Cancer/Pathology
Overarching aims

**Aim 1.** To determine if the incidence of specific types of cancers is increased among HIV-infected women as compared to HIV-uninfected women and to the general population, and whether cancer incidence and survival are affected by use of HAART.

**Aim 2:** To investigate risk factors for specific cancers (breast, cervical, lung cancer, and non-Hodgkin lymphoma) with an emphasis on potential strategies for cancer prevention and cancer therapy.

**Aim 3.** To collect fresh-frozen tissue from biopsies of the cervix, vagina, and vulva and accompanying blood specimens and oral rinses for donation to the NCI-sponsored AIDS Cancer and Specimen Resource (ACSR). For select malignancies, to collect and donate paraffin-embedded formalin-fixed tissue specimens from WIHS women with confirmed incident cancers.

Overall Research Design and Methods: For the start of WIHS V, there are no newly proposed cancer-specific concept sheets that have requested additional funding. There are, however, several existing cancer and HPV-related projects that require the current infrastructure and activities outlined below.

We will continue to identify and confirm all cancers that occur in the WIHS participants using the following ascertainment methods: (1) searches of statewide cancer registries, (2) medical record confirmation of self-reported cancer diagnoses, and (3) WIHS-initiated gynecologic biopsies. Cancers that are initially identified by self-report or death certificate via a National Death Index (NDI) search will be classified as ‘confirmed cancers’ only if they are subsequently confirmed by medical record review or cancer registry matching. The state cancer registry matches are performed every two years and the NDI is matched every year.

We will document the diagnosis date, primary site/tumor type, and cancer treatment information for each cancer identified from the medical records or the WIHS gynecologic biopsy. For all cancers documented via the state cancer registries, we also obtain the ICD-O-3 coded tumor site, histological type, tumor behavior (in-situ or malignant), and treatment information directly from the registry. The Cancer WG will continue to attempt to obtain detailed pathology reports and, when deemed necessary, available biopsy specimens to confirm or refute the information obtained from the original source.

WIHS continues to be a major donator to the ACSR of tissue, blood, and oral rinses from HIV-infected and comparative group of HIV-uninfected women. Our protocol involves donations from at least 10 women per WIHS site, per WIHS visit, who undergo colposcopy. If a lesion is present, the colposcopist is to biopsy the lesion, split it in two, send one section for clinical pathology review and flash-freeze the other section in liquid nitrogen. Another biopsy of nonlesion tissue is then collected and flash-frozen; also blood is collected for plasma and PBMCs, and an oral rinse is collected and frozen. These specimens are then sent to either the west coast or east coast ACSR repository according to the WHIS protocol. Corresponding demographic and clinical data are also transmitted to the ACSR by the WIHS data center (WDMAC).

Progress highlights: During WIHS IV, we were able to look more closely as specific cancers, such as cervical, lung and breast, and below are three examples of these investigations.

**Long-term incidence of cervical cancer in women with human immunodeficiency virus.** Massad LS, Seaberg EC, Watts DH, Minkoff H, Levine AM, Henry D, Colie C, Darragh TM, Hessol NA. Cancer. 2009 Feb 1;115(3):524-30. Massad et al. reported that among women with HIV in a prospective study that incorporated cervical cancer prevention measures, the incidence of invasive cervical cancer (ICC) was not significantly higher than that in a comparison group of HIV-uninfected women.

**HIV as a risk factor for lung cancer in women: data from the Women's Interagency HIV Study.** Levine AM, Seaberg EC, Hessol NA, Preston-Martin S, Silver S, Cohen MH, Anastos K, Minkoff H, Orenstein J, Dominguez G, Watts DH. J Clin Oncol. 2010 Mar 20;28(9):1514-9. Levine et al. reported that the incidence rates of lung cancer were similar among HIV-infected and uninfected WIHS women. Lung cancer standardized incidence ratios (SIRs) were increased in both HIV-infected and -uninfected women compared with population expectations, but did not differ by HIV status. Among HIV-infected women, lung cancer incidence rates were similar in pre-HAART and HAART eras.
**HIV tropism and decreased risk of breast cancer.** Hessol NA, Napolitano LA, Smith D, Lie Y, Levine A, Young M, Cohen M, Minkoff H, Anastos K, D'Souza G, Greenblatt RM, Goedert JJ. PLoS One. 2010 Dec 16;5(12):e14349. Hessol and colleagues used both WIHS and HERS data and found that low breast cancer risk with among women with HIV infection was specifically linked to CXCR4-using variants of HIV. These variants are thought to exclusively bind to and signal through a receptor that is commonly expressed on hyperplastic and neoplastic breast duct cells.

For WIHS IV a heightened focused was placed on collaborations to increase the power and scientific validity of the cancer initiatives. Below are two recent publications resulting from the NA-ACCORD collaboration.


**Collaborations within and external to WIHS:** The WIHS Cancer/Pathology working group works closely with the WIHS HPV working group (many of the members overlap) to ensure the WIHS data is collected and used to the best of its ability and that newly proposed projects do not overlap. The Chairs of the WIHS Cancer/Pathology and MACS Malignancy working groups are also in close contact and are members of both working groups. In addition, the Chairs of the WIHS Cancer/Pathology and HPV working groups are active members of the NA-ACCORD Malignancy working group and serve as advisors to the NA-ACCORD regarding the WIHS.

**Collaborations with funding external to WIHS:** The WIHS will continue to serve as a platform for RO-1 related studies; two recently funded studies are described below.

Strickler H, PI. **Grant title: Molecular Methods for Cervical Cancer Screening in HIV+ Women.** The overall specific aims are: 1) to determine the relative sensitivity, specificity, PPV, and NPV of several promising molecular assays for detection of cervical pre-cancer in HIV(+) women; 2) to assess these assays in combination with one another as well as in combination with routine cytology and HC2, to determine the optimal cervical cancer screening approach in HIV(+) women; 3) to collect and store appropriate specimens from HIV(+) women to test future cervical cancer screening methods when they become available.

Silverberg M, Dubrow R, PIs. **Grant title: Antiretroviral therapy strategies to lower cancer risk in HIV-infected persons.** The overarching goal of the current proposal is to formulate evidence-based recommendations about the optimal CD4 T-cell count at which to initiate ART and the optimal ART regimen, in order to would minimize cancer incidence among HIV-infected persons.

