Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients

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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 United States, including 16,899 kidney transplants, 6,291 liver transplants, 2,333 heart transplants, and 1,770 lung transplants. Although transplant outcomes have improved dramatically over time, substantial morbidity results from chronic immunosuppressive therapy administered to prevent graft rejection.

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

Objective To describe the overall pattern of cancer following solid organ transplantation.

Design, Setting, and Participants Cohort study using linked data on solid organ transplant recipients from the US Scientific Registry of Transplant Recipients (1987-2008) and 13 state and regional cancer registries.

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

Results The registry linkages yielded data on 175,732 solid organ transplants (58.4% for kidney, 21.6% for liver, 10.0% for heart, and 4.0% for lung). The overall cancer risk was elevated with 10,656 cases and an incidence of 1375 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 for 32 different malignancies, some related to known infections (eg, anal cancer, Kaposi sarcoma) and others unrelated (eg, melanoma, thyroid and lip cancers). The most common malignancies with elevated risk were non-Hodgkin lymphoma (n=1,504; incidence: 194.0 per 100,000 person-years; SIR, 7.54 [95% CI, 7.17-7.93]; EAR, 168.3 [95% CI, 158.6-178.4] per 100,000 person-years) and cancers of the lung (n=1,344; incidence: 173.4 per 100,000 person-years; SIR, 1.97 [95% CI, 1.86-2.08]; EAR, 85.3 [95% CI, 76.2-94.8] per 100,000 person-years), liver (n=930; incidence: 120.0 per 100,000 person-years; SIR, 11.56 [95% CI, 10.83-12.33]; EAR, 109.6 [95% CI, 102.0-117.6] per 100,000 person-years), and kidney (n=752; incidence: 97.0 per 100,000 person-years; SIR, 4.65 [95% CI, 4.32-4.99]; EAR, 76.1 [95% CI, 69.3-83.3] per 100,000 person-years). Lung cancer risk was elevated for recipients of a kidney, liver, heart, or lung transplant have an increased risk for diverse infection-related and unrelated cancers.

Conclusion Compared with the general population, recipients of a kidney, liver, heart, or lung transplant have an increased risk for diverse infection-related and unrelated cancers.

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CANCER RISK AMONG US SOLID ORGAN TRANSPLANT RECIPIENTS

Cancer is a major adverse outcome of solid organ transplantation.\(^2\) Previous studies have demonstrated an overall 2- to 4-fold elevated risk of cancer.\(^3\)\(^-\)\(^9\) Excess risk is largely due to immunosuppression, with a spectrum of cancer resembling that seen with human immunodeficiency virus (HIV) infection, another immunosuppressing condition.\(^1\) Risks are especially high for malignancies caused by viral infections, including non-Hodgkin lymphoma 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 also are 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,\(^9\) prior linkage studies of cancer following transplantation included 2000 to 11 000 recipients,\(^5\)\(^-\)\(^9\) which is not large enough to accurately estimate risk for less common cancers. Also, these previous studies have been limited mostly 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 US 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 4 most common malignancies for which risk is elevated in transplant recipients and which together comprise more than 40% of all cases.

 METHODS

US Transplant Registry and Linkage With Cancer Registries

The 1984 National Organ Transplant Act established the US Organ Procurement and Transplantation Network (OPTN). Transplant programs are required to be OPTN members to perform solid organ transplantation in the United States. 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). The SRTR contains data on all US solid organ transplant recipients since 1987 and includes demographic characteristics, medical indication for transplant, and characteristics of transplanted organs. Additional vital status information is obtained through linkage with the US Social Security Death Master File.


Following each linkage, investigators retained information regarding cancer cases that matched to SRTR transplant recipients. Our 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 area of Washington State, and Texas. It was reviewed and exempted from human subjects approval by the Health Resources and Services Administration and the North Carolina cancer registry.

