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Cancer-Attributable Mortality among Solid Organ Transplant Recipients in the United States, 1987-2014

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Abstract

Background: Solid organ transplant recipients have an elevated risk of cancer. Quantifying deaths attributable to cancer can inform priorities to reduce cancer burden.

Methods: Linked transplant and cancer registry data were used to identify incident cancers and deaths among solid organ transplant recipients in the United States (1987–2014). Population-attributable fractions (PAFs) of deaths due to cancer and corresponding cancer-attributable mortality rates were estimated using Cox models.

Results: Among 221,962 transplant recipients, 15,012 developed cancer. Thirteen percent of deaths (PAF=13.2%) were attributable to cancer, corresponding to a cancer-attributable mortality rate of 516 per 100,000 person-years. Lung cancer was the largest contributor to mortality (PAF=3.1%), followed by non-Hodgkin lymphoma (NHL, PAF=1.9%), colorectal cancer (PAF=0.7%), and kidney cancer (PAF=0.5%). Cancer-attributable mortality rates increased with age at transplantation, reaching 1229 per 100,000 person-years among recipients 65+ years old. NHL was the largest contributor among children (PAF=4.1%) and lung cancer among 50+ year-olds (PAFs=3.7–4.3%). Heart recipients had the highest PAF (16.4%), but lung recipients had the

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highest cancer-attributable mortality rate (1241 per 100,000 person-years). Overall, mortality attributable to cancer increased steadily with longer time since transplant, reaching 15.7% of deaths (810 per 100,000 person-years) 10+ years post-transplant. Comparison of cancer-attributable mortality rates with specified causes of death indicated that some deaths recorded as other causes might instead be caused by cancer or its treatment.

Conclusions: Cancer is a substantial cause of mortality among solid organ transplant recipients, with major contributions from lung cancer and NHL. Cancer-attributable mortality increases with age and time since transplant, so cancer deaths will become an increasing burden as recipients live longer.

Precis:

Cancer is a substantial cause of mortality among solid organ transplant recipients, with major contributions from lung cancer and NHL. There are opportunities to reduce cancer mortality among solid organ transplant recipients through prevention and tailored screening.

Keywords

cancer; mortality; transplant; attributable fraction

Introduction

Solid organ transplant recipients have increased cancer risk compared with the general population.[1] Excess risk varies by cancer type and is largely due to immunosuppression from medications used to prevent rejection, underlying medical comorbidities, and end-stage organ disease. Recipients have elevated risk for both virus-related cancers (e.g., non-Hodgkin lymphoma [NHL], caused by Epstein-Barr virus [EBV]) and virus-unrelated cancers (e.g., lung and kidney cancers).[1] Moreover, the transplant population in the United States has doubled since the late 1980s due to an increasing number of transplants and improved survival.[2] Understanding long-term health risks, including cancer, is critical.

Cancer mortality is an important measure of burden, since it reflects the final downstream outcome accounting for cancer incidence, treatment, and survival following cancer diagnosis. For many cancers, patients with a previous transplant have an increased risk of dying from cancer compared to those without a transplant.[3,4] Immunosuppression associated with transplantation may impair control of the primary tumor or metastases. Studies conducted outside of the US have shown that the population of transplant recipients overall has a 2–3-fold elevated mortality from cancer compared to the general population.[5–8]

Cancer mortality is usually estimated using cause of death (COD) information. However, such estimates depend on accurate classification and reporting by physicians. Determining single underlying CODs can be difficult, since death may be precipitated by multiple causes and determination of the underlying COD is often subjective.[9] This may be especially true for deaths in transplant recipients, who have multiple health conditions.

An alternative approach to estimating cancer-related mortality is to compare the overall mortality of individuals with and without cancer, attributing excess deaths in the former

group to cancer. This statistical calculation leads to a population-attributable fraction (PAF), which describes the proportion of all deaths attributable to cancer. The PAF depends only on ascertainment of incident cancer diagnoses and overall mortality, thus avoiding the need for COD. Further, the cancer-attributable mortality rate can be derived from the PAF.

Population-based estimates can help quantify the cancer burden in the transplant population and identify specific cancers and subgroups that might benefit from intervention. In this study, we estimated the fraction of deaths attributed to cancer and corresponding cancer-attributable mortality rates among US transplant recipients.

Methods

The Transplant Cancer Match (TCM{TA \l “TCM: Transplant Cancer Match” \s “TCM” \c 1}) Study links the US Scientific Registry of Transplant Recipients (SRTR) with state and regional cancer registries.[1] SRTR data include recipient demographic and transplant characteristics, vital status and organ function. COD is based on clinical information reported by transplant centers and updated over time, so recipients may have multiple CODs. Seventeen cancer registries provided data on incident cancers (excluding non-melanoma skin cancer) covering approximately half of the US transplant population (see Table 1 footnote). The TCM Study was approved by institutional review boards at the National Cancer Institute and participating cancer registries.