**New Directions for WIHS V:** Now that WIHS follow-up time has increased, the numbers of new cancers has grown, and the study population is reaching the age where rate of several common tumors begins to rapidly rise, we are better positioned to evaluate the impact of host and viral risk factors on these malignancies. One new area of investigation for the WIHS focuses on modifiable risk factors for cancer which could lead to interventional studies of cancer prevention. Another area leverages the recently completed genotyping of five million single nucleotide polymorphisms (SNPs) in all participants, which will permit the identification of risk alleles for ancestry and candidate genes associated with cancer risk.
HIV Tropism and Decreased Risk of Breast Cancer

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Abstract

Background: During the first two decades of the U.S. AIDS epidemic, and unlike some malignancies, breast cancer risk was significantly lower for women with human immunodeficiency virus (HIV) infection compared to the general population. This deficit in HIV-associated breast cancer could not be attributed to differences in survival, immune deficiency, childbearing or other breast cancer risk factors. HIV infects mononuclear immune cells by binding to the CD4 molecule and to CCR5 or CXCR4 chemokine coreceptors. Neoplastic breast cells commonly express CXCR4 but not CCR5. In vitro, binding HIV envelope protein to CXCR4 has been shown to induce apoptosis of neoplastic breast cells. Based on these observations, we hypothesized that breast cancer risk would be lower among women with CXCR4-tropic HIV infection.

Methods and Findings: We conducted a breast cancer nested case-control study among women who participated in the WHIS and HERS HIV cohort studies with longitudinally collected risk factor data and plasma. Cases were HIV-infected women (mean age 46 years) who had stored plasma collected within 24 months of breast cancer diagnosis and an HIV viral load ≥500 copies/mL. Three HIV-infected control women, without breast cancer, were matched to each case based on age and plasma collection date. CXCR4-tropism was determined by a phenotypic tropism assay. Odds ratios (OR) and 95% confidence intervals (CI) for breast cancer were estimated by exact conditional logistic regression. Two (9%) of 23 breast cancer cases had CXCR4-tropic HIV, compared to 19 (28%) of 69 matched controls. Breast cancer risk was significantly and independently reduced with CXCR4 tropism (adjusted odds ratio, 0.10, 95% CI 0.002–0.84) and with menopause (adjusted odds ratio, 0.08, 95% CI 0.001–0.83). Adjustment for CD4+ cell count, HIV viral load, and use of antiretroviral therapy did not attenuate the association between infection with CXCR4-tropic HIV and breast cancer.

Conclusions: Low breast cancer risk with HIV is specifically linked to CXCR4-using variants of HIV. These variants are thought to exclusively bind to and signal through a receptor that is commonly expressed on hyperplastic and neoplastic breast duct cells. Additional studies are needed to confirm these observations and to understand how CXCR4 might reduce breast cancer risk.


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Competing Interests: Two authors, LAN and YL, are employed by Monogram Biosciences. All other authors declare that they have no competing interests. This does not alter the authors’ adherence to all PLoS ONE policies on sharing data and materials.

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Introduction

Human immunodeficiency virus type-1 (HIV) envelope protein binds to the CD4 receptor and to chemokine coreceptors CCR5 or CXCR4, leading to infection and destruction of the CD4-bearing immune cells: T lymphocytes and macrophages [1]. Although HIV infection increases the risk of several malignancies,[2] from 1980–2002 breast cancer risk in the United States was 31% lower among women with AIDS compared to the general population [3]. This cancer deficit was unrelated to crude measures of immune deficiency, was most pronounced before 1996, and gradually disappeared with improving antiretroviral therapy (ART) [3].
The CXCR4 receptor is commonly expressed not only on immune cells, but also on hyperplastic and especially on malignant breast duct cells [4–6]. CXCR4 may play an essential role in metastasis and, indirectly, earlier stages of tumor growth [4,5,7–9]. Linking HIV with breast cancer was the observation that programmed cell death (apoptosis) was induced in human breast cancer cell lines through binding of CXCR4-tropic, but not CCR5-tropic, HIV envelope protein [10]. Based on both the pattern of breast cancer risk in women with AIDS and the in vitro findings that CXCR4-tropic HIV induced apoptosis of breast cancer cells, we postulated that HIV strains tropic for CXCR4 may account for the reduction in breast cancer observed in HIV-infected women. To test this hypothesis, we studied HIV tropism in women with breast cancer and in matched controls.

**Methods**

**Cohorts, Covariate Data and Specimens, and Ethics Statement**

The study population was drawn from two large multisite longitudinal studies of HIV infection in women in the United States, the Women’s Interagency HIV Study (WIHS) and the HIV Epidemiology Research Study (HERS). Study protocols were reviewed and approved by the institutional review boards, and written informed consent was obtained from the participants.

The WIHS is a prospective study of HIV infection in women, conducted in New York City, Washington D.C., Chicago, Southern California and the San Francisco Bay Area. The WIHS methods and baseline cohort characteristics have been previously described [11]. Briefly, between October 1994 and November 1995, 2056 HIV-infected and 569 uninfected women were enrolled. A second enrollment between October 2001 and September 2002, added 737 HIV-infected and 406 HIV-uninfected women [12]. Follow-up of the women enrolled in the WIHS is ongoing.

The HERS was a collaborative, multicenter (Baltimore, MD; Bronx, NY; Providence, RI; and Detroit, MI) prospective study that enrolled 671 HIV-seropositive and 439 HIV-seronegative women with acknowledged HIV risk behavior from April 1993 to January 1995. Women were enrolled on the basis of either eligibility to receive a physical examination, and provided multiple gynecologic and blood specimens. Among HIV-infected women, blood samples collected at the core study visit were tested for CD4+ lymphocytes and HIV RNA load.

**Selection of Cases and Controls**

Breast cancer cases were identified and confirmed through medical records and state cancer registry matches, and date of diagnosis determined. In the WIHS, cancers were identified from January 1993 through June 2009 and in the HERS from April 1993 through March 2000. Cases for the current investigation were HIV-infected women for whom we had stored plasma samples that were within 24 months (either before or after) of their cancer diagnosis and in which the HIV RNA viral load was 500 copies/mL or greater. A random sample program selected three HIV-infected control women who did not have breast cancer, had HIV RNA viral loads ≤500 copies/mL, and who matched to each case based on cohort, age (plus or minus 2 years), and date of plasma specimen collection (within six months).

**HIV Tropism Determination**

The primary independent variable was HIV coreceptor usage (tropism), which was determined by the original Trofile assay (Monogram Biosciences, South San Francisco CA. Figure S1). Women were classified as having exclusively CCR5-tropic HIV (“R5”) or as having CXCR4-tropic HIV (“X4” or dual/mixed tropism “R5/X4”). The original Trofile assay has >99% sensitivity to detect low levels of CXCR4 and CCR5 variants that comprise at least 5–10% of a viral population, and the positive and negative predictive value of the assay has been verified in clinical trials of CCR5 antagonists [14].

