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Title
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Permalink
https://escholarship.org/uc/item/94z85638

Journal
AIDS, 29(10)

ISSN
0269-9370

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Publication Date
2015-06-19

DOI
10.1097/qad.0000000000000690

Peer reviewed

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HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2016 June 19.

Published in final edited form as:

AIDS. 2015 June 19; 29(10): 1183–1193. doi:10.1097/QAD.0000000000000690.

LUNG CANCER INCIDENCE AND SURVIVAL AMONG HIV-INFECTED AND UNINFECTED WOMEN AND MEN

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Abstract

Objectives—To determine the lung cancer incidence and survival time among HIV-infected and uninfected women and men.

Design—Two longitudinal studies of HIV infection in the United States.

Methods—Data from 2,549 women in the Women's Interagency HIV Study (WIHS) and 4,274 men in the Multicenter AIDS Cohort Study (MACS), all with a history of cigarette smoking, were analyzed. Lung cancer incidence rates and incidence rate ratios were calculated using Poisson regression analyses. Survival time was assessed using Kaplan-Meier and Cox proportional hazard analyses.

Results—Thirty-seven women and 23 men developed lung cancer (46 HIV-infected and 14 HIV-uninfected) during study follow-up. In multivariable analyses, the factors that were found to be

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Disclosure statement: The authors have no conflicts of interest to disclose.

Meeting presentation: An earlier version of this study was presented at the 13th International Conference on Malignancies in AIDS and other Acquired Immunodeficiencies (ICMAOI), Bethesda, MD; National Cancer Institute: Bethesda, MD, 2011; Abstract 025

Human Participant Protection

Study protocols and consent materials were reviewed and approved by the institutional review boards at each of the collaborating institutions and informed consent was obtained from the participants.

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independently associated with a higher lung cancer incidence rate ratios were older age, less education, 10 or more pack-years of smoking, and a prior diagnosis of AIDS pneumonia (vs. HIV-uninfected women). In an adjusted Cox model that allowed for different hazard functions for each cohort, a history of injection drug use was associated with shorter survival, and a lung cancer diagnosis after 2001 was associated with longer survival. In an adjusted Cox model restricted to HIV-infected participants, nadir CD4 lymphocyte cell count <200 was associated with shorter survival time.

Conclusions—Our data suggest that pulmonary damage and inflammation associated with HIV infection may be etiologic for the increased risk of lung cancer. Encouraging and assisting younger HIV-infected smokers to quit and to sustain cessation of smoking is imperative to reduce the lung cancer burden in this population.

Keywords

AIDS; HIV infection; incidence; lung cancer; survival

INTRODUCTION

The use of highly active antiretroviral therapy (HAART) among HIV-infected individuals has led to a considerable decrease in the incidence of AIDS-defining cancers, most notably Kaposi sarcoma and non-Hodgkin lymphoma [1, 2]. Compared to the pre-HAART era, HIV-infected adults in the HAART era have experienced an increased incidence and proportional mortality for certain non-AIDS defining malignancies, including lung cancer [3-6]. This increase is partially due to longer life expectancy since the introduction of HAART, allowing HIV-infected individuals to reach older ages when the incidence rates of several common tumors, including lung cancer, begin to rise [7, 8]. Additionally, HIV-infected adults are more likely to smoke tobacco than the general population [9-14], and almost all HIV-infected patients with lung cancer reported to date have had a history of cigarette smoking [12, 13, 15-17].

While several studies have reported a higher incidence of lung cancer among people with HIV and AIDS as compared to population estimates [2, 4, 18], it is unclear whether this increase is due to HIV or to other risk factors for lung cancer such as cigarette smoking [12, 19]. A study comparing HIV-infected with -uninfected participants from the Women's Interagency HIV Study (WIHS) observed that the lung cancer incidence rates were similar in the two groups after adjusting for smoking history [12]. A study comparing cancer incidence in the Multicenter AIDS Cohort Study (MACS) found that compared to HIV-uninfected men who have sex with men, HIV-infected men had elevated but not significantly different rates of lung cancer when controlling for history of cigarette smoking [19]. Both these prior studies in the WIHS and the MACS were limited by a relatively small number of incident lung cancer cases (N=14 in the WIHS and N=15 in the MACS) and neither study considered risk factors such as prior lung disease or AIDS diagnosis in their analyses.

HIV-related immunosuppression can lead to chronic immune activation, inflammation, and immune system dysfunction which can increase the risk of developing lung cancer [20, 21].

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Yet the relationship between CD4 lymphocyte count, duration of immunodeficiency, and lung cancer risk is uncertain; with some studies finding an association between CD4 lymphocytes <200 [22-24] or duration of severe immunodeficiency [25] and incident lung cancer while others have not [13, 15, 26, 27].

Pre-existing lung disease, both infectious and non-infectious diseases, including asthma, has been associated with a trend toward increased lung cancer risk [15, 28]. Consistent with these trends, a study investigating the role of AIDS-defining pulmonary infections on the subsequent risk of lung cancer reported that HIV-infected individuals with recurrent pneumonia were at significantly higher lung cancer risk than those without this history, after adjusting for age, race, sex, HIV acquisition mode, CD4 lymphocyte count, and AIDS diagnosis year [29]. These studies suggest that factors other than HIV infection or immunodeficiency may increase the risk of lung cancer in HIV-infected individuals.

The aims of this investigation were to determine the incidence, risk factors, and survival time for lung cancer among the participants in two longitudinal studies of HIV infection in United States (US) women and men. Both cohort studies include a comparison group of HIV-uninfected at-risk individuals. We hypothesized that the observed increased incidence of lung cancer among HIV-infected individuals would primarily be due to cigarette smoking and secondarily to pre-existing pulmonary disease.

