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Risk of lip cancer after solid organ transplantation in the United States

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Abstract

Solid organ transplant recipients have an increased risk of lip cancer, but the reasons are uncertain. Using data from the Transplant Cancer Match Study, we describe the epidemiology of lip cancer among 261,500 transplant recipients in the United States. Two-hundred thirty-one lip cancers were identified, corresponding to elevated risks for both invasive and *in situ* lip cancers (standardized incidence ratios of 15.3 and 26.2, respectively). Invasive lip cancer incidence was associated with male sex (adjusted incidence rate ratio [aIRR] 2.01, 95%CI 1.44–2.82), transplanted organ (0.33, 0.20–0.57, for liver transplants and 3.07, 1.96–4.81, for lung transplants, compared with kidney transplants), and racial/ethnic groups other than non-Hispanic whites (0.09, 0.04–0.20). In addition, incidence increased with age and during the first three years following transplant, and was higher in recipients prescribed cyclosporine/azathioprine maintenance therapy (aIRR 1.79, 95%CI 1.09–2.93, compared with use of tacrolimus/mycophenolate mofetil) and following a diagnosis of cutaneous squamous cell carcinoma (4.21, 2.69–0.94). The elevation in lip cancer incidence is consistent with an effect of immunosuppression. Notably, the very strong associations with white race and history of prior skin cancer point to an important role for ultraviolet radiation exposure, and cyclosporine and azathioprine may contribute as photosensitizing or DNA damaging agents.

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1. Introduction

In the United States, nearly 30,000 individuals receive a transplant yearly, and more than 300,000 Americans are living with a solid organ transplant (1). The success of transplantation relies upon the use of immunosuppressive medications to prevent organ rejection (2). However, the general inhibition of the immune system makes patients more susceptible to infections and cancer (2). Following transplantation, cancer risk increases 2–3 fold compared to the general population (3). Risks are especially increased for cancers associated with viral infections, such as non-Hodgkin lymphomas (caused by Epstein-Barr virus) and anogenital cancers (caused by human papillomavirus [HPV]) (4–7).

Transplant recipients have a markedly elevated risk of lip cancer, with standardized incidence ratios (SIRs) from different countries indicating 13- to 66-fold increased incidence compared with the general population (3, 6, 8–12). Lip cancers occur on either the external lip (vermillion border) or the mucosal lip (internal surface, contiguous with the oral cavity) and are predominantly squamous cell carcinomas (SCCs) (13, 14). Ultraviolet radiation (UVR) is an important cause of cancers of the external lip (15), while mucosal lip cancers are related to alcohol and tobacco consumption (16). There has been interest in whether HPV may contribute to some cases, although results are inconclusive (17, 18). Among transplant recipients, elevated lip cancer risk has been associated with UVR exposure, use of cyclosporine or azathioprine as maintenance immunosuppressive therapy, higher dose and prolonged duration of immunosuppression, and increasing time since transplantation (14, 19).

However, as lip cancer is a rare malignancy, there are consequently few studies on lip cancer among transplant recipients (14, 19), and risk factors are not well documented. In the present study, we used data from the Transplant Cancer Match (TCM) Study to describe the epidemiology of lip cancer among transplant recipients in the United States.

2. Materials and Methods

The TCM Study is described in detail elsewhere (https://transplantmatch.cancer.gov/) (6). Briefly, this study links the Scientific Registry of Transplant Recipients (SRTR), a national registry of all US solid organ transplants since 1987, with 17 population-based cancer registries. The TCM Study was approved by the institutional review board at the National Cancer Institute (NCI) and, as required, by each participating cancer registry.

The SRTR collects information from transplant centers on transplant recipient demographic characteristics and clinical data. Cancer registries collect information on all cancers diagnosed within their geographic area (other than keratinocyte carcinomas arising at non-genital sites, i.e., cutaneous basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]). Although cutaneous BCC and SCC are not captured by cancer registries, these diagnoses are reported by transplant centers following transplantation and included in the SRTR. We previously assessed the accuracy of SRTR reports of BCC and SCC in relation to Medicare claims (20). We found that 14% of BCC cases and 22% of SCC cases reported to Medicare were captured by the SRTR, 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 skin cancers. Overall, cancer registries participating in the TCM Study provide data for approximately 50% of US transplant recipients.

Our population included all recipients who received transplants during 1987–2014 and who resided in an area covered by a TCM cancer registry at the time of listing or transplantation. We restricted the study to individuals of the major racial/ethnic groups (non-Hispanic white, non-Hispanic black, Hispanic, and Asian/Pacific Islander) to allow comparisons with general population lip cancer rates. From the SRTR, we obtained information on immunosuppressive agents used for induction and the baseline maintenance regimen prescribed at the time of transplantation (categorized as including cyclosporine and/or azathioprine, excluding use of tacrolimus and mycophenolate mofetil; tacrolimus and/or mycophenolate mofetil, excluding cyclosporine and azathioprine; and other regimens).