**Statistical Analyses**

All analyses were pre-specified. Contingency table analyses were conducted to compare the distribution of participant characteristics by case-control status, and chi-square or Fisher exact tests measured statistical significance. Paired t-tests were used to measure equality of means for continuous variables. Unadjusted and adjusted exact conditional, matched-pair, logistic regression was performed. The following continuous variables were transformed for the regression analyses: body mass index was divided by 10, CD4+ cell count was divided by 100, and HIV viral load was the log_{10}. Variables that were significant at the P-value <0.10 level in the unadjusted regression models were included in the adjusted analysis. Statistical analyses were performed using SAS® software version 9.2 [15].

**Results**

There were 29 confirmed breast cancer cases identified, 27 in the WIHS and 2 in the HERS. Of 29 confirmed breast cancer cases, three were excluded due to HIV viral load <500 copies/mL, and tropism results could not be determined in three others. A total of 23 breast cancer cases, who had a mean age of 46 years, were included in the analyses. Nearly all of these cancers were invasive infiltrating ductal carcinoma, and they were distributed across the years 1993–2009 (Table 1). Of 69 randomly selected controls, tropism could not be determined in seven, who were replaced with other cohort participants using the same random selection program.

**HIV Tropism in Cases and Controls**

The characteristics of the 23 cases and 69 controls with HIV tropism results are shown in Table S1. Only 2 (9%) breast cancer cases had CXCR4-tropic HIV, compared to 19 (28%) of the matched controls (Fisher’s exact P = 0.09, Table S1). Two of the seven replacement controls had CXCR4-tropic HIV, for a prevalence of 29%, essentially the same as the originally selected controls. Compared to participants with CCR5-tropic HIV, those with CXCR4-tropic HIV had lower mean CD4+ counts (213.5 vs 389.8 cells/μL, P = 0.001) but similar mean HIV viral loads (4.4 vs 4.1 log_{10} copies/mL, P = 0.21). In addition, tropism was not associated with history of clinical AIDS or HIV viral load (P = 0.26).

**Breast Cancer Risk by HIV Tropism and Other Variables**

In unadjusted exact conditional regression analysis of 20 variables (Table S1), breast cancer was marginally inversely associated with CXCR4-tropic HIV (Odds Ratio (OR) = 0.20, 95% confidence interval (CI) 0.02–1.1) as well as menopause (OR = 0.13, 95% CI 0.003–1.0), defined as not having a menstrual
Discussion

These findings show that the odds of breast cancer in women with CXCR4-tropic HIV were 90% lower than in women with CCR5-tropic HIV. This is large enough to account for most of the breast cancer deficit for women with AIDS in the United States. Our findings support the hypothesis that the low breast cancer incidence observed in women with HIV/AIDS is specifically linked to HIV variants that bind to CXCR4, a receptor that is commonly expressed on hyperplastic and neoplastic breast cells. This hypothesis was developed from three observations: 1) the utilization of CXCR4 as the coreceptor for HIV X4 and R5/X4 strains; 2) the common and often high level expression of CXCR4 in breast neoplasia; and 3) the induction of apoptosis of breast cancer cells by the specific binding of CXCR4-tropic HIV to CXCR4.

CXCR4 in Breast Neoplasia

Our data showing a reduced risk of breast cancer among women with CXCR4-tropic HIV may reflect an effect of CXCR4 at an intermediate stage of breast neoplasia. Muller and colleagues first observed that CXCR4 is commonly and often highly expressed in primary breast cancers and in breast cancer cell lines. This observation has been replicated and extended by many others, as reviewed by Luker and Luker. Mammary stem cells express CXCR4 mRNA, as well as many other genes, although the relevance of this to breast neoplasia is speculative. Notably, CXCR4 protein was observed by Schmid and colleagues in 13 of 14 cases of ductal carcinoma in situ of the breast, as well as in 13 of 14 areas of atypical ductal hyperplasia of the breast. However, Schmid et al did not detect CXCR4 protein in normal breast epithelium, consistent with scanty or absent mRNA expression in cell lines derived from mammary epithelial tissue.

Overall, these data imply that normal epithelial breast cells would have few targets for, and thus probably not be directly affected by, CXCR4-tropic HIV envelope.

CXCR4 by Cell Type

The possibility that CXCR4-tropic HIV might inhibit tumor-promoting macrophages and that CXCR4 may differ between mononuclear and breast cells should be considered. CXCR4-tropic HIV envelope first binds to a CD4 epitope on T lymphocytes or macrophages and then undergoes a conformational change that allows the virus to bind to surface CXCR4 and enter the cell, causing death by various means including apoptosis. CXCR4-mediated apoptosis of uninfected bystander cells that do not express CD4 has been reported, but this phenomenon commonly involves a degree of interaction with CD4-bearing cells. In vitro experiments have reported that CD4-independent interaction of CXCR4-tropic HIV mediates apoptosis of breast cells, apparently requiring no CD4 expression or interaction to mediate conformational change of HIV and occurring without evidence of in vitro or ex vivo breast cell infection by HIV. Conformational differences in the orientation or folding of surface CXCR4, including conformational differences between immune versus breast cells, may be functionally important. The additional possibility of HIV infection of breast cells should also be considered.

Assessment of Potential Survivorship, Competing Risk, and Screening Biases

Women with HIV infection may have other causes of morbidity and mortality that prevent them from being diagnosed with breast cancer or living long enough to develop breast cancer. With the increasing availability and potency of ART, these competing causes of morbidity and mortality are reduced, and thus HIV-infected women are living longer and reaching the age of higher breast cancer incidence. By matching the controls to the cases on date of plasma collection we controlled for temporal trends in the availability and potency of ART. We also matched the controls to the age of the cases. CD4+ cell counts were significantly lower in our participants who had CXCR4-tropic HIV. This accords with the well known tendency for patients infected with CXCR4-tropic virus to have more rapid HIV disease progression compared to those infected with only CCR5-tropic virus. However, CXCR4-tropic HIV was not significantly associated with HIV viral load or history of clinical AIDS. Moreover, in multivariable models that included CD4 cell count, use of ART, or HIV viral load, the significance level for CXCR4-tropic HIV was not attenuated. As a result, we have considered and minimized competing risk as much as possible and still found a significant association between CXCR4-tropic HIV and reduced risk of breast cancer.

