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Article

Risk of Rare Cancers Among Solid Organ Transplant Recipients

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Abstract

Background: Immunosuppressed solid organ transplant recipients (SOTRs) have elevated rates of certain rare cancers caused by viruses. Evaluating risk of rare cancers among SOTRs may provide etiological clues for additional cancers linked to poor immunity and viral infections. **Methods:** We performed a cohort study of 262 455 SOTRs (1987-2014) from the US SOTR registry linked to 17 population-based cancer registries. First cancers in SOTRs were categorized using an established classification scheme based on site and histology. Standardized incidence ratios (SIRs) compared risk in SOTRs with the general population. We used Poisson regression to calculate incidence rate ratios according to immune-related SOTR characteristics, including time since transplant (ie, duration of immunosuppression). All statistical tests were 2-sided. **Results:** We examined 694 distinct cancer subtypes, with 33 manifesting statistically significantly elevated SIRs (Bonferroni $P < 7.2 \times 10^{-5}$). All 33 are rare (incidence <6 per 100 000 person-years) and several have known viral etiology (eg, Merkel cell carcinoma: SIR = 24.7, 95% confidence interval [CI] = 20.8 to 29.1). Additional cancers that were increased include squamous cell carcinomas of the lip (SIR range = 18.3-19.8), eye and adnexa (SIR = 13.8, 95% CI = 7.9 to 22.3), salivary gland (SIR = 9.3, 95% CI = 6.1 to 13.5), and nasal cavity and sinuses (SIR = 4.5, 95% CI = 2.8 to 6.8); sebaceous adenocarcinoma (SIR = 34.3, 95% CI = 26.3 to 44.0); malignant fibrous histiocytoma (15.4); and subtypes of bladder, kidney, lung, and colon cancer (SIR range = 3.2-13.3). Incidence of several cancers increased over time since transplant ($P_{trend} < .05$), including squamous cell carcinomas of the lip, salivary gland, and anogenital sites. **Conclusions:** SOTRs experience elevated rates of several rare cancers. Because some of these cancers exhibit aggressive behavior with poor outcomes, it is important to further characterize the role of immunity and the potential involvement of oncogenic viruses to improve prevention and treatment.

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Several cancers caused by viruses, including Kaposi sarcoma (KS; caused by KS-associated herpesvirus) and Merkel cell carcinoma (MCC; caused by Merkel cell polyomavirus), are rare in the general population but overrepresented among immunosuppressed individuals (eg, individuals with HIV infection and solid organ transplant recipients [SOTRs]) (1–6). HIV causes immunosuppression through depletion of CD4+ T cells, whereas SOTRs are administered immunosuppressive medications to prevent rejection. In an immunocompetent person, oncogenic viruses are controlled or eliminated by the immune system, whereas immunity loss can allow persistent infection and genetic damage leading to cancer.

The greatly elevated incidence of KS and MCC in HIV-infected people pointed to their viral etiology and led to the discovery of the implicated viruses (2, 7, 8). Identification of additional rare cancers with such elevations is hampered by the difficulty in assembling suitably large immunosuppressed populations. Additionally, classification of cancers solely by the organ of origin can mask important etiological differences. Different cancer subtypes arising within an organ may be distinct disease entities, in which case grouping them would hamper discovery of risk factors for rare subtypes (eg, non-Hodgkin lymphoma subtypes) (9). We use the terms "cancer entity," "cancer subtype," and "rare cancer" interchangeably in this article, because the determination when a subtype is sufficiently distinct to be considered a separate biologic entity is ambiguous, and many cancer subtypes are rare.

Certain skin cancers, especially cutaneous squamous cell carcinoma (SCC), are substantially more elevated in SOTRs compared with both the general population as well as individuals

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with HIV (7, 8, 10). Notably, some SOTR medications are photosensitizing, potentially accelerating ultraviolet radiation (UVR) damage (11–13). Cutaneous SCC has an extremely high tumor mutational burden (14), and the excess risk in SOTRs may be a result of loss of immunosurveillance. Therefore, UVR exposure may be another mechanism by which some cancers are very elevated among SOTRs.

Immunocompromised SOTRs are an ideal population in which to identify overrepresented rare cancers that may be linked to poor immunity, viral infections, or UVR exposure. In this study, we systematically evaluated the risk of a large number of different cancers among SOTRs using a classification scheme that separately captures distinct cancer subtypes.

Methods

Data Source

We used data from the Transplant Cancer Match (TCM) Study (6), a linkage between the Scientific Registry of Transplant Recipients (SRTR) and multiple state and regional cancer registries. The SRTR contains information from all US SOTRs since 1987, including demographic data, transplant characteristics, and initial immunosuppressive regimen. We used data from 17 linked cancer registries to identify cancer cases in SOTRs during 1987-2014.

Cancer Classification

All first invasive cancers in participating TCM cancer registries were categorized using the classification scheme described by Gatta et al. (15). That study used data from a European consortium of 80 cancer registries and included more than 9 million cancer cases. All cancers in that study were classified by experts into a hierarchical 3-level classification scheme based on site and histology. Level-3 cancers are site-histology combinations that the World Health Organization classifies as distinct cancer subtypes (eg, mucinous adenocarcinoma of the lung). Level-2 cancers are collections of level-3 cancers sharing similar clinical treatment and research profiles (eg, lung adenocarcinoma). Level-1 cancers are grouped level-2 cancers considered to require similar clinical expertise (eg, lung carcinoma). Many level-3 cancers and some level-2 and level-1 cancers are considered rare in the general population (incidence <6 per 100 000 person-years) (15).