To create a proxy variable for UVR exposure, we linked recipient zip codes of residence at the time of listing/transplantation to the National Aeronautics and Space Administration Total Ozone Mapping Spectrometer database (21). These data provide satellite-based estimates of ambient cloud-adjusted UVR on a 1 degree latitude by 1 degree longitude grid. Daily average at noontime during 1982–1992 was calculated to account for fluctuations in the 11-year solar cycle.

Invasive and *in situ* lip cancers were identified from the linked cancer registries. We included all lip cancers coded using the International Classification of Diseases for Oncology (third edition) as arising on the external lip (topography codes C00.0–00.2, C00.6), mucosal lip (C00.3–00.5), or unspecified or overlapping locations (C00.8–00.9) (22). We excluded cancers classified as arising on the skin of the lip (C44.0), as these are considered skin cancers. SCC of the lip was captured using morphology codes (8050–8084).

To assess the validity of lip cancer diagnoses, pathology reports and other documentation from 41 cases were reviewed by staff at five participating cancer registries. Following review, one case was determined to be a misclassified skin cancer (topography C44.0) and excluded. Two other cases had their subsites reclassified (from C00.2 to C00.1, and from C00.9 to C00.1). In total, 231 lip cancers were included in this study. Of the 123 lip cancers with information on reporting source, 99 (80.5%) were diagnosed in hospitals.

Follow-up of recipients started at the date of transplantation and ended at the earliest of lip cancer diagnosis, death, transplant failure/retransplantation, loss to follow-up, or end of cancer registry coverage. For recipients with multiple transplants, person-time was calculated separately for each transplant.

We computed SIRs to compare lip cancer incidence among recipients with the expected incidence using general population incidence rates stratified according to age, sex, race/ethnicity, calendar year, and cancer registry region. We present SIRs for lip cancer separately according to tumor behavior (invasive and *in situ*) and subsite (external vs. internal lip). In addition, we calculated SIRs separately for non-Hispanic whites and other racial/ethnic groups.

Because lip cancers were predominantly SCCs, we focused our analyses of risk factors on invasive lip SCCs (combining all subsites). We used Poisson regression to estimate adjusted incidence rate ratios (aIRRs) mutually adjusted for all of the evaluated demographic and clinical factors (Table 3). Cutaneous BCC and SCC diagnoses were considered time-dependent variables in the Poisson model. Because the associations with age at transplant and time since transplant appeared nonlinear, we assessed models using cubic splines. These suggested a single change in slope for these variables, so we fitted the relationships using piecewise linear models with a single knot (age at transplant: knot at 20 years old; time since transplant: knot at 3 years).

We also show aIRRs separately for invasive external and mucosal lip SCC. Finally, in an analysis restricted to non-Hispanic whites (among whom most cases occurred), we used backwards selection to identify significant independent risk factors for invasive lip SCC. Stata (release 15, StataCorp, College Station, TX) and SAS (version 9.3, SAS Institute, Cary, NC) were used for statistical analyses.

3. Results

The study included 261,500 individuals who received 283,832 organ transplants, contributing 1.43 million person-years of follow-up (median 3.96 years, interquartile range 1.43–7.55). As shown in Table 1, transplant recipients were predominantly males (61.5%) and non-Hispanic whites (62.5%), with a median age at transplant of 49.0 years. The most common transplanted organ was the kidney (58.0%) followed by liver (21.8%), heart (9.5%), and lung (4.6%).

Overall, 231 lip cancers were diagnosed during follow-up (incidence 16.2 per 100,000 person-years). Of these, 206 were invasive cancers (89.2%) and 25 were *in situ* cases (10.8%). Both invasive and *in situ* lip cancers were predominantly SCC (98.5% and 88.0%, respectively), with the external lip the most common subsite (82.3% and 77.3% of invasive and *in situ* cases, respectively). The majority of invasive lip cancers were diagnosed at localized stage (90.8%), while the remainder had regional (1.5%), distant (0.5%), or unspecified stage (7.3%).

Table 2 presents SIRs for lip cancer. Compared to the general population, risks were elevated for both invasive lip cancer (SIR 15.3, 95%CI 13.3–17.6), and *in situ* lip cancer (SIR 26.2, 17.0–38.9). Similar elevations were observed specifically for SCC of the lip (SIR 16.2 for invasive cancer, 29.5 for *in situ* cancer), SCC of the external lip (SIR 17.2 for invasive cancer, 27.7 for *in situ* cancer), and SCC of the mucosal lip (SIR 14.8 for invasive cancer, 38.2 for *in situ* cancer). In addition, we calculated SIRs for invasive SCC according to race/ethnicity. The elevation in non-Hispanic whites was much greater (SIR 17.5, 95%CI 15.1–20.1) than in other racial/ethnic groups, although their risk was still elevated (SIR 5.7, 95%CI 2.1–12.4).