Invasive first cancers in transplant recipients were identified from the linked cancer registries and classified as previously described.[10] The study cohort comprised recipients who resided in areas covered by participating cancer registries at the time of transplant, received their first transplant during a period of cancer registry coverage, and did not previously have cancer recorded in the cancer registry. Prior cancers were those diagnosed before transplant or within 90 days post-transplant (since those likely developed pre-transplantation). Follow-up thus started 90 days post-transplant, and ended at the earliest of death, loss to follow-up by the SRTR, or end of cancer registry coverage. Since we sought to quantify the impact of cancer on mortality once a transplant is performed, we did not censor follow-up if the transplanted organ failed or the person received a subsequent transplant.

We calculated the PAF as the fraction of deaths attributable to cancer among this cohort of transplant recipients. Specifically, $PAF = p_d \times [(\mathrm{HR}-1)/\mathrm{HR}]$ where p_d is the proportion of all deaths preceded by cancer diagnosis, and HR is the hazard ratio that quantifies the risk of death associated with a cancer diagnosis.[11] We estimated HRs using Cox proportional hazards models with cancer as a time-dependent variable. Models were additionally adjusted for age at transplant, sex, race/ethnicity, transplanted organ, and calendar year of transplant (see Table 2 footnote). The time scale was time since transplant starting 90 days post-transplant. We calculated the cancer-attributable mortality rate as PAF × overall mortality rate (i.e., attributable deaths per 100,000 person-years). The variance of the PAF was calculated using an influence function-based approach.[12] 95% confidence intervals were computed as PAF +/− 1.96 × standard error.

We present results for all cancers combined and separately for selected cancers. We selected cancer sites that show elevated incidence among transplant recipients and were expected to have sufficient cases and subsequent deaths for the PAF calculations.[1] Breast and prostate cancers were included because these are common among the US general population. We include grouped results for cancers with infectious etiology (NHL, Hodgkin lymphoma, nasopharynx, liver, stomach, Kaposi sarcoma, anus, vulva, cervix, penis, vagina, and oropharynx including tonsil). The HR for each cancer or grouping was estimated using a separate model, in which recipients without the cancer of interest were considered unaffected. We also show PAF results for subgroups of the cohort defined by age at transplant, sex, race/ethnicity, transplanted organ, and time since transplant.

Our Cox models were adjusted for recipient demographic characteristics. However, if there was substantial residual confounding, then PAFs would not accurately reflect mortality that should be attributed to cancer. We considered that tobacco use could be a strong confounder of the association between lung cancer and mortality. Since the SRTR does not have complete information on tobacco use, we calculated a bias factor to adjust the HR for smoking (see Supplemental Appendix for details).[13] This method relies on external estimates of the relative risk of death for smokers vs. non-smokers and smoking prevalence among recipients. In a second analysis, we assessed possible confounding by obesity by estimating HRs further adjusted for body mass index (BMI) overall and for cancers known to be associated with overweight or obesity (i.e., NHL, colorectum, breast, kidney, liver).[14]

We hypothesized that differences between cancer-attributable mortality rates (calculated using PAFs) and cancer-specific mortality rates (calculated using CODs) may arise because some deaths with non-cancer COD were actually caused by cancer. To estimate this proportion, we applied our PAF methodology separately for five mortality outcomes based on different COD categories recorded in the SRTR (cancer, infection, graft failure, other, unknown). Specifically, we repeated the analyses, but instead of overall mortality we examined cause-specific mortality based on how the SRTR coded the COD. HRs were then estimated separately for each mortality outcome. For each Cox model, the events were deaths due to the specified outcome, and other individuals (including those who died of other causes) were censored at the end of follow-up. These results correspond to the proportion of deaths attributable to cancer for the specified COD category, and the sum of the five cancer-attributable mortality rates corresponds closely to the overall cancer-attributable mortality rate.

Finally, we compared CODs from the SRTR to CODs from cancer registries.[15] Analyses were restricted to deceased recipients with cancer who resided in areas covered by 12 cancer registries providing CODs. The kappa statistic was used to quantify agreement and should be close to 1.00 if both the SRTR and cancer registries accurately capture cancer-related deaths in these individuals.

Computations were performed using SAS software version 9.4.

Results

The study included 221,962 solid organ transplant recipients (Table 1). Mean age at transplant was 45 years. The majority of recipients were male (61%) and non-Hispanic white (61%). The most commonly transplanted organs were kidney (62%), liver (18%), heart (10%), and lung (5%).