Screening bias may account for a fraction of the breast cancer deficit. During ages 40–49, history of screening mammography was reported by a smaller fraction of HIV-positive women in our WIHS cohort (64%) compared to the general population (79%). Screening mammography history after age 50 was nearly identical in the WIHS and general populations, although the data were sparse. Whether mammography screening is related to HIV tropism is unknown.

Table 1. Histopathology and years of diagnosis of the 23 breast cancer cases in the WIHS and HERS cohort studies.

<table>
<thead>
<tr>
<th>Tumor description*</th>
<th>Total Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive infiltrating ductal carcinoma</td>
<td>16</td>
</tr>
<tr>
<td>Invasive infiltrating ductal and lobular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma in situ</td>
<td>2</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>1</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Not specified</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data obtained from medical records (pathology reports) and cancer registries (histology and behavior). doi:10.1371/journal.pone.0014349.t001

period for one year or more. Breast cancer was not associated with any other variables (exact P-values all >0.1), including CD4+ cell count, HIV viral load, ART, race/ethnicity, and classical breast cancer risk factors (Figure 1). In multivariable analysis, cancer risk was reduced in women with CXCR4-tropic HIV (adjusted OR = 0.10, 95% CI 0.002–0.84) and with menopause (adjusted OR = 0.08, 95% CI 0.001–0.83). In additional multivariable analyses, the adjusted OR and significance level for CXCR4-tropic HIV was not attenuated by the inclusion of CD4+ cell count, use of ART, or HIV viral load in the regression models.

Cancer incidence observed in women with HIV/AIDS is specifically related to HIV tropism is unknown.
Trends in HIV Tropism and ART Use

Initial HIV infection with HIV subtype B is almost always CCR5-tropic, with CXCR4-tropic virus emerging later, a shift that may be retarded by highly active ART (HAART) [1]. We postulate that gradual increases in HAART use and efficacy since 1996 may have been sufficient to account for the increasing trend in breast cancer incidence [3]. In 2008, 71% of HIV-infected women in the WIHS cohort were receiving HAART [N. Hessol, unpublished data]. The observed 28% prevalence of CXCR4-using HIV in our control group and 90% lower risk of breast cancer associated with these HIV strains, would account for most of the breast cancer deficit in women with AIDS [3,22].

Limitations and Contrary Data

We lacked ex vivo data to support the epidemiologic association with CXCR4-tropic HIV. In addition to the reported induction of apoptosis,[10] induction of various growth factors could contribute to or account for the association. [7–9] Our study was very small and limited to U.S. women who may not be representative of the global HIV epidemic. In our evaluation of classical breast cancer risk factors, we observed a lower risk associated with menopause. This association is not surprising, especially in a population with a mean age of 46 years, because early menopause is known to decrease the risk of breast cancer [23]. Despite our hypothesis-driven study that included many potential risk and confounding factors, and our exclusion of survivorship and other potential biases by matching and statistical adjustment, the association between CXCR4-tropic virus and breast cancer may be spurious due to an unmeasured viral or other exogenous or endogenous risk factor.

It should be noted that during severe immune deficiency, when CXCR4-tropic HIV is most prevalent, risks for Kaposi sarcoma and central nervous system lymphoma are very high despite tumor expression of CXCR4 [24,25]. Nevertheless, these particular malignancies are distinct as they are known to be driven by herpes virus transformation and thus may not utilize CXCR4 as a major means of oncogenesis and metastasis. It is possible that our observed association of CXCR4-tropic HIV is unique to breast neoplasia due to conformational heterogeneity or variable surface expression of CXCR4 epitopes on neoplastic breast duct cells [10,19].

Summary and Implications

We found a 90% lower risk of breast cancer for women who have circulating CXCR4-tropic HIV envelope, which points to the possibility of a novel protective interaction between a specific viral protein and cancer risk. The prototype selective antagonist of CXCR4, AMD3100 (Plerixafor) [26], was reported to inhibit apoptosis of breast cancer cells by CXCR4-tropic HIV [10], and other inhibitors of CXCR4 are currently in development to treat various cancers [27–29]. However, derivative studies should also consider indirect pathways, such as blockade of pro-carcinogenic effects of chemokines expressed by tumor-infiltrating macrophages [17]. Continued studies of molecular interactions [8–10], of patients with malignancies, and of populations at risk for these diseases are needed to develop insight into the roles of CXCR4 in breast and other cancers, which may lead to new approaches for prevention or treatment.
Monogram Biosciences supported tropism testing and all assays were performed by the Monogram Clinical Reference Laboratory. We are sincerely thankful to the women who consented to be part of this study. We are also grateful to Dr. Peter Bacchetti, University of California San Francisco, and to Drs. Anil Chaturvedi and Nilanjan Chatterjee, National Cancer Institute, for their statistical assistance.

References


Table S1. Characteristics of the 23 breast cancer cases and 69 controls in the WIHS and HERS cohort studies.

<table>
<thead>
<tr>
<th>Participant characteristic</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCR4-tropic</td>
<td>2 (8.7)</td>
<td>19 (27.5)</td>
<td>0.09*</td>
</tr>
<tr>
<td>Menstrual period in the last 12 months</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (73.9)</td>
<td>38 (55.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (26.1)</td>
<td>31 (44.9)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA viral load [mean log\text{10}]</td>
<td>[3.96]</td>
<td>[4.21]</td>
<td>0.24**</td>
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<td>6 (26.1)</td>
<td>21 (30.4)</td>
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<tr>
<td>CD4+ cell count/ mm\text{3} [mean]</td>
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<td>[342]</td>
<td>0.58**</td>
</tr>
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<td>&lt;200</td>
<td>4 (17.4)</td>
<td>23 (33.3)</td>
<td>0.39*</td>
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<tr>
<td>200 – 499</td>
<td>14 (60.9)</td>
<td>33 (47.8)</td>
<td></td>
</tr>
<tr>
<td>≥500</td>
<td>5 (21.7)</td>
<td>13 (18.8)</td>
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<tr>
<td>Current HIV therapy</td>
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<tr>
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<tr>
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<tr>
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<td>4 (5.8)</td>
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<tr>
<td>Ever used ART</td>
<td></td>
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<td>15 (65.2)</td>
<td>54 (78.3)</td>
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<td>8 (34.8)</td>
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<td>[46.0]</td>
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<td>41-50</td>
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<td>5 (7.3)</td>
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<td>Controls</td>
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<td>&gt;13</td>
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<td>1-2</td>
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<td>≥3</td>
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<td>3-13 drinks per week</td>
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<td>≥14 drinks per week</td>
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<td>Body mass index</td>
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<td>Normal 19.8-26.0</td>
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<td>Overweight 26.1-29.0</td>
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<td>Ever used oral contraceptives</td>
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<td>No</td>
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<td>22 (31.9)</td>
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<td>Ever used hormone replacement therapy</td>
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* Fisher's exact test; ** Equality of mean
HIV As a Risk Factor for Lung Cancer in Women: Data From the Women’s Interagency HIV Study


ABSTRACT

Purpose

Prior reports of an increased risk of lung cancer in HIV-infected individuals have not always included control groups, nor considered other risk factors such as tobacco exposure. We sought to determine the role of HIV infection and highly active antiretroviral therapy (HAART) on lung cancer incidence in 2,651 HIV-infected and 898 HIV-uninfected women from the Women’s Interagency HIV Study (WIHS).