We classified cancers in TCM cancer registries using the most specific classification level to which the cancer could be categorized, resulting in consideration of 694 entities. As an initial screen, we selected those classified cancers for which there were at least 5 cases matched to SOTRs in the SRTR and where at least 0.18% of cases occurred among SOTRs. This threshold was chosen because SOTRs contributed 0.034% of person-time in the general population of areas covered by TCM cancer registries, so that a prevalence of 0.034% × 5 = 0.18% of prior transplantation among cancer cases corresponded to an approximately fivefold elevated risk. We excluded KS and hematologic malignancies because their associations with immunosuppression in SOTRs have been studied (3, 4, 6, 16, 17). We could not examine basal cell and squamous cell skin cancers because they are not captured by cancer registries.

Statistical Analysis

For these initially selected cancers, we calculated standardized incidence ratios (SIRs) as the observed number of cases in the TCM SOTR population divided by the expected number. For the expected number, we applied cancer incidence rates from the general population to the transplant cohort, stratified by sex, age in 5-year intervals, race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian), calendar year, and cancer registry. We considered only first reported cancers.

For SIR and incidence rate calculations, follow-up of SOTRs began at the latest of transplantation or start of cancer registry coverage. Before the 2001 publication of the World Health Organization International Classification of Diseases for Oncology, Third Edition (18), some histologies were not considered malignant, and therefore tumors with those histologies were not reported before 2001. For cancers specified by those histology codes, follow-up began at the earliest of transplantation or January 1, 2001. Follow-up ended at the earliest of death, organ failure or retransplant, loss to follow-up, or the last date of cancer registry coverage. Transplant recipients with HIV and follow-up in Hispanics before 1992 (when expected counts were unavailable) were further excluded. For liver cancer, we excluded follow-up occurring less than 90 days after a liver transplant because liver cancer is an indication for a liver transplant, and liver cancers observed shortly after liver transplantation may reflect an incorrect diagnosis date. We identified cancers for which the SIR was statistically significantly different from 1.00, using a 2-sided Bonferroni P value of .05/N, where N = 694 was the number of initially screened entities. We also calculated excess absolute risk, which is defined as the difference between the observed and expected incidence.

If immunosuppression explains the excess cancer risk in SOTRs, the incidence of these cancers could vary by factors related to the intensity or duration of immunosuppression, including transplanted organ, time since transplantation, and whether induction immunosuppression therapy was used. Immunosuppression therapy is most intensive for lung and heart transplants compared with other transplanted organs. Immunosuppression is greatest immediately following transplantation, so assessment of risk in relation to time since transplantation can distinguish between effects of intensive short-term vs lower level long-term immunosuppression. Induction therapy, which occurs immediately after transplantation, causes intense immunosuppression for 1-2 years, but because it decreases the need for later antirejection therapy, individuals who receive induction may require less intensive long-term immunosuppression. For cancers with statistically significantly elevated SIRs and at least 15 cases in the transplant population, we used Poisson regression to calculate unadjusted incidence rate ratios (IRRs) comparing incidence among SOTRs according to transplanted organ, receipt of induction therapy, and time since transplantation. Poisson models with a likelihood ratio test were used to calculate P_{trend} values for time since transplantation. All statistical tests were 2-sided, and a P less than .05 was considered statistically significant. Time since transplantation was coded as the following: 0-1.9 years = 1; 2-4.9 years = 2; 5-9.9 years = 3; 10+ years = 4.

Results

There were a total of 15 462 031 first cancer cases identified in TCM cancer registries, which we categorized into 770 uniquely specified cancer entities, 76 of which were KS or hematological

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malignancies. Of the remaining 694 categories, 485 were level-3, 164 were level-2, and 45 were level-1 cancers. Fifty-four of these cancer entities had at least 5 cases diagnosed in SOTRs and approximately 5-fold or higher elevated risk in SOTRs (Supplemental Table 1, available online).

We evaluated risk of these cancers in a cohort of 262 455 SOTRs followed for 1 393 047 person-years during 1987-2014. The median age at transplantation was 48 years and 60.8% of SOTRs were male. The most commonly transplanted organ was the kidney (61.9%), followed by liver (16.6%) and heart and/or lung (15.5%), and 48.0% received induction therapy.

Of the 54 cancer entities that were considered, 33 showed SIRs in SOTRs that were statistically significantly elevated ($P < .05/694$ or 7.2×10^{-5}) (Table 1). Most of these entities were of epithelial origin, although a few were sarcomas or neuroendocrine tumors. Renal cell carcinomas (RCCs) of the kidney were the most common cases, specifically including clear cell (n = 379), papillary (n = 324), and renal cell adenocarcinomas (n = 396). Other frequent cancers in SOTRs included MCC (n = 140) and SCCs of the lip (n = 192), oropharynx (n = 161), and anal canal (n = 122). All 33 cancer entities are considered rare cancers in the Gatta classification.

