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Spectrum of Cancer Risk among U.S. Solid Organ Transplant Recipients: The Transplant Cancer Match Study

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Abstract

Context—Solid organ transplant recipients have elevated cancer risk due to immunosuppression and oncogenic viral infections. Since most prior research has concerned kidney recipients, large studies that include recipients of differing organs can inform cancer etiology.

Objective—Describe the overall pattern of cancer among solid organ transplant recipients.

Design—Cohort study using linked data from the U.S. Scientific Registry of Transplant Recipients (1987–2008) and 13 state/regional cancer registries.

Participants and Setting—Solid organ transplant recipients in the U.S.

Main Outcome Measure—Standardized incidence ratios (SIRs) and excess absolute risks (EARs) assessing relative and absolute cancer risk in transplant recipients compared to the general population.

Results—Registry linkages yielded data on 175,732 solid organ transplants (58.4% kidney, 21.6% liver, 10.0% heart, 4.0% lung). Overall cancer risk was elevated (N=10,656 cases, incidence 1374.7 per 100,000 person-years; SIR 2.10, 95%CI 2.06–2.14; EAR 719.3, 95%CI 693.3–745.6, per 100,000 person-years). Risk was increased ($p<0.001$) for 32 different malignancies, some related to known infections (e.g., anal cancer, Kaposi sarcoma) and others unrelated (e.g., melanoma, thyroid and lip cancers). The most common malignancies with elevated risk were non-Hodgkin lymphoma (N=1504, incidence 194.0; SIR 7.54, 95%CI 7.17–7.93; EAR 168.3, 95%CI 158.6–178.4) and cancers of the lung (N=1344, incidence 173.4; SIR 1.97, 95%CI 1.86–2.08; EAR 85.3, 95%CI 76.2–94.8), liver (N=930, incidence 120.0; SIR 11.56, 95%CI 10.83–12.33; EAR 109.6, 95%CI 102.0–117.6), and kidney (N=752, incidence 97.0; SIR 4.65, 95%CI 4.32–4.99; EAR 76.1, 95%CI 69.3–83.3). Lung cancer risk was most elevated in lung recipients (SIR 6.13, 95%CI 5.18–7.21) but also increased among other recipients (SIR 1.46, 95%CI 1.34–1.59 for kidney; 1.95, 1.74–2.19 for liver; 2.67, 2.40–2.95 for heart). Liver cancer was elevated only among liver recipients (SIR 43.83, 95%CI 40.90–46.91), who manifested exceptional risk in the first 6 months (SIR 508.97, 95%CI 474.16–545.66) and continuing two-fold excess for 10–15 years (SIR 2.22, 95%CI 1.57–3.04). Among kidney recipients, kidney cancer was elevated (SIR 6.66, 95%CI 6.12–7.23) and bimodal in onset. Kidney cancer was also increased in liver and heart recipients (SIR 1.80, 95%CI 1.40–2.29, and 2.90, 2.32–3.59, respectively).

Conclusions—Recipients of a kidney, liver, heart, or lung transplant have an increased risk for diverse infection-related and unrelated cancers, compared with the general population.

Introduction

Solid organ transplantation provides life-saving therapy for patients with end-stage organ disease. In 2010, a total of 28,664 transplants were performed in the U.S., including 16,899 kidney, 6291 liver, 2333 heart, and 1770 lung transplants (1). Although transplant outcomes have improved dramatically over time, substantial morbidity results from chronic immunosuppressive therapy administered to prevent graft rejection.

Cancer is a major adverse outcome of solid organ transplantation (2). Previous studies have demonstrated an overall 2–4-fold elevated risk of cancer (3–11). Excess risk is largely due to immunosuppression, with a spectrum of cancer resembling that seen with human immunodeficiency virus (HIV) infection, another immunosuppressing condition (11). Risks are especially high for malignancies caused by viral infections, including non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (both due to Epstein Barr virus [EBV]), Kaposi sarcoma (human herpesvirus 8), anogenital cancers (human papillomavirus), and liver cancer (hepatitis C and B viruses). Certain other malignancies, such as cancers of the lung, kidney, skin, and thyroid, are also increased in transplant recipients.

Linkage of population-based transplant and cancer registries from the same geographic region can allow for systematic ascertainment of cancer outcomes in a large representative population of recipients. Except for a recent study from the United Kingdom with 37,616

transplant recipients (4), prior linkage studies of cancer following transplantation included 2000–11,000 recipients (3;5–9), which is not large enough to accurately estimate risk for less common cancers. Also, these previous studies have mostly been limited to kidney recipients. As a result, it is unclear how cancer risk varies according to the transplanted organ.

A better understanding of cancer risk in transplant recipients would help clarify the role of the immune system, infections, and other factors in the development of malignancy, and could identify opportunities to improve transplant safety. To this end, we conducted the Transplant Cancer Match Study, a linkage of the U.S. solid organ transplant registry with state and regional cancer registries. We herein present an initial overview of cancer risk in recipients of all organ types, based on data for more than 175,000 transplant recipients. In addition, we provide further details for the four most common malignancies for which risk is elevated in transplant recipients and which together comprise over 40% of all cases.

Methods

Overview of the U.S. transplant registry and linkage with cancer registries

The 1984 National Organ Transplant Act established the U.S. Organ Procurement and Transplantation Network (OPTN). Transplant programs are required to be OPTN members to perform solid organ transplantation in the U.S. The OPTN collects information from transplant centers and organ procurement organizations regarding transplant candidates, recipients, and donors. At 6 months after transplant and at yearly intervals, transplant centers provide follow-up data on recipients' vital status and graft function. These data are provided monthly by the OPTN to the Scientific Registry of Transplant Recipients (SRTR, http://www.srtr.org). The SRTR thus includes data on all U.S. solid organ transplant recipients since 1987, including demographic characteristics, medical indication for transplant, and characteristics of transplanted organs. Additional vital status information is obtained through linkage with the U.S. Social Security Death Master File.

During December 2008 through June 2010, we linked the SRTR with 13 U.S. population-based cancer registries, covering the states of California (years of complete cancer data: 1988–2008), Colorado (1988–2006), Connecticut (1973–2006), Georgia (1995–2008), Hawaii (1973–2007), Illinois (1986–2007), Iowa (1973–2007), Michigan (1985–2006), New Jersey (1979–2006), New York (1976–2007), North Carolina (1990–2007), and Texas (1995–2006), and the Seattle-Puget Sound area of Washington state (1974–2008). Database linkages between the SRTR and cancer registries were accomplished using a computer-based probabilistic matching algorithm followed by a manual review of potential matches. Variables incorporated in the match included name, sex, date of birth, and social security number.

Following each linkage, investigators retained information regarding cancer cases that matched to SRTR transplant recipients. The study was approved by human subjects committees at the National Cancer Institute and the following cancer registries: California, Colorado, Connecticut, Georgia, Hawaii, Illinois, Iowa, Michigan, New Jersey, New York, Seattle-Puget Sound, and Texas. It was reviewed and exempted from human subjects approval at the Health Resources and Services Administration and the North Carolina cancer registry.

Statistical analyses

As of June 2010, the SRTR included 458,834 U.S. solid organ transplants. Of these, 442,629 were during 1987–2008, a period for which cancer registries in our study provided data on incident cancers. We evaluated cancer risk among the cohort of transplant recipients who

resided in the geographic areas covered by the cancer registries and who were followed during the periods when cancer ascertainment was considered at least 95% complete. Residence of transplant recipients was determined based on the location recorded in the SRTR at the time of transplant (32.1%) or listing as a candidate (61.4%); 6.6% had missing information and were excluded. Thus, through linkages with the 13 population-based cancer registries, and after exclusions based on geographic and temporal coverage, data on cancer risk were available for 176,974 transplants (40.0% of 442,629 transplants). Finally, we restricted analysis to individuals of the major race/ethnicity groups (non-Hispanic white, non-Hispanic black, Hispanic, and Asian/Pacific Islander) to allow comparison with general population cancer rates. Exclusion of persons of race/ethnicity outside the major categories (N=1242 transplants) yielded the final cohort of 175,732 transplants.

