Original Article

Comparing cancer incidence in an observational cohort of Medicaid beneficiaries with and without HIV, 2001-2015

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ABSTRACT

Background. Life expectancy among people with HIV (PWH) is increasing, making chronic conditions—including cancer—increasingly relevant. Among PWH, cancer burden has shifted from AIDS-defining cancers (ADCs) toward non-AIDS-defining cancers (NADCs).

Setting. We described incidence of cancer in a claims-based cohort of Medicaid beneficiaries. We included 43,426,043 Medicaid beneficiaries (180,058 with HIV) from 14 US states, aged 18-64, with >6 months of enrollment (with no dual enrollment in another insurance) and no evidence of a prior cancer.

Methods. We estimated cumulative incidence of site-specific cancers, NADCs, and ADCs by baseline HIV status, using age as the time scale and accounting for death as a competing risk. We compared cumulative incidence across HIV status to estimate risk differences. We examined cancer incidence overall and by sex, race/ethnicity, and calendar period.

Results. PWH had a higher incidence of ADCs, infection-related NADCs, and death. For NADCs like breast, prostate, and colon cancer, incidence was similar or higher among PWH below age 50 but higher among those without HIV by age 65. Incidence of lung and head and neck cancer was always higher for female beneficiaries with HIV, while the curves crossed for male beneficiaries. We saw only small differences in incidence trends by race/ethnicity.

Conclusion. Our findings suggest an increased risk of certain NADCs at younger ages among PWH, even when compared against other Medicaid beneficiaries, and highlight the importance of monitoring PWH for ADCs and NADCs. Future work should explore possible mechanisms explaining the differences in incidence for specific cancer types.

KEY WORDS

Human immunodeficiency virus; Medicaid; AIDS-defining cancer; non-AIDS-defining cancer
INTRODUCTION

Since the introduction of effective antiretroviral therapy (ART) in 1996, there have been steady declines in mortality among people with HIV (PWH) in the United States (US).\textsuperscript{1,2} As life expectancy increases, the population of PWH is aging. One study estimated that nearly half of PWH in the US were aged 50 or older,\textsuperscript{3} and this percentage will only increase over time. Consequently, chronic conditions (e.g., cancer, hypertension, and diabetes) are on the rise among PWH, and understanding how HIV infection and HIV care interact with management of these conditions is a critical area of research.

Cancer has long been a major comorbid condition for PWH, particularly AIDS-defining cancers (ADCs). In the modern ART era, incidence of ADCs has decreased, and the cancer burden in PWH has shifted toward non-AIDS-defining cancers (NADCs).\textsuperscript{3,4} NADCs are now a leading cause of death among PWH.\textsuperscript{5–11} Compared to the general US population, PWH have higher rates of lung cancer (partly due to elevated rates of smoking)\textsuperscript{3} and NADCs with infectious causes, due to worse immune control of infections with potentially carcinogenic pathogens (e.g., human papillomavirus, HPV). Conversely, PWH have lower incidence of several common NADCs, including breast, prostate, and colorectal cancer.\textsuperscript{4} Nonetheless, PWH have been shown to have advanced stage at diagnosis, worse outcomes, and higher cancer-specific mortality than the general population.\textsuperscript{12–14}

Here, we evaluated the burden of cancer in Medicaid, which is consequential for multiple reasons. Medicaid is a public, state-administered insurance source for individuals in the US who are low income or have disabilities and the largest source of health insurance for PWH. Approximately 40\% of PWH in the US are covered by Medicaid, compared to 13\% of the general population.\textsuperscript{15} The Medicaid population is diverse and includes a comparison group of people without HIV with similar socioeconomic status, access to care, and risk factor burden.\textsuperscript{16} Medicaid also provides an important complement to the existing HIV cohorts in the US, which are often tied to academic care centers.\textsuperscript{17} Finally, Medicaid provides a large sample size to examine burden in a wide variety of cancers by HIV status – even among
subgroups defined by sex and race/ethnicity and at younger ages than many other data sources. Specifically, we examined incidence of ADCs, NADCs, and site-specific cancers among more than 43 million Medicaid beneficiaries, including more than 180,000 with HIV.

