell lymphoma (DLBCL), the most common non-Hodgkin lymphoma among transplant recipients. We included only first cancer diagnoses, which could have been a first and only cancer (sequence 0) or first of multiple cancers (sequence 1).

The cohort of these cancer patients was followed from cancer diagnosis until the earlier of death or loss of follow-up or December 31, 2014. Individuals who received a transplant after cancer diagnosis initiated follow-up as non-recipients and were censored at the time of transplant. We excluded liver cancers diagnosed within 0–180 days after liver transplantation, because such cases are mostly cancers that were the indication for the liver transplant but which cancer registries record with a diagnosis date shortly after the transplant[11].

Although we present results for overall mortality, the primary outcome was cancer-specific mortality, with death due to cancer defined as described by Howlader et al[12]. The algorithm uses the tumor sequence number, primary site, and COD to classify deaths as attributable to the cancer when the COD incorrectly specifies another cancer or related condition. We calculated overall mortality and cancer-specific mortality rates stratified by cancer site and transplant status. Cox regression was used to estimate the association (hazard ratio) between transplant status and mortality outcomes. Primary adjusted models included adjustment for sex, age, race, SEER summary cancer stage, and diagnosis year (Table 2). Because treatment of transplant recipients and cancer patients has changed over time, we performed secondary analyses restricted to cancers occurring in 2002 or later.

We performed additional analyses of cancer-specific mortality accounting for appropriate (Table S2) first course cancer treatment using data provided by cancer registries, restricting these analyses to cancer registries and calendar years when treatment data were at least 90% complete (Table 1/Table S2). We also performed analyses in which we restricted to local stage cancers of the breast, colorectum, lung, prostate, and kidney, as well as melanoma and

DLBCL, for which individuals were documented as having received treatment modalities appropriate for curative intent.

Additionally, we examined cancer-specific mortality for kidney, lung, and liver cancers among transplant recipients who received that organ vs. a different organ (e.g., for kidney cancers in kidney recipients vs. recipients of other organs). Finally, to examine whether other biological characteristics of tumors affected associations with mortality, we performed analyses for breast cancers stratified by estrogen receptor (ER) status (available 2004 or later), for CRC separately for colon and rectal cancers, and for lung cancers stratified by adenocarcinoma, squamous cell carcinoma, other non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC) histology.

Results

Our cohort contained 11,416 cancer patients with a prior transplant and 7,136,060 cancer patients without a transplant (34.6 million person-years of follow-up) (Table 1). Compared with cancer patients without a transplant, those with a prior transplant were younger at diagnosis (median age 59 versus 66 years) and more likely to be male (68.5% versus 53.3%) and of black race (16.5% versus 9.1%). The distribution of cancer diagnoses differed, with a larger fraction of patients with a prior transplant comprised of DLBCL and kidney cancer (Table 1). The timing of cancer diagnoses also differed by transplant status with non-transplant recipients more likely to be diagnosed in earlier calendar years than transplant recipients (median year 2000 versus 2005). Compared to patients without a transplant, those with a transplant were more likely to be diagnosed with distant-stage tumors (23.7% versus 19.1%). Cancer patients with a prior transplant were less likely to receive surgical treatment (57.8% versus 61.3%) and radiation treatment (23.8% versus 29.7%).

Among these cancer patients, overall mortality was 209 vs. 118 per 1000 person-years in those with vs. without a prior transplant, respectively, and cancer-specific mortality was 114 vs. 73 in these two groups. However, mortality rates varied greatly across cancer types (Table S1, Table 2). Across cancer sites, overall mortality rates were generally higher in cancer patients with a prior transplant than in those without a prior transplant (Table S1), and associations with overall mortality strengthened and were all statistically significant after multivariate adjustment (adjusted HRs [aHRs] 1.37–5.19), except for liver cancer (aHR 0.93, 95%CI 0.79–1.08). The strongest associations between transplantation and overall mortality were for patients with thyroid cancer (aHR 5.19, 95%CI 4.35–6.19), melanoma (3.87, 3.47–4.31), and breast cancer (3.34, 3.04–3.67).