For each area, transplant recipients were considered at risk of cancer beginning at transplantation or start of cancer registry coverage (whichever came last). Follow-up ended at death, failure of a transplanted organ, a subsequent transplant, loss to follow-up, or last date of cancer registry coverage (whichever came first). Individuals were not censored when they developed a first cancer and could develop multiple cancers of different types. The unit of analysis was the transplant, and individuals were considered at risk separately during successive transplant episodes. The overall transplant cohort was constructed by combining data from each registry area.

Invasive cancers were classified using the Surveillance, Epidemiology, and End Results (SEER) program “site recode with Kaposi sarcoma and mesothelioma” (http://seer.cancer.gov/), except that we separately considered cancers of poorly specified histology (because these could represent undiagnosed cases of post-transplant lymphoproliferative disorder) and collapsed some rare categories. Based on a recent review by the International Agency for Research on Cancer (12), we considered the following malignancies to be related to infections: non-Hodgkin lymphoma, Hodgkin lymphoma, and nasopharyngeal cancer (due to Epstein Barr virus); cancers of the cervix, vulva, vagina, penis, anus, and oropharynx including tonsil (human papillomavirus); liver cancer (hepatitis B and C viruses); Kaposi sarcoma (human herpesvirus 8); and stomach (*Helicobacter pylori*). In geographic areas outside the U.S., biliary tract and bladder cancers are linked to parasites, but these were considered unrelated to infections for our analyses. For purposes of presentation, other cancers were considered unrelated to infections, although evidence of variable strength supports links to infections for some additional subtypes (e.g., Merkel cell polyomavirus for Merkel cell carcinoma of the skin).

Observed cancers in the transplant cohort were determined through the linkage with the cancer registry. These observed counts were compared with the expected number, calculated by applying general population cancer rates to person-time at risk among transplant recipients. Specifically, person-time in the cohort was stratified by sex, age, race/ethnicity, calendar year, and cancer registry area. We then applied general population cancer rates for each stratum to the corresponding increment of person-time and summed the resulting products for each person, yielding expected counts for the overall cohort or subgroups of interest. We used strata of single calendar years and evaluated age in five-year intervals (0–4, 5–9, …, 80–84, 85+ years). For each cancer registry area, general population cancer rates for whites, blacks, and Asians/Pacific Islanders were calculated using the cancer registry’s case counts and U.S. census population estimates. For Hispanics, we used cancer rates from SEER to calculate expected counts. Because SEER data on Hispanics were available only beginning in 1992, we restricted analysis for Hispanic transplant recipients to those years. For Kaposi sarcoma, we used SEER rates from 1973–1979 to calculate expected counts for all recipients, because general population rates of Kaposi sarcoma since 1980 have been

strongly influenced by the HIV epidemic (13). We present observed and expected incidence rates based on these case counts and the total follow-up time in the cohort.

To measure relative risk of cancer in transplant recipients compared to the general population, we calculated a standardized incidence ratio (SIR) for each cancer type (i.e., observed/expected cases). We also calculated excess absolute risk (EAR = observed incidence minus expected incidence) to measure absolute cancer risk attributable to transplant. Ninety-five percent confidence intervals (CIs) for the SIR and EAR were derived using an exact method that assumes that the observed counts follow a Poisson distribution (14). We focus on SIRs with an exact p-value less than 0.001 (Bonferroni correction for multiple comparisons, based on approximately 50 cancer types).

We performed additional analyses for the four most common cancers for which SIRs were significantly elevated (NHL, and cancers of the lung, liver, and kidney). For these cancers, we compared incidence across strata defined by sex, age, and transplanted organ (kidney, liver, heart, or lung). We used univariate Poisson regression models to test for heterogeneity in incidence across these strata. We also present SIRs based on these strata. We also calculated SIRs in eight successive time intervals (1–180, 181–360, 361–720, 721–1080, 1081–1440, 1441–1800, 1801–3600, and 3601–5400 days after transplant [i.e., approximately 0.01–0.50, 0.51–1.00, 1.01–2.00, 2.01–3.00, 3.01–4.00, 4.01–5.00, 5.01–10.00, and 10.01–15.00 years after transplant]), for the overall cohort and subgroups defined by transplanted organ.

Results

Overview of transplant recipients and cancer risk

We evaluated cancer risk in a cohort of 175,732 transplants (39.7% of the U.S. total during 1987–2008). Recipients included in the study were similar to those excluded (Table 1), except that included recipients were limited to four major racial/ethnic groups (and had a larger fraction of Hispanics and Asians/Pacific Islanders) and were more likely to be transplanted during 1995–2004. Most included recipients were male (60.90%), and the median age at transplant was 47 years. The most common transplanted organs were kidney (58.42%), liver (21.56%), heart (10.01%), and lung (3.99%).

Transplant recipients were linked to 10,656 malignancy diagnoses during follow-up, corresponding to an overall doubling of cancer risk compared with the general population (SIR 2.10, 95%CI 2.06–2.14). Overall cancer incidence in transplant recipients was 1375 per 100,000 person-years, corresponding to an EAR of 719.3 (95%CI 693.3–745.6) per 100,000 person-years.

As shown in Table 2, SIRs were significantly elevated ($p<0.001$) for most infection-related malignancies, including NHL, Kaposi sarcoma, Hodgkin lymphoma, and cancers of the liver, stomach, oropharynx, anus, vulva, and penis. Risks of cervical, nasopharyngeal, and vaginal cancers were not significantly increased. Among infection-unrelated malignancies, SIRs were significantly elevated ($p<0.001$) for cancers of the lung, kidney, colorectum, thyroid, urinary bladder, other oral cavity and pharynx sites, skin (non-melanoma, non-epithelial), pancreas, lip, esophagus, larynx, soft tissue, salivary gland, small intestine, testis, intrahepatic bile duct and other biliary sites, and eye/orbit, and for melanoma, plasma cell neoplasms, acute myeloid leukemia, and chronic myeloid leukemia. In contrast, risk was decreased for breast cancer and, to a lesser extent, prostate cancer.

Additional analyses for NHL and cancers of the lung, liver, and kidney

We conducted additional analyses for the four most common malignancies with elevated risk: NHL (N=1504, incidence 194.0; SIR 7.54, 95%CI 7.17–7.93; EAR 168.3, 95%CI 158.6–178.4), and cancers of the lung (N=1344, incidence 173.4; SIR 1.97,95%CI 1.86–2.08; EAR 85.3, 95%CI 76.2–94.8), liver (N=930, incidence 120.0; SIR 11.56, 95%CI 10.83–12.33; EAR 109.6, 95%CI 102.0–117.6), and kidney (N=752, incidence 97.0; SIR 4.65, 95%CI 4.32–4.99; EAR 76.1, 95%CI 69.3–83.3).

Among transplant recipients, incidence of these four cancers was higher in males than females and increased steeply with age (Table 3). NHL was an exception to this pattern: both younger and older recipients (age 0–34 or 50+ years at transplant) had higher incidence than middle-aged recipients (age 35–49 years). SIRs for NHL, liver cancer, and kidney cancer were especially elevated for the youngest recipients, reflecting large increases relative to the general population.

As shown in Table 3, NHL incidence was highest in lung recipients, intermediate in liver and heart recipients, and lowest in kidney recipients. For the other three malignancies, incidence was greatest in recipients of the corresponding organ (Table 3). This difference by transplanted organ was most pronounced for liver cancer, with 89.4% of cases arising in liver recipients.

For NHL, risk was elevated for both nodal and extranodal lymphomas (SIR 6.08, 95%CI 5.68–6.51, and 10.72, 9.93–11.56, respectively; Table 2). As shown in Table 3, the elevation in NHL risk was greatest among lung recipients (SIR 18.73, 95%CI 15.59–22.32), but substantial elevations were also seen for other recipients (SIR 6.05, 95%CI 5.59–6.54 for kidney; 7.77, 6.99–8.61 for liver; 7.79, 6.89–8.79 for lung). Among all recipients together and for each organ separately, NHL risk was highest in the first year after transplant, then fell, and increased again to a plateau beginning at 4–5 years after transplant (Figure 1).