METHODS

Study Sample

We obtained Medicaid Analytic eXtract (MAX) data from the Centers for Medicare and Medicaid Services for beneficiaries enrolled in 14 states, 2001-2015. MAX data were available through 2015 for California (CA), Georgia (GA), New York (NY), and Pennsylvania (PA); through 2014 for Massachusetts (MA), Ohio (OH), Texas (TX), and Washington (WA); and through 2013 for Alabama (AL), Colorado (CO), Florida (FL), Illinois (IL), Maryland (MD), and North Carolina (NC). Our data covered two years of Medicaid Expansion for CA and NY and one year for MA, OH, PA, and WA.

We included beneficiaries aged 18-64 years, who had >6 months of continuous enrollment in Medicaid (without dual enrollment in Medicare or private insurance) and no cancer diagnosis prior to baseline (evidenced by the presence of 1 diagnosis code for any cancer in either the inpatient, outpatient, or long-term care files). Baseline for follow-up was defined as six months from the start of the first enrollment period. Beneficiaries aged 65 or older were excluded because the vast majority are dually enrolled in Medicare. We only considered a beneficiary’s first enrollment period where the inclusion criteria were met because, if a beneficiary experienced a coverage lapse, it was possible for cancer to occur during the lapse. Beneficiaries were considered lost to follow-up when they disenrolled from Medicaid. All beneficiaries were administratively censored on September 30, 2015 (the last date for International Classification of Diseases 9th Edition coding).
Our exposure was HIV status at baseline, based on the presence of an inpatient claim or outpatient claim (with a 2nd outpatient claim within two years) with an HIV-related diagnosis code prior to baseline.20–22 Our outcome was first cancer diagnosis, defined by the presence of an inpatient claim or outpatient claim (with a 2nd outpatient claim within two years) of the relevant cancer type. We examined cancer types which are common in the general US population or among PWH. The specific types examined were anal, breast, cervical, colon, head and neck, Hodgkin’s lymphoma, kidney, Kaposi’s sarcoma, larynx, leukemia, liver, lung, non-Hodgkin’s lymphoma, oropharynx, pancreatic, and prostate. See Table S1 for the codes used to define HIV status and cancer diagnoses. We also examined incidence of all cancers listed in Table S1 combined, all ADCs (cervical, Kaposi’s sarcoma, and non-Hodgkin’s lymphoma), all NADCs listed in Table S1, and infection-related NADCs.23

Statistical Analysis

Our analyses were guided by a framework for descriptive studies.24 We described our study sample by estimating, stratified by HIV status, the median and interquartile range of age at baseline and the number and proportion of beneficiaries by sex (female, male), race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, Asian/Pacific Islander, Other/Unknown), and state of residence. We estimated the standardized mean difference, to compare these characteristics across HIV status (using the R package tableone). We used survival analysis to examine time to first cancer by HIV status. We estimated cumulative incidence (risk) curves overall and by HIV status, using the Aalen-Johansen estimator to account for death as a competing event (using the survfit function from the R survival package).25,26 We treated incidence of any other cancer type as a competing event. Following the example of previous analyses of cancer incidence among PWH, we used continuous age as our time scale, with 18 years as the minimum age and 65 years as the maximum.27 Individuals were considered late entries if they enrolled in Medicaid at >18 years of age and were censored when they reached 65
years of age. We took the difference between the risk curves for those with and without HIV to estimate crude risk differences (RD). We obtained estimates overall and stratified by sex, select race/ethnicity categories (non-Hispanic white, non-Hispanic Black, Hispanic), and calendar period (2001-2005, 2005-2010, 2010-2015).

In a supplementary analysis, we restricted our sample to beneficiaries who were classified as being eligible for Medicaid with full benefits. Restricted benefits occur for a variety of reasons, and coverage under restricted benefits varies by state. If a beneficiary is not dually enrolled in Medicare or private insurance and has full benefits, we can be as certain as possible that their health care encounters will appear in our data.

All analyses were carried out in R version 4.0.5 (The R Foundation, Vienna, Austria).

RESULTS

There were 43,426,043 Medicaid beneficiaries (including 180,058 PWH) who met our eligibility criteria, with a median follow-up of 13 months (interquartile range: 12, 24). Baseline characteristics differed by HIV status (Table 1). PWH were older (median: 42.3 years) than beneficiaries without HIV (median: 28.0 years). Almost two-thirds of beneficiaries without HIV were female (65.0%), while only one-third with HIV were female (35.9%). PWH were more likely to be non-Hispanic Black than beneficiaries without HIV (47.8% vs. 17.4%) and less likely to be non-Hispanic white (23.7% vs. 32.8%) or Hispanic (10.5% vs. 32.5%). Nearly half of beneficiaries without HIV lived in CA (46.8%), while NY was the largest contributor of PWH (36.7%).