Statistical Analyses

As of June 2010, the SRTR included 458 834 US solid organ transplants. Of these, 442 629 were during 1987-2008, a period for which the cancer registries included 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 up 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 for cancer beginning at transplantation or start of cancer registry coverage (whichever came last). Follow-up ended at death,
failure of a transplanted organ, a sub-
sequent transplant, loss to follow-up,
or last date of cancer registry coverage
(whichever came first). Individuals
were not censored when they devel-
oped 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 trans-
plant 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 meso-
theloma,” with the exception of can-
cers of poorly specified histology that
were considered separately because
these could represent undiagnosed cases
of posttransplant lymphoproliferative
disorder; some rare categories were col-
lapsed. Based on a recent review by the
International Agency for Research on
Cancer,13 we considered the following
malignancies to be related to infe-
tions: non-Hodgkin lymphoma, Hodg-
kin lymphoma, and nasopharyngeal
cancer (due to EBV); cancers of the cer-
vix, vulva, vagina, penis, anus, and oro-
pharynx including tonsil (human pap-
ilomavirus); liver cancer (hepatitis B
and C viruses); Kaposi sarcoma (hu-
man herpesvirus 8); and stomach can-
cer (Helicobacter pylori). In geo-
graphic areas outside the United States,
biliary tract and bladder cancers are
linked to parasites, but these were con-
sidered unrelated to infections for our
analyses. For the purposes of presen-
tation, other cancers were considered
unrelated to infections, although evi-
dence of variable strength supports links
to infections for some additional sub-
types (eg, 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 ap-
plying general population cancer rates
to person-time at risk among trans-
plant 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 incre-
ment of person-time and summed the
resulting products for each person,
yielding expected counts for the over-
all cohort or subgroups of interest. We
used strata of single calendar years and
evaluated age in 5-year intervals (0-4,
5-9, . . . , 80-84, and ≥85 years). For
each cancer registry area, general popu-
lation cancer rates for whites, blacks,
and Asians/Pacific Islanders were cal-
culated using the cancer registry’s case
counts and US census population esti-
mates. For Hispanics, we used cancer
rates from SEER to calculate expected
case counts. Because SEER data on His-
panics were available only beginning in
1992, we restricted the analysis for His-
panic transplant recipients to those
years. For Kaposi sarcoma, we used
SEER rates from 1973-1979 to calcu-
late expected counts for all recipients
because general population rates of Ka-
posi sarcoma since 1980 have been
strongly influenced by the HIV epi-
demic.13 We present observed and ex-
pected incidence rates based on these
case counts and the total follow-up time
in the cohort.

To measure the relative risk of can-
cer in transplant recipients compared
with the general population, we calcu-
lated a standardized incidence ratio
(SIR) for each cancer type (ie, observed/
expected cases). We also calculated ex-
cess absolute risk (EAR; observed in-
cidence minus expected incidence) to
measure absolute cancer risk attribut-
able to transplant. Ninety-five percent
CIs for the SIR and EAR were derived
using an exact method that assumes the
observed counts follow a Poisson dis-
tribution.14 We focus on SIRs with an
exact P value of less than .001 (Bon-
ferroni correction for multiple com-
parisons based on approximately 50
cancer types).

We performed additional analyses for
the 4 most common cancers for which
SIRs were significantly elevated (non-
Hodgkin lymphoma and cancers of the
lung, liver, and kidney). For these can-
cers, we compared incidence across
strata defined by sex, age, and trans-
planted organ (kidney, liver, heart, or
lung). We used univariate Poisson re-
gression models to test for heteroge-

Results

Transplant Recipients

We evaluated cancer risk in a cohort of
175,732 transplants (39.7% of the
US total during 1987-2008). Recipi-
ents included in the study were simi-
lar to those excluded (Table 1),
except that included recipients were
limited to 4 major racial/ethnic
groups (and had a larger fraction of
Hispanics and Asians/Pacific Island-
ers) and were more likely to receive
transplants during 1995-2004. Most
of the 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, which
corresponded to an EAR of 719.3
(95% CI, 693.3-745.6) per 100,000
person-years.

SIRs were significantly elevated
(P<.001) for most infection-related
malignancies, including non-Hodgkin
lymphoma, Kaposi sarcoma, Hodgkin

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lymphoma, and cancers of the liver, stomach, oropharynx, anus, vulva, and penis (Table 2). Risks of cervical, nasopharyngeal, and vaginal cancers were not significantly increased. Among non–infection-related malignancies (Table 3), SIRs were significantly elevated (P < .001) for cancers of the lung, kidney, colorectum, thyroid, urinary bladder, other oral cavity and pharynx sites, skin (nonmelanoma, nonepithelial), 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.

**Analyses for Non-Hodgkin Lymphoma and Cancers of the Lung, Liver, and Kidney**

We conducted additional analyses for the 4 most common malignancies with elevated risk: 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] per 100 000 person-years), and cancers of the lung (n = 1344; incidence: 173.4 per 100 000 person-years; SIR, 1.97 [95% CI, 1.86-2.08]; EAR, 85.3 [95% CI, 76.2-94.8] per 100 000 person-years), liver (n = 1344; incidence: 77.5 per 100 000 person-years; SIR, 22.32 [95% CI, 20.19-24.55]; EAR, 58.9 [95% CI, 51.3-66.5] per 100 000 person-years; SIR, 18.73 [95% CI, 15.59-21.83]; EAR, 109.6 [95% CI, 96.1-123.3] per 100 000 person-years), and kidney (n = 752; incidence: 102.0-117.6 per 100 000 person-years; SIR, 4.65 [95% CI, 4.32-4.99]; EAR, 76.1 [95% CI, 69.3-83.3] per 100 000 person-years).

Among transplant recipients, the incidence of these 4 cancers was higher in males than in females and increased steeply with age (Table 4). Non-Hodgkin lymphoma was an exception to this pattern: both younger and older recipients (age: 0-34 years or ≥50 years at transplant) had higher incidence than middle-aged recipients (age: 35-49 years). The SIRs for non-Hodgkin lymphoma, liver cancer, and kidney cancer were especially elevated for the youngest recipients, reflecting large increases relative to the general population.

