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HPV-Related Cancers after Solid Organ Transplantation in the US

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Abstract

Transplant recipients have elevated cancer risk including risk of human papillomavirus (HPV)-associated cancers of the cervix, anus, penis, vagina, vulva, and oropharynx. We examined the incidence of HPV-related cancers in 187,649 U.S. recipients in the Transplant Cancer Match Study. Standardized incidence ratios (SIRs) compared incidence rates to the general population, and incidence rate ratios (IRR) compared rates across transplant subgroups. We observed elevated incidence of HPV-related cancers (SIRs: *in situ* 3.3–20.3, invasive 2.2–7.3), except for invasive cervical cancer (SIR 1.0). Incidence increased with time since transplant for vulvar, anal, and penile cancers (IRRs 2.1–4.6 for 5+ vs. <2 years). Immunophenotype, characterized by decreased incidence with HLA DRB1:13 and increased incidence with B:44, contributed to susceptibility at several sites. Use of specific immunosuppressive medications was variably associated with incidence; for example, tacrolimus, was associated with reduced incidence for some anogenital cancers (IRRs 0.4–0.7) but increased incidence of oropharyngeal cancer (IRR 2.1). Thus, specific features associated with recipient characteristics, transplanted organs, and medications are associated with incidence of HPV-related cancers after transplant. The absence of increased incidence of invasive cervical cancer highlights the success of cervical screening in this population and suggests a need for screening of other HPV-related cancers.

Keywords

HPV-related cancer; organ transplant cohort; Transplant Cancer Match study; immunosuppression

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Supplemental Information

Additional Supporting Information may be found in the online version of this article.

INTRODUCTION

Solid organ transplant recipients are at increased risk of several pathogen-associated cancers, including those caused by infection with human papillomavirus (HPV), Epstein Barr virus, and hepatitis B and C viruses. These virus-related cancers emerge in the setting of immune suppression maintained by drugs that prevent rejection of transplanted organs. The level of immune suppression varies by factors such as type of organ, level of HLA matching between donor and recipient, and drug regimen (1).

HPV is the central etiologic agent in cervical and anal cancers and is causally associated with subsets of vaginal, vulvar, penile, and oropharyngeal cancers (2;3). The mechanism by which HPV oncoproteins contribute to genetic instability and cancer in the transplant setting is likely similar to that in the immune competent population, but time to development of HPV-related cancers may be accelerated by iatrogenic immune suppression. Published studies of cancers arising after solid organ transplant, including a meta-analysis (4) and a large study in England (5), indicate that HPV-related malignancies occur in substantial excess after solid organ transplantation.

The U.S. Transplant Cancer Match (TCM) Study (http://transplantmatch.cancer.gov/) is an ongoing linkage between the nationwide U.S. organ transplant registry and 15 state and local cancer registries (6). The TCM Study found that solid organ transplant recipients are at approximately 2-fold increased risk of any type of cancer compared to the general population (6). Further, the risks for pathogen-associated cancers, such as non-Hodgkin lymphoma, liver cancer, and Kaposi sarcoma, were sharply elevated. In this analysis we focused on the excess incidence for HPV-related malignancies, namely *in situ* and invasive cervical, anal, penile, vaginal, vulvar, and oropharyngeal cancers, among transplant recipients in the TCM Study.

METHODS

Detailed methods for the ongoing TCM Study were published (6). This report extends our prior study by including estimates of cancer risk related to demographic and transplant-associated risk factors, immune-related factors, and medications. We also included *in situ* cancers in this study but not in our prior report. We linked national transplant and cancer registry data. The Scientific Registry of Transplant Recipients (SRTR), which provides complete ascertainment of the US transplant population, includes information on transplant characteristics and demographics. The cancer registries all comply with the high standards of the CDC National Program of Cancer Registries and/or the NCI Surveillance, Epidemiology and End Results Program, which sponsor the cancer registries used in this match. Vital status information was obtained through linkage with the US Social Security Death Master File. The cancer registries were analyzed for all malignancies after transplant until death, failure of a transplanted organ, a subsequent transplant, loss to follow up, or last date of cancer registry coverage. Thus, malignancies arising after graft failure and cessation of immunosuppression would not be included.

The current analysis was restricted to recipients transplanted at 18 years of age or older, since HPV-related cancers are very rare at younger ages. We divided person-time among transplant recipients according to several time-varying characteristics, such as calendar year and transplant number, so recipients were included more than once if they received more than one transplant. The study was approved by human subjects' committees at participating cancer registries, as required, and at the National Cancer Institute.

The HPV-related cancers examined in this study include *in situ* and invasive cervical, vaginal, vulvar, anal, and penile cancers. Invasive cancers of the oropharynx, defined to include base of tongue, tonsils, and other oropharynx sites (7), were also included; cancers at other oral sites are less likely to be HPV-related. *In situ* cancers of the oropharynx were excluded due to inconsistent reporting across registries. We restricted this report to case groups with 25 or more cases, and therefore excluded invasive vaginal cancers (n=10).

