Title

Risk of smoking-related cancers among women and men living with and without HIV.

Journal

AIDS, 35(1)

ISSN

0269-9370

Authors

Hessol, Nancy A
Barrett, Benjamin W
Margolick, Joseph B
et al.

Publication Date

2021

DOI

10.1097/qad.0000000000002717

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

AIDS. 2021 January 01; 35(1): 101–114. doi:10.1097/QAD.0000000000002717.

RISK OF SMOKING-RELATED CANCERS AMONG WOMEN AND MEN LIVING WITH AND WITHOUT HIV

Nancy A. HESSOL[1,2], **Benjamin W. BARRETT**[3], **Joseph B. MARGOLICK**[4], **Michael PLANKEY**[5], **Shehnaz K. HUSSAIN**[6], **Eric C. SEABERG**[3], **L. Stewart MASSAD**[7]

[1]Department of Clinical Pharmacy, University of California, San Francisco, CA, USA

[2]Chicago Cook County Clinical Research Site of the MWCCS, Chicago, IL, USA

[3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[4]Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[5]Department of Medicine, Georgetown University, Washington DC, USA

[6]Cedars-Sinai Cancer and Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

[7]Department of Obstetrics and Gynecology, Washington University School of Medicine in St Louis, St Louis, MO, USA

Abstract

OBJECTIVES: We investigated whether the effect of smoking on the incidence of smoking-related cancers differs by HIV-infection status, if sex modifies the impact of risk factors for smoking-related cancers, and the sex-specific attributable risk of smoking on cancer incidence.

DESIGN: Data from two large prospective studies in the United States were analyzed: 6,789 men in the Multicenter AIDS Cohort Study from 1984–2018 and 4,423 women in the Women's Interagency HIV Study from 1994–2018.

METHODS: Incidence rates (IRs), relative risks, and adjusted population attributable fractions (PAFs) were calculated for smoking-related cancers.

RESULTS: During study follow-up, there were 214 incident smoking-related cancers in the men and 192 in the women. The age-adjusted IRs for smoking-related cancers were higher in the women (392/100,000) than for the men (198/100,000; $p<0.01$) and higher for people living with HIV (PLWH, 348/100,000) than for those without HIV (162/100,000; $p<0.01$). Unadjusted IRs in

Address for correspondence and reprints: Nancy A. Hessol, University of California San Francisco, Department of Clinical Pharmacy, 3333 California Street, Suite 420, San Francisco, CA 94143-0613. Nancy.Hessol@ucsf.edu.

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

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.

Supplemental Digital Content 1. Table that lists the incident cancers diagnosed in the MACS and WIHS. Pdf

PLWH were higher than in those without HIV when stratifying by cumulative pack-years of smoking (all p-values<0.01). In adjusted interaction models, the effects of cumulative pack-years of smoking were significantly stronger in women. The adjusted PAFs for smoking-related cancers were non-significantly higher in the women than in the men (39% vs. 28%; p=0.35).

CONCLUSIONS: HIV looks to be an independent risk factor for smoking-related cancers and women appear to have a greater risk than men. These results highlight the need for interventions to help PLWH, especially women, quit smoking and sustain cessation to reduce their risk of smoking-related cancers.

Keywords

cancer; HIV infection; incidence; risk factors; sex differences; smoking

INTRODUCTION

As people living with HIV (PLWH) are aging, largely due to effective ART, cancer - particularly non-AIDS defining cancer - has become a more common cause of morbidity and mortality.[1] The high prevalence of cancer risk factors among PLWH, especially tobacco use, contributes to the increased risk of cancer. In the United States (U.S.), the estimated percentage of adult PLWH who smoke was twice that of the U.S. general population and the smoking prevalence varied by HIV risk behavior groups.[2–4] A better understanding of the contribution of smoking to the development of cancer in PLWH can help promote smoking cessation among smokers living with HIV.

In 2010, approximately 29% of all cancer deaths in the U.S. were attributable to cigarette smoking.[5] The contribution of smoking to the cancer burden among PLWH is less well-defined. In a study of PLWH in Denmark, the estimated percentage of smoking-related cancer diagnoses attributable to smoking was 91%.[6]

A limitation of prior studies investigating cancer risk in PLWH has been the lack of an appropriate comparison group, which has traditionally been the general population. People LWH are very different from the general population and thus comparisons are confounded by other cancer risk factors like cigarette smoking, Human Papilloma Virus (HPV) and Hepatitis C Virus (HCV) infection, and substance use. For example, women in the Women's Interagency HIV Study (WIHS) had a high prevalence of smoking (more than twice the national average) independent of HIV status.[7] Similarly, the prevalence of smoking in the men with and without HIV in the Multicenter AIDS Cohort Study (MACS) is almost twice as high as the national average.[8]

The present study has the unique advantage of a highly similar HIV-uninfected comparison group, as well as the ability to precisely adjust for potential confounders and examine sex-related differences. This investigation had three aims. First, to determine whether the effect of smoking on the incidence of smoking-related cancers differs by HIV-infection status among participants in the MACS and WIHS. We hypothesized that for a given smoking history, the incidence of smoking-related cancers would be higher among PLWH vs. those without HIV.[6] Second, to determine whether sex modifies the impact of cancer risk factors

among WIHS and MACS participants. We hypothesized that the adjusted risk of smoking-related cancers would be higher among women (both with and without HIV) than among men.[9] Third, to estimate the sex-specific attributable risk of smoking on smoking-related cancers among women in the WIHS and men in the MACS. We hypothesized that approximately 50% of smoking-related cancers would be prevented if PLWH refrained from smoking.[10]

METHODS

Study population

Data collected through September 30, 2019, from participants in two U.S. HIV/AIDS cohort studies, the WIHS and the MACS, were used for this investigation. The WIHS is a multi-site prospective cohort study of 4,982 women with or at risk for HIV established in 1994. Women were enrolled at one of eleven centers across the U.S. and returned at 6-month intervals for a standardized interview-based questionnaire, physical examination including pelvic exam, Pap test with referral for colposcopy for any abnormality, and collection of blood for laboratory testing and storage. Detailed information about the WIHS study methodology and baseline characteristics of enrollees has been published.[11, 12]

The MACS is a multi-site prospective cohort study of 7,358 men who reported having had sex with men. Men were enrolled, starting in 1984, at four metropolitan areas in the U.S. Details about the recruitment and characteristics of the MACS cohort have been reported elsewhere.[13] Participants returned at 6-month intervals for a detailed interview, physical examination, and collection of blood for laboratory testing and storage.

Participants who had at least one follow-up visit, reported their history of tobacco use, and entered the study without a prior or prevalent (diagnosed within six months of study enrollment) smoking-related cancer were included in these analyses (6,789 men and 4,423 women). All analyses were performed using data collected through September 30, 2019, but follow-up was censored on December 31, 2018 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 [14]). The institutional review boards of each institution approved these studies; all participants provided written informed consent.

Cancer diagnosis

Cancer diagnoses were ascertained using medical records, cancer registry matches, and death certificates. Each confirmed cancer was classified according to the SEER site recoding scheme, which is based on the International Classification of Diseases for Oncology 3rd edition, [15] and all cancers with an initial diagnosis date that was at least six months after enrollment into the cohort study (to account for a lag time in diagnosis) were further classified as ‘incident’ cancers. We then identified smoking-related incident cancers: lung/bronchus, larynx, liver, colon, rectum, small intestine, kidneys, oral cavity, nose and middle ear, acute myeloid leukemia, cervix, vagina, vulva, penis, anus, pancreas, esophagus, bladder, and stomach.[16–18] We created a single combined endpoint where the first

occurrence of any of these cancers was treated as an event. Those who developed a non-smoking-related cancer continued in follow-up.

Risk factors for cancer

The independent variables included several known cancer risks, such as tobacco use, alcohol consumption, illicit substance use, body mass index (BMI), and coinfection with HPV and HCV. Other variables included sociodemographic characteristics, behavioral factors, characteristics of HIV infection, geographic region, and calendar period. For further details regarding independent variables, see Appendix.