Associations for cancer-specific mortality were attenuated compared with associations for overall mortality; however, after adjustment for demographic factors and tumor stage, cancer-specific mortality remained significantly elevated in transplant recipients for all examined cancers except esophageal, liver, laryngeal, thyroid, prostate cancers and myeloma (Table 2). The strongest elevations in cancer-specific mortality associated with transplantation were for patients with melanoma (aHR 2.59, 95%CI 2.18–3.00), breast cancer (1.88, 1.61–2.19), bladder cancer (1.85, 1.58–2.17), and colorectal cancer (1.77,

1.60–1.96). Analyses restricted to cancers occurring in 2002–2014 yielded similar, and in some instances, qualitatively stronger results (Table S3).

Adjustment for first-course cancer treatment did not strongly affect associations between transplantation status and cancer-specific mortality (Table S2), and some associations were stronger, e.g., for melanoma (aHR 3.01, 95%CI 2.54–3.56) and breast cancer (2.23, 95% CI 1.89–2.62). Analyses restricted to patients with local stage cancers receiving treatment modalities appropriate for curative intent yielded similar or slightly stronger associations, compared with first-course treatment adjustment (Table 3). Specifically, prior transplantation was significantly associated with higher cancer-specific mortality for all examined cancers, with especially strong associations seen for melanoma (aHR 3.82, 2.94–4.97) and CRC (2.77, 2.07–3.70). Transplant status was significantly associated with cancer-specific mortality among individuals with local stage prostate cancers who received surgery or radiation treatment (aHR 1.60, 95%CI 1.12–2.29), despite the lack of association for prostate cancer overall (Table 2).

We also assessed cancer-specific mortality for cancers arising in an organ among individuals who had a prior transplant of that organ (Table 4). For kidney cancer, excess cancer-specific morality was observed among both patients with a prior kidney transplant (aHR 1.23, 95%CI 1.08, 1.40) and those who received other organs (aHR 1.21, 0.93–1.58). Similarly, for lung cancer, both lung recipients and recipients of other organs had elevated cancer-specific mortality (aHR 1.45, 95%CI 1.20–1.75, and 1.35, 1.27–1.42, respectively). In contrast, liver recipients had more favorable cancer-specific mortality than liver cancer patients without a transplant (aHR 0.59, 95%CI 0.44–0.80), but there was no difference between recipients of other organs and non-recipients (1.02, 0.81–1.27).

For breast cancer (Table 4), transplant recipients had elevated cancer-specific mortality regardless of ER status, but the association appeared qualitatively stronger for ER positive breast cancers (aHR 2.94, 95%CI 2.16–4.00) than ER negative breast cancers (2.21, 1.56–3.15). Among individuals with colorectal cancer (Table 4), patients with prior transplant had higher cancer-specific mortality than patients without a transplant, for both colon cancer (aHR 1.81, 95%CI 1.62–2.03) and rectal cancer (1.59, 1.26–2.02). With respect to lung cancer (Table 4), there was some heterogeneity by subtype in associations of cancer-specific mortality with transplant status, varying from no association for squamous cell cancer (aHR 1.09, 95%CI 0.98–1.20) to elevated mortality for adenocarcinoma, other NSCLC, and SCLC (aHRs 1.47–1.67).

Discussion

In this large population-based study, we examined how the presence of a prior organ transplant among cancer patients affected overall and cancer-specific mortality. Overall mortality was higher in transplant recipients, which was expected because this population is at risk of dying from complications of end-stage organ disease and transplantation. For most of the evaluated cancer sites, transplant-recipients also had elevated cancer-specific mortality. In particular, cancer-specific mortality was strongly elevated for melanoma, breast cancer, and bladder cancer.

