

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, 6291 liver transplants, 2333 heart transplants, and 1770 lung transplants.¹ Although transplant outcomes have improved dramatically over time, substantial

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=1504; 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=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=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 most elevated in lung recipients (SIR, 6.13 [95% CI, 5.18-7.21]) but also increased among other recipients (kidney: SIR, 1.46 [95% CI, 1.34-1.59]; liver: SIR, 1.95 [95% CI, 1.74-2.19]; and heart: SIR, 2.67 [95% CI, 2.40-2.95]). Liver cancer risk 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 a 2-fold excess risk for 10 to 15 years thereafter (SIR, 2.22 [95% CI, 1.57-3.04]). Among kidney recipients, kidney cancer risk was elevated (SIR, 6.66 [95% CI, 6.12-7.23]) and bimodal in onset time. Kidney cancer risk also was increased in liver recipients (SIR, 1.80 [95% CI, 1.40-2.29]) and heart recipients (SIR, 2.90 [95% CI, 2.32-3.59]).

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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morbidity results from chronic immunosuppressive therapy administered to prevent graft rejection.

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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.³⁻¹¹ 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 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,⁴ prior linkage studies of cancer following transplantation included 2000 to 11 000 recipients,^{3,5-9} 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.

During December 2008 through June 2010, we linked the SRTR with 13 US 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 can-

cer 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 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," with the exception of cancers of poorly specified histology that were considered separately because these could represent undiagnosed cases of posttransplant lymphoproliferative disorder; some rare categories were collapsed. 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 EBV); 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 cancer (*Helicobacter pylori*). In geographic areas outside the United States, biliary tract and bladder cancers are linked to parasites, but these were considered unrelated to infections for our analyses. For the purposes of presentation, other cancers were considered unrelated to infections, although evidence of variable strength supports links to infections for some additional subtypes (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 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 5-year intervals (0-4, 5-9, . . . , 80-84, and ≥ 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 US census population estimates. For Hispanics, we used cancer rates from SEER to calculate expected case counts. Because SEER data on Hispanics were available only beginning in 1992, we restricted the 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 the relative risk of cancer in transplant recipients compared with the general population, we calculated a standardized incidence ratio (SIR) for each cancer type (ie, 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 CIs for the SIR and EAR were derived using an exact method that assumes the observed counts follow a Poisson distribution.¹⁴ We focus on SIRs with an exact *P* value of less than .001 (Bonferroni correction for multiple comparisons 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 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 8 successive time intervals (1-180, 181-360, 361-720, 721-1080, 1081-1440, 1441-1800, 1801-3600, and 3601-5400 days after transplant; ie, 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, respectively, after transplant) for the overall cohort and subgroups defined by transplanted organ.

RESULTS

Transplant Recipients and Cancer Risk

We evaluated cancer risk in a cohort of 175 732 transplants (39.7% of the US total during 1987-2008). Recipients included in the study were similar 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 Islanders) 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

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 (non-melanoma, 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

($n=930$; 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).

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

	No. (%) of Transplant Recipients	
	Included (n = 175 732)	Excluded (n = 266 897)
Sex		
Male	107 027 (60.90)	164 473 (61.62)
Female	68 705 (39.10)	102 424 (38.38)
Age at transplant, y		
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)	6026 (2.26)
Other or unknown ^a	0	4326 (1.62)
Transplanted organ		
Kidney	102 654 (58.42)	161 002 (60.32)
Kidney and pancreas	6165 (3.51)	9607 (3.60)
Pancreas	1639 (0.93)	3631 (1.36)
Liver	37 888 (21.56)	50 894 (19.07)
Heart	17 593 (10.01)	26 860 (10.06)
Lung	7013 (3.99)	10 900 (4.08)
Heart and lung	388 (0.22)	563 (0.21)
Other or multiple	2392 (1.36)	3440 (1.29)
Transplant		
First	160 383 (91.27)	242 691 (90.93)
Second	14 079 (8.01)	21 863 (8.19)
\geq Third	1270 (0.72)	2343 (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)

