Immunological and infectious risk factors for lung cancer in US veterans with HIV: a longitudinal cohort study

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Summary

Background HIV infection is independently associated with risk of lung cancer, but few data exist for the relation between longitudinal measurements of immune function and lung-cancer risk in people living with HIV.

Methods We followed up participants with HIV from the Veterans Aging Cohort Study for a minimum of 3 years between Jan 1, 1998, and Dec 31, 2012, and used cancer registry data to identify incident cases of lung cancer. The index date for each patient was the later of the date HIV care began or Jan 1, 1998. We excluded patients with less than 3 years’ follow-up, prevalent diagnoses of lung cancer, or incomplete laboratory data. We used Cox regression models to investigate the relation between different time-updated lagged and cumulative exposures (CD4 cell count, CD8 cell count, CD4/CD8 ratio, HIV RNA, and bacterial pneumonia) and risk of lung cancer. Models were adjusted for age, race or ethnicity, smoking, hepatitis C virus infection, alcohol use disorders, drug use disorders, and history of chronic obstructive pulmonary disease and occupational lung disease.

Findings We identified 277 cases of incident lung cancer in 21 666 participants with HIV. In separate models for each time-updated 12 month lagged, 24 month simple moving average cumulative exposure, increased risk of lung cancer was associated with low CD4 cell count (p trend=0.001), low CD4/CD8 ratio (p trend=0.0001), high HIV RNA concentration (p=0.004), and more cumulative bacterial pneumonia episodes (12 month lag only; p trend=0.0004). In a mutually adjusted model including these factors, CD4/CD8 ratio and cumulative bacterial pneumonia episodes remained significant (p trends 0.003 and 0.004, respectively).

Interpretation In our large HIV cohort in the antiretroviral therapy era, we found evidence that dysfunctional immune activation and chronic inflammation contribute to the development of lung cancer in the setting of HIV infection. These findings could be used to target lung-cancer prevention measures to high-risk groups.

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Introduction Lung cancer is the most common non-AIDS-defining cancer and a leading cause of cancer death in people with HIV.1-3 HIV infection is independently associated with risk of lung cancer after accounting for established risk factors such as age, smoking, and chronic obstructive pulmonary disease (COPD).4 Several factors have been tentatively linked to the increased risk of lung cancer associated with HIV infection, including immunosuppression (ie, low CD4 cell count) and recurrent lung infections.5

Findings from studies of the relation between severity of HIV-related immunosuppression as measured by CD4 cell count and lung-cancer risk have been mixed, with several previous studies showing an association6,7 and others8 no association. Many previous studies have been limited by retrospective approaches, small numbers of cases of lung cancer, an absence of data about smoking, or static, insensitive measures of immunosuppression, such as baseline CD4 cell count.

Immunosuppression places people with HIV at increased risk of bacterial pneumonia.9 An association between history of bacterial pneumonia and raised lung-cancer risk has been noted in both the general population10 and people living with HIV.11 However, no investigators have previously attempted to disentangle the relations between CD4 cell count, history of bacterial pneumonia, and risk of lung cancer. In addition to low CD4 cell count, other clinically available markers of immune impairment include CD8 cell count and ratio of CD4 cell count to CD8 cell count (a low ratio has been associated with immunosenescence and abnormal immune activation in HIV-negative people12). In patients with HIV, a persistently low CD4/CD8 ratio has been associated with increased risk of all-cause mortality, non-AIDS mortality, and incidence of non-AIDS-defining cancer.13,14 However, the ratio has not been previously assessed as a predictor of lung-cancer risk.

In this study we used data from a large, national HIV cohort from the era of antiretroviral therapy (ART) to assess the relations between lagged and cumulative markers of immune function and cumulative bacterial pneumonia episodes and risk of lung cancer.