Cancer-attributable mortality

Recipients were followed for a median of 4.6 years, during which 15,012 recipients developed a first cancer and 8,123 of those with cancer died. Overall, 16.6% of deaths were preceded by a cancer diagnosis.

The adjusted HR for death following a cancer diagnosis was 4.79, so the PAF for cancer-attributable mortality was $p_d \times [(\mathrm{HR}-1)/\mathrm{HR}] = 0.166 \times [(4.79-1)/4.79] = 13.2\%$ (95%CI: 12.4, 13.9), corresponding to a cancer-attributable mortality rate of 516 deaths per 100,000 person-years (Table 2).

Lung cancer was the largest contributor to cancer-attributable mortality (PAF=3.1%; Table 2) and had the highest cancer-attributable mortality rate (121 per 100,000 person-years). This was followed by NHL (PAF=1.9%), colorectal cancer (PAF=0.7%), and kidney cancer (PAF=0.5%). Since men with prostate cancer had nominally lower risk of death than men without prostate cancer (adjusted HR=0.99), the resulting PAF was negative. Three percent of deaths were attributed to cancers of infectious etiology (cancer-attributable mortality rate 116 per 100,000 person-years), while the remaining cancers of non-infectious etiology contributed almost 10% of deaths (388 per 100,000 person-years). Results for subgroups of the cohort and individual cancers are presented in Supplementary Table 1 and graphically in figures.

PAFs increased with age at transplant, from 6.1% of deaths among children to 15.5% of deaths among recipients aged 50+ years (Table 2, Figure 1). Cancer-attributable mortality rates also increased steeply with age, reaching 1229 per 100,000 person-years among recipients 65+ years old at transplant. In the youngest age group, NHL was the largest single contributor to cancer-attributable mortality (PAF=4.1%, Figure 1). In the oldest age groups, however, lung cancer was the largest contributor (PAFs=3.7–4.3% among 50+ year-olds) along with NHL (1.7%), kidney cancer (0.5–0.6%), and colorectal cancer (0.8–1.1%).

The PAF was higher among males than females (14.4% vs. 11.1%, Table 2). Among males, the largest contributor was lung cancer (PAF=3.4%) followed by NHL (PAF=2.1%). Although these cancers were also the largest contributors in females, their contribution was lower (PAF=2.5% and 1.6%, respectively) (Supplementary Figure 1 and Supplementary Table 1).

PAFs varied by race/ethnicity with non-Hispanic whites having the highest PAF (14.2%), followed by Asian/Pacific Islanders (13.8%). Non-Hispanic blacks and Hispanics had lower PAFs (10.2–10.7%). Although there was some variability, lung cancer and NHL made the

greatest contributions across the racial/ethnic groups (PAFs 1.4–4.1% and 0.9–2.8% respectively; Supplementary Figure 2 and Supplementary Table 1).

PAFs varied by transplanted organ, from 16.4% among heart recipients to 9.8% among recipients of other (miscellaneous) organs (Figure 2 and Table 2). Lung recipients had the highest overall mortality and thus the highest cancer-attributable mortality rate (1241 per 100,000 person-years). Heart recipients had the next highest cancer-attributable mortality rate (891 per 100,000 person-years), followed by liver recipients (531 per 100,000 person-years). NHL and lung cancer were major contributors across all organs (PAF=1.7–3.1% for NHL, 1.0–4.6% for lung cancer). The proportion of deaths attributed to kidney cancer among kidney recipients was low (PAF=0.6%). The PAF for liver cancer was small among liver recipients (0.5%), however, this was almost double compared to recipients of other organs (0.1%−0.3%, Figure 2 and Supplementary Table 1).

Overall mortality was high 3 months-2 years post-transplant, decreased 2–5 years post-transplant, and then increased subsequently (Figure 3 and Table 2). PAFs increased over time, from 8.1% (3 months-2 years post-transplant) to 16.0% and 15.7% (5–10 years and 10+ years post-transplant, respectively). Thus, the cancer-attributable mortality rate increased over time, reaching 810 per 100,000 person-years during 10+ years post-transplant. For lung cancer, PAFs increased from 1.8% within 2 years of transplant to approximately 4% for 2+ years post-transplant, and cancer-attributable mortality for lung cancer increased over time from 68 to 168 per 100,000 person-years (Figure 3). The PAF for NHL was 2.1% during 3 months-2 years post-transplant, decreased slightly to 1.5% during 2–5 years post-transplant, then increased again to approximately 2% for 5+ years post-transplant (Figure 3 and Supplementary Table 1).