As shown in Table 1, the strongest elevations were observed for sebaceous adenocarcinoma (SIR = 34.3, 95% confidence interval [CI] = 26.3 to 44.0) and malignant nodular hidradenoma (SIR = 20.4, 95% CI = 8.20 to 42.0), which are both adnexal carcinomas of the skin; MCC (SIR = 24.7, 95% CI = 20.8 to 29.1); and leiomyosarcoma of the head and neck (SIR = 26.5, 95% CI = 13.7 to 46.4). Other strong associations (SIRs in the 10-19 range) were observed for SCCs of the lip, anal canal, and eye and adnexa; malignant fibrous histiocytoma of the head and neck; sclerosing sweat duct adnexal carcinoma of the skin; micropapillary transitional cell carcinoma and signet ring cell adenocarcinoma of the bladder; and papillary adenocarcinoma and collecting duct carcinoma of kidney. More modest associations (SIRs = 2.2-10) were observed for specific cancers of the salivary gland (SCC and mucoepidermoid carcinoma), oropharynx (SCC), colon (signet ring cell adenocarcinoma), nasal cavity and sinuses (SCC), lung (mucinous and papillary adenocarcinomas), bladder (adenocarcinoma not otherwise specified [NOS]), nonmelanoma skin (adnexal carcinoma NOS, soft tissue sarcoma), breast (in males), vulva and vagina (SCC), penis (SCC), kidney (renal cell adenocarcinoma, RCC chromophobe type), endocrine organs (well-differentiated carcinoid), and intrahepatic bile tract (cholangiocarcinoma). Because SIRs were very large, excess absolute risks were close to the observed incidence rates (Table 1).

Of the 33 cancer entities listed in Table 1, 25 had at least 15 cases identified in SOTRs and were assessed in additional analyses. As shown in Table 2, compared with recipients of other organs, those receiving heart and/or lung transplants experienced particularly elevated risks of SCC of the nasal cavity and sinuses (IRR = 4.0, 95% CI = 1.7 to 9.5) and soft tissue sarcomas of the skin (IRR = 4.1, 95% CI = 2.4 to 7.1). Heart and/or lung recipients also experienced higher incidence of SCCs of the lip or salivary gland and adnexal skin cancers (NOS and sebaceous adenocarcinoma). In contrast, a lower incidence of clear cell adenocarcinoma of the kidney occurred among heart and/or lung recipients compared with those receiving other organs.

As shown in Table 3, receipt of induction therapy was associated with a 1.5- to 3-fold increased risk of RCC subtypes (papillary adenocarcinoma: IRR = 2.0, 95% CI = 1.6 to 2.5; clear cell adenocarcinoma: IRR = 1.7, 95% CI = 1.4 to 2.1), sebaceous adenocarcinoma (IRR = 1.9, 95% CI = 1.1 to 3.1), and cholangiocarcinoma of the intrahepatic bile duct (IRR = 2.9, 95% CI = 1.4 to 6.0). In contrast, individuals receiving induction therapy experienced lower incidence of SCCs of the lip, anal canal, and nasal cavity or sinuses.

Incidence increased over time since transplant for several cancers ($P_{trend} < .05$; Table 4), including SCCs of the lip, salivary gland, anal canal, and vulva or vagina, with rates of salivary gland SCC increasing especially sharply ($P_{trend} < .001$). Incidence of nasal cavity and sinus SCC increased initially but then stabilized, whereas incidence of papillary adenocarcinoma of the kidney and well-differentiated endocrine carcinoid tumors only began increasing more than 5 years after transplantation. Incidence of sebaceous adenocarcinoma and MCC increased steadily over time since transplant.

Discussion

In this study, we systematically identified specific cancer entities that were elevated among SOTRs using a detailed classification hierarchy that incorporated information on cancer site and histology. Thirty-three cancer entities were statistically significantly increased, all of which are considered rare in the general population (incidence <6 per 100 000 person-years) (15). In addition to some novel findings, we replicated established associations with immunosuppression, lending support to this approach. For example, cancers of the oropharynx, anus, vulva or vagina, and penis, which showed elevated SIRs in our transplant population, are also elevated among HIV-infected people and are known to be caused by human papillomavirus (HPV) (4, 5, 19). Our findings support a role for immunosuppression and oncogenic viruses in the etiology of certain rare cancers.

Of the 33 cancer entities that were elevated in transplant recipients, the strongest increases (SIRs in the 13-34 range) were observed for sebaceous adenocarcinoma (a subtype of adnexal skin cancer), SCCs of the lip and eye and adnexa (including the conjunctiva), leiomyosarcoma of the head and neck, malignant fibrous histiocytoma sarcoma of the head and neck, and MCC. Increased risk for each of these has also been observed in HIV-infected individuals (20–23), and some of these associations were identified in a prior assessment of histologically defined cancers among HIV-infected people (20). MCC is caused by Merkel cell polyomavirus, and many leiomyosarcomas arising in immunosuppressed individuals are Epstein-Barr virus positive (23–26). Although our initial finding was for leiomyosarcoma of the head and neck, SOTRs in our study also had elevated incidence for leiomyosarcomas at other sites, albeit substantially attenuated (N = 29, SIR = 1.7, 95% CI = 1.2 to 2.5). There is limited evidence that some HPV types may contribute to sebaceous carcinoma and SCCs of the lip and conjunctiva (27–31).