For lung cancer, the elevated risk was greatest among lung recipients (SIR 6.13, 95%CI 5.18–7.21) but was also present for recipients of other organs (SIR 1.46, 95%CI 1.34–1.59 for kidney; 1.95, 1.74–2.19 for liver; 2.67, 2.40–2.95 for heart). Among transplant recipients overall, lung cancer risk increased gradually over time, but the pattern varied by transplanted organ (Figure 2). Risk for lung recipients was especially high in the first 6 months after transplant (SIR 11.17, 95%CI 7.48–16.04) and persisted at a lower level throughout follow-up (Figure 2). Excluding the first 6 months, lung cancer risk was elevated 5.5-fold in lung recipients compared with the general population (SIR 5.53, 95%CI 4.58–6.63). As shown in Figure 2, recipients of other organs had smaller elevations in risk that were somewhat constant (kidney and liver recipients) or gradually increasing over time (heart recipients).

For liver cancer, liver recipients had a strongly elevated risk compared to the general population (SIR 43.83, 95%CI 40.90–46.91). Among liver recipients, 95.4% of liver cancers were diagnosed in the first 6 months after transplant, leading to remarkable risk during this interval (SIR 508.97, 95%CI 474.16–545.66). Nonetheless, liver cancer risk remained elevated among liver recipients throughout subsequent follow-up, albeit at a much lower level (SIR 2.22, 95%CI 1.57–3.04, excluding the first 6 months after transplantation; Figure 3). Among recipients of other organs, liver cancer risk showed no elevation (Table 3, Figure 3).

Kidney cancer risk was highest in kidney recipients (SIR 6.66, 95%CI 6.12–7.23), but was also elevated among liver and heart recipients (SIRs 1.80, 95%CI 1.40–2.29, and 2.90, 2.32–3.59, respectively). Among all recipients, kidney cancer risk showed a bimodal pattern over time (Figure 4). The early peak was largely due to the high risk during the first year among

kidney recipients (SIRs 7.28–10.28), and a second peak in risk was seen during years 4–15 after kidney transplant. Patterns over time were similar for liver and heart recipients, although SIRs were lower (Figure 4).

Discussion

In this large population-based study of U.S. transplant recipients, we observed a two-fold overall increased risk of cancer, corresponding to an excess absolute risk attributable to transplantation of approximately 0.7% per year. The spectrum of cancer risk was broad, including numerous infection-related and unrelated malignancies. NHL and cancers corresponding to three commonly transplanted organs (kidney, liver, and lung) together comprised 43% of all cancer cases in recipients, compared with 21% in the U.S. general population (15).

Elevated risks were seen for NHL and a variety of other malignancies associated with persistent viral infections. These increases resemble the cancer risks associated with HIV infection (11) and appear related to poor immune control of known oncogenic viruses. The absence of increased risk for cervical cancer (caused by human papillomavirus) may reflect Pap smear screening of recipients and prompt treatment of precancerous lesions (16). Although we did not see an elevated risk of nasopharyngeal cancer (linked to EBV), our study included relatively few Asians, who may be uniquely predisposed (17). Risk was elevated for gastric cancer, caused by the bacterium *Helicobacter pylori.*

Risk was also increased for certain malignancies without established links to infections. A few (e.g., melanoma, plasma cell neoplasms including multiple myeloma and plasmacytomas) are increased in HIV-infected populations (11) and may reflect loss of immune surveillance or the effects of chronic inflammation or immune activation. Some may be caused by yet unknown infections. Notably, transplant recipients appear prone to several cancers (e.g., colorectum, thyroid, and lip) that are not increased or occur much less often with HIV infection (11). The elevated risk of bladder cancer among transplant recipients (but not HIV-infected individuals) may be related to underlying medical conditions leading to transplantation (e.g., analgesic nephropathy) (18;19).

NHL was the most common malignancy in U.S. transplant recipients. Among transplant recipients, NHL represents one extreme of EBV-driven proliferative disease (termed “post-transplant lymphoproliferative disorder”, PTLD), which ranges from benign hyperplasia and infectious mononucleosis to lymphoid malignancy (20). The most common NHL subtype among both transplant recipients and HIV-infected individuals is diffuse large B-cell lymphoma, and most cases are EBV-positive (20;21). Bimodal onset of NHL and PTLD following organ transplantation (Figure 1) has been described previously (21;22), and risk factors differ somewhat for early-onset and late-onset PTLD, supporting etiologic heterogeneity (23). NHL risk was most pronounced among young transplant recipients, who are susceptible to primary EBV infection following transplantation (23–25). As reported previously (26), NHL risk was especially high among lung recipients, possibly as a result of the intensity of immunosuppression or the large amount of lymphoid tissue conveyed within the lung graft.

Lung cancer risk was most elevated among lung recipients, perhaps due to smoking-related lung diseases (e.g., chronic obstructive pulmonary disease) that may be the indication for lung transplant. Among lung recipients, the majority of whom receive single-lung transplants, most lung cancers arise in the remaining native lung (27;28). However, some cancers observed in the first 6 months may reflect delayed reports of cancers discovered in the explanted lung (29;30). Discounting these early cancers, lung cancer risk increased over

time among lung recipients (Figure 2), suggesting a cumulative effect of transplantation. We found lower, but still elevated, risks of lung cancer among kidney and liver recipients. Unfortunately, the SRTR does not include data on tobacco use. The elevated risk of lung cancer among HIV-infected people, independent of tobacco use, suggests that chronic immunosuppression, pulmonary inflammation, or repeated lung infections contribute to development of this malignancy (31).

Elevated risk of liver cancer was observed only among liver recipients. The extraordinary risk in the first six months after liver transplant is probably an artifact of delayed recognition or reporting of liver cancer. Liver cancer is a common complication of end-stage liver disease (32), and liver transplantation is an accepted therapy for localized liver cancer (33). We therefore suspect that the vast majority of early cancers were prevalent cases from the explanted liver. After excluding these early cancers, we still observed a two-fold increase in liver cancer among liver recipients followed for up to 15 years. Some late-onset liver cancers may represent recurrent disease or new cases related to diabetes mellitus or infection with hepatitis C or B virus (particularly common among liver recipients) (34).

The elevated risk of kidney cancer among kidney recipients is well described (3–5;7–11). Some early cases arise as a result of malignant transformation of cysts that develop in end-stage kidneys prior to transplantation (35;36). However, the elevated risk of late-onset kidney cancers, including those arising in non-kidney recipients, is not readily explained. The recent U.K. study also found an elevated risk of kidney cancer among non-kidney recipients (4). It is possible that nephrotoxic or directly carcinogenic effects of some immunosuppressive medications may contribute to cancers arising in the donor kidney (in kidney recipients) or the relatively normal kidneys in other recipients (37;38). In comparison, the absence of an increased risk of kidney cancer in HIV-infected people is striking and argues against a major role for chronic immunosuppression (19).

Strengths of the Transplant Cancer Match Study include its large size and (despite minor differences from the excluded recipients) representative sampling of the U.S. transplant population. Inclusion of non-kidney recipients allowed comparison of cancer risk across transplanted organs. Our study was more than four times larger than the recent U.K. study (4), which allowed us to stratify our analyses of cancer risk over time according to the transplanted organ. Also, the large sample size allowed stable estimates of risk for rare cancers, which were not presented by Collett *et al.* (4).