Statistical Analysis—Study participants were characterized at baseline using standard descriptive statistics. Smoking-related cancer incidence rates (IRs) were computed as the number of observed incident cancers divided by person-years of follow-up, where follow-up time was measured from six months after the baseline visit until the earliest of the first smoking-related cancer diagnosis, death, or date of the last study visit. Incidence rates of smoking-related cancers were adjusted for age and compared by cumulative pack-years smoked lagged by 10 years (since smoking-related cancers take at least 10 years to manifest) [19], years since smoking cessation, HIV status, and sex (MACS vs. WIHS). HIV serostatus was considered as a time-varying variable to allow for the possibility of HIV seroconversion during follow-up (see Appendix).

Smoking-related cancer IR comparisons were quantified using the incidence rate ratio (IRR) and performed using exact Poisson regression wherever possible. For the IRR analyses, the dependent (outcome) variable for this investigation was smoking-related cancer, yes or no. The effects of HIV-related variables were examined in two ways. First, unadjusted models were stratified by HIV serostatus. Second, pooled univariate models included indicator variables for HIV infection with and without the exposure of interest, compared to the HIV-uninfected reference group. All variables collected at each study visit (see Appendix) were evaluated using time-varying covariates. Interaction terms were added to the final multiple regression models to determine whether a covariate effect differed significantly by sex.

To explore the possibility that higher AIDS-related morbidity and mortality during the pre- and early ART era lowered the smoking-related cancer incidence rates and altered the effects of certain risk factors on cancer incidence, we repeated the multivariable analyses using only follow-up time accrued between 2001 and 2018 (the modern ART treatment era). Since several of the smoking-related cancers may also have viral etiologies, we repeated the age-adjusted IR and adjusted IRR analyses and excluded anal, cervix, gum and mouth, larynx, liver, penis, pharyngeal, salivary gland, stomach, tongue, tonsil, and vagina/vulva cancers from the definition of smoking-related cancers to see how this impacted the association between smoking history and the development of smoking-related malignancies. Last, since anal cancers were three times more common in men than women, we repeated the adjusted population attributable fraction (PAF) analyses excluding anal cancers from the definition of smoking-related cancers to assess sex differences for the remaining smoking-related malignancies.

Pooled as well as stratified (MACS and WIHS) relative risks and adjusted PAFs were calculated for 1) all incident smoking-related cancers; 2) cancers strongly associated with smoking (lung/bronchus and larynx; average PAF range in men and women combined 78-97%); 3) cancers moderately associated with smoking (esophagus, gum and mouth, lip, nose and middle ear, pharyngeal, and lower urinary tract; PAF range 31-60%); and 4) cancers weakly associated with smoking (acute myeloid leukemia, anal, cervix, colon/rectum, liver, pancreas, penis, salivary gland, small intestine, stomach, tongue, tonsil, and vagina/vulva; PAF range 8-25%).[20] For additional details regarding the PAF models and SAS macro [21], see Appendix. All analyses were performed using SAS 9.4.[22]

RESULTS

Of the potentially eligible participants enrolled in the MACS (7,358) and the WIHS (4,982), 569 men and 559 women were excluded due to either no accrual of follow-up time (473 men and 376 women), lack of information about pack-years of smoking (89 men and 148 women) or because they had a smoking-related cancer prior to or within six months of their baseline visit (7 men and 35 women).

The remaining 4,423 WIHS and 6,789 MACS participants exhibited many significant differences at baseline (Table 1). Most notably, men were enrolled in earlier years and at younger ages; were more likely to be non-Latinx white and HIV-uninfected; had more education, higher household incomes, lower BMIs, and more lifetime sex partners; and consumed more alcohol (all $p<0.01$). Women were more likely to smoke and had a higher prevalence of HCV, HIV, lower CD4 cell counts, higher HIV viral loads, and a greater prevalence of clinical AIDS (all p-values<0.01).

Smoking-related cancer incidence

We observed 214 smoking-related incident cancers among the MACS participants and 192 among the WIHS (see Table, Supplemental Digital Content 1). The majority of smoking-related cancers were lung/bronchus and were diagnosed in the modern ART era. Seven men and eight women had more than one primary smoking-related malignancy.

The age-adjusted IR for smoking-related cancers was higher among PLWH than participants without HIV ($p<0.01$) and higher among women than men ($p<0.01$; Table 2). Among those who smoked, incidence ratios among PLWH were higher than among those without HIV when stratifying by cumulative pack-years of smoking (all p-values<0.01). When the smoking-related cancer IRs among all women were compared to all men, the IRR was 2.0 (95% CI: 1.6-2.4). For women with HIV vs. men with HIV the IRR was 1.6 (95% CI: 1.2-2.0) and for women without HIV vs. men without HIV the IRR was 2.0 (95% CI: 1.3-3.0). Ten or more years since cessation of smoking resulted in a reduced IR of smoking-related cancers ($p<0.01$).

In unadjusted analysis and for participants without HIV, IRRs for smoking-related cancers were higher for older ages, non-Latinx blacks compared to non-Latinx whites, increasing cumulative pack-years of smoking compared to never smokers, those with a history of injecting drugs, and those with HCV at baseline (Table 3). People without HIV with more

years of education also had lower unadjusted IRRs for smoking-related cancers. Similar results were seen for PLWH, with higher unadjusted IRRs for smoking-related cancers associated with older age, non-Latinx blacks, higher cumulative pack-years of smoking, history of injecting drugs, and HCV infection at baseline. Lower IRRs were associated with more years of education, as well as greater household income. In PLWH, higher IRRs were associated with having a prior AIDS diagnosis and exposure to ART, and lower IRRs associated with having CD4 cell counts ≥200.

In adjusted analyses combining participants with and without HIV, the variables that remained significantly associated with an increased IRR for smoking-related cancer were ages 40 and above, 11 or more cumulative pack-years of smoking, and having HIV with or without a prior AIDS diagnosis (Table 4, column 2). Factors associated with a decreased IRR for smoking-related cancers were annual household income ≥$30,000 and for PLWH, having CD4 cell counts >200. Significant cohort interactions (Table 4, column 3) were observed for age 40-49 years (effect stronger in the WIHS), other race (effect stronger in the MACS), smoking 1-20 cumulative pack-years (effect stronger in the WIHS), and among PLWH for CD4 cell counts of 200-500 cells (effect stronger in the MACS). In analyses that were restricted to only those alive in the modern ART era (year ≥2001), exposures significantly associated with an increased or decreased risk of smoking-related cancers (Table 4, columns 4 and 5) were highly similar to those for all years (Table 4, columns 2 and 3). Additionally, PLWH in the modern ART era who had a detectable HIV viral load had a lower risk for these cancers (Table 4, column 4).

Excluding virus-associated cancers from the definition of smoking-related cancers did not affect the association between smoking and smoking-related cancer risk, but did affect the observed differences between PLWH and people without HIV (data not shown). This suggests that PLWH are more likely to develop virus-associated cancers than people without HIV, and that those cancers may have contributed to the higher incidence of smoking-related cancers in PLWH. Excluding just anal cancer from the definition of smoking-related cancers strengthened the association between smoking and smoking-related cancer incidence among both the men and the women equally (data not shown).

Based on adjusted PAF models with cumulative pack-years groups of 0-5 pack-years (reference), 6-20 pack-years, and >20 pack-years, an estimated 34% (95% CI: 21–46%) of all smoking-related cancers were attributable to smoking cigarettes among all participants, 31% (95% CI: 15–45%) among PLWH, and 41% (95% CI: 13–60%) among participants without HIV (Figure 1). The adjusted PAFs were non-significantly higher in the women than in men: 39% vs. 28% for all participants (p=0.35), 34% vs. 25% among PLWH (p=0.58), and 67% vs. 27% among those without HIV (p=0.11). When virus-associated cancers were removed from these analyses, the point estimates were higher in all groups but still well within the 95% CI of the full sample results (data not shown).