Except for SCC of the conjunctiva, all of the cancers mentioned in the previous paragraph manifest more strongly increased risk in our transplant population than reported previously for HIV. This observation suggests that additional etiologic factors contribute to these malignancies among SOTRs. Notably, the aforementioned cancers (like cutaneous SCC) develop on sunlight-exposed tissues, and UVR is etiologically important for SCC of the lip and conjunctiva, sebaceous adenocarcinoma, and MCC. Risks of lip SCC and MCC are increased in association with cyclosporine or azathioprine maintenance therapy among SOTRs (32–34). Both medications are classified as carcinogens by the International Agency for Research on Cancer (35), and azathioprine is photosensitizing and causes DNA damage with UVR exposure (12, 13). Sebaceous

Table 1. SIRs for cancer subtypes that occur at increased incidence among transplant recipients[a]

Cancer type, grouped by organ (Gatta classification level)	Observed cases	SIR (95% CI)	Observed incidence[b]	EAR[b]
Oral cavity or pharynx				
Lip, SCC with variants of lip (2)[a]	29	19.79 (13.26 to 28.43)	2.08	1.98
Lip, SCC with variants of lip, SCC (3)[a]	163	18.30 (15.60 to 21.33)	11.71	11.07
Salivary gland, epithelial tumors, mucoepidermoid carcinoma (3)[a]	18	4.32 (2.56 to 6.82)	1.29	0.99
Salivary gland, epithelial tumors, SCC (3)[a]	27	9.25 (6.09 to 13.45)	1.94	1.73
Oropharynx, SCC with variants, SCC (3)[a]	161	2.23 (1.90 to 2.60)	11.56	6.38
Digestive system				
Colorectum, adenocarcinoma, signet ring cell carcinoma (3)[a]	31	4.45 (3.02 to 6.31)	2.23	1.73
Anal canal, SCC with variants (2)[a]	117	6.10 (5.05 to 7.32)	8.40	7.03
Anal canal, SCC with variants, verrucous carcinoma (3)[a]	5	18.76 (6.09 to 43.78)	0.36	0.34
Liver and IBT, cholangiocarcinoma of IBT (2)[a]	33	2.63 (1.81 to 3.69)	2.37	1.47
Respiratory system				
Nasal cavity and sinuses, SCC with variants, SCC (3)[a]	21	4.47 (2.76 to 6.83)	1.51	1.17
Lung, adenocarcinoma, mucinous adenocarcinoma (3)[a]	21	3.21(1.99 to 4.91)	1.51	1.04
Lung, adenocarcinoma, papillary adenocarcinoma NOS (3)[a]	19	3.55 (2.14 to 5.54)	1.36	0.98
Soft tissue sarcoma				
Sarcoma of head and neck, leiomyosarcoma (3)[a]	12	26.54 (13.71 to 46.36)	0.86	0.83
Sarcoma of head and neck, malignant fibrous histiocytoma (3)[a]	8	15.41 (6.65 to 30.36)	0.57	0.54
Nonmelanoma skin cancer				
Adnexal carcinoma of skin (1)[a]	15	9.76 (5.46 to 16.10)	1.08	0.97
Adnexal carcinoma of skin, malignant nodular hidradenoma (3)[a]	7	20.39 (8.20 to 42.01)	0.50	0.48
Adnexal carcinoma of skin, sclerosing sweat duct carcinoma (3)[a]	6	13.39 (4.91 to 29.14)	0.43	0.40
Adnexal carcinoma of skin, sebaceous adenocarcinoma (3)[a]	62	34.34 (26.33 to 44.02)	4.45	4.32
NET, endocrine carcinoma, MCC (3)[a]	140	24.67 (20.75 to 29.11)	10.06	9.65
Soft tissue sarcoma (2)[a]	53	6.46 (4.84 to 8.45)	3.81	3.22
Breast, male[c]	30	2.35 (1.59 to 3.36)	2.15	2.06
Genital system[c]				
Vulva and vagina, SCC with variants (2)[a]	79	6.76 (5.35 to 8.42)	14.21	12.11
Penis, SCC with variants, SCC (3)[a]	21	3.53 (2.18 to 5.39)	2.51	1.80
Urinary system				
Bladder, adenocarcinoma with variants (2)	15	6.17 (3.45 to 10.18)	1.08	1.50
Bladder, adenocarcinoma, signet ring cell carcinoma (3)	6	10.59 (3.89 to 23.05)	0.43	0.65
Bladder, TCC, TCC micropapillary (3)	7	14.18 (5.70 to 29.22)	0.50	0.78
Kidney, RCC, clear cell adenocarcinoma NOS (3)	379	3.78 (3.41 to 4.19)	27.22	33.34
Kidney, RCC, collecting duct carcinoma (3)	6	10.33 (3.79 to 22.48)	0.43	0.65
Kidney, RCC, papillary adenocarcinoma NOS (3)	324	13.30 (11.89 to 14.83)	23.27	35.83
Kidney, RCC, renal cell adenocarcinoma (3)	396	3.65 (3.30 to 4.03)	28.44	34.39
Kidney, RCC, RCC chromophobe type (3)	25	2.90 (1.87 to 4.28)	1.80	1.96
Eye and adnexa, SCC with variants, squamous carcinoma (3)[a]	16	13.75 (7.86 to 22.32)	1.15	1.77
NET, well-differentiated endocrine tumors: carcinoid (2)[a]	28	2.40 (1.59 to 3.46)	2.01	1.95

[a]Cancer incidence rates for expected counts were stratified by sex, age in 5-year intervals, race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian), calendar year, and cancer registry. CI = confidence interval; EAR = excess absolute risk; IBT = intrahepatic bile tract; MCC = Merkel cell carcinoma; NET = neuroendocrine tumor; NOS = not otherwise specified; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SIR = standardized incidence ratio; TCC = transitional cell carcinoma.