While the present overview provides an overall picture of cancer risk, a limitation is that we could not present detailed analyses for individual cancers. Future analyses will focus on specific cancers that occur excessively and examine associations with medical conditions and individual immunosuppressive medications. We identified malignancies through linkage with population-based cancer registries, which assured largely complete ascertainment. However, because cancer data were not available for the entire U.S., we would have missed cancers if recipients moved away from their state or region after their transplant. SRTR follow-up data regarding recipients' residence are largely missing before 2003, but due to changes in data collection policies, these data are more than 95% complete for subsequent years. Based on addresses for the subset followed in 2003–2008, we estimate that the proportion of transplant recipients who were not residing in their initial state or region was 2.3% at 6 months, 2.9% at 1 year, 3.9% at 3 years, 4.6% at 5 years, and 5.8% at 10 years. Because this outmigration would have led to proportionate decreases in ascertainment of cancer, these results indicate that our cancer risk estimates were not greatly affected even after extended follow-up after transplant.

We note that patterns of cancer risk in transplant recipients may partly reflect artifacts of cancer screening. For example, decreased breast and prostate cancer risk may arise from screening before transplant, leading to removal of prevalent cancers or deferral of transplant in candidates with cancer. Additionally, transplant recipients may appear to have elevated risk for some cancers (e.g., melanoma, kidney and thyroid cancers) because of heightened medical surveillance (39). Finally, we could not evaluate squamous cell and basal cell skin cancers, because these tumors are not collected by cancer registries.

In conclusion, this large-scale registry linkage study documents a wide spectrum of cancer risk among transplant recipients. Some malignancies arise from the loss of immunologic control of oncogenic viruses, but others are unrelated to known infections. Additional contributing factors for some cancers may include other effects of chronic immune disturbance or inflammation, underlying medical conditions, or medication toxicity. Our findings should stimulate research into carcinogenic mechanisms associated with organ transplantation. The elevated risk for a broad range of malignancies among transplant recipients, coupled with improvements in long-term survival, should encourage further development of approaches to prevention and early detection of cancer targeted to this population.

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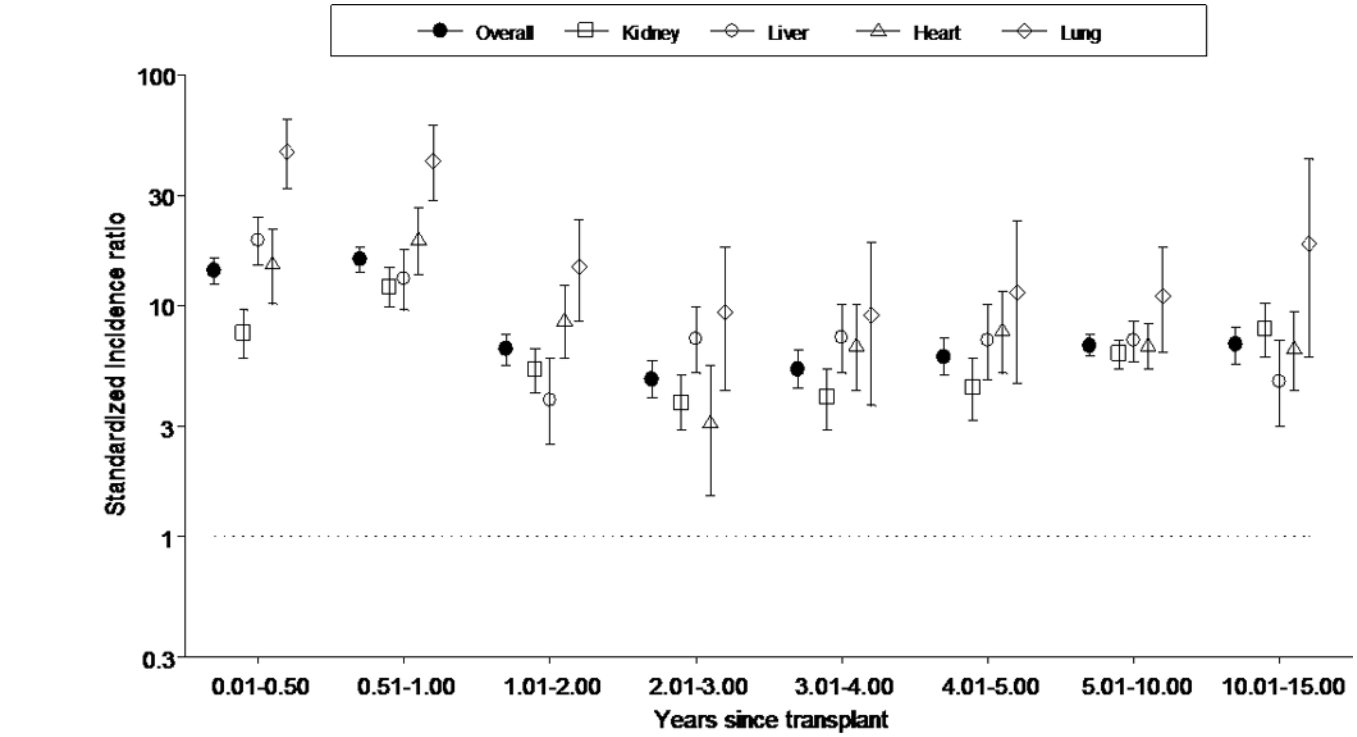
Reference List

1. Organ Procurement and Transplantation Network. http://optn.transplant.hrsa.gov/. 5-5-2011.
2. Vajdic CM, van Leeuwen MT. Cancer incidence and risk factors after solid organ transplantation. Int J Cancer. 2009; 125:1747–1754. [PubMed: 19444916]
3. Birkeland SA, Storm HH, Lamm LU, Barlow L, Blohme I, Forsberg B, et al. Cancer risk after renal transplantation in the Nordic countries, 1964–1986. Int J Cancer. 1995; 60:183–189. [PubMed: 7829213]

4. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant. 2010; 10:1889–1896. [PubMed: 20659094]
5. Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer incidence among Canadian kidney transplant recipients. Am J Transplant. 2007; 7:941–948. [PubMed: 17331115]
6. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006; 296:2823–2831. [PubMed: 17179459]
7. Adami J, Gäbel H, Lindelöf B, Ekström K, Rydh B, Glimelius B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer. 2003; 89:1221–1227. [PubMed: 14520450]
8. Kyllonen L, Salmela K, Pukkala E. Cancer incidence in a kidney-transplanted population. Transpl Int. 2000; 13 Suppl 1:S394–S398. [PubMed: 11112040]
9. Serraino D, Piselli P, Angeletti C, Minetti E, Pozzetto A, Civati G, et al. Risk of Kaposi's sarcoma and of other cancers in Italian renal transplant patients. Br J Cancer. 2005; 92:572–575. [PubMed: 15668710]
10. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant. 2004; 4:905–913. [PubMed: 15147424]
11. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007; 370:59–67. [PubMed: 17617273]
12. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009; 10:321–322. [PubMed: 19350698]
13. Chaturvedi AK, Mbulaiteye SM, Engels EA. Underestimation of relative risks by standardized incidence ratios for AIDS-related cancers. Ann Epidemiol. 2007; 18:230–234. [PubMed: 18083545]
14. Breslow, NE.; Day, NE. The design and analysis of cohort studies. Lyon: International Agency for Research on Cancer; 1987. Statistical methods in cancer research, volume II.
15. Surveillance, Epidemiology, and End Results(SEER) Program. (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases (November 2010 submission). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2011. Ref Type: Report
16. Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. J Am Soc Nephrol. 2000; 11 Suppl 15:S1–S86. S1–86. [PubMed: 11044969]
17. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2006; 15:1765–1777. [PubMed: 17035381]
18. Swindle P, Falk M, Rigby R, Petrie J, Hawley C, Nicol D. Transitional cell carcinoma in renal transplant recipients: the influence of compound analgesics. Br J Urol. 1998; 81:229–233. [PubMed: 9488064]
19. Layman AB, Engels EA. Kidney and bladder cancers among people with AIDS in the United States. J Acquir Immune Defic Syndr. 2008; 48:365–367. [PubMed: 18580342]
20. Harris, NL.; Swerdlow, SH.; Frizzera, G.; Knowles, DM. Post-transplant lymphoproliferative disorders. In: Jaffe, ES.; Harris, NL.; Stein, H.; Vardiman, JW., editors. Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001. p. 264-269.
21. van Leeuwen MT, Grulich AE, Webster AC, McCredie MR, Stewart JH, McDonald SP, et al. Immunosuppression and other risk factors for early and late non-Hodgkin lymphoma after kidney transplantation. Blood. 2009; 114:630–637. [PubMed: 19443660]
22. Faull RJ, Hollett P, McDonald SP. Lymphoproliferative disease after renal transplantation in Australia and New Zealand. Transplantation. 2005; 80:193–197. [PubMed: 16041263]
23. Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. Am J Hematol. 2011; 86:206–209. [PubMed: 21264909]