Our results are consistent with previous studies examining cancer mortality in immunosuppressed populations. Miao et al.[8] examined several cancer sites using data from the Israel Penn International Transplant Tumor Registry (IPITTR). They generally reported similar if slightly stronger associations to those we observed, with the exception of prostate cancer (for which they documented a very strong elevation in cancer-specific mortality). However, IPITTR is not a population-based study and had substantially fewer cases than our study, and Miao et al. excluded a large fraction of cases that lacked stage information. Our results showing elevated cancer-specific mortality in transplant recipients with melanoma are similar to those reported by Robbins et al.[13] using an earlier version of TCM data and Vajdic et al.[14] for Australian patients.

HIV infection causes immunosuppression similar to that observed in transplant recipients, through depletion of CD4-positive T-cells. A comprehensive study reported that HIV-infected individuals with cancer generally experienced higher cancer-specific mortality than HIV-uninfected cancer patients[15]. Those findings are largely mirrored by our results, although the associations were generally weaker in HIV-infected individuals than in our study. No elevation in cancer-specific mortality was reported for HIV-infected individuals with DLBCL[15], which may reflect the misclassification of some DLBCL deaths as due to acquired immunodeficiency syndrome.

As a result of their close follow-up for post-transplant medical care, transplant recipients are likely to receive timely work-up and diagnosis of cancer. In turn, this early diagnosis would be expected to result in a relatively early stage at cancer diagnosis. Overall, however, we observed a slight shift to more advanced stage at diagnosis for all cancers as a group (Table 1). Transplant recipients with cancer in our study were also less likely to receive surgery and radiation therapy than other cancer patients. Differences in stage and treatment were partly driven by the distribution of cancers in the two groups, as individual cancer sites varied considerably with respect to stage and therapy (data not shown). Shiels et al. previously observed a shift towards earlier stage at diagnosis among cancer patients with a prior transplant for a number of individual cancer sites[16]. Nonetheless, the associations with elevated cancer-specific mortality that we demonstrate were present for individual cancer sites with adjustment for stage and cancer treatment, and certain estimates appeared stronger when we restricted to patients with local stage cancers who received treatment appropriate for curative intent as well as for cancer cases treated recently (2002–2014).

Our results support a model in which immunosuppression, attributable to medications given to prevent organ rejection, increases cancer-specific mortality. Immunity is increasingly recognized as critical to cancer control. In particular, heightened immune function as reflected by the presence of tumor infiltrating lymphocytes (TILs) is associated with lower mortality in patients with melanoma[17], colorectal cancer[18,19], bladder cancer[20], and breast cancer[21–23], and with favorable tumor features, such absence of lymph node metastases in melanoma[24] and chemotherapeutic response in breast cancer[23,25,26]. However, we are not aware of any data regarding the presence of TILs in tumors among transplant recipients. Additionally, immunotherapy, in particular monoclonal antibodies that target programmed death-ligand 1 (PD-L1) and its receptor PD-1 on T-cells, is increasingly used to manage advanced stage cancers including melanoma, bladder cancer, and lung cancer[27]. Finally,

immunosuppressive drugs may directly contribute to cancer-specific mortality among transplant recipients by promoting tumor invasiveness, angiogenesis, and metastasis[5–7].

The emerging understanding of how TILs and immunotherapy influence prognosis for the aforementioned cancers make the strong associations for melanoma, bladder cancer, and breast cancer more intriguing. Moreover, in the study by Shiels et al.[16], melanoma and bladder cancer presented at more distant stages among both transplant recipients and HIV-infected individuals than among cancer patients in the general population.

With the exception of prostate cancer, we observed stronger associations with cancer-specific mortality for cancers with typically better prognoses, such as local stage cancers and ER-positive breast cancers, compared with associations for more lethal cancers like pancreatic cancer. This pattern may be attributable to the small relative impact immunosuppression has on mortality in very aggressive cancers. Additionally, apparently curable cancers may be differentially susceptible to micro-metastases in immunosuppressed individuals, whereby a seemingly good prognosis cancer is more serious than staging would indicate[28]. Alternatively, the algorithm may have differentially misclassified some deaths as cancer-specific deaths because of cause of death errors. Although this algorithm has been validated for a range of cancer sites and demographic groups in the general population[12], its performance in a transplant population is unknown. Differentially misclassifying more deaths as cancer-attributable in transplant recipients could have had a relatively large impact on analyses of less aggressive cancers. The reason for the observed heterogeneity across the lung cancer subtypes was unclear.

