HHS Public Access

Author manuscript

Cancer Res. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Cancer Res. 2017 August 01; 77(15): 4196–4203. doi:10.1158/0008-5472.CAN-16-3291.

Risk of second malignancies in solid organ transplant recipients who develop keratinocyte cancers

Rachel D. Zamoiski[1], **Elizabeth Yanik**[1], **Todd M. Gibson**[2], **Elizabeth K. Cahoon**[1], **Margaret M. Madeleine**[3], **Charles F. Lynch**[4], **Sally Gustafson**[5], **Marc T. Goodman**[6], **Melissa Skeans**[5], **Ajay K. Israni**[7], **Eric A. Engels**[1], and **Lindsay M. Morton**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

[2]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN

[3]Public Health Science, Fred Hutchinson Cancer Research Center, Seattle, WA

[4]Department of Epidemiology, University of Iowa, Iowa City, IA

[5]Scientific Registry of Transplant Recipients, Minneapolis, MN

[6]Cancer Prevention and Control Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

[7]Department of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN

Abstract

Solid organ transplant recipients have increased risk for developing keratinocyte cancers (KC), including cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), in part as a result of immunosuppressive medications administered to prevent graft rejection. In the general population, KC are associated with increased risks of subsequent malignancy, however, the risk in organ transplant populations has not been evaluated. We addressed this question by linking the U.S. Scientific Registry of Transplant Recipients, which includes data on KC occurrence, with 15 state cancer registries. Risk of developing malignancies after KC was assessed among 118,440 Caucasian solid organ transplant recipients using multivariate Cox regression models. Cutaneous SCC occurrence (n=6169) was associated with 1.44-fold increased risk [95% confidence interval (CI): 1.31–1.59] for developing later malignancies. Risks were particularly elevated for non-cutaneous SCC, including those of the oral cavity/pharynx [hazard ratio (HR)=5.60, 95%CI: 4.18–7.50] and lung (HR=1.66, 95%CI: 1.16–2.31). Cutaneous SCC was also associated with increased risk of human papillomavirus-related cancers, including anal cancer (HR=2.77, 95%CI: 1.29–5.96) and female genital cancers (HR=3.43, 95%CI: 1.44–8.19). In contrast, BCC (n=3669) was not associated with overall risk of later malignancy (HR=0.98, 95%CI: 0.87–1.12) including any SCC. Our results suggest that transplant recipients with cutaneous SCC, but not BCC, have an

Corresponding Author: Lindsay M. Morton, PhD, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Room 7E-454, MSC 9778, Bethesda, MD 20892-9778; mortonli@mail.nih.gov; Phone: +1.240.276.7377; Fax: +1.240.276.7840.

Conflict of interest statement: The authors have no conflicts of interest to disclose.

increased risk of developing other SCC. These findings somewhat differ from those for the general population and suggest a shared etiology for cutaneous SCC and other SCC in the setting of immunosuppression. Cutaneous SCC occurrence after transplantation could serve as a marker for elevated malignancy risk.

Keywords

keratinocyte cancer; second cancers; solid organ transplantation; squamous cell cancers; survivorship

Introduction

Keratinocyte carcinomas (KCs), including cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common malignancy in the United States (1). In the general population, BCC is more common than SCC, accounting for about 80% of all KC diagnoses (2). Exposure to ultraviolet radiation (UVR) is the primary risk factor for both SCC and BCC (2,3). Although BCC and SCC are rarely fatal, they can metastasize, and patients with metastatic SCC have poor prognoses (2). Individuals in the general population with a history of KC have increased risk of developing a variety of cancers, including melanoma, oral cancers, and non-Hodgkin lymphoma (NHL) (4–8).

Solid organ transplant recipients have greatly increased risk of KC compared with the general population (9), with estimated risks increased over 100-fold for SCC and 10-fold for BCC (10–12). KC risk is related to the use of immunosuppressive drugs to prevent rejection of transplanted organs, with higher risks seen in those recipients who receive higher levels of immunosuppressive therapy (13) and for longer durations (12). Solid organ transplant recipients are also at elevated risk of developing a range of other malignancies throughout the body (14,15). Overall risk of new malignancy after solid organ transplantation is approximately two-fold higher than in the general population, though increases for specific infection-related malignancies including NHL, anogenital cancers, and Kaposi sarcoma are even higher (14–20).

In 2015, 30,973 people underwent solid organ transplantation in the United States, and approximately 300,000 organ transplant recipients were alive with a functioning transplanted organ in 2014 (21). Because transplant recipients have unique exposures due to risk factors for transplant and immunosuppressive treatment and high risk for developing new malignancies, prior studies on the risk of malignancy following KC may not be generalizable to transplant recipients. We therefore utilized a large-scale, population-based study to describe the risk of malignancy following cutaneous BCC or SCC in 118,440 individuals who received a solid organ transplant during 1987–2011.

Methods

Study population and transplantation data

The Transplant Cancer Match Study, described in detail previously (14), links the Scientific Registry of Transplant Recipients (SRTR) with population-based cancer registries to provide

systematic ascertainment of malignancy among solid organ transplant recipients in the United States. Sixteen registries were included in the analysis: the states of California (years of data inclusion with ≥95% complete case ascertainment, 1988–2008), Colorado (1988–2009), Connecticut (1973–2009), Florida (1981–2009), Georgia (1995–2010), Hawaii (1973–2007), Iowa (1973–2009), Illinois (1986–2007), Kentucky (1995–2011), Michigan (1985–2009), North Carolina (1990–2010), New Jersey (1979–2010), New York (1976–2010), Texas (1995–2010), and Utah (1973–2008), as well as the Seattle/Puget Sound area of Washington State (1974–2008). The SRTR includes information on all solid organ transplants in the United States starting in 1987. For this analysis, data derived from the SRTR included basic demographic and transplantation data, health information at the time of transplantation [body-mass index (BMI), history of diabetes, Epstein-Barr virus (EBV) antibody status], and baseline data on receipt of specific types of induction and maintenance immunosuppressive medications to prevent graft rejection (Table 1).

