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Immunodeficiency, AIDS-related pneumonia, and risk of lung cancer among HIV-infected individuals

Julia L. Marcus, PhD, MPH¹, Wendy A. Leyden, MPH¹, Chun R. Chao, PhD², Michael A. Horberg, MD, MAS³, Daniel B. Klein, MD⁴, Charles P. Quesenberry Jr, PhD¹, William J. Towner, MD⁵, and Michael J. Silverberg, PhD, MPH¹

¹Kaiser Permanente Northern California, Oakland, CA

²Kaiser Permanente Southern California, Pasadena, CA

³Kaiser Permanente Mid-Atlantic States, Rockville, MD

⁴Kaiser Permanente Northern California, Hayward, CA

⁵Kaiser Permanente Southern California, Los Angeles, CA

Abstract

Objective—To clarify the role of immunodeficiency and pneumonia in elevated lung cancer risk among HIV-infected individuals.

Design—Cohort study of HIV-infected and HIV-uninfected adults in a large integrated healthcare system in California during 1996–2011.

Methods—We used Poisson models to obtain rate ratios (RR) for lung cancer associated with HIV infection, overall and stratified by recent CD4 cells/ μ L (HIV-uninfected as reference group), with chi-square tests for trends across CD4 strata. Fully adjusted models included demographics, cancer risk factors (smoking, drug/alcohol abuse, overweight/obesity), and prior pneumonia.

Results—Among 24,768 HIV-infected and 257,600 HIV-uninfected individuals, the lung cancer rate per 100,000 person-years was 66 (n=80 events) for HIV-infected and 33 (n=506 events) for HIV-uninfected individuals (RR 2.0, 95% confidence interval [CI]: 1.7–2.2). Overall, HIV-infected individuals were at increased risk of lung cancer after adjustment for demographics and cancer risk factors (RR 1.4, 95% CI: 1.1–1.7), but not after additional adjustment for pneumonia (RR 1.2, 95% CI: 0.9–1.6). Lower CD4 counts were associated with higher risk of lung cancer in unadjusted and demographics-adjusted models ($P<0.001$ for all), but this trend did not remain after adjustment for cancer risk factors and pneumonia. Compared with HIV-uninfected individuals, HIV-infected individuals with CD4 <200 cells/ μ L were not at increased risk of lung cancer in fully adjusted models.

Corresponding author and requests for reprints: Michael J. Silverberg, Kaiser Permanente Northern California, Division of Research, 2000 Broadway, Oakland, CA 94612, USA. Tel: +1 510-891-3801; fax: +1 510-891-3508; michael.j.silverberg@kp.org.

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Conclusions—The increased lung cancer risk among HIV patients is attributable to differences in demographics, risk factors such as smoking, and history of pneumonia. Immunodeficiency does not appear to have an independent effect on lung cancer risk.

Keywords

HIV; acquired immunodeficiency syndrome; CD4; lung neoplasms; smoking; pneumonia

Introduction

As life expectancy for HIV-infected individuals in developed countries improves [1, 2], non-AIDS-defining cancers increasingly contribute to morbidity and mortality, with a particularly high burden of lung cancer [3-8]. The increased risk of lung cancer among HIV-infected individuals [3-8] may be partly attributable to a higher prevalence of traditional risk factors, most notably smoking [9], yet several studies have found a higher risk of lung cancer in this population even after adjustment for smoking [10-13]. The remaining increased risk may be explained by HIV-associated factors, such as immunodeficiency or a higher incidence of pulmonary infections that increase lung cancer risk, possibly as a result of inflammation [14-16]. However, studies of the impact of immunodeficiency on lung cancer have had mixed results [10, 17-19], and those that have examined the role of pneumonia have had few lung cancer cases [10, 20] or lacked an internal HIV-uninfected comparison group [15, 21].

Clarification of the role of immunodeficiency and pneumonia in lung cancer risk could help target lung cancer screening and prevention efforts to the highest-risk subsets of HIV-infected patients [22]. We previously found that HIV infection and immunodeficiency were associated with an increased risk of lung cancer, with attenuated results after adjustment for smoking [17]. Here, we extend that work by evaluating the role of pneumonia in a larger cohort with longer follow-up. Specifically, we assessed whether HIV infection confers an increased risk of lung cancer after adjustment for demographic characteristics, cancer risk factors such as smoking, and prior pneumonia. We also determined whether immunodeficiency has an independent effect on lung cancer incidence among HIV patients.