[b]Observed incidence rates and EARs are per 100 000 person-years. These estimates are restricted to men for breast and penile cancers and women for cancer of the vulva and vagina. There were 1 392 320 person-years in the total cohort, including 836 327 for men and 555 993 for women.

[c]Sex-specific incidence and EAR were calculated.

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adenocarcinoma is a component of the Muir-Torre syndrome, a variant of Lynch syndrome caused by germline mismatch repair gene defects (36), and mismatch repair–deficient cells may be especially prone to genetic damage caused by azathioprine (37).

Additional associations were observed for 3 bladder cancer subtypes and SCCs of the salivary gland and nasal cavity and sinuses. Emerging evidence suggests that BK polyomavirus causes a proportion of bladder cancers in SOTRs (38). The SIRs that we estimated for the 3 bladder cancer subtypes (6-fold to 14-fold elevations) were stronger than previously reported for bladder cancer overall (typically in the 1.5-3.3 range) (4, 6), perhaps because of the added specificity gained by focusing on these subtypes. HPV may contribute to a subset of nasal cavity and sinus cancers (39–41). Limited evidence supports an etiologic contribution of Epstein-Barr virus for salivary gland SCC (42). Alternatively, salivary gland SCCs may represent misdiagnosed cases of cutaneous SCCs arising on the face (43), which occur at markedly increased incidence and are highly invasive in SOTRs (44).

Risks of RCC and colorectal cancer are elevated SOTRs (4, 6), and our findings for specific subtypes are therefore expected. These cancers are not increased in HIV-infected people (4, 5), arguing that nonimmunologic factors are important. The risk of clear cell adenocarcinoma of the kidney was lower among heart and lung recipients, which is consistent with kidney cancers arising in kidney recipients as a result of end-stage renal

Table 2. Associations between transplanted organ and cancer incidence among transplant recipients[a]

Cancer type	Other transplanted organs (reference) No. (IR)	Heart and/or lung transplants No. (IR)	IRR (95% CI)	P[b]
Oral cavity or pharynx				
Lip, SCC with variants of lip	110 (9.4)	53 (24.2)	2.6 (1.9 to 3.6)	<.001
Lip, SCC with variants of lip, SCC	17 (1.5)	12 (5.5)	3.8 (1.8 to 7.9)	.001
Salivary gland, epithelial tumors, mucoepidermoid carcinoma	16 (1.4)	2 (0.9)	0.7 (0.2 to 2.9)	.57
Salivary gland, epithelial tumors, SCC	18 (1.5)	9 (4.1)	2.7 (1.2 to 6.0)	.02
Oropharynx, SCC with variants, SCC	134 (11.4)	27 (12.3)	1.1 (0.7 to 1.6)	.72
Digestive system				
Colon, adenocarcinoma, signet ring cell carcinoma	22 (1.9)	9 (4.1)	2.2 (1.0 to 4.8)	.06
Anal canal, SCC with variants	92 (7.8)	25 (11.4)	1.5 (0.9 to 2.3)	.11
Liver and IBT, cholangiocarcinoma of IBT	28 (2.4)	5 (2.3)	1.0 (0.4 to 2.5)	.93
Respiratory system				
Nasal cavity and sinuses, SCC with variants, SCC	12 (1.0)	9 (4.1)	4.0 (1.7 to 9.5)	.003
Lung, adenocarcinoma, mucinous adenocarcinoma	15 (1.3)	6 (2.7)	2.1 (0.8 to 5.5)	.14
Lung, adenocarcinoma, papillary adenocarcinoma NOS	13 (1.1)	6 (2.7)	2.5 (0.9 to 6.5)	.09
Nonmelanoma skin cancer				
Adnexal carcinoma of skin	10 (0.9)	5 (2.3)	2.7 (0.9 to 7.8)	.09
Adnexal carcinoma of skin, sebaceous adenocarcinoma	45 (3.8)	17 (7.8)	2.0 (1.2 to 3.5)	.02
NET, endocrine carcinoma, MCC	113 (9.6)	27 (12.3)	1.3 (0.8 to 2.0)	.26
Soft tissue sarcoma	30 (2.6)	23 (10.5)	4.1 (2.4 to 7.1)	<.001
Breast, male	24 (2.1)	6 (2.7)	1.3 (0.6 to 3.3)	.53
Genital system				
Vulva and vagina, SCC with variants	67 (5.7)	12 (5.5)	1.0 (0.5 to 1.8)	.89
Penis, SCC with variants, SCC	17 (1.5)	4 (1.8)	1.3 (0.4 to 2.4)	.68
Urinary system				
Bladder, adenocarcinoma with variants	14 (1.2)	1 (0.5)	0.4 (0.1 to 2.9)	.28
Kidney, RCC, clear cell adenocarcinoma NOS	339 (28.9)	40 (18.3)	0.6 (0.5 to 0.9)	.004
Kidney, RCC, papillary adenocarcinoma NOS	282 (24.0)	42 (19.2)	0.8 (0.6 to 1.1)	.16
Kidney, RCC, renal cell adenocarcinoma	331 (28.2)	65 (29.7)	1.1 (0.8 to 1.4)	.71
Kidney, RCC, RCC chromophobe type	22 (1.9)	3 (1.4)	0.7 (0.2 to 2.4)	.60
Eye and adnexa, SCC with variants, squamous carcinoma	13 (1.1)	3 (1.4)	1.2 (0.4 to 4.3)	.75
NET, well-differentiated endocrine tumors: carcinoid	21 (1.8)	7 (3.2)	1.8 (0.8 to 4.2)	.26