Methods

A prospective study of the incidence rates of lung cancer was conducted, with cases identified through medical records, death certificates, and state cancer registries. Standardized incidence ratios (SIRs) were calculated to compare lung cancer incidence among HIV-infected and uninfected WIHS participants, with population-based expectations using the Surveillance, Epidemiology, and End Results registry. Behavioral characteristics in the WIHS were compared to US women by age and race adjusting the population-based data from the National Health and Nutritional Examination Survey (NHANES) III.

Results

Incidence rates of lung cancer were similar among HIV-infected and uninfected WIHS women. Lung cancer SIRs were increased in both HIV-infected and uninfected women compared with population expectations, but did not differ by HIV status. Among HIV-infected women, lung cancer incidence rates were similar in pre-HAART and HAART eras. All WIHS women with lung cancer were smokers; the risk of lung cancer increased with cumulative tobacco exposure. WIHS women were statistically more likely to smoke than US women studied in NHANES III.

Conclusion

HIV infection is strongly associated with smoking behaviors that increase lung cancer risk. The role of HIV itself remains to be clarified.

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INTRODUCTION

Highly active antiretroviral therapy (HAART) has been associated with a remarkable decline in the incidence of AIDS-defining cancers.1-3 However, an increase in certain non-AIDS defining cancers, including lung cancer, has been reported.4-8 The number of HIV-infected persons with lung cancer is relatively small, and not all studies have confirmed an increase in risk.9-11

Factors associated with development of lung cancer in HIV-infected persons have included history of cigarette smoking, lung disease,8 and prolonged duration of HIV infection. The actual role of profound HIV-related immunodeficiency remains unclear.5,8,11-13

Given these uncertainties, we wished to ascertain the incidence of lung cancer among HIV-infected women enrolled in the Women’s Interagency HIV Study (WIHS) in the pre-HAART versus HAART eras, comparing incidence data to that from a group of HIV-uninfected WIHS participants, all of whom were observed over prolonged periods, and in whom behavioral characteristics were carefully documented. We also examined risk factors and disease characteristics of lung cancer among HIV-infected versus uninfected participants.

METHODS

Study Cohort

WIHS is a cohort study of women with or at risk for HIV infection, observed at six sites (Bronx/Manhattan,
NY; Brooklyn, NY; Metropolitan Washington, DC, and surrounds; Northern California; Southern California; and Chicago, IL. The cohort included 3,766 women enrolled during two recruitment waves: October 1994 to November 1995, and October 2001 to September 2002. HIV-infected and -uninfected women were recruited from similar sources and frequency matched on age, race/ethnicity, and risk for HIV acquisition. Semi-annual visits included interviewer-administered questionnaires, physical and gynecological examinations, and collection of biologic specimens. Study protocols were reviewed and approved by each institutional review board; informed consent was obtained from all participants.

The 3,678 women who gave additional written consent for cancer ascertainment through state registries were eligible. We excluded three women with lung cancer before enrollment, and another 126 women without known lung cancer, seen only at baseline. All analyses were conducted using the remaining 3,549 women (94%), and were based on data entered into the database by March 31, 2008; follow-up was censored on September 30, 2006, to allow for lags in reporting and confirmation of incident cancers.

Study Outcome

All incident lung cancers were confirmed through medical record reviews of self-reported lung cancers, and/or through matching to statewide cancer registries (most recently performed in 2008), and the national death index. Lung cancer pathology reports were reviewed.

Exposures and Potential Confounders

The primary independent variables included HIV serostatus, history of tobacco use, and HAART use. HIV serology was tested by enzyme-linked immunosorbent assay with Western blot confirmation. Smoking history was summarized at baseline using a categoric variable indicating never/former/current use; and, among current smokers, quantification of the total cumulative exposure in pack-years (total number of years smoking cigarettes times the average number of packs smoked/day). To account for selection by indication bias resulting from the administration of HAART to women with more advanced HIV, the population effectiveness of HAART at reducing lung cancer incidence was assessed by comparing the incidence rates during the pre-HAART (1994 to 1996) and HAART (1997 to 2006) eras. The onset of the HAART era was set at 1997, since ≥ 25% of HIV-infected participants first reported HAART use at that time. We also evaluated age, sex, race, education, income, employment status, insurance coverage, history of alcohol consumption, body mass index (BMI), CD4 cell count, and HIV RNA levels.

External Comparison Groups

SEER. Surveillance, Epidemiology and End Results (SEER) is an ongoing population-based surveillance program, documenting cancer incidence and survival using selected US state cancer registries. We used age-, sex-, and race-specific cancer incidence data from SEER from 1994 to 2004 to estimate the number of lung cancers expected in WIHS. The SEER “site recode” number 22030 was used to identify lung cancer cases in SEER, including cancers with International Classification of Diseases O-2 site codes C34.0 to C34.9.

National Health and Nutrition Examination Survey III. The third National Health and Nutrition Examination Survey (NHANES III) used a complex multistage cluster sampling of the US civilian, noninstitutionalized population to develop a cohort to investigate risk factors to explain differences in health in the US population. A random sample was selected and interviews were conducted in three waves from 1988 to 1994. We used the NHANES III cohort to obtain population-based estimates of the prevalence of identified lung cancer risk factors.