Table 3 presents risk factors for invasive SCC of the lip (all subsites combined). Incidence was significantly higher in males compared to females (aIRR 2.01, 95%CI 1.44–2.82). Racial/ethnic groups other than non-Hispanic whites had greatly decreased incidence (aIRR

0.09, 95%CI 0.04–0.20). Compared with kidney recipients, incidence was lower in liver recipients (aIRR 0.33, 95%CI 0.20–0.57), similar in heart recipients (aIRR 0.98, 95%CI 0.67–1.42), and increased for lung recipients (aIRR 3.07, 95%CI 1.96–4.81).

Figure 1 depicts unadjusted associations with age at transplantation and time since transplantation. Incidence increased steeply until age 20 then leveled off (Figure 1A), and the median age at diagnosis of invasive lip SCC was 50 years. The pattern incidence can also be seen in Table 3, where aIRRs indicate increases in incidence of 41% per year of age up to age 20 (aIRR 1.41, 95%CI 0.96–2.09) and 1% per year of age subsequently (aIRR 1.01, 95%CI 1.00–1.02). As shown in Figure 1B and Table 3, incidence increased strongly in the first 3 years after transplantation at 71% per year (aIRR 1.71, 95%CI 1.40–2.08). After the first 3 years, incidence appeared to level off, and in the adjusted models this corresponded to a slight decrease of −4% per year (aIRR 0.96, 95%CI 0.92–1.00).

Incidence declined across calendar periods (p-trend=0.01, Table 3). Incidence was also lower in individuals who received anti-interleukin-2 antibody induction therapy (aIRR 0.47, 95%CI 0.24–0.94) compared to those who did not receive induction therapy. Among baseline maintenance immunosuppressive regimens, incidence was higher for individuals who received cyclosporine and/or azathioprine (aIRR 1.79, 95%CI 1.09–2.93) compared to those who had only received tacrolimus and/or mycophenolate mofetil.

A diagnosis of cutaneous SCC was associated with increased incidence of lip cancer (aIRR 4.21, 95%CI 2.69–6.58). Although incidence was also higher in recipients with cutaneous BCC (Table 3), there was no association after multivariate adjustment (aIRR 0.95, 95%CI 0.47–1.91). Finally, UVR exposure as assessed by residence at the time of listing/transplantation was not associated with lip cancer incidence (Table 3). In addition, we found no interaction between cyclosporine/azathioprine use and UVR exposure with respect to the incidence of lip SCC (not shown).

Since most invasive SCCs were located on the external lip, aIRRs were similar for invasive external SCC of the lip for most risk factors (Table 3). For invasive SCC of the mucosal lip, there were few cases (N=29), so most aIRRs were not precisely estimated. However, the pattern was largely similar to that for external lip SCC, with the possible exception of an attenuated association with cutaneous SCC (aIRR 1.49, 95%CI 0.32–6.94). Of note, incidence of mucosal lip SCC was strongly increased among recipients who received cyclosporine/azathioprine as baseline maintenance therapy compared to a tacrolimus/mycophenolate mofetil regimen (aIRR 5.24, 95%CI 1.14–24.2).

Table 4 presents independent risk factors for invasive SCC of the lip among non-Hispanic white recipients. As UVR exposure, induction therapy, and cutaneous BCC diagnosis were the least significant variables, they were removed from the final model following backwards selection. Associations for the remaining risk factors were similar in magnitude to those shown in Table 3, for SCC overall, SCC of the external lip, and SCC of the mucosal lip.

4. Discussion

With the increasing success of transplantation, recipients are living longer with functional grafts. However, use of immunosuppressive medications is associated with adverse effects, including susceptibility to development of some cancers. In our study of more than 260,000 US transplant recipients, we found an elevated risk of lip cancer, most cases of which were invasive SCCs.

The risk that we observed for invasive lip cancer was very high, corresponding to a 15-fold higher incidence compared with the general population, and the increase for *in situ* cancers was even stronger (SIR 26.2). Similarly, prior studies of solid organ transplant recipients conducted in several countries have demonstrated SIRs in the range of 13–66 for invasive lip cancer (3, 6, 8–12). In contrast, risk of lip cancers is elevated to a lesser degree among individuals diagnosed with acquired immunodeficiency syndrome (AIDS) and others infected with human immunodeficiency virus (HIV), who have a compromised immune system comparable to transplant recipients. Among HIV-infected individuals, SIRs for invasive lip cancer are typically in the range of 2–6 (3, 23). Thus, while the elevated SIR in both transplant recipients and people with HIV/AIDS supports a role for immunosuppression in the development of lip cancer, the much greater elevation among transplant recipients suggests that additional factors are also important (3).