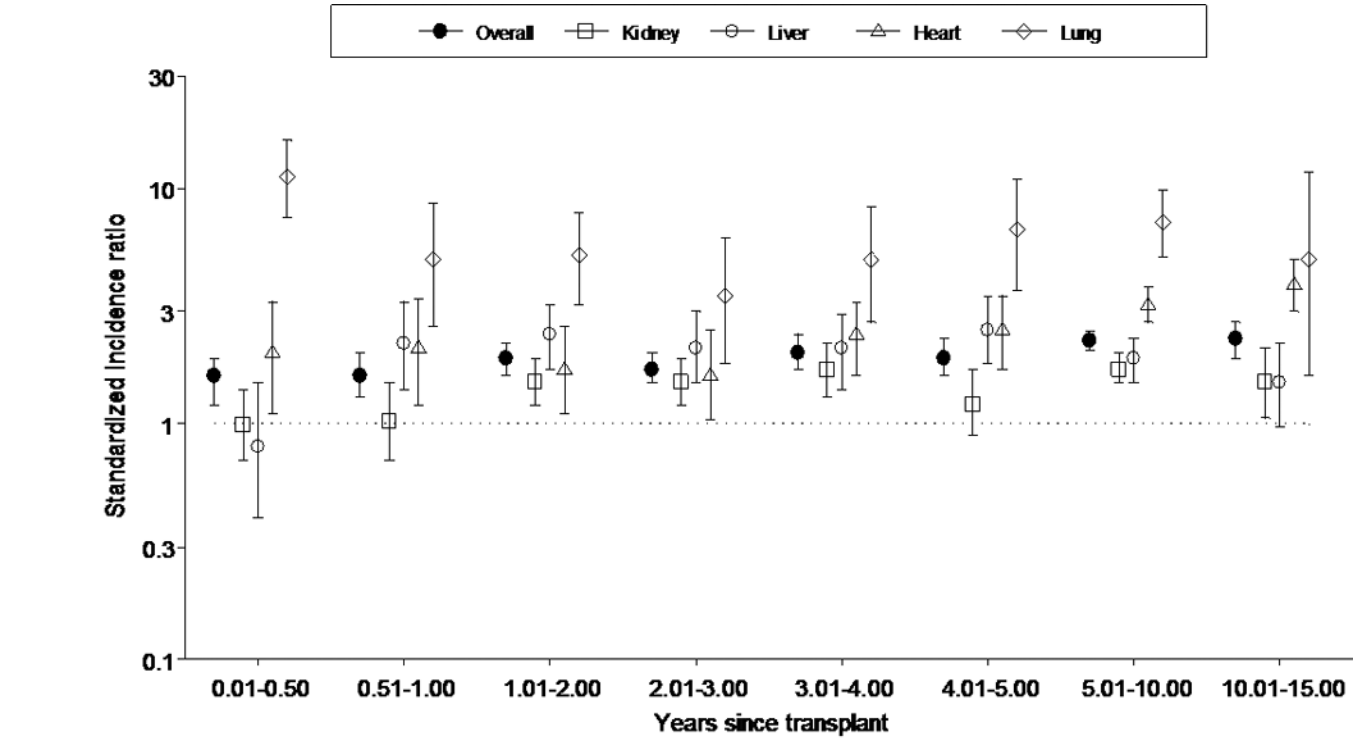
24. Cockfield SM. Identifying the patient at risk for post-transplant lymphoproliferative disorder. Transpl Infect Dis. 2001; 3:70–78. [PubMed: 11395972]
25. Andreone P, Gramenzi A, Lorenzini S, Biselli M, Cursaro C, Pileri S, et al. Posttransplantation lymphoproliferative disorders. Arch Intern Med. 2003; 163:1997–2004. [PubMed: 14504111]
26. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004; 4:222–230. [PubMed: 14974943]
27. Minai OA, Shah S, Mazzone P, Budev MM, Sahoo D, Murthy S, et al. Bronchogenic carcinoma after lung transplantation: characteristics and outcomes. J Thorac Oncol. 2008; 3:1404–1409. [PubMed: 19057264]
28. Dickson RP, Davis RD, Rea JB, Palmer SM. High frequency of bronchogenic carcinoma after single-lung transplantation. J Heart Lung Transplant. 2006; 25:1297–1301. [PubMed: 17097492]
29. Ritchie AJ, Mussa S, Sivasothy P, Stewart S. Single-lung transplant complicated by unexpected explant carcinoma: a management dilemma. J Heart Lung Transplant. 2007; 26:1206–1208. [PubMed: 18022089]
30. Abrahams NA, Meziane M, Ramalingam P, Mehta A, DeCamp M, Farver CF. Incidence of primary neoplasms in explanted lungs: long-term follow-up from 214 lung transplant patients. Transplant Proc. 2004; 36:2808–2811. [PubMed: 15621155]
31. Engels EA. Inflammation in the development of lung cancer: epidemiological evidence. Expert Rev Anticancer Ther. 2008; 8:605–615. [PubMed: 18402527]
32. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999–2008. Am J Transplant. 2010; 10:1003–1019. [PubMed: 20420649]
33. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334:693–699. [PubMed: 8594428]
34. Hoffmann CJ, Subramanian AK, Cameron AM, Engels EA. Incidence and risk factors for hepatocellular carcinoma after solid organ transplantation. Transplantation. 2008; 86:784–790. [PubMed: 18813102]
35. Goh A, Vathsala A. Native renal cysts and dialysis duration are risk factors for renal cell carcinoma in renal transplant recipients. Am J Transplant. 2011; 11:86–92. [PubMed: 20973916]
36. Heinz-Peer G, Schoder M, Rand T, Mayer G, Mostbeck GH. Prevalence of acquired cystic kidney disease and tumors in native kidneys of renal transplant recipients: a prospective US study. Radiology. 1995; 195:667–671. [PubMed: 7753991]
37. de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. Am J Kidney Dis. 2000; 35:333–346. [PubMed: 10676738]
38. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. Transplantation. 2004; 77:1777–1782. [PubMed: 15223891]
39. Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst. 2010; 102:605–613. [PubMed: 20413742]



All recipients	231	246	179	118	115	113	379	114
Kidney recipients	70	107	83	53	47	44	171	55
Liver recipients	71	45	24	39	35	30	97	23
Heart recipients	30	38	32	11	23	25	77	28
Lung recipients	35	29	17	9	7	7	16	5

Figure 1.

