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Lung Cancer in Persons with HIV

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Abstract

Purpose of Review—Lung cancer is emerging as a leading cause of death in HIV infected persons. This review will discuss the latest scientific evidence regarding the mechanisms driving lung cancer risk in HIV infection, the clinical presentation of lung cancer in HIV infected persons, and recent data regarding the outcomes, treatment and prevention of lung cancer in this group.

Recent Findings—Increased risk of lung cancer in HIV infected persons is primarily due to higher smoking rates, but emerging evidence also implicates immunosuppression and inflammatory processes. Lung cancer outcomes may be worse in HIV infected persons in the anti-retroviral era but this may stem, in part, from treatment disparities. Early detection of lung cancer using chest computed tomography (CT) is being increasingly adopted for smokers in the general population and recent studies suggest it may be safe and efficacious in HIV infected smokers.

Summary—Lung cancer is an important complication associated with chronic HIV infection. It is associated with unique HIV-related causal mechanisms, and may be associated with worse outcomes in some HIV infected persons. Smoking cessation and early cancer detection with chest CT are likely to benefit HIV infected smokers.

Keywords

Lung cancer; HIV; Non-small cell lung cancer; Non-AIDS Defining Cancer; Lung cancer screening

Introduction

Lung cancer is a leading non-AIDS defining cancer (NADC) and is the most frequent cause of cancer deaths in HIV infected persons[1–3]. This is largely related to higher smoking rates among HIV infected persons, but also due to independent, HIV-related increased lung cancer risk[4]. With improved HIV disease control, larger numbers of patients are surviving long enough to develop and die from lung cancer[4–6].

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Conflicts of interest

The authors report no potential conflicts of interest related to this work.

Several key questions exist regarding lung cancer in the setting of HIV infection. The mechanisms driving increased lung cancer risk (beyond higher rates of smoking) in HIV infected persons remain largely unclear and are an area of active investigation. Additionally, prognosis of HIV infected persons who develop lung cancer has been shown to be worse than uninfected persons in several studies, but it is not known if this is related to treatment disparities, lung cancer therapy intolerance, greater risk of treatment toxicity, or competing risk from AIDS and non-AIDS-related morbidity. Last, lung cancer prevention and early detection, an area of major clinical interest in HIV uninfected persons, is an emerging area of study for HIV infected persons.

In this review we will provide an update on the recent scientific literature regarding lung cancer in HIV infected persons, with a focus on these key areas of ongoing uncertainty.

Incidence of Lung Cancer in HIV Infection

Lung cancer incidence has been consistently reported as greater in HIV infected persons than uninfected persons[4, 7]. Recent estimates from the multi-cohort North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) suggest that lung cancer cumulative incidence rates in HIV infected persons continue to rise, but that this increase may reflect decreasing rates of all-cause mortality among HIV infected persons. This NA-ACCORD analysis showed, however, that the underlying hazard of lung cancer is decreasing, possibly due to population-wide changes in smoking behavior and improved immune control in HIV infected persons[6]. An overall decrease in the crude incidence of lung cancer in HIV infected persons was noted in the Veterans Aging Cohort Study (VACS) in the late ART era when compared to earlier ART-era periods, consistent with hazard observations from NA-ACCORD[8].

Lung Cancer Risk in HIV Infected Persons

Lung cancer is a unique NADC; unlike most other malignancies (eg. anal cancer, hepatocellular carcinoma, lymphoma) with increased frequency in the setting of HIV it has no known predisposing viral co-infection[9]. Although some of the excess in lung cancer risk in HIV+ persons is due to an increased prevalence of smoking[4, 10], multiple studies have shown that independent factors specifically associated with HIV infection also contribute to this increased risk[4, 5, 11, 12].

Traditional Lung Cancer Risk Factors: Age, Smoking, Obstructive Lung Disease

HIV infected smokers appear to develop lung cancer at an earlier age than uninfected persons[7, 13]. Smoking continues to be a major risk factor for lung cancer in the HIV infected population[14], where smoking rates continue to exceed the general population[15, 16]. Although some early evidence suggested that HIV infected persons may develop lung cancer with less smoking exposure[5], it is still unclear whether smoking has greater impact on lung cancer risk in HIV infected persons compared to uninfected persons.