Non-Hodgkin lymphoma incidence was highest in lung recipients, intermediate in liver and heart recipients, and lowest in kidney recipients (Table 4). For the other 3 malignancies, incidence was greatest in recipients of the corresponding organ. This difference by transplanted organ was most pronounced for liver cancer, with 89.4% of cases arising in liver recipients. For non-Hodgkin lymphoma, risk was elevated for both nodal lymphomas (SIR, 6.08 [95% CI, 5.68-6.51]) and extranodal lymphomas (SIR, 10.72 [95% CI, 9.93-11.56]) (Table 2). The elevation in risk for non-Hodgkin lymphoma was greatest among lung recipients (SIR, 18.73 [95% CI, 15.59-22.32]), but substantial elevations also were seen for other recipients (kidney: SIR, 6.05 [95% CI, 5.59-6.54]; liver: SIR, 7.77 [95% CI, 6.99-8.61]; and lung: SIR, 7.79 [95% CI, 6.89-8.79]) (Table 4). Among all recipients together and for each organ separately, non-Hodgkin lymphoma risk was highest in the first year after transplant, then decreased, and increased again to a plateau beginning at 4-5 years after transplant (Figure 1).

### Table 1. Characteristics of US Solid Organ Transplant Recipients From 1987 Through 2008

<table>
<thead>
<tr>
<th>Characteristics of US Solid Organ Transplant Recipients From 1987 Through 2008</th>
<th>Included (n = 175,732)</th>
<th>Excluded (n = 266,897)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong> Male</td>
<td>107,027 (60.90)</td>
<td>164,473 (61.62)</td>
</tr>
<tr>
<td><strong>Age at transplant, y</strong> 0-17</td>
<td>13,813 (7.86)</td>
<td>19,265 (7.22)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong> White, non-Hispanic</td>
<td>106,895 (60.83)</td>
<td>189,289 (70.92)</td>
</tr>
<tr>
<td><strong>Transplanted organ</strong> Kidney 102,654 (58.42)</td>
<td>161,002 (60.32)</td>
<td>Kidney and pancreas 6165 (3.51)</td>
</tr>
<tr>
<td><strong>Transplant</strong> First 160,383 (91.27)</td>
<td>242,691 (90.93)</td>
<td>Second 14,079 (8.01)</td>
</tr>
</tbody>
</table>

aIndicates persons of race/ethnicity outside the major categories.
For lung cancer, the elevated risk was greatest among lung recipients (SIR, 6.13 [95% CI, 5.18-7.21]) but also was present for recipients of other organs (kidney: SIR, 1.46 [95% CI, 1.34-1.59]; liver: SIR, 1.95 [95% CI, 1.74-2.19]; heart: SIR, 2.67 [95% CI, 2.40-2.95]). 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]). Recipients of other organs had smaller elevations in risk that were somewhat constant (kidney and liver recipients) or gradually increasing over time (heart recipients) (Figure 2).

For liver cancer, liver recipients had a strongly elevated risk compared with 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 transplantation, 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 4 and 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 recipients (SIR, 1.80 [95% CI, 1.40-2.29]) and heart recipients (SIR, 2.90 [95% CI, 2.32-3.59]). 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 (SIR range, 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).

**COMMENT**

In this large, population-based study of US transplant recipients, we observed a 2-fold overall increased risk of cancer, corresponding to an EAR attributable to transplantation of approximately 0.7% per year. The spectrum of cancer risk was broad, including numerous infection-related and unrelated malignancies. Non-Hodgkin lymphoma and cancers corresponding to 3 commonly transplanted organs (kidney, liver, and lung) together comprised 43% of all cancer cases in transplant recipients compared with 21% in the US general population.

Elevated risks were seen for non-Hodgkin lymphoma and a variety of other malignancies associated with persistent viral infections. These increases resemble the cancer risks associated with HIV infection 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 Papanicolaou test screening of recipients and prompt treatment of precancerous lesions. 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 to this cancer.