METHODS

Study population

Data from participants in two US HIV/AIDS cohort studies, the WIHS and the Multicenter AIDS Cohort Study (MACS), were used for this investigation. In the WIHS cohort, recruitment of HIV-infected and -uninfected women occurred in 1994-1995 and again in 2001-2002, for a total of 3,766 women (2,791 HIV-infected and 975 HIV-uninfected). Data for the WIHS were collected from the following six centers: Brooklyn, Bronx, Washington D.C., Chicago, the Los Angeles area, and the San Francisco Bay area. Women in the WIHS returned at 6-month intervals for a standardized interview-based questionnaire, physical examination, and collection of blood for laboratory testing and storage. Detailed information about the WIHS study methodology, quality assurance, and baseline characteristics of enrollees has been published [30, 31].

The MACS recruited a total of 6,972 men (2,943 HIV-infected and 4,029 HIV-uninfected) during three recruitment periods: from April 1984 through March 1985, from April 1987 through September 1991, and from October 2001 through August 2003. Men who reported having had sex with men were enrolled at one of four metropolitan areas in the US (Baltimore, MD and Washington, DC; Chicago, IL; Pittsburgh, PA; and Los Angeles, CA). The details about the recruitment and characteristics of the MACS cohort have been reported elsewhere [32]. Participants in the MACS returned at 6-month intervals for a detailed interview, physical examination, neuropsychological testing, and collection of blood for laboratory testing and storage.

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All analyses were performed using data collected through September 30, 2012, but follow-up was censored on September 30, 2011, to allow for cancer reporting delays (Federal and state law requires all new cancer diagnoses to be reported to the cancer registries within 180 days [33]). The individual institutional review boards of each institution involved approved these studies; all participants provided written informed consent.

Lung cancer diagnosis

Ascertainment of lung cancer cases was obtained via: 1) searches of statewide cancer registries, 2) medical record confirmation of self-reported cancer diagnoses, and 3) death certificates. The eight of the nine sites performed their state cancer registry matches between 2010 and 2012, with one site match in 2008. For this analysis, four participants who had lung cancer diagnosed more than four years after their last study visit were censored as being cancer-free at the time of their last study visit due to missing data preceding their cancer diagnosis.

Risk factors for cancer

The lung cancer risk factors included in this analysis were study cohort (WIHS women or MACS men), age, race/ethnicity (African American vs. all other), history of injection drug use (ever vs. never), educational attainment (a high school degree or less vs. more than high school degree), body mass index (kg/m^2 per 10 unit increase), pack-years of smoking, history of asthma (excluded from MACS multiple regression analysis due to 32% missing data), calendar time, HAART use, and prior clinical AIDS diagnosis. Among the AIDS diagnoses, additional categorization was made for AIDS-related pneumonias; *Pneumocystis jiroveci* pneumonia (PCP) and recurrent bacterial pneumonia. Laboratory measures included HIV antibody status, nadir and peak CD4 lymphocyte count ($cells/mm^3$), and quantitative plasma HIV-RNA levels. HIV medications were categorized as HAART or non-HAART using guidelines published by the United States Department of Health and Human Services at the time of the study visit [34].

Statistical Analysis

All but one incident lung cancer occurred among participants who had reported a history of cigarette smoking at enrollment, therefore we restricted this study to the 6,823 (2,549 WIHS, 4,274 MACS) participants who reported having smoked at least 100 cigarettes prior to their baseline study visit. Study participants were characterized at baseline using standard descriptive statistics. Lung cancer incidence rates (IR) were computed as the number of observed incident cancers divided by the number of person-years of follow-up, where follow-up time was measured from the baseline visit until the earliest of the lung cancer diagnosis, death, or the date of the last study visit on or prior to September 30, 2011. Lung cancer IR comparisons were quantified using the incidence rate ratio (IRR) and performed using exact Poisson regression wherever possible, and asymptotic results were obtained and reported when exact methods failed. To examine the effects of HIV-related factors such as HAART exposure, low CD4 lymphocyte count, and prior AIDS diagnosis, we created separate indicator variables for HIV infection with and without the exposure of interest (e.g., HIV-infected and HAART-naïve vs. HIV-infected and HAART-exposed), and then

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compared the lung cancer IR for each group to that of the HIV-uninfected reference group. We also assessed the association between lung cancer and a prior AIDS pneumonia diagnosis and lagged the AIDS pneumonia diagnosis for up to five years to examine the possibility that those with a prior history of AIDS pneumonia might have had their lung cancer diagnosed earlier (diagnostic bias) than those without pneumonia due to an expanded pulmonary work-up of their AIDS pneumonia. All cofactors that varied over time were evaluated using time-varying covariates. We also added interaction terms to the final multiple regression models to determine whether the effect of any covariate differed significantly between WIHS and MACS.

Survival following lung cancer diagnosis was analyzed using Kaplan-Meier methods and Cox proportional hazards models for the combined WIHS/MACS cohort. Except for age which was calculated on the date of lung cancer diagnosis, participant characteristics were measured at the last study visit prior to diagnosis. For the multiple regression analysis, we forced cohort, age, and HIV status into the model and then examined the effects of geographic location, race, pack-years, more than a high school education, history of IDU, and lung cancer histology on survival. The final model included the factors forced into the model plus those that remained significant at the 0.05 level. The proportionality assumption was assessed by testing for an interaction between each covariate and the natural logarithm of time.

Two sensitivity analyses were performed to explore the possibility that higher AIDS-related morbidity and mortality during the pre-HAART era might have lowered the lung cancer incidence rates and altered the effects of certain risk factors on lung cancer incidence. We first repeated the multivariable analyses using only follow-up time accrued between 1995 through 2011, and then performed a competing risks analysis [35] of lung cancer incidence where death due to any cause was treated as a competing event. All analyses were performed using SAS 9.3 [36], STATA 12 [37], or StatXact 10.0 [38]. Statistical significance was inferred from p-values less than 0.05 using a two-sided test.