Methods

Study design, setting, and population

The study population was a previously described cohort [17] of HIV-infected and HIV-uninfected members of Kaiser Permanente (KP) Northern and Southern California (KPNC and KPSC, respectively), large integrated healthcare systems providing comprehensive medical services to over 30% of insured Californians [23]. Briefly, HIV-uninfected adults were frequency-matched 10:1 to HIV-infected adults by age (five-year groups), sex, medical center, and initial calendar year of follow-up. The start of follow-up for each subject was the earliest date on or after January 1, 1996 (January 1, 2000, for KPSC) when eligibility criteria were met. For this analysis, subjects were followed until the earliest of lung cancer, health plan disenrollment, death, or December 31, 2011.

The institutional review boards at KPNC and KPSC approved this study with a waiver of written informed consent.

Study measurements

HIV status was obtained from KP HIV registries, which include all known cases of HIV/AIDS since the early 1980s for KPNC and 2000 for KPSC. Lung cancer diagnoses were ascertained from KP cancer registries, which use standardized methods for reporting to the Surveillance, Epidemiology, and End Results program registry [24].

Demographic and risk factor data were extracted from the clinical and administrative databases constituting KP's electronic health record (EHR), including age; sex; race/ethnicity; CD4 counts; health plan enrollment periods; and inpatient or outpatient clinical diagnoses, including smoking/tobacco use (International Classification of Disease Codes, version 9 [ICD-9]: 305.1, V15, V65, 649, internal social history codes), drug/alcohol abuse (ICD-9: 291, 292, 303-305.0, 305.2-305.5), overweight/obesity (ICD-9: 278, 259.9, V85, internal weight/height codes), and pneumonia, defined as *Pneumocystis jiroveci* pneumonia (ICD-9: 136.3) or 2 episodes of bacterial or other pneumonia (ICD-9: 481-486) <12 months apart. Pneumonia events included both presumptive diagnoses and those confirmed by laboratory testing or radiology.

Statistical analysis

Demographic characteristics for analyses included age (<40, 40-49, 50-64, 65 years), sex, race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, other; with imputed data where missing [27, 28]), calendar era (1996-1999, 2000-2003, 2004-2007, 2008-2009, 2010-2011), and KP region (KPNC, KPSC). Cancer risk factors were smoking, drug/alcohol abuse, and overweight/obesity, all defined as ever/never from two years prior to baseline through the end of follow-up. Time-dependent variables were age; calendar era; recent CD4 count; and any history of pneumonia, including two years prior to baseline through the end of follow-up; these were updated continuously except for CD4 counts, which were updated at six-month intervals.

We first computed lung cancer incidence rates per 100,000 person-years by HIV status. Adjusted rate ratios (RR) for HIV status were then obtained from three Poisson regression models including 1) HIV status, age, sex, race/ethnicity, calendar era, and KP region, 2) additional terms for smoking, drug/alcohol abuse, and overweight/obesity, and 3) an additional term for prior pneumonia. Next, we compared the risk of lung cancer in HIV-infected individuals stratified by recent CD4 count with the risk among HIV-uninfected individuals (reference group), using chi-square tests for trend in the RR across CD4 strata. Because pneumonia and CD4 decline may be clinical symptoms of undiagnosed lung cancer (i.e., reverse causation), we ran the CD4-stratified models with 12-month and 36-month lagged CD4 and pneumonia variables, such that CD4 counts and pneumonia diagnoses during the 12 and 36 months prior to lung cancer diagnosis were excluded.

Analyses were conducted in SAS 9.3 (Cary, North Carolina, USA). Statistical tests were two-sided, and statistical significance was defined as $P < 0.05$.

Results

Among 24,768 HIV-infected and 257,600 HIV-uninfected individuals, there were 121,115 and 1,502,391 person-years of follow-up, with a mean of 4.9 and 5.8 person-years per subject, respectively. The mean age was approximately 40 years, and 90% were men. A higher proportion of HIV-infected compared with HIV-uninfected individuals were White (56.2% vs. 44.1%) or Black (17.8% vs. 10.4%), and a lower proportion were Hispanic (21.0% vs. 27.3%) or Asian/Pacific Islander (4.3% vs. 16.1%; $P<0.001$ overall). Compared with HIV-uninfected individuals, HIV-infected patients more frequently had a history of smoking (45.2% vs. 31.1%; $P<0.001$) and drug/alcohol abuse (20.6% vs. 8.6%; $P<0.001$), and less frequently had a history of overweight/obesity (47.5% vs. 52.9%; $P<0.001$). The most common HIV-transmission risk group was men who have sex with men (74.7%). HIV-infected patients had been known to be HIV-infected for an average of 3.8 years at baseline, with a mean CD4 count of 410 cells/ μ L.