The study population included first transplant recipients who resided in participating cancer registry catchment areas. We excluded individuals who had a transplant prior to the beginning of registry coverage (n=6,156), had a cancer diagnosis other than KC or *in situ* cancer reported to a cancer registry preceding the transplant (n=13,242), were diagnosed with liver cancer <6 months after liver transplantation (because these were likely prevalent cancers; n=719) (14), or were known to be infected with human immunodeficiency virus (HIV) at the time of transplantation (n=96). In addition, because over 95% of KC diagnoses occurred among whites, we excluded non-white individuals (n=78,309). The final analytic population included 118,440 white individuals with a first transplant, followed during 1987–2011.

Although UVR exposure is an important determinant of KC risk, we had no individual measures of exposure to UVR. We therefore used ambient UVR linked to residence at the time of entry onto the transplant waitlist or at transplantation as a proxy for UVR exposure. Residential zip codes were linked to the National Aeronautics and Space Administration (NASA) Total Ozone Mapping Spectrometer (TOMS) database, which provides satellite-based estimates of ambient cloud-adjusted UVR on a 1° latitude by 1° longitude grid (22). We averaged daily at noontime between 1982 and 1992 to account for fluctuations in the 11-year solar cycle. UVR exposure was grouped into quartiles based on the study population distribution at baseline.

BCC and SCC ascertainment

Occurrence of KC (BCC and SCC) is not captured by cancer registries but is ascertained in transplant recipients based on patient medical records, as reported in yearly transplant center follow-up reports included in the SRTR. We validated SRTR data on KC diagnoses using Medicare claims for the subset of Medicare-eligible individuals (23). We found that 14% of BCC cases and 22% of SCC cases reported to Medicare were captured by the SRTR (Supplementary Table S1), indicating low sensitivity. However, 71% of the BCCs and 73% of the SCCs in the SRTR were confirmed by Medicare claims, indicating a high positive predictive value of SRTR-documented KCs.

Malignancy data

Data for cancers other than KCs were obtained from the 15 linked cancer registries. Malignant cancers were coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (Supplementary Table S2) (1). We considered risk for malignancy overall as well as specific types or groupings that occurred in at least 100 recipients in our study population. Non-KC skin cancers are captured by cancer registries, and thus were evaluated in this analysis as a cancer outcome. Morphology codes further distinguished squamous and non-squamous oral cavity/pharyngeal, esophageal, lung, and bladder cancers; diffuse large B-cell lymphoma from other NHLs; and Merkel cell carcinoma from other types of non-KC skin cancer (Table 2 footnote, most commonly sebaceous adenocarcinoma, dermatofibrosarcoma, and malignant fibrous histiocytoma).

Statistical analysis

Follow-up began on the date of transplantation and ended at the first of: cancer registry cancer diagnosis, graft failure, re-transplantation, loss to follow-up, end of registry coverage, or death. We first estimated the relative risk of developing BCC or SCC among transplant recipients in association with key demographic and transplant-related factors using hazard ratios (HRs) and 95% confidence intervals (CIs) derived from Cox regression analyses with age as the time scale. As specified *a priori*, models were adjusted for sex, year of transplantation, type of organ transplanted, and time since transplantation (as a time-dependent covariate). Using similar models, we then estimated the relative risk of developing cancer after KC among transplant recipients. The occurrences of BCC and SCC were each included in the model as time-dependent variables, recording the first instance of each type of KC.

Additional potential confounders evaluated were BMI, diabetes, induction medications, baseline maintenance medications, and ambient UVR quartiles. However, inclusion of these factors did not meaningfully change (>10%) the BCC or SCC risk estimates, thus they were excluded from the final models. We also conducted secondary analyses with three time-dependent covariates for KC occurrence: BCC only, SCC only, and both BCC + SCC in order to assess potential differences in risk among individuals who developed both BCC and SCC compared to BCC alone or SCC alone. Individuals who developed BCC before SCC were included in the BCC only group until the development of SCC, and vice-versa for those who developed SCC before BCC.

Analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The majority of 118,440 solid organ transplant recipients in our study population were male (62.6%), and the most commonly transplanted organ was kidney (51.5%) followed by liver (21.9%) (Table 1). The median age at transplantation was 49 years. Following transplantation, a total of 8056 recipients developed KC, including 3669 with BCC and 6169 with SCC (1782 recipients developed both).

As shown in Table 1, the proportion of individuals who developed KC increased with increasing age at transplantation. Males had higher KC risk than females, and risk increased with more recent year of transplantation. Liver recipients had the lowest risk of KC, and lung recipients had the highest risk, with the elevated risk among lung recipients particularly evident for SCC. Receipt of monoclonal antibodies was also associated with increased KC risk, whereas inverse associations were observed among individuals receiving maintenance therapy with mTOR inhibitors, as well as among individuals with diabetes. UVR exposure was also associated with increased risk of KC.