Assessment of confounding

Our calculations to assess the potential confounding by tobacco use yielded a bias factor of 1.67 which, when applied to lung cancer, resulted in an HR further adjusted for smoking of 6.28. Although this is lower than the HR of 10.42 used in our primary analyses, it results in a similar PAF (2.5% vs. 3.1%). Similarly, the adjusted HR overall and for the cancer sites associated with overweight and obesity were not greatly affected by adjustment for BMI and yielded similar PAFs. Specifically, the overall HR further adjusted for BMI was 4.87 (vs. 4.79), and HRs for specific cancers changed between −9.5% and 2.1%.

Comparison of cancer-attributable and cancer-specific mortality rates

Based on SRTR CODs, we calculated a cancer-specific mortality rate of 368 per 100,000 person-years, substantially lower than the above cancer-attributable mortality rate (516 per 100,000 person-years). PAFs for each of five mortality outcomes were assessed separately. With COD specified as cancer, a high proportion of deaths (PAF=74%) were attributed to cancer, as expected (Table 3). Notably, additional deaths were also attributed to cancer among deaths with other CODs. Specifically, we attributed to cancer 4.2% of deaths with infection recorded as the COD, 4.2% of deaths with graft failure as the COD, 5.6% of deaths with other recorded CODs, and 9.4% of unknown CODs. The sum of the cancer-attributable

mortality rates across the five COD categories was 491 per 100,000 person-years, close to the overall cancer-attributable mortality rate (516 per 100,000 person-years).

Finally, we conducted an analysis restricted to 12 cancer registries that provided CODs for cancer cases (N=165,839). In this subgroup, approximately 25% of deceased recipients with cancer had missing or unknown CODs in the SRTR or cancer registry. There were 4943 recipients with a cancer diagnosis who subsequently died and had CODs specified in both the SRTR and cancer registry. Of these, 2773 (56%) had cancer listed as the COD in the SRTR and 2807 (57%) had cancer listed as the COD in the cancer registry. However, only 2062 (42%) had cancer listed as the COD in both the SRTR and cancer registry (kappa=0.40).

Discussion

Among US solid organ transplant recipients, 13.2% of deaths were attributed to cancer, of which almost half were attributable to NHL and lung, kidney, and colorectal cancers. The PAF depends on cancer incidence and its impact on mortality. The two cancer sites with the highest PAFs (lung cancer and NHL) are both common and associated with high mortality in transplant recipients. Moreover, transplant recipients have worse survival following cancer diagnosis than cancer patients in the general population,[3] contributing further to cancer-attributable mortality.

Immunosuppression plays a major role in malignancy after transplant.[16] Indeed, we found that lung and heart recipients, who generally receive intensive immunosuppression, had the highest cancer-attributable mortality. Lung and heart recipients had high PAFs for NHL, a cancer strongly associated with EBV, and for lung cancer, which is linked to smoking and, among lung recipients, end-stage lung disease.[17] Among the overall cohort, the cancer-attributable mortality rate also increased with time since transplant, and lung cancer and NHL contributed prominently greater than five years post-transplant. This pattern partly reflects rising incidence of these cancers with longer duration since transplant and prolonged exposure to immunosuppressant medications.[1,18,19]

Among children, NHL was the single largest contributor to cancer-attributable mortality. NHL, when it occurs in transplant recipients, is a type of post-transplant lymphoproliferative disorder (PTLD), which among young recipients results from primary EBV infection.[20–22] Other cancers such as lung and colorectal cancers become more common with age and so contribute more to mortality in older recipients. In addition, the PAF was higher among males compared to females for all cancer sites combined and for individual cancers, although the relative ranking of cancer sites was similar. While there were some differences in PAFs among the racial/ethnic groups, lung cancer and NHL comprised the largest contributors for each group.

PAF calculations rely on a causal relationship between cancer and excess mortality, and a key assumption is that the association between cancer and death is estimated without confounding. The bias factor analysis showed that, although tobacco use is associated with lung cancer, it does not introduce a large bias into the estimate of the PAF. Similarly, obesity

did not greatly affect the HR estimates. Nonetheless, it is possible that residual confounding by other unmeasured factors affected our results. Confounding likely explains the slightly negative PAF for prostate cancer since it is implausible that prostate cancer lowers the risk of death. Most prostate cancer cases are diagnosed through screening, and many detected cancers are indolent.[23,24] The lower mortality observed in our study among recipients with prostate cancer thus probably reflects the relative health of men offered screening.