^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 trans-

plant, 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.¹⁵

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 infection¹¹ 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.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 predis-

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

Cancer Site	No. of Cases		SIR (95% CI)	P Value	Incidence/100 000 Person-Years ^a		EAR/100 000 Person-Years (95% CI)
	Observed	Expected			Observed	Expected	
Non-Hodgkin lymphoma	1504	199.4	7.54 (7.17 to 7.93)	<.001	194.0	25.7	168.3 (158.6 to 178.4)
Nodal	831	136.6	6.08 (5.68 to 6.51)	<.001	107.2	17.6	89.6 (82.4 to 97.1)
Extranodal	673	62.8	10.72 (9.93 to 11.56)	<.001	86.8	8.1	78.7 (72.3 to 85.5)
Liver	930	80.5	11.56 (10.83 to 12.33)	<.001	120.0	10.4	109.6 (102.0 to 117.6)
Stomach	152	90.9	1.67 (1.42 to 1.96)	<.001	19.6	11.7	7.9 (4.9 to 11.3)
Kaposi sarcoma	120	2.0	61.46 (50.95 to 73.49)	<.001	15.5	0.3	15.2 (12.6 to 18.3)
Oropharynx including tonsil	106	52.8	2.01 (1.64 to 2.43)	<.001	13.7	6.8	6.9 (4.4 to 9.7)
Anus	90	15.4	5.84 (4.70 to 7.18)	<.001	11.6	2.0	9.6 (7.3 to 12.3)
Hodgkin lymphoma	85	23.7	3.58 (2.86 to 4.43)	<.001	11.0	3.1	7.9 (5.7 to 10.5)
Vulva	58	7.6	7.60 (5.77 to 9.83)	<.001	7.5	1.0	6.5 (4.7 to 8.7)
Cervix	45	43.6	1.03 (0.75 to 1.38)	.88	5.8	5.6	0.2 (-1.4 to 2.1)
Penis	22	5.3	4.13 (2.59 to 6.26)	<.001	2.8	0.7	2.2 (1.1 to 3.6)
Nasopharynx	8	8.3	0.96 (0.42 to 1.90)	>.99	1.0	1.1	0 (-0.6 to 1.0)
Vagina	7	3.0	2.35 (0.94 to 4.84)	.07	0.9	0.4	0.5 (0 to 1.5)
Total ^b	10 656	5080.6	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.

^aIncludes 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.

^bIncludes non-infection-related malignancies presented in Table 3.

posed.¹⁷ 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 includ-

ing multiple myeloma and plasmacytomas) are increased in HIV-infected populations¹¹ 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, trans-

plant recipients appear prone to several cancers (eg, 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)