RESULTS

The baseline characteristics of the WIHS and MACS participants who reported a history of cigarette smoking are described in Table 1. Compared to the men, notable differences for the women at the time of enrollment include a higher proportion of African-Americans, less education, a lower cumulative number of smoking pack-years, and higher proportions with a history of asthma and injection drug use. In addition, WIHS participants were significantly more likely to be infected with HIV and, among those with HIV, to have lower CD4 lymphocyte counts.

Lung cancer histology

Of the 60 lung cancers, histology was known for 48 (80%). The most common histologic type was adenocarcinoma (n=23) followed by non-small cell carcinoma (n=9) and squamous cell carcinoma (n=8). Histologic type did not differ significantly by HIV status (exact p-value=0.85) or between cohorts (exact p-value=0.39).

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Lung cancer incidence

We observed 37 incident lung cancers (31 in HIV-infected participants and 6 in HIV-uninfected participants) among 2549 WIHS participants and 23 incident lung cancers (15 HIV-infected and 8 HIV-uninfected) among 4274 MACS participants (Table 2). The average age at diagnosis was 52.1 for the HIV-infected women and 51.3 for the HIV-uninfected women and 49.6 for the HIV-infected men and 54.4 for the HIV-uninfected men. Overall, the lung cancer IR was significantly higher among the women than the men ($p<0.0001$) and higher among HIV-infected participants than uninfected participants ($p=0.001$; Table 2).

In unadjusted analyses, lung cancer IRs were significantly higher in both cohorts among older participants and those who had accumulated >30 pack-years of smoking exposure. Lung cancer IRs were also elevated among African-Americans and those with a history of IDU among women and among less educated men (Table 3). While women with a history of asthma also had a significantly higher lung cancer IR, the data were not available to evaluate this risk factor among men.

HIV infection was not significantly associated with unadjusted lung cancer IRs in either cohort, but the IRRs suggested a two-fold higher incidence for HIV-infected men and women (Table 3). When we combined the two cohorts, HIV infection was significantly associated with lung cancer incidence (IRR=2.64, 95% CI=1.43-5.21). Among MACS participants infected with HIV, the unadjusted results indicate that higher lung cancer incidence was associated with lower CD4 T-cell counts, higher peak HIV RNA levels, and a prior AIDS diagnosis (Table 3).

In multivariable analyses of the combined WIHS and MACS participants using all data (1984-2011), the factors that were found to be independently associated with a higher lung cancer IR were older age, less education, 10 or more pack-years of smoking, and prior AIDS pneumonia diagnosis (Table 4). The association between lung cancer incidence and a prior AIDS pneumonia diagnosis remained significant even when the pneumonia diagnosis was lagged by up to five years (data not shown). By testing interaction terms we determined that none of the effects of the risk factors included in the multiple regression analysis differed significantly between WIHS and MACS participants. Finally, in a subgroup analysis restricted to the women in the WIHS, lung cancer incidence was also independently associated with a history of asthma (IRR=2.44, 95% CI=1.17-5.06).

Of the 31 incident lung cancers among HIV-infected women in the WIHS, 20 reported a prior AIDS diagnosis of which 14 consisted of pneumonia; all 14 were diagnosed with repeated bacterial pneumonia and seven were also diagnosed with PCP. Of the 15 incident lung cancers among HIV-infected men in the MACS, six reported a prior AIDS diagnosis of which three were pneumonia; all three were diagnosed with PCP and one was also diagnosed with repeated bacterial pneumonia.

Lung cancer survival

We examined survival following lung cancer diagnosis in 56 of the 60 cases, excluding four participants who had no follow-up time after lung cancer diagnosis. In cohort-stratified

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Kaplan-Meier survival time analyses of these 56 cases, there were 45 deaths with an estimated median survival of 9.5 months for women in the WIHS and 6.2 months for men in the MACS, log-rank p-value 0.71.

In unadjusted Cox proportional hazard analyses among these 56 cases, the only factor associated with longer survival time was being diagnosed in 2001-2011 (vs. 1984-1994, HR=0.31, 95% CI=0.14-0.70; Table 5). In the final multivariable Cox model adjusted for cohort, age, and HIV infection, two variables remained significant: more recent calendar period (2001-2011) was associated with improved survival (HR=0.23, 95% CI=0.07-0.71) and history of IDU was associated with shorter survival time (HR=2.98, 95% CI=1.28-6.95; Table 5). When the final adjusted model was restricted to the 42 HIV-infected cases and evaluated for the effect of HAART use, prior AIDS diagnosis, prior AIDS-pneumonia, HIV viral load, and CD4 lymphocyte count, the only HIV disease measure found to be independently associated with survival at the p=0.05 level was nadir CD4 lymphocyte cell count <200 (HR=2.55, 95% CI=1.09-5.95).

Sensitivity analyses for both lung cancer incidence and survival were performed using a study sample that was restricted to HAART era observations (1995-2011), which included 37 lung cancer cases and 24,330 person-years of observation in the WIHS and 14 lung cancer cases and 21,871 person-years of observation in the MACS. In this restricted cohort, the estimated IRRs were similar to those obtained using the entire cohort, although the confidence intervals around the estimates were larger and education was not statistically significant (Table 4). Examination of interactions between cohort and each of the other covariates in the model revealed that the effect of nadir CD4 lymphocyte cell count <200 differed significantly between the two cohorts (IRR=1.04, 95% CI=0.48-2.24 in WIHS vs. IRR=4.19, 95% CI=1.29-13.59 in MACS). We also found that the lung cancer incidence results obtained when death was treated as a competing risk were analogous to those reported in Table 4 (supplemental Table 1). Finally, the results of the survival analyses remained comparable to those obtained from the full study sample (data not shown).

