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Pulmonary infections and risk of lung cancer among persons with AIDS

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Abstract

Lung cancer risk is significantly increased among persons with AIDS (PWA), and increased smoking may not explain all of the elevated risk, suggesting a role for additional co-factors. We investigated whether AIDS-defining pulmonary infections [recurrent pneumonia, *Pneumocystis jirovecii* pneumonia (PCP), and pulmonary tuberculosis] affected the risk of subsequent lung cancer over 10 years after AIDS onset among 322,675 PWA whose records were linked with cancer registries in 11 U.S. regions. We assessed lung cancer hazard ratios (HR) using Cox regression, and indirectly adjusted HRs for confounding by smoking. Individuals with recurrent pneumonia (n=5317) were at significantly higher lung cancer risk than those without [HR=1.63, 95%CI=1.08-2.46, adjusted for age, race, sex, HIV acquisition mode, CD4 count, and AIDS diagnosis year]. This association was especially strong among young PWA (<50 years HR=1.99 vs. ≥50 years HR=1.10) and was significantly elevated during 5-10 years after recurrent pneumonia diagnosis (HR= 2.41; 95% CI=1.07-5.47). Although attenuated, HRs for recurrent pneumonia remained non-significantly elevated after indirect adjustment for smoking. Lung cancer risk was unrelated to tuberculosis [(n=13,878) HR=1.12, 95%CI=0.82-1.53] or PCP [(n=69,771) HR=0.97, 95%CI=0.80-1.18]. The increased lung cancer risk associated with recurrent pneumonia supports the hypothesis that chronic pulmonary inflammation arising from infections contributes to lung carcinogenesis.

Keywords

HIV/AIDS; Lung cancer; Pulmonary infections; Inflammation; Recurrent pneumonia; Tuberculosis; *Pneumocystis jirovecii* pneumonia

Background

Lung cancer is the third most common cancer in the United States among persons with AIDS (PWA) during the era of highly active antiretroviral therapies (HAART) [1]. PWA have a 2-5 fold increased risk of lung cancer when compared to the general population [1]. Frequent smoking among PWA explains only part of this increased risk. Even with adjustment for smoking, lung cancer risk is significantly elevated among PWA [2-4], suggesting that additional factors might act in concert with smoking to increase lung cancer risk in this population.

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Conflict of interest statement
Authors declare no conflict of interest.

Chronic inflammation is increasingly recognized as a risk factor for lung cancer [5]. Inflammatory conditions such as chronic obstructive pulmonary disease, asthma, pneumonia, and tuberculosis are associated with increased lung cancer risk [6-11]. Notably, owing to HIV-related immunosuppression, these infections and pulmonary inflammatory conditions are common among PWA, including an accelerated form of smoking-related emphysema [12], *Pneumocystis jirovecii* pneumonia (PCP), and tuberculosis [5, 13]. Chronic inflammation arising from pulmonary infections could potentiate the effects of smoking in increasing lung cancer risk among PWA [5].

Using data from the U.S. HIV/AIDS Cancer Match Study, we recently showed that lung cancer risk was substantially elevated among PWA and the increased risk persisted even after indirect adjustment for smoking, particularly among young PWA [4]. We hypothesize that pulmonary infections and ensuing inflammation could partially explain the high lung cancer risk among PWA, and test this hypothesis in the current study by investigating whether AIDS-defining pulmonary infections—pulmonary tuberculosis, PCP, and recurrent pneumonia—are related to lung cancer risk.

Materials and Methods

Study subjects

AIDS registry surveillance data on 322,675 persons with AIDS diagnoses during 1977-2002 were linked with cancer registries in 11 U.S. regions [4]. Incident lung cancers were identified using data from the cancer registries. Pulmonary neoplasms classified as Kaposi sarcoma, non-Hodgkin lymphoma, and cancers with non-specific ICD-O3 codes (8000-8005) were not considered as lung cancers, and thus were excluded from the analyses. Data on AIDS-defining pulmonary infections—recurrent pneumonia (defined as 2 or more episodes of pneumonia during a 1-year period), tuberculosis, and PCP [14]—occurring at AIDS onset (defined as the 0-3 months after the AIDS registration date) or subsequently were available from the AIDS registries. Other pulmonary infections are not captured by HIV/AIDS registries and were thus not examined.

Statistical analyses

We assessed lung cancer risk over a 10-year period, spanning the 4-120 months after AIDS onset. Follow-up began at the 4th month after AIDS onset or beginning of cancer registry coverage and ended at the earliest occurrence of lung cancer, death, end of cancer registry coverage, or the 120th month after AIDS onset. We used Cox regression to assess the relationship between recurrent pneumonia, tuberculosis, and PCP (considered as time-dependent exposures) with subsequent lung cancer risk. These analyses were conducted for all lung cancers and separately by histology: squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, and other histologies [15]. Additionally, we assessed the relationship by time interval between pulmonary infection and lung cancer diagnosis (i.e., latency) : <1 year, 1 to <5 years, and 5+ years. After excluding the first year of follow-up, we calculated a p-value for trend in HRs across the following latency intervals: 2 to <3, 3 to <4, 4 to <5, and 5+ years. Because reporting of AIDS-defining pulmonary infections could have varied by AIDS-relative time (at AIDS-onset vs. after AIDS onset) as well as across calendar time (given the revised CDC definition in 1993 and the introduction of HAART in 1996), we conducted two sensitivity analyses to evaluate whether our results were robust to these potential changes. We conducted analyses stratified by timing of the pulmonary infection relative to AIDS onset (at vs. after AIDS) as well as analyses stratified by the calendar year of pulmonary infection (pre-HAART [1977-1995] vs. HAART [1996-2002]). All models were adjusted for age at AIDS onset, race, sex, mode of HIV acquisition, CD4 T-cell count at AIDS onset, and

year of AIDS diagnosis (before 1990, 1990-1995, and 1996-2002). All statistical tests were two-sided and statistical significance was assessed at $p<0.05$.

Because smoking information was unavailable, we performed indirect adjustment for smoking using the methods described by Steenland and Greenland [16]. Briefly, we obtained estimates from the literature for the prevalence of smoking among individuals with or without pneumonia, and the relative risk (RR) for the association of smoking with lung cancer [2, 17-20]. This information was used to calculate a bias factor reflecting the effect of tobacco use on lung cancer risk and thereby adjust hazard ratios (HRs) from the Cox models for confounding by smoking. Additional details are provided in the supplemental statistical appendix.

Results

The study included 322,675 PWA with a median age at AIDS diagnosis of 37 years and median CD4 T-cell count at AIDS onset of 111 cells/mm^3 (Table 1). The age at AIDS onset, and the proportions of females, blacks and Hispanics, and of those who acquired HIV infection through heterosexual contact increased over time. In a previous publication from this study, we found that lung cancer incidence was significantly higher among older PWA, African-Americans, men, and injection-drug users (data not shown), and incidence did not significantly vary across calendar time or CD4 T-cell count at AIDS onset [4].

Recurrent pneumonia, tuberculosis, and PCP were reported at or after AIDS onset among 5,317 (1.7%), 13,878 (4.3%), and 69,771 (21.6%) individuals, respectively. Incidence of recurrent pneumonia was similar between 1990-1995 and 1996-2002 (chi-square p=0.41), whereas incidence of tuberculosis and PCP was significantly lower during 1996-2002 than 1990-1995 (chi-square p <0.0001 and <0.0001, respectively). Compared to PWA without the respective pulmonary infection, median CD4 count at AIDS diagnosis was significantly lower among those with tuberculosis (median 81 vs. 112 cells/mm^3, $p<0.0001$) or PCP (median 40 vs. 120 cells/mm^3, $p<0.0001$) and marginally lower among those with recurrent pneumonia (median 100 vs. 111 cells/mm^3, p=0.08).

Over 10 years of follow-up after AIDS onset (1,032,256 person-years), 853 lung cancers were observed (82.6 cases per 100,000 person-years). Individuals with recurrent pneumonia were at significantly higher lung cancer risk than those without (Table 2; HR=1.63, 95% CI=1.08-2.46, p=0.02). Recurrent pneumonia was not associated with a specific histologic subtype of lung cancer, although the risk tended to be increased for adenocarcinoma (p=0.08) and lung cancers of uncommon histologies (p=0.05). The elevated lung cancer risk varied little with time since recurrent pneumonia (p-trend=0.443); notably, 5-10 years after a diagnosis of recurrent pneumonia, lung cancer risk was significantly increased more than 2-fold (HR= 2.41, 95% CI= 1.07-5.47, p=0.04). Recurrent pneumonia was associated with increased lung cancer risk among younger PWA (<50 years at AIDS onset; HR=1.99, 95% CI= 1.26-3.16, p=0.003), but not among older PWA (age ≥50 years; HR=1.10, 95% CI= 0.45-2.69, p=0.83). However, this difference by age at AIDS onset was not statistically significant (p-interaction=0.20). The association of recurrent pneumonia with lung cancer risk did not significantly differ by calendar time (pre-HAART vs. HAART, p=0.74) or by the timing of pneumonia diagnosis relative to AIDS onset (at AIDS onset vs. after AIDS onset, p=0.67).

Lung cancer risk was not related to tuberculosis (HR=1.11, 95% CI=0.81-1.51, p=0.52) or PCP (HR=0.98, 95% CI= 0.80-1.19, p=0.81, both overall or for specific lung cancer histologies (Table 2). Although overall cancer risk was not associated with tuberculosis, significantly increased lung cancer risk was observed within the first year after tuberculosis diagnosis (HR=2.01, 95% CI= 1.21-3.34, p=0.007).

We indirectly adjusted the HR for the association of recurrent pneumonia with lung cancer risk for confounding by smoking (Table 3). Although the HR for the recurrent pneumonia-lung cancer association remained elevated after adjustment for smoking, this association did not retain statistical significance under assumptions of 70% or higher prevalence of smoking among individuals with recurrent pneumonia (i.e., 10% higher prevalence than in those without). These analyses show that confounding by smoking could account for part of the elevated lung cancer risk among individuals with recurrent pneumonia.

Discussion

Pulmonary infections with mycobacteria and *Pneumocystis jirovecii* as well as recurrent pneumonia caused by bacterial agents such as Streptococcus pneumoniae, Hemophilus influenzae, Staphylococcus aureus, and *Chlamydia pneumoniae* are common among PWA [13]. Given accumulating evidence that smoking may not explain all of the increased lung cancer risk among PWA [2-4], we evaluated whether pulmonary infections could explain part of the association. Consistent with this hypothesis, we found that individuals with recurrent pneumonia had a significantly increased risk of lung cancer. Notably, lung cancer risk was significantly elevated 5-10 years after a recurrent pneumonia diagnosis, thus arguing against reverse causality (i.e., that pneumonia arose as a manifestation of lung cancer). Additionally, our previous observation that the excess risk of lung cancer was especially strong among young PWA [4] indicated a role for additional co-factors among young individuals. Our current observation that recurrent pneumonia was associated with increased lung cancer risk among younger, but not older, PWA supports the conclusion that pulmonary infections might explain the high lung cancer risk among young PWA.

Ascertainment and reporting of AIDS-defining pulmonary infections may have varied across both calendar time and between the AIDS-onset period and the years of subsequent follow-up, which could bias our results. However, our observations that the incidence of recurrent pneumonia among PWA was similar between the pre-HAART and the HAART eras and that the recurrent pneumonia-lung cancer association did not differ by calendar time or AIDS-relative time, argue against a major bias arising from changes in ascertainment or reporting of recurrent pneumonia.

The lack of a significant relationship between AIDS-associated tuberculosis and lung cancer risk contrasts with previous reports of an association among individuals without HIV infection [11, 21, 22]. Our observation of an increased risk of lung cancer within one year following a tuberculosis diagnosis suggests a non-causal association and points to the role of either an ascertainment bias (i.e., detection of lung cancer by chest radiographs among persons with tuberculosis) or reverse causality (i.e., that subclinical lung cancer facilitated the reactivation of latent tuberculosis infection).

Cigarette smoking increases the risk of pulmonary infections such as recurrent pneumonia and tuberculosis [23]. Therefore, confounding by smoking could explain, in part, the association of recurrent pneumonia with increased lung cancer risk. Indeed, our analyses that incorporated indirect adjustment for smoking indicated that a 10% difference in the prevalence of smoking between PWA without pneumonia and individuals with recurrent pneumonia could account for the significantly elevated lung cancer risk. Nonetheless, we note that effect estimates for the recurrent pneumonia association remained elevated, although not statistically significantly so, across a range of hypothetical smoking prevalence estimates, indicating that confounding by smoking may not explain all of the elevated risk. Likewise, the lack of association between lung cancer and tuberculosis, which is also related to smoking, also argues against confounding by smoking being the entire explanation for the recurrent pneumonia association.

The pulmonary infections we evaluated—tuberculosis, PCP, and recurrent pneumonia—are more common among HIV-infected individuals with low CD4 T-cell counts than those with relatively higher CD4 counts [13]. Although recurrent pneumonia was associated with both low CD4 counts and lung cancer, lung cancer risk was previously noted to be unrelated to CD4 count at AIDS onset among PWA overall [4]. The low range of CD4 counts among PWA in our study may have masked an association between immunosuppression and lung cancer risk. Indeed, a recent study among HIV-infected individuals reported strong associations of immunosuppression with increased lung cancer risk [24]. Likewise, we previously found that lung cancer risk increased significantly from 5 years before to 5 years after AIDS onset, which could be an alternative measure for the degree of immunosuppression, or perhaps an indicator of recurrent or persistent pulmonary inflammation [4].

The limitations of our study should be noted. Importantly, our assessment of pulmonary infections was based on AIDS registry data, not on our own direct assessment of infection status. Additionally, we did not have information on the smoking behaviors of PWA. Our analyses that incorporated indirect adjustment for smoking showed that confounding by smoking could potentially explain part of the significant association of recurrent pneumonia with increased lung cancer risk. Furthermore, we could not adjust for either duration or intensity of smoking. Therefore, the possibility of residual confounding by smoking cannot be ruled out. Our study also has several strengths, including a large sample size, population-based surveillance, and prospective evaluation of the association of pulmonary infections with lung cancer.

In conclusion, lung cancer risk was significantly elevated among PWA who had recurrent pneumonia, suggesting a role for pulmonary infections and inflammation in lung carcinogenesis. Additional studies utilizing biological markers for pulmonary infections and inflammation, along with detailed information on smoking behaviors, are needed to further characterize the mechanisms of increased lung cancer risk among PWA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of individuals diagnosed with AIDS in the United States during 1977-2002 (N=322,675)

Characteristics	Total	AIDS diagnosis year		
		Before 1990	1990-1995	1996-2002
	N(%)	N(%)	N(%)	N(%)
Sex				
Male	259,904(80.6)	54765(89.1)	134,819(80.9)	70,320(74.3)
Female	62,771(19.5)	6688(10.9)	31,784(19.1)	24,299(25.7)
Age at AIDS onset (years)				
<15	4,171(1.3)	1136(1.9)	2,309(1.4)	726(0.8)
15-29	50,121(15.5)	12,021(19.6)	26,366(15.8)	11,734(12.4)
30-39	145,408(45.1)	29,556(48.1)	75,958(45.6)	39,894(42.2)
40-49	88,982(27.6)	13,631(22.2)	45,465(27.3)	29,886(31.6)
50+	33,993(10.5)	5,109(8.3)	16,505(9.9)	12,379(13.1)
Race/ethnicity				
White	127,535(39.5)	33,327(54.23)	67,160(40.3)	27,048(28.6)
Black	121,860(37.8)	17,156(27.9)	61,480(36.9)	43,224(45.7)
Hispanic	69,190(21.4)	10,354(18.9)	35,987(21.6)	22,849(24.2)
Other	4,090(1.3)	616(1.0)	1,976(1.2)	1,498(1.6)
CD4 Count at AIDS onset, cells/mm^3				
0-49	58,348(18.1)	809 (1.3)	33,829(20.3)	23,710(25.1)
50-99	31,829(9.9)	638(1.0)	18,157(10.9)	13,034(13.8)
100-149	32,691(10.1)	718(1.2)	18,047(10.8)	13,926(14.7)
150-199	44,612(13.8)	1,061(1.7)	24,490(14.7)	19,061(20.2)
200+	28,828(8.9)	1,006(1.6)	15,404(9.3)	12,418(13.1)
Missing	126,367(39.2)	57,221(93.1)	56,676(34.0)	12,470(13.2)
Mode of HIV acquisition				
MSM	142,312(44.1)	36,561(59.5)	74,300(44.6)	31,451(33.2)
IDU	85,462(26.5)	14,234(23.2)	49,073(29.5)	22,155(23.4)
MSM+IDU	16,487(5.1)	4,133(6.7)	8,909(5.4)	3,445(3.6)
Heterosexual	35,471(11.0)	2,335(3.8)	17,584(10.6)	15,552(16.4)
Other categories or unknown	42,943(13.3)	4,190(6.8)	16,737(10.1)	22,016(23.3)
Pulmonary infections occurring at AIDS onset or during follow-up [#]				
Recurrent pneumonia	5,317(1.7)	308(0.5)	3,234(1.9)	1,775(1.9)
Pulmonary tuberculosis	13,878(4.3)	2,938(4.8)	8,475(5.1)	2,465(2.6)
Pnemocystitis jirovecii pneumonia	69,771(21.6)	24,499(39.9)	34,552(20.8)	10,738(11.3)
No pulmonary infection	238,678(74.0)	35,226(57.3)	123,131(73.9)	80,321(84.9)

Abbreviations: MSM men who have sex with men and IDU injection drug users.

[#]Infections are not mutually exclusive.

Table 2

Association of lung cancer with pulmonary infections among persons with AIDS[&]

	Recurrent pneumonia		Pulmonary tuberculosis		*Pnemocystitis jirovecii* pneumonia	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Overall lung cancer risk during 4-120 months after AIDS onset	1.63(1.08-2.46)	0.019	1.11(0.81-1.51)	0.520	0.98(0.80-1.19)	0.806
Overall lung cancer risk during 4-120 months after AIDS onset by lung cancer subtype [#]						
Squamous cell carcinoma	0.98(0.31-3.07)	0.967	1.56(0.89-2.75)	0.099	0.82(0.53-1.28)	0.385
Small cell carcinoma	2.23(0.53-9.31)	0.273	1.95(0.74-5.10)	0.176	1.09(0.53-2.24)	0.817
Large cell carcinoma	0.88(0.12-6.41)	0.900	1.39(0.49-3.94)	0.531	1.44(0.77-2.67)	0.250
Adenocarcinoma	1.78(0.94-3.36)	0.077	0.88(0.50-1.55)	0.655	1.12(0.83-1.51)	0.456
Uncommon/unknown histologies	2.02(0.99-4.12)	0.053	0.79(0.40-1.56)	0.500	0.74(0.48-1.12)	0.152
Lung cancer risk stratified by time since pulmonary infection						
< 1 year	1.62(0.67-3.93)	0.282	2.01(1.21-3.34)	0.007	1.31(0.93-1.84)	0.123
1 to < 5 years	1.42(0.82-2.47)	0.213	0.79(0.50-1.26)	0.792	0.91(0.71-1.18)	0.475
5 to 10 years	2.41(1.07-5.47)	0.035	1.13(0.60-2.16)	0.702	0.76(0.47-1.23)	0.268
p-trend [#]		*0.443*		*0.882*		*0.301*
Lung cancer risk according to age at AIDS onset						
< 50 years	1.99(1.26-3.16)	0.003	1.10(0.75-1.60)	0.638	1.03(0.82-1.29)	0.812
≥ 50 years	1.10(0.45-2.69)	0.827	1.26(0.74-2.17)	0.393	0.80(0.55-1.18)	0.265
Lung cancer risk according to calendar period of pulmonary infection						
Pre-HAART era (1977-1995)	1.59(0.97-2.62)	0.069	1.05(0.75-1.48)	0.764	0.94(0.76-1.17)	0.565
HAART era (1996-2002)	1.77(0.88-3.60)	0.112	1.09(0.51-2.32)	0.821	1.03(0.67-1.57)	0.906
Lung cancer risk according occurrence of pulmonary infection relative to AIDS onset						
At AIDS onset	1.22(0.72-2.08)	0.458	1.05(0.74-1.48)	0.789	0.92(0.75-1.14)	0.445
After AIDS onset	1.46(0.78-2.72)	0.236	1.08(0.61-1.91)	0.797	1.07(0.74-1.53)	0.735

[&]Models were adjusted for age, sex, race, mode of HIV acquisition, CD4 count at AIDS onset, and calendar year of AIDS onset.

[#]After excluding the first year of follow-up, we calculated a p-value for trend in HRs across the following latency intervals: 2 to <3, 3 to < 4, 4 to < 5, and 5+ years.

Table 3

Smoking indirect adjusted hazard rate ratio (HR) of the association between recurrent pneumonia and lung cancer

Prevalence of smoking among individuals with pneumonia[a]	Smoking associated RR=21.3[b]	
	Bias factor	Smoking adjusted HR (95% CI)
0.65	1.08	1.52 (1.00-2.31)
0.70	1.15	1.42 (0.93-2.14)
0.75	1.23	1.33 (0.88-2.03)
0.80	1.31	1.25 (0.83-1.90)
0.90	1.46	1.12 (0.74-1.70)

[a] Prevalence of smokers among individuals without pneumonia was fixed to 0.60

[b] Thun et al.'s estimate for the RR associating smoking with lung cancer in men[20] was applied for both men and women, because men comprised the majority of our cohort.