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

Cancer Site	No. of Cases		SIR (95% CI)	P Value	Incidence/100 000 Person-Years ^a		EAR/100 000 Person-Years (95% CI)
	Observed	Expected			Observed	Expected	
Lung	1344	682.8	1.97 (1.86 to 2.08)	<.001	173.4	88.1	85.3 (76.2 to 94.8)
Prostate	1039	1126.9	0.92 (0.87 to 0.98)	.009	134.0	145.4	-11.3 (-19.4 to -2.9)
Kidney	752	161.8	4.65 (4.32 to 4.99)	<.001	97.0	20.9	76.1 (69.3 to 83.3)
Colorectum	627	504.9	1.24 (1.15 to 1.34)	<.001	80.9	65.1	15.8 (9.5 to 22.3)
Breast	481	567.9	0.85 (0.77 to 0.93)	<.001	62.1	73.3	-11.2 (-16.6 to -5.4)
Melanoma	381	160.3	2.38 (2.14 to 2.63)	<.001	49.2	20.7	28.5 (23.7 to 33.7)
Thyroid	238	80.8	2.95 (2.58 to 3.34)	<.001	30.7	10.4	20.3 (16.5 to 24.4)
Urinary bladder	225	148.1	1.52 (1.33 to 1.73)	<.001	29.0	19.1	9.9 (6.2 to 14.0)
Skin (nonmelanoma, nonepithelial)	184	13.3	13.85 (11.92 to 16.00)	<.001	23.7	1.7	22.0 (18.7 to 25.7)
Pancreas	157	107.3	1.46 (1.24 to 1.71)	<.001	20.3	13.8	6.4 (3.4 to 9.8)
Other oral cavity and pharynx	149	58.2	2.56 (2.17 to 3.01)	<.001	19.2	7.5	11.7 (8.8 to 15.1)
Lip	130	7.7	16.78 (14.02 to 19.92)	<.001	16.8	1.0	15.8 (13.0 to 18.9)
Plasma cell neoplasms	118	64.3	1.84 (1.52 to 2.20)	<.001	15.2	8.3	6.9 (4.3 to 9.9)
Acute myeloid leukemia	102	33.9	3.01 (2.45 to 3.65)	<.001	13.2	4.4	8.8 (6.4 to 11.6)
Larynx	97	60.8	1.59 (1.29 to 1.95)	<.001	12.5	7.8	4.7 (2.3 to 7.4)
Esophagus	96	61.5	1.56 (1.26 to 1.91)	<.001	12.4	7.9	4.4 (2.1 to 7.2)
Uterine corpus	94	109.3	0.86 (0.70 to 1.05)	.15	12.1	14.1	-2.0 (-4.3 to 0.7)
Soft tissue including heart	65	28.8	2.25 (1.74 to 2.87)	<.001	8.4	3.7	4.7 (2.8 to 7.0)
Salivary gland	56	12.3	4.55 (3.44 to 5.91)	<.001	7.2	1.6	5.6 (3.9 to 7.8)
Ovary	54	56.7	0.95 (0.72 to 1.24)	.79	7.0	7.3	-0.3 (-2.1 to 1.8)
Small intestine	50	20.6	2.43 (1.80 to 3.20)	<.001	6.5	2.7	3.8 (2.1 to 5.8)
Brain	45	59.6	0.76 (0.55 to 1.01)	.06	5.8	7.7	-1.9 (-3.5 to 0.1)
Testis	40	20.4	1.96 (1.40 to 2.67)	<.001	5.2	2.6	2.5 (1.1 to 4.4)
Other biliary	39	15.9	2.45 (1.74 to 3.35)	<.001	5.0	2.1	3.0 (1.5 to 4.8)
Intrahepatic bile duct	38	6.6	5.76 (4.08 to 7.91)	<.001	4.9	0.9	4.1 (2.6 to 5.9)
Chronic myeloid leukemia	38	10.9	3.47 (2.46 to 4.77)	<.001	4.9	1.4	3.5 (2.1 to 5.3)
Chronic lymphocytic leukemia	23	38.9	0.59 (0.38 to 0.89)	.008	3.0	5.0	-2.0 (-3.1 to -0.6)
Gallbladder	22	11.0	2.00 (1.25 to 3.02)	.005	2.8	1.4	1.4 (0.4 to 2.9)
Eye and orbit	21	7.6	2.78 (1.72 to 4.24)	<.001	2.7	1.0	1.7 (0.7 to 3.2)
Renal pelvis	17	8.3	2.05 (1.20 to 3.29)	.01	2.2	1.1	1.1 (0.2 to 2.4)
Acute lymphocytic leukemia	17	8.2	2.06 (1.20 to 3.30)	.01	2.2	1.1	1.1 (0.2 to 2.4)
Mesothelioma	15	11.5	1.30 (0.73 to 2.15)	.37	1.9	1.5	0.4 (-0.4 to 1.7)
Bones and joints	14	7.1	1.98 (1.09 to 3.33)	.03	1.8	0.9	0.9 (0.1 to 2.1)
Other acute leukemia	5	2.3	2.20 (0.71 to 5.13)	.16	0.6	0.3	0.4 (-0.1 to 1.2)
Acute monocytic leukemia	4	1.7	2.35 (0.64 to 6.01)	.19	0.5	0.2	0.3 (-0.1 to 1.1)
Miscellaneous specified malignancies	546	172.1	3.17 (2.91 to 3.45)	<.001	70.4	22.2	48.2 (42.4 to 54.4)
Tumors with poorly specified histology	206	97.9	2.11 (1.83 to 2.41)	<.001	26.6	12.6	14.0 (10.4 to 17.8)
Total ^b	10 656	5080.6	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.