DISCUSSION

Lung cancer incidence is significantly higher among HIV-infected individuals than the general population [2, 4, 18, 39], yet the precise role of HIV and immune suppression remains somewhat elusive. By analyzing data from cohort studies of HIV-infected and HIV-uninfected at-risk participants, and then incorporating information on HIV status, CD4 lymphocyte count, prior AIDS diagnosis, prior lung disease, age, education, and pack-years of smoking, we were better able to address the independent contribution of HIV infection to the increased the rate of lung cancer among HIV-infected individuals. We found that approximately two-thirds of the effect of HIV infection was explained by a diagnosis of prior AIDS-pneumonia. Our results are consistent with other studies that have reported an increased risk of lung cancer among HIV-infected adults with prior lung disease and/or AIDS pneumonia [15, 28, 29].

Reasons why the increased risk of lung cancer among HIV-infected persons may not be fully explained by the number of pack-years of smoking include lung damage from chronic

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or recurrent infections (which are more common in HIV-infected persons), an aberrant inflammatory response, or an HIV-mediated increase in susceptibility to tobacco carcinogens [15, 40]. Inflammatory pulmonary disease and infections have been shown to play a role in the development of lung cancer in the general population [41], and this has also been observed among HIV-infected individuals, particularly in association with recurrent pneumonias [29]. Chronic or recurrent infections (such as HIV and pneumonia, respectively), as well as chronic inflammation from smoking, can induce inflammatory and genetic changes that lead to the development of lung cancer in susceptible individuals.

Our observation that lung cancer survival has improved over time may be due to several recent trends, including 1) increased pulmonary disease screening for people with HIV and thus the potential for earlier diagnosis of lung cancer; 2) widespread use of HAART before, during and after lung cancer treatment, thus preventing inter-current infection and treatment delays, as well as progression to AIDS; and 3) increased use and efficiency of cancer treatment in HIV-infected individuals over time. Other studies of HIV-infected adults have also reported longer lung cancer survival time for those diagnosed more recently [17, 42-44].

Our study has a few limitations. First, the women in the WIHS differed from the men in the MACS on a number of measured and unmeasured potential risk factors for the development of lung cancer. While we might be able to control for notable differences, such as race, we are unable to completely rule out differences that may be due to environmental factors, such as secondhand smoke, or health-related behaviors, such as diet and exercise. Second, all participants in this study had history of smoking and thus we did not asses the lung cancer risk among non-smokers. However, there was only one case of lung cancer in a cigarette non-smoker and that person reported a long history of smoking marijuana. Third, stage at cancer diagnosis and lung cancer treatment data was not available for 57% and 100% the men, respectively, and 23% and 22% of the women, respectively, and thus we were unable to evaluate the effect of cancer stage or treatment on survival time. Finally, our results may not be applicable to all people living with, or at risk for HIV infection, especially those living in developing countries where tobacco use, environmental factors, and lung cancer diagnosis or treatment may differ from those in the US.

Despite these limitations, our study is unique in many ways. A large number of study participants was included (over 6,800 men and women), with many person-years of follow-up (69,738 person-years). A rich database was available, and included both HIV-infected participants as well as similar HIV-uninfected comparison groups. Our investigation spanned both pre-HAART and HAART time periods thus allowing for temporal comparisons. Additionally, the two cohorts were comprised of a racial/ethnic mix which is quite diverse and fairly representative of men and women with living with HIV nationally.

In summary, using data from two of the largest longitudinal studies of HIV infection among men and women in the US, we found that HIV infection alone was not an independent risk factor for lung cancer, but that the amount of cigarette smoking over time, and prior AIDS pneumonia among HIV-infected adults were major contributors for the development of lung cancer. Older age and pack-years of smoking were the strongest risk factors for lung cancer.

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Thus, encouraging and assisting younger HIV-infected smokers to quit and to sustain cessation of smoking is imperative to reduce the lung cancer burden in this population. Practitioners treating HIV-infected smokers have an ideal opportunity to teach their patients that serious and life-threatening health conditions may be exacerbated by smoking and can be ameliorated by quitting [45-48]. A better understanding of the role and consequence of HIV-related lung disease on lung cancer pathogenesis is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Nancy A. Hessol contributed to the design and execution of the project, interpretation of results, and writing of the manuscript. Otoniel MartÍnez-Maza contributed to the execution of the project and writing of the manuscript. Alexandra M. Levine contributed to the design and execution of the project, interpretation of the results, and writing of the manuscript. Alison Morris contributed to the interpretation of the results and writing of the manuscript. Joseph B. Margolick contributed to the execution of the project, interpretation of results, and writing of the manuscript. Mardge H. Cohen contributed to the execution of the project and writing of the manuscript. Lisa P. Jacobson contributed to the design and execution of the project and writing of the manuscript. Eric C. Seaberg was the statistician and analyst of this project and contributed to the design and execution of the project, interpretation of results, and writing of the manuscript.

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington DC Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases (UO1-AI-35004, UO1-AI-31834, UO1-AI-34994, UO1-AI-34989, UO1-AI-34993, and UO1-AI-42590) and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (UO1-HD-32632). The study is co-funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Funding is also provided by the National Center for Research Resources (UCSF-CTSI Grant Number UL1 RR024131). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Data in this manuscript were also collected by the Multicenter AIDS Cohort Study (MACS) with centers (Principal Investigators) at The Johns Hopkins Bloomberg School of Public Health (Joseph B. Margolick, Lisa P. Jacobson), Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services (John P. Phair, Steven M. Wolinsky), University of California, Los Angeles (Roger Detels), and University of Pittsburgh (Charles R. Rinaldo). The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute. UO1-AI-35042, UL1-RR025005 (GCRC), UO1-AI-35043, UO1-AI-35039, UO1-AI-35040, UO1-AI-35041.