The cancer-specific mortality rate based on CODs from the SRTR was substantially lower than our cancer-attributable mortality rate estimate (368 vs. 516 per 100,000 person-years). We believe this reflects inaccurate determination of CODs, because recipients may appear to die from non-cancer CODs, such as infection or graft failure, that are actually downstream effects of cancer or its treatment. Indeed, Table 3 shows 4% of deaths with CODs recorded as infection and 4% as graft failure were attributable to recipients' cancer diagnoses. In addition, 5% of deaths with other causes and 9% of deaths of unknown cause were attributable to cancer, and numerically these contributed substantially to the overall cancer-attributable mortality rate. Furthermore, our comparison of CODs from the SRTR and cancer registries yielded only modest agreement (kappa=0.40), indicating that assigning CODs is difficult and that likely neither source is entirely accurate in distinguishing cancer from non-cancer deaths.

Strengths of our study include a large sample representative of the US transplant population, including recipients of all organ types. We obtained incident cancer information from population-based cancer registries that ascertain cancers in their catchment areas. We assessed potential confounding of PAFs and compared our results with cancer-specific mortality rates derived from CODs. A limitation of our study is that cancer registries do not collect information on non-melanoma skin cancers. While these cause substantial morbidity among transplant recipients,[25,26] they are not often fatal and therefore would not greatly contribute to mortality. Also, some cancers may have been missed by the cancer registries, if the linkage did not match the cancer to the recipient, or if recipients migrated from the catchment area. However, outmigration is uncommon.[1]

There are opportunities to reduce cancer mortality in transplant recipients through prevention and screening. Most cancer screening guidelines for recipients follow recommendations for the general population, but our results indicate that more tailored guidelines would be useful.[27] Given the high PAF for NHL (4% among children and about 2% among adults), this cancer should be a priority. Since high levels of circulating EBV load can be used as a marker of PTLD, there may be opportunities to use this biomarker to screen for NHL, especially in pediatric recipients.[28] Treating underlying liver disease (e.g., with direct-acting antiviral medications for hepatitis C virus infection) and screening for liver cancers in high-risk recipients should also be considered,[27,29] including among liver recipients, among whom liver cancer contributes the most to mortality. Finally, cancer prevention strategies aimed at modifying lifestyle cancer risk factors, especially smoking cessation but also sun protection,[30] should be prioritized to reduce mortality from lung cancer and melanoma.

In conclusion, cancer causes substantial mortality among transplant recipients. About 13% of deaths are attributable to cancer, with about 5% of deaths from NHL and lung cancer combined. Cancer-attributable mortality increases with age and time since transplant, indicating that deaths from cancer will increase in the future as survival following transplantation improves. Further research aimed at cancer prevention, screening, and treatment will be required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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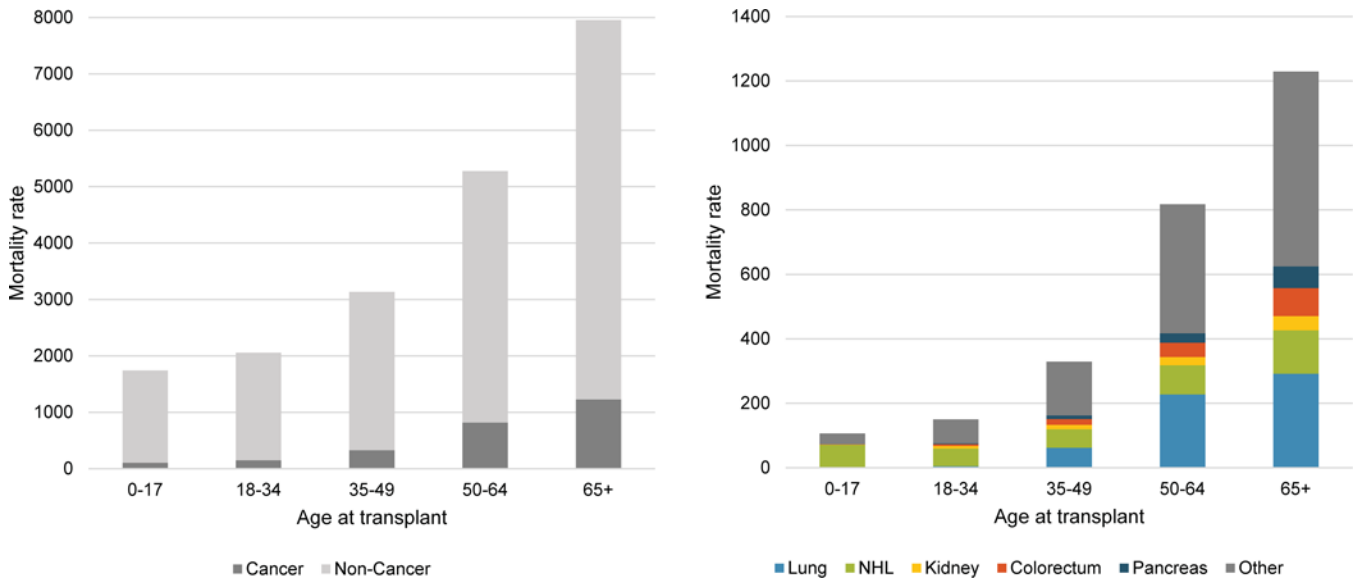

Figure 1: Cancer-attributable mortality rates, according to age at transplant

The left panel displays cancer and non-cancer mortality rates per 100,000 person-years according to age at transplant. The right panel displays cancer-attributable mortality rates per 100,000 person-years according to the age at transplant for each cancer site.