After adjustment for sex, type of organ transplanted, year of transplantation, and follow-up time, recipients with SCC after transplantation had 1.44-fold (95%CI 1.31–1.59) increased overall risk of developing a new malignancy compared with recipients without SCC (Table 2). Cancers of the oral cavity/pharynx were the most common malignancy among individuals with SCC (n=155), with risk increased 5.34-fold (95%CI: 4.02–7.08). When considering histologic subtypes of oral cavity/pharyngeal cancers, associations were somewhat stronger for squamous than for non-squamous cancers (n=475, HR=5.60, 95%CI: 4.18–7.50 *versus* n=45, HR=3.00, 95%CI: 1.01–8.93). When considering subsite within the oral cavity, the associations were consistent for SCC of the lip (HR=4.13, 95%CI: 2.43–7.00) and tongue (HR=3.58, 95%CI: 1.82–7.05). A reported diagnosis of cutaneous SCC after transplantation also was associated with an increased risk of SCC of the lung (HR=1.66, 95%CI: 1.16–2.37), but not non-squamous cell lung cancer (HR=1.00, 95%CI: 0.71–1.39). Other sites with increased risk after a diagnosis of cutaneous SCC included anal cancer (HR=2.77, 95%CI: 1.29–5.96), human papillomavirus (HPV)-related female genital cancers (defined as cancer of the cervix, vulva, or vagina) (HR=3.43, 95%CI 1.44–8.19), melanoma (HR=1.75, 95%CI: 1.17–2.62), Merkel cell carcinoma (HR=3.58, 95%CI: 1.96–6.53), and other non-epithelial skin cancers (not including Merkel cell carcinoma, melanoma, BCC, or SCC) (HR=3.78, 95%CI: 2.17–6.59). Finally, diagnosis of cutaneous SCC after transplantation was inversely associated with NHLs other than DLBCL (HR=0.41, 95%CI: 0.19–0.89), whereas there was no significant association for DLBCL (HR= 1.13, 95%CI: 0.72–1.80).

In contrast to the risk patterns observed for cutaneous SCC, a diagnosis of BCC after transplantation was not associated with overall cancer risk (HR=0.98, 95%CI: 0.87–1.12) (Table 2). However, associations were observed for several specific malignancies. The highest significantly elevated risk occurred for Merkel cell carcinoma (HR=2.10, 95%CI: 1.05–4.22), whereas there was no significant association for melanoma (HR=1.35, 95%CI: 0.82–2.22). Among individuals who had a diagnosis of BCC after transplantation, risk was borderline elevated for prostate cancer (HR=1.37, 95%CI: 1.01–1.87) and was decreased for oral cavity/pharyngeal cancers and colon cancers (Table 2). Risk for non-squamous oral cavity/pharyngeal cancers was elevated, but the increased risk was not statistically significant (HR=3.07, 95%CI: 0.96–9.80).

In secondary analyses that considered separately risks after BCC only, SCC only, and BCC +SCC, findings for SCC were largely unchanged, but the inverse associations with BCC were no longer evident (Supplementary Table S3). Additional models adjusted for potential confounders (BMI, diabetes, EBV serostatus, induction medications, maintenance

medications, and UVR exposure) and models that stratified by transplanted organ (kidney, liver, heart, other) resulted in no meaningful change in the associations between BCC or SCC for any of the subsequent cancer outcomes (data not shown). As a sensitivity analysis, we evaluated the association of cutaneous SCC with oral cavity/pharyngeal cancer separately for the sites known or suspected to be associated with human papillomavirus (HPV; i.e., cancers of the tonsil and oropharynx) versus other sites within the oropharynx; both showed increased risk (HR=6.08, 95%CI: 2.69–13.71 and HR=5.20, 95%CI: 3.84–7.03 respectively).

Discussion

In this study of 118,440 solid organ transplant recipients in the United States, we present novel evidence of associations between KC and subsequent malignancy risk, observing somewhat different patterns than those observed in the general population. Among transplant recipients, risk of overall malignancy was increased after developing cutaneous SCC, but not after BCC. Remarkably, risks were specifically elevated after cutaneous SCC for a number of other non-cutaneous SCC, including oral cavity/pharyngeal cancers, lip cancer, tongue cancer, and lung cancer, whereas BCC was not associated with increased risk of any squamous cell cancers. The results suggest a shared carcinogenic mechanism for cutaneous SCC and other SCC at different sites in the body among transplant recipients, and highlight a population of individuals with increased risk of developing new malignancies. In the general population, risk is increased after both BCC and SCC for a wide variety of cancers, particularly Hodgkin lymphoma, NHL, and leukemia, as well as overall malignancies (4–8). These associations were not evident in our study of transplant recipients.

One possible explanation for our findings is that increased risks of both SCC and other malignancies are most evident among individuals with higher levels of immunosuppression (24–27). However, a number of observations suggest that the degree of immunosuppression alone cannot explain our results. First, both induction therapy and organ type are correlated with immunosuppression level and were themselves associated with increased risk of KC in our study. Nonetheless, the associations of cutaneous SCC with subsequent malignancies remained consistent in models adjusted for receipt of induction therapy or stratified by type of organ transplanted (data not shown). Second, if cutaneous SCC were solely a marker of immunosuppression, we would expect to also see an increased risk of NHL after SCC, since risk of NHL is greatly increased with immunosuppression (28,29). Studies in the general population also have reported an increased risk of NHL after cutaneous SCC (6). In contrast, we found a decreased risk of NHL after cutaneous SCC.

It is plausible that immunosuppression combined with a specific infectious agent, possibly HPV, may explain our findings. HPV has been associated with cutaneous SCC in some studies (30) and causes cancers of the oropharynx and tonsil, anus, and female genital tract (31,32), all of which we observed to be increased after SCC. However, further research is needed to explore the potential role of infections in cutaneous SCC and other squamous cancers because the association of skin cancers with HPVs is not established, and recent evidence supports variation in the observed HPV-cancer associations by HPV genus (33,34).

Additionally, we found increased risk of both HPV-related and non-HPV-related oral cancers, suggesting that if HPV is playing a role, it is not the only causative factor. Finally, lung cancer is not known to be caused by HPV, so this would not explain the increased risk of squamous cell lung cancer after cutaneous SCC.

Another possible explanation for our findings is shared germline genetic susceptibility to SCC and other squamous cell cancers, including the possibility of susceptibility to DNA damaging effects of immunosuppressing medications. Cyclosporine, an immunosuppressing drug, has been shown to inhibit DNA repair, which could provide a plausible mechanism for these associations (35). However, shared susceptibility among squamous malignancies is poorly understood (36). We also did not see associations between cyclosporine or azathioprine, which are photosensitizing (37,38), and KC risk.