REFERENCES

1. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS. 2006; 20:1645–1654. [PubMed: 16868446]
2. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008; 123:187–194. [PubMed: 18435450]
3. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol. 2006; 24:1383–1388. [PubMed: 16549832]
4. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. AIDS. 2007; 21:207–213. [PubMed: 17197812]

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5. Shiels MS, Cole SR, Mehta SH, Kirk GD. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. J Acquir Immune Defic Syndr. 2010; 55:510–515. [PubMed: 20838223]
6. Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. Clin Infect Dis. 2010; 51:957–962. [PubMed: 20825305]
7. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. Ann Intern Med. 2010; 153:452–460. [PubMed: 20921544]
8. Crothers K, Huang L, Goulet JL, Goetz MB, Brown S, Rodriguez-Barradas M, et al. HIV Infection and Risk for Incident Pulmonary Diseases in the Combination Antiretroviral Therapy Era. Am J Respir Crit Care Med. Feb 1; 2011 183(3):388–95. [PubMed: 20851926]
9. Saves M, Chene G, Ducimetiere P, Leport C, Le Moal G, Amouyel P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clin Infect Dis. 2003; 37:292–298. [PubMed: 12856222]
10. Rahmanian S, Wewers ME, Koletar S, Reynolds N, Ferketich A, Diaz P. Cigarette smoking in the HIV-infected population. Proc Am Thorac Soc. 2011; 8:313–319. [PubMed: 21653534]
11. Cadranel J, Garfield D, Lavole A, Wislez M, Milleron B, Mayaud C. Lung cancer in HIV infected patients: facts, questions and challenges. Thorax. 2006; 61:1000–1008. [PubMed: 17071836]
12. Levine AM, Seaberg EC, Hessol NA, Preston-Martin S, Silver S, Cohen MH, et al. HIV as a risk factor for lung cancer in women: data from the Women's Interagency HIV Study. J Clin Oncol. 2010; 28:1514–1519. [PubMed: 20177022]
13. Clifford GM, Lise M, Franceschi S, Egger M, Bouchardy C, Korol D, et al. Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Br J Cancer. 2012; 106:447–452. [PubMed: 22240797]
14. Hessol NA, Weber KM, D'Souza G, Burton D, Young M, Milam J, et al. Smoking Cessation and Recidivism in the Women's Interagency Human Immunodeficiency Virus Study. Am J Prev Med. 2014
15. Kirk GD, Merlo C, O' Driscoll P, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis. 2007; 45:103–110. [PubMed: 17554710]
16. Ruiz M. Lung cancer in HIV-infected patients: the experience of an urban clinic. J Int Assoc Physicians AIDS Care (Chic). 2010; 9:214–217. [PubMed: 20798400]
17. Bearz A, Vaccher E, Martellotta F, Spina M, Talamini R, Lleshi A, et al. Lung cancer in HIV positive patients: the GICAT experience. Eur Rev Med Pharmacol Sci. 2014; 18:500–508. [PubMed: 24610616]
18. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009; 52:611–622. [PubMed: 19770804]
19. Seaberg EC, Wiley D, Martinez-Maza O, Chmiel JS, Kingsley L, Tang Y, et al. Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007. Cancer. 2010; 116:5507–5516. [PubMed: 20672354]
20. Dubrow R, Silverberg MJ, Park LS, Crothers K, Justice AC. HIV infection, aging, and immune function: implications for cancer risk and prevention. Curr Opin Oncol. 2012; 24:506–516. [PubMed: 22759737]
21. Shcherba M, Shuter J, Haigentz M Jr. Current questions in HIV-associated lung cancer. Curr Opin Oncol. 2013; 25:511–517. [PubMed: 23942294]
22. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20:2551–2559. [PubMed: 22109347]
23. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007; 370:59–67. [PubMed: 17617273]
24. Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009; 10:1152–1159. [PubMed: 19818686]

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25. Kesselring A, Gras L, Smit C, van Twillert G, Verbon A, de Wolf F, et al. Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy. Clin Infect Dis. 2011; 52:1458–1465. [PubMed: 21628488]
26. Sigel K, Wisnivesky J, Gordon K, Dubrow R, Justice A, Brown ST, et al. HIV as an independent risk factor for incident lung cancer. AIDS. 2012; 26:1017–1025. [PubMed: 22382152]
27. Lavole A, Wislez M, Antoine M, Mayaud C, Milleron B, Cadranel J. Lung cancer, a new challenge in the HIV-infected population. Lung Cancer. 2006; 51:1–11. [PubMed: 16300854]
28. Palacios R, Pascual J, Cabrera E, Lebron JM, Guerrero-Leon MA, del Arco A, et al. Lung cancer in HIV-infected patients. Int J STD AIDS. 2014; 25:239–243. [PubMed: 23970654]
29. Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. J Acquir Immune Defic Syndr. 2010; 55:375–379. [PubMed: 20736841]
30. Bacon MC, von Wyl V, Alden C, Sharp G, Robison E, Hessol N, et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol. 2005; 12:1013–1019. [PubMed: 16148165]
31. Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, et al. The Women's Interagency HIV Study. WIHS Collaborative Study Group. Epidemiology. 1998; 9:117–125. [PubMed: 9504278]
32. Kaslow R, Ostrow D, Detels R, Phair J. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. 1987; 126:310–318. [PubMed: 3300281]
33. Hofferkamp, J. Standards for Cancer Registries Volume III: Standards for Completeness, Quality, Analysis, Management, Security and Confidentiality of Data. North American Association of Central Cancer Registries; Springfield, Ill: Aug. 2008
34. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. 2004 Updated 3/23/04.
35. Fine J, Gray R. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999; 94:496–509.
36. SAS Institute Inc.. SAS/STAT User's Guide, Version 9.3. SAS Institute Inc.; Cary, North Carolina: 2010.
37. StataCorp.. Stata Statistical Software: Release 12. StataCorp LP; College Station, TX: 2011.
38. Cytel Software Corporation. StatXact 10.0. Cytel Software Corporation; Cambridge, MA: 2012.
39. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. AIDS. 2014; 28:881–890. [PubMed: 24300545]
40. Morris A, George MP, Crothers K, Huang L, Lucht L, Kessinger C, et al. HIV and chronic obstructive pulmonary disease: is it worse and why? Proc Am Thorac Soc. 2011; 8:320–325. [PubMed: 21653535]
41. Bobba RK, Holly JS, Loy T, Perry MC. Scar carcinoma of the lung: a historical perspective. Clin Lung Cancer. 2011; 12:148–154. [PubMed: 21663856]
42. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol. 2007; 165:1143–1153. [PubMed: 17344204]
43. Hakimian R, Fang H, Thomas L, Edelman MJ. Lung cancer in HIV-infected patients in the era of highly active antiretroviral therapy. J Thorac Oncol. 2007; 2:268–272. [PubMed: 17409796]
44. Lavole A, Chouaid C, Baudrin L, Wislez M, Raguin G, Pialoux G, et al. Effect of highly active antiretroviral therapy on survival of HIV infected patients with non-small-cell lung cancer. Lung Cancer. 2009; 65:345–350. [PubMed: 19135758]
45. Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ. Treating Tobacco Use and Dependence: 2008 Update. US Department of Health and Human Services. May.2008
46. Ebbert JO, Sood A, Hays JT, Dale LC, Hurt RD. Treating tobacco dependence: review of the best and latest treatment options. J Thorac Oncol. 2007; 2:249–256. [PubMed: 17410050]

