Published in final edited form as:

Oral Oncol. 2017 May ; 68: 60–66. doi:10.1016/j.oraloncology.2017.03.004.

RISK FACTORS FOR OROPHARYNX CANCER IN A COHORT OF HIV-INFECTED VETERANS

Erin Y. Chew, BS¹, Christine M. Hartman, PhD², Peter A. Richardson, PhD², Jose P. Zevallos, MD, MPH^{3,4}, Andrew G. Sikora, MD, PhD⁵, Jennifer R. Kramer, PhD², and Elizabeth Y. Chiao, MD, MPH^{1,2}

¹One Baylor Plaza, Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, TX, USA, 77030

²2002 Holcombe Boulevard, Center of Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA, 77030

³170 Manning Drive, CB# 7070 Department of Otolaryngology-Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 27514

⁴170 Rosenau Hall CB, #7400 Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, 27514

⁵One Baylor Plaza, Department of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, Houston, TX, USA, 77030

Abstract

Objective: To evaluate HIV-related and other clinical risk factors associated with oropharynx cancer (OPSCC) in HIV-infected U.S. Veterans.

Methods: Retrospective cohort study utilizing Veterans Affairs HIV Clinical Case Registry (CCR) data from 1985–2010. Outcome was incident OPSCC as indicated by 1 inpatient or 2 outpatient ICD-9 codes. Cox proportional hazard models were used to determine hazard ratios (HR) and 95% confidence intervals (CI) for each risk factor on the time to OPSCC diagnosis.

Results: A total of 40,996 HIV-infected male veterans were included in the cohort with 97 cases of OPSCC. The age adjusted incidence rate was 23.2/100,000 [95% CI 17.8 to 29.2]. Age >50 (aHR=3.8, 95% CI 1.9 to 7.8), recent CD4 <200 (aHR=3.8, 95% CI 2.0 to 7.3), and undetectable HIV viral loads 40–79% of the time (aHR=1.8, 95% CI 1.1 to 3.0) were associated with an increased risk of OPSCC. Era of HIV diagnosis, utilization of cART, nadir CD4 count, race, smoking history, and previous risk of HPV disease, including condyloma or invasive squamous cell carcinoma of the anus (SCCA) were *not* associated with increased risk of OPSCC.

Conclusion: Patients who were older at beginning of follow up, had lower CD4 counts around the time of OPSCC diagnosis, and moderate HIV viral control during follow-up had an increased

Corresponding author: Elizabeth Y. Chiao, M.D., M.P.H., Michael E. DeBakey VA Medical Center, HSR&D Center of Innovation (152), 2002 Holcombe Boulevard, Houston, TX 77030, echiao@bcm.edu, Phone: 713-791-1414 ext. 10356.

Conflict of Interest Statement: None declared

risk of OPSCC. Other HPV-related diseases such as SCCA and condyloma did not increase the risk for OPSCC.

Keywords

oropharynx cancer; HIV; epidemiology; combined antiretroviral therapy; HIV-related immune suppression; human papilloma virus; oral cancer; Head and Neck cancer

INTRODUCTION

Since the introduction of combination anti-retroviral therapy (cART) in 1996, the epidemiology of HIV related morbidity and mortality has changed. The incidence of AIDS-defining malignancies such as Kaposi's Sarcoma and certain types of non Hodgkin's lymphoma [1,2] has declined and the mortality rate of HIV-infected individuals from associated opportunistic infections has decreased by 70% [3]. However, evidence suggests that there has been no significant decrease in risk of human papilloma virus (HPV)-related cancers [4,5]. In fact, the incidence of other non AIDS-defining malignancies (NADM) including HPV-related head and neck squamous cell carcinoma (HNSCC) has increased in HIV-infected individuals in the post-cART era [3,6–9].

The prevalence of oropharyngeal squamous cell carcinoma (OPSCC) has increased at an epidemic rate of 225% from 1988 to 2004 [10]. Recent data has shown that 3 of 4 newly diagnosed OPSCC are associated with HPV and that the prevalence of OPSCC is expected to overtake that of cervical cancer by the year 2020 [11,12]. OPSCC affects nearly 20,000 patients annually in US alone [13]. The substantial rise in incidence of OPSCC in the general population [14–16] has also occurred concurrently in the HIV-infected population over the past two decades [3,11,17,18].

Furthermore, HIV-infected patients, have a 3-fold higher standardized incidence of HPV-related OPSCC compared to the uninfected population which may be mediated by immunosuppression [19–21]. Like cervical cancer in women and squamous cell carcinoma of the anus (SCCA), OPSCC is etiologically associated with HPV infections, especially the high risk genotypes [22–24]. HIV infected individuals have a high prevalence of oral HPV infection (approximately 14–45%) [25–27]. Previous studies have shown that viral control and immune reconstitution are important risk factors for the development of other viral mediated NADM such as Hodgkin's lymphoma (HL), hepatocellular carcinoma (HCC), and SCCA [28–30]. For example, HIV viral load as measured by the percent of time with undetectable HIV viral load is associated with a decreased risk of SCCA and HL in HIV-infected individuals [28,30]. However, it is unclear if similar HIV-related and immunologic risk factors are associated with the risk for HPV-related OPSCC.