^aIncludes 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.

^bIncludes 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

	Cancer Site			
	Non-Hodgkin Lymphoma	Lung Cancer	Liver Cancer	Kidney Cancer
Observed Cases (Observed Incidence Rate/100 000 Person-Years)				
Sex ^a				
Male	994 (213.5)	890 (191.2)	739 (158.7)	547 (117.5)
Female	510 (164.7)	454 (146.6)	191 (61.7)	205 (66.2)
Age at transplant, y ^a				
0-34	412 (201.5)	10 (4.9)	27 (13.2)	57 (27.9)
35-49	395 (150.5)	243 (92.6)	216 (82.3)	288 (109.7)
≥50	697 (226.1)	1091 (353.9)	687 (222.9)	407 (132.0)
Transplanted organ ^a				
Kidney	635 (141.6)	517 (115.3)	48 (10.7)	565 (126.0)
Liver	365 (217.4)	300 (178.7)	831 (495.0)	67 (39.9)
Heart	267 (283.1)	364 (386.0)	13 (13.8)	85 (90.1)
Lung	125 (532.7)	147 (626.4)	4 (17.0)	8 (34.1)
Expected Cases (Expected Incidence Rate/100 000 Person-Years)				
Sex				
Male	139.7 (30.0)	488.2 (104.9)	68.6 (14.7)	124.5 (26.7)
Female	59.7 (19.3)	194.6 (62.8)	11.9 (3.8)	37.3 (12.0)
Age at transplant, y				
0-34	9.0 (4.4)	3.8 (1.9)	1.0 (0.5)	3.4 (1.7)
35-49	44.5 (17.0)	88.6 (33.8)	17.9 (6.8)	34.3 (13.1)
≥50	145.9 (47.3)	590.4 (191.5)	61.6 (20.0)	124.0 (40.2)
Transplanted organ				
Kidney	105.0 (23.4)	354.0 (78.9)	44.5 (9.9)	84.9 (18.9)
Liver	47.0 (28.0)	153.7 (91.6)	19.0 (11.3)	37.2 (22.2)
Heart	34.3 (36.3)	136.5 (144.8)	12.8 (13.5)	29.3 (31.0)
Lung	6.7 (28.4)	24.0 (102.1)	2.0 (8.4)	5.4 (22.9)
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, y				
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)

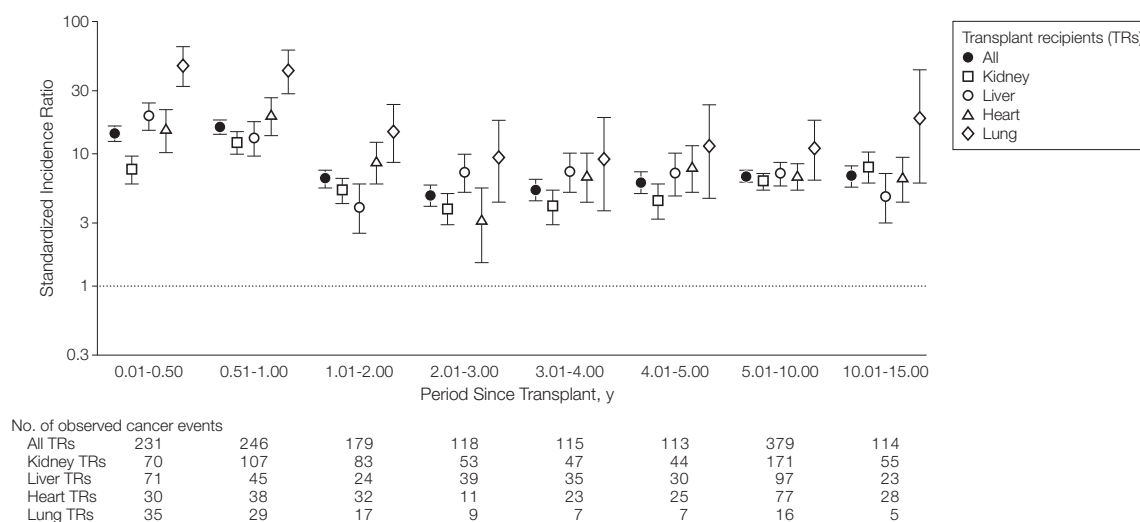
^aTest of heterogeneity based on Poisson regression yielded *P* values of less than .001 for all of the comparisons in this category (eg, *P* < .001 for the comparison between male and female for non-Hodgkin lymphoma and cancers of the lung, liver, and kidney).