Data from the SRTR were available from 1987 to 2009. Cancers were identified through the linkage with cancer registries, so analysis was restricted to recipients residing in a cancer registry region. Follow-up started at transplantation or start of cancer registry coverage (whichever was later) and ended at death, graft failure, re-transplantation, loss to follow-up by the transplant registry, or end of cancer registry coverage. This yielded a cohort of 187,649 transplants for record linkage to the cancer registries. Of note, *in situ* cervical cancer surveillance was stopped by most registries after 1995, but two registries collected data until 2008. Analyses of *in situ* cervical cancers were therefore restricted to 17,010 women residing in registry regions while this cancer was actively being ascertained. Geographic registry regions were defined as described in our prior paper (6), except for *in situ* cervical cancer analyses for which we further restricted the cohort to women who were followed during a period when this cancer type was ascertained by cancer registries.

In addition to the SRTR variables used to characterize the recipients and their transplant, we examined several surrogate measures of immunity. These included the number of transplants (1 versus 2+) and level of HLA mismatch across the three loci used for matching (HLA*A, *B, and *DR). We also constructed two HLA-family group variables for DRB1:13 and B:44, which compared recipients with zero copies of each allele to those with one or (rarely) two copies. These specific HLA variables were constructed to test for associations with decreased risk (DRB1:13) or increased risk (B:44), based on associations previously seen for cervical cancer (8;9). We focused our analysis on these two alleles because we wanted to limit multiple comparisons. Based on prior studies, these alleles represent the most consistent finding (DRB1:13) and highest risk estimate (B:44) associated with cervical cancer across the polymorphic HLA region. We investigated associations with history of diabetes mellitus for transplants after 1995, when data on diabetes were most complete. We also examined alcoholic liver disease as an underlying cause of liver transplant, using diagnosis codes available in the transplant database.

We present incidence rates and standardized incidence ratios (SIRs) separately for *in situ* and invasive cancers. The SIR is defined as the ratio of the observed incidence to the incidence expected based on general population rates. Expected counts were derived by applying cancer rates from the cancer registries, specific to sex, age, race/ethnicity, and

calendar year, to person-time at risk among recipients. Incidence rates were calculated as observed counts divided by the person-time at risk accumulated in specific strata within the cohort. Incidence rates were compared across strata using Poisson regression to calculate incidence rate ratios (IRRs).

RESULTS

Selected characteristics of the 187,649 solid organ transplant recipients and the subset followed for *in situ* cervical cancers are described in Table 1. Over half of the recipients were male and white, and the most frequently transplanted organ was the kidney and/or pancreas (59.4% kidney alone; 4.8% kidney and pancreas, or pancreas alone). Compared to the full cohort, the women in the smaller subset followed for *in situ* cervical cancer were younger at transplant and more often received their transplant between 1987 and 1994.

In the total cohort, we observed 890 HPV-related cancers, including 500 *in situ* and 390 invasive cancers. The most common HPV-related cancer site was the vulva (n=350). Compared to the general population, transplant recipients had significantly elevated incidence of *in situ* and invasive cancers at all sites except invasive cervix (Table 2). Among *in situ* cancers, we observed the smallest increases for cervical cancer (SIR 3.3), larger increases for vaginal (SIR 10.6) and anal cancers (SIR 11.6), and the largest increases for penile cancers (SIR 18.6) and vulvar (SIR 20.3). The SIRs for invasive cancers were lower, and ranged from no increased incidence (SIR 1.0) for cervical cancer, to the highest incidence for invasive vulvar cancer (SIR 7.3). Median age at diagnosis was younger for *in situ* compared to invasive cases for cancers of the cervix (6.5 years younger), vulva (10 years), and anus (11 years), but 3 years older for men with *in situ* compared to invasive penile cancer. The time from transplant to diagnosis was similar for *in situ* and invasive cancers and ranged from a median of 2.6 to 5.7 years.

Table 3 presents IRRs comparing incidence of these cancers for subgroups of recipients defined by demographic and transplant-related characteristics; counts and incidence rates for each cancer type are detailed in Supplemental Table 1. Among transplant recipients, anal cancer incidence was higher in women than men (*in situ* IRR 3.0 and invasive IRR 1.8); in contrast, oropharyngeal cancer incidence was lower in women than men (IRR 0.4). Compared to recipients who were 50+ years old at time of transplant, younger recipients (18–34 years old) had higher incidence of *in situ* cervical, vulvar, and anal cancers (IRRs 4.7, 4.1, and 4.7, respectively) and also invasive cervical cancer (IRR 2.4). In contrast, lower incidence of *in situ* penile cancer (IRR 0.4) and invasive oropharyngeal cancer (IRR 0.1) was observed among the younger recipients.

Compared to white women, Hispanic women had higher incidence of *in situ* cervical cancer (IRR 2.8). Hispanics did not have higher incidence for other *in situ* or invasive cancers, including invasive cervical cancer (IRR 1.3). Reduced incidence was noted for *in situ* vulvar, invasive vulvar, and oropharyngeal cancers for non-white compared with white recipients.