There is limited research examining the HIV-related immune factors associated with OPSCC incidence in a cohort of individuals receiving cART. Given the increased life expectancy of HIV-infected individuals in the post cART era, the population of HIV and HPV co-infected individuals who are at risk for OPSCC is expected to rise [24]. It is therefore important to identify the clinical and HIV-related immune risk factors with oropharynx cancer.

The Veterans Affairs (VA) is the largest integrated health care system in the United States and is also the largest provider of HIV care in the United States [31]. The VA maintains system wide clinical information and death data in the national registry of HIV-infected patients. Using these resources, we conducted a retrospective cohort study within the VA Clinical Case Registry to determine the incidence of oropharynx cancer in the HIV-infected population and to evaluate the effect of HIV related immune status on the incidence of OPSCC.

METHODS

Data Sources

The VA HIV Clinical Case Registry (CCR) is a nation-wide registry that contains health-related information on all known HIV-infected individuals using VA services. It was established in 1992, and has been described elsewhere [32]. The CCR draws on the electronic medical records of over 60,000 HIV-infected patients cared for by the VA since the registry's inception and includes all demographic, laboratory, pharmacy, outpatient clinic visit, and hospitalization data and dates of death. For this study, VA death data were supplemented with data from the Social Security and VA vital status files, and CCR race data were supplemented with data from the national inpatient treatment file and outpatient clinics' files. This study was approved by the Institutional Review Board of Baylor College of Medicine and Affiliated Institutions, the Michael E. DeBakey VA Medical Center Research and Development Committee, and the VA CCR administration.

Subjects

The study population consisted of HIV infected veterans whose health-related information was collected from the HIV CCR dating from January 1, 1996 to December 31, 2010. Only patients who had well-documented vital statistics and HIV diagnosis dates were included. Patients who were aged more than 18 years, with at least 1 confirmed date for (1) HIV test (HIV-1 Elisa, Western Blot, or HIV viral load), (2) ICD-9 for HIV (042 or V08), or at least 1 prescription for antiretroviral therapy, were eligible for inclusion in the cohort. Female veterans were excluded from the overall cohort because they were a very small percentage of the population (<2%). We included only those patients who were alive in 1996 (cART era) and those who had at least 1 CD4 count. Patients were censored at death, at the date of their last recorded health care encounter, or at the end of the study period. Figure 1 shows the study flow chart.

Definition of Variables

The VA Inpatient and Outpatient Medical SAS Datasets were used to identify OPSCC patients using ICD-9 codes. ICD-9 codes for OPSCC include: 146 (malignant neoplasm of oropharynx), 146.0 (malignant neoplasm of the tonsil), 146.1 (malignant neoplasm of the tonsillar fossa), 146.2 (malignant neoplasm of the tonsillar pillars), 146.6 (malignant neoplasm of the lateral wall of the oropharynx), 146.7 (malignant neoplasm of the posterior wall of the oropharynx), 146.8 (malignant neoplasm of other specified sites of oropharynx), 141.0 (malignant neoplasm of base of tongue), 141.6 (malignant neoplasm of the tongue). Patients were required to have two ICD codes within 6 months if they had only outpatient

diagnoses. The ICD-9 codes for OPSCC were validated by conducting a detailed electronic medical record review on a sample of 200 subjects that met the ICD-9 criteria and treated at the MEDVAMC-between 2000 and 2012. The positive predictive value (PPV) of OPSCC ICD-9 codes was calculated as the percentage of patients with ICD-9 codes for OPSCC that had histologically confirmed squamous cell carcinoma of the oropharynx in the medical record. The PPV was found to be 86%. Invasive SCCA was defined as 1 inpatient or 2 outpatient ICD-9 codes of '154.2' and '154.3.' Condyloma was defined as 1 inpatient or 2 outpatient ICD-9 codes of '78.11.'

We defined cART therapy as filled VA pharmacy prescriptions for any combination of 2 nucleoside reverse transcriptase inhibitor drugs and one of the following: a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, or an integrase inhibitor drug. In addition, any combination of drugs from 2 of the following classes was considered cART: non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and entry inhibitors. Only Food and Drug administration drugs approved before January 1, 2011 were included in the cART definition. cART era of diagnosis was defined by the first year of HIV diagnosis and indicated as either pre-HAART (1985–1995), early HAART (1996–200), or late HAART (2001–2010). Percent cART is the percentage of time in follow-up that the veteran had a valid cART prescription.

The most recent CD4 count, nadir CD4 count, percent of time with an undetectable HIV viral load, and whether the patient ever had cART were all time-updated variables for survival analysis. When reporting clinical statistics (Table 2), these variables were defined as the most recent value recorded before the event or censor date. A plasma HIV viral load <500 copies per milliliter was considered to be “undetectable.” The nadir CD4 cell count was defined as the lowest CD4 count ever. Percent of time with an undetectable HIV viral load was calculated as the overall percent of time each individual had an undetectable HIV viral load during follow-up. Time-updated variables were evaluated at an interval of at least every 7 days. The index date, or beginning of follow up, was assigned as the earliest date after 1/1/1996. Subjects were followed from first visit after 1/1/1996 until the earliest of OPSCC diagnosis, lost to follow up, death or, 1/31/2010.