The 40% reduction in cancer-specific mortality observed for liver cancers that developed in liver recipients was surprising. One possible explanation is that liver recipients were under close surveillance, and any liver cancers developing after transplantation were detected when they were small and amenable to treatment. Additionally, the transplanted liver in which liver cancers arose was from a healthy donor. In contrast, lung cancers in lung recipients and kidney cancers in kidney recipients generally arise in a native, damaged organ left in place at transplantation[29–32], which may contribute to the poor outcomes.

Our study has several strengths. It is the largest and most comprehensive examination of the association between transplant status and cancer mortality, and our sample of cancer patients was population-based, incorporating all cases reported to central cancer registries in 11 US areas. Additionally, we utilized an algorithm previously validated for the general population to more accurately classify deaths attributable to cancer[12].

There are also several limitations. Information on some tumor characteristics, such as grade and molecular features, was unavailable or missing for some cases, which prevented us from assessing their impact. For example, there was a suggestion of more ER negative breast cancers among transplant recipients, but ER status was missing for ~15% of individuals, and there were too few data on human epidermal growth factor receptor 2 status of breast cancer cases to evaluate. Additionally, we only had data from cancer registries on the first course of cancer treatment, and data on some treatment modalities (especially chemotherapy) were likely incomplete. Registry treatment data also lack granularity. For example, we have no

information on treatment tolerance, length of treatment, or specific medications or procedures.

In conclusion, we provide evidence that transplant recipients who develop cancer generally have higher mortality due to their cancer than other cancer patients. As transplant recipients continue to live longer with improved outcomes, cancer will likely increase as a cause of morbidity and mortality in this population. More research is needed to understand whether tumors arising in this population are affected by the patients' immunosuppression. Finally, additional work is needed to identify optimal treatment regimens in cancer patients with a prior transplant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Characteristics of cancer patients according to transplant status *

Characteristic	Cancer patients with prior transplant (n = 11,416)		Cancer patients without prior transplant (n=7,136,060)	
	n	%	n	%
Sex				
Female	3,596	31.5	3,336,109	46.8
Male	7,820	68.5	3,799,951	53.3
Age at diagnosis (years)				
< 40	910	8.0	316,983	4.4
40–49	1,545	13.5	682,091	9.6
50–59	3,252	28.5	1,349,555	18.9
60–69	4,086	35.8	1,961,454	27.5
70–79	1,509	13.2	1,869,434	26.2
80+	114	1.0	956,543	13.4
Race				
White	8,286	72.6	5,856,905	82.1
Black	1,881	16.5	652,504	9.1
Other	1,249	10.9	626,651	8.8
Cancer site				
Oral Cavity/pharynx	696	6.1	213,384	3.0
Colorectum	942	8.3	1,011,114	14.2
Esophagus	140	1.2	86,465	1.2
Stomach	240	2.1	152,174	2.1
Liver	202	1.8	90,753	1.3
Pancreas	232	2.0	189,175	2.7
Larynx	170	1.5	82,874	1.2
Lung	1,910	16.7	1,131,970	15.9
Melanoma	552	4.8	333,779	4.7
Breast	858	7.5	1,473,944	20.7
Prostate	1,607	14.1	1,455,712	20.4
Bladder	350	3.1	236,360	3.3
Kidney	1,562	13.7	235,833	3.3
Thyroid	399	3.5	199,586	2.8
DLBCL	1,353	11.9	132,852	1.9
Myeloma	203	1.8	110,085	1.5
Stage at diagnosis				
Local	5,906	51.7	3,534,550	49.5
Regional	2,248	19.7	1,757,969	24.6
Distant	2,704	23.7	1,363,898	19.1
Unknown	558	4.9	479,643	6.7
Year of diagnosis				