Compared to kidney and/or pancreas recipients, liver recipients had a higher incidence of oropharyngeal cancer (IRR 4.4). We investigated the incidence of oropharyngeal cancer among liver recipients by reason for transplant, and found an elevated incidence associated with alcoholic liver disease as the indication for transplant (IRR 5.4, 95% CI 3.3–8.9, compared with other liver recipients). Heart and/or lung recipients had higher incidence of *in situ* penile cancer (IRR 2.7) and invasive vulvar (IRR 1.9), anal (IRR 1.8), and oropharyngeal (IRR 2.0) cancers. Strikingly, incidence of *in situ* and invasive vulvar, anal, and penile cancers all increased with duration of time since transplant, but this pattern was not present for *in situ* or invasive cervical, *in situ* vaginal, or invasive oropharyngeal cancers (Table 3).

In Table 4, we explored immune markers related to cancer incidence. Receiving a second transplant was associated with increased incidence of *in situ* vulvar (IRR 2.0) and anal cancers (*in situ* IRR 4.4 and invasive IRR 2.1), but not invasive vulvar cancer (IRR 1.7). HLA mismatch between donor and recipient (*HLA-A*, *-B,* and *-DRB1* loci) was associated with reduced incidence of vaginal cancer (IRR 0.2 for 5–6 vs. 0–2 mismatches); only oropharyngeal cancer was associated with number of mismatches in the predicted direction (IRR 1.9 for 3 or more mismatches). DRB1:13 carriage was associated with marginally decreased incidence of cervical cancer (*in situ* IRR 0.4 and invasive IRR 0.4), and this decrease was also noted for *in situ* vulvar (IRR 0.4) and anal cancers (*in situ* IRR 0.5 and invasive IRR 0.6). Carriage of B:44 was associated with increased incidence for anal cancer (*in situ* IRR 1.8 and invasive IRR 1.7) and penile cancer (*in situ* IRR 1.9), but not cervical cancer.

There was a significantly increased incidence of vulvar cancer associated with pancreas transplants (counted as pancreas alone or pancreas plus kidney compared to kidney alone, *in situ* IRR 3.1, 95% CI 2.2–4.4 and invasive IRR 2.6, 95% CI 1.1–5.3). However, a history of diabetes mellitus was not significantly associated with incidence of HPV-related cancers (Table 4).

As shown in Table 5, the maintenance immunosuppressive medications cyclosporine and azathioprine were related to increased incidence of *in situ* vulvar, *in situ* penile, and invasive anal cancers. In contrast, we observed decreased incidence with tacrolimus or mycophenolate at these same sites. An inverse pattern was observed for oropharyngeal cancer and these maintenance drugs, so that decreased incidence was associated with cyclosporine and azathioprine and increased incidence with tacrolimus. Almost all transplant recipients (over 90%) received maintenance regimens that included corticosteroids. Corticosteroid use was associated with strongly increased incidence of *in situ* anal cancer (IRR 5.3) but not for invasive anal cancer (IRR 1.2) or other cancers. In contrast, sirolimus, a newer drug, was used as a maintenance medication for fewer than 10% of transplant recipients. A decreased incidence of invasive anal cancer (IRR 0.2) associated with sirolimus was based on exposure of one case and the estimate had wide confidence intervals. Use of induction medications after transplant was associated with decreased incidence of invasive cervical cancer (IRR 0.5) and oropharynx cancer (IRR 0.7 We evaluated the induction medications by mechanisms of action (monoclonal antibody, polyclonal antibody, and interleukin 2 receptor antagonists), to investigate the two significant findings. None of

the individual types of induction medications was significantly associated with a decreased incidence of invasive cervical cancer. The decreased incidence of oropharyngeal cancer was associated with monoclonal antibodies (n=2 exposed cases, IRR 0.2, 95% CI 0.0–0.5), but not other types of induction.

DISCUSSION

HPV is the known cause of cervical cancer (10) and is causally related to substantial subsets of vaginal, vulvar, anal, penile, and oropharyngeal cancers (2;11). We used the Transplant Cancer Match Study data to explore the excess incidence of HPV-related cancers among U.S. solid organ transplant recipients. Compared to the general population, transplant recipients had especially high incidence of *in situ* cancers (SIRs ranging from 3-fold higher for cervical cancer to 20-fold for vulvar and penile cancers), and increased incidence (SIRs 2- to 7-fold) for most invasive cancers, with the exception of cervical cancer.

We observed that most *in situ* HPV-related cancers occurred at younger ages than invasive cancers, reflecting a continuum of progressively disrupted epithelium along a gradient from persistent HPV infection to pre-invasive *in situ* cancer to invasive cancer (12). Higher incidence of *in situ* cancers may partly reflect the increased frequency of interactions that transplant recipients have with medical professionals who monitor their health and immune status after transplant. Thus, it may be that HPV-related cancers come to clinical attention earlier and more often among transplant recipients. Indeed, the lack of increased incidence for invasive cervical cancer points to effective surveillance and treatment of cervical neoplasia in this population.