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47. Taylor KL, Cox LS, Zincke N, Mehta L, McGuire C, Gelmann E. Lung cancer screening as a teachable moment for smoking cessation. Lung Cancer. 2007; 56:125–134. [PubMed: 17196298]

48. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. Health Educ Res. 2003; 18:156–170. [PubMed: 12729175]

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Table 1

Characteristics of WIHS and MACS participants with a history of cigarette smoking at enrollment.

	WIHS		MACS		
Baseline characteristics	**N**	**%**	**N**	**%**	**p-value**
All	2549	100	4274	100	
Geographic location					**<0.0001**
East coast	1335	52.4	1020	23.9	
Central US	343	13.5	2004	46.9	
West coast	871	34.2	1250	29.2	
Enrollment period					0.14
1984-1995	1924	75.5	3293	77.1	
2001-2003	625	24.5	981	22.9	
Age					**<0.0001**
<40	1740	68.3	3212	75.2	
40-49	708	27.8	853	20.0	
50+	101	3.9	209	4.9	
Race					**<0.0001**
White	420	16.5	3000	70.2	
Black	1478	58.0	836	19.6	
Hispanic	573	22.5	377	8.8	
Other	78	3.1	58	1.4	
Education					**<0.0001**
≤ High school	1801	70.9	1001	23.6	
> High school	738	29.1	3238	76.4	
BMI (kg/m^2)					**<0.0001**
<25	1115	44.4	2991	70.1	
25-30	731	29.1	977	22.9	
>30	668	26.6	296	6.9	
Cumulative pack-years of cigarette use					**<0.0001**
<10	1346	55.9	1625	39.1	
10 to 20	579	24.0	852	20.5	
20 to 30	280	11.6	684	16.4	
>30	205	8.5	999	24.0	
Unknown	139	--	114	--	
History of asthma					**<0.0001**
No	1836	72.4	2633	90.4	

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	WIHS		MACS		
Yes	701	27.6	281	9.6	
Unknown*	12	--	1360	--	
Recreational drug use					**<0.0001**
Never	189	7.4	502	11.8	
Ever	2360	92.6	3767	88.2	
Unknown	0	--	5	--	
Injection drug use					**<0.0001**
Never	1472	**57.8**	3535	87.9	
Ever	1077	42.2	487	12.1	
Unknown	0	--	252	--	
HIV-infected					
No	674	26.4	2414	56.5	**<0.0001**
Yes	1875	73.6	1860	43.5	
CD4 T-cells at baseline (cells/ul, HIV+ only)					**0.0001**
<200	459	**24.8**	144	**7.8**	
200 to 500	828	**44.7**	666	36.0	
>500	566	30.6	1039	56.2	
Unknown	22	--	11	--	
HIV RNA level at baseline (copies/m , HIV+ only)					**<0.0001**
<400	274	**14.7**	280	18.4	
401 to 10,000	522	29.7	359	23.6	
> 10,000	1034	55.6	882	58.0	
Unknown**	15	--	339	--	
HAART-experienced (HIV+ only)					**<0.0001**
No	1643	87.6	1533	82.4	
Yes	232	12.4	327	17.6	

* MACS did not document history of asthma at enrollment after 1985.

** MACS did not measure HIV RNA in all HIV-infected participants during the 1980's.

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Table 2

Lung cancer incidence during follow-up among current and former smokers in the WIHS and the MACS.

	Baseline		Lung cancer incidence					
	N	%	N	P-yrs	IRper 100,000	95% CI		p-value
Cohort								
WIHS	2549[a]	37	37[b]	24376	151.8	106.9	209.2	<0.0001
MACS	4274	63	23[c]	45362	50.7	32.1	76.1	
HIV status								
Infected	3735	55	46	38645	119.0	87.2	158.8	0.001
Uninfected	3088	45	14	31093	45.0	24.6	75.6	
Total	6823	100	60	69738	86.0	65.7	110.7	

P-yrs = Person-years; IR = incidence rate; CI = confidence interval.

[a] Excludes 3 WIHS participants with lung cancer diagnosed prior to enrollment.

[b] Includes 31 HIV-infected and 6 HIV-uninfected women.

[c] Includes 15 HIV-infected and 8 HIV-uninfected men.

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Table 3

Unadjusted lung cancer IRs among the 6823 current and former smokers in the WIHS and the MACS.