Data Analysis

Primary outcome was overall survival to oropharynx cancer. Additionally, we calculated crude incidence rates in the overall cohort and stratified by cART utilization and current CD4 count. The age distribution from the US 2000 Census was used to calculate age adjusted OPSCC incidence rates. Descriptive analyses with Chi-square and Fisher's exact tests were used to characterize and compare the demographic and disease characteristics of the non-cancer and cancer groups. Cox proportional hazard regression analysis was used to calculate the effect of demographic and HIV-specific variables use on time to cancer. The multivariate hazard ratios (HR) were calculated with both the inclusion and exclusion of patients censored by death prior to the diagnosis of OPSCC or lost to follow up. SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

OPSCC Incidence

Table 1 shows the age-adjusted incidence of OPSCC among HIV infected veterans. The overall unadjusted incidence of OPSCC in this cohort was 32.7/100,000 [95% CI 26.5 to 39.9]. The age adjusted incidence of OPSCC for the cohort was 23.2/100,000 [95% CI 17.8 to 29.2]. The age-adjusted incidence for all patients who received cART was 21.9/100,000 [95% CI 16.4 to 28.5] compared to 31.3/100,000 [95% CI 15.5 to 52.4] who never received cART. Incidence of OPSCC was lowest in patients with current CD4 counts >350 (15.3/100,000 [95% CI 10.0 to 21.7]) as compared to those with CD4 counts 200–350 (27.7/100,000 [95% CI 14.7 to 47.3]) and <200 (46.5/100,000 [95% CI 29.9 to 68.1]). Figure 2 is a Kaplan-Meier plot displaying the cumulative incidence of OPSCC diagnosis over time stratified by CD4 cell count. Patients with a CD4<200 have a significantly higher cumulative incidence of OPSCC over time compared to those with higher CD4 counts ($P=0.0001$).

Study Cohort

There were 40,966 male veterans identified in the complete cohort with a total of 282,100 person-years of follow up, and of these, 97 were diagnosed with OPSCC. Table 2 shows the descriptive and clinical characteristics for the overall study cohort and those diagnosed with OPSCC. The mean age at HIV diagnosis in the total cohort was 44.9 years with 50% of the cohort Black, 36% White, and 14% Hispanic, unknown, or other. Approximately one-third were diagnosed in the pre-cART era (33%), 29% in the early-cART era (1996–2000), and 39% in the late cART era (2001–2010). The majority of patients received cART (80%) and most had a valid prescription for cART 0–39% of the time (53%). Fifty-two percent of the patients had a recent CD4 >350, 18% had a CD4 count between 200–350, and 30% had a CD4 count <200. A majority of patients had a past or current smoking history (84%) and no previous diagnosis of SCCA (93%) or condyloma (99%).

As seen in Table 2, patients who developed OPSCC were significantly different from patients who did not develop OPSCC in the following variables: age at beginning of follow up, era of HIV diagnosis, and recent CD4 cell count. Eighty-nine percent of patients who developed OPSCC were older than 40 years at the beginning of follow up. Approximately 73% of patients who did not develop OPSCC were older than 40. Compared to the percentage of patients who developed OPSCC (47%), a smaller percentage of patients who did not develop OPSCC were diagnosed in the pre-cART era (33%). Forty percent of patients who developed OPSCC had a recent CD4 cell count <200. Comparatively, thirty percent of patients who did not develop OPSCC had a recent CD4 cell count <200.

Multivariate and Univariate Analysis of Factors Associated with Increased Risk of OPSCC

Table 3 includes the results of the univariate and multivariate survival analysis for OPSCC risk. In the univariate survival analysis, age >40 at beginning of follow up, recent CD4 count <200, and nadir CD4 count <200 were independently associated with increased risk for OPSCC. Compared to those aged less than 40 at beginning of follow up, patients aged 40–49 years old and aged >50 had a higher risk of OPSCC [hazard ratio (HR), 4.0; $P<0.0001$].

and HR, 3.7; $P=0.0003$, respectively]. Compared to those who had a CD4 cell count >350 , those with CD4 counts <200 had a markedly increased risk of OPSCC (HR, 2.9; $P<0.001$). Furthermore, those with a nadir CD4 cell count <200 also had an increased risk of OPSCC (HR, 1.7; $P=0.01$) compared to those with a nadir CD4 cell count >350 .

In the multivariate survival analysis for OPSCC risk, significant predictors for OPSCC included older age, recent CD4 count <200 , and percent time with undetectable HIV viral load 40–79%. Compared with patients who were less than 40 years of age at beginning of follow up, individuals aged 40–49 had a HR of 3.8 ($P<0.0001$) for OPSCC and those aged greater than 50, had a HR of 3.8 ($P<0.001$). Compared to those who had a current CD4 count >350 , those who had a current CD4 count <200 had a HR of 3.8 of OPSCC ($P<0.0001$). For those who had a current CD4 count 200–350, however, the increased risk for OPSCC was not significant (HR, 1.4; $P=0.24$). Patients who had an undetectable HIV viral load 40–79% of the time had an increased risk (HR, 1.8; $P=0.02$) for OPSCC as compared to patients with an undetectable HIV viral load 0–39% of the time. However, undetectable viral loads 80–100% of the time were associated with an increased risk for OPSCC (HR, 1.5; $P=0.25$), but this did not reach significance. Era of HIV diagnosis, ever having cART, and nadir CD4 were not associated with significant risk for OPSCC. Additionally, race, smoking history and previous risk of HPV disease, specifically, condyloma or anal cancer were not associated with risk of OPSCC.