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,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 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).³⁴

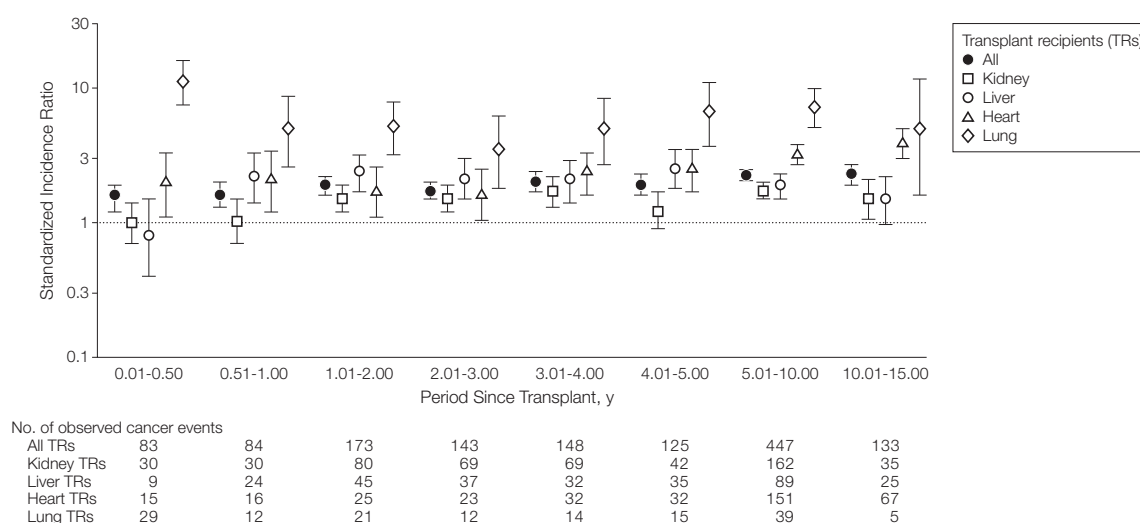
The elevated risk of kidney cancer among kidney recipients is well described.^{3-5,7-11} Some early cases arise as a result of malignant transformation of cysts that develop in end-stage kidneys prior to transplantation.^{35,36} However, the elevated risk of late-onset kidney cancers, including those arising in recipients of other organs, is not readily explained. The recent UK study also found an elevated risk of kidney cancer among

Figure 1. Risk of Non-Hodgkin Lymphoma Following Transplantation



The corresponding expected cancer case counts are presented in the eTable at <http://www.jama.com>.

Figure 2. Risk of Lung Cancer Following Transplantation



The corresponding expected cancer case counts are presented in the eTable at <http://www.jama.com>.