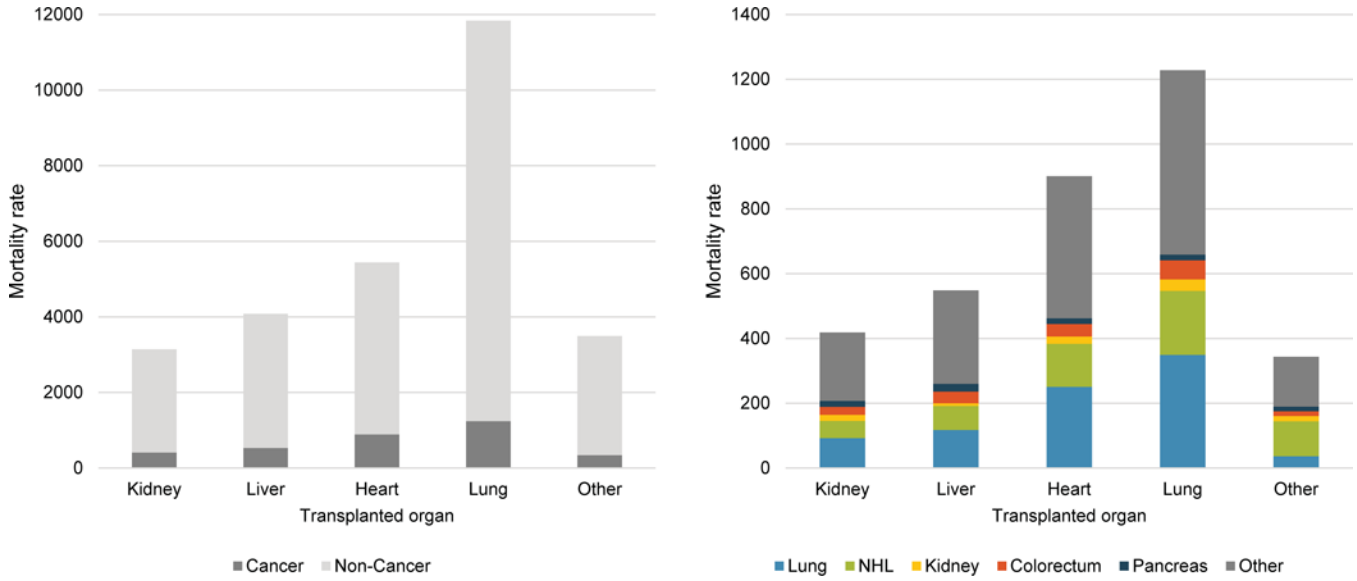

Figure 2: Cancer-attributable mortality rates, according to transplanted organ

The left panel displays cancer and non-cancer mortality rates per 100,000 person-years according to transplanted organ. The right panel displays cancer-attributable mortality rates per 100,000 person-years according to the transplanted organ for each cancer site.