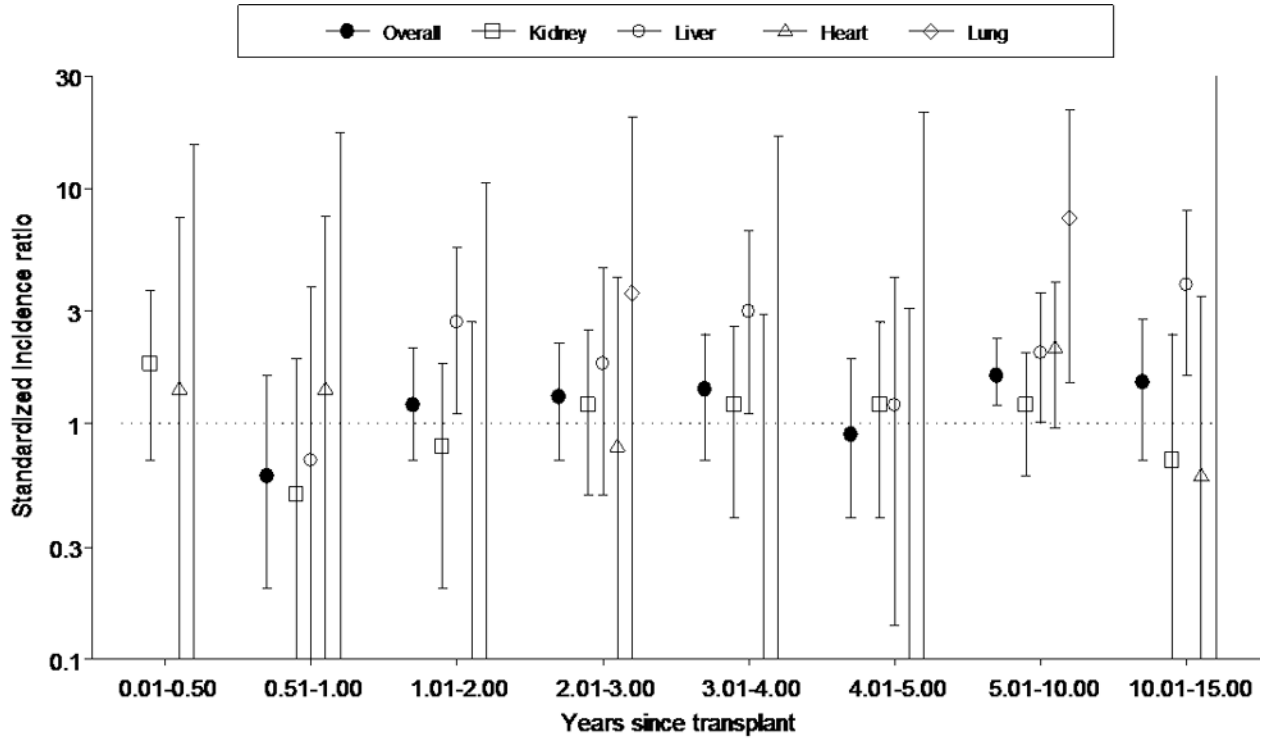
Risk of non-Hodgkin lymphoma following transplantation. Standardized incidence ratios and associated 95% confidence intervals are shown according to time since transplantation and transplanted organ. The vertical axis shows the standardized incidence ratios on a log-scale. Results are presented for all transplants (solid circle), kidney transplants (open square), liver transplants (open circle), heart transplants (open triangle), and lung transplants (open diamond). The number of observed cancer events is shown below the figure; corresponding expected counts are presented in eTable 1.



All recipients	83	84	173	143	148	125	447	133
Kidney recipients	30	30	80	69	69	42	162	35
Liver recipients	9	24	45	37	32	35	89	25
Heart recipients	15	16	25	23	32	32	151	67
Lung recipients	29	12	21	12	14	15	39	5

Figure 2.

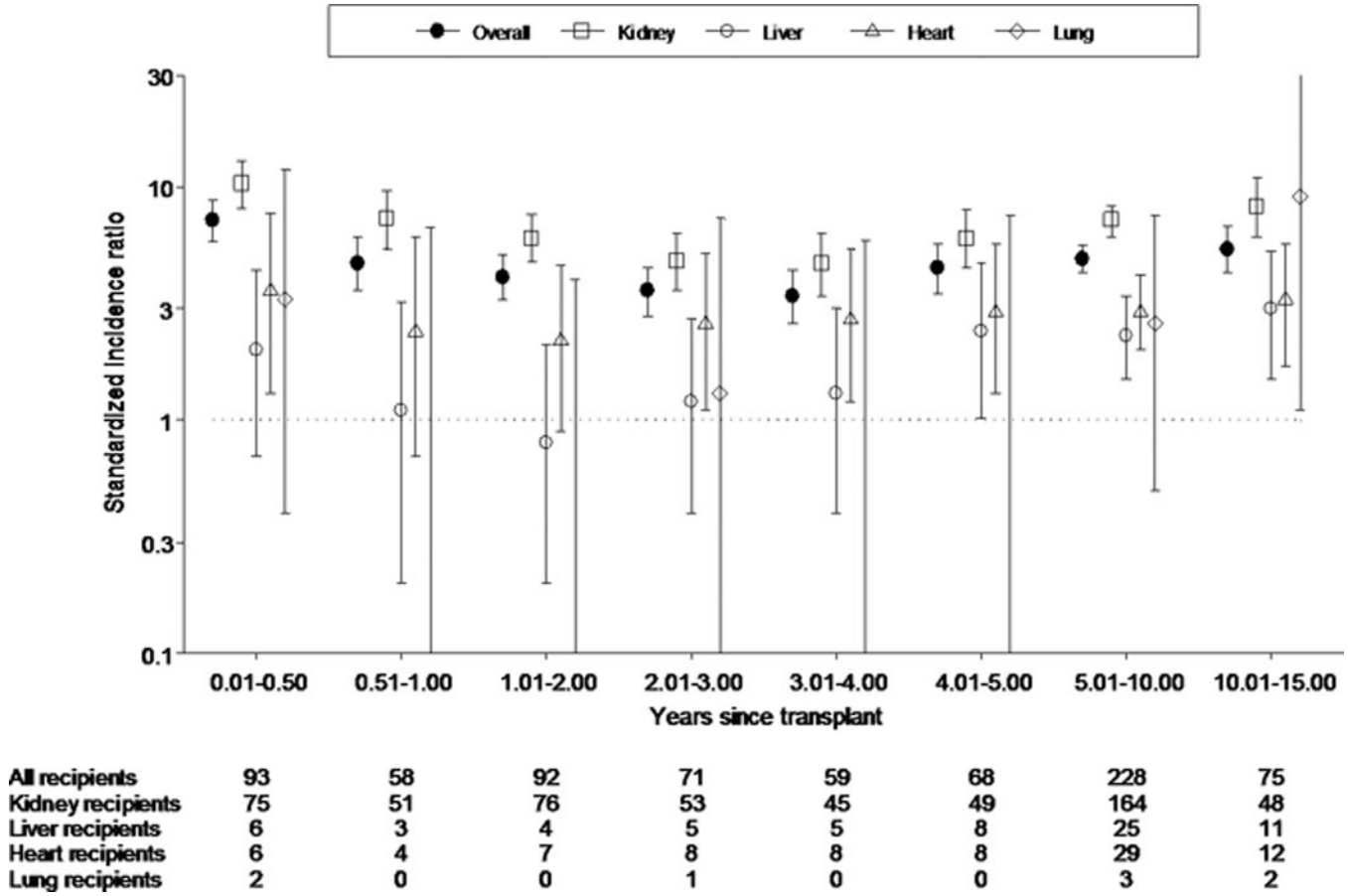
Risk of lung cancer following transplantation. Standardized incidence ratios and associated 95% confidence intervals are shown according to time since transplantation and transplanted organ. The vertical axis shows the standardized incidence ratios on a log-scale. Results are presented for all transplants (solid circle), kidney transplants (open square), liver transplants (open circle), heart transplants (open triangle), and lung transplants (open diamond). The number of observed cancer events is shown below the figure; corresponding expected counts are presented in eTable 1.



All recipients	833	4	14	13	12	7	37	10
Kidney recipients	7	2	5	7	6	5	14	2
Liver recipients	793	1	7	4	6	2	11	7
Heart recipients	1	1	0	1	0	0	9	1
Lung recipients	0	0	0	1	0	0	3	0

Figure 3.