	WIHS						MACS				
	# Lung Cancers	P-yrs	IR*	IRR (95% CI)	p-value		# Lung Cancers	P-yrs	IR*	IRR (95% CI)	p-value
Geographic location											
Central US	**6**	3320	180.7	1			9	20253	44.4	1	
East coast	18	12904	139.5	0.77 (0.29, 2.38)	0.73		5	10617	47.1	1.06 (0.28, 3.52)	1.00
West coast	13	8152	159.5	0.88 (0.31, 2.83)	0.97		9	14493	62.1	1.40 (0.49, 3.97)	0.63
Calendar year											
1984-1994	--	--	--				9	23491	38.3	1	
1995-2000	12	9671	124.1	1			5	7189	69.6	1.82 (0.48, 6.03)	0.43
2001-2011	25	14705	170.0	1.37 (0.66, 2.99)	0.47		9	14682	61.3	1.60 (0.56, 4.55)	0.44
Age											
<40	**2**	9172	21.8	1			2	18532	10.8	1	
40-49	13	10194	127.5	**5.85 (1.32, 53.36)**	**0.01**		9	15169	59.3	**5.50 (1.14, 52.30)**	**0.03**
50-59	17	4291	396.2	**18.17 (4.31, 162.07)**	**<0.0001**		8	8525	93.8	**8.70 (1.74, 84.02)**	**0.005**
60+	**5**	719	695.5	**31.88 (5.22, 334.96)**	**<0.0001**		4	3136	127.5	**11.82 (1.69, 130.71)**	**0.01**
Race											
Non-Black	**9**	10116	89.0	1			19	39314	48.3	1	
Black	28	14360	196.4	**2.21 (1.01, 5.32)**	**0.046**		4	6037	66.3	1.37 (0.34, 4.12)	0.73
Education											
> High school	**7**	7369	95.0	1			13	36940	35.2	1	
≤ High school	30	16946	177.0	1.86 (0.80-5.03)	0.18		10	8220	121.7	**3.46 (1.36-8.53)**	**0.009**
BMI											
<25	21	9885	212.4	1			18	32907	54.7	1	
25-30	**7**	7010	99.9	0.47 (0.17, 1.15)	0.11		0	2429	0.0	0.0 (0.0, 3.08)	0.56
>30	**8**	7420	107.8	0.51 (0.19, 1.19)	0.14		5	10018	49.0	0.91 (0.26, 2.55)	1.0

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	WIHS						MACS				
	# Lung Cancers	P-yrs	IR*	IRR (95% CI)	p-value		# Lung Cancers	P-yrs	IR*	IRR (95% CI)	p-value
Cumulative pack-years											
<10	**2**	11365	17.6	1			**2**	14609	13.7	1	
10 to 19	14	6144	227.9	**12.95 (2.97, 117.45)**	**<0.0001**		**1**	7975	12.5	0.92 (0.02, 17.60)	1.00
20 to 29	**6**	2940	204.1	**11.60 (2.07, 117.45)**	**0.003**		**2**	7112	28.1	2.05 (0.15, 28.33)	0.79
>=30	13	2583	503.3	**28.59 (6.48, 261.13)**	**<0.0001**		18	14448	124.6	**9.10 (2.18, 80.88)**	**0.0004**
Unknown	**2**						0				
History of asthma (WIHS only)											
No	15	15183	98.8	1			--				
Yes	22	9170	239.9	**2.43 (1.20, 5.03)**	**0.01**		--				
Recreational drug use											
Never	**4**	2662	240.6	1			**2**	3147	63.5	1	
Ever	33	22713	145.3	0.60 (0.21, 2.35)	0.49		21	42207	49.8	0.78 (0.19, 6.89)	0.96
Injection drug use											
Never	13	14506	89.6	1			18	39565	45.5	1	
Ever	24	9870	243.2	**2.71 (1.33, 5.80)**	**0.005**		**5**	5583	89.6	1.97 (0.57, 5.50)	0.29
HIV											
Infected	**6**	6634	90.4	1			**8**	24459	32.7	1	
Uninfected	31	17742	174.7	1.93 (0.79, 5.66)	0.18		15	20903	71.6	2.19 (0.87, 5.98)	0.10
Current CD4 (cells/ul, HIV+ only)											
<200	**9**	3340	269.4	2.21 (0.76, 6.58)	0.16		**5**	2625	72.3	**4.73 (1.02, 23.86)**	**0.047**
200 to 500	14	7793	179.7	1.47 (0.58, 4.05)	0.51		**6**	8297	72.3	1.80 (0.43, 8.65)	0.54
>500	**8**	6560	122.0	1			**4**	9937	40.3	1	
Nadir CD4 (cells/ul, HIV+ only)											
<200	17	7242	234.7	1.28 (0.42, 5.21)	0.90		8	5161	155.0	**8.00** (1.07, 355.31)	**0.04**
200 to 500	10	8279	120.8	0.66 (0.19, 2.87)	0.66		6	10532	57.0	2.94 (0.36, 135.37)	0.54