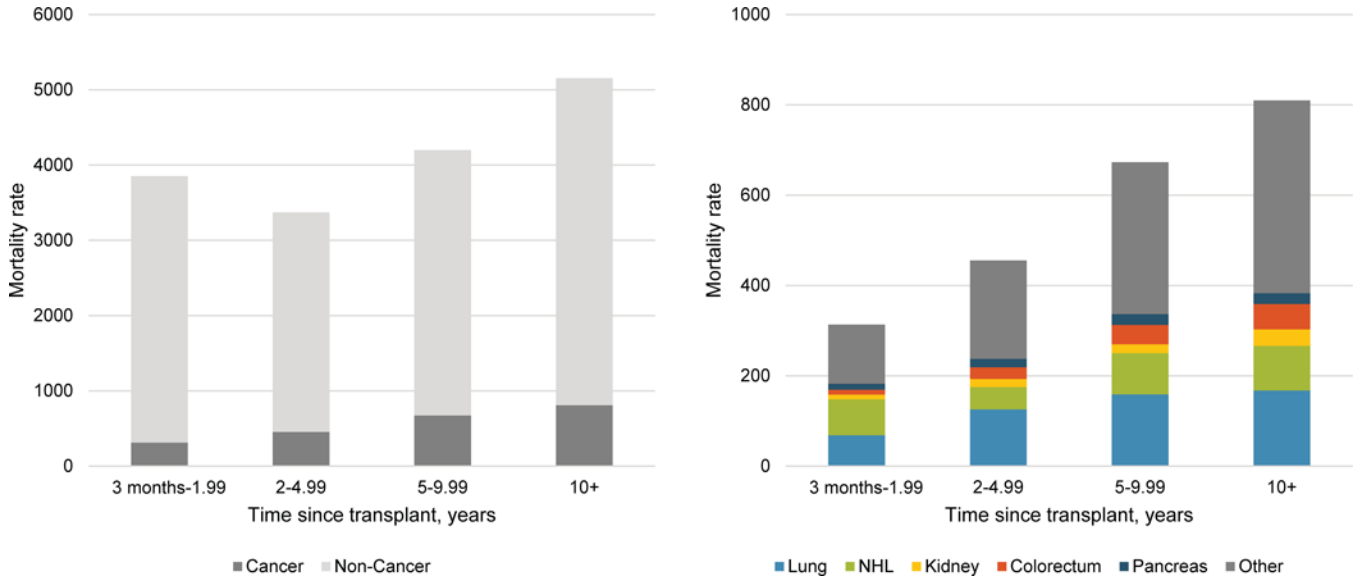

Figure 3: Cancer-attributable mortality rates, according to time since transplant

The left panel displays cancer and non-cancer mortality rates per 100,000 person-years according to years since transplant. The right panel displays cancer-attributable mortality rates per 100,000 person-years according to years since transplant for each cancer site.

Table 1:

Characteristics of 221,962 solid organ transplant recipients in the United States (1987–2014)

	N	%
Age at transplant, years		
0–17	16,707	7.5
18–34	34,997	15.8
35–49	67,595	30.5
50–64	82,092	37.0
65+	20,571	9.3
Sex		
Female	86,734	39.1
Male	135,228	60.9
Race/ethnicity		
Non-Hispanic white	134,535	60.6
Non-Hispanic black	40,114	18.1
Hispanic	33,726	15.2
Asian/Pacific islander	12,146	5.5
Other	1,441	0.7
Transplanted organ		
Kidney	136,534	61.5
Liver	39,155	17.6
Heart	22,912	10.3
Lung	10,467	4.7
Other	12,894	5.8
Year of transplant		
1987–1994	32,257	14.5
1995–1999	49,140	22.1
2000–2004	58,297	26.3
2005–2008	50,901	22.9
2009–2014	31,367	14.1

This study includes data from 17 US population-based cancer registries: California (years of cancer registry data 1988–2012), Colorado (1988–2009), Connecticut (1973– 2009), Florida (1981–2009), Georgia (1995–2010), Hawaii (1973–2007), Illinois (1986– 2013), Iowa (1973–2009), Kentucky (1995–2011), Michigan (1985–2009), New Jersey (1979–2010), New York (1976– 2010), North Carolina (1990–2010), Pennsylvania (1985–2013), Texas (1995–2010), Utah (1973–2008), and the Seattle-Puget Sound area of Washington State (1974– 2014)

Table 2:

Cancer-attributable mortality among solid organ transplant recipients

		Cancer cases	Deaths	Deaths with prior cancer, P_d (%)	HR*	PAF (%)	95%CI	Cancer-attributable mortality rate
Overall		15012	48831	16.6	4.79	13.2	(12.4, 13.9)	516
Cancer site	Lung	2033	48831	3.4	10.42	3.1	(2.8, 3.4)	121
	NHL	2240	48831	2.4	4.58	1.9	(1.6, 2.2)	75
	Colorectum	877	48831	1.0	3.48	0.7	(0.6, 0.9)	29
	Kidney	1184	48831	0.8	2.42	0.5	(0.3, 0.6)	18
	Pancreas	273	48831	0.5	31.6	0.5	(0.4, 0.6)	19
	Stomach	233	48831	0.4	14.0	0.4	(0.2, 0.5)	14
	Breast	801	48831	0.6	1.79	0.3	(0.1, 0.4)	10
	Bladder	345	48831	0.4	4.21	0.3	(0.2, 0.4)	12
	Melanoma	581	48831	0.5	2.26	0.3	(0.2, 0.4)	11
	Liver	177	48831	0.3	13.35	0.3	(0.2, 0.4)	10
	Myeloma	173	48831	0.2	6.88	0.2	(0.1, 0.3)	8
	Esophagus	153	48831	0.3	11.06	0.2	(0.1, 0.3)	9
	Larynx	174	48831	0.2	3.27	0.1	(0.1, 0.2)	6
	Thyroid	339	48831	0.1	1.40	0.0	(0.0, 0.1)	2
	Prostate	1686	48831	1.0	0.99	0.0	--	−1
	Infectious etiology†	3355	48831	3.7	4.81	3.0	(2.6, 3.3)	116
	Non-infectious etiology	11657	48831	12.9	4.30	9.9	(9.3, 10.5)	388
Age at transplant, years	0–17	438	1809	7.5	5.58	6.1	(2.5, 9.8)	107
	18–34	1016	4300	8.9	5.56	7.3	(4.9, 9.7)	151
	35–49	3637	12858	13.1	5.09	10.5	(9.1, 11.9)	329
	50–64	7736	22937	19.7	4.70	15.5	(14.5, 16.5)	818
	65+	2185	6927	20.3	4.17	15.5	(13.8, 17.1)	1229
Sex	Female	4972	18023	14.1	4.78	11.1	(10.0, 12.2)	404
	Male	10040	30808	18.1	4.79	14.4	(13.4, 15.3)	590
Race/ethnicity	Non-Hispanic white	10754	33733	18.0	4.78	14.2	(13.4, 15.1)	600