The most frequently occurring HPV-related cancers in the study were vulvar cancers (n=350). Increased incidence for this cancer was associated with earlier age at transplant, increased time since transplant, and use of the older drugs cyclosporine and azathioprine. The second most frequent cancer was anal cancer (n=156), which shared most risk factors with vulvar cancer. Anal cancer occurred more frequently in women than men, which reflects the sex ratio of anal cancer in the general population (13). This is in contrast to the pattern seen for anal cancer among HIV-infected populations, in which men-who-have-sex-with-men are a large subgroup and shift the sex ratio toward men (14). The third most frequent cancer was oropharyngeal cancer (n=144), of which 81.3% occurred in men. In men and women combined, oropharyngeal cancer incidence was higher with older age at transplant, non-white race, non-kidney organ transplant, increased HLA mismatch, and use of tacrolimus.

Two findings support the idea that cumulative duration of immunosuppression contributes to the risk of these cancers. First, longer time since transplant (5+ years) was associated with increased incidence of *in situ* and invasive vulvar, anal, and penile cancers. Second, the incidence of *in situ* vulvar and anal cancers was higher with second or later transplants than with first transplants. The degree of incompatibility between donor and recipient, and thus the intensity of immunosuppression required to prevent rejection, depends on the level of HLA mismatch (15). However, HLA mismatch seems unlikely to be an important predictor

for HPV-related cancers, as only incidence of oropharyngeal cancer increased with the number of mismatches (IRR 1.9).

We assessed two HLA markers that are putative markers of susceptibility to HPV, based on prior studies in immunocompetent women demonstrating associations with cervical cancer risk. DRB1:13 was associated with decreased risk for cervical cancer in prior studies (8), and in this study it was associated with a significantly lower incidence of *in situ* vulvar cancer (IRR 0.4). Although results for other sites were inconclusive, DRB1:13 was also associated with lower incidence of cervical, anal, and penile cancers. HLA-B:44, an allele related to increased risk of cervical cancer in a U.S. population-based study (9), was associated with elevated incidence of *in situ* vaginal, anal, penile, and invasive anal cancers in our study, although most of these increases were not statistically significant.

Some HPV-related cancers may occur more frequently in recipients with specific medical conditions. For example, we observed an increased incidence of oropharyngeal cancer among liver recipients compared to kidney recipients, and incidence was even higher in the subset who had alcoholic cirrhosis as the indication for liver transplant (IRR 5.4 vs. other indications among liver recipients). Alcohol is a key risk factor in oropharyngeal cancer (16), and our finding supports that damage from alcohol contributes in the transplant setting as well (17). Likewise, smoking is a risk factor common to HPV-related squamous cell cancers, including cervical, penile, vulvar, anal, and oropharyngeal cancers (13;16). Increased incidence of these cancers among heart and/or lung recipients may be attributable in part to tobacco-related conditions that commonly lead to these transplants. In addition, we found a significantly increased incidence of vulvar cancer associated with pancreas transplants, which suggested that type 1 diabetes mellitus, the common indication for pancreas transplant, might contribute to cancer incidence. However, among recipients overall, we found no association between history of diabetes and incidence of any HPV-related cancers.

Maintenance immune suppressive drug regimens generally include a combination of agents that work together to prevent graft rejection: calcineurin inhibitors (tacrolimus or cyclosporine), anti-metabolites (mycophenolate or azathioprine), and corticosteroids (prednisone). Current maintenance regimens, combining tacrolimus and mycophenolate, have largely replaced the older regimen, cyclosporine and azathioprine, though both combinations are still used (18) (19). In our study, the older regimen drugs were associated with approximately 2-fold increased incidence of the anogenital cancers. In contrast, the newer regimen was associated with reduced incidence of anogenital cancers. Opposite impacts of the two calcineurin inhibitors were seen for oropharyngeal cancers (i.e., increased incidence with tacrolimus and decreased with cyclosporine). These observations suggest that although the drugs act through the same general pathway, they are not identical in their effects.(20)

Corticosteroids were associated with 5-fold excess of *in situ* anal cancer and 3-fold borderline excess of invasive vulvar cancer. Outside of the transplant setting, corticosteroids have been associated with excess skin cancer (21). Cancers at anogenital sites sometimes occur on cutaneous skin, and increased risk of these cancers may be related to this subset.

Sirolimus is a member of a new class of drugs, mTOR inhibitors, and is considered to have anti-cancer effects (22;23). We observed a significant decreased incidence of invasive anal cancer (IRR 0.2) that was not seen for *in situ* anal cancer; but we note that only one transplant recipient with anal invasive cancer received sirolimus. Various anti-lymphoproliferative induction therapies have been in use among transplant patients since the early 1990s (19), and induction was associated with reduced incidence of invasive cervical cancer (IRR 0.5) and oropharyngeal cancer (IRR 0.7). The potential positive impact of induction needs to be replicated in other studies.