The crude lung cancer rate per 100,000 person-years was 66 for HIV-infected individuals (80 events) and 33 for HIV-uninfected individuals (506 events), with an unadjusted RR of 2.0 (95% confidence interval [CI]: 1.7-2.2; Table 1). Compared with HIV-uninfected individuals, HIV-infected individuals were at increased risk of lung cancer after adjustment for demographic characteristics (RR 1.9, 95% CI: 1.5-2.4) and additional adjustment for smoking, drug/alcohol abuse, and overweight/obesity (RR 1.4, 95% CI: 1.1-1.7), but were no longer at increased risk in fully adjusted models including any prior pneumonia (RR 1.1, 95% CI: 0.9-1.5).

Lung cancer risk increased as recent or lagged CD4 count decreased, in both unadjusted and demographics-adjusted models ($P<0.001$ for all), but this trend was not significant after adjustment for cancer risk factors and pneumonia. Compared with HIV-uninfected individuals, HIV-infected individuals with recent CD4 ≥ 500 cells/ μ L had no excess risk of lung cancer in unadjusted or adjusted models. For HIV-infected individuals with recent CD4 200-499 cells/ μ L, lung cancer incidence was elevated compared with HIV-uninfected individuals after adjustment for demographics and cancer risk factors (RR 1.4, 95% CI: 1.0-2.0; $P=0.039$), but not after adjustment for pneumonia (RR 1.3, 95% CI: 0.9-1.6). For HIV-infected individuals with recent CD4 <200 cells/ μ L, lung cancer risk was higher compared with HIV-uninfected individuals after adjustment for demographics and cancer risk factors (RR 2.2, 95% CI: 1.3-3.6), but not after adjustment for pneumonia (RR 1.6, 95% CI: 0.9-2.6). Similarly, in models using 12-month lagged CD4 and pneumonia variables, HIV-infected individuals with CD4 <200 cells/ μ L were at increased risk of lung cancer compared with HIV-uninfected individuals after adjustment for demographics (RR 2.7, 95% CI: 1.5-4.8), but not after adjustment for cancer risk factors (RR 1.7, 95% CI: 0.9-3.1) and pneumonia (RR 1.4, 95% CI: 0.7-2.6), with similar results for 36-month lagged CD4 and pneumonia measurements.

Discussion

In this large cohort of HIV-infected and matched HIV-uninfected adults from the same healthcare system, we found an increased risk of lung cancer for HIV-infected individuals

after adjustment for age, sex, race/ethnicity, smoking, overweight/obesity, and drug/alcohol abuse, but not after additional adjustment for prior pneumonia. We extend previous studies by including an HIV-uninfected control group, allowing us to determine the extent to which pneumonia explained the excess risk of lung cancer among HIV patients relative to HIV-uninfected individuals. Although we observed an increased risk of lung cancer at lower CD4 counts in unadjusted analyses, this association did not remain in fully adjusted models. Our results suggest that the increased risk of lung cancer among HIV-infected individuals is attributable to differences in demographic characteristics, cancer risk factors such as smoking, and pneumonia, and that immunodeficiency does not have an independent effect on lung cancer risk in this population.

We found that prior pneumonia drove the remaining risk of lung cancer among HIV-infected individuals after adjustment for smoking and other cancer risk factors, consistent with previous studies identifying pneumonia as a risk factor for lung cancer among HIV-infected patients [15, 20]. Pneumonia risk is higher in HIV infection [29], and inflammation during pulmonary infection may subsequently contribute to lung cancer risk [16]. Indeed, in a study of two HIV cohorts, Hessol et al. found that approximately two-thirds of the effect of HIV infection on lung cancer risk was explained by prior pneumonia [20].

There are several limitations to our study. First, because cancer risk factors were collected from the EHR, there may have been some misclassification and we could not analyze these variables in detail. For example, variables that captured current smoking or pack years, rather than ever smoking, would likely have explained even more of the excess risk of lung cancer among HIV-infected individuals in our study. Second, we may have missed mild cases of pneumonia that were undiagnosed, and pneumonia ascertainment may have varied across the cohort. For example, if pneumonia was more likely to be diagnosed among lung cancer cases as a result of increased interaction with the healthcare system, we may have overestimated the association of pneumonia with lung cancer; however, we minimized the potential for differential misclassification by using lagged measurements of pneumonia. Finally, our subjects were mostly male, reflecting the epidemiology of the HIV epidemic in California.