When cancer types were stratified by the strength of their association with smoking, the adjusted PAF estimates were 85% (95% CI: 60–94%), 19% (95% CI: −24–47%), and 14% (95% CI: −6–30%) for cancers strongly, moderately, and weakly associated with smoking, respectively (Figure 1). In these stratified analyses, the adjusted PAFs were not significantly

different for women compared to men. The removal of virus-associated malignancies increased the point estimate for cancers strongly associated with smoking while the point estimates for cancers moderately and weakly associated with smoking fluctuated but all were still within the 95% CI of the total sample (data not shown).

DISCUSSION

With over 139,500 person-years of follow-up, this is one of the largest cohort studies to examine the contribution of smoking on the cancer burden among PLWH relative to highly similar people without HIV. Among those with a history of smoking, the observed incidence of smoking-related cancers was significantly higher among PLWH than participants without HIV, as hypothesized in our aim 1. This reaffirms that HIV infection is associated with a higher risk of smoking-related cancers beyond what would be expected from cigarette smoking alone, a finding reported in previous studies.[6, 23–25] However, these prior studies did not have a highly similar comparison group of participants without HIV or detailed smoking and other behavioral histories, as in the present study.

In both minimally and fully adjusted analyses, we observed that women have a higher risk of smoking-related cancers than men. The reasons for this are unclear and the exact mechanism may be confounded by unmeasured factors that might differentially and adversely affect women - such as the environment (air pollution and second-hand smoke), genetics, physiology, and hormones. The majority of the women in this study were African American and had fewer pack-years of smoking than the men. Studies indicate that African American smokers have a higher risk for lung cancer compared to whites, [26] and this racial difference is most pronounced at lower levels of daily cigarette consumption.[27] In addition, women appear to have a higher incidence of lung cancer than men. [28–30] This may be due to an increased susceptibility to tobacco carcinogens among women, smaller lung size in women, or the effect of hormones in carcinogenesis, such as the role of estrogens as promoters of lung cancer.[29, 31, 32]

In our PAF models that pooled men and women, an estimated 31% (95% CI: 15–45%) of all smoking-related cancers were attributed to smoking more than 5 pack-years in a lifetime among PLWH. This is within the range reported by other studies of PLWH[10, 33, 34], although we found higher estimates for women than for men. Our investigation has the added advantage of a more precise adjustment for smoking, as well as adjustment for other important confounders such as CD4 cell count, HIV viral load detectability, and exposure to ART. Varying degrees of association between smoking and smoking-related cancers likely influenced our PAF estimates. When smoking-related cancers were stratified by strength of association, the estimated PAF for cancers strongly associated with smoking (lung, bronchus, and larynx) was 74% among men and 87% among women. When we removed laryngeal cancers from this group (a virus-associated cancer[35]), the PAF was 86% for men and 93% for women suggesting that inclusion of virus-related cancers may dilute the effect of smoking on these cancers. Our estimates for lung and bronchial cancers are higher than estimates reported in other studies of the general population (men 75–84% and women 70–79%).[16] Our estimates were similar to another study of PLWH (82–98% for lung cancer)

[10] which supports the interpretation that HIV is a risk factor for cancers that are strongly associated with smoking.

There is a substantial burden of smoking-related cancers among PLWH and unless the high prevalence of cigarette smoking is reduced, this will likely increase over time due to increasing longevity among PLWH on ART. One study reported that among PLWH who adhere to ART, smoking is projected to be a much greater health threat than HIV.[36] Another study assessed the impact of smoking cessation on cancer risk among PLWH and observed that the lung cancer IR was reduced by more than half but was still elevated five years after cessation (from an adjusted IRR of 19.08 to 8.69), while the incidence of other smoking-related cancers was found to decline to that of non-smokers after 1–2 years of cessation (from an adjusted IRR of 2.06 to 1.32).[37]

In addition to smoking-related cancers, preventing the initiation of smoking and smoking cessation lessens the burden for all smoking-related diseases. For PLWH this is especially important given the elevated risk for several other diseases that can be exacerbated by smoking, including CVD, pulmonary infections, COPD, and pneumonia.[33, 38–40]

This investigation was not without limitations. First, certain smoking-related cancers, such as gum and mouth, had very few events – perhaps due to competing causes of death among PLWH. Our risk estimates for smoking-related cancers may therefore be biased towards the null. Despite this limitation, we were able to demonstrate significantly elevated risk of these cancers among PLWH compared to highly similar people without HIV. Second, these two cohorts of men and women differed in other ways besides sex and we were unable to adjust for unmeasured risk factors such as the living environment (second hand smoke, air pollution, etc.), which may have contributed to their cancer burden. Nevertheless, we were able to adjust our analyses for many other potential risk factors – far more than most other studies that have investigated the cancer burden in PLWH. Last, as per WIHS protocol the women received screening for cervical, vaginal, and vulvar cancers. Screening may have led to treatment of pre-cancers and reduced the cancer burden for these malignancies. Earlier cancer detection from screening may have also resulted in those cancers occurring at lower cumulative pack-years of smoking and therefore attenuated the effect estimates between smoking and smoking-related cancer incidence.

The strengths of this longitudinal study include a large and diverse sample with many person-years of follow-up, a highly similar comparison group of people without HIV infection, detailed baseline and follow-up social and clinical histories, and a study period that spans the pre-ART, early ART, and current ART era. Notably, the adjusted IRR point estimates for smoking-related cancer risk factors among participants in the modern ART era were virtually identical to the estimates among participants across all years, indicating that these have not dramatically changed since the introduction of potent therapy. Because of these strengths, we were able to do what few, if any, have been able to do before us: compare men to women and those with and without HIV, as well as to fully adjust our models for a multitude of potential cancer-causing risk factors.

Our results, along with those from prior well-designed observational studies, provide strong evidence of the excess risk of smoking-related cancers among PLWH who smoke compared to smokers without HIV. What is novel in our study are the sex differences, with women LWH having a greater risk of smoking-related cancers than men LWH. These data lend strong support for integrating smoking cessation interventions into ongoing HIV programs and educating PLWH, especially women, about the harm of smoking and the benefits of quitting to reduce their risk of smoking-related cancers. There is indisputable evidence of the harm caused by smoking in PLWH and an equally clear opportunity for health care providers to intervene as part of comprehensive care of PLWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Data in this manuscript were collected by the MACS/WIHS Combined Cohort Study (MWCCS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). MWCCS (Principal Investigators): Atlanta CRS (Ighovwerha Ofotokun, Anandi Sheth, and Gina Wingood), U01-HL146241; Baltimore CRS (Todd Brown and Joseph Margolick), U01-HL146201; Bronx CRS (Kathryn Anastos and Anjali Sharma), U01-HL146204; Brooklyn CRS (Deborah Gustafson and Tracey Wilson), U01-HL146202; Data Analysis and Coordination Center (Gypsyamber D'Souza, Stephen Gange and Elizabeth Golub), U01-HL146193; Chicago-Cook County CRS (Mardge Cohen and Audrey French), U01-HL146245; Chicago-Northwestern CRS (Steven Wolinsky), U01-HL146240; Connie Wofsy Women's HIV Study, Northern California CRS (Bradley Aouizerat and Phyllis Tien), U01-HL146242; Los Angeles CRS (Roger Detels), U01-HL146333; Metropolitan Washington CRS (Seble Kassaye and Daniel Merenstein), U01-HL146205; Miami CRS (Maria Alcaide, Margaret Fischl, and Deborah Jones), U01-HL146203; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo), U01-HL146208; UAB-MS CRS (Mirjam-Colette Kempf and Deborah Konkle-Parker), U01-HL146192; UNC CRS (Adaora Adimora), U01-HL146194. The MWCCS is funded primarily by the National Heart, Lung, and Blood Institute (NHLBI), with additional co-funding from the Eunice Kennedy Shriver National Institute Of Child Health & Human Development (NICHD), National Human Genome Research Institute (NHGRI), National Institute On Aging (NIA), National Institute Of Dental & Craniofacial Research (NIDCR), National Institute Of Allergy And Infectious Diseases (NIAID), National Institute Of Neurological Disorders And Stroke (NINDS), National Institute Of Mental Health (NIMH), National Institute On Drug Abuse (NIDA), National Institute Of Nursing Research (NINR), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). MWCCS data collection is also supported by UL1-TR000004 (UCSF CTSA), UL1-TR003098 (Johns Hopkins Institute for Clinical and Translational Research (ICTR), P30-AI-050409 (Atlanta CFAR), P30-AI-050410 (UNC CFAR), and P30-AI-027767 (UAB CFAR).