COPD is a risk factor for lung cancer, independent of smoking, in HIV uninfected persons[17, 18]. HIV infected persons appear to be at greater risk of developing COPD,

possibly due to higher smoking rates[19], increased lung inflammation due to dysfunctional or increased levels of pulmonary CD8 activity[20, 21] or deleterious effects of recurrent or chronic lung infections[22–24]. COPD appears also to be an independent lung cancer risk factor for HIV infected persons[25], but there is no published data regarding COPD severity and lung cancer risk in HIV+ persons. Further investigation regarding the role of COPD in the development of lung cancer in the setting of HIV is warranted to better understand the interplay of immunologic and inflammatory factors that may be responsible for the increased lung cancer risk in this population.

HIV Specific Risk Factors: Immunosuppression, Inflammation, Viral Oncogenesis and Anti-retrovirals

Immunosuppression as measured by low CD4 count measures has shown limited association with lung cancer incidence when investigated as a static exposure, a finding noted in early studies[4, 11], as well as a recent analysis of lung cancer predictors that combined data from the Womens Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS)[7]. When evaluated as a longitudinal exposure, however, low CD4 measures appear to have a more robust independent association with lung cancer[26, 27]. In one of the largest analyses of immunologic risk factors for non-AIDS cancers (NADCs), Hleyhel et al. found that HIV infected persons who did not recover their CD4 count to at least 500 cells/mm³ were at increased risk of lung cancer[26].

Inflammation, both locally in the lung and systemically, has also been investigated as a contributor to the increased lung cancer risk in HIV infection. Lung infections have been proposed as an acute inflammatory insult potentially contributing to the development of lung cancer in HIV infected persons[28]. In the recent WIHS/MACS study, preceding pneumonia (even lagged 5 years) was an independent predictor of lung cancer[7]. Chronic inflammation within the lung related to HIV may also play a role in lung cancer development. Various mechanisms have been linked to pulmonary chronic inflammation in HIV including CD8 infiltration and dysregulation[20, 21], viral impairment of epithelial integrity[29] and lung microbiome alterations[30, 31] although direct correlations between lung chronic inflammation and subsequent lung cancer risk have not been proven in HIV infected persons. It has also been suggested that HIV and smoking may have synergistic effects promoting lung inflammation, but this has received limited evaluation to date, and has not been linked to lung cancer risk[32]. Systemic inflammation associated with HIV infection has also been implicated in cancer risk; proinflammatory cytokines have been found to be elevated prior to lung cancer diagnosis in HIV infected persons[33].

Direct viral oncogenesis has been proposed as a mechanism for lung cancer in HIV infection. The lung may serve as a compartment where HIV activity may not reflect systemic viral suppression[34]. This theory is supported by recent work from Cribbs et al. showing that 70% of a cohort of 23 HIV infected non-smokers with ART-mediated viral suppression had measurable proviral DNA in alveolar macrophages[35]. There has been no clear evidence of direct HIV oncogenesis in the lungs, however; early studies suggested that HIV viral proteins may have some direct oncogenic activity (not specific to lung cancer) via

viral proteins[36, 37], but data from a mouse model of HIV failed to confirm direct lung tumorigenesis[38].

There have been no notable associations between ART exposure and increased lung cancer risk. The international Strategic Timing of Antiretroviral Treatment (START) trial found a significant decrease in all-cancer risk with immediate ART initiation compared to delayed initiation and a trend towards a decrease in NADC risk (15% of NADCs in START were lung cancers)[39]. D:A:D study investigators evaluated ART and lung cancer risk and found no overall or drug class-specific increased risk associated with ART[40]. Bruyand et al. hypothesized that P450 cytochrome inhibitors (such as protease inhibitors) might influence the metabolism of lung carcinogens thereby increasing lung cancer risk, but did not find an association within the French Hospital Database (FHDH)[41].