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**Table 2. Risk of Infection-Related Malignancies in US Transplant Recipients**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>No. of Cases</th>
<th></th>
<th>Incidence/100 000 Person-Years&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>EAR/100 000 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>SIR (95% CI)</td>
<td>P Value</td>
<td>Observed</td>
</tr>
<tr>
<td><strong>Non-Hodgkin lymphoma</strong></td>
<td>1504</td>
<td>1374.7</td>
<td>7.54 (7.17 to 7.93)</td>
<td>&lt;.001</td>
<td>194.0</td>
</tr>
<tr>
<td>Nodal</td>
<td>831</td>
<td>655.4</td>
<td>6.08 (5.68 to 6.51)</td>
<td>&lt;.001</td>
<td>107.2</td>
</tr>
<tr>
<td>Extranodal</td>
<td>723</td>
<td>719.3</td>
<td>10.72 (9.93 to 11.56)</td>
<td>&lt;.001</td>
<td>86.6</td>
</tr>
<tr>
<td>Liver</td>
<td>930</td>
<td>893.4</td>
<td>11.56 (10.83 to 12.33)</td>
<td>&lt;.001</td>
<td>120.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>152</td>
<td>152.0</td>
<td>1.67 (1.42 to 1.96)</td>
<td>&lt;.001</td>
<td>19.6</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>120</td>
<td>120.0</td>
<td>61.46 (50.96 to 73.49)</td>
<td>&lt;.001</td>
<td>15.5</td>
</tr>
<tr>
<td>Oropharynx including tonsil</td>
<td>106</td>
<td>69.4</td>
<td>2.01 (1.64 to 2.43)</td>
<td>&lt;.001</td>
<td>13.7</td>
</tr>
<tr>
<td>Anus</td>
<td>90</td>
<td>67.8</td>
<td>5.84 (4.70 to 7.18)</td>
<td>&lt;.001</td>
<td>11.6</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>85</td>
<td>64.4</td>
<td>5.38 (2.96 to 4.43)</td>
<td>&lt;.001</td>
<td>11.0</td>
</tr>
<tr>
<td>Vulva</td>
<td>58</td>
<td>46.7</td>
<td>7.60 (5.77 to 9.83)</td>
<td>&lt;.001</td>
<td>7.5</td>
</tr>
<tr>
<td>Cervix</td>
<td>45</td>
<td>34.8</td>
<td>1.03 (0.75 to 1.38)</td>
<td>.88</td>
<td>5.8</td>
</tr>
<tr>
<td>Penis</td>
<td>22</td>
<td>13.3</td>
<td>4.13 (2.59 to 6.26)</td>
<td>&lt;.001</td>
<td>2.8</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>8</td>
<td>7.0</td>
<td>0.96 (0.42 to 1.90)</td>
<td>&gt;.99</td>
<td>1.0</td>
</tr>
<tr>
<td>Vagina</td>
<td>7</td>
<td>7.0</td>
<td>2.35 (0.94 to 4.84)</td>
<td>.07</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10 656</td>
<td>5080.6</td>
<td>2.10 (2.06 to 2.14)</td>
<td>&lt;.001</td>
<td>1374.7</td>
</tr>
</tbody>
</table>

Abbreviations: EAR, excess absolute risk; SIR, standardized incidence ratio.

<sup>a</sup>Includes 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. Cancer types are listed in order of decreasing frequency.

[1] Includes non-infection-related malignancies presented in Table 3.

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posed. Risk was elevated for gastric cancer, caused by the bacterium *Helicobacter pylori*. Risk also was increased for certain malignancies without established links to infections. A few (eg, melanoma, plasma cell neoplasms including multiple myeloma and plasmacytomas) are increased in HIV-infected populations 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 (eg, colorectum, thyroid, and lip) that are not increased or occur much less often with HIV infection. The elevated risk of bladder cancer among transplant recipients (but not HIV-infected individuals)