A potential role for UVR exposure also should be considered in the interpretation of our results. UVR induces DNA damage (39), and laboratory studies suggest that skin cancers induced by UVR exposure are more likely to grow in immunocompromised hosts (40). While it is unlikely that UVR is the mechanism responsible for the increased risk of non-skin cancers seen in this study, UVR may explain the clustering of BCC and SCC with increased risk of melanoma, Merkel cell carcinoma, and other skin cancers (the majority of which were either sebaceous carcinoma or fibroxanthoma, data not shown). Similar to BCC and SCC, Merkel cell carcinoma is associated with immune deficiency, male predominance, older age, and UVR exposure (41,42). While less common, sebaceous carcinoma and fibroxanthoma are also associated with immunodeficiency and UVR exposure (43–46). However, adjustment for ambient UVR based on residential location did not materially change our risk estimates for other cutaneous malignancies after BCC and SCC, possibly due to limitations in our UVR exposure measure.

Although primary analyses showed a decreased risk of oral cavity/pharyngeal and colon cancers after BCC, these associations were not present in secondary analyses that included variables for BCC only, SCC only, and combined BCC+SCC, pointing away from a biological relationship with BCC. Instead, one possibility is that once a person develops SCC, clinicians may alter a patient's immunosuppressive regimen (e.g. decreasing the doses, or switching to an mTOR inhibitor), which may reduce subsequent risk for non-skin cancers (47,48). In contrast, the increased risks after SCC were not meaningfully different in secondary analyses.

The primary limitation of our study was the reliance on SRTR data for ascertainment of KC diagnoses. Our comparisons with Medicare claims demonstrated that KC reports in the SRTR are likely to be valid cases, although the majority of KC cases are not captured in the SRTR. Because this under-reporting would likely bias the risk estimates toward the null hypothesis, our risk estimates are likely conservative, and we may have missed additional significant associations. Although we restricted analyses to cancers with at least 100 cases (excluding salivary gland tumors, e.g.), false negative findings are possible due to low power for rare cancers or associations with only weakly elevated risks. Additionally, cancer risks may have been under-ascertained due to patient migration outside cancer registry areas or failure of linkage, though this under-ascertainment is likely to have been small (49,50). False

positive results also are possible due to multiple comparisons, and chance could explain some borderline associations. Finally, we lacked information on smoking history, which is related to SCC (51). and our UVR exposure metric was limited because it reflected residence at the time of transplant, rather than during childhood (52), and we lacked information on sun sensitivity factors (e.g., Fitzpatrick skin type), time spent outdoors, or sun shielding behaviors, though UVR is unlikely to confound non-cutaneous cancer risk estimates.

The strengths of this study include a large sample size from around the United States representing a wide age range and several types of organ transplants, as well as reliable and complete cancer ascertainment based on cancer registry diagnoses. We also had histologic information, which allowed us to consider cutaneous SCC and BCC separately and differentiate cancer outcomes by squamous cell versus non-squamous cell histology. The availability of UVR exposure data, although imperfect, is also a strength of this study.

In this large, population-based study of solid organ transplant recipients in the United States, we found that SCC increased risk for additional cancers more so than BCC, and remarkably, cutaneous SCC increased risk for other squamous cell cancers whereas BCC did not. In the general population, many types of cancer besides squamous cell cancers are increased after cutaneous SCC, suggesting that the increase in squamous cell cancers after SCC is unique to transplant recipients or those who are immunosuppressed. These results support shared risk factors and common carcinogenic mechanisms in cutaneous SCC and other squamous cell cancers in immunosuppressed individuals, and that a diagnosis of SCC in transplant recipients could potentially serve as a marker for elevated risk for developing certain malignancies. Future studies should focus on clarifying potential shared risk factors of all squamous cell cancers and identifying optimal prevention and surveillance guidelines for KCs and other cancers in solid organ transplant recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the support and assistance provided by individuals at the Health Resources and Services Administration (Monica Lin), the SRTR (Bertram Kasiske, Paul Newkirk, Jon Snyder), and the following cancer registries: the states of California (Tina Clarke), Colorado (Jack Finch), Connecticut (Lou Gonsalves), Florida (Brad Wohler), Georgia (Rana Bayakly), Hawaii (Brenda Hernandez), Iowa, Illinois (Lori Koch), Michigan (Glenn Copeland), New Jersey (Xiaoling Niu), New York (Amy Kahn), North Carolina (Chandrika Rao), Texas (Leticia Nogueria), and Utah (Janna Harrell), and the Seattle-Puget Sound area of Washington. We also thank analysts at Information Management Services for programming support (David Castenson, Matthew Chaloux, Michael Curry, Ruth Parsons).

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, Health Resources and Services Administration, SRTR, cancer registries, or their contractors.

Financial Support: This research was supported in part by the Intramural Research Program of the National Cancer Institute. The SRTR is currently operated under contract number HHSH250201500009C (Health Resources and Services Administration) by the Minneapolis Medical Research Foundation, Minneapolis, MN. Previously the SRTR was managed under contracts HHSH250201000018C and HHSH234200537009C. The following cancer registries were supported by the SEER Program of the National Cancer Institute: California (contracts

HHSN261201000036C, HHSN261201000035C, and HHSN261201000034C), Connecticut (HHSN261201000024C), Hawaii (HHSN261201000037C, N01-PC-35137, and N01-PC-35139), Iowa (HSN261201000032C and N01-PC-35143), New Jersey (HHSN261201300021I, N01-PC-2013-00021), Seattle-Puget Sound (N01-PC-35142), and Utah (HHSN2612013000171). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: California (agreement 1U58 DP000807-01), Colorado (U58 DP000848-04), Georgia (5U58DP003875-01), Illinois (5U58DP003883-03), Maryland (U58DP12-1205 3919-03), Michigan (5U58DP003921-03), New Jersey (5U58/DP003931-02), New York (U58DP003879), North Carolina (U58DP000832) and Texas (5U58DP000824-04). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, Massachusetts (Massachusetts Cancer Prevention and Control Cooperative Agreement 5458DP003920), New Jersey, New York (including the Cancer Surveillance Improvement Initiative), Texas, Utah, and Washington, as well as the University of Utah and Fred Hutchinson Cancer Research Center in Seattle, WA.