We would like to acknowledge the National Program of Cancer Registries of the Centers for Disease Control and Prevention (CDC) for the funds that helped support the collection and availability of the cancer registry data and thank the following state cancer registries for their help: AL, CA, FL, GA, IL, MD, MS, NY, NC, OH, PA, and VA. The authors assume full responsibility for analyses and interpretations of these data.

Sources of funding: National Institutes of Health

APPENDIX

Pack-years of smoking were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Cumulative pack-years of smoking was constructed by summing collected smoking pack-year data. In cases of missing pack-year data, values of cumulative pack-years were interpolated using per-person observed smoking trends. Cumulative pack-years of smoking was then lagged by 10 years for use in analyses. Data values for lagged cumulative pack-years that were within the 10 year lag window were interpolated using per-person historical smoking data collected by the studies,

such as age started smoking, age quit smoking, and average number of cigarette packs smoked per day. Smoking status at a study visit was coded as never, former, and current. Years since smoking cessation was calculated only for former smokers, and the year count reset if an individual quit smoking for a period but then restarted.

Age was categorized as <40 years, 40–49 years, 50–59 years, and ≥60 years. Alcohol consumption since last study visit was categorized as abstainer, zero to seven drinks/week, seven to 12 drinks/week, and greater than 12 drinks/week. Illicit substance use since last study visit was subdivided into smoking, injecting, or taking an illicit drug not through smoking/injection. BMI was measured per visit. Coinfection with HPV at a study visit was divided into any HPV and oncogenic HPV. WIHS participants were tested far more frequently for HPV than MACS participants.

Race/ethnicity was recorded at study enrollment, and categorized as non-Latinx white, non-Latinx black, and other. Educational attainment was also recorded at enrollment, and coded into high school or less, some college, college graduate, and at least some postgraduate education. Household income was measured at each study visit, and categorized as less than $29,999 and $30,000 and above. Missing values of household income were interpolated with data collected within six months of the missing value.

Geographic region was categorized as west coast, east coast, and Midwest and based on the location of study recruitment. Calendar period was categorized as before 1996 and with three year intervals from then on. History of injection drug use was coded as positive if an individual reported to ever having used injection drugs. Lifetime number of sexual partners was treated as time-varying, and updated with each round of newly collected data at a study visit.

HIV serostatus was assessed at each study visit. CD4 cell count and HIV RNA level were measured at each study visit. CD4 cell count was explored as cell count at a visit, pre-ART nadir CD4 cell count, and post-ART nadir CD4 cell count. HIV RNA level was examined with a variable indicating if the HIV viral load was detectable (defined as > 500 copies/ml, as this was the common cutoff among all HIV viral load assays used throughout study follow-up), if the viral load was below or above 4,000 copies/ml, and the peak HIV viral load. ART use was collected at each study visit, and analyzed as a variable indicating exposure to ART. Similarly, a prior history of clinical AIDS (using the CDC case definition, [41] and excluding those individuals whose AIDS diagnosis was based solely on CD4 cell count) was collected at each study visit, and analyzed as a time-varying covariate.

An individual contributed person-time to the HIV serostatus group they belonged to at a given study visit. In the event of a seroconversion during follow-up (443 men and 17 women), the date of seroconversion was defined as the midpoint between the last HIV seronegative test and the first HIV seropositive test. Person-time occurring before the date of seroconversion was added to the HIV seronegative group and person-time occurring after the date of seroconversion was applied to the HIV seropositive group.

PAFs were calculated relative to a model with all cumulative pack-year values (lagged by 10 years) set to 0–5 pack-years, and were adjusted for age, race/ethnicity, annual household

income, alcohol use, history of injection drug use, baseline hepatitis C infection status, HIV status, and study cohort. The HIV seropositive-specific model did not adjust for history of clinical AIDS, and instead adjusted for CD4 cell count, detectable HIV viral load, and exposure to ART. To assess the contribution of smoking-related cancers that also had viral etiologies, we repeated the PAF analyses and removed this subset of malignancies. The PAFs were calculated using a SAS macro provided by Laaksonen and colleagues.[21]

REFERENCES

1. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst 2011; 103(9):753–762. [PubMed: 21483021]
2. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med 2015; 162(5):335–344. [PubMed: 25732274]
3. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current Cigarette Smoking Among Adults - United States, 2005–2015. MMWR Morb Mortal Wkly Rep 2016; 65(44):1205–1211. [PubMed: 27832052]
4. Lifson AR, Lando HA. Smoking and HIV: prevalence, health risks, and cessation strategies. Curr HIV/AIDS Rep 2012; 9(3):223–230. [PubMed: 22618079]
5. Jacobs EJ, Newton CC, Carter BD, Feskanich D, Freedman ND, Prentice RL, et al. What proportion of cancer deaths in the contemporary United States is attributable to cigarette smoking? Ann Epidemiol 2015; 25(3):179–182 e171. [PubMed: 25487970]
6. Helleberg M, Gerstoft J, Afzal S, Kronborg G, Larsen CS, Pedersen C, et al. Risk of cancer among HIV-infected individuals compared to the background population: impact of smoking and HIV. AIDS 2014; 28(10):1499–1508. [PubMed: 24785952]
7. 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.
8. Akhtar-Khaleel WZ, Cook RL, Shoptaw S, Surkan P, Stall R, Beyth RJ, et al. Trends and Predictors of Cigarette Smoking Among HIV Seropositive and Seronegative Men: The Multicenter Aids Cohort Study. AIDS Behav 2016; 20(3):622–632. [PubMed: 26093780]
9. Hessol NA, Martinez-Maza O, Levine AM, Morris A, Margolick JB, Cohen MH, et al. Lung cancer incidence and survival among HIV-infected and uninfected women and men. AIDS 2015; 29(10):1183–1193. [PubMed: 25888645]
10. Altekruse SF, Shiels MS, Modur SP, Land SR, Crothers KA, Kitahata MM, et al. Cancer burden attributable to cigarette smoking among HIV-infected people in North America. AIDS 2018; 32(4):513–521. [PubMed: 29239891]
11. 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(9):1013–1019. [PubMed: 16148165]
12. 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(2):117–125. [PubMed: 9504278]
13. 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]
14. Hofferkamp J Standards for Cancer Registries Volume III: Standards for Completeness, Quality, Analysis, Management, Security and Confidentiality of Data. In. Springfield, Ill: North American Association of Central Cancer Registries; 8 2008.
15. Surveillance E, and End Results (SEER) Program. Surveillance Research Program, Cancer Statistics Branch In. SEER 9 Regs Public-Use (1973–2001) ed: National Cancer Institute, Division of Cancer Control and Population Science; 2004.

16. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018; 68(1):31–54. [PubMed: 29160902]
17. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.
18. Moore TO, Moore AY, Carrasco D, Vander Straten M, Arany I, Au W, et al. Human papillomavirus, smoking, and cancer. J Cutan Med Surg 2001; 5(4):323–328. [PubMed: 11907844]
19. Peto J That the effects of smoking should be measured in pack-years: misconceptions 4. Br J Cancer 2012; 107(3):406–407. [PubMed: 22828655]
20. Freedman ND, Abnet CC, Caporaso NE, Fraumeni JF Jr., Murphy G, Hartge P, et al. Impact of changing US cigarette smoking patterns on incident cancer: risks of 20 smoking-related cancers among the women and men of the NIH-AARP cohort. Int J Epidemiol 2016; 45(3):846–856. [PubMed: 26411408]
21. Laaksonen MA, Virtala E, Knekt P, Oja H, Harkanen T. SAS Macros for Calculation of Population Attributable Fraction in a Cohort Study Design. J Stat Softw 2011; 43(7):1–25.
22. SAS Institute Inc. SAS/STAT User's Guide, Version 9.4. In. Cary, North Carolina: SAS Institute Inc.; 2014.
23. Kirk GD, Merlo C, P OD, 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(1):103–110. [PubMed: 17554710]
24. 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(4):510–515. [PubMed: 20838223]
25. 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(8):1017–1025. [PubMed: 22382152]
26. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin 2004; 54(2):78–93. [PubMed: 15061598]
27. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med 2006; 354(4):333–342. [PubMed: 16436765]
28. Thomas L, Doyle LA, Edelman MJ. Lung cancer in women: emerging differences in epidemiology, biology, and therapy. Chest 2005; 128(1):370–381. [PubMed: 16002959]
29. Henschke CI, Yip R, Miettinen OS. Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer. JAMA 2006; 296(2):180–184. [PubMed: 16835423]
30. Pakkala S, Chen Z, Rimland D, Owonikoko TK, Gunthel C, Brandes JR, et al. Human immunodeficiency virus-associated lung cancer in the era of highly active antiretroviral therapy. Cancer 2011.
31. Marquez-Garban DC, Pietras RJ. Estrogen-signaling pathways in lung cancer. Adv Exp Med Biol 2008; 617:281–289. [PubMed: 18497051]
32. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. J Natl Cancer Inst 1996; 88(3–4):183–192. [PubMed: 8632492]
33. Althoff KN, Gebo KA, Moore RD, Boyd CM, Justice AC, Wong C, et al. Contributions of traditional and HIV-related risk factors on non-AIDS-defining cancer, myocardial infarction, and end-stage liver and renal diseases in adults with HIV in the USA and Canada: a collaboration of cohort studies. Lancet HIV 2019; 6(2):e93–e104. [PubMed: 30683625]
34. Lifson AR, Neuhaus J, Arribas JR, van den Berg-Wolf M, Labriola AM, Read TR. Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial. Am J Public Health 2010; 100(10):1896–1903. [PubMed: 20724677]

35. Li X, Gao L, Li H, Gao J, Yang Y, Zhou F, et al. Human papillomavirus infection and laryngeal cancer risk: a systematic review and meta-analysis. J Infect Dis 2013; 207(3):479–488. [PubMed: 23175764]

36. Reddy KP, Kong CY, Hyle EP, Baggett TP, Huang M, Parker RA, et al. Lung Cancer Mortality Associated With Smoking and Smoking Cessation Among People Living With HIV in the United States. JAMA Intern Med 2017; 177(11):1613–1621. [PubMed: 28975270]

37. Shepherd L, Ryom L, Law M, Petoumenos K, Hatleberg CI, d'Arminio Monforte A, et al. Cessation of Cigarette Smoking and the Impact on Cancer Incidence in Human Immunodeficiency Virus-infected Persons: The Data Collection on Adverse Events of Anti-HIV Drugs Study. Clin Infect Dis 2019; 68(4):650–657. [PubMed: 29912335]

38. Bigna JJ, Kenne AM, Asangbeh SL, Sibetcheu AT. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. Lancet Glob Health 2018; 6(2):e193–e202. [PubMed: 29254748]

39. Benard A, Mercie P, Alioum A, Bonnet F, Lazaro E, Dupon M, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000–2007. PLoS One 2010; 5(1):e8896. [PubMed: 20126646]

40. Fitzpatrick ME, Kunisaki KM, Morris A. Pulmonary disease in HIV-infected adults in the era of antiretroviral therapy. AIDS 2018; 32(3):277–292. [PubMed: 29194119]

41. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection--United States, 2014. MMWR Recomm Rep. 2014;63(RR-03):1–10.

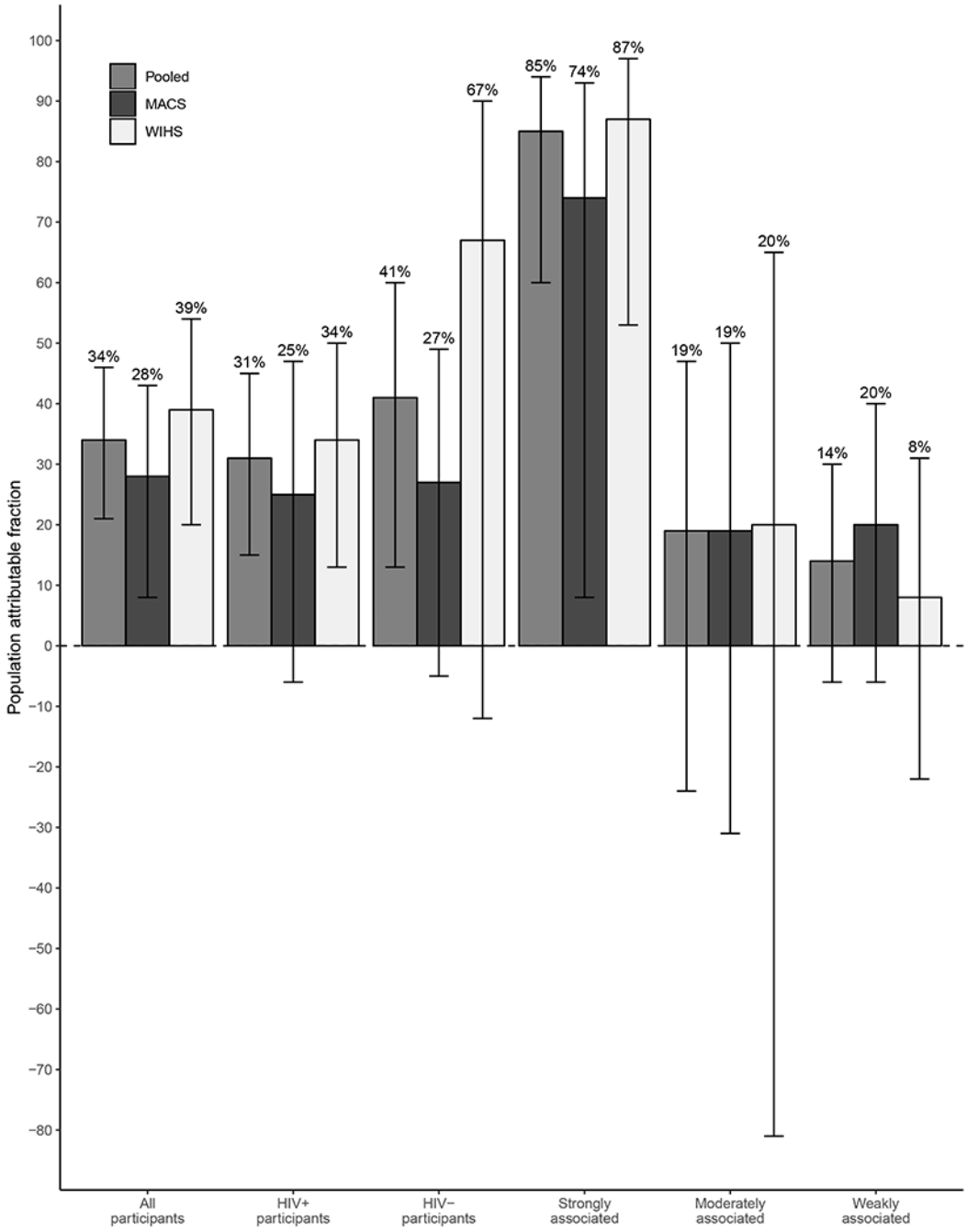

Figure 1. Adjusted population attributable fractions of smoking on smoking-related cancer incidence in the MACS and WIHS

PAFs were calculated among all participants for all smoking-related cancers (“All participants”), among HIV seropositive participants for all smoking-related cancers (“HIV+ participants”), among HIV seronegative participants for all smoking-related cancers (“HIV- participants”), and among all participants for smoking-related cancers strongly, moderately, or weakly associated with smoking (“Strongly associated”, “Moderately associated”, and “Weakly associated”, respectively). Bars indicate 95% CIs.

MACS = Multicenter AIDS Cohort Study; WIHS = Women's Interagency HIV Study CI = confidence interval; PAF = population attributable fraction

Table 1.

Baseline characteristics of participants in the MACS and WIHS.