There were strengths and limitations in this analysis. The large size of the TCM population provided sufficient cases to examine separately *in situ* and invasive cancers. A limitation of our study is that tumor tissue was unavailable, so we could not determine the HPV status of tumors. Our hypothesis was that transplant-related immunosuppression increases the incidence of the HPV-related subset, and that most of the excess cancers are HPV-related. However, without knowing which cases were HPV-positive, the incidence estimates included a small number of HPV-negative cases. In addition, information about duration of medication use and intensity of immune suppression was not available, which may have been of interest if, for example, high doses of specific drugs were related to specific outcomes. Another concern is the possibility that type 1 error from multiple comparisons might have led to some significant associations in this study. The probability of false positive results is lower for some of the associations presented, for which we had *a priori* hypotheses and demonstrated consistent associations across multiple sites. In addition, although we do not have systematic information on recipients moving out of the area where they were transplanted, we do have an estimate of 6% at 10 years after transplantation from a sample in our prior study (6). The SIRs may therefore be underestimated by a small amount. Finally, some of the results were based on a very small numbers of events, as such, misclassifications of the types of cancers could dramatically alter estimates. Thus these findings, although statistically significant, should be interpreted with caution.

The absence of an increased incidence of invasive cervical cancer is likely due to effective cytologic screening (i.e., routine use of Pap smears). The target group for screening in the U.S. is women 21–65 years old, with cytology initially recommended every 3 years. For women over 30 years old, a longer interval of 5 years between screens is suggested when cytology and HPV co-testing are negative (24). The Kidney Disease: Improving Global Outcomes group suggested that screening for cervical cancer in transplant recipients should follow the general population guidelines (25). However, screening for women with transplants may be performed outside the guidelines if the patient and provider determine it is clinically indicated (26).

Anal cytological screening is available for people who are at high risk of anal cancer, including men-who-have-sex-with-men, HIV-infected individuals, women with vulvar neoplasia, and transplant recipients (27). A cost-benefit analysis of anal cytology in HIV-infected men-who-have-sex-with-men indicated that screening would be effective in that population (28), and screening might be useful for transplant recipients as well. Others consider anal cytology screening to be of unclear benefit until more is known about the natural history of anal precursor lesions (29). HPV16 cotesting with anal cytology may be

predictive of low grade lesions at risk of progression (30), and might be a beneficial adjunct to testing in the transplant setting. No guidelines for screening transplant recipients for vulvar, penile, vaginal, or oropharyngeal neoplasia have been established. Our study and others suggest that screening could be focused; for example, it may be most feasible to begin inspection of external genitalia starting at 2 years post-transplant or limit evaluation of the oropharynx to liver recipients with a history of alcoholism. Future guidelines developed by expert groups would also need evidence that screening for HPV-related cancers leads to timely and effective treatment.

In conclusion, our findings point to the importance of demographic characteristics, medical conditions, genetics (HLA), duration of immunosuppression, and use of specific immunosuppressive medications as possible risk factors for HPV-related cancers. With cervical cancer screening as a model, it is possible that screening for other HPV-related cancers would facilitate identification of pre-cancerous lesions, thereby preventing development of invasive cancers and improving outcomes for transplant recipients. Future studies may focus on elucidating specific underlying conditions and other exposures that participate in causing HPV-related cancers in solid organ transplant recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SIR	standardized incidence rate
IRR	incidence rate ratio

References

1. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003; 348:1681–1691. [PubMed: 12711744]
2. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006; 24 (Suppl 3):S3-11–S3/25. [PubMed: 16949997]
3. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El GF, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009; 10:321–322. [PubMed: 19350698]
4. 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]
5. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant. 2010; 10:1889–1896. [PubMed: 20659094]
6. 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; 306:1891–1901. [PubMed: 22045767]
7. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008; 26:612–619. [PubMed: 18235120]
8. Hildesheim A, Wang SS. Host and viral genetics and risk of cervical cancer: a review. Virus Res. 2002; 89:229–240. [PubMed: 12445662]
9. Madeleine MM, Johnson LG, Smith AG, Hansen JA, Nisperos BB, Li S, et al. Comprehensive analysis of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci and squamous cell cervical cancer risk. Cancer Res. 2008; 68:3532–3539. [PubMed: 18451182]
10. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; 189:12–19. [PubMed: 10451482]
11. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005; 14:467–475. [PubMed: 15734974]
12. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: Updating the natural history of HPV and anogenital cancer. Vaccine. 2006; 24 (Suppl 3):S3-42–S3/51. [PubMed: 16950017]
13. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004; 101:270–280. [PubMed: 15241823]
14. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009; 101:1120–1130. [PubMed: 19648510]
15. Opelz G, Dohler B. Effect of human leukocyte antigen compatibility on kidney graft survival: comparative analysis of two decades. Transplantation. 2007; 84:137–143. [PubMed: 17667803]
16. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007; 356:1944–1956. [PubMed: 17494927]
17. Duvoux C, Delacroix I, Richardet JP, Roudot-Thoraval F, M+¬treau JM, Fagniez PL, et al. Increased incidence of oropharyngeal squamous cell carcinomas after liver transplantation for alcoholic cirrhosis. Transplantation. 1999; 67:418–421. [PubMed: 10030289]