References

1. Howlader, N., Noone, A., Krapcho, M., Miller, D., Bishop, K., Altekruse, S., et al. SEER Cancer Statistics Review, 1975–2013. National Cancer Institute; Bethesda, MD: 2016.
2. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. The New England journal of medicine. 2001; 344:975–83. [PubMed: 11274625]
3. Wong CS, Strange RC, Lear JT. Basal cell carcinoma. BMJ. 2003; 327:794–8. [PubMed: 14525881]
4. Cantwell MM, Murray LJ, Catney D, Donnelly D, Autier P, Boniol M, et al. Second primary cancers in patients with skin cancer: a population-based study in Northern Ireland. Br J Cancer. 2009; 100:174–7. [PubMed: 19127269]
5. Chen J, Ruczinski I, Jorgensen TJ, Yenokyan G, Yao Y, Alani R, et al. Nonmelanoma skin cancer and risk for subsequent malignancy. Journal of the National Cancer Institute. 2008; 100:1215–22. [PubMed: 18728282]
6. Robsahm TE, Karagas MR, Rees JR, Syse A. New malignancies after squamous cell carcinoma and melanomas: a population-based study from Norway. BMC Cancer. 2014; 14:210. [PubMed: 24645632]
7. Rees JR, Zens MS, Gui J, Celaya MO, Riddle BL, Karagas MR. Non melanoma skin cancer and subsequent cancer risk. PloS one. 2014; 9:e99674. [PubMed: 24937304]
8. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010; 19:1686–95.
9. Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. Journal of the American Academy of Dermatology. 1999; 40:177–86. [PubMed: 10025742]
10. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. The New England journal of medicine. 2003; 348:1681–91. [PubMed: 12711744]
11. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation. 1990; 49:506–9. [PubMed: 2316011]
12. Krynitz B, Edgren G, Lindelof B, Baecklund E, Brattstrom C, Wilczek H, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008--a Swedish population-based study. International journal of cancer Journal international du cancer. 2013; 132:1429–38. [PubMed: 22886725]
13. Dantal J, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. Lancet. 1998; 351:623–8. [PubMed: 9500317]
14. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. Jama. 2011; 306:1891–901. [PubMed: 22045767]
15. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007; 370:59–67. [PubMed: 17617273]

16. Vajdic CM, van Leeuwen MT. Cancer incidence and risk factors after solid organ transplantation. International journal of cancer Journal international du cancer. 2009; 125:1747–54. [PubMed: 19444916]
17. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. Jama. 2006; 296:2823–31. [PubMed: 17179459]
18. Serraino D, Angeletti C, Carrieri MP, Longo B, Piche M, Piselli P, et al. Kaposi's sarcoma in transplant and HIV-infected patients: an epidemiologic study in Italy and France. Transplantation. 2005; 80:1699–704. [PubMed: 16378064]
19. Serraino D, Piselli P, Angeletti C, Minetti E, Pozzetto A, Civati G, et al. Risk of Kaposi's sarcoma and of other cancers in Italian renal transplant patients. British journal of cancer. 2005; 92:572–5. [PubMed: 15668710]
20. Madeleine MM, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-related cancers after solid organ transplantation in the United States. Am J Transplant. 2013; 13:3202–9. [PubMed: 24119294]
21. OPTN/SRTR 2015 Annual Data Report. Am J Transplant. 2017; 17:1–564.
22. National Aeronatics and Space Administration: Total Ozone Mapping Spectrometer Data Product: Erythemal UV Exposure. Greenbelt, MD: Goddard Space Flight Center; 2004.
23. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence Estimate of Nonmelanoma Skin Cancer (Keratinocyte Carcinomas) in the U.S. Population, 2012. JAMA dermatology. 2015; 151:1081–6. [PubMed: 25928283]
24. Kayamba V, Bateman AC, Asombang AW, Shibemba A, Zyambo K, Banda T, et al. HIV infection and domestic smoke exposure, but not human papillomavirus, are risk factors for esophageal squamous cell carcinoma in Zambia: a case-control study. Cancer Med. 2015; 4:588–95. [PubMed: 25641622]
25. Persson EC, Shiels MS, Dawsey SM, Bhatia K, Anderson LA, Engels EA. Increased risk of stomach and esophageal malignancies in people with AIDS. Gastroenterology. 2012; 143:943–50. e2. [PubMed: 22796240]
26. Beachler DC, Abraham AG, Silverberg MJ, Jing Y, Fakhry C, Gill MJ, et al. Incidence and risk factors of HPV-related and HPV-unrelated Head and Neck Squamous Cell Carcinoma in HIV-infected individuals. Oral Oncol. 2014; 50:1169–76. [PubMed: 25301563]
27. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. AIDS. 2007; 21:207–13. [PubMed: 17197812]
28. Clarke CA, Morton LM, Lynch C, Pfeiffer RM, Hall EC, Gibson TM, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. Br J Cancer. 2013; 109:280–8. [PubMed: 23756857]
29. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS. 2014; 28:2313–8. [PubMed: 25111081]
30. Shamanin V, zur Hausen H, Lavergne D, Proby CM, Leigh IM, Neumann C, et al. Human papillomavirus infections in nonmelanoma skin cancers from renal transplant recipients and nonimmunosuppressed patients. Journal of the National Cancer Institute. 1996; 88:802–11. [PubMed: 8637046]
31. Auluck A, Hislop G, Bajdik C, Poh C, Zhang L, Rosin M. Trends in oropharyngeal and oral cavity cancer incidence of human papillomavirus (HPV)-related and HPV-unrelated sites in a multicultural population: the British Columbia experience. Cancer. 2010; 116:2635–44. [PubMed: 20336792]
32. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006; 24(Suppl 3):S3/11–25.
33. Karagas MR, Nelson HH, Sehr P, Waterboer T, Stukel TA, Andrew A, et al. Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. Journal of the National Cancer Institute. 2006; 98:389–95. [PubMed: 16537831]
34. Agalliu I, Gapstur S, Chen Z, Wang T, Anderson RL, Teras L, et al. Associations of Oral alpha-, beta-, and gamma-Human Papillomavirus Types With Risk of Incident Head and Neck Cancer. JAMA Oncol. 2016