### Table 3. Risk of Non-infection-Related Malignancies in US Transplant Recipients

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>No. of Cases</th>
<th>SIR (95% CI)</th>
<th>P Value</th>
<th>Incidence/100,000 Person-Years</th>
<th>EAR/100,000 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1344</td>
<td>682.8 1.97 (1.86 to 2.08)</td>
<td>&lt;.001</td>
<td>565.2 173.4</td>
<td>88.1 85.3 (76.2 to 94.8)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1039</td>
<td>1126.9 0.92 (0.87 to 0.98)</td>
<td>.009</td>
<td>134.0 145.4</td>
<td>−11.3 (−19.4 to −2.9)</td>
</tr>
<tr>
<td>Kidney</td>
<td>752</td>
<td>161.8 4.65 (4.32 to 4.90)</td>
<td>&lt;.001</td>
<td>97.0 20.9</td>
<td>76.1 (69.3 to 83.3)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>627</td>
<td>504.9 1.24 (1.15 to 1.34)</td>
<td>&lt;.001</td>
<td>80.9 65.1</td>
<td>15.8 (9.5 to 22.3)</td>
</tr>
<tr>
<td>Breast</td>
<td>481</td>
<td>567.9 0.85 (0.77 to 0.93)</td>
<td>&lt;.001</td>
<td>62.1 73.3</td>
<td>−11.2 (−16.6 to −5.4)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>381</td>
<td>160.3 2.39 (2.14 to 2.63)</td>
<td>&lt;.001</td>
<td>49.2 20.7</td>
<td>28.5 (23.7 to 33.7)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>238</td>
<td>80.8 2.95 (2.58 to 3.34)</td>
<td>&lt;.001</td>
<td>30.7 10.4</td>
<td>20.3 (16.5 to 24.4)</td>
</tr>
<tr>
<td>Uterine bladder</td>
<td>225</td>
<td>148.1 1.52 (1.33 to 1.73)</td>
<td>&lt;.001</td>
<td>29.0 19.1</td>
<td>9.9 (6.2 to 14.0)</td>
</tr>
<tr>
<td>Skin (nonmelanoma, nonepithelial)</td>
<td>184</td>
<td>13.3 13.85 (11.92 to 16.00)</td>
<td>&lt;.001</td>
<td>23.7 1.7</td>
<td>22.0 (18.7 to 25.7)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>157</td>
<td>107.3 1.46 (1.24 to 1.71)</td>
<td>&lt;.001</td>
<td>20.3 13.8</td>
<td>6.4 (3.4 to 9.8)</td>
</tr>
<tr>
<td>Lip</td>
<td>130</td>
<td>77.7 16.78 (14.02 to 19.92)</td>
<td>&lt;.001</td>
<td>16.8 1.0</td>
<td>15.8 (13.0 to 18.9)</td>
</tr>
<tr>
<td>Plasma cell neoplasms</td>
<td>118</td>
<td>64.3 1.84 (1.52 to 2.20)</td>
<td>&lt;.001</td>
<td>15.2 8.3</td>
<td>6.9 (4.3 to 9.9)</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>102</td>
<td>33.9 3.01 (2.45 to 3.65)</td>
<td>&lt;.001</td>
<td>13.2 4.4</td>
<td>8.8 (6.4 to 11.6)</td>
</tr>
<tr>
<td>Larynx</td>
<td>97</td>
<td>60.8 1.59 (1.29 to 1.95)</td>
<td>&lt;.001</td>
<td>12.5 7.8</td>
<td>4.7 (2.3 to 7.4)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>96</td>
<td>61.5 1.56 (1.26 to 1.91)</td>
<td>&lt;.001</td>
<td>12.4 7.9</td>
<td>4.4 (2.1 to 7.2)</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>94</td>
<td>109.3 0.86 (0.70 to 1.05)</td>
<td>.15</td>
<td>12.1 14.1</td>
<td>−2.0 (−4.3 to 0.7)</td>
</tr>
<tr>
<td>Soft tissue including heart</td>
<td>65</td>
<td>28.8 2.25 (1.74 to 2.87)</td>
<td>&lt;.001</td>
<td>8.4 3.7</td>
<td>4.7 (2.8 to 7.9)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>56</td>
<td>12.3 4.55 (3.44 to 5.91)</td>
<td>&lt;.001</td>
<td>7.2 1.6</td>
<td>5.6 (3.9 to 7.8)</td>
</tr>
<tr>
<td>Ovary</td>
<td>54</td>
<td>56.7 0.95 (0.72 to 1.24)</td>
<td>.79</td>
<td>7.0 7.3</td>
<td>−0.3 (−2.1 to 1.8)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>50</td>
<td>20.6 2.43 (1.80 to 3.20)</td>
<td>&lt;.001</td>
<td>6.5 2.7</td>
<td>3.8 (2.1 to 5.8)</td>
</tr>
<tr>
<td>Brain</td>
<td>45</td>
<td>59.6 0.76 (0.55 to 1.01)</td>
<td>.06</td>
<td>5.8 7.7</td>
<td>−1.9 (−3.5 to 0.1)</td>
</tr>
<tr>
<td>Testis</td>
<td>40</td>
<td>20.4 1.96 (1.40 to 2.67)</td>
<td>&lt;.001</td>
<td>5.2 2.6</td>
<td>2.5 (1.1 to 4.4)</td>
</tr>
<tr>
<td>Other biliary</td>
<td>39</td>
<td>15.9 2.45 (1.74 to 3.35)</td>
<td>&lt;.001</td>
<td>5.0 2.1</td>
<td>3.0 (1.5 to 4.8)</td>
</tr>
<tr>
<td>Intrahepatic bile duct</td>
<td>38</td>
<td>6.6 5.76 (4.08 to 7.91)</td>
<td>&lt;.001</td>
<td>4.9 0.9</td>
<td>4.1 (2.6 to 5.9)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>38</td>
<td>10.9 3.47 (2.46 to 4.77)</td>
<td>&lt;.001</td>
<td>4.9 1.4</td>
<td>3.5 (2.1 to 5.3)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>23</td>
<td>38.9 0.59 (0.38 to 0.89)</td>
<td>.008</td>
<td>3.0 5.0</td>
<td>−2.0 (−3.1 to −0.6)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>22</td>
<td>11.0 2.00 (1.25 to 3.02)</td>
<td>.005</td>
<td>2.8 1.4</td>
<td>1.4 (0.4 to 2.9)</td>
</tr>
<tr>
<td>Eye and orbit</td>
<td>21</td>
<td>7.6 2.78 (1.72 to 4.24)</td>
<td>&lt;.001</td>
<td>2.7 1.0</td>
<td>1.7 (0.7 to 3.2)</td>
</tr>
<tr>
<td>Renal pelvis</td>
<td>17</td>
<td>8.3 2.06 (1.20 to 3.29)</td>
<td>.01</td>
<td>2.2 1.1</td>
<td>1.1 (0.2 to 2.4)</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>17</td>
<td>8.2 2.06 (1.20 to 3.30)</td>
<td>.01</td>
<td>2.2 1.1</td>
<td>1.1 (0.2 to 2.4)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>15</td>
<td>11.5 1.30 (0.73 to 2.15)</td>
<td>.37</td>
<td>1.9 1.5</td>
<td>0.4 (−0.4 to 1.7)</td>
</tr>
<tr>
<td>Bones and joints</td>
<td>14</td>
<td>7.1 1.98 (1.09 to 3.30)</td>
<td>.03</td>
<td>1.8 0.9</td>
<td>0.9 (0.1 to 2.1)</td>
</tr>
<tr>
<td>Other acute leukemia</td>
<td>5</td>
<td>2.3 2.90 (0.71 to 5.13)</td>
<td>.16</td>
<td>0.6 0.3</td>
<td>0.4 (−0.1 to 1.2)</td>
</tr>
<tr>
<td>Acute monocytic leukemia</td>
<td>4</td>
<td>1.7 2.35 (0.64 to 6.01)</td>
<td>.19</td>
<td>0.5 0.2</td>
<td>0.3 (−0.1 to 1.1)</td>
</tr>
<tr>
<td>Miscellaneous specified malignancies</td>
<td>546</td>
<td>172.1 3.17 (2.91 to 3.45)</td>
<td>&lt;.001</td>
<td>70.4 22.2</td>
<td>48.2 (42.4 to 54.4)</td>
</tr>
<tr>
<td>Tumors with poorly specified histology</td>
<td>206</td>
<td>97.9 2.11 (1.83 to 2.41)</td>
<td>&lt;.001</td>
<td>26.6 12.6</td>
<td>14.0 (10.4 to 17.8)</td>
</tr>
</tbody>
</table>