Our results point to an etiologic role for UVR, since many of the significant risk factors for lip cancer were indicators of UVR effects. The majority of lip cancers were in non-Hispanic whites, and the incidence was much higher among non-Hispanic whites than other racial/ethnic groups. Skin pigmentation is a result of melanocyte activity and provides protection against UVR (24). In addition, we observed a strong association between diagnosis of a cutaneous SCC and subsequent incidence of lip cancer, as we reported in a previous study that utilized TCM data (20). BCC was also associated with lip cancer incidence, but the association was attenuated when we adjusted for cutaneous SCC and other factors. UVR is a strong risk factor for cutaneous SCC and BCC in the general population (25, 26), so the association with SCC may indicate that certain transplant recipients who are especially susceptible to UVR-induced skin damage are those most likely to develop lip cancer. On the other hand, the ecological measurement of UVR exposure that we used was not significantly associated with the risk of lip cancer. Because this measure captures the average ambient UVR levels at the place where individuals lived around the time of transplantation, it does not capture UVR levels where they lived earlier or later in life or behaviors related to sun exposure (e.g., time spent outdoors, use of protective clothes and sunscreen, tanning). Therefore, misclassification of UVR exposure may explain the lack of association of this measure with lip cancer (27).

UVR exposure is likely important, but it cannot by itself explain the strong elevation in lip cancer incidence, since transplant recipients as a group are unlikely to be substantially more exposed to UVR than the general population. Although all maintenance medications have a major immunosuppressive effect, some also have photosensitizing or other DNA damaging effects that may contribute directly to the occurrence of lip cancer. We observed an association of maintenance therapy with cyclosporine and/or azathioprine with increased lip

cancer incidence. Although use of these medications has declined markedly over time, their association with lip cancer incidence persisted after adjustment for calendar year of transplantation. Importantly, azathioprine and cyclosporine are classified as human carcinogens by the International Agency for Research on Cancer (IARC), at least in part because of non-immunosuppressive effects (28). Metabolism of azathioprine results in the incorporation of 6-thioguanine into DNA, and 6-thioguanine DNA is a chromophore that absorbs ultraviolet A radiation, producing highly damaging reactive oxygen species (29). Furthermore, use of azathioprine is associated with increased skin sensitivity to UVR (30). Cyclosporine has been described as a promotor of tumor growth through induction of transforming growth factor β and vascular endothelial growth factor (31, 32). Cyclosporine also interferes directly with DNA repair (33, 34).

A direct DNA-damaging effect of these medications may explain the association of cyclosporine/azathioprine maintenance therapy with lip cancer, especially since the association was strongest for mucosal lip cancer and the interior of the lip is not highly exposed to UVR. Several additional findings are also indirectly consistent with an effect of maintenance medications on the incidence of lip cancer. First, the increasing risk of lip cancer with greater time since transplant is consistent with effects of long-term duration of exposure to these medications. Second, the associations with transplanted organs may reflect medication dose, as liver transplantation typically requires less immunosuppression, and lung transplantation requires more immunosuppression, compared to kidney transplantation.

Although IARC has classified the link between UVR and lip cancer as causal, prior studies on UVR exposure and lip cancer in transplant recipients are limited, probably because of the rarity of lip cancer. van Leeuwen et al. (14) showed that UVR is a risk factor for lip cancer in Australia, using race and residential latitude as surrogates for exposure. In the general population, several studies have shown strong associations between lip cancer and outdoor occupations (35), such as agricultural work (35, 36). In addition, we and van Leeuwen et al. (14) observed that male kidney transplant recipients were at greater risk of developing lip cancer than females. In the US general population, the male-to-female ratio for incidence is among the highest for lip cancer when compared with other cancer sites (37). It has been suggested that the excess of lip cancer in males could reflect greater tobacco or alcohol consumption, outdoor occupational exposure, or hormonal differences between the sexes (37).

Although our findings point to the importance of factors other than immunosuppression, we cannot entirely rule out a contribution of immunosuppression. Immunosuppression is thought to be most relevant in increasing the risk of cancers caused by viruses. Mucosal lip cancer is a type of oral cavity cancer, and the possibility of HPV playing a role has been raised based on the etiologic contribution of mucosal HPVs (alpha genus, especially HPV-16) to oropharyngeal cancer (38). External lip cancers arising on the vermillion border share similarities with cutaneous SCCs, and there has been interest in whether cutaneous HPVs (beta or gamma genera) are involved in these skin cancers (39). At this time, however, the causal relationship between HPV and skin cancer is unclear (40). Since the presence of HPV in lip cancer tumors has been reported in small case series only (17, 41, 42), no definite conclusions can be drawn on a causal role.