Statistical Analyses

Baseline characteristics in WIHS were quantified descriptively. Comparisons between HIV-infected and -uninfected women were performed using χ² tests of homogeneity and trend. Lung cancer incidence rates were estimated as the number of incident cancers divided by total number of person-years (PYs) follow-up. Statistical comparisons between HIV-infected and -uninfected women, and between the pre-HAART and HAART eras, assumed a Poisson distribution for lung cancer incidence rates. To compare the observed number

### Table 1. Baseline Characteristics of the WIHS Participants at Study Entry by HIV Status (N = 3,549)

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<thead>
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<th>Characteristic</th>
<th>HIV Positive</th>
<th>HIV Negative</th>
<th>P</th>
</tr>
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<td>898</td>
<td>100.0</td>
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<tr>
<td>Age group, years</td>
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<td></td>
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<tr>
<td>&lt; 30</td>
<td>622</td>
<td>23.5</td>
<td>360</td>
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<tr>
<td>30-39</td>
<td>1,265</td>
<td>47.7</td>
<td>340</td>
</tr>
<tr>
<td>40-49</td>
<td>651</td>
<td>24.6</td>
<td>176</td>
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<td>50+</td>
<td>112</td>
<td>4.3</td>
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<td>Race/ethnicity</td>
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<td>Non-Hispanic Black</td>
<td>1,499</td>
<td>56.5</td>
<td>492</td>
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<td>396</td>
<td>14.9</td>
<td>126</td>
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<td>Latina/Hispanic</td>
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<td>25.7</td>
<td>247</td>
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<td>75</td>
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<td>Highest education level attained</td>
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<td>Post-HS education</td>
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<td>Annual household income, $</td>
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<td>Fewer than 6,000</td>
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<td>27.1</td>
<td>271</td>
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<td>6,000-11,999</td>
<td>862</td>
<td>33.5</td>
<td>236</td>
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<td>12,000-29,999</td>
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<td>315</td>
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<td>Alcohol consumption during past 12 months, drinks per week</td>
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<td>Does not drink alcohol</td>
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<td>787</td>
<td>30.4</td>
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<tr>
<td>3 or more</td>
<td>569</td>
<td>22.0</td>
<td>263</td>
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<td>Among drinkers, No. of drinks/week</td>
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<td>Mean</td>
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<td>8.9</td>
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<td>1.0-9.0</td>
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<td>Lifetime cigarette consumption among current smokers, pack-years</td>
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<td>Lower than 10</td>
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<tr>
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<td>15.7</td>
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</tr>
<tr>
<td>Median</td>
<td>9.0</td>
<td>7.5</td>
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</tr>
<tr>
<td>IQR</td>
<td>3.8-16.5</td>
<td>2.5-15.0</td>
<td></td>
</tr>
</tbody>
</table>

Body mass index, kg/m²

| Lower than 20.0 | 225          | 8.8          | 74   | 8.6  |
| 20.0-24.9 | 871          | 34.1         | 271  | 31.3 |
| 25.0-29.9 | 758          | 29.7         | 247  | 28.5 | .04* |
| 30.0 or higher | 697          | 27.3         | 274  | 31.6 |
| Mean | 27.3         | 28.2         |
| SD | 6.8          | 7.3          |
| Median | 25.9         | 26.5         |
| IQR | 22.4-30.5    | 22.9-32.1    |

Abbreviations: WIHS, Women’s Interagency HIV Study; HS, high school; SD, standard deviation; IQR, interquartile range.

*Test of trend.
of lung cancers in the WIHS to the expected number documented by SEER between January 1, 1994, and December 31, 2004, we computed standardized incidence ratios (SIRs)\(^20\) and exact 95% CIs\(^21\) adjusted for age (5-year categories), sex, and race (African American, Latino/Hispanic, other white, and other). SIRs by HIV serostatus and calendar time were compared using SIR regression. Because of the small number of observed lung cancer cases, all incidence analyses were performed using exact statistical methods. Possible differences in behavioral or demographic characteristics between WIHS and US women were determined comparing baseline characteristics. Data from WIHS Cohort incidence ratios (SIRs)\(^20\) and exact 95% CIs\(^21\) adjusted for age (5-year categories), sex, and race (African American, Latino/Hispanic, other white, and other). SIRs by HIV serostatus and calendar time were compared using SIR regression. Because of the small number of observed lung cancer cases, all incidence analyses were performed using exact statistical methods. Possible differences in behavioral or demographic characteristics between WIHS and US women were determined comparing baseline characteristics. Data from WIHS participants were compared with the NHANES III women, the WIHS participants had significantly lower pack-years compared to NHANES III women (median, 7.5 vs 10.0 PYs; \(P = .008\)).

**Comparison of WIHS to the US Population**

Fourteen incident lung cancers were observed in WIHS, while between four and five were expected based on population-based age and race-specific rates from SEER (Table 4). Overall, the SIR for lung cancer in WIHS was 3.0 (95% CI, 1.7 to 5.1). The excess lung cancer burden did not vary by HIV status (exact \(P = .85\)), nor by pre-HAART versus HAART eras (exact \(P = .96\)).

Because other recognized risk factors for lung cancer might explain the excess incidence rate in WIHS, we compared the WIHS cohort characteristics to those in the age- and race-adjusted US female population, using NHANES III data, reweighted to match the age and race distributions of WIHS. Our adjustment yielded identical age and race distributions in the two cohorts (data not shown). When compared with the NHANES III women, the WIHS participants had significantly (\(P < .05\)) less education, lower annual household incomes, were less likely to be employed, have medical insurance coverage, or have a BMI higher than 30. A higher percentage of WIHS participants had consumed alcohol during the past 12 months (54.4% vs 37.5%). A higher percentage of WIHS participants (both HIV infected and uninfected) had history of smoking cigarettes (68.0% vs 37.2%; \(P < .001\)). Among current smokers at enrollment in the two studies, the cumulative exposure (pack-years) was more than 50% higher in WIHS.

**RESULTS**

**WIHS Cohort**

Median age at enrollment of all 3,549 WIHS participants was 34.9 years (interquartile range [IQR], 29.3 to 40.4), and was higher in HIV-infected women (35.6 vs 32.4 years; \(P < .001\); Table 1). The racial/ethnic composition of both groups was similar. At their baseline visit, HIV-infected women were less likely to be currently employed, or to drink alcohol, and were more likely to have medical insurance (including Medicaid) than the HIV-uninfected comparators. The HIV-infected women had lower baseline BMI. Two thirds of WIHS participants reported a history of smoking. While fewer HIV-infected than uninfected women were current smokers, the median lifetime cigarette consumption for current smokers was higher among HIV-infected women. The median lifetime cigarette consumption among all WIHS women who reported smoking at enrollment was 8.4 pack-years (IQR, 3.5 to 16.0).