Characteristic	Cancer patients with prior transplant (n = 11,416)		Cancer patients without prior transplant (n=7,136,060)	
	n	%	n	%
1987–1996	1,061	9.3	2,148,823	30.1
1997–2001	2,204	19.3	1,551,233	21.7
2002–2005	2,533	22.2	1,280,815	18.0
2006–2009	3,304	28.9	1,360,411	19.1
2010–2014	2,314	20.3	794,778	11.1
Surgical therapy†				
Yes	6,055	57.8	3,654,689	61.3
No	4,158	39.7	2,140,106	35.9
Unknown	261	2.5	168,546	2.8
Radiation therapy†				
Yes	2,489	23.8	1,770,427	29.7
No	7,525	71.8	3,844,285	64.5
Unknown	460	4.4	348,629	5.9
Chemotherapy†				
Yes	2,663	25.4	1,514,814	25.4
No	7,296	69.7	4,114,024	69.0
Unknown	515	4.9	334,503	5.6

Abbreviations: DLBCL, diffuse large B-cell lymphoma

*The cohort includes cancer cases from the following cancer registries that provided information on vital status and cause of death: California (years of cancer diagnosis and follow-up 1988–2012);Colorado (1988–2009);Connecticut (1987–2009);Georgia (1995–2010);Illinois (1987–2013);Iowa (1987–2009);Kentucky (1995–2011);New Jersey (1987–2010);Pennsylvania (1987–2013);Seattle (1987–2014);Texas (1995–2010).

†Treatment information was available for all cancer registries for all calendar years of diagnosis, with the exception of Pennsylvania (data restricted to 1998–2013), Kentucky (2004–2011) and Illinois (2005–2013).

Table 2:

Association between transplant status and cancer-specific mortality

Cancer site, and transplant status	Cancer-specific deaths	Cancer-specific mortality rate*	HR	95%CI	aHR	95%CI
Oral cavity/pharynx						
Recipient	207	77.1	0.87	(0.76, 1.00)	1.21	(1.06, 1.39)
Non-recipient	75,916	78.0	1	referent	1	referent
Colorectum						
Recipient	369	132.4	1.38	(1.25, 1.53)	1.77	(1.6, 1.96)
Non-recipient	372,567	76.5	1	referent	1	referent
Esophagus						
Recipient	87	416.3	0.81	(0.66, 1.00)	1.10	(0.89, 1.36)
Non-recipient	65,094	439.9	1	referent	1	referent
Stomach						
Recipient	160	497.4	1.25	(1.07, 1.46)	1.47	(1.26, 1.71)
Non-recipient	102,930	301.0	1	referent	1	Referent
Liver						
Recipient	118	392.1	0.74	(0.62, 0.89)	0.81	(0.68, 0.97)
Non-recipient	63,953	606.1	1	referent	1	Referent
Pancreas						
Recipient	195	1165.9	1.24	(1.08, 1.43)	1.46	(1.27, 1.68)
Non-recipient	164,347	900.6	1	referent	1	Referent
Larynx						
Recipient	51	101.5	1.14	(0.87, 1.50)	1.24	(0.94, 1.63)
Non-recipient	29,927	69.8	1	referent	1	Referent
Lung						
Recipient	1,355	537.6	1.08	(1.03, 1.14)	1.35	(1.29, 1.43)
Non-recipient	870,934	424.9	1	referent	1	Referent
Melanoma						
Recipient	152	73.3	2.54	(2.17, 2.98)	2.59	(2.18, 3.00)
Non-recipient	47,660	22.6	1	referent	1	Referent
Breast						
Recipient	162	46.8	1.56	(1.34, 1.82)	1.88	(1.61, 2.19)
Non-recipient	265,229	27.0	1	referent	1	Referent
Prostate						
Recipient	101	14.4	0.71	(0.58, 0.86)	1.07	(0.88, 1.30)
Non-recipient	188,303	20.4	1	referent	1	Referent
Bladder						
Recipient	152	158.6	1.86	(1.58, 2.18)	1.85	(1.58, 2.17)
Non-recipient	75,981	61.7	1	referent	1	Referent
Kidney						
Recipient	284	54.3	0.66	(0.59, 0.75)	1.23	(1.09, 1.38)
Non-recipient	71,838	68.4	1	referent	1	Referent