Risk of liver cancer following transplantation. Standardized incidence ratios and associated 95% confidence intervals are shown according to time since transplantation and transplanted organ. The vertical axis shows the standardized incidence ratios on a log-scale. Results are presented for all transplants (solid circle), kidney transplants (open square), liver transplants (open circle), heart transplants (open triangle), and lung transplants (open diamond). The number of observed cancer events is shown below the figure; corresponding expected counts are presented in eTable 1. Standardized incidence ratios are off-scale and therefore not presented for 0.01–0.50 years after transplantation, for all transplants combined (standardized incidence ratio 126.11, 95%CI 117.69–134.98) and for liver transplants (standardized incidence ratio 508.97, 95%CI 474.16–545.66). For some other estimates, the standardized incidence ratio was zero and so cannot be shown on the log-scale. When the standardized incidence ratio was zero, the upper confidence limit is displayed, with the exception of the estimate for lung transplants at 10.01–15.00 years after transplant, for which the upper limit is also off-scale (95% upper confidence interval 49.64).



All recipients	93	58	92	71	59	68	228	75
Kidney recipients	75	51	76	53	45	49	164	48
Liver recipients	6	3	4	5	5	8	25	11
Heart recipients	6	4	7	8	8	8	29	12
Lung recipients	2	0	0	1	0	0	3	2

Figure 4.

Risk of kidney cancer following transplantation. Standardized incidence ratios and associated 95% confidence intervals are shown according to time since transplantation and transplanted organ. The vertical axis shows the standardized incidence ratios on a log-scale. Results are presented for all transplants (solid circle), kidney transplants (open square), liver transplants (open circle), heart transplants (open triangle), and lung transplants (open diamond). The number of observed cancer events is shown below the figure; corresponding expected counts are presented in eTable 1. For some estimates, the standardized incidence ratio was zero and so cannot be shown on the log-scale. When the standardized incidence ratio was zero, the upper confidence limit is displayed, with the exception of the estimate for lung transplants at 10.01–15.00 years after transplant, for which the upper limit is also off-scale (95% upper confidence interval 32.73).

Table 1

Characteristics of included and excluded U.S. solid organ transplant recipients (1987–2008)

Characteristic	Included transplants N (%) (% of total)	Excluded transplants N (%)
Total	175,732 (100.00)	266,897 (100.00)
Sex		
Male	107,027 (60.90)	164,473 (61.62)
Female	68,705 (39.10)	102,424 (38.38)
Age at transplant, years		
0–17	13,813 (7.86)	19,265 (7.22)
18–34	29,444 (16.76)	45,443 (17.03)
35–49	55,837 (31.77)	85,973 (32.21)
50–64	62,815 (35.74)	95,705 (35.86)
65+	13,823 (7.87)	20,511 (7.68)
Race/ethnicity		
White, non-Hispanic	106,895 (60.83)	189,289 (70.92)
Black, non-Hispanic	29,928 (17.03)	48,827 (18.29)
Hispanic	28,263 (16.08)	18,429 (6.90)
Asian/Pacific Islander	10,646 (6.06)	6,026 (2.26)
Other/unknown	0 (0.00)	4,326 (1.62)
Transplanted organ		
Kidney	102,654 (58.42)	161,002 (60.32)
Kidney and pancreas	6,165 (3.51)	9,607 (3.60)
Pancreas	1,639 (0.93)	3,631 (1.36)
Liver	37,888 (21.56)	50,894 (19.07)
Heart	17,593 (10.01)	26,860 (10.06)
Lung	7,013 (3.99)	10,900 (4.08)
Heart and lung	388 (0.22)	563 (0.21)
Other or multiple	2,392 (1.36)	3,440 (1.29)
Transplant number		
First	160,383 (91.27)	242,691 (90.93)
Second	14,079 (8.01)	21,863 (8.19)
Third or higher	1,270 (0.72)	2,343 (0.88)
Calendar year of transplant		
1987–1994	34,583 (19.68)	74,943 (28.08)
1995–1999	46,110 (26.24)	55,041 (20.62)
2000–2004	56,888 (32.37)	65,202 (24.43)
2005–2008	38,151 (21.71)	71,711 (26.87)

Table 2

Cancer risk in U.S. transplant recipients

Cancer site*	Observed cases	Expected cases	SIR†	95% lower CI	95% upper CI	P-value	Observed incidence, per 100,000 person-years	Expected incidence, per 100,000 person-years	EAR, per 100,000 person-years	95% upper CI	95% lower CI
Infection-related malignancies											
NHL	1504	199.4	7.54	7.17	7.93	<0.0001	194.0	25.7	168.3	158.6	178.4
Nodal NHL	831	136.6	6.08	5.68	6.51	<0.0001	107.2	17.6	89.6	82.4	97.1
Extranodal NHL	673	62.8	10.72	9.93	11.56	<0.0001	86.8	8.1	78.7	72.3	85.5
Liver	930	80.5	11.56	10.83	12.33	<0.0001	120.0	10.4	109.6	102.0	117.6
Stomach	152	90.9	1.67	1.42	1.96	<0.0001	19.6	11.7	7.9	4.9	11.3
Kaposi sarcoma	120	2.0	61.46	50.95	73.49	<0.0001	15.5	0.3	15.2	12.6	18.3
Oropharynx including tonsil	106	52.8	2.01	1.64	2.43	<0.0001	13.7	6.8	6.9	4.4	9.7
Anus	90	15.4	5.84	4.70	7.18	<0.0001	11.6	2.0	9.6	7.3	12.3
Hodgkin lymphoma	85	23.7	3.58	2.86	4.43	<0.0001	11.0	3.1	7.9	5.7	10.5
Vulva	58	7.6	7.60	5.77	9.83	<0.0001	7.5	1.0	6.5	4.7	8.7
Cervix	45	43.6	1.03	0.75	1.38	0.88	5.8	5.6	0.2	−1.4	2.1
Penis	22	5.3	4.13	2.59	6.26	<0.0001	2.8	0.7	2.2	1.1	3.6
Nasopharynx	8	8.3	0.96	0.42	1.90	1.00	1.0	1.1	0.0	−0.6	1.0
Vagina	7	3.0	2.35	0.94	4.84	0.07	0.9	0.4	0.5	0.0	1.5
Infection-unrelated malignancies											
Lung	1344	682.8	1.97	1.86	2.08	<0.0001	173.4	88.1	85.3	76.2	94.8
Prostate	1039	1126.9	0.92	0.87	0.98	0.009	134.0	145.4	−11.3	−19.4	−2.9
Kidney	752	161.8	4.65	4.32	4.99	<0.0001	97.0	20.9	76.1	69.3	83.3
Colorectum	627	504.9	1.24	1.15	1.34	<0.0001	80.9	65.1	15.8	9.5	22.3
Breast	481	567.9	0.85	0.77	0.93	0.0002	62.1	73.3	−11.2	−16.6	−5.4
Melanoma	381	160.3	2.38	2.14	2.63	<0.0001	49.2	20.7	28.5	23.7	33.7
Thyroid	238	80.8	2.95	2.58	3.34	<0.0001	30.7	10.4	20.3	16.5	24.4
Urinary bladder	225	148.1	1.52	1.33	1.73	<0.0001	29.0	19.1	9.9	6.2	14.0
Skin (non-melanoma, non-epithelial)	184	13.3	13.85	11.92	16.00	<0.0001	23.7	1.7	22.0	18.7	25.7
Pancreas	157	107.3	1.46	1.24	1.71	<0.0001	20.3	13.8	6.4	3.4	9.8