DISCUSSION

In this large cohort of HIV-infected veterans, older age, lower CD4 counts around the time of OPSCC diagnosis, and having a moderate amount of time with undetectable HIV viral loads were significant predictors for OPSCC. Additionally, HPV infections in other sites, specifically condyloma and previous history of SCCA did not impact risk for developing OPSCC. Our findings suggest that development of OPSCC may have different immunologic risk factors compared to other HPV-related cancers such as SCCA in the HIV population.

Our findings are well supported by previous studies that have evaluated the impact of immunosuppression on HPV related head and neck cancers [21,33]. The age-standardized incidence rate of OPSCC in our cohort (23.2/100,000) was higher than the previously published incidence for HPV-related HNSCC (10.7/100,000) [21]. This may be explained by our unique population of veterans who fall within range of the birth cohort for the highest risk for OPSCC. In addition, our finding that older age is associated with an increased risk for OPSCC aligns with a recent study conducted by Beachler et al. [21]. They found that older age >40 had the strongest impact on both HPV related and unrelated HNSCC. Lower CD4 counts around the time of OPSCC diagnosis was also found to be associated with an increased risk of OPSCC in Beachler's study, which found an association between reduced baseline CD4 cell counts and both HPV and HPV unrelated HNSCC. The findings of our study are also supported by Silverberg et al. who found that recent CD4 <200 had a higher relative risk for oral cavity and oropharynx cancers among HIV individuals [33].

Of note, these previous studies, did not attempt to quantify the role of the amount of time on effective cART, as measured by undetectable HIV viral loads or the risk of HNSCC or

OPSCC. By using the variable “percent time with undetectable HIV viral load,” our study was uniquely able to measure the cumulative effect of HIV viral load on the risk of OPSCC. Our finding that a moderate amount of percent time with undetectable viral loads is associated with an increased risk for OPSCC, however, is somewhat supported by Silverberg et al.’s study which used a single HIV viral load at the time of cancer diagnosis. They did not find a clear dose-response relationship between recent HIV viral loads and relative risk for oral cavity/pharynx cancer among HIV infected individuals compared to HIV uninfected individuals. The highest risk was found in patients with viral loads between 501–9,999 copies/mL compared to viral loads <500 copies/mL and >10,000 copies/mL.

The cause for increased OPSCC incidence in the HIV-infected population in the post-cART era has been unclear [34]. Our study demonstrates that there may be an effect of poor immune reconstitution on the development of OPSCC. One possible explanation for increased OPSCC incidence in the post-cART era is the improvement in survival due to antiretroviral treatment along with an only partial recovery in immune status allowing for a greater number of cancers to manifest clinically [34]. Uncontrolled HIV replication is associated with immunodeficiency and decreased ability to clear latent viral co-infections [35]. HIV infected individuals thus may experience longer durations of persistent HPV infection [36], which has been observed to be cyclically linked with HIV proliferation and cellular immune deficit [37]. HIV and HPV genes may reciprocally interact, resulting in an increasing HPV viral load, increasing the potential for malignant progression [38]. However, our finding that the group of patients with 80–100% of time with undetectable HIV viral did not have a lower risk of OPSCC than those with <40% undetectable HIV viral load, but those with 40–79% time undetectable HIV viral load had a significantly higher risk for OPSCC demonstrates that the relationship between HIV and HPV may be more complicated.

Our findings with respect to HIV related immune factors on the development of OPSCC are somewhat different from other HPV related malignancies in HIV infected individuals. For example, previously published results using HIV-infected veterans from the CCR examining the effect of HIV viral control on the risk of SCCA demonstrated that percent of time with undetectable viral load was significantly associated with reduction of SCCA risk but current CD4 count was not [28]. In contrast, the current study found that individuals with 80–100% percent of time with undetectable viral load was not significantly associated with decreased OPSCC risk. Rather, moderate amounts of time with an undetectable viral load (between 40–80% of follow-up time) were associated with an *increased* risk for OPSCC. Demonstrating that unlike SCCA HIV viral load suppression alone did not decrease OPSCC risk. Additionally, unlike SCCA, a low current CD4 count (rather than a low nadir CD4 count) increased the risk of OPSCC. This demonstrates that although both OPSCC and SCCA are both mediated by HPV infection, the impact of immunosuppression by HIV affects the risk of each cancer differently.

Our findings suggest that although increasing access to cART effectively reduces circulating HIV viral loads, the immune system may fail to fully recover oral HPV-specific immunity, which then increases the risk for oral HPV persistence and development of OPSCC. Interestingly, we also found that other HPV related diseases such as SCCA or condyloma

were not associated with an increased risk of oropharynx cancer. Studies in both HIV-negative men and women have demonstrated minimal concordance between HPV anogenital and oral infections [39,40], demonstrating that there is little cross-contamination of HPV infection between these sites [41]. Taken together, it appears that in immunosuppressed individuals, the mechanisms of HPV-related oncogenesis may differ between the oropharynx and other anogenital sites.

Our study has several limitations. First, it was a retrospective cohort and thus may be subject to unmeasured confounders such as sexual behavior and alcohol use. However, we attempted to adjust for this through ICD-9 codes identifying individuals with a history of both alcohol and drug use. Our study also utilized ICD-9 codes for the definitions of covariates such as condyloma and SCCA, however the ICD-9 code for SCCA has been previously validated, and we have previously utilized the ICD-9 code for condyloma in association with SCCA incidence [28,42]. Additionally, we lacked information about the tumor HPV status of OPSCC cases. Although a recent case series study suggests that HPV is detected in the majority of oropharyngeal cancers in HIV infected individuals [43], there were likely several HPV-negative OPSCCs in our cohort. Finally, this study was limited to male veterans, thus these data may not be completely generalizable to the other populations of HIV-infected individuals.