Cancer site, and transplant status		Cancer-specific deaths	Cancer-specific mortality rate*	HR	95%CI	aHR	95%CI
Thyroid							
	Recipient	14	7.8	0.85	(0.50, 1.44)	1.42	(0.84, 2.39)
	Non-recipient	9,350	8.0	1	referent	1	Referent
DLBCL							
	Recipient	449	112.4	0.92	(0.84, 1.01)	1.31	(1.20, 1.44)
	Non-recipient	56,983	108.8	1	referent	1	Referent
Myeloma							
	Recipient	74	129.8	0.73	(0.58, 0.92)	1.11	(0.88, 1.39)
	Non-recipient	61,262	178.5	1	referent	1	referent

Abbreviations: HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; DLBCL, diffuse large B-cell lymphoma

*Mortality rate per 1000 person-years.

† Cox regression models were adjusted for sex, age (<40,40–84 in 5 year increments,85+), race (white,black,other), stage (local,regional,distant,unknown), and diagnosis year (1987–1991,1992–1996,1997–2001,2002–2005,2006–2009, 2010–2014).

Table 3:

Association between transplant status and cancer-specific mortality among local-stage cancer patients receiving curative treatment *

Cancer site, and transplant status	Cancer-specific deaths	Cancer-specific mortality rate†	aHR1‡	95%CI	aHR2§	95%CI
Colorectum						
Recipient	46	38.2	2.59	(1.94, 3.47)	2.77	(2.07, 3.70)
Non-recipient	32,305	19.3	1	referent	1	referent
Lung						
Recipient	117	123.6	1.46	(1.22, 1.75)	1.66	(1.38, 1.99)
Non-recipient	47,405	85.7	1	referent	1	referent
Melanoma						
Recipient	56	37.8	3.88	(2.98, 5.04)	3.82	(2.94, 4.97)
Non-recipient	16,595	10.5	1	referent	1	referent
Breast						
Recipient	36	17.1	1.99	(1.43, 2.76)	2.08	(1.50, 2.88)
Non-recipient	50,563	9.9	1	referent	1	referent
Prostate						
Recipient	30	7.3	1.64	(1.14, 2.34)	1.60	(1.12, 2.29)
Non-recipient	36,891	7.9	1	referent	1	referent
Kidney						
Recipient	78	19.9	1.52	(1.22, 1.90)	1.56	(1.25, 1.96)
Non-recipient	10,396	17.2	1	referent	1	referent
DLBCL						
Recipient	49	67.7	1.54	(1.16, 2.04)	1.44	(1.09, 1.91)
Non-recipient	6,120	53.0	1	referent	1	referent

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma

*Analyses were restricted to local stage cancers. Curative treatment is defined as receipt of surgery for colorectal, breast, and kidney cancers and melanoma; surgery or radiation therapy for lung and prostate cancers; and chemotherapy for DLBCL.

†Mortality rate per 1000 person-years.

‡Cox regression models were adjusted for age (<40,40–84 in 5 year increments,85+), sex, race (white,black,other), stage (local,regional,distant,unknown), and diagnosis year (1987–1991, 1992–1996, 1997–2001, 2002–2005, 2006–2009, 2010–2014).

§Cox regression models were adjusted for factors in HR1 plus additional treatment received including: surgery received (yes,no,unknown), radiotherapy received (yes,no,unknown), chemotherapy received (yes,no,other). Breast and prostate cancer models were also adjusted for hormone therapy (yes,no,unknown). DLBCL was not adjusted for surgery, but was adjusted for immune therapy (yes,no,unknown).

Table 4:

Cancer-specific mortality associations related to transplanted organ or cancer-specific biological features.