Cancer site*	Observed cases	Expected cases	SIR†	95% lower CI	95% upper CI	P-value	Observed incidence, per 100,000 person-years	Expected incidence, per 100,000 person-years	EAR, per 100,000 person-years	95% upper CI	95% lower CI
Other oral cavity and pharynx	149	58.2	2.56	2.17	3.01	<0.0001	19.2	7.5	11.7	8.8	15.1
Lip	130	7.7	16.78	14.02	19.92	<0.0001	16.8	1.0	15.8	13.0	18.9
Plasma cell neoplasms	118	64.3	1.84	1.52	2.20	<0.0001	15.2	8.3	6.9	4.3	9.9
Acute myeloid leukemia	102	33.9	3.01	2.45	3.65	<0.0001	13.2	4.4	8.8	6.4	11.6
Larynx	97	60.8	1.59	1.29	1.95	<0.0001	12.5	7.8	4.7	2.3	7.4
Esophagus	96	61.5	1.56	1.26	1.91	0.0001	12.4	7.9	4.4	2.1	7.2
Uterine corpus	94	109.3	0.86	0.70	1.05	0.15	12.1	14.1	−2.0	−4.3	0.7
Soft tissue including heart	65	28.8	2.25	1.74	2.87	<0.0001	8.4	3.7	4.7	2.8	7.0
Salivary gland	56	12.3	4.55	3.44	5.91	<0.0001	7.2	1.6	5.6	3.9	7.8
Ovary	54	56.7	0.95	0.72	1.24	0.79	7.0	7.3	−0.3	−2.1	1.8
Small intestine	50	20.6	2.43	1.80	3.20	<0.0001	6.5	2.7	3.8	2.1	5.8
Brain	45	59.6	0.76	0.55	1.01	0.06	5.8	7.7	−1.9	−3.5	0.1
Testis	40	20.4	1.96	1.40	2.67	0.0002	5.2	2.6	2.5	1.1	4.4
Other biliary	39	15.9	2.45	1.74	3.35	<0.0001	5.0	2.1	3.0	1.5	4.8
Intrahepatic bile duct	38	6.6	5.76	4.08	7.91	<0.0001	4.9	0.9	4.1	2.6	5.9
Chronic myeloid leukemia	38	10.9	3.47	2.46	4.77	<0.0001	4.9	1.4	3.5	2.1	5.3
Chronic lymphocytic leukemia	23	38.9	0.59	0.38	0.89	0.008	3.0	5.0	−2.0	−3.1	−0.6
Gallbladder	22	11.0	2.00	1.25	3.02	0.005	2.8	1.4	1.4	0.4	2.9
Eye and orbit	21	7.6	2.78	1.72	4.24	0.0001	2.7	1.0	1.7	0.7	3.2
Renal pelvis	17	8.3	2.05	1.20	3.29	0.01	2.2	1.1	1.1	0.2	2.4
Acute lymphocytic leukemia	17	8.2	2.06	1.20	3.30	0.01	2.2	1.1	1.1	0.2	2.4
Mesothelioma	15	11.5	1.30	0.73	2.15	0.37	1.9	1.5	0.4	−0.4	1.7
Bones and joints	14	7.1	1.98	1.09	3.33	0.03	1.8	0.9	0.9	0.1	2.1
Other acute leukemia	5	2.3	2.20	0.71	5.13	0.16	0.6	0.3	0.4	−0.1	1.2
Acute monocytic leukemia	4	1.7	2.35	0.64	6.01	0.19	0.5	0.2	0.3	−0.1	1.1
Other/unspecified malignancies											
Miscellaneous specified malignancies	546	172.1	3.17	2.91	3.45	<0.0001	70.4	22.2	48.2	42.4	54.4
Tumors with poorly specified histology	206	97.9	2.11	1.83	2.41	<0.0001	26.6	12.6	14.0	10.4	17.8
Total	10,656	5080.6	2.10	2.06	2.14	<0.0001	1374.7	655.4	719.3	693.3	745.6

Abbreviations: CI confidence interval, EAR excess absolute risk, NHL, non-Hodgkin lymphoma, SIR standardized incidence ratio

*The table lists invasive cancers arising during 775,147 person-years. Incidence is presented for the entire cohort, but can be calculated separately for males or females for sex-specific malignancies based on follow up of 465,521 person-years in males and 309,626 person-years in females. Cancers are grouped into infection-related, infection-unrelated, and other/unspecified categories; within categories, cancers are listed in order of decreasing frequency.

†Standardized incidence ratios are underlined when the p-value was less than 0.001, corresponding to the Bonferroni level of statistical significance.

Table 3

Risk of selected cancers in subgroups of transplant recipients

Category of recipient	NHL		Lung cancer		Liver cancer		Kidney cancer	
A. Observed incidence rate, per 100,000 person-years (observed cases)*								
Sex								
Male	213.5	(994)	191.2	(890)	158.7	(739)	117.5	(547)
Female	164.7	(510)	146.6	(454)	61.7	(191)	66.2	(205)
p-value†	<0.0001		<0.0001		<0.0001		<0.0001	
Age at transplant, years								
0–34	201.5	(412)	4.9	(10)	13.2	(27)	27.9	(57)
35–49	150.5	(395)	92.6	(243)	82.3	(216)	109.7	(288)
50+	226.1	(697)	353.9	(1091)	222.9	(687)	132.0	(407)
p-value†	<0.0001		<0.0001		<0.0001		<0.0001	
Transplanted organ								
Kidney	141.6	(635)	115.3	(517)	10.7	(48)	126.0	(565)
Liver	217.4	(365)	178.7	(300)	495.0	(831)	39.9	(67)
Heart	283.1	(267)	386.0	(364)	13.8	(13)	90.1	(85)
Lung	532.7	(125)	626.4	(147)	17.0	(4)	34.1	(8)
p-value†	<0.0001		<0.0001		<0.0001		<0.0001	
B. Expected incidence rate, per 100,000 person-years (expected cases)*								
Sex								
Male	30.0	(139.7)	104.9	(488.2)	14.7	(68.6)	26.7	(124.5)
Female	19.3	(59.7)	62.8	(194.6)	3.8	(11.9)	12.0	(37.3)
Age at transplant, years								
0–34	4.4	(9.0)	1.9	(3.8)	0.5	(1.0)	1.7	(3.4)
35–49	17.0	(44.5)	33.8	(88.6)	6.8	(17.9)	13.1	(34.3)
50+	47.3	(145.9)	191.5	(590.4)	20.0	(61.6)	40.2	(124.0)
Transplanted organ								
Kidney	23.4	(105.0)	78.9	(354.0)	9.9	(44.5)	18.9	(84.9)
Liver	28.0	(47.0)	91.6	(153.7)	11.3	(19.0)	22.2	(37.2)
Heart	36.3	(34.3)	144.8	(136.5)	13.5	(12.8)	31.0	(29.3)

Category of recipient	NHL		Lung cancer		Liver cancer		Kidney cancer	
Lung	28.4	(6.7)	102.1	(24.0)	8.4	(2.0)	22.9	(5.4)
C. Standardized incidence ratio (95%CI)								
Sex								
Male	7.11	(6.68–7.57)	1.82	(1.71–1.95)	10.78	(10.02–11.58)	4.39	(4.03–4.77)
Female	8.54	(7.82–9.32)	2.33	(2.12–2.56)	16.06	(13.86–18.50)	5.50	(4.77–6.30)
Age at transplant, years								
0–34	45.86	(41.54–50.51)	2.62	(1.26–4.83)	27.55	(18.16–40.09)	16.63	(12.60–21.55)
35–49	8.87	(8.02–9.79)	2.74	(2.41–3.11)	12.09	(10.53–13.81)	8.39	(7.45–9.41)
50+	4.78	(4.43–5.15)	1.85	(1.74–1.96)	11.15	(10.33–12.02)	3.28	(2.97–3.62)
Transplanted organ								
Kidney	6.05	(5.59–6.54)	1.46	(1.34–1.59)	1.08	(0.80–1.43)	6.66	(6.12–7.23)
Liver	7.77	(6.99–8.61)	1.95	(1.74–2.19)	43.83	(40.90–46.91)	1.80	(1.40–2.29)
Heart	7.79	(6.89–8.79)	2.67	(2.40–2.95)	1.02	(0.54–1.74)	2.90	(2.32–3.59)
Lung	18.73	(15.59–22.32)	6.13	(5.18–7.21)	2.04	(0.56–5.22)	1.49	(0.64–2.94)

Abbreviations: CI confidence interval, NHL non-Hodgkin lymphoma

* P-values are tests of heterogeneity based on Poisson regression.