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	WIHS						MACS				
	# Lung Cancers	P-yrs	IR*	IRR (95% CI)	p-value		# Lung Cancers	P-yrs	IR*	IRR (95% CI)	p-value
>500	4	2173	184.1	1			1	5165	19.4	1	
Current HIV RNA (copies/ml, HIV+ only)											
≤400	10	7384	135.4	1			4	5492	72.8	1	
401 to 10, 000	10	4479	223.3	1.65 (0.62, 4.41)	0.37		1	2375	42.1	0.58 (0.01, 5.84)	1.00
10, 001 to 100, 000	6	3621	165.7	1.22 (0.37, 3.72)	0.88		4	3189	125.5	1.72 (0.32, 9.24)	0.66
> 100, 000	4	1362	293.7	2.17 (0.50, 7.52)	0.32		0	1216	0.0	0.0 (0.0, 6.84)	0.90
Unknown	1						0				
Peak HIV RNA (copies/ml, HIV+ only)											
<10, 000	6	4665	128.6	1			0	4915	0.0	1	
10, 001 to 100, 000	14	7100	197.2	1.53 (0.55, 4.87)	0.52		5	7798	64.1	∞ (0.58, ∞)	0.17
> 100, 000	11	5892	186.7	1.45 (0.49, 4.78)	0.63		8	5570	143.6	00 (1.51, ∞)	**0.01**
Unknown	0						2				
HAART experienced (HIV+ only)											
No	9	6107	147.4	1			8	12981	61.6	1	
Yes	22	11635	189.1	1.28 (0.57, 3.16)	0.67		7	7922	88.4	1.43 (0.44, 4.53)	0.65
Prior AIDS diagnosis (HIV+ only)											
No	11	9578	114.8	1			9	18472	48.7	1	
Yes	20	8164	245.0	2.13 (0.97, 4.93)	0.06		6	2431	246.8	5.07 (1.48, 15.94)	**0.01**

* IR: Incidence rate per 100, 000 person-years.

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Table 4

Multiple regression models for lung cancer incidence, WIHS and MACS combined.

	All years (1984-2011)			HAART era (1995-2011)		
	IRR	**95% CI**	**p-value for interaction with cohort***	**IRR**	**95% CI**	**p-value for interaction with cohort***
MACS vs. WIHS	0.59	0.27-1.29		0.54	0.23-1.25	
Calendar period						
1984 - 2000	**1**					
1995 - 2000				**1**		
2001-2011	0.80	0.42-1.53	0.52	0.82	0.41-1.64	0.61
Age						
<40	**1**			**1**		
40-49	**3.27**	**1.09-9.82**	0.76	3.95	0.89-17.59	NE**
50-59	**7.04**	**2.25-22.07**	0.90	**8.51**	**1.85-39.07**	NE**
60 and older	**11.52**	**3.23-41.09**	0.78	**15.98**	**3.15-80.98**	NE**
Black vs. non-Black Race	1.86	0.98-3.54	0.65	1.83	0.93-3.60	0.61
IDU (ever vs. never)	0.98	0.53-1.80	0.59	1.02	0.54-1.95	0.48
Education (≤ high school vs. > high school)	**2.29**	**1.20-4.39**	0.25	1.95	0.96-3.98	0.44
BMI (per 10 unit increase)	0.70	0.40-1.20	0.86	0.67	0.38-1.19	0.56
Pack-years of smoking						
<10	**1**			1		
10-30	**4.75**	**1.62-13.96**	0.14	**4.69**	**1.59-13.85**	0.16
>30	**11.09**	**3.72-33.11**	0.35	**8.73**	**2.85-26.73**	0.15
HIV and AIDS						
HIV-uninfected	1			1		
HIV+, AIDS-free	1.79	0.80-4.03	0.75	1.71	0.64-4.57	0.74
HIV+, Prior AIDS (not pneumonia)	0.93	0.39-2.22	0.08	0.82	0.32-2.07	0.14
HIV+, Prior AIDS pneumonia	**3.56**	**1.67-7.61**	0.22	**3.51**	**1.61-7.67**	0.08
Nadir CD4 (< 200 vs. >=200) ***	1.37	0.71-2.63	0.13	1.46	0.73-2.92	**0.03**
HAART (experienced vs. naïve) ***	0.72	0.34-1.52	0.80	0.74	0.32-1.67	0.60

BMI = body mass index; CI = confidence interval; HIV+ = HIV-infected; HIV- = HIV-uninfected; IDU = injection drug use; IRR = incidence rate ratio; NE = not evaluable.

* The p-value for an interaction between the given covariate and cohort tests whether the effect of the covariate differs between MACS and WIHS.

** Not evaluable because no lung cancers were diagnosed in MACS participants younger than 40 years old during the HAART era.

*** The nadir CD4 and HAART experience effects correspond only to HIV-infected participants.

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Table 5

Unadjusted and adjusted Cox proportional hazard analysis of survival following lung cancer diagnosis.

Characteristics at lung cancer diagnosis	# deaths/ participants**	Unadjusted		Adjusted *	
		HR	95% CI	HR	95% CI
Cohort					
WIHS MACS	29/36 16/20	1 1.12	0.61-2.07	1 1.18	0.44-3.13
Geographic location					
East/Central West	26/34 19/22	1 1.18	0.65-2.16		
Calendar period					
1984-1994 1995-2000 2001-2011	9/9 16/16 20/31	1 0.50 0.31	0.21-1.16 **0.14-0.70**	1 0.34 0.23	0.11 – 1.13 **0.07 – 0.71**
Decade of age at diagnosis	45/56	0.80	0.54-1.21	0.79	0.48-1.31
Black Race					
No Yes	19/27 26/29	1 1.04	0.57-1.88		
Cumulative pack-years (per 10 pack-years)	45/56	0.96	0.84-1.10		
≤ High school education					
No Yes	14/19 31/37	1 1.71	0.90-3.25		
Ever injected drugs					
No Yes	22/30 23/26	1 1.65	0.88-3.12	1 **2.98**	**1.28 - 6.95**
HIV infected					
No Yes	11/14 34/42	1 0.76	0.38-1.51	1 0.61	0.29 – 1.30
Histologic Type					
Adenocarcinoma Squamous cell carcinoma Non-small cell carcinoma All others/Unknown	14/21 8/8 8/8 15/19	1 1.62 1.39 1.10	0.68 – 3.86 0.69 – 3.93 0.24 – 1.90		

HR = hazard ratio; CI = confidence interval.

* The covariates for study cohort, age, and HIV infection were forced into the adjusted model.

** Excludes 4 participants with no follow-up after lung cancer diagnosis.