**Total**: 10,656 508.6 2.10 (2.06 to 2.14) <.001 1374.7 655.4 719.3 (693.3 to 745.6)

Abbreviations: EAR, excess absolute risk; SIR, standardized incidence ratio.

*Includes 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. Cancer types are listed in order of decreasing frequency.

**Includes infection-related malignancies presented in Table 2.**
may be related to underlying medical conditions leading to transplantation (eg, analgesic nephropathy).18,19

Non-Hodgkin lymphoma was the most common malignancy in US transplant recipients. Among transplant recipients, non-Hodgkin lymphoma represents one extreme of EBV-driven proliferative disease (termed posttransplant lymphoproliferative disorder), which ranges from benign hyperplasia and infectious mononucleosis to lymphoid malignancy.20 The most common non-Hodgkin lymphoma subtype among both transplant recipients and HIV-infected individuals is diffuse large B-cell lymphoma, and most cases have detectable EBV in tumor cells.20,21 Bimodal onset of non-Hodgkin lymphoma and posttransplant lymphoproliferative disorder following organ transplantation (Figure 1) has been described previously,21,22 and risk factors differ somewhat for early-onset and late-onset posttransplant lymphoproliferative disorder, supporting etiological heterogeneity.23 Non-Hodgkin lymphoma risk was most pronounced among young transplant recipients, who are susceptible to primary EBV infection following transplantation.23-25 As reported previously,26 non-Hodgkin lymphoma 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 (eg, 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, liver, and heart recipients. However, 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