18. Meier-Kriesche HU, Li S, Gruessner RW, Fung JJ, Bustami RT, Barr ML, et al. Immunosuppression: evolution in practice and trends, 1994–2004. Am J Transplant. 2006; 6:1111–1131. [PubMed: 16613591]
19. OPTN. The Organ Procurement and Transplantation Network (OPTN) maintains the only national patient waiting list and features the most comprehensive data available in any single field of medicine. US Department of Health and Human Sevices; 2011. [cited 2011 Jul 5];Available from: URL: http://optn.transplant.hrsa.gov/
20. Almawi WY, Melemedjian OK. Clinical and mechanistic differences between FK506 (tacrolimus) and cyclosporin A. Nephrol Dial Transplant. 2000; 15:1916–1918. [PubMed: 11096132]
21. Karagas MR, Cushing GL Jr, Greenberg ER, Mott LA, Spencer SK, Nierenberg DW. Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer. 2001; 85:683–686. [PubMed: 11531252]
22. Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin Transplant. 2004; 18:446–449. [PubMed: 15233824]
23. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012; 367:329–339. [PubMed: 22830463]
24. Moyer VA. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012; 156:880–91. W312. [PubMed: 22711081]
25. Kasiske BL, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. Kidney Int. 2010; 77:299–311. [PubMed: 19847156]
26. Wong G, Chapman JR, Craig JC. Cancer screening in renal transplant recipients: what is the evidence? Clin J Am Soc Nephrol. 2008; 3 (Suppl 2):S87–S100. [PubMed: 18309007]
27. Etienney I, Vuong S, Si-Mohamed A, Flejou JF, Atienza P, Bauer P. Value of cytologic Papanicolaou smears and polymerase chain reaction screening for human papillomavirus DNA in detecting anal intraepithelial neoplasia: Comparison with histology of a surgical sample. Cancer. 2012; 118:6031–6038. [PubMed: 22674290]
28. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. JAMA. 1999; 281:1822–1829. [PubMed: 10340370]
29. Patel HS, Silver AR, Northover JM. Anal cancer in renal transplant patients. Int J Colorectal Dis. 2007; 22:1–5. [PubMed: 16133005]
30. Walts AE, Thomas P, Bose S. Anal cytology: is there a role for reflex HPV DNA testing? Diagn Cytopathol. 2005; 33:152–156. [PubMed: 16078257]

Table 1

Selected characteristics of Transplant Cancer Match study cohort*

	Total Cohort		CIS Cohort	
Characteristic	**N**	**%**	**N**	**%**
Sex				
Male	115,614	61.6	0	0
Female	72,035	38.4	17,010	100
Age at Transplant				
18–34	33,443	17.8	4,279	25.2
35–49	63,831	34.0	6,234	36.6
50+	90,375	48.2	6,497	38.2
Race/Ethnicity				
White, Non-Hispanic	117,502	62.6	11,302	66.4
Black, Non-Hispanic	31,527	16.8	2,839	16.7
Hispanic	28,073	15.0	1,952	11.5
Asian/Pacific Islander	10,547	5.6	917	5.4
Transplanted Organ**				
Kidney and/or pancreas	119,756	63.8	11,624	68.3
Liver	39,784	21.2	3,558	20.9
Heart and/or Lung	25,877	13.8	1,716	10.1
Other	2,232	1.2	112	0.7
Transplant Number				
First	171,337	91.3	15,691	92.2
Second	14,991	8.0	1,226	7.2
Third or Higher	1,321	0.7	93	0.5
Year of Transplant				
1987–1994	35,049	18.7	9,120	53.6
1995–1999	48,193	25.7	5,000	29.4
2000–2009	104,407	55.6	2,890	17.0

* Data represent all transplants combined (1987–2009) and separately for those followed for *in situ* cervical cancer (CIS).

** Kidney and/or pancreas transplants combine recipients with kidney alone, kidney/pancreas, or pancreas only; “other” transplants include intestine transplants and individuals who received other multiple organs (such as kidney and liver).

Table 2

HPV-related cancers among U.S. organ transplant recipients

Outcome	N	Incidence Rate	SIR	(95% CI)	Age at diagnosis, median years	Time from transplant to cancer, median years
***In reply to: situ* cancers**						
Cervix	71	144.9	3.3	(2.6–4.2)	38	2.6
Vagina	34	10.4	10.6	(7.4–14.8)	50.5	3.4
Vulva	284	86.5	20.3	(18.0–22.8)	42	4.1
Anus	53	6.3	11.6	(8.7–15.2)	43	4.4
Penis	58	11.4	18.6	(14.1–24.0)	59	5.7
Invasive cancers						
Cervix	52	15.8	1.0	(0.8–1.3)	44.5	3.8
Vulva	66	20.1	7.3	(5.6–9.2)	52	4.1
Anus	103	12.3	5.4	(4.4–6.6)	54	5.3
Penis	25	4.9	3.9	(2.5–5.7)	56	4.7
Oropharynx	144	17.2	2.2	(1.8–2.5)	56	3.5

Incidence rates are per 100,000 person-years; SIR, standardized incidence ratio

Table 3

Incidence rate ratios (IRR) for demographic and transplant-related risk factors for HPV-related cancers among U.S. organ transplant recipients