**Lung Cancer Incidence**

With 25,000 PYs follow-up, and median follow-up for individual women of 5.8 years (IQR, 4.8 to 12.1), we observed 14 incident lung cancers, yielding an overall lung cancer incidence rate of 56.0 per 100,000 PYs (Table 2). The incidence rates did not differ by HIV status (exact \(P = .58\)). Further, incidence rates did not differ between pre-HAART and HAART eras in the cohort as a whole (exact \(P = .81\)) or in the HIV-infected women.

Unadjusted lung cancer incidence rates were significantly associated with older age (Table 3). Further, lung cancer incidence was highest among non-Hispanic blacks when compared with the combined nonblack groups (incidence rate ratio, 10.1; 95% CI, 1.5 to 431; Table 3). Black women were significantly more likely to be current smokers at baseline (59% vs 45%; \(P < .001\)) but among current smokers, black women reported significantly lower pack-years compared to nonblack women (median, 7.5 vs 10.0 PYs; \(P = .008\)).

**Table 2. Unadjusted Lung Cancer Incidence in the Women’s Interagency HIV Study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All</th>
<th>Pre-HAART Era:1994-1996</th>
<th>HAART Era:1997-2003</th>
<th>Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed No. with cancer</td>
<td>14</td>
<td>3</td>
<td>11</td>
<td>0.71</td>
<td>0.19 to 3.97</td>
</tr>
<tr>
<td>PYs per 100,000 PYs</td>
<td>25,000</td>
<td>4,059</td>
<td>20,941</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR per 100,000 PYs</td>
<td>56.0</td>
<td>73.9</td>
<td>52.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed No. with cancer</td>
<td>12</td>
<td>2</td>
<td>10</td>
<td>1.03</td>
<td>0.22 to 9.69</td>
</tr>
<tr>
<td>PYs per 100,000 PYs</td>
<td>18,825</td>
<td>3,221</td>
<td>15,604</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR per 100,000 PYs</td>
<td>63.7</td>
<td>62.1</td>
<td>64.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed No. with cancer</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.16</td>
<td>0.002 to 12.3</td>
</tr>
<tr>
<td>PYs per 100,000 PYs</td>
<td>6,175</td>
<td>838</td>
<td>5,337</td>
<td>1.97</td>
<td>0.52</td>
</tr>
<tr>
<td>IR per 100,000 PYs</td>
<td>32.4</td>
<td>119.3</td>
<td>18.7</td>
<td>3.42</td>
<td></td>
</tr>
<tr>
<td>Rate ratio for HIV positive v HIV negative</td>
<td>1.97</td>
<td>0.52</td>
<td>3.42</td>
<td>0.44 to 18.1</td>
<td>0.03 to 30.7</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td>0.44 to 18.1</td>
<td>0.03 to 30.7</td>
</tr>
</tbody>
</table>

Abbreviations: HAART, highly active antiretroviral therapy; PY, person-years; IR, incidence rate.
Risk Factors for Lung Cancer

Among the characteristics that differed between the age- and race-adjusted WIHS participants and US female population from NHANES III, only smoking history and pack-years of smoking were significantly associated with lung cancer in WIHS. No lung cancers occurred among WIHS women who had never smoked, and a dose-response relationship between pack-years and lung cancer incidence rate was clearly observed among both HIV-infected and uninfected current smokers, though the latter group did not reach statistical significance (Table 3). When stratifying by pack-years, we also found a significant dose-response relationship with lung cancer incidence rates. Among HIV-uninfected women, lung cancers were only observed among women with at least 20 pack-years while the majority of lung cancers in HIV-infected women occurred in those with history of 10 to 20 pack-years of smoking.

The 14 WIHS participants with lung cancer had a median cumulative smoking exposure of 18.9 pack-years, significantly higher than the 9.7 pack-years among the women who smoked but did not develop lung cancer (P = .002). Pack-years of smoking did not differ by HIV status among lung cancer cases. There was no difference between age of onset of smoking for either HIV-infected (17.3 years) or HIV-uninfected current smokers (17.9 years), or for WIHS women with or without incident lung cancer.

History of previous injection drug use (IDU) was present in both HIV-uninfected women and three of the 12 HIV-infected women with lung cancer, while three additional HIV infected women reported current IDU. The incidence rate for lung cancer among those with current or prior history of IDU was 96.5/100,000 PYs, versus 36.1/100,000 PYs in those without IDU (incidence rate ratio, 2.67; 95% CI, 0.81 to 7.35), and adjustment for age and pack-years did not statistically alter this result.

Clinical Data Among the WIHS Women With Lung Cancer

The median age at lung cancer diagnosis in the 12 HIV infected women was 53.3 years (range, 36 to 64). All were non-Hispanic black, with a median of 15.5 pack-years smoking exposure (range, 10.0 to 96.3 pack-years). Median CD4 cells and plasma HIV-1 RNA levels at the WIHS visit before lung cancer diagnosis were 276/mm³ (range, 0 to 893/mm³) and 3,400 copies/mL (range, 550 to 310,000 copies/mL). Prior AIDS defining conditions were present in eight (67%). At the visit before diagnosis of lung cancer, two patients were taking HAART, three were on combination ART, and seven were taking no antiretroviral therapy. Pathologic types of lung cancer included adenocarcinoma, poorly differentiated nonsmall cell, and squamous cell carcinoma, all equally distributed. Advanced cancer (stage IIIB or IV) was diagnosed in seven of 14 (50%), while stage I or II was present in 6.

Table 3. Unadjusted Lung Cancer Incidence in WIHS by Age, Race, Smoking History, and HIV Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Lung Cancers</th>
<th>Pys</th>
<th>IR/100,000 PYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (P &lt; .0001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger than 30</td>
<td>0</td>
<td>2,442</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>1</td>
<td>9,444</td>
<td>10.6</td>
</tr>
<tr>
<td>40-49</td>
<td>4</td>
<td>9,247</td>
<td>43.3</td>
</tr>
<tr>
<td>50 and older</td>
<td>9</td>
<td>3,067</td>
<td>293.4</td>
</tr>
<tr>
<td>Race (P = .056)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>13</td>
<td>14,047</td>
<td>92.5</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>0</td>
<td>3,804</td>
<td>0</td>
</tr>
<tr>
<td>Latina</td>
<td>1</td>
<td>6,408</td>
<td>15.6</td>
</tr>
<tr>
<td>Other groups</td>
<td>0</td>
<td>741</td>
<td>0</td>
</tr>
<tr>
<td>Second race comparison (P = .007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>13</td>
<td>14,047</td>
<td>92.5</td>
</tr>
<tr>
<td>All others</td>
<td>1</td>
<td>10,953</td>
<td>9.1</td>
</tr>
<tr>
<td>Cigarette smoking history (Overall (P = .003))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
<td>7,419</td>
<td>0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1</td>
<td>3,889</td>
<td>25.7</td>
</tr>
<tr>
<td>Current smoker</td>
<td>13</td>
<td>13,576</td>
<td>95.8</td>
</tr>
<tr>
<td>HIV negative (P = .50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
<td>1,770</td>
<td>0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0</td>
<td>749</td>
<td>25.7</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2</td>
<td>3,626</td>
<td>55.2</td>
</tr>
<tr>
<td>HIV positive (P = .007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0</td>
<td>5,648</td>
<td>0</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1</td>
<td>3,140</td>
<td>31.8</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11</td>
<td>9,951</td>
<td>110.5</td>
</tr>
</tbody>
</table>