In summary, our study demonstrates that older age and low recent CD4 counts <200 increase the risk for OPSCC in HIV-infected veterans. We also found that previous HPV diseases including SCCA and condyloma do not increase the risk for OPSCC. Although SCCA and OPSCC are both HPV-mediated cancers, our study suggests that they may be associated with different immunologic mechanisms which predominate in the oral cavity or the anal canal. Alternatively, the interaction between HIV and HPV in the oropharynx may not be the same as the interaction between HPV and HIV-related immunosuppression in other anatomic sites. The information from this study demonstrates that older age and CD4 count <200 are specific risk factors that can alert health care professionals to consider OPSCC screening, including careful evaluation of oropharyngeal symptoms, and oral exams for HIV-infected individuals with these risks. Clinical studies evaluating the optimal approaches to the detection and prevention of OPSCC and other HPV-associated malignancies among HIV-infected individuals are necessary.

Acknowledgments

Funding Support: Drs. Elizabeth Chiao and Jennifer Kramer received research funding for this project through a 2011 developmental grant from the Baylor-UT Houston Center for AIDS Research (CFAR), an NIH-funded program (NIH P30 CA125123). This work was also supported in part by the Center for Innovations in Quality, Effectiveness and Safety (#CIN 13–413).

REFERENCES

- [1]. Besson C, Goubar A, Gabarre J, Rozenbaum W, Pialoux G, Châtelet FP, Katlama C, Charlotte F, Dupont B, Brousse N, Huerre M, Mikol J, Camparo P, Mokhtari K, Tulliez M, Salmon-Céron D, Boué F, Costagliola D, Raphaël M, Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy, *Blood* 98 (2001) 2339–2344. [PubMed: 11588028]

- [2]. International Collaboration on HIV and Cancer, Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults, *J. Natl. Cancer Inst* 92 (2000) 1823–1830. [PubMed: 11078759]
- [3]. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, Bhatia K, Uldrick TS, Yarchoan R, Goedert JJ, Engels EA, Cancer burden in the HIV-infected population in the United States, *J. Natl. Cancer Inst* 103 (2011) 753–762. doi:10.1093/jnci/djr076. [PubMed: 21483021]
- [4]. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, Goedert JJ, Cancer risk in people infected with human immunodeficiency virus in the United States, *Int. J. Cancer* 123 (2008) 187–194. doi:10.1002/ijc.23487. [PubMed: 18435450]
- [5]. Dal Maso L, Polesel J, Serraino D, Lise M, Piselli P, Falcini F, Russo A, Intrieri T, Vercelli M, Zambon P, Tagliabue G, Zanetti R, Federico M, Limina RM, Mangone L, De Lisi V, Stracci F, Ferretti S, Piffer S, Budroni M, Donato A, Giacomini A, Bellù F, Fusco M, Madeddu A, Vitarelli S, Tessori R, Tumino R, Suligoi B, Franceschi S, Cancer and AIDS Registries Linkage (CARL) Study, Pattern of cancer risk in persons with AIDS in Italy in the HAART era, *Br. J. Cancer* 100 (2009) 840–847. doi:10.1038/sj.bjc.6604923. [PubMed: 19223894]
- [6]. Herida M, Mary-Krause M, Kaphan R, Cadranel J, Poizot-Martin I, Rabaud C, Plaisance N, Tissot-Dupont H, Boue F, Lang J-M, Costagliola D, Incidence of Non-AIDS-Defining Cancers Before and During the Highly Active Antiretroviral Therapy Era in a Cohort of Human Immunodeficiency Virus-Infected Patients, *J. Clin. Oncol* 21 (2003) 3447–3453. doi:10.1200/JCO.2003.01.096. [PubMed: 12972519]
- [7]. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ, HIV/AIDS Cancer Match Study, Trends in cancer risk among people with AIDS in the United States 1980–2002, *AIDS Lond. Engl* 20 (2006) 1645–1654. doi:10.1097/01.aids.0000238411.75324.59.
- [8]. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, Holmberg SD, Brooks JT, Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators, Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003, *Ann. Intern. Med* 148 (2008) 728–736. [PubMed: 18490686]
- [9]. Piketty C, Selinger-Leneman H, Grabar S, Duvivier C, Bonmarchand M, Abramowitz L, Costagliola D, Mary-Krause M, FHDH-ANRS CO 4, Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy, *AIDS Lond. Engl* 22 (2008) 1203–1211. doi:10.1097/QAD.0b013e3283023f78.
- [10]. Pytynia KB, Dahlstrom KR, Sturgis EM, Epidemiology of HPV-associated oropharyngeal cancer, *Oral Oncol* 50 (2014) 380–386. doi:10.1016/j.oraloncology.2013.12.019. [PubMed: 24461628]
- [11]. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML, Human papillomavirus and rising oropharyngeal cancer incidence in the United States, *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol* 29 (2011) 4294–4301. doi:10.1200/JCO.2011.36.4596.
- [12]. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, Roberts S, Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region, *Head Neck* 35 (2013) 747–755. doi: 10.1002/hed.22015. [PubMed: 22267298]
- [13]. Siegel R, Naishadham D, Jemal A, Cancer statistics, 2013, *CA. Cancer J. Clin* 63 (2013) 11–30. doi:10.3322/caac.21166.
- [14]. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML, Human papillomavirus and survival of patients with oropharyngeal cancer, *N. Engl. J. Med* 363 (2010) 24–35. doi:10.1056/NEJMoa0912217. [PubMed: 20530316]
- [15]. Mehanna H, Jones TM, Gregoire V, Ang KK, Oropharyngeal carcinoma related to human papillomavirus, *BMJ* 340 (2010) c1439. [PubMed: 20339160]
- [16]. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, Moore-Higgs GJ, Greene BD, Speer TW, Cassisi NJ, Million RR, Squamous cell carcinoma of the oropharynx:

surgery, radiation therapy, or both, *Cancer* 94 (2002) 2967–2980. doi:10.1002/cncr.10567. [PubMed: 12115386]

- [17]. 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. Off. J. Am. Soc. Clin. Oncol* 26 (2008) 612–619. doi:10.1200/JCO.2007.14.1713.
- [18]. 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* 116 (2010) 2635–2644. doi: 10.1002/cncr.25087. [PubMed: 20336792]
- [19]. Fakhry C, D'souza G, Sugar E, Weber K, Goshu E, Minkoff H, Wright R, Seaberg E, Gillison M, Relationship between prevalent oral and cervical human papillomavirus infections in human immunodeficiency virus-positive and -negative women, *J. Clin. Microbiol* 44 (2006) 4479–4485. doi:10.1128/JCM.01321-06. [PubMed: 17021055]
- [20]. Marais DJ, Passmore J-AS, Denny L, Sampson C, Allan BR, Williamson A-L, Cervical and oral human papillomavirus types in HIV-1 positive and negative women with cervical disease in South Africa, *J. Med. Virol* 80 (2008) 953–959. doi:10.1002/jmv.21166. [PubMed: 18428143]
- [21]. Beachler DC, Abraham AG, Silverberg MJ, Jing Y, Fakhry C, Gill MJ, Dubrow R, Kitahata MM, Klein MB, Burchell AN, Korthuis PT, Moore RD, D'Souza G, Incidence and risk factors of HPV-related and HPV-unrelated Head and Neck Squamous Cell Carcinoma in HIV-infected individuals, *Oral Oncol* 50 (2014) 1169–1176. doi:10.1016/j.oraloncology.2014.09.011. [PubMed: 25301563]
- [22]. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML, Case-control study of human papillomavirus and oropharyngeal cancer, *N. Engl. J. Med* 356 (2007) 1944–1956. doi:10.1056/NEJMoa065497. [PubMed: 17494927]
- [23]. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R, Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers, *J. Natl. Cancer Inst* 100 (2008) 407–420. doi:10.1093/jnci/djn025. [PubMed: 18334711]
- [24]. Gillison ML, Oropharyngeal cancer: a potential consequence of concomitant HPV and HIV infection, *Curr. Opin. Oncol* 21 (2009) 439–444. doi:10.1097/CCO.0b013e32832f3e1b. [PubMed: 19587593]
- [25]. Coutlée F, Trottier AM, Ghattas G, Leduc R, Toma E, Sanche G, Rodrigues I, Turmel B, Allaire G, Ghadirian P, Risk factors for oral human papillomavirus in adults infected and not infected with human immunodeficiency virus, *Sex. Transm. Dis* 24 (1997) 23–31. [PubMed: 9018780]
- [26]. Kreimer AR, Alberg AJ, Daniel R, Gravitt PE, Viscidi R, Garrett ES, Shah KV, Gillison ML, Oral human papillomavirus infection in adults is associated with sexual behavior and HIV serostatus, *J. Infect. Dis* 189 (2004) 686–698. doi:10.1086/381504. [PubMed: 14767823]
- [27]. Cameron JE, Mercante D, O'Brien M, Gaffga AM, Leigh JE, Fidel PL, Hagensee ME, The impact of highly active antiretroviral therapy and immunodeficiency on human papillomavirus infection of the oral cavity of human immunodeficiency virus-seropositive adults, *Sex. Transm. Dis* 32 (2005) 703–709. [PubMed: 16254546]
- [28]. Chiao EY, Hartman CM, El-Serag HB, Giordano TP, The impact of HIV viral control on the incidence of HIV-associated anal cancer, *J. Acquir. Immune Defic. Syndr* 1999 63 (2013) 631–638. doi:10.1097/QAI.0b013e3182968fa7.
- [29]. Kramer JR, Kowalkowski MA, Duan Z, Chiao EY, The effect of HIV viral control on the incidence of hepatocellular carcinoma in veterans with hepatitis C and HIV coinfection, *J. Acquir. Immune Defic. Syndr* 1999 68 (2015) 456–462. doi:10.1097/QAI.0000000000000494.
- [30]. Kowalkowski MA, Mims MP, Amiran ES, Lulla P, Chiao EY, Effect of Immune Reconstitution on the Incidence of HIV-Related Hodgkin Lymphoma, *PLoS ONE* 8 (2013) e77409. doi:10.1371/journal.pone.0077409. [PubMed: 24098586]
- [31]. Backus L, Mole L, Chang S, Deyton L, The Immunology Case Registry, *J. Clin. Epidemiol* 54 Suppl 1 (2001) S12–15. [PubMed: 11750204]

