Oral Oncology 68 (2017) 60–66

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Risk factors for oropharynx cancer in a cohort of HIV-infected veterans

Erin Y. Chew [a], Christine M. Hartman [b], Peter A. Richardson [b], Jose P. Zevallos [c,d], Andrew G. Sikora [e], Jennifer R. Kramer [b], Elizabeth Y. Chiao [a,b,*]

[a] One Baylor Plaza, Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, TX 77030, USA
[b] 2002 Holcombe Boulevard, Center of Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX 77030, USA
[c] 170 Manning Drive, CB# 7070 Department of Otolaryngology-Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514, USA
[d] 170 Rosenau Hall CB, #7400 Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514, USA
[e] One Baylor Plaza, Department of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, Houston, TX 77030, USA

ARTICLE INFO

Article history:
Received 22 January 2017
Accepted 11 March 2017
Available online 23 March 2017

Keywords:
Oropharynx cancer
HIV
Epidemiology
Combined antiretroviral therapy
HIV-related immune suppression
Human papilloma virus
Oral cancer
Head and neck cancer

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 to 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 17.8–29.2]. Age > 50 (aHR = 3.8, 95% CI 1.9–7.8), recent CD4 < 200 (aHR = 3.8, 95% CI 2.0–7.3), and undetectable HIV viral loads 40–79% of the time (aHR = 1.8, 95% CI 1.1–3.0) 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 risk of OPSCC. Other HPV-related diseases such as SCCA and condyloma did not increase the risk for OPSCC.

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

* Corresponding author at: Michael E. DeBakey VA Medical Center, HSR&D Center of Innovation (152), 2002 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail address: echiao@bcm.edu (E.Y. Chiao).

http://dx.doi.org/10.1016/j.oraloncology.2017.03.004
1368-8375/

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 conduced 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. Fig. 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

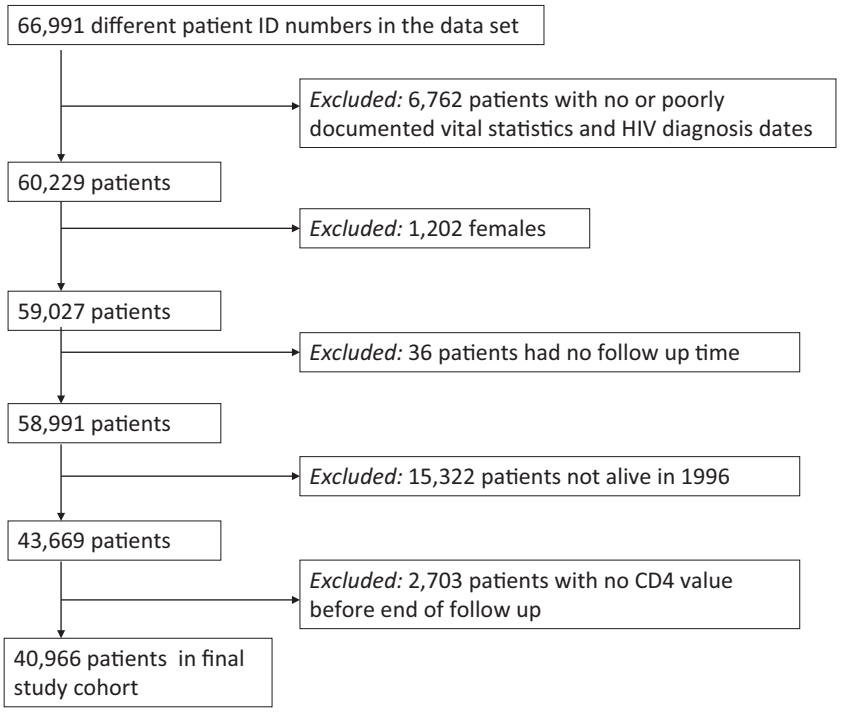

Fig. 1. Selection criteria to generate final study cohort.