Table 4. Standardized Incidence Ratios for Lung Cancer Incidence in the Women’s Interagency HIV Study Compared With the Surveillance, Epidemiology and End Results Program

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observed Person-Years</th>
<th>No. of Lung Cancers</th>
<th>Observed Expected</th>
<th>Standardized Incidence Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>25,000</td>
<td>14</td>
<td>4.60</td>
<td>3.04</td>
<td>1.66 to 5.10</td>
</tr>
<tr>
<td>HIV positive</td>
<td>18,825</td>
<td>12</td>
<td>3.65</td>
<td>3.28</td>
<td>1.70 to 5.74</td>
</tr>
<tr>
<td>HIV negative</td>
<td>6,175</td>
<td>2</td>
<td>0.95</td>
<td>2.11</td>
<td>0.25 to 7.61</td>
</tr>
<tr>
<td>Pre-HAART era (1994-1996)</td>
<td>4,059</td>
<td>3</td>
<td>0.48</td>
<td>6.22</td>
<td>1.28 to 18.19</td>
</tr>
<tr>
<td>HIV positive</td>
<td>3,221</td>
<td>2</td>
<td>0.40</td>
<td>4.97</td>
<td>0.60 to 17.96</td>
</tr>
<tr>
<td>HIV negative</td>
<td>838</td>
<td>1</td>
<td>0.08</td>
<td>12.57</td>
<td>0.32 to 70.05</td>
</tr>
<tr>
<td>HAART era (1997-2006)</td>
<td>20,941</td>
<td>11</td>
<td>4.12</td>
<td>2.67</td>
<td>1.33 to 4.78</td>
</tr>
<tr>
<td>HIV positive</td>
<td>15,604</td>
<td>10</td>
<td>3.25</td>
<td>3.08</td>
<td>1.47 to 5.66</td>
</tr>
<tr>
<td>HIV negative</td>
<td>5,337</td>
<td>1</td>
<td>0.87</td>
<td>1.15</td>
<td>0.03 to 6.40</td>
</tr>
</tbody>
</table>

Abbreviation: HAART, highly active antiretroviral therapy.
two; staging information was unavailable in five. Median survival from diagnosis of lung cancer was 14.1 months (range, 3.0 to 62 months) with one women remaining alive, at 28 months.

The two HIV-uninfected WIHS women with incident lung cancer were 46 and 56 years of age, with 25.0 and 30.9 PYs smoking history. One was non-Hispanic black while the other was Latina. Survival was 1.6 and 8 months from diagnosis.

DISCUSSION

We found a substantially increased risk of lung cancer among both HIV-infected and at-risk uninfected women compared with population-based expectations. A possible explanation is the high rate of cigarette smoking in WIHS women, reported by approximately twice as likely to smoke as age- and race-matched women, studied as part of NHANES III. While multiple other behavioral and demographic differences between WIHS and NHANES III women were found, only smoking was significantly associated with incident lung cancer. Several prior reports have also documented a strong history of tobacco exposure in their HIV-infected patients who developed lung cancer.

As previously noted, we found that WIHS women were almost twice as likely to smoke as age- and race-matched women, studied as part of NHANES III. While multiple other behavioral and demographic differences between WIHS and NHANES III women were found, only smoking was significantly associated with incident lung cancer. Thus, when compared to population-based controls, any increase in the incidence of lung cancer among HIV-infected women could be explained by differences in history of tobacco exposure.

When comparing lung cancer incidence rates between HIV-infected women in the WIHS and the internal group of HIV-uninfected women, no differences were apparent. Of importance, all women with lung cancer had strong histories of tobacco exposure, thus serving to explain the equivalent increase in lung cancer among both HIV-infected and uninfected women, when compared with population-based expectations. Of note, both HIV-infected and -uninfected WIHS participants were statistically more likely to smoke than the NHANES III/US female population. Nonetheless, HIV-uninfected women with lung cancer had smoked for 25 and 30 PYs, while those infected with HIV had 10 to 20 PY smoking history. It is possible that HIV may accelerate the development of lung cancer.

Several studies have shown a significant increase in lung cancer among HIV-infected patients after the introduction of HAART. The remarkable prolongation in survival due to HAART may have allowed evaluation of the potential role of cigarette smoking as a cause for the increase in lung cancer among WIHS women. The WIHS study followed a large cohort prospectively for up to 12 years, and all cancer diagnoses were confirmed. However, details of treatment or response were not available. Furthermore, despite our large database of more than 3,500 women and 25,000 PYs of follow-up, the small number of incident lung cancers limited the statistical power. Nonetheless, a prospective comparison between HIV-infected women, and HIV-uninfected women with similar lifestyles was possible, augmenting the study design. Further, the careful documentation of tobacco exposure, and the ability to compare our data with behavioral data from age- and race-matched US women (NHANES III) allowed evaluation of the potential role of cigarette smoking as a cause for the increase in lung cancer among WIHS women.

We have demonstrated that WIHS participants, whether HIV-infected or at-risk but uninfected, have a significantly increased risk of lung cancer when compared with the rates expected in the general population, while no difference in lung cancer rates among HIV-infected versus uninfected women was seen. Of importance, both HIV-infected and -uninfected WIHS participants were significantly more likely to have smoked than the NHANES III/US female population. All WIHS women with lung cancer had history of smoking, and the risk of cancer increased with increasing smoking exposure. The development of lung cancer among HIV-infected women appears very strongly correlated with tobacco exposure. As such, the development and implementation of smoking cessation programs aimed at HIV-infected persons will be of increasing importance. The precise role of HIV infection, per se, in terms of the development or progression of lung cancer awaits further clarification.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.
8

REFERENCES


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Provision of study materials or patients: Alexandra M. Levine, Nancy A. Hessol, Susan Preston-Martin, Mardge H. Cohen, Kathryn Anastos, Howard Minkoff