- [32]. Giordano TP, Gifford AL, White AC, Suarez-Almazor ME, Rabeneck L, Hartman C, Backus LI, Mole LA, Morgan RO, Retention in care: a challenge to survival with HIV infection, *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am* 44 (2007) 1493–1499. doi:10.1086/516778.
- [33]. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, Towner WJ, Dubrow R, Quesenberry CP, Neugebauer RS, Abrams DI, HIV Infection, Immunodeficiency, Viral Replication, and the Risk of Cancer, *Cancer Epidemiol. Biomarkers Prev* 20 (2011) 2551–2559. doi:10.1158/1055-9965.EPI-11-0777. [PubMed: 22109347]
- [34]. Clifford GM, Polesel J, Rickenbach M, on behalf of the S.H.C. Study, Maso LD, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, Bordoni A, Weck DD, Franceschi S, Cancer Risk in the Swiss HIV Cohort Study: Associations With Immunodeficiency, Smoking, and Highly Active Antiretroviral Therapy, *J. Natl. Cancer Inst* 97 (2005) 425–432. doi:10.1093/jnci/dji072. [PubMed: 15770006]
- [35]. Engels EA, Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities, *AIDS Lond. Engl* 23 (2009) 875–885. doi:10.1097/QAD.0b013e328329216a.
- [36]. Critchlow CW, Hawes SE, Kuypers JM, Goldbaum GM, Holmes KK, Surawicz CM, Kiviat NB, Effect of HIV infection on the natural history of anal human papillomavirus infection, *AIDS Lond. Engl* 12 (1998) 1177–1184.
- [37]. Arany I, Tyring SK, Systemic immunosuppression by HIV infection influences HPV transcription and thus local immune responses in condyloma acuminatum, *Int. J. STD AIDS* 9 (1998) 268–271. [PubMed: 9639204]
- [38]. Dolei A, Curreli S, Marongiu P, Pierangeli A, Gomes E, Bucci M, Serra C, Degener AM, Human immunodeficiency virus infection in vitro activates naturally integrated human papillomavirus type 18 and induces synthesis of the L1 capsid protein, *J. Gen. Virol* 80 (Pt 11) (1999) 2937–2944. doi:10.1099/0022-1317-80-11-2937. [PubMed: 10580055]
- [39]. Cañadas MP, Bosch FX, Junquera ML, Ejarque M, Font R, Ordoñez E, de Sanjosé S, Concordance of prevalence of human papillomavirus DNA in anogenital and oral infections in a high-risk population, *J. Clin. Microbiol* 42 (2004) 1330–1332. [PubMed: 15004111]
- [40]. Smith EM, Ritchie JM, Yankowitz J, Wang D, Turek LP, Haugen TH, HPV prevalence and concordance in the cervix and oral cavity of pregnant women, *Infect. Dis. Obstet. Gynecol* 12 (2004) 45–56. doi:10.1080/10647440400009896. [PubMed: 15739817]
- [41]. King EM, Gilson R, Beddows S, Soldan K, Panwar K, Young C, Jit M, Edmunds WJ, Sonnenberg P, Oral human papillomavirus (HPV) infection in men who have sex with men: prevalence and lack of anogenital concordance, *Sex. Transm. Infect* 91 (2015) 284–286. doi:10.1136/sextrans-2014-051955. [PubMed: 25887283]
- [42]. Chiao EY, Giordano TP, Richardson P, El-Serag HB, Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era, *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol* 26 (2008) 474–479. doi:10.1200/JCO.2007.14.2810.
- [43]. D'souza G, Carey TE, William WN, Nguyen ML, Ko EC, Riddell J, Pai SI, Gupta V, Walline HM, Lee JJ, Wolf GT, Shin DM, Grandis JR, Ferris RL, Epidemiology of head and neck squamous cell cancer among HIV-infected patients, *J. Acquir. Immune Defic. Syndr* 1999 65 (2014) 603–610. doi:10.1097/QAI.0000000000000083.

Highlights

- Older age and low recent CD4 counts <200 increase the risk for OPSCC in HIV-infected veterans
- Previous HPV diseases including SCCA and condyloma do not increase the risk for OPSCC
- OPSCC may have different immunologic risk factors compared to other HPV-related cancers

Figure 1.
Selection criteria to generate final study cohort

Figure 2.
Kaplan-Meier plot displaying the cumulative incidence of OPSCC diagnosis over time stratified by CD4 cell count.

Table 1.

Age-Adjusted Incidence of OPSCC Among a Cohort of HIV-Infected United States Veterans

	Number of Cancers	Person-years Follow-up	Age-Adjusted Incidence of OPSCC per 100,000 Person-Years (Lower and Upper Confidence Intervals)
Complete Cohort	97	296,370	23.2 (17.8 to 29.2)
Overall cART Cohort	78	266,440	21.9 (16.4 to 28.5)
Never cART Cohort	19	29,931	31.3 (15.5 to 52.4)
Current CD4 count			
<200	39	64,299	46.5 (29.9 to 68.1)
200–350	19	54,856	27.7 (14.7 to 47.3)
>350	39	177,215	15.3 (10.0 to 21.7)

Table 2.