Two additional findings deserve brief comment. First, we observed that the incidence of lip cancer increased with age at transplantation. Similar increases are observed for many other cancers, and for lip cancer this pattern may reflect the age-related accumulation of genetic damage from UVR or other exposures. Second, lip cancer incidence was reduced in recipients who were administered induction therapy with interleukin-2 antagonists. The reason for this protective association is unclear, but it may be a marker for the ability of transplant providers to subsequently reduce the dose of maintenance immunosuppressive medications which may themselves be carcinogenic.

A strength of this study is the evaluation of a large cohort representative of all US transplant recipients. The cohort size allowed us to study lip cancer in detail, and assess risk factors using multivariate analysis. Although some important risk factors were available from the TCM Study for analyses, a limitation is that we lacked information on doses and changes over time in maintenance immunosuppressive medications. We also lacked data on tobacco and alcohol consumption, which are important risk factors in the general population, as well as tumor HPV status. Another potential issue is that some lip cancers actually may have been misdiagnosed skin cancers arising near the lip. However, we reviewed pathology reports from five participating cancer registries and confirmed the accuracy of most of these cases, suggesting that others that we could not review were also accurately reported. Finally, it is possible that we underestimated the incidence of lip cancer in transplant recipients, because cases would not have been reported to cancer registries if dermatologists or other providers considered them skin cancers. We observed that 80.5% of lip cancers in transplant recipients were reported by hospitals. If there was a greater likelihood of hospital work-up among transplant recipients, compared with other cases in the general population, this might have led to greater reporting for those cancers to cancer registries. This would have caused us to overestimate the SIRs, but should not have affected the validity of our risk factor analyses. To the extent that treatment patterns and registry ascertainment of cancer cases vary, the SIRs assessed in cohort studies in different countries could be affected.

In conclusion, there is a markedly high incidence of lip cancer among transplant recipients. Our analyses support that UVR exposure is an important risk factor, and transplant recipients should be counseled on practices to minimize sun exposure, such as use of protective clothing and sunscreen (including lip sunscreen or lipstick that provides documented protection against UVR) when spending time outdoors. Transplant recipients should receive regular skin cancer screening which should include examination of the lip.

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Abbreviations

AIDS	acquired immunodeficiency syndrome
aIRR	adjusted incidence rate ratio
AZA	azathioprine
BCC	basal cell carcinoma
CI	confidence interval
CS	cyclosporine
DNA	deoxyribonucleic acid
HIV	human immunodeficiency virus
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IRR	incidence rate
MMF	mycophenolate mofetil
NCI	National Cancer Institute
SCC	squamous cell carcinoma
SIR	standardized incidence ratio
SOT	solid organ transplantation
SRTR	Scientific Registry of Transplant Recipients

TAC	tacrolimus
TCM	Transplant Cancer Match study
UVR	ultraviolet radiation

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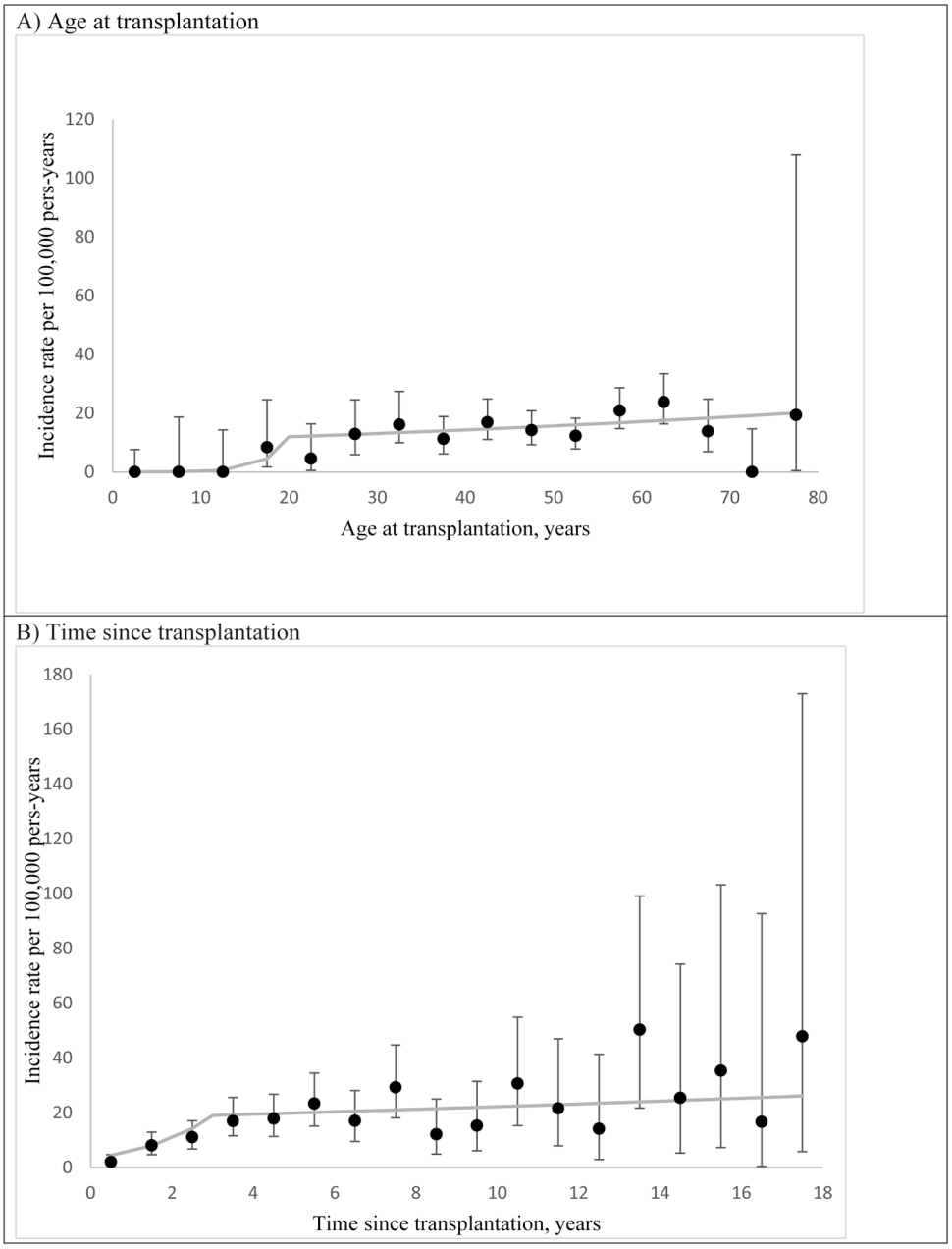