Table 4. Risk of Selected Cancers in Subgroups of Transplant Recipients

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Non-Hodgkin Lymphoma</th>
<th>Lung Cancer</th>
<th>Liver Cancer</th>
<th>Kidney Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed Cases</strong></td>
<td>Observed Incidence Rate/100 000 Person-Years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>994 (213.5)</td>
<td>890 (191.2)</td>
<td>739 (158.7)</td>
<td>547 (117.5)</td>
</tr>
<tr>
<td>Female</td>
<td>510 (164.7)</td>
<td>454 (146.6)</td>
<td>191 (61.7)</td>
<td>205 (66.2)</td>
</tr>
<tr>
<td>Age at transplant, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-34</td>
<td>412 (201.5)</td>
<td>10 (4.9)</td>
<td>27 (13.2)</td>
<td>57 (27.9)</td>
</tr>
<tr>
<td>35-49</td>
<td>395 (150.5)</td>
<td>243 (92.6)</td>
<td>216 (82.3)</td>
<td>298 (109.7)</td>
</tr>
<tr>
<td>≥50</td>
<td>697 (226.1)</td>
<td>1091 (353.9)</td>
<td>687 (222.9)</td>
<td>407 (132.0)</td>
</tr>
<tr>
<td>Transplanted organ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>635 (141.6)</td>
<td>517 (115.3)</td>
<td>48 (10.7)</td>
<td>565 (126.0)</td>
</tr>
<tr>
<td>Liver</td>
<td>365 (217.4)</td>
<td>300 (178.7)</td>
<td>831 (495.0)</td>
<td>67 (39.9)</td>
</tr>
<tr>
<td>Heart</td>
<td>267 (283.1)</td>
<td>364 (386.0)</td>
<td>13 (13.8)</td>
<td>85 (90.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>125 (532.7)</td>
<td>147 (626.4)</td>
<td>4 (17.0)</td>
<td>8 (34.1)</td>
</tr>
<tr>
<td><strong>Expected Cases</strong></td>
<td>Expected Incidence Rate/100 000 Person-Years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>139.7 (30.0)</td>
<td>488.2 (104.9)</td>
<td>68.6 (14.7)</td>
<td>124.5 (26.7)</td>
</tr>
<tr>
<td>Female</td>
<td>59.7 (19.3)</td>
<td>194.6 (62.8)</td>
<td>11.9 (8.8)</td>
<td>37.3 (12.3)</td>
</tr>
<tr>
<td>Age at transplant, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-34</td>
<td>9.0 (4.4)</td>
<td>3.8 (1.9)</td>
<td>1.0 (0.5)</td>
<td>3.4 (1.7)</td>
</tr>
<tr>
<td>35-49</td>
<td>44.5 (17.0)</td>
<td>88.6 (33.8)</td>
<td>17.9 (6.8)</td>
<td>34.3 (13.1)</td>
</tr>
<tr>
<td>≥50</td>
<td>145.9 (47.3)</td>
<td>590.4 (191.5)</td>
<td>61.6 (20.3)</td>
<td>124.0 (40.2)</td>
</tr>
<tr>
<td>Transplanted organ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>105.0 (23.4)</td>
<td>364.0 (78.9)</td>
<td>44.5 (6.9)</td>
<td>84.9 (18.9)</td>
</tr>
<tr>
<td>Liver</td>
<td>47.0 (28.0)</td>
<td>153.7 (91.6)</td>
<td>19.0 (11.3)</td>
<td>37.2 (22.2)</td>
</tr>
<tr>
<td>Heart</td>
<td>34.3 (36.3)</td>
<td>136.5 (144.8)</td>
<td>12.8 (13.5)</td>
<td>29.3 (31.3)</td>
</tr>
<tr>
<td>Lung</td>
<td>6.7 (28.4)</td>
<td>24.0 (102.1)</td>
<td>2.0 (8.4)</td>
<td>5.4 (22.9)</td>
</tr>
<tr>
<td><strong>Standardized Incidence Ratio (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7.11 (6.68-7.57)</td>
<td>1.82 (1.71-1.95)</td>
<td>10.78 (10.02-11.58)</td>
<td>4.99 (4.03-4.77)</td>
</tr>
<tr>
<td>Female</td>
<td>8.54 (7.82-9.32)</td>
<td>2.33 (2.12-2.56)</td>
<td>16.06 (13.86-18.50)</td>
<td>5.50 (4.77-6.30)</td>
</tr>
<tr>
<td>Age at transplant, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-34</td>
<td>45.86 (41.54-50.51)</td>
<td>2.62 (1.29-4.83)</td>
<td>27.55 (18.16-40.09)</td>
<td>16.63 (12.60-21.55)</td>
</tr>
<tr>
<td>35-49</td>
<td>8.87 (6.02-9.79)</td>
<td>2.74 (2.41-3.11)</td>
<td>12.09 (10.53-13.81)</td>
<td>8.39 (7.45-9.41)</td>
</tr>
<tr>
<td>≥50</td>
<td>4.78 (4.43-5.15)</td>
<td>1.85 (1.74-1.96)</td>
<td>11.15 (10.33-12.02)</td>
<td>3.28 (2.97-3.62)</td>
</tr>
<tr>
<td>Transplanted organ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>6.05 (5.59-6.54)</td>
<td>1.46 (1.34-1.59)</td>
<td>1.08 (0.80-1.43)</td>
<td>6.66 (6.12-7.23)</td>
</tr>
<tr>
<td>Liver</td>
<td>7.77 (6.90-8.61)</td>
<td>1.95 (1.74-2.19)</td>
<td>43.83 (40.90-46.91)</td>
<td>1.80 (1.40-2.29)</td>
</tr>
<tr>
<td>Heart</td>
<td>7.97 (6.89-8.79)</td>
<td>2.67 (2.40-2.95)</td>
<td>1.02 (0.54-1.74)</td>
<td>2.90 (2.32-3.59)</td>
</tr>
<tr>
<td>Lung</td>
<td>18.73 (15.59-22.32)</td>
<td>6.13 (5.18-7.21)</td>
<td>2.04 (0.56-5.22)</td>
<td>1.49 (0.64-2.94)</td>
</tr>
</tbody>
</table>

*Test of heterogeneity based on Poisson regression yielded P values of less than .001 for all of the comparisons in this category (eg, P<.001 for the comparison between male and female for non-Hodgkin lymphoma and cancers of the lung, liver, and kidney).