[a]Only cancer types with at least 15 cases in the transplant group were evaluated. CI = confidence interval; IBT = intrahepatic bile tract; IR = incidence rate; IRR = incidence rate ratio; MCC = Merkel cell carcinoma; NET = neuroendocrine tumor; NOS = not otherwise specified; RCC = renal cell carcinoma; SCC = squamous cell carcinoma.
[b]P values were based on a Wald test and were 2-sided.

disease in the native kidneys (45). We observed increased risk for signet cell carcinoma of the colorectum. JC polyomavirus may contribute to the etiology of some colon cancers, but evidence is sparse (46, 47). Additionally, primary sclerosing cholangitis and cystic fibrosis, which cause end-stage organ disease and are indications for liver and lung transplantation, respectively, are strong risk factors for colorectal cancer in SOTRs (48).

Lung cancer risk was elevated to a similar magnitude as described in HIV-infected persons (4, 5). We speculate that immunosuppression increases the risk of pneumonia and promotes chronic inflammation and lung damage (49). The increased risk of male breast cancer that we observed may be a spurious association attributable to increased medical engagement of SOTRs relative to the general population.

Our additional analyses support a role of immunosuppression in some cancers. Increasing cancer incidence with prolonged time since transplantation highlights the importance of chronic immunosuppression for some cancers. The risk of anal cancer increased over time since transplant, which, interestingly, corresponds to the prior observation in HIV-infected people that there is a 6- to 7-year lag in the effects of immunosuppression on anal cancer incidence (50, 51). MCC, SCC of the lip, and sebaceous carcinoma also increased steadily in incidence over time, consistent with cumulative damage from UVR and, potentially, a synergistic interaction with immunosuppression or other medication effects. Heart and lung recipients had markedly increased rates of SCC of the nasal cavity and sinuses and soft tissue sarcomas of the skin compared with other SOTRs, suggesting that intensity of immunosuppression is important in their development. Induction therapy was associated with decreased risk of SCCs of the lip and anal canal. Induction therapy often results in less organ rejection treatment after transplant and thus lower long-term immunosuppression, so these observations are consistent with our findings that the risk of both cancers increased over time since transplant.

Our study has several strengths, including its large size and population-based ascertainment of cancer. The linkage of cancer registries to the US transplant registry enabled us to identify rare cancers that may be attributable to immunosuppression. We systematically and agnostically evaluated a large number of cancer entities with a classification scheme previously used to assess rare cancers in Europe (15). We identified cancers with known elevations in SOTRs and HIV-infected people, supporting

Table 3. Associations between receipt of induction therapy and cancer incidence among transplant recipients[a]

Cancer type	No induction (reference)	Induction therapy		
	No. (IR)	No. (IR)	IRR (95% CI)	P[b]
Oral cavity or pharynx				
Lip, SCC with variants of lip	22 (2.7)	7 (1.2)	0.5 (0.2 to 1.1)	.06
Lip, SCC with variants of lip, SCC	117 (14.2)	46 (8.1)	0.6 (0.4 to 0.8)	.001
Salivary gland, epithelial tumors, mucoepidermoid carcinoma	9 (1.1)	9 (1.6)	1.5 (0.6 to 3.7)	.43
Salivary gland, epithelial tumors, SCC	18 (2.2)	9 (1.6)	0.7 (0.3 to 1.6)	.42
Oropharynx, SCC with variants, SCC	102 (12.4)	59 (10.4)	0.8 (0.6 to 1.2)	.27
Digestive system				
Colon, adenocarcinoma, signet ring cell carcinoma	20 (2.4)	11 (1.9)	0.8 (0.4 to 1.7)	.54
Anal canal, SCC with variants	81 (9.8)	36 (6.3)	0.6 (0.4 to 1.0)	.02
Liver and IBT, cholangiocarcinoma of IBT	11 (1.3)	22 (3.9)	2.9 (1.4 to 6.0)	.003
Respiratory system				
Nasal cavity and sinuses, SCC with variants, SCC	17 (2.1)	4 (0.7)	0.3 (0.1 to 1.0)	.03
Lung, adenocarcinoma, mucinous adenocarcinoma	9 (1.1)	12 (2.1)	1.9 (0.8 to 4.6)	.13
Lung, adenocarcinoma, papillary adenocarcinoma NOS	11 (1.3)	8 (1.4)	1.1 (0.4 to 2.6)	.91
Nonmelanoma skin cancer				
Adnexal carcinoma of skin	10 (1.2)	5 (0.9)	0.7 (0.3 to 2.1)	.55
Adnexal carcinoma of skin, sebaceous adenocarcinoma	27 (3.3)	35 (6.2)	1.9 (1.1 to 3.1)	.01
NET, endocrine carcinoma, MCC	87 (10.6)	53 (9.3)	0.9 (0.6 to 1.2)	.47
Soft tissue sarcoma	32 (3.9)	21 (3.7)	1.0 (0.6 to 1.7)	.86
Breast, male	20 (2.4)	10 (1.8)	0.7 (0.3 to 1.6)	.40
Genital system				
Vulva and vagina, SCC with variants	47 (5.7)	32 (5.6)	1.0 (0.6 to 1.5)	.95
Penis, SCC with variants, SCC	14 (1.7)	7 (1.2)	0.7 (0.3 to 1.8)	.48
Urinary system				
Bladder, adenocarcinoma with variants	6 (0.7)	9 (1.6)	2.2 (0.8 to 6.1)	.14
Kidney, RCC, clear cell adenocarcinoma NOS	175 (21.3)	204 (35.9)	1.7 (1.4 to 2.1)	<.001
Kidney, RCC, papillary adenocarcinoma NOS	136 (16.5)	188 (33.1)	2.0 (1.6 to 2.5)	<.001
Kidney, RCC, renal cell adenocarcinoma	230 (27.9)	166 (29.2)	1.0 (0.9 to 1.3)	.67
Kidney, RCC, RCC chromophobe type	14 (1.7)	11 (1.9)	1.1 (0.5 to 2.5)	.75
Eye and adnexa, SCC with variants, squamous carcinoma	12 (1.5)	4 (0.7)	0.5 (0.2 to 1.5)	.18
NET, well-differentiated endocrine tumors: carcinoid	20 (2.4)	8 (1.4)	0.6 (0.3 to 1.3)	.18