Figure 1.

Association of lip cancer with A) age at transplantation, and B) time since transplantation.

Table 1.

Characteristics of solid organ transplant recipients in the United States Transplant Cancer Match Study (N=283,832)

Characteristic	Number of transplants (% of total)
Sex	
Female	109,357 (38.5)
Male	174,475 (61.5)
Age at transplantation, years	
0-17	20,533 (7.2)
18-34	42,661 (15.0)
35-49	84,526 (29.8)
50-64	107,769 (38.0)
65+	28,343 (10.0)
Race/ethnicity	
White, non-Hispanic	177,493 (62.5)
Black, non-Hispanic	49,523 (17.5)
Hispanic	41,231 (14.5)
Asian/Pacific Islander	15,585 (5.5)
Transplanted organ	
Kidney	164,528 (58.0)
Liver	61,908 (21.8)
Heart	26,916 (9.5)
Lung	12,948 (4.6)
Other/multiple	17,532 (6.2)
Transplant number	
First	261,500 (92.1)
Second or higher	22,332 (7.9)
Calendar year of transplantation	
1987-1994	36,949 (13.0)
1995-1999	59,728 (21.0)
2000-2004	73,436 (25.9)
2005-2009	82,705 (29.1)
2010-2014	31,014 (10.9)

Participating registries include the following, with years of coverage in parentheses: California (1988-2012), Colorado (1988-2009), Connecticut (1973-2009), Florida (1981-2009), Georgia (1995-2010), Hawaii (1973-2007), Illinois (1986-2013), Iowa (1973-2009), Kentucky (1995-2011), Michigan (1985-2009), New Jersey (1979-2010), New York (1976-2010), North Carolina (1990-2010), Pennsylvania (1985-2013), Seattle-Puget sound area of Washington (1974-2014), Texas (1995-2010), and Utah (1973-2008).

Table 2.

Standardized incidence ratios for lip cancer among US solid organ transplant recipients

Behavior of lip cancer	Histology and subsite of lip cancer	Observed cases	SIR (95%CI)
Invasive			
	Overall	206	15.3 (13.3-17.6)
	SCC, all subsites	203	16.2 (14.0-18.5)
	SCC, external	167	17.2 (14.6-19.9)
	SCC, mucosal	29	14.8 (9.9-21.3)
	SCC, overlapping/unspecified	7	7.9 (3.2-16.3)
In situ			
	Overall	25	26.2 (17.0-38.9)
	SCC all subsites	22	29.5 (18.4-44.4)
	SCC, external	17	27.7 (16.2-44.6)
	SCC, mucosal	5	38.2 (12.5-89.8)

Abbreviations: CI, confidence intervals; SCC, squamous cell carcinoma; SIR, standardized incidence ratio.

Table 3.