	MACS	WIHS	P-value
	N (Percent)		
Geographic region of recruitment site			< **0.01**
West coast	1964 (28.93)	1266 (28.62)	
East coast	3264 (48.08)	2641 (59.71)	
Midwest	1561 (22.99)	516 (11.67)	
Enrollment cohort			< **0.01**
1984 - 1987	5302 (78.10)	0 (0.00)	
1994 - 1995	0 (0.00)	2301 (52.02)	
2001 - 2002	1149 (16.92)	957 (21.64)	
2010+	338 (4.98)	1165 (26.34)	
Race/ethnicity			< **0.01**
Non-Latinx white	4929 (72.62)	591 (13.36)	
Non-Latinx black	1129 (16.63)	2763 (62.47)	
Other	729 (10.74)	1069 (24.17)	
Baseline educational attainment			< **0.01**
High school or less	1234 (18.30)	2924 (66.23)	
Some college	1991 (29.52)	1159 (26.25)	
College graduate	1505 (22.31)	233 (5.28)	
At least some postgraduate education	2015 (29.87)	99 (2.24)	
Annual household income			< **0.01**
< $29,999	1072 (71.99)	3711 (86.50)	
≥ $30,000	417 (28.01)	579 (13.50)	
Smoking status			< **0.01**
Never	2690 (39.62)	1532 (34.64)	
Former	1335 (19.66)	559 (12.64)	
Current	2764 (40.71)	2332 (52.72)	
Alcohol use			< **0.01**
Abstainer	574 (8.61)	1957 (44.88)	
> 0 to 7 drinks/week	3767 (56.49)	1788 (41.00)	
> 7 to 12 drinks/week	715 (10.72)	183 (4.20)	
> 12 drinks/week	1612 (24.18)	433 (9.93)	
Smoked an illicit drug			< **0.01**
No	2617 (38.55)	2951 (66.72)	
Yes	4172 (61.45)	1472 (33.28)	
Injected an illicit drug			< **0.01**
No	6255 (92.13)	4145 (93.71)	
Yes	534 (7.87)	278 (6.29)	

	MACS	WIHS	P-value
	N (Percent)		
Took an illicit drug other than through smoking/injection			< **0.01**
No	3119 (45.94)	4306 (97.35)	
Yes	3670 (54.06)	117 (2.65)	
Any HPV *			
No		1534 (50.43)	
Yes		1508 (49.57)	
Oncogenic HPV *			
No		2294 (75.41)	
Yes		748 (24.59)	
Hepatitis C virus			< **0.01**
No	6375 (94.65)	3414 (80.96)	
Yes	360 (5.35)	803 (19.04)	
HIV infection			< **0.01**
No	3805 (56.05)	1150 (26.00)	
Yes	2984 (43.95)	3273 (74.00)	
CD4 cell count/μl (PLWH only)			< **0.01**
< 200	185 (6.34)	595 (18.61)	
200 - 500	1073 (36.78)	1368 (42.78)	
> 500	1659 (56.87)	1235 (38.62)	
HIV viral load detectable (PLWH only)			< **0.01**
No	481 (45.16)	1063 (33.42)	
Yes	584 (54.84)	2118 (66.58)	
HIV viral load ≥ 4,000 copies/ml (PLWH only)			< **0.01**
No	592 (55.59)	1526 (47.91)	
Yes	473 (44.41)	1659 (52.09)	
Exposure to ART (PLWH only)			< **0.01**
No	2473 (82.88)	2327 (71.10)	
Yes	511 (17.12)	946 (28.90)	
History of clinical AIDS (PLWH only)			< **0.01**
No	2969 (99.50)	2636 (80.54)	
Yes	15 (0.50)	637 (19.46)	
Pre-ART nadir CD4 cell/μl count (PLWH only)			< **0.01**
< 200	1497 (50.37)	1004 (43.22)	
≥ 200	1475 (49.63)	1319 (56.78)	
Post-ART nadir CD4 cell/μl count (PLWH only)			< **0.01**
< 200	389 (28.21)	1098 (40.13)	
≥ 200	990 (71.79)	1638 (59.87)	
Peak HIV viral load (PLWH only)			< **0.01**

	MACS	WIHS	P-value
	N (Percent)		
≤ 10,000 copies/ml	563 (20.01)	1041 (31.81)	
> 10,000 copies/ml	2251 (79.99)	2232 (68.19)	
	Median (IQR)		
Cumulative pack-years smoked (never smokers excluded)	14.70 (4.58-28.84)	7.75 (3.00-15.50)	< **0.01**
Years since smoking cessation	5.00 (1.00-8.25)	1.27 (0.30-5.78)	< **0.01**
Age (years)	33.37 (28.28-39.42)	36.77 (30.63-43.52)	< **0.01**
BMI (kg/m^2)	23.30 (21.70-25.50)	27.20 (23.40-33.10)	< **0.01**
Lifetime number of sexual partners	102.00 (34.00-400.00)	11.00 (5.00-35.00)	< **0.01**
Total number of participants	6789	4423	

Bold indicates statistically significant.

HPV= human papilloma virus; MACS = Multicenter AIDS Cohort Study; PLWH = people living with HIV; WIHS = Women's Interagency HIV Study.

*: MACS participants not tested for HPV at baseline visit.

Due to missing values, participant frequencies within variable categories may not sum to total participant counts.

Table 2.

Smoking-related cancer incidence among participants in the MACS and WIHS.

	Baseline			Smoking-related cancer incidence			
	N	**%**		**N**	**P-yrs**	**IR per 100,000* [95% CI]**	**P-value**
HIV infection							
Seronegative [ref]	4955	44		118	63642	162.2 [133.6, 196.9]	
Seropositive	6257	56		271	75883	347.6 [303.1, 398.5]	< **0.01**
Cohort							
MACS [ref]	6789	61		206	92047	197.5 [169.4, 230.3]	
WIHS	4423	39		183	47477	391.6 [333.7, 459.6]	< **0.01**
Cumulative pack-years†							
Never smokers [ref]	6271	56		86	64947	141.7 [114.1, 175.9]	
1 - 10	2391	21		81	32684	266.0 [212.4, 333.1]	< **0.01**
11 - 20	1205	11		65	16740	373.2 [290.1, 480.0]	< **0.01**
21 - 30	647	6		47	10634	379.5 [282.0, 510.7]	< **0.01**
> 30	698	6		110	14521	480.3 [388.3, 594.1]	< **0.01**
Years since smoking cessation‡							
< 10 [ref]	1632	89		59	23216	260.3 [192.8, 351.6]	
10 - 19	144	8		15	10909	100.1 [57.9, 172.9]	< **0.01**
≥ 20	62	3		24	7994	132.0 [81.0, 215.1]	< **0.01**
Cohort by HIV serostatus							
MACS seronegative [ref]	3805	34		85	50542	138.3 [110.3, 173.4]	
MACS seropositive	2984	27		121	41505	279.0 [230.8, 337.4]	< **0.01**
WIHS seronegative [ref]	1150	10		33	13100	276.3 [195.5, 390.5]	
WIHS seropositive	3273	29		150	34377	434.1 [364.4, 517.2]	**0.02**
Cumulative pack-years by HIV serostatus†							
Never smokers seronegative [ref]	2871	26		37	31805	116.6 [84.1, 161.6]	
Never smokers seropositive	3400	30		49	33142	170.6 [128.5, 226.5]	0.08
1 - 10 seronegative [ref]	881	8		14	12591	122.4 [72.3, 207.1]	

	Baseline			Smoking-related cancer incidence			
	N	%		N	P-yrs	IR per 100,000* [95% CI]	P-value
1 - 10 seropositive	1510	13		67	20091	358.8 [280.3, 459.2]	< **0.01**
11 - 20 seronegative [ref]	505	5		13	6683	190.1 [110.1, 328.5]	
11 - 20 seropositive	700	6		52	10057	497.6 [375.9, 658.7]	< **0.01**
21 - 30 seronegative [ref]	310	3		11	4645	201.2 [110.9, 365.2]	
21 - 30 seropositive	337	3		36	5989	527.8 [376.9, 739.2]	< **0.01**
> 30 seronegative [ref]	388	3		43	7918	329.8 [240.1, 453.0]	
> 30 seropositive	310	3		67	6602	668.1 [515.6, 865.7]	< **0.01**
Years since smoking cessation by HIV serostatus‡							
< 10 seronegative [ref]	789	43		15	10131	152.8 [90.2, 259.1]	
< 10 seropositive	843	46		44	13085	348.0 [248.3, 487.8]	< **0.01**
10 - 19 seronegative [ref]	49	3		7	5354	93.2 [43.2, 201.5]	
10 - 19 seropositive	95	5		8	5555	106.7 [51.8, 220.0]	0.79
≥ 20 seronegative [ref]	24	1		5	4171	48.3 [19.1, 121.8]	
≥ 20 seropositive	38	2		19	3823	228.6 [135.2, 386.4]	< **0.01**
Total	11212	100		389	139524	278.8 [252.4, 307.9]	

Bold indicates statistically significant.