Descriptive and Clinical Characteristics of the Overall Cohort and Stratified by OPSCC

Variable	Overall N=40,966	OPSCC Cases N=97	No OPSCC N=40,869	P
	N (%)	N (%)	N (%)	
Age at Beginning of Follow Up				
<40	11095 (27)	11 (11)	11084 (27)	0.006
40–49	16953 (41)	58 (60)	16895 (41)	
50 and above	12918 (32)	28 (29)	12890 (32)	
Race				
White	14765 (36)	34 (35)	14731 (36)	0.500
Black	20474 (50)	53 (55)	20421 (50)	
Hispanic/unknown/other	5727 (14)	10 (10)	5717 (14)	
Era of HIV diagnosis				
Pre-cART (1985–1995)	13479 (33)	46 (47)	13433 (33)	<0.0001
Early cART (1996–2000)	11692 (29)	34 (35)	11658 (29)	
Late cART (2001–2010)	15795 (39)	17 (18)	15778 (39)	
Percent cART*				
0–39%	21661 (53)	47 (48)	21614 (53)	0.170
40–79%	12603 (31)	38 (39)	12565 (31)	
80–100%	6702 (16)	12 (12)	6690 (16)	
Ever cART*				
No	32619 (80)	19 (20)	8328 (20)	0.847
Yes	8347 (20)	78 (80)	32541 (80)	
Recent CD4 cell count*				
>350	21238 (52)	39 (40)	21198 (52)	0.053
200–350	7334 (18)	19 (20)	7315 (18)	
<200	12394 (30)	39 (40)	12355 (30)	
Nadir CD4 cell count*				
CD4 ≥ 200	17145 (42)	36 (37)	17109 (42)	0.344
CD4 < 200	23821 (58)	61 (63)	23760 (58)	
% Time with undetectable HIV VL*				
0–39%	20748 (50)	50 (52)	20698 (51)	0.144
40–79%	10861 (27)	32 (33)	10829 (27)	
80–100%	9357 (23)	15 (15)	9342 (23)	
Smoking History				
Non-smoker	6632 (16)	12 (12)	6620 (16)	0.307

		Overall	OPSCC Cases	No OPSCC	P
Variable		N=40,966	N=97	N=40,869	
Past or Current		34334 (84)	85 (88)	34249 (84)	
Condyloma Diagnosis					
	No	38288 (93)	88 (91)	38200 (93)	0.274
	Yes	2678 (7)	9 (9)	2669 (7)	
SCCA Diagnosis					
	No	40458 (99)	94 (97)	40364 (99)	0.099
	Yes	508 (1)	3 (3)	505 (1)	

*
Value at event or censor date

Table 3.

Univariate and Multivariate Survival Analysis of OPSCC Risk among HIV-infected Veterans

	Univariate HR and 95% CI N=40,966 (97 Cancers)	P	Multivariate HR and 95% CI N=40,966 (97 Cancers)	P
Age at Beginning of Follow Up				
<40	1		1	
40–49	4.0 (2.1 to 7.7)	<0.0 001	3.8 (2.0 to 7.3)	<0.0 001
50 and above	3.7 (1.8 to 7.4)	0.0003	3.8 (1.9 to 7.8)	0.0003
Race				
White	1		1	
Black	1.2 (0.8 to 1.8)	0.50	1.1 (0.7 to 1.8)	0.59
Hispanic/Unknown/other	1.0 (0.5 to 1.9)	0.88	0.9 (0.5 to 1.8)	0.79
Era of HIV Diagnosis				
Pre-cART (1985–1995)	1		1	
Early cART (1996–2000)	0.9 (0.6 to 1.4)	0.67	0.9 (0.6 to 1.4)	0.58
Late cART (2001–2010)	0.8 (0.4 to 1.4)	0.40	0.7 (0.4 to 1.3)	0.25
Ever cART *				
No	1		1	
Yes	1.3 (0.7 to 2.2)	0.43	1.0 (0.6 to 1.9)	0.91
Recent CD4 cell count *				
>350	1		1	
200–350	1.3 (0.8 to 2.3)	0.35	1.4 (0.8 to 2.6)	0.24
<200	2.9 (1.9 to 4.5)	<0.001	3.8 (2.0 to 7.3)	<0.0001
Nadir CD4 cell count *				
CD4 ≥ 200	1		1	
CD4 < 200	1.7 (1.1 to 2.6)	0.01	0.8 (0.4 to 1.4)	0.43
% Time with undetectable HIV VL *				
0–39%	1		1	
40–79%	1.5 (0.9 to 2.3)	0.11	1.8 (1.1 to 3.0)	0.02
80–100%	1.0 (0.6 to 1.8)	0.94	1.5 (0.8 to 2.8)	0.25
Smoking History				
Non-smoker	1		1	
Past or Current	1.5 (0.8 to 2.8)	0.18	1.3 (0.7 to 2.4)	0.41
Condyloma Diagnosis				
No	1		1	
Yes	1.0 (0.5 to 1.9)	0.89	1.0 (0.5 to 2.1)	0.99
SCCA Diagnosis				
No	1		1	

	Univariate HR and 95% CI N=40,966 (97 Cancers)	<i>P</i>	Multivariate HR and 95% CI N=40,966 (97 Cancers)	<i>P</i>
Yes	1.8 (0.6 to 5.8)	0.30	1.7 (0.5 to 5.6)	0.38

* Time-updated variables

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript