Lung Cancer Mortality Associated With Smoking and Smoking Cessation Among People Living With HIV in the United States

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IMPORTANCE

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OBJECTIVE

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DESIGN ,
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40 4.3 4.5. ,
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MAIN OUTCOMES AND MEASURES 80
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RESULTS 40- - ,
, , 28.9%, 23.0%, 18.8%,
; 40 , 7.9%, 6.1%, 4.3%;
, 1.6%. ,
27.8%, 20.9%, 16.6%; , 7.5%, 5.2%, 3.7%;
, 1.2%. -
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, 59 900 (9.3%)
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CONCLUSIONS AND RELEVANCE

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ntiretroviral therapy (ART) has dramatically improved the life expectancy of people living with human immunodeficiency virus (HIV) (PLWH), with a concomitant shift in morbidity and mortality from AIDS to non-AIDS diseases.[1,2] Much of the non-AIDS disease burden is tobacco-related. Over 40% of PLWH in the United States smoke cigarettes, more than double the smoking prevalence in the general population.[3-7] Among PLWH undergoing ART, smoking now reduces life expectancy more than HIV itself.[8-10]

Tobacco use and HIV together may accelerate the development of lung cancer.[11-14] The risk of lung cancer is increased by the presence of HIV through mechanisms likely involving chronic inflammation, immunomodulation, and other infections.[11,15-19] Lung cancer is the leading cause of cancer death among PLWH undergoing ART and is among the leading causes of death overall in this population.[13,20]

Despite the high smoking prevalence and the risk of lung cancer and other tobacco-related diseases, smoking cessation programs generally have not been successfully implemented in HIV care. As the population of PLWH in the United States ages, estimates of projected comorbidities can help guide where to direct attention and resources in HIV care. We sought to understand the likely impact of smoking cessation on lung cancer mortality among PLWH in HIV care in the United States. We compared the risk of lung cancer death against the risks of death from other causes as a function of smoking exposure.

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-US model, a validated, widely published Monte Carlo microsimulation of HIV disease and treatment.[10,21-23] After populating the model with published data, we projected lung cancer mortality among PLWH in HIV care according to smoking exposure. We defined smoking exposure by both smoking status (current, former, or never) and, for current and former smokers, intensity (heavy, moderate, or light) based on number of cigarettes per day. We accounted for competing risks of death from AIDS-related and non-AIDS-related causes, the latter stratified by smoking exposure. We modeled cohorts of 1 million men or women of a particular smoking exposure entering HIV care at a specific age (eg, 30, 40, or 50 years).

The primary outcome was cumulative lung cancer mortality by age 80 years. We combined the model-generated estimates with published epidemiologic data to project the total expected lung cancer deaths among PLWH in care in the United States.

Model Overview

For this analysis, an individual enters the model at the time of linkage to HIV care and is followed until death or age 80 years, whichever comes first. The model draws randomly from user-defined initial distributions of CD4 count and HIV

RNA and tracks clinical outcomes as an individual transitions monthly through states of disease progression and treatment. Probabilities of transition between HIV-related health states depend on factors including current CD4 count and HIV RNA. All individuals are ART

likely to survive long enough to develop lung cancer. Recognizing that smoking emerges as an important competing risk in the presence of virologic suppression, we assumed, in the base case, complete ART adherence and no loss to follow-up from HIV care. These in-care individuals are more likely to participate in a smoking cessation intervention. In sensitivity analysis, we relaxed this assumption, accounting for reported rates of ART nonadherence and loss to follow-up (Supplement).[27] Additional specifications are described elsewhere.[23,27]

Model Validation

There are few published data on smoking-related mortality specific to PLWH. We therefore pursued 2 validation strategies. First, we compared our model-generated cumulative lung cancer mortality among HIV-uninfected people to results reported in general population studies in Western Europe.[28,29] Second, we compared our model-generated cumulative lung cancer mortality among PLWH (accounting for ART nonadherence and loss to follow-up) with the modeled cumulative lung cancer incidence reported by the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (Supplement).[30,31]

Input Parameters

Cohort Characteristics

We simulated PLWH reflecting those initiating HIV care in the United States[25,32-39] (**Table 1** and Supplement). In the base case, we assumed the same CD4 distribution regardless of cohort age at entry to care.

Cohort Stratifications by Smoking Exposure

Smoking intensity for current and former smokers was based on number of cigarettes per day as derived by Rosenberg et al,[25] who categorized US smokers into quintiles of cigarettes per day stratified by sex, age, and 5-year birth cohort, through the year 2000.[25] Among current and former smokers, we considered the fifth, third, and first quintiles to be heavy, moderate, and light smokers. For example, among 40-year-old men, heavy, moderate, and light smokers consumed 35, 18, and 2 cigarettes per day, respectively (Table 1). These quantities changed with age according to published data (Supplement).[25]

Lung Cancer Mortality

To derive monthly lung cancer mortality by smoking exposure, we combined US general population data on lung cancer mortality rates in 2000 (to match the latest year of the lung cancer–deleted life tables[25]), lung cancer mortality risk ratios for current and former smokers (further stratified by smoking intensity) vs never smokers, and the proportions of current, former, and never smokers in the population (Supplement).[25,36,40-42] Compared with never smokers, the lung cancer mortality risk ratio for male and female current moderate smokers was 23.6 and 24.2, respectively, and for those who quit at age 40 years, it was 4.3 and 4.5.

The derived smoking exposure-stratified lung cancer rates were not specific to PLWH. Therefore, in the base case, we accounted for an HIV-associated independent risk of lung

Table 1. Input Parameters for Model Simulations of Smoking and Lung Cancer Among People Living With HIV in the United States

Parameter	Patient Characteristic Category				Source
HIV- and ART-related parameters	Base case				
CD4 count at entry to HIV care, cells/μL, mean (SD)	360 (280)				Althoff et al[32]
First-line ART suppression (dolutegravir/abacavir/lamivudine), <50 copies/mL at 48 wk, %	87				Walmsley et al[33] and Raffi et al[34]
Virologic failure for suppressed patients (dolutegravir/abacavir/lamivudine), % per month	0.1				Raffi et al[35]
Smoking and non-AIDS-related parameters	Men		Women		
Cigarettes per day at age 40 years, No.[a]					Rosenberg et al[25]
Heavy smokers	35		28		
Moderate smokers	18		14		
Light smokers	2		2		
Lung cancer mortality RR vs never smokers					Thun et al[36]
Current smokers					
Heavy smokers	32.4		36.1		
Moderate smokers	23.6		24.2		
Light smokers	15.8		16.7		
Former smokers (quit at age 40 years)					
Heavy smokers	5.8		6.8		
Moderate smokers	4.3		4.5		
Light smokers	2.9		3.1		
Lung cancer mortality RR, people with HIV vs HIV-uninfected people (independent of smoking)[b]	1.7		1.7		Sigel et al[11]
Lung cancer–deleted, non-AIDS-related mortality RR, people with HIV vs HIV-uninfected people (independent of smoking)[c]	1.0		1.0		Triant et al,[37] Freiberg et al,[38] and Althoff et al[39]
Monthly lung cancer–deleted, non-AIDS-related mortality probability in men only,[d] $\times 10^{-4}$	Age 40 y	Age 50 y	Age 60 y	Age 70 y	Rosenberg et al[25]
Current smokers					
Heavy smokers	6.1	8.6	17.1	40.1	
Moderate smokers	3.9	7.0	16.2	38.6	
Light smokers	3.0	5.4	11.2	26.7	
Former smokers (quit at age 40 years)					
Heavy smokers	6.1	5.6	9.0	20.3	
Moderate smokers	3.9	4.3	7.9	19.2	
Light smokers	3.0	3.5	7.1	18.6	
Never smokers	1.7	2.7	6.7	18.5	

Model Validation

For HIV-uninfected people, model-generated cumulative lung cancer mortalities by age 75 years for current heavy smokers were 24.5% and 19.5% for men and women, respectively; these values are similar to those reported in the United Kingdom, 24.4% and 18.5% (eTables 1 and 2 in the Supplement).[28] For 20-year-old PLWH in the United States, our model-generated cumulative lung cancer mortality by age 75 years was 5.0%, while the modeled cumulative lung cancer incidence reported by NA-ACCORD was 3.7% (Supplement).[30]

Base Case

Among men, cumulative lung cancer mortality by age 80 years for heavy, moderate, and light current smokers entering HIV care at age 40 years was 28.9%, 23.0%, and 18.8%, respectively; for heavy, moderate, and light former smokers who quit smoking at age 40 years, it was 7.9%, 6.1%, and 4.3%; and for never smokers, it was 1.6%. Among women, the corresponding respective cumulative lung cancer mortality for heavy,

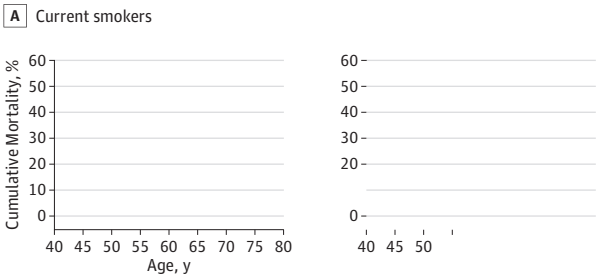
moderate, and light current smokers was 27.8%, 20.9%, and 16.6%; for heavy, moderate, and light former smokers who quit at age 40 years, it was 7.5%, 5.2%, and 3.7%; for never smokers, it was 1.2% (**Table** and **Figure 1**). Cumulative lung cancer mortality for ART-adherent current and never smokers varied little by age at entry to HIV care, with slightly higher results among those entering care at older ages owing to survival bias (Table 2).

Risk of Mortality From Lung Cancer vs Other Causes

Risks of mortality from lung cancer vs other causes varied by smoking exposure. For men who entered HIV care at age 40 years, adhered to the ART regimen, and continued to smoke at a moderate ("average") level, cumulative mortality from lung cancer was 10 times that from AIDS-related causes (23.0% vs 2.3%; **Figure** A). The mortality for former smokers in this category is illustrated in Figure 2B, and for never smokers, it is illustrated in eFigure 2A in the Supplement. For women who entered HIV care at age 40 years, adhered to the ART regimen, and continued to smoke at a moderate ("average") level, cumulative mortality from lung cancer was 8 times that from AIDS-related causes (20.9% vs 2.5%). Depending on sex and smoking intensity, ART-adherent

mulative lung cancer mortality (22.7%) was similar to AIDS-related mortality (23.0%); for women, the corresponding results were 21.6% vs 25.5% (eTable 5 in the Supplement).

Figure 2. Cumulative Mortality by Cause Among Men Entering HIV Care at Age 40 Years



Varying HIV-Associated Risks of Lung Cancer and of Other Non–AIDS-Related Mortality

Model-generated cumulative mortality varied depending on the HIV-associated risk ratios applied for lung cancer and for other non-AIDS-related causes. For male and female current moderate smokers, cumulative lung cancer mortality varied from 10.5% to 23.0%, and cumulative other non-AIDS-related mortality varied from 45.7% to 78.0%. The lower numbers reflected scenarios assuming no direct influence of HIV on these causes of death (**Table**).

Population-Level Impact

Applying sex- and age-specific, model-projected results to the approximately 644 200 PLWH aged 20 to 64 years in care in the United States (including current, former, and never smokers), 59 900 lung cancer deaths by age 80 years are expected (9.3% of this population) if smoking status does not change. If 20% of the 273 200 current smokers quit, their lung cancer risk would decrease to that of former smokers, and 6900 (11.5%) lung cancer deaths could be averted.

Using a microsimulation model, we found that ART-adherent PLWH in the United States who smoke cigarettes are 6 to 13 times more likely to die from lung cancer than from AIDS-related causes. Even when accounting for reported rates of ART nonadherence and loss to follow-up, we found that nearly 10% of PLWH initially linked to HIV care (including both smokers and nonsmokers) are expected to die from lung cancer if smoking habits do not change. Smoking cessation could substantially reduce lung cancer risk for an individual and avert many lung cancer deaths at the population level.

People with HIV whose virus is suppressed now have a life expectancy approaching that of HIV-uninfected people.[44] However, life expectancy gaps persist, and smoking is a key driver of this difference.[45] This smoking footprint will likely grow as PLWH age and develop lung cancer and other smoking-associated diseases. Lung cancer was already the leading cause of death in a study of PLWH in France in 2010; the smoking

prevalence among PLWH is similar in France and the United States.[3,20,46]

In stratifying mortality risks by smoking status and intensity, our results can inform important conversations between clinicians and PLWH who smoke, helping both clinician and patient understand the patient's risks of different diseases and the potential benefits of smoking cessation. Recognizing the increased risk of death from lung cancer vs that from traditionally feared AIDS-related causes may motivate a smoker to quit smoking,[47] although this is not always the case. Our analyses also accounted for the smoking-conferred increase in risk of death from causes besides lung cancer and AIDS—this includes other cancers, other lung diseases, and cardiovascular disease. Our results provide evidence for HIV care programs and policymakers to include smoking cessation interventions as a key component of the comprehensive care of PLWH. Though smoking cessation is challenging, smoking prevalence among the US general population has decreased substantially in recent decades, from 42% in 1965 to 15% in 2015.[7,48] While the current smoking prevalence among PLWH is much higher than that among HIV-uninfected people, a similar proportion of smokers in the 2 groups want to quit, offering hope for a potential decrease in smoking prevalence in PLWH as well.[49]

Perhaps counterintuitively, lung cancer risk is linked to adherence to HIV therapy. Those who are not ART-adherent are more likely to die of AIDS-related causes before developing lung cancer. Nonetheless, even when accounting for reported rates of ART nonadherence and loss to follow-up from HIV care, we found that for male heavy smokers, the risk of dying from lung cancer is similar to the risk of dying from AIDS-related causes.

Limitations

Our results are subject to limitations inherent in the assumptions and simplifications of any model-based study. These include the following: (1) using data from the US general population in 2000 in the absence of smoking-stratified lung cancer data for PLWH; (2) uncertainty around the HIV-conferred risk of lung cancer, which could be lower or higher than what we applied in this analysis, and could vary by age[11,13-17,50]; (3) assuming no relationship between CD4 count and lung cancer risk, given conflicting reports affected by confounders such as smoking intensity[15,19,51-54]; (4) assuming that the HIV-associated increase in lung cancer mortality is similar to the increase in incidence, since median survival after lung cancer diagnosis is short[11,40]; (5) not accounting for disparities between PLWH and HIV-uninfected people in mortality after lung cancer diagnosis[17,55-58]; (6) not examining race: African American men are overrepresented among PLWH in the United States and may be more susceptible to lung cancer than people of other races[31,59]; (7) not differentiating by HIV transmission risk category: the national survey data for smoking prevalence among PLWH indicated little difference by sexual transmission risk category, but there were few injection drug users[3]; (8) not accounting for possibly higher average daily cigarette consumption among PLWH who smoke compared with HIV-uninfected people who smoke[11]; (9) assuming, in the base case, that smoking status does not change over time; and (10) not examining a potential impact on mortality from lung cancer screening with computed tomography.[60,61] Estimating smoking-attributable mortality for various diseases would be informative, but the data for non-AIDS, non–lung cancer outcomes were too limited to do so. The smoking-conferred risk of death from smoking-related diseases may be even greater than that applied in our analyses, especially in PLWH.[43] Though the model-generated estimates may be influenced by input parameter uncertainty, the magnitude of smoking-related harm with respect to lung cancer and other non-AIDS-related mortality, and the magnitude of the benefit from smoking cessation, remain robust, as shown in our sensitivity analysis.

In conclusion, there is a large expected burden of lung cancer among PLWH in the United States because (1) the smoking prevalence is very high in this population; (2) HIV itself increases the risk of lung cancer; and (3) PLWH are increasingly living long enough to develop lung cancer. For PLWH who adhere to ART, smoking is a much greater threat to their health than HIV itself. Clinicians caring for PLWH should offer guideline-based behavioral and pharmacologic treatments for tobacco use.[62] Lung cancer is now a leading cause of death among PLWH, but smoking cessation can greatly reduce the risk. Lung cancer prevention, especially through smoking cessation, should be a priority in the comprehensive care of PLWH.

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