[a]Only cancer types with at least 15 cases in the transplant group were evaluated. CI = confidence interval; IBT = intrahepatic bile tract; IR = incidence rate; IRR = incidence rate ratio; MCC = Merkel cell carcinoma; NET = neuroendocrine tumor; NOS = not otherwise specified; RCC = renal cell carcinoma; SCC = squamous cell carcinoma.

[b]P values were based on a Wald test and were 2-sided.

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our approach and lending credence for our novel findings. By comparing our associations with those in HIV-infected individuals, we generated hypotheses about etiologic factors that contribute to elevated cancer risk in the transplant population.

A study limitation is that we could not account for increased medical care that transplant recipients receive relative to the general population. Because SOTRs are frequently followed at tertiary care hospitals and academic medical centers, they may be less likely to have a rare cancer misdiagnosed or coded in a nonspecific manner. This bias would tend to increase SIRs for unusual cancer types, although it is unlikely to be extreme enough to fully explain the strongest elevations. Finally, because we lacked detailed longitudinal treatment information, we could not examine carcinogenic effects of individual immunosuppressive maintenance medications.

In conclusion, this study identified specific rare cancers that are overrepresented in the SOTR population. Some of these cancers may be increased as a result of immunosuppression and loss of immunosurveillance. It will be important to assess tumor tissues in these cases for candidate or unknown viruses or high tumor mutational burden from UVR or other exposures (14, 52, 53). Notably, rare cancers (including some of the entities we identify) have been described as aggressive and having poor outcomes regardless of diagnosis stage (54–56), highlighting the importance of further research to improve prevention and treatment and to understand how transplant status affects survival from these rare cancers.

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Table 4. Associations between time since transplant and cancer incidence rates among transplant recipients[a]