	In situ cancers, IRR (95%CI)					Invasive cancers, IRR (95%CI)				
	Cervix N=71	**Vagina N=34**	**Vulva N=284**	**Anus N=53**	**Penis N=58**	**Cervix N=52**	**Vulva N=66**	**Anus N=103**	**Penis N=25**	**Oropharynx N=144**
Sex										
Male				1.0				1.0		1.0
Female				**3.0 (1.7–5.4)**				**1.8 (1.3–2.7)**		**0.4 (0.2–0.5)**
Age at transplant										
18–34	**4.7 (2.5–9.3)**	1.8 (0.8–3.9)	**4.1 (3.0–5.6)**	**4.7 (2.3–10)**	**0.4 (0.1–1.0)**	**2.4 (1.2–4.8)**	1.0 (0.5–1.8)	0.7 (0.4–1.3)	0.7 (0.2–2.1)	**0.1 (0.0–0.2)**
35–49	1.6 (0.8–3.4)	0.8 (0.3–1.8)	**1.8 (1.3–2.5)**	**2.2 (1.1–4.8)**	0.8 (0.4–1.3)	1.4 (0.7–2.7)	0.9 (0.5–1.5)	0.9 (0.6–1.3)	1.1 (0.5–2.5)	0.8 (0.5–1.1)
50+	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Race/Ethnicity										
White	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Black	1.6 (0.8–2.9)	0.6 (0.2–1.6)	**0.7 (0.5–1.0)**	1.4 (0.7–2.8)	1.2 (0.6–2.5)	0.9 (0.4–1.9)	0.9 (0.5–1.7)	0.7 (0.4–1.2)	1.1 (0.3–3.3)	**0.5 (0.3–0.8)**
Hispanic	**2.8 (1.4–5.1)**	0.5 (0.1–1.6)	0.8 (0.5–1.1)	1.2 (0.5–2.4)	1.0 (0.5–2.1)	1.3 (0.6–2.5)	**0.2 (0.0–0.5)**	0.5 (0.3–1.0)	2.4 (0.9–5.9)	**0.4 (0.2–0.8)**
Asian/Pac Islander	2.0 (0.7–4.6)	0.0	0.7 (0.4–1.2)	1.1 (0.3–3.1)	0.0	1.6 (0.5–3.7)	**0.2 (0.0–0.9)**	0.5 (0.1–1.2)	1.0 (0.1–4.8)	**0.2 (0.0–0.6)**
Organ										
Kidney and/or Pancreas	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Liver	0.7 (0.4–1.4)	0.9 (0.3–2.2)	**0.5 (0.3–0.7)**	0.8 (0.3–1.5)	1.1 (0.5–2.3)	1.2 (0.6–2.3)	**0.3 (0.1–0.7)**	1.2 (0.7–2.0)	0.6 (0.1–1.7)	**4.4 (3.1–6.4)**
Heart, Lung	1.0 (0.4–2.0)	2.2 (0.9–5.0)	1.4 (1.0–1.9)	0.6 (0.2–1.4)	**2.7 (1.5–4.8)**	1.8 (0.8–3.7)	**1.9 (1.0–3.4)**	**1.8 (1.1–2.9)**	1.1 (0.4–2.8)	**2.0 (1.2–3.2)**
Other	0.8 (0.0–3.6)	1.8 (0.1–8.8)	**2.8 (1.6–4.6)**	3.3 (0.8–9.1)	0.0	**5.1 (1.5–12.9)**	1.6 (0.3–5.2)	2.2 (0.5–5.8)	2.6 (0.1–12.7)	3.3 (1.0–8.1)
Time since transplant, years										
<2	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2–5	1.5 (0.9–2.6)	1.3 (0.6–3.1)	**1.9 (1.4–2.6)**	**2.1 (1.0–4.7)**	2.1 (0.9–5.1)	0.9 (0.4–1.8)	1.8 (0.9–3.6)	**2.4 (1.3–4.5)**	**3.4 (1.1–15.3)**	1.1 (0.7–1.6)
5+	1.1 (0.5–2.0)	1.1 (0.5–2.7)	**2.1 (1.5–2.9)**	**2.3 (1.1–5.2)**	**4.6 (2.3–10.8)**	1.4 (0.7–2.7)	**2.4 (1.3–4.7)**	**3.8 (2.2–6.9)**	**4.4 (1.4–19.2)**	1.2 (0.8–1.8)

Table 4

Incidence rate ratios (IRR) for immune-related risk factors for HPV-related cancers among U.S. organ transplant recipients