	Cancer Deaths	Cancer-specific mortality rate	HR	95%CI	aHR1*	95%CI
Analyses for selected cancers, by transplanted organ						
Kidney cancer						
Kidney recipient	230	52.4	0.65	(0.57, 0.74)	1.23	(1.08, 1.40)
Non-kidney recipient	54	64.3	0.74	(0.57, 0.97)	1.21	(0.93, 1.58)
Non-recipient	71,838	68.4	1		1	
Lung cancer						
Lung recipient	107	421.8	0.86	(0.71, 1.04)	1.45	(1.20, 1.75)
Non-lung recipient	1,248	550.5	1.11	(1.05, 1.17)	1.35	(1.27, 1.42)
Non-recipient	870,934	424.9	1		1	
Liver cancer						
Liver recipient	42	298.0	0.61	(0.45, 0.82)	0.59	(0.44, 0.80)
Non-liver recipient	76	475.1	0.85	(0.68, 1.06)	1.02	(0.81, 1.27)
Non-recipient	63,953	606.1	1		1	
Analyses for selected cancers, by biological features of the cancer						
Breast cancer†						
ER positive cases						
Recipient	41	41.7	1.95	(1.43, 2.64)	2.94	(2.16, 4.00)
Non-recipient	28,141	21.6	1	referent	1	referent
ER negative cases						
Recipient	31	105.3	1.77	(1.25, 2.52)	2.21	(1.56, 3.15)
Non-recipient	17,735	56.6	1		1	referent
Colorectal cancer						
Colon cancer						
Recipient	301	147.6	1.48	(1.32, 1.66)	1.81	(1.62, 2.03)
Non-recipient	259,781	76.2	1	referent	1	referent
Rectal cancer						
Recipient	68	91.0	1.05	(0.82, 1.33)	1.59	(1.26, 2.02)
Non-recipient	112,786	77.2	1	referent	1	referent
Lung cancer‡						
Adenocarcinoma						
Recipient	468	564.5	1.28	(1.17, 1.40)	1.56	(1.42, 1.70)
Non-recipient	283,598	346.1	1	referent	1	referent
Squamous cell						
Recipient	399	363.6	0.87	(0.79, 0.96)	1.09	(0.98, 1.20)
Non-recipient	190,938	383.7	1	referent	1	referent
Other NSCLC						
Recipient	329	752.6	1.17	(1.05, 1.30)	1.47	(1.32, 1.64)

	Cancer Deaths	Cancer-specific mortality rate	HR	95%CI	aHR1*	95%CI
Non-recipient	238,823	561.1	1	referent	1	referent
SCLC						
Recipient	154	1445.6	1.63	(1.39, 1.91)	1.67	(1.42, 1.95)
Non-recipient	152,187	719.3	1	referent	1	referent

Abbreviations: HR,hazard ratio;aHR,adjusted hazard ratio;CI,confidence interval;ER,estrogen receptor;NSCLC,non-small cell lung cancer;SCLC,small cell lung cancer

*Cox models were adjusted for age (<40,40–84 in 5 year increments,85+), sex, race (white,black,other), stage (local,regional,distant,unknown), and diagnosis year (1987–1991,1992–1996,1997–2001,2002–2005,2006–2009, 2010–2014).

†Cases were restricted to diagnosis dates 2004–2014. ER status was missing for breast cancers in 15.3% of transplant recipients and 16.6% of non-recipients.

‡Adenocarcinoma was identified with histology codes: {8140,8141,8143–8145,8147,8190, 8250,8255,8260, 8262,8263,8290,8320,8323,8480,8481,8570–8574,8576}; squamous cell was identified with histology codes: 8052,8070–8076,8078; other NSCLC was identified with histology codes: {8010–8015,8020–8022,8030–8035,8040,8046,8050,8051,8082:8084,8146,8210,8230,8231,8244,8246,8251–8254,8280,8310, 8313,8315, 8330,8333,8341,8345,8350,8500,8510,8512,8520,8521,8525,8530,8550,8551,8560,8562,8575,9015}; SCLC was defined with histology codes: 8041–8045.