Clinical Characteristics of Lung Cancer

ART-era lung cancer in HIV infected persons appears to have similar presenting clinical characteristics when compared to uninfected persons. Distributions of cancer stage at presentation and histologic subtypes have been similar by HIV status in data from large cohort studies[42–44]. There are limited published data regarding the prevalence of clinically relevant oncogenic mutations found in lung cancers from HIV infected persons. A recent study described the largest cohort to date, finding 3.3% *EGFR* mutations and 29% *KRAS* mutations in a cohort of 63 HIV infected lung cancer patients[45]. Although the investigators did not compare these rates to uninfected comparators, these rates do not appear to differ markedly from expected rates in uninfected persons.

Lung Cancer Treatment and Prognosis

The effects of HIV infection on lung cancer treatment tolerability, toxicity and effectiveness are not well known. Patients with serious comorbid conditions such as HIV are substantially underrepresented in clinical trials of cancer therapies[46–48] and no prospective data have been published regarding lung cancer treatment in HIV infected patients. Several small series and cohorts have reported treatment effectiveness estimates and complication rates for lung cancer therapies in HIV infected patients. Surgical resection is the standard-of-care for early stage lung cancer, and a large ART-era analysis from the Veterans Affairs Health System found that HIV infected patients may continue to experience more frequent surgical complications than uninfected patients[49], although results specific to lung cancer surgery were limited. A comparative study evaluating lung cancer surgical outcomes in a cohort of 22 HIV infected patients compared to uninfected comparators demonstrated more frequent surgical complications and poorer post-surgical survival[25]. Adjuvant therapies may also be associated with greater harms in HIV infected patients; lung cancer chemotherapy outcomes were evaluated in a French cohort (n=56) and treatment was associated with a substantial number of deaths (12%)[50]. An Italian study described lung cancer treatments in their HIV infected patients (n=68) and found an expected amount of major complications but commented that HIV infected patients received fewer cycles of chemotherapy than indicated[51].

These factors may have led to lung cancer treatment disparities in HIV infected lung cancer patients compared to uninfected patients. Lung cancer treatment was often withheld in the pre-ART era due to poor overall prognosis[51] and several large recent analyses have suggested that treatment disparities persist during the ART-era (Table 1). In a cohort of patients at Kaiser Permanente California diagnosed with cancer from 1996–2011, those who were HIV infected were less likely to receive treatment for lung cancer than HIV uninfected patients (64% vs. 76%, respectively); for unclear reasons, this disparity was not observed for any other NADCs. In the same study, only 16% of HIV infected patients with lung cancer underwent surgery compared to 28% of HIV uninfected[44]. A study of patients diagnosed with cancer from 1995–2009 found that 60.3% of those with both lung cancer and HIV received treatment for lung cancer compared to 77.5% of those with lung cancer who were uninfected[55]. Similar disparities were found in other population-based cohorts of HIV infected and uninfected lung cancer cases[52, 53]. The cause of these treatment disparities remains unclear; they may be in part related to sociodemographic factors[52], perception of greater risk or diminished benefits associated with treatment due to perceived underlying life expectancy, or a lack of specific guidance regarding lung cancer treatment in the setting of HIV.

The effect of HIV infection on lung cancer-specific prognosis has not been fully determined. Single and multi-center retrospective studies of lung cancer survival in the late ART-era have demonstrated a limited effect of HIV on outcomes. In contrast, population-based studies of lung cancer outcomes in HIV infected persons have generally shown poorer cancer-specific survival associated with HIV infection (Table 2). In an analysis of Medicare enrollees diagnosed with lung cancer from 1996–2007, the HIV infected subjects demonstrated worse lung cancer-specific survival even after accounting for potential confounders (including lung cancer treatment) and competing risks[42]. Other population-based studies have shown similar results: HIV infected patients diagnosed with lung cancer between 1996–2010 and 1995–2009 in two population-based analyses had worse survival compared to their uninfected counterparts after adjustment[55, 56]. The Kaiser Permanente HIV cohort also reported worse lung cancer survival in HIV infected persons compared to uninfected persons but this difference appears to be related to treatment disparities[44]. In general, population-based analyses have lacked detailed information about cancer treatment and patient-level HIV clinical information such as viral suppression or CD4 count, and therefore the direct effects of HIV on lung cancer prognosis remain unclear.

Lung Cancer Prevention and Early Detection

Smoking Cessation

Smoking cessation is the most effective method to prevent lung cancer in HIV infected persons. Most published studies of lung cancer in HIV infected persons have shown nearly 100% smoking rates[50, 60–62]. In addition, HIV infected persons lose more life-years from smoking than HIV infection. In a Danish study, HIV infected subjects lost a median of 12 years of life due to smoking, while the median years lost was 5.1 due to HIV in non-smokers, reinforcing the public health importance of smoking cessation in this population[63].

Behavioral and pharmacologic smoking cessation interventions have demonstrated efficacy in HIV infected smokers. Several programs in HIV infected smokers have shown that when self-efficacy is increased, chances of smoking cessation are improved[64–66]. In a recent meta-analysis of randomized controlled trials evaluating behavioral interventions for tobacco use in HIV infected smokers these interventions, particularly those with eight or more sessions, had a modest but significant effect on smoking cessation[67]. Pharmacologic agents that have shown smoking cessation efficacy in the general population, including varenicline, bupropion and nicotine replacement therapy, have also been evaluated in HIV infected smokers as part of smoking cessation programs with evidence of safety and efficacy[64, 68–70].

Lung Cancer Early Detection with Computed Tomography

In 2011, the randomized National Lung Screening trial (NLST) demonstrated a significant all-cause mortality reduction of 6.7% and a lung cancer mortality reduction of 20% with three annual low dose chest tomography (CT) examinations versus simple chest radiography in high risk subjects from the general population[71]. Since the publication of NLST results, several studies have attempted to clarify the benefits, harms and optimal indications associated with lung cancer screening using low dose chest CT in HIV infected persons.

Initial studies of chest imaging in HIV infected persons showed high rates of incidental lung abnormalities, possibly due to a higher prevalence of lung infections, suggesting potentially higher rates of false-positive lung cancer screening tests[72]. A prospective study of asymptomatic HIV infected Veterans compared the prevalence of clinically significant pulmonary nodules on baseline chest CT with the NLST and found that only subjects with CD4 counts below 200 cells/mm³ had more significant nodules than the first round of screening in the NLST[73].

Two lung cancer screening clinical trials using chest CT in HIV infected smokers have been published to date[74, 75]. The first study was conducted in Baltimore between 2006 and 2013, and enrolled a cohort with significant smoking history (median 34 pack-years) but was younger than the NLST (median age 48) [74]. Baseline screen positivity (a general measure of harms associated with screening, as most positive screens are false-positives) was broadly similar to NLST (14%). During 678 person-years of follow-up, only one lung cancer was found on an incident screening, although adherence to the study protocol was low.

The second lung cancer screening trial was a French National Agency of AIDS Research (ANRS) sponsored study[75]. Between 2011 and 2012, 442 subjects from 13 clinical centers underwent a single baseline chest CT. Median age was 49.8 years, median smoking was 30 pack-years, median CD4 level was 574 cells/mm³, and all subjects had nadir CD4 counts < 350 cells/mm³. In contrast to the Baltimore cohort, 10 lung cancers were diagnosed, of which 9 were screen detected (60% were early stage cancers). Most subjects with lung cancer were younger than 55 years old, and would not have been screened according to the NLST criteria. The number of subjects needed to detect one lung cancer in this study was 49, which compares favorably to estimates in the general population[76]. Baseline rates of screen positivity were also broadly similar to NLST (21%) with low rates of diagnostic procedures performed.

It is not known if HIV infected smokers will benefit from lung cancer screening at younger ages; this should be further assessed. Lung cancer risk-prediction models including traditional and emerging immunologic risk factors in HIV infected populations are also needed to focus screening efforts.

Conclusion

Lung cancer is a major source of morbidity and mortality for HIV infected persons. The increased risk of lung cancer in HIV infected persons is related to high rates of smoking and may also be associated with HIV-specific etiologies including immunodeficiency and inflammatory processes. Lung cancer outcomes for HIV infected persons have lagged uninfected persons during the ART-era and cancer treatment disparities contribute to decreased survival. Smoking cessation and lung cancer screening with chest CT scanning have emerging data supporting clinical implementation for appropriate groups of HIV infected smokers. Future research should further address lung cancer risk in this population as well as identify and optimize effective prevention and treatment methods.