	***In situ* cancers, IRR (95%CI)**					**Invasive cancers, IRR (95%CI)**				
	Cervix (N=71)	**Vagina (N=34)**	**Vulva (N=284)**	**Anus (N=53)**	**Penis (N=58)**	**Cervix (N=52)**	**Vulva (N=66)**	**Anus (N=103)**	**Penis (N=25)**	**Oropharynx (N=144)**
Transplant number										
First	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2nd +	0.9 (0.3–2.1)	1.2 (0.3–3.4)	**2.0 (1.4–2.7)**	**4.4 (2.2–7.9)**	1.6 (0.6–3.5)	1.3 (0.5–3.0)	1.7 (0.8–3.4)	**2.1 (1.2–3.6)**	1.2 (0.2–4.2)	1.1 (0.6–2.0)
HLA mismatch										
0 to 2	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3 to 4	1.2 (0.7–2.1)	0.8 (0.4–1.8)	1.0 (0.7–1.4)	1.0 (0.5–2.1)	1.4 (0.7–3.0)	1.1 (0.5–2.6)	0.9 (0.5–1.7)	0.7 (0.4–1.2)	0.8 (0.3–2.3)	**1.9 (1.1–3.4)**
5 to 6	0.9 (0.4–1.7)	**0.2 (0.1–0.7)**	1.1 (0.8–1.5)	0.9 (0.4–2.1)	0.9 (0.4–2.2)	1.8 (0.8–4.1)	0.7 (0.3–1.3)	0.6 (0.4–1.1)	0.7 (0.2–2.3)	**1.9 (1.1–3.6)**
DRB1:13										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.4 (0.1–1.1)	1.9 (0.8–4.2)	**0.4 (0.3–0.6)**	0.5 (0.1–1.2)	0.5 (0.2–1.2)	0.4 (0.1–1.0)	0.9 (0.4–1.7)	0.6 (0.3–1.2)	1.1 (0.3–2.9)	1.3 (0.8–2.0)
B:44										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.9 (0.5–1.6)	1.4 (0.6–3.1)	1.3 (0.9–1.7)	1.8 (1.0–3.4)	**1.9 (1.1–3.3)**	1.1 (0.5–2.1)	0.9 (0.5–1.7)	**1.7 (1.1–2.6)**	1.1 (0.4–2.7)	0.9 (0.6–1.5)
Diabetes mellitus*										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.0 (0.3–2.6)	0.6 (0.2–1.6)	1.0 (0.7–1.5)	0.7 (0.3–1.6)	0.9 (0.4–2.0)	0.8 (0.3–1.8)	1.4 (0.7–2.7)	0.6 (0.3–1.2)	0.8 (0.2–2.8)	0.6 (0.4–1.0)

*Data available only for transplants in years 1995 and later.

Table 5

Incidence rate ratios for immunosuppressive medications and risk for HPV-related cancers among U.S. organ transplant recipients

	In situ cancers, IRR (95%CI)					Invasive cancers, IRR (95%CI)				
	Cervix (N=71)	**Vagina (N=34)**	**Vulva (N=284)**	**Anus (N=53)**	**Penis (N=58)**	**Cervix (N=52)**	**Vulva (N=66)**	**Anus (N=103)**	**Penis (N=25)**	**Oropharynx (N=144)**
Cyclosporine										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.1 (0.6–1.9)	1.1 (0.5–2.1)	**1.4 (1.1–1.8)**	1.1 (0.6–1.8)	**2.3 (1.3–4.2)**	1.4 (0.8–2.4)	1.1 (0.7–1.9)	1.4 (0.9–2.1)	1.2 (0.5–2.7)	**0.6 (0.4–0.8)**
Tacrolimus										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.8 (0.4–1.4)	1.0 (0.5–2.0)	**0.7 (0.6–0.9)**	0.8 (0.5–1.4)	**0.4 (0.2–0.7)**	0.7 (0.4–1.2)	0.9 (0.6–1.5)	**0.6 (0.4–1.0)**	1.0 (0.4–2.3)	**2.1 (1.5–2.9)**
Azathioprine										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.2 (0.7–1.9)	1.5 (0.7–2.9)	**1.8 (1.4–2.2)**	1.4 (0.8–2.4)	**2.4 (1.4–4.1)**	1.4 (0.8–2.5)	**2.0 (1.2–3.2)**	**1.7 (1.1–2.5)**	1.2 (0.5–2.6)	0.7 (0.5–1.0)
Mycophenolate										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.7 (0.4–1.3)	1.0 (0.5–2.0)	**0.8 (0.6–1.0)**	1.0 (0.6–1.7)	**0.6 (0.3–1.0)**	0.6 (0.3–1.1)	0.9 (0.5–1.4)	0.7 (0.5–1.1)	1.2 (0.5–2.6)	0.9 (0.6–1.3)
Sirolimus										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.0 (0.1–4.7)	0.6 (0.0–2.8)	1.0 (0.6–1.7)	1.6 (0.5–4.0)	1.1 (0.3–2.9)	0.8 (0.1–2.6)	--	**0.2 (0.0–0.9)**	1.7 (0.3–5.8)	0.9 (0.3–1.8)
Corticosteroids										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.7 (0.4–1.7)	1.0 (0.4–4.0)	1.2 (0.8–2.0)	**5.3 (1.2–93.1)**	1.4 (0.6–4.7)	0.6 (0.3–1.5)	3.0 (0.9–18.3)	1.2 (0.6–2.7)	2.5 (0.5–45.5)	1.2 (0.7–2.4)
Induction medications										
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	1.1 (0.6–1.8)	0.9 (0.4–1.8)	1.0 (0.8–1.2)	1.1 (0.6–1.9)	1.0 (0.6–1.7)	**0.5 (0.3–0.9)**	1.0 (0.6–1.7)	0.8 (0.5–1.2)	0.8 (0.3–1.8)	**0.7 (0.5–0.9)**