MACS = Multicenter AIDS Cohort Study; WIHS = Women's Interagency HIV Study; P-years = person-years; IR = incidence rate; CI = confidence interval.

*: All estimates adjusted for age.

†: Lagged by 10 years.

‡: Study population limited to former smoking participants.

Table 3.

Unadjusted smoking-related cancer incidence rates among participants in the MACS and WIHS, stratified by HIV serostatus.

	HIV Seronegative						HIV Seropositive				
	No. cancers	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**		**No. cancers**	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**
Geographic region of recruitment site											
West coast [ref]	32	18801	170.2				91	24545	370.7		
East coast	76	34552	220.0	1.3 [0.8, 2.0]	0.26		140	36518	383.4	1.0 [0.8, 1.4]	0.86
Midwest	10	10288	97.2	0.6 [0.3, 1.2]	0.15		40	14819	269.9	0.7 [0.5, 1.1]	0.11
Calendar period											
Before 1996 [ref]	22	24454	90.0				21	16983	123.7		
1996 - 1999	4	4046	98.9	1.1 [0.3, 3.2]	1.00		27	9632	280.3	2.3 [1.2, 4.2]	< **0.01**
2000 - 2003	8	7921	101.0	1.1 [0.4, 2.6]	0.92		29	9288	312.2	2.5 [1.4, 4.7]	< **0.01**
2004 - 2007	15	8180	183.4	2.0 [1.0, 4.1]	0.06		47	11664	402.9	3.3 [1.9, 5.7]	< **0.01**
2008 - 2011	30	7279	412.1	4.6 [2.6, 8.3]	< **0.01**		60	10275	583.9	4.7 [2.8, 8.2]	< **0.01**
2012 - 2015	23	6762	340.1	3.8 [2.0, 7.1]	< **0.01**		47	10017	469.2	3.8 [2.2, 6.7]	< **0.01**
2016 - 2018	16	5001	319.9	3.6 [1.7, 7.1]	< **0.01**		40	8024	498.5	4.0 [2.3, 7.2]	< **0.01**
Age (years)											
< 40 [ref]	8	20781	38.5				22	24679	89.1		
40 - 49	18	19444	92.6	2.4 [1.0, 6.4]	0.05		74	26996	274.1	3.1 [1.9, 5.2]	< **0.01**
50 - 59	44	14239	309.0	8.0 [3.7, 19.7]	< **0.01**		117	17876	654.5	7.3 [4.6, 12.2]	< **0.01**
≥ 60	48	9178	523.0	13.6 [6.4, 33.3]	< **0.01**		58	6332	916.0	10.3 [6.2, 17.6]	< **0.01**
Race/ethnicity											
Non-Latinx white [ref]	67	43512	154.0				107	34094	313.8		
Non-Latinx black	39	12910	302.1	2.0 [1.3, 3.0]	< **0.01**		122	27476	444.0	1.4 [1.1, 1.9]	**0.01**
Other	12	7207	166.5	1.1 [0.5, 2.0]	0.90		42	14312	293.5	0.9 [0.6, 1.3]	0.79
Baseline educational attainment											
High school or less [ref]	46	14332	321.0				146	30342	481.2		
Some college	26	16147	161.0	0.5 [0.3, 0.8]	< **0.01**		74	22555	328.1	0.7 [0.5, 0.9]	< **0.01**
College graduate	15	13132	114.2	0.4 [0.2, 0.6]	< **0.01**		22	10979	200.4	0.4 [0.3, 0.7]	< **0.01**
At least some postgraduate education	31	19770	156.8	0.5 [0.3, 0.8]	< **0.01**		29	11879	244.1	0.5 [0.3, 0.8]	< **0.01**

	HIV Seronegative						HIV Seropositive				
	No. cancers	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**		**No. cancers**	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**
Annual household income											
< $29,999 [ref]	35	19640	178.2				147	39335	373.7		
≥ $30,000	33	25318	130.3	0.7 [0.4, 1.2]	0.24		42	20961	200.4	0.5 [0.4, 0.8]	< **0.01**
BMI (kg/m^2)											
Under or normal weight (< 25) [ref]	24	20864	115.0				76	26627	285.4		
Overweight (25 - 29)	18	19427	92.7	0.8 [0.4, 1.5]	0.59		51	20883	244.2	0.9 [0.6, 1.2]	0.44
Obese (≥ 30)	17	13877	122.5	1.1 [0.5, 2.1]	0.96		29	16224	178.7	0.6 [0.4, 1.0]	**0.04**
Smoking status											
Never [ref]	16	20340	78.7				20	22155	90.3		
Former	27	21242	127.1	1.6 [0.8, 3.2]	0.17		57	22372	254.8	2.8 [1.7, 5.0]	< **0.01**
Current	24	18163	132.1	1.7 [0.9, 3.4]	0.14		92	26447	347.9	3.9 [2.4, 6.6]	< **0.01**
Cumulative pack-years *											
Never smokers [ref]	37	31805	116.3				49	33141	147.9		
1 - 10	14	12592	111.2	1.0 [0.5, 1.8]	1.00		67	20092	333.5	2.3 [1.5, 3.3]	< **0.01**
11 - 20	13	6682	194.6	1.7 [0.8, 3.2]	0.16		52	10057	517.1	3.5 [2.3, 5.3]	< **0.01**
21 - 30	11	4644	236.9	2.0 [0.9, 4.1]	0.07		36	5989	601.1	4.1 [2.6, 6.4]	< **0.01**
> 30	43	7918	543.1	4.7 [2.9, 7.5]	< **0.01**		67	6603	1014.7	6.9 [4.7, 10.1]	< **0.01**
Years since smoking cessation †											
< 10 [ref]	15	10131	148.1				44	13085	336.3		
10 - 19	7	5354	130.7	0.9 [0.3, 2.3]	0.98		8	5555	144.0	0.4 [0.2, 0.9]	**0.03**
≥ 20	5	4171	119.9	0.8 [0.2, 2.3]	0.90		19	3823	497.0	1.5 [0.8, 2.6]	0.20
Alcohol use											
Abstainer [ref]	14	12615	111.0				89	25881	343.9		
> 0 to 7 drinks/week	31	32542	95.3	0.9 [0.4, 1.7]	0.74		54	33666	160.4	0.5 [0.3, 0.7]	< **0.01**
> 7 to 12 drinks/week	10	6883	145.3	1.3 [0.5, 3.2]	0.65		9	4644	193.8	0.6 [0.2, 1.1]	0.12
> 12 drinks/week	10	7467	133.9	1.2 [0.5, 2.9]	0.80		16	6018	265.9	0.8 [0.4, 1.3]	0.41
Smoked an illicit drug											
No [ref]	108	44170	244.5				210	51565	407.3		

AIDS. Author manuscript; available in PMC 2022 January 01.