35. Han W, Soltani K, Ming M, He YY. Deregulation of XPC and CypA by cyclosporin A: an immunosuppression-independent mechanism of skin carcinogenesis. Cancer prevention research. 2012; 5:1155–62. [PubMed: 22846842]
36. Mulherkar R, Kirtane BM, Ramchandani A, Mansukhani NP, Kannan S, Naresh KN. Expression of enhancing factor/phospholipase A2 in skin results in abnormal epidermis and increased sensitivity to chemical carcinogenesis. Oncogene. 2003; 22:1936–44. [PubMed: 12673199]
37. Hofbauer GF, Attard NR, Harwood CA, McGregor JM, Dziunycz P, Iotzova-Weiss G, et al. Reversal of UVA skin photosensitivity and DNA damage in kidney transplant recipients by replacing azathioprine. Am J Transplant. 2012; 12:218–25. [PubMed: 21943390]
38. O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science. 2005; 309:1871–4. [PubMed: 16166520]
39. Sinha RP, Hader DP. UV-induced DNA damage and repair: a review. Photochem Photobiol Sci. 2002; 1:225–36. [PubMed: 12661961]
40. Fisher MS, Kripke ML. Systemic alteration induced in mice by ultraviolet light irradiation and its relationship to ultraviolet carcinogenesis. Proc Natl Acad Sci U S A. 1977; 74:1688–92. [PubMed: 300876]
41. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. Lancet. 2002; 359:497–8. [PubMed: 11853800]
42. Clarke CA, Robbins HA, Tatalovich Z, Lynch CF, Pawlish KS, Finch JL, et al. Risk of merkel cell carcinoma after solid organ transplantation. J Natl Cancer Inst. 2015; 107
43. Dowd MB, Kumar RJ, Sharma R, Murali R. Diagnosis and management of sebaceous carcinoma: an Australian experience. ANZ J Surg. 2008; 78:158–63. [PubMed: 18269479]
44. Iorizzo LJ 3rd, Brown MD. Atypical fibroxanthoma: a review of the literature. Dermatol Surg. 2011; 37:146–57. [PubMed: 21269345]
45. McCoppin HH, Christiansen D, Stasko T, Washington C, Martinez JC, Brown MD, et al. Clinical spectrum of atypical fibroxanthoma and undifferentiated pleomorphic sarcoma in solid organ transplant recipients: a collective experience. Dermatol Surg. 2012; 38:230–9. [PubMed: 22129349]
46. Lanoy E, Dores GM, Madeleine MM, Toro JR, Fraumeni JF Jr, Engels EA. Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. AIDS. 2009; 23:385–93. [PubMed: 19114864]
47. Yanik EL, Siddiqui K, Engels EA. Sirolimus effects on cancer incidence after kidney transplantation: a meta-analysis. Cancer Med. 2015; 4:1448–59. [PubMed: 26108799]
48. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. New Engl J Med. 2012; 367:329–39. [PubMed: 22830463]
49. Engels EA, Pfeiffer RM, Fraumeni JF, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011; 306:1891–901. [PubMed: 22045767]
50. Yanik EL, Nogueira LM, Koch L, Copeland G, Lynch CF, Pawlish KS, et al. Comparison of cancer diagnoses between the US solid organ transplant registry and linked central cancer registries. Am J Transplant. 2016
51. Leonardi-Bee J, Ellison T, Bath-Hextall F. Smoking and the risk of nonmelanoma skin cancer: systematic review and meta-analysis. Archiv Dermatol. 2012; 148:939–46.
52. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control. 2001; 12:69–82. [PubMed: 11227927]

Cancer Res. Author manuscript; available in PMC 2018 August 01.

Table 1

Characteristics of 118,440 solid organ transplant recipients and associations with KC, BCC, and SCC