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Elevated risk of liver cancer was observed only among liver transplant recipients. The extraordinary risk in the first 6 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, and liver transplantation is an accepted therapy for localized liver cancer. 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 2-fold increase in liver cancer among liver recipients followed up for as long as 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).

The elevated risk of kidney cancer among kidney recipients is well described. Some early cases arise as a result of malignant transformation of cysts that develop in end-stage kidneys prior to transplantation. However, the elevated risk of late-onset kidney cancers, including those arising in recipients of other organs, is not readily explained. The recent UK study also found an elevated risk of kidney cancer among
recipients of other organs. 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 recipients of other organs. 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.

Strengths of the Transplant Cancer Match Study include its large size and (despite minor differences from the excluded recipients) representative sampling of the US transplant population. Inclusion of non-kidney recipients allowed comparison of cancer risk across transplanted organs. Our study was more than 4 times larger than the re-

Figure 3. Risk of Liver Cancer Following Transplantation

<table>
<thead>
<tr>
<th>Period Since Transplant, y</th>
<th>Standardized Incidence Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01-0.50</td>
<td></td>
</tr>
<tr>
<td>0.51-1.00</td>
<td></td>
</tr>
<tr>
<td>1.01-2.00</td>
<td></td>
</tr>
<tr>
<td>2.01-3.00</td>
<td></td>
</tr>
<tr>
<td>3.01-4.00</td>
<td></td>
</tr>
<tr>
<td>4.01-5.00</td>
<td></td>
</tr>
<tr>
<td>5.01-10.00</td>
<td></td>
</tr>
<tr>
<td>10.01-15.00</td>
<td></td>
</tr>
</tbody>
</table>

The corresponding expected cancer case counts are presented in the eTable at http://www.jama.com. Standardized incidence ratios (SIRs) are off-scale and therefore not presented for 0.01-0.50 years after transplantation, for all transplants combined (SIR, 126.11 [95% CI, 117.69-134.98]), and for liver transplants (SIR, 508.97 [95% CI, 474.16-545.66]). For some other estimates, the SIR was zero and cannot be shown on the log scale. When the SIR 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 the scale (95% upper CI: 49.64).

Figure 4. Risk of Kidney Cancer Following Transplantation

<table>
<thead>
<tr>
<th>Period Since Transplant, y</th>
<th>Standardized Incidence Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01-0.50</td>
<td></td>
</tr>
<tr>
<td>0.51-1.00</td>
<td></td>
</tr>
<tr>
<td>1.01-2.00</td>
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<td>2.01-3.00</td>
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<tr>
<td>3.01-4.00</td>
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<tr>
<td>4.01-5.00</td>
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<tr>
<td>5.01-10.00</td>
<td></td>
</tr>
<tr>
<td>10.01-15.00</td>
<td></td>
</tr>
</tbody>
</table>

The corresponding expected cancer case counts are presented in the eTable at http://www.jama.com. For some estimates, the standardized incidence ratio was zero and cannot be shown on the log scale. When the standardized incidence ratio was zero, the upper confidence limit is displayed. Also, for the estimate for lung transplants at 10.01-15.00 years after transplant, the upper limit is off the scale (95% upper CI: 32.73).
CANCER RISK AMONG US SOLID ORGAN TRANSPLANT RECIPIENTS

Analysis and interpretation of data: Engels, Pfeiffer, Fraumeni, Kasiske, Israni, Snyder, Wolfe, Goodrich, Bayakly, Clarke, Copeland, Finch, Fleissner, Goodman, Kahn, Koch, Lynch, Madeleine, Pavlish, Rao, Williams, Castanconi, Curry, Parsons, Fant, Lin.

Drafting of the manuscript: Engels.

Critical revision of the manuscript for important intellectual content: Pfeiffer, Fraumeni, Kasiske, Israni, Snyder, Wolfe, Goodrich, Bayakly, Clarke, Copeland, Finch, Fleissner, Goodman, Kahn, Koch, Lynch, Madeleine, Pavlish, Rao, Williams, Castanconi, Curry, Parsons, Fant, Lin.

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Study supervision: Engels, Fant, Lin.

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cent UK study,† 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.† 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 ensured largely complete ascertainment. However, because cancer data were not available for the entire United States, we could have missed cancers if recipients moved away from their state or region after their transplant. The 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 up 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 after their transplants. 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 posttransplant.

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 (eg, melanoma, cancers of the kidney or thyroid) because of heightened medical surveillance. 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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Author Contributions: Dr Engels had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Engels, Pfeiffer, Fraumeni, Wolfe, Fant, Lin.

Acquisition of data: Kasiske, Israni, Snyder, Wolfe, Goodrich, Bayakly, Clarke, Copeland, Finch, Fleissner, Goodman, Kahn, Koch, Lynch, Madeleine, Pavlish, Rao, Williams.

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