Risk factors for invasive lip squamous cell carcinoma among US transplant recipients

	SCC (N=203)			SCC external lip (N=167)			SCC mucosal lip (N=29)		
Characteristics	**N**	**Incidence**	**aIRR (95%CI)**	**N**	**Incidence**	**aIRR (95%CI)**	**N**	**Incidence**	**aIRR (95%CI)**
Sex									
Female	45	8.0	Reference	36	6.4	Reference	6	1.1	Reference
Male	158	18.2	**2.01 (1.44-2.82)**	131	15.1	**2.08 (1.43-3.03)**	23	2.7	2.39 (0.96-5.95)
Age at transplantation									
Per year, age <20 years	3	2.3	1.41 (0.96-2.09)	2	1.6	1.43 (0.92-2.22)	0	-	-
Per year, age ≥20 years	200	15.4	1.01 (1.00-1.02)	165	12.7	1.01 (1.00-1.03)	29	2.2	1.03 (0.99-1.06)
Transplanted organ									
Kidney	101	12.3	Reference	83	10.1	Reference	17	2.1	Reference
Liver	17	5.3	**0.33 (0.20-0.57)**	16	5.0	**0.36 (0.21-0.63)**	1	0.3	0.15 (0.02-1.16)
Heart	45	28.1	0.98 (0.67-1.42)	36	22.5	0.93 (0.62-1.41)	5	3.1	0.64 (0.23-1.81)
Lung	27	56.4	**3.07 (1.96-4.81)**	21	43.9	**2.90 (1.75-4.80)**	5	10.4	**3.62 (1.23-10.7)**
Other/multiple	13	16.4	1.31 (0.72-2.37)	11	13.9	1.28 (0.67-2.44)	1	1.3	0.82 (0.11-6.4)
Race/ethnicity									
White, non-Hispanic	197	21.0	Reference	164	17.5	Reference	26	2.8	Reference
Other	6	1.2	**0.09 (0.04-0.20)**	3	0.6	**0.05 (0.02-0.16)**	3	0.6	0.30 (0.09-1.02)
Years since transplantation									
Per year, <3 years	42	30.3	**1.71 (1.40-2.08)**	37	26.7	**1.64 (1.33-2.02)**	5	**3.6**	**1.94 (1.10-3.42)**
Per year, ≥3 years	161	12.5	0.96 (0.92-1.00)	129	10.0	**0.95 (0.90-0.99)**	24	1.9	0.99 (0.88-1.11)
Calendar year of transplantation[a]									
1987-1994	80	30.1	Reference	65	24.5	Reference	12	4.5	Reference
1995-1999	75	18.0	0.78 (0.55-1.11)	63	15.1	0.78 (0.53-1.15)	9	2.2	0.60 (0.23-1.57)
2000-2004	29	6.8	**0.46 (0.27-0.79)**	22	5.2	**0.40 (0.21-0.73)**	6	1.4	0.74 (0.20-2.70)
2005-2009	18	6.5	0.51 (0.26-1.01)	15	5.4	**0.46 (0.22-0.99)**	2	0.7	0.58 (0.09-3.95)
2010-2014	1	2.3	0.19 (0.03-1.45)	1	2.3	0.20 (0.03-1.58)	0	0	-
Skin BCC diagnosis									
No	194	13.7	Reference	158	11.2	Reference	28	2.0	Reference

	SCC (N=203)			SCC external lip (N=167)			SCC mucosal lip (N=29)		
Characteristics	**N**	**Incidence**	**aIRR (95%CI)**	**N**	**Incidence**	**aIRR (95%CI)**	**N**	**Incidence**	**aIRR (95%CI)**
Yes	9	58.5	0.95 (0.47-1.91)	8	52.1	1.02 (0.48-2.16)	1	6.5	0.89 (0.11-7.08)
Skin SCC diagnosis									
No	174	12.3	Reference	140	9.9	Reference	27	1.9	Reference
Yes	29	148.9	**4.21 (2.69-6.58)**	26	133.5	**4.95 (3.06-8.01)**	2	10.0	1.49 (0.32-6.94)
Induction therapy									
None	144	17.1	Reference	120	14.3	Reference	19	2.3	Reference
Monoclonal	21	27.5	1.09 (0.68-1.75)	17	22.3	1.13 (0.63-1.79)	3	3.9	1.24 (0.36-4.33)
Polyclonal	25	10.5	0.78 (0.50-1.21)	21	8.8	0.77 (0.48-1.25)	4	1.7	1.07 (0.35-3.24)
Anti-interleukin-2 antibody	10	4.7	**0.47 (0.24-0.94)**	6	2.8	**0.34 (0.14-0.80)**	3	1.4	0.99 (0.25-3.93)
Other/multiple	3	5.0	0.55 (0.17-1.81)	2	3.4	0.41 (0.10-1.74)	0	0	-
Baseline maintenance therapy regimen[b]									
TAC/MMF	42	5.9	Reference	38	5.4	Reference	3	0.4	Reference
CS/AZA	120	30.2	**1.79 (1.09-2.93)**	98	24.7	1.46 (0.86-2.48)	18	4.5	**5.24 (1.14-24.2)**
Other/multiple	41	12.6	1.07 (0.66-1.75)	30	9.2	0.85 (0.49-1.46)	8	2.5	3.53 (0.83-15.0)
UVR exposure[c]									
Quartile 1	60	15.8	Reference	50	13.2	Reference	7	2.3	Reference
Quartile 2	38	10.6	0.88 (0.59-1.33)	32	8.9	0.93 (0.60-1.45)	1	0.3	0.49 (0.13-1.84)
Quartile 3	68	18.5	**1.49 (1.05-2.12)**	56	15.2	**1.48 (1.01-2.18)**	8	3.0	1.60 (0.63-4.11)
Quartile 4	37	11.4	0.98 (0.65-1.49)	28	8.6	0.90 (0.57-1.44)	4	1.5	1.49 (0.55-4.04)