	HIV Seronegative						HIV Seropositive				
	No. cancers	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**		**No. cancers**	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**
Yes	10	19471	51.4	0.2 [0.1, 0.4]	< **0.01**		61	24317	250.9	0.6 [0.5, 0.8]	< **0.01**
Injected an illicit drug											
No [ref]	118	63013	187.3				265	74212	357.1		
Yes	0	629	110.5	0.6 [−∞, 2.6]	0.62		6	1670	359.3	1.0 [0.4, 2.2]	1.00
Took illicit drugs other than through smoking/injection											
No [ref]	112	50417	222.1				257	62667	410.1		
Yes	6	13225	45.4	0.2 [0.1, 0.5]	< **0.01**		14	13215	105.9	0.3 [0.1, 0.4]	< **0.01**
History of injection drug use											
No [ref]	100	59434	168.3				204	65911	309.5		
Yes	18	4207	427.9	2.5 [1.4, 4.2]	< **0.01**		67	9964	672.4	2.2 [1.6, 2.9]	< **0.01**
Any HPV											
No [ref]	0	457	151.7				0	836	82.9		
Yes	3	1240	215.1	1.4 [0.2, ∞]	0.78		4	2388	153.4	1.9 [0.3, ∞]	0.60
Oncogenic HPV											
No [ref]	1	1117	89.5				1	1864	53.6		
Yes	2	581	344.2	3.8 [0.2, 226.8]	0.54		3	1360	220.6	4.1 [0.3, 215.9]	0.41
Lifetime number of sexual partners											
< 30 [ref]	33	10845	304.3				86	21916	392.4		
30 - 59	12	10328	116.2	0.4 [0.2, 0.8]	< **0.01**		45	11518	390.7	1.0 [0.7, 1.4]	1.00
60 - 89	9	6458	139.4	0.5 [0.2, 1.0]	**0.04**		26	5452	476.9	1.2 [0.8, 1.9]	0.44
≥ 90	64	36010	177.7	0.6 [0.4, 0.9]	**0.02**		114	36996	308.1	0.8 [0.6, 1.1]	0.11
Hepatitis C virus at baseline											
No [ref]	99	60196	164.5				188	64552	291.2		
Yes	19	3060	620.9	3.8 [2.2, 6.2]	< **0.01**		75	10185	736.4	2.5 [1.9, 3.3]	< **0.01**
CD4 cell/μl count (HIV seropositive only)											
< 200 [ref]	-						37	9455	391.3		
200 - 500	-						72	25197	285.7	0.7 [0.5, 1.1]	0.15
> 500	-						59	31825	185.4	0.5 [0.3, 0.7]	< **0.01**

AIDS. Author manuscript; available in PMC 2022 January 01.

	HIV Seronegative						HIV Seropositive				
	No. cancers	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**		**No. cancers**	**P-yrs**	**IR per 100,000**	**IRR [95% CI]**	**P-value**
HIV viral load detectable (HIV seropositive only)											
No [ref]	-						104	33789	307.8		
Yes	-						55	24050	228.7	0.7 [0.5, 1.0]	0.09
HIV viral load ≥ 4,000 copies/ml (HIV seropositive only)											
No [ref]	-						119	39778	299.2		
Yes	-						40	18074	221.3	0.7 [0.5, 1.1]	0.11
Exposure to ART (HIV seropositive only)											
No [ref]	-						85	29323	289.9		
Yes	-						186	46559	399.5	1.4 [1.1, 1.8]	**0.02**
History of clinical AIDS (HIV seropositive only)											
No [ref]	-						132	55726	236.9		
Yes	-						139	20156	689.6	2.9 [2.3, 3.7]	**< 0.01**
Pre-ART nadir CD4 cell/μl count (HIV seropositive only)											
< 200 [ref]	-						120	28689	418.3		
≥ 200	-						139	40954	339.4	0.8 [0.6, 1.0]	0.11
Post-ART nadir CD4 cell/μl count (HIV seropositive only)											
< 200 [ref]	-						124	23331	531.5		
≥ 200	-						82	37673	217.7	0.4 [0.3, 0.5]	**< 0.01**
Peak HIV viral load (copies/ml, HIV seropositive only)											
≤ 10,000 [ref]	-						55	14776	372.2		
> 10,000	-						207	59889	345.6	0.9 [0.7, 1.3]	0.67
Total	118	63642	185.4				271	75882	357.1		

Bold indicates statistically significant.

MACS = Multicenter AIDS Cohort Study; WIHS = Women's Interagency HIV Study; P-years = person-years; IR = incidence rate; IRR = incidence rate ratio; CI = confidence interval

*: Lagged by 10 years.

†: Study population limited to former smoking participants.

Table 4.

Adjusted smoking-related cancer incidence rate ratios among participants in the MACS and WIHS.

	All years (1984-2018)		Modern ART years (2001-2018)	
	IRR [95% CI]	**P-value for cohort interaction***	**IRR [95% CI]**	**P-value for cohort interaction***
Age (years)				
< 40 [ref]				
40 - 49	**2.0 [1.1, 3.6]**	**0.05**	1.9 [0.8, 4.2]	0.24
50 - 59	**4.9 [2.8, 8.7]**	0.11	**3.9 [1.8, 8.4]**	0.37
≥ 60	**6.6 [3.6, 12.1]**	0.18	**5.7 [2.6, 12.7]**	0.56
Race/ethnicity				
Non-Latinx white [ref]				
Non-Latinx black	1.2 [0.8, 1.8]	0.74	1.2 [0.8, 1.9]	0.89
Other	0.6 [0.3, 1.2]	**0.04**	0.6 [0.3, 1.3]	**0.04**
Annual household income				
< $29,999 [ref]				
≥ $30,000	**0.6 [0.4, 0.8]**	0.58	**0.6 [0.4, 0.9]**	0.44
Cumulative pack-years†				
Never smokers [ref]				
1 - 10	1.3 [0.8, 2.1]	**0.02**	1.3 [0.8, 2.2]	**0.02**
11 - 20	**2.0 [1.2, 3.2]**	**0.04**	1.7 [0.9, 2.9]	**0.03**
21 - 30	**2.7 [1.7, 4.4]**	0.20	**2.4 [1.4, 4.1]**	0.28
> 30	**3.4 [2.1, 5.3]**	0.06	**3.3 [2.0, 5.3]**	0.08
Alcohol use				
Abstainer [ref]				
> 0 to 7 drinks/week	0.7 [0.5, 1.1]	0.17	0.8 [0.6, 1.2]	0.22
> 7 to 12 drinks/week	0.9 [0.4, 1.7]	0.53	0.6 [0.3, 1.5]	0.63
> 12 drinks/week	1.2 [0.8, 2.0]	0.68	1.4 [0.8, 2.3]	0.73
History of injection drug use				
No [ref]				

	All years (1984-2018)		Modern ART years (2001-2018)	
	IRR [95% CI]	**P-value for cohort interaction***	**IRR [95% CI]**	**P-value for cohort interaction***
Yes	1.2 [0.8, 1.7]	0.38	1.2 [0.8, 1.8]	0.75
Hepatitis C virus at baseline				
No [ref]				
Yes	1.1 [0.7, 1.7]	0.21	1.2 [0.8, 1.9]	0.26
HIV status				
Seronegative [ref]				
Seropositive and no history of clinical AIDS	**1.5 [1.1, 2.2]**	0.67	1.5 [1.0, 2.2]	0.75
Seropositive and history of clinical AIDS	**3.0 [2.0, 4.4]**	0.92	**2.7 [1.7, 4.2]**	0.62
CD4 cell count/μl (PLWH only)				
< 200 [ref]				
200 - 500	**0.5 [0.3, 0.9]**	**0.03**	**0.5 [0.3, 0.9]**	0.16
> 500	**0.3 [0.2, 0.6]**	0.20	**0.3 [0.2, 0.6]**	0.65
HIV viral load detectable (PLWH only)				
No [ref]				
Yes	0.8 [0.5, 1.2]	0.43	**0.4 [0.2, 0.9]**	**0.05**
Exposure to ART (PLWH only)				
No [ref]				
Yes	1.1 [0.7, 1.9]	0.67	0.8 [0.4, 1.6]	0.61

Bold indicates statistically significant.

MACS = Multicenter AIDS Cohort Study; PLWH = people living with HIV; WIHS = Women's Interagency HIV Study; IRR = incidence rate ratio; CI = confidence interval.

*: Tests whether the effect of the given covariate differs between MACS and WIHS.

†: Lagged by 10 years.