Cancer outcome	0-1.9 years	2-4.9 years		5-9.9 years		10+ years		
	No. (IR)	No. (IR)	IRR (95% CI)	No. (IR)	IRR (95% CI)	No. (IR)	IRR (95% CI)	P_{trend}[b]
Oral cavity or pharynx								
Lip, SCC with variants of lip	6 (1.4)	6 (1.4)	1.0 (0.3 to 3.0)	13 (3.5)	2.5 (1.0 to 6.6)	4 (2.7)	1.9 (0.6 to 6.9)	.06
Lip, SCC with variants of lip, SCC	21 (4.9)	55 (12.4)	2.5 (1.5 to 4.2)	59 (16.0)	3.3 (2.0 to 5.4)	28 (19.0)	3.9 (2.2 to 6.8)	<.001
Salivary gland, epithelial tumors, mucoepidermoid carcinoma	5 (1.2)	7 (1.6)	1.4 (0.4 to 4.3)	4 (1.1)	0.9 (0.3 to 3.5)	2 (1.4)	1.2 (0.2 to 6.0)	.99
Salivary gland, epithelial tumors, SCC	2 (0.5)	9 (2.0)	4.3 (0.9 to 20.1)	8 (2.2)	4.7 (1.0 to 22.0)	8 (5.4)	11.6 (2.5 to 54.8)	.001
Oropharynx, SCC with variants, SCC	48 (11.2)	53 (11.9)	1.1 (0.7 to 1.6)	43 (11.7)	1.0 (0.7 to 1.6)	17 (11.5)	1.0 (0.6 to 1.8)	.88
Digestive system								
Colon, adenocarcinoma, signet ring cell carcinoma	6 (1.4)	8 (1.8)	1.3 (0.5 to 3.7)	12 (3.3)	2.3 (0.9 to 6.2)	5 (3.4)	2.4 (0.7 to 8.0)	.05
Anal canal, SCC with variants	14 (3.3)	37 (8.3)	2.6 (1.4 to 4.7)	35 (9.5)	2.9 (1.6 to 5.4)	31 (21.0)	6.5 (3.4 to 12.1)	<.001
Liver and IBT, cholangiocarcinoma of IBT	7 (1.6)	13 (2.9)	1.8 (0.7 to 4.5)	8 (2.2)	1.3 (0.5 to 3.7)	5 (3.4)	2.1 (0.7 to 6.6)	.34
Respiratory system								
Nasal cavity and sinuses, SCC with variants, SCC	1 (0.2)	7 (1.6)	6.8 (0.8 to 54.9)	11 (3.0)	12.8 (1.7 to 99.3)	2 (1.4)	5.8 (0.5 to 64.2)	.02
Lung, adenocarcinoma, mucinous adenocarcinoma	6 (1.4)	3 (0.7)	0.5 (0.1 to 1.9)	9 (2.4)	1.8 (0.6 to 4.9)	3 (2.0)	1.5 (0.4 to 5.8)	.23
Lung, adenocarcinoma, papillary adenocarcinoma NOS	6 (1.4)	9 (2.0)	1.5 (0.5 to 4.1)	4 (1.1)	0.8 (0.2 to 2.8)	0 (0.0)	0.0 (0.0 to 0.0)	.23
Nonmelanoma skin cancer								
Adnexal carcinoma of skin	2 (0.5)	3 (0.7)	1.5 (0.2 to 8.7)	6 (1.6)	3.5 (0.7 to 17.3)	4 (2.7)	5.8 (1.1 to 31.8)	.02
Adnexal carcinoma of skin, sebaceous adenocarcinoma	7 (1.6)	18 (4.0)	2.5 (1.0 to 5.9)	23 (6.2)	3.8 (1.6 to 8.9)	14 (9.5)	5.8 (2.4 to 14.4)	<.001
NET, endocrine carcinoma, MCC	21 (4.9)	40 (9.0)	1.8 (1.1 to 3.1)	52 (14.1)	2.9 (1.7 to 4.8)	27 (18.3)	3.7 (2.1 to 6.6)	<.001
Soft tissue sarcoma	10 (2.3)	21 (4.7)	2.0 (1.0 to 4.3)	17 (4.6)	2.0 (0.9 to 4.3)	5 (3.4)	1.5 (0.5 to 4.3)	.26
Breast, male	6 (1.4)	15 (3.4)	2.4 (0.9 to 6.2)	7 (1.9)	1.4 (0.5 to 4.1)	2 (1.4)	1.0 (0.2 to 4.8)	.99
Genital system								
Vulva and vagina, SCC with variants	14 (3.3)	25 (5.6)	1.7 (0.9 to 3.3)	28 (7.6)	2.3 (1.2 to 4.4)	12 (8.1)	2.5 (1.2 to 5.4)	.005
Penis, SCC with variants, SCC	3 (0.7)	9 (2.0)	2.9 (0.8 to 10.7)	3 (0.8)	1.2 (0.2 to 5.8)	6 (4.1)	5.8 (1.5 to 23.3)	.07
Urinary system								
Bladder, adenocarcinoma with variants	5 (1.2)	5 (1.1)	1.0 (0.3 to 3.3)	5 (1.4)	1.2 (0.3 to 4.0)	0 (0.0)	0.0 (0.0 to 0.0)	.51
Kidney, RCC, clear cell adenocarcinoma NOS	121 (28.1)	108 (24.3)	0.9 (0.7 to 1.1)	97 (26.3)	0.9 (0.7 to 1.2)	53 (35.9)	1.3 (0.9 to 1.8)	.34
Kidney, RCC, papillary adenocarcinoma NOS	83 (19.3)	61 (13.7)	0.7 (0.5 to 1.0)	114 (30.9)	1.6 (1.2 to 2.1)	66 (44.7)	2.3 (1.7 to 3.2)	<.001
Kidney, RCC, renal cell adenocarcinoma	143 (33.3)	109 (24.5)	0.7 (0.6 to 0.9)	113 (30.6)	0.9 (0.7 to 1.2)	31 (21.0)	0.6 (0.4 to 0.9)	.08
Kidney, RCC, RCC chromophobe type	9 (2.1)	4 (0.9)	0.4 (0.1 to 1.4)	10 (2.7)	1.3 (0.5 to 3.2)	2 (1.4)	0.7 (0.1 to 3.0)	.87
Eye and adnexa, SCC with variants, squamous carcinoma	4 (0.9)	3 (0.7)	0.7 (0.2 to 3.2)	6 (1.6)	1.8 (0.5 to 6.2)	3 (2.0)	2.2 (0.5 to 9.8)	.18
NET, well-differentiated endocrine tumors: carcinoid	5 (1.2)	6 (1.4)	1.2 (0.4 to 3.8)	9 (2.4)	2.1 (0.7 to 6.3)	8 (5.4)	4.7 (1.5 to 14.2)	.004

[a]Only types with at least 15 cases in the transplant group were evaluated. CI = confidence interval; IBT = intrahepatic bile tract; IR = incidence rate; IRR = incidence rate ratio; MCC = Merkel cell carcinoma; NET = neuroendocrine tumor; RCC = renal cell carcinoma; SCC = squamous cell carcinoma.
[b]P values were based on a likelihood ratio test and were 2-sided.

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