	Study population (n=118,440)		KC (BCC, SCC, or both) (n=8056)					BCC (n=3669)*					SCC (n=6169)*				
	N (%)		N (%)		HR (95%CI)			N (%)		HR (95%CI)			N (%)		HR (95%CI)		
Gender																	
Female	44316	(37.4)	2057	(25.5)	0.62	(0.59 –	0.65)	908	(24.8)	0.62	(0.57 –	0.67)	1502	(24.4)	0.58	(0.55 –	0.62)
Male	74124	(62.6)	5999	(74.5)		ref		2761	(75.3)		ref		4667	(75.7)		ref	
Transplanted organ																	
Kidney	61028	(51.5)	3554	(44.1)		ref		1677	(45.7)		ref		2649	(42.9)		ref	
Kidney-pancreas	5789	(4.9)	281	(3.5)	1.14	(1.01 –	1.29)	128	(3.5)	1.11	(0.93 –	1.34)	200	(3.2)	1.12	(0.96 –	1.29)
Liver	25977	(21.9)	1066	(13.2)	0.58	(0.54 –	0.63)	476	(13.0)	0.56	(0.51 –	0.62)	797	(12.9)	0.59	(0.54 –	0.63)
Heart	15268	(12.9)	2052	(25.5)	1.62	(1.53 –	1.71)	1007	(27.5)	1.62	(1.49 –	1.76)	1585	(25.7)	1.60	(1.50 –	1.70)
Lung	7818	(6.6)	965	(12.0)	2.61	(2.43 –	2.81)	316	(8.6)	1.80	(1.60 –	2.04)	836	(13.6)	3.08	(2.85 –	3.34)
Other or multiple transplants†	2560	(2.2)	138	(1.7)	1.54	(1.30 –	1.82)	65	(1.8)	1.54	(1.20 –	1.97)	102	(1.7)	1.57	(1.29 –	1.92)
Age at transplant‡																	
0–5 years	3402	(2.9)	2	(0.0)				0	(0.0)				2	(0.0)			
6–19 years	5749	(4.9)	29	(0.4)				10	(0.3)				22	(0.4)			
20–39 years	24827	(21.0)	868	(10.8)				406	(11.1)				642	(10.4)			
40–64 years	72883	(61.5)	5937	(73.7)				2688	(73.3)				4550	(73.8)			
65–87 years	11579	(9.8)	1220	(15.1)				565	(15.4)				953	(15.5)			
Year of transplant																	
1987–1996	33226	(28.1)	2174	(27.0)		ref		978	(26.7)		ref		1746	(28.3)		ref	
1997–2001	31969	(27.0)	2300	(28.6)	1.57	(1.47 –	1.66)	1134	(30.9)	1.79	(1.63 –	1.95)	1709	(27.7)	1.46	(1.36 –	1.57)
2002–2005	26458	(22.3)	1871	(23.2)	3.13	(2.91 –	3.36)	822	(22.4)	3.34	(3.00 –	3.72)	1411	(22.9)	3.07	(2.83 –	3.33)
2006–2011	26787	(22.6)	1711	(21.2)	11.19	(10.29 –	12.17)	735	(20.0)	12.50	(11.00 –	14.22)	1303	(21.1)	12.00	(10.89 –	13.22)
Diabetes																	
No	69208	(58.4)	5054	(62.7)		ref		2302	(62.7)		ref		3832	(62.1)		ref	
Yes	24351	(20.6)	1404	(17.4)	0.80	(0.75 –	0.85)	648	(17.7)	0.80	(0.73 –	0.87)	1048	(17.0)	0.82	(0.76 –	0.88)
Missing	24881	(21.0)	1598	(19.8)	0.82	(0.76 –	0.89)	719	(19.6)	0.81	(0.72 –	0.92)	1289	(20.9)	0.85	(0.77 –	0.93)
Induction therapy																	

	Study population (n=118,440)		KC (BCC, SCC, or both) (n=8056)					BCC (n=3669)*					SCC (n=6169)*				
	N (%)		N (%)		HR (95%CI)			N (%)		HR (95%CI)			N (%)		HR (95%CI)		
Anti-IL-2 antibody	18545	(15.7)	1316	(16.3)	1.04	(0.98 –	1.11)	594	(16.2)	1.04	(0.95 –	1.15)	998	(16.2)	1.05	(0.97 –	1.13)
Monoclonal antibody	5830	(4.9)	494	(6.1)	1.24	(1.13 –	1.37)	239	(6.5)	1.24	(1.08 –	1.42)	379	(6.1)	1.23	(1.10 –	1.37)
Polyclonal antibody	19584	(16.5)	1339	(16.6)	1.16	(1.09 –	1.24)	573	(15.6)	1.06	(0.96 –	1.16)	1021	(16.6)	1.19	(1.10 –	1.28)
Other or more than one drug	4790	(4.0)	268	(3.3)	1.11	(0.98 –	1.26)	119	(3.2)	1.04	(0.86 –	1.26)	194	(3.1)	1.10	(0.94 –	1.27)
No induction	69691	(58.8)	4639	(57.6)		ref		2144	(58.4)		ref		3577	(58.0)		ref	
Baseline maintenance therapy regimen§																	
Cyclosporine and azathioprine	23771	(20.1)	1984	(24.6)	1.04	(0.96 –	1.13)	890	(24.3)	1.08	(0.95 –	1.23)	1638	(26.6)	1.07	(0.97 –	1.18)
Tacrolimus and mycophenolate	40409	(34.1)	2568	(31.9)		ref		1120	(30.5)		ref		1933	(31.3)		ref	
Other	54260	(45.8)	3504	(43.5)	0.88	(0.83 –	0.94)	1659	(45.2)	0.96	(0.88 –	1.05)	2598	(42.1)	0.85	(0.79 –	0.91)
Baseline maintenance therapy with mTOR inhibitor																	
No	112611	(95.1)	7748	(96.2)		ref		3522	(96.0)		ref		5946	(96.4)		ref	
Yes	5829	(4.9)	308	(3.8)	0.86	(0.76 –	0.96)	147	(4.0)	0.88	(0.74 –	1.04)	223	(3.6)	0.85	(0.74 –	0.97)
UVR quartile‖																	
Q1	34053	(28.8)	2144	(26.6)		ref		948	(25.8)		ref		1622	(26.3)		ref	
Q2	25173	(21.3)	1442	(17.9)	0.93	(0.87 –	1.00)	642	(17.5)	0.91	(0.82 –	1.00)	1092	(17.7)	0.91	(0.84 –	0.98)
Q3	29677	(25.1)	2180	(27.1)	1.22	(1.15 –	1.30)	1003	(27.3)	1.18	(1.08 –	1.29)	1675	(27.2)	1.16	(1.09 –	1.24)
Q4	29533	(24.9)	2290	(28.4)	1.28	(1.21 –	1.36)	1076	(29.3)	1.19	(1.09 –	1.30)	1780	(28.9)	1.15	(1.07 –	1.23)

Models are Cox regression models, with age as the time scale, adjusted for sex, year of transplantation, type of organ transplanted, and time since transplantation.

Abbreviations: KC = keratinocytic carcinoma; BCC = basal cell carcinoma; SCC = squamous cell carcinoma; IL-2 = interleukin-2; mTOR = mammalian target of rapamycin; UVR = ultraviolet radiation; Q = quartile

*BCC and SCC categories each include 1,782 individuals who had both BCC and SCC.

†Multiple transplants refers to more than one transplant at the date of the first transplant.

‡HRs not calculated for age at transplant because the model uses age as the time scale.