		Cancer cases	Deaths	Deaths with prior cancer, P_d (%)	HR*	PAF (%)	95%CI	Cancer-attributable mortality rate
	Non-Hispanic black	2241	8074	13.4	4.11	10.2	(8.5, 11.8)	423
	Hispanic	1411	5062	13.0	5.61	10.7	(8.3, 13.0)	303
	Asian/Pacific islander	531	1665	16.0	7.34	13.8	(9.0, 18.6)	350
	Other	75	297	14.8	6.13	12.4	(3.4, 21.4)	506
Transplanted organ	Kidney	8028	23024	16.6	4.67	13.1	(11.9, 14.3)	410
	Liver	2781	9966	15.8	5.63	13.0	(11.6, 14.5)	531
	Heart	2628	8141	20.9	4.60	16.4	(14.8, 17.9)	891
	Lung	942	5066	13.9	4.04	10.5	(9.2, 11.8)	1241
	Other	633	2634	11.8	5.80	9.8	(7.0, 12.6)	342
Time since transplant‡	3 months-1.99 years	4159	14847	8.9	11.60	8.1	(6.4, 9.9)	313
	2–4.99 years	6863	13543	16.1	6.27	13.5	(11.3, 15.7)	456
	5–9.99 years	8017	13904	21.3	4.04	16.0	(14.1, 18.0)	673
	10+ years	4411	6537	25.5	2.61	15.7	(13.0, 18.4)	810

HR=Hazard ratio; PAF=Population-attributable fraction; CI=Confidence interval

*Hazard ratios are computed using time since transplant as the time scale and are adjusted for sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, other), organ transplanted (kidney, liver, heart, lung, other), calendar year of transplant (1987–1994, 1995–1999, 2000–2004, 2005–2008, 2009–2014) and age at transplant. Since the effect of age on mortality was non-linear, age was modeled as a piecewise linear function with knots at age 5 and 19 years.

Overall and cancer-attributable mortality rates are per 100,000 person-years. Cancers are ordered by PAF.

†NHL, Hodgkin lymphoma, nasopharynx, liver, stomach, Kaposi sarcoma, anus, vulva, cervix, penis, vagina, and oropharynx including tonsil.

‡Cancer case numbers sum to 23,450 because both prevalent and incident cases are captured in each interval.

Table 3:

PAF and cancer-attributable mortality for five mortality outcomes

Mortality outcome category defined by COD in SRTR	Deaths	Mortality rate	Deaths with prior cancer, P_d (%)	HR*	PAF (%)	Cancer-attributable mortality rate
Cancer	4584	368	74.4	138	73.8	272
Infection	6683	537	7.4	2.3	4.2	23
Graft failure	6001	482	7.5	2.3	4.2	20
Other causes	20154	1619	9.7	2.4	5.6	90
Missing	11409	916	13.8	3.2	9.4	86
Overall	48831	--	--	--	--	491

HR=Hazard ratio; PAF=Population-attributable fraction

*Hazard ratios are computed using time since transplant as the time scale and are adjusted for sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, other), organ transplanted (kidney, liver, heart, lung, other), calendar year of transplant (1987–1994, 1995–1999, 2000–2004, 2005–2008, 2009–2014) and age at transplant. Since the effect of age on mortality was non-linear, age was modeled as a piecewise linear function with knots at age 5 and 19 years.

Overall and cancer-attributable mortality rates are per 100,000 person-years