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Key Points

- HIV infected persons are at greater risk of lung cancer than uninfected persons
- High smoking rates in HIV infected persons are the largest contributor to lung cancer risk but emerging evidence also suggests immunosuppression and inflammation may also contribute to risk.
- In the ART-era HIV infected persons appear to continue to experience lung cancer treatment disparities compared to uninfected persons.
- Early clinical trials of computed tomography-based lung cancer screening have demonstrated safety in HIV infected smokers.

Table 1

Recent Studies of Lung Cancer Treatment Disparities in US HIV Infected Persons

Study	Lung Cancer Diagnosis Years	HIV+ Lung Cancers (N)	HIV- Lung Cancers (N)	% HIV + treated	% HIV – treated	Other/Notes
Marcus et al. 2015[44]	1996–2011	80	507	64%	76%	Lung cancer only NADC with treatment disparities: Lung surgery 16% (HIV+) vs. 28% (HIV–)
Suneja et al. 2016[52]	2003–2011	1420	353156	67.3%	86.4%	Adjusted OR* = 2.46 (95% CI 2.19–2.76)
Suneja et al. 2014[53]	1996–2010	581	260652	65.1%	75.9%	Adjusted OR* = 2.18 (95% CI 1.80–2.64)
Lee et al. 2013[54]	1998–2007	174	3480	58.0%	59.6%	HIV not independently associated with receipt of guidance concordant treatment
Suneja et al. 2013[55]	1995–2009	337	156593	60.3% (lung)	77.5%	Adjusted OR* = 0.39 (95% CI 0.30–0.52)

OR: Odds Ratio, NADC: Non-AIDS Defining Cancer

* Odds ratio for lung cancer treatment associated with lack of HIV infection

** Odds ratio for lung cancer treatment associated with HIV infection

Table 2

Recent Studies of Lung Cancer Outcomes in HIV Infected Persons

Study	Study Period	HIV+ Lung Cancers (N)	HIV- Lung Cancers (N)	Overall Survival	Other Outcome Measures Associated with HIV+
Crequit et al. 2016[45]	1996–2013	73	N/A	13.2 months	• <i>EGFR</i> mutations associated with better survival
Coghill et al. 2015[56]	1996–2010	1058	327866	–	•HR for lung cancer-specific mortality = 1.28 (95% CI 1.17–1.39)
Hleyhel et al. 2015[57]	1992–2009	446	N/A	–	•5 year OS for lung cancer = 16%
Marcus et al. 2015[44]	1996–2011	80	507	–	•5 year OS for lung cancer = 9.5% •Adjusted HR for lung cancer-specific mortality = 1.3 (95% CI 1.0–1.7)
Bearz et al. 2014[51]	1986–2003	68	N/A	–	N/A
Gotti et al. 2014[58]	1998–2012	35	N/A	3.7 months	•1 year OS for lung cancer = 28%
Worm et al. 2013[59]	2004–2010	140	N/A	–	•1 year OS for lung cancer = 42%
Sigel et al. 2013[42]	1996–2007	267	1428	6 months	•Adjusted HR for OS = 1.9 (1.6–2.2)
Hoffmann et al. 2013[60]	2000–2010	72	N/A	13 months	•Worse survival associated with lower PS, low CD4, IVDU route of HIV infection
Suneja et al. 2013[55]	1995–2009	337	156593	–	•Adjusted HR for lung cancer-specific mortality = 1.34 (95% CI 1.15–1.56) •Adjusted HR for lung cancer-specific mortality including treatment 1.25 (95% CI 1.06–1.47)

SMR: Standardized Mortality Ratio, HR: Hazard Ratio, OS: Overall Survival, PS: Performance Status, IVDU: Intravenous Drug Use, ART: Anti-retroviral Therapy, HR: Hazard Ratio, CI: Confidence Interval

* Compared to general population rates.

** Hazard ratios associated with HIV infection for all cause mortality.