Methods

Study population We used data from the Veterans Aging Cohort Study (VACS), a large HIV cohort assembled from national...
Veterans Affairs administrative and clinical databases. The full VACS included more than 48 000 veterans living with HIV receiving Veterans Affairs care between 1996 and 2012, but we restricted our analysis to 40 973 patients receiving care between Jan 1, 1998, and Dec 31, 2012, because during this period the database contained the most complete data about immune markers. For our analysis, the index date for each patient was the later of the date HIV care began or Jan 1, 1998. Because we were interested in associations between longitudinal exposures to different measures of immune function and risk of lung cancer, we further restricted the cohort by excluding patients with less than 3 years of follow-up or with a prevalent lung-cancer diagnosis (appendix p 1). We then excluded patients for whom laboratory data were incomplete during the study period. Each patient was then followed up until the date of their last available laboratory measurement (carried forward 365 days), diagnosis of lung cancer, death, or Dec 31, 2012. The Institutional Review Boards of the Veterans Affairs Connecticut Healthcare System and the Yale University School of Medicine approved this research (they waived the need for informed consent).

Procedures
We linked VACS data with the Veterans Affairs Central Cancer Registry (VACCR), which ascertains almost 90% of cancer cases diagnosed or treated by Veterans Affairs in patients living with HIV.\(^6\) We used VACCR data to identify pathologically confirmed incident cases of lung carcinoma among cohort members. We established patients’ baseline characteristics on the basis of the period from 12 months before the index date until 6 months afterwards. Baseline characteristics were demographic variables (ie, age, sex, and race or ethnicity), clinical diagnoses (COPD, occupational lung disease, alcohol and drug use disorders, bacterial pneumonia, tuberculosis, and Pneumocystis jirovecii pneumonia) identified from relevant diagnostic codes (appendix p 2), chronic hepatitis C virus infection (based on relevant laboratory tests and diagnosis codes and considered present if found at any time during follow-up), smoking status (current, former, or never) determined from a clinical-reporting system based on previously validated methods,\(^7\) use of ART and specific ART drug classes identified from the Veterans Affairs pharmacy database, CD4 cell count, CD8 cell count, CD4/CD8 ratio, and HIV RNA concentration.

We collected longitudinal laboratory data for all participants during the observation period, and organised longitudinal values by the month and year in which they were reported. For months when no laboratory measures were available for a patient, we used linear interpolation to assign imputed values.\(^8\) Initial laboratory values were carried back 90 days. Final values were carried forward either 365 days or until cancer diagnosis or censoring, whichever came first. If a patient had a gap of more than 547 days between laboratory tests, the value before the gap was carried forward for 365 days and then the patient was censored.

We identified all episodes of bacterial pneumonia after the index date from inpatient admissions (>90 days apart) on the basis of relevant diagnosis codes. Longitudinal exposure was measured by cumulative counts of episodes (including baseline episodes).

Statistical analysis
We compared baseline characteristics of patients who developed lung cancer with those of patients who did not develop lung cancer during follow-up with the Wilcoxon

Research in context
Evidence before this study
We searched Google Scholar with the terms “lung cancer” and “HIV” for articles published in English between Jan 1, 1997, and Aug 1, 2016 (the date of our final search). We selected studies in which risk factors for lung cancer were assessed in patients living with HIV during the antiretroviral therapy era. Studies of the relation between CD4 cell count and lung-cancer risk had mixed results, and most studies included small numbers of cancer cases. Bacterial pneumonia was assessed as a risk factor for lung cancer in people with HIV in two previous studies, but this risk was not clarified in the context of immunosuppression. We found no studies in which the relation between the ratio of CD4 cell count to CD8 cell count and risk of lung cancer was examined.

Added value of this study
The Veterans Aging Cohort Study is a large US cohort of people with HIV, for whom detailed cancer and exposure data are available. We showed that cumulative low CD4/CD8 ratio, a novel risk factor for lung cancer, was the most robust independent immunological predictor of increased risk of lung cancer in this cohort. Additionally, cumulative episodes of bacterial pneumonia were directly associated with risk of lung cancer, even after immunological factors were accounted for.

Implications of all the available evidence
Our findings suggest that, in people with HIV, abnormal immune activation, as represented by low CD4/CD8 ratio, and previous episodes of bacterial pneumonia might have roles in the development of lung cancer, the leading cause of cancer death in this population. These risk factors, along with smoking history, age, and chronic obstructive pulmonary disease, could be used to target high-risk groups with lung-cancer prevention measures, such as CT-based screening.
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