Our study also has several strengths. First, we used a large cohort of HIV-infected and matched HIV-uninfected individuals from the same healthcare system, thus minimizing the selection biases that can be introduced by using an external comparison group. Second, the HIV and cancer registries allowed for near-perfect case ascertainment for HIV infection and lung cancer. Third, we used lagged CD4 and pneumonia variables to account for potential reverse causation. Fourth, matching by medical center minimized potential confounding by environmental causes of cancer. Finally, the KP membership mirrors the age, sex, and race/ethnicity distributions of the California statewide population [30, 31], and the demographics of HIV-infected KP members are comparable to those of reported AIDS cases in California [32]. Thus, our results are likely to be generalizable to other insured individuals.

In summary, we found that the increased risk of lung cancer among HIV-infected individuals is largely explained by differences in demographics, cancer risk factors such as smoking, and a higher risk of pneumonia. We did not observe an independent effect of

immunodeficiency on lung cancer risk. Our results suggest that HIV patients with pneumonia may be good candidates for lung cancer screening, and that smoking cessation efforts, early antiretroviral therapy initiation, and pneumococcal vaccination and *Pneumocystis jiroveci* chemoprophylaxis may reduce the burden of lung cancer in this population.

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JLM and MJS had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. MJS was responsible for the overall conception and design of the study. WAL collected, assembled, and analyzed the data. CPQ provided statistical expertise. JLM drafted the article. CC and MJS were responsible for administrative, technical, and logistic support. All coauthors were responsible for interpretation of the data, critical revision of the article, and final approval of the article.

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Table 1
Rate ratios^a (95% CI) for lung cancer by HIV status and stratified by CD4 count, Kaiser Permanente California, 1996-2011

HIV-infected (HIV-uninfected reference)				P-value
Unadjusted			2.0 (1.7-2.2)	<0.001
Adjusted				
Demographics			1.9 (1.5-2.4)	<0.001
Demographics and cancer risk factors			1.4 (1.1-1.7)	0.014
Demographics, cancer risk factors, and prior pneumonia			1.1 (0.9-1.5)	0.37
Recent CD4 cells/μL (HIV-uninfected reference)				P_{trend}^b
	<200	200-499	500	
Unadjusted	3.1 (1.9-5.1)	2.2 (1.6-3.0)	1.5 (1.0-2.2)	<0.001
Adjusted				
Demographics	3.3 (2.0-5.5)	2.0 (1.4-2.8)	1.4 (0.9-2.1)	<0.001
Demographics and cancer risk factors	2.2 (1.3-3.6)	1.4 (1.0-2.0)	1.0 (0.7-1.6)	0.12
Demographics, cancer risk factors, and prior pneumonia	1.6 (0.9-2.6)	1.2 (0.8-1.7)	0.9 (0.6-1.4)	0.76
Recent CD4 cells/μL, 12 months prior (HIV-uninfected reference)				P_{trend}^b
	<200	200-499	500	
Unadjusted	2.8 (1.5-5.0)	2.0 (1.4-2.9)	1.7 (1.1-2.5)	<0.001
Adjusted				
Demographics	2.7 (1.5-4.8)	1.7 (1.2-2.5)	1.5 (1.0-2.3)	<0.001
Demographics and cancer risk factors	1.7 (0.9-3.1)	1.2 (0.8-1.7)	1.1 (0.7-1.7)	0.29
Demographics, cancer risk factors, and pneumonia >12 months prior	1.4 (0.7-2.6)	1.1 (0.7-1.6)	1.0 (0.7-1.6)	0.76
Recent CD4 cells/μL, 36 months prior (HIV-uninfected reference)				P_{trend}^b
	<200	200-499	500	
Unadjusted	2.4 (1.2-4.9)	2.3 (1.6-3.4)	1.4 (0.8-2.4)	<0.001
Adjusted				
Demographics	2.2 (1.1-4.5)	1.9 (1.3-2.8)	1.2 (0.7-2.0)	0.008
Demographics and cancer risk factors	1.4 (0.7-2.9)	1.3 (0.9-1.9)	0.9 (0.5-1.5)	0.58
Demographics, cancer risk factors, and pneumonia >36 months prior	1.2 (0.6-2.5)	1.2 (0.8-1.8)	0.8 (0.5-1.4)	0.98

CI, confidence interval.

^aRate ratios estimated by Poisson regression models with HIV-uninfected reference group. Demographic variables were age, sex, race/ethnicity, calendar era of study entry, and Kaiser Permanente region, and risk factors were smoking, drug/alcohol abuse, and overweight/obesity.

^bP-values for trend obtained from chi-square tests for trend.