§"Cyclosporine and azathioprine" includes all individuals taking cyclosporine or azathioprine and not taking tacrolimus or mycophenolate. "Tacrolimusand mycophenolate" includes all individuals taking tacrolimus or mycophenolate and not taking cyclosporine or azathioprine.

‖UVR information was missing for 4 individuals.

Table 2

Associations of KC with risk of other malignancies among 118,440 solid organ transplant recipients

		BCC				SCC			
	n cases	n (with BCC)	HR (95%CI)*			n (with SCC)	HR (95%CI)*		
Overall malignancies	9977	491	0.98	(0.87 –	1.12)	1001	***1.44***	***(1.31 –***	***1.59)***
Oral cavity and pharynx	520	37	***0.58***	***(0.34 –***	***0.97)***	155	***5.34***	***(4.02 –***	***7.08)***
Squamous†	475	31	***0.43***	***(0.24 –***	***0.79)***	142	***5.60***	***(4.18 –***	***7.50)***
Non-squamous	45	6	3.07	(0.96 –	9.80)	13	***3.00***	***(1.01 –***	***8.93)***
Lip	163	19	0.60	(0.23 –	1.55)	54	***4.02***	***(2.37 –***	***6.81)***
Squamous†	160	19	0.60	(0.23 –	1.56)	54	***4.13***	***(2.43 –***	***7.00)***
Non-squamous	3	0	0.00	-		0	0.00	-	
Tongue	116	7	0.80	(0.27 –	2.36)	30	***3.49***	***(1.78 –***	***6.86)***
Squamous†	112	7	0.80	(0.27 –	2.38)	30	***3.58***	***(1.82 –***	***7.05)***
Non-squamous	4	0	0.00	-		0	0.00	-	
Esophagus	123	3	0.82	(0.24 –	2.75)	10	0.87	(0.34 –	2.27)
Squamous†	32	0	0.00	-		2	0.00	-	
Non-squamous	91	3	0.95	(0.28 –	3.25)	8	1.02	(0.38 –	2.71)
Stomach	130	3	0.57	(0.13 –	2.43)	8	1.08	(0.42 –	2.77)
Colon	449	7	***0.38***	***(0.15 –***	***0.93)***	27	1.14	(0.70 –	1.88)
Rectum	118	2	0.38	(0.05 –	2.87)	10	0.84	(0.26 –	2.77)
Anus	103	8	1.10	(0.37 –	3.29)	22	***2.77***	***(1.29 –***	***5.96)***
Pancreas	152	6	1.72	(0.71 –	4.15)	6	0.68	(0.26 –	1.79)
Larynx	103	7	0.78	(0.18 –	3.43)	16	1.08	(0.37 –	3.16)
Lung	1419	58	1.00	(0.73 –	1.37)	108	1.25	(0.98 –	1.59)
Squamous†	455	24	0.96	(0.58 –	1.57)	54	***1.66***	***(1.16 –***	***2.37)***
Non-squamous	964	34	1.03	(0.69 –	1.55)	54	1.00	(0.71 –	1.39)
Kidney	641	30	0.96	(0.55 –	1.68)	41	0.74	(0.45 –	1.21)
Bladder	271	18	0.99	(0.51 –	1.90)	31	1.59	(0.97 –	2.60)
Squamous†	9	0	0.00	-		0	0.00	-	
Non-squamous	262	18	1.00	(0.52 –	1.92)	31	1.61	(0.98 –	2.65)

	n cases	n (with BCC)	BCC HR (95%CI)*			n (with SCC)	SCC HR (95%CI)*		
Prostate	975	100	***1.37***	***(1.01 –***	***1.87)***	146	0.87	(0.65 –	1.17)
Breast (female)	494	17	1.35	(0.70 –	2.64)	22	1.10	(0.60 –	2.02)
Uterus	103	6	1.98	(0.46 –	8.53)	7	0.40	(0.05 –	3.12)
Female HPV-related genital	115	3	0.35	(0.05 –	2.68)	19	***3.43***	***(1.44 –***	***8.19)***
Thyroid	230	7	0.23	(0.03 –	1.71)	15	1.93	(0.88 –	4.24)
Melanoma	499	44	1.35	(0.82 –	2.22)	71	***1.75***	***(1.17 –***	***2.62)***
Other skin‡	214	39	***1.74***	***(1.06 –***	***2.86)***	74	***3.69***	***(2.45 –***	***5.55)***
MCC	103	20	***2.10***	***(1.05 –***	***4.22)***	30	***3.58***	***(1.96 –***	***6.53)***
Other	111	19	1.44	(0.71 –	2.95)	44	***3.78***	***(2.17 –***	***6.59)***
NHL	1492	27	0.67	(0.39 –	1.13)	54	0.79	(0.54 –	1.18)
DLBCL§	901	16	0.56	(0.27 –	1.15)	35	1.13	(0.72 –	1.80)
Other NHL	591	11	0.85	(0.39 –	1.83)	19	0.41	(0.19 –	0.89)
Myeloma	115	4	1.19	(0.40 –	3.52)	10	1.22	(0.49 –	3.03)
Acute leukemia	125	1	0.42	(0.06 –	3.20)	3	0.91	(0.28 –	3.02)

Abbreviations: KC = keratinocytic carcinoma; BCC = basal cell carcinoma; SCC = squamous cell carcinoma; HPV = human papillomavirus; MCC = Merkel cell carcinoma; NHL = non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma

*Cox regression models with age as the time scale, adjusted for sex, year of transplantation, type of organ transplanted, and time since transplantation. BCC and SCC are time-dependent variables each included in the same model.

†Internal squamous cell cancers were identified using SEER histology codes 8052, 8070–8078, 8083, and 8084.

‡Histology codes were used to define Merkel cell carcinoma (8247) and other types of skin cancer (8123, 8140, 8200, 8390, 8400–8402, 8407, 8409, 8410, 8413, 8560, 8800–8802, 8830, 8832, 8890, and 9120).

§Histology codes were used to define DLBCL (9678–9680, 9684, 9688, 9712, 9737, 9738).