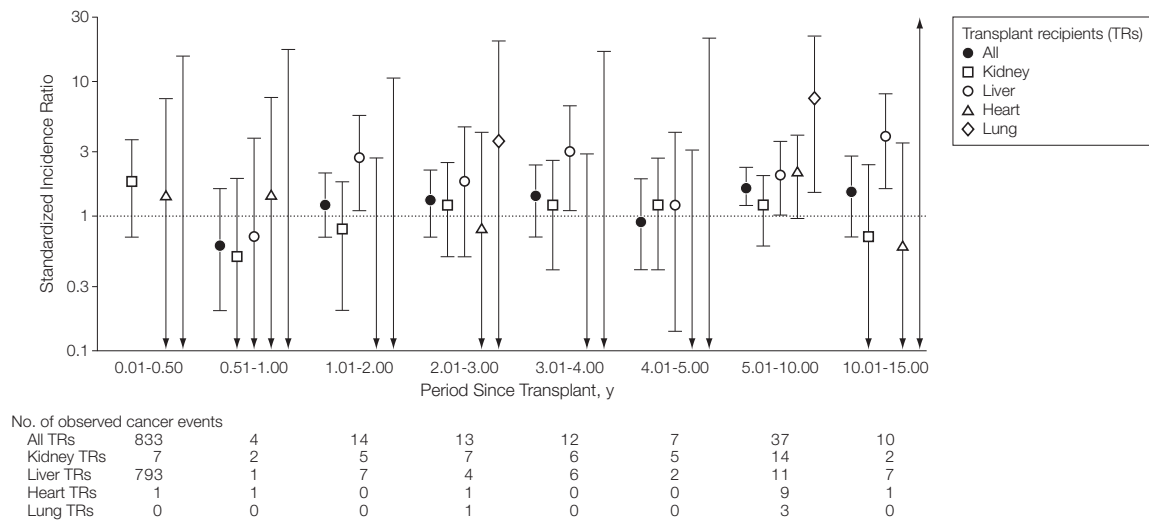
recipients of other organs.⁴ It is possible that nephrotoxic or directly carcinogenic effects of some immunosuppressive medications may contribute to cancers arising in the donor kidney (in kidney recipients) or the relatively normal kidneys in recipients of other or-

gans.^{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

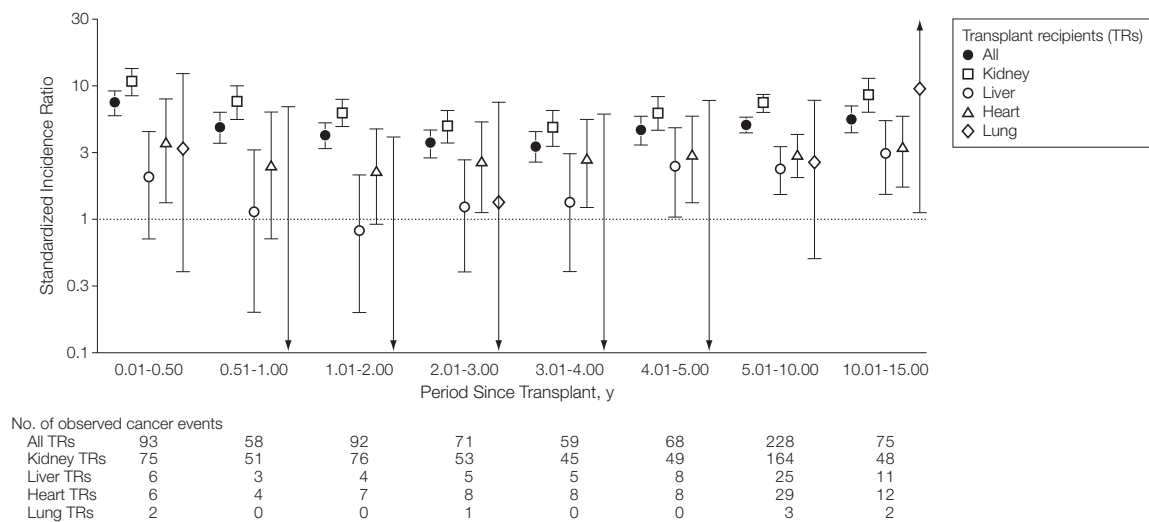
(despite minor differences from the excluded recipients) representative sampling of the US transplant population. Inclusion of non-kidney recipients allowed comparison of cancer risk across transplanted organs. Our study was more than 4 times larger than the re-

Figure 3. Risk of Liver Cancer Following Transplantation



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



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).

cent UK 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 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.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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