[*] Abbreviations: aIRR, adjusted incidence rate ratio; AZA, azathioprine; BCC, basal cell carcinoma; CI, confidence intervals; CS, cyclosporine; MMF, mycophenolate mofetil; SCC, squamous cell carcinoma; TAC, tacrolimus; UVR, ultraviolet radiation. Incidence rates are reported as events per 100,000 person-years of follow-up. IRRs were derived from multivariate Poisson regression models, and characteristics under study are mutually adjusted.

[a] The p-trend for calendar year of transplantation is 0.01.

[b] "CS/AZA" includes all individuals taking cyclosporine or azathioprine and not taking tacrolimus or mycophenolate mofetil. "TAC/MMF" includes all individuals taking tacrolimus or mycophenolate mofetil and not taking cyclosporine or azathioprine.

[c] Quartiles of UVR are based on residential zip codes at the time of listing or transplantation (see Methods). Quartile 1 corresponds to the lowest and quartile 4 to the highest UVR exposure.

Table 4.

Risk factors for invasive lip squamous cell carcinoma among non-Hispanic whites US transplant recipients

	SCC (N=203)	SCC external lip (N=167)	SCC mucosal lip (N=29)
Characteristics	**aIRR (95%CI)**	**aIRR (95%CI)**	**aIRR (95%CI)**
Sex			
Female	Reference	Reference	Reference
Male	**1.93 (1.37-2.71)**	**2.02 (1.38-2.94)**	2.14 (0.85-5.42)
Age at transplantation			
Per year, age <20 years	1.41 (0.95-2.08)	1.42 (0.91-2.20)	-
Per year, age ≥20 years	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.03 (1.00-1.06)
Transplanted organ			
Kidney	Reference	Reference	Reference
Liver	**0.37 (0.22-0.63)**	**0.41 (0.24-0.71)**	0.15 (0.02-1.18)
Heart	1.04 (0.72-1.52)	1.01 (0.67-1.52)	0.60 (0.19-1.86)
Lung	**3.12 (1.99-4.90)**	**2.88 (1.73-4.78)**	**3.98 (1.37-11.6)**
Other/multiple	1.34 (0.75-2.43)	1.31 (0.71-2.54)	0.82 (0.11-6.30)
Years since transplantation			
Per year, <3 years	**1.71 (1.40-2.08)**	**1.62 (1.32-2.00)**	**2.15 (1.17-3.96)**
Per year, ≥3 years	**0.95 (0.91-0.99)**	**0.95 (0.90-0.99) 99)**	0.94 (0.83-1.08)
Calendar year of transplantation			
1987-1994	Reference	Reference	Reference
1995-1999	0.73 (0.53-1.07)	0.75 (0.51-1.11)	0.47 (0.17-1.31)
2000-2004	**0.37 (0.21-0.63)**	**0.32 (0.18-0.59)**	0.51 (0.13-1.95)
2005-2009	**0.37 (0.19-0.73)**	**0.32 (0.15-0.68)**	0.41 (0.06-2.73)
2010-2014	0.14 (0.02-1.07)	0.15 (0.02-1.15)	-
Skin SCC diagnosis			
No	Reference	Reference	Reference
Yes	**4.15 (2.65-6.50)**	**4.99 (3.10-8.03)**	0.88 (0.11-6.89)
Baseline maintenance therapy regimen			
TAC/MMF	Reference	Reference	Reference
CS/AZA	**1.78 (1.09-2.93)**	1.54 (0.91-2.63)	4.11 (0.84-20.1)
Other/multiple	1.08 (0.66-1.77)	0.90 (0.52-1.54)	3.04 (0.70-13.3)

*Abbreviations: aIRR, adjusted incidence rate ratio; AZA, azathioprine; CI, confidence intervals; CS, cyclosporine; MMF, mycophenolate mofetil; SCC, squamous cell carcinoma; TAC, tacrolimus.