All Cancers Combined

PWH had a higher incidence of all cancers combined from age 18 to 65 than beneficiaries without HIV (Table 2). Cancer incidence among PWH increased steadily with age, while incidence among
beneficiaries without HIV began to increase dramatically around age 50 (Table 2). Across all ages examined, the RD comparing PWH to those without HIV was higher in male beneficiaries, compared to female beneficiaries (Table 2), and when looking at Hispanic beneficiaries, compared to non-Hispanic white and non-Hispanic Black beneficiaries (Table S2). Death was an important competing event among PWH in this time period (Table S3), and non-Hispanic Black PWH had a higher risk of death than any other group (Figure 1). Incidence of death among PWH decreased consistently across calendar time (Figure S1).

**AIDS-Defining Cancers**

Among PWH, ADCs were more common at younger ages, with incidence plateauing around age 50 (risk: 12.23%; 95% CI: 11.54, 12.93) (Figure 1, Table 2). Male PWH had a higher incidence of ADCs than female PWH; at age 65, incidence was 14.54% (95% CI: 13.46, 15.62) among male PWH but 9.99% (95% CI: 9.07, 10.91) among female PWH (Table 2). Incidence of ADCs among beneficiaries without HIV remained low at all ages (Table 2, Figure 1). Findings were similar when stratified by sex (Figure 1). When stratifying by race/ethnicity, we saw the largest differences in incidence of ADCs by HIV status among Hispanic beneficiaries, partly due to lower incidence of cancer in Hispanic beneficiaries without HIV (Table S2). Incidence of ADCs consistently decreased among PWH across calendar time (Table S4). Among male and female PWH, non-Hodgkin’s lymphoma was the most common ADC, followed by cervical cancer for female PWH and Kaposi’s sarcoma for male PWH (Table S5). Site-specific ADC incidence among PWH was similar when stratified by race (Table S6).

**Non-AIDS-Defining Cancers**

The combined incidence of NADCs among PWH increased consistently across all ages, resulting in NADC incidence overtaking ADC incidence by age 52 (Figure 1). While NADC incidence among
beneficiaries without HIV was low at younger ages, incidence increased rapidly starting at age 50, such that incidence by age 65 nearly reached incidence among PWH (Table 2). Like for ADCs, we saw the largest differences in incidence of NADCs by HIV status among Hispanic beneficiaries, again due to the lower incidence of NADCs among Hispanic beneficiaries without HIV (Table S2). Incidence of NADCs by age 65 increased over calendar time among PWH but remained similar among those without HIV (Table S4). Among beneficiaries with full Medicaid benefits, incidence of NADCs was marginally elevated at age 65 for beneficiaries with and without HIV, with a RD of 0.19% (95% CI: -0.52, 0.89), compared to 0.74% (95% CI: 0.07, 1.42) in the main analysis (Table S7).

When examining infection-associated NADCs, PWH had a higher incidence than those without HIV across all ages (Table 2). Incidence of infection-associated NADCs was higher among male than female beneficiaries, regardless of HIV status, and the RD across HIV status was further from the null among male beneficiaries. Infection-associated NADC incidence was higher among non-Hispanic white PWH at age 65 (Table S2) than the other race/ethnicity categories. Incidence of infection-associated NADCs increased across calendar time for PWH who were 50 and older but remained stable among those without HIV over time (Table S4).

**Site-Specific NADCs**

By age 65, lung cancer was the most common NADC among female (3.55%; 95% CI: 3.21, 3.93) and male (3.04%; 95% CI: 2.76, 3.34) PWH and the second most common NADC among female (2.50%; 95% CI: 2.47, 2.54%) and male (3.51%; 95% CI: 3.46, 3.56) beneficiaries without HIV (Table S8). Lung cancer incidence was higher among female PWH than those without HIV at all ages; incidence was higher among male PWH than those without HIV until age 62 (Figure 2). Among non-Hispanic white and non-Hispanic Black beneficiaries, lung cancer incidence curves merged for beneficiaries with and
without HIV at the oldest ages; among Hispanic beneficiaries, lung cancer incidence remained higher among PWH compared to those without (Table S9, Figure S2).

Breast cancer was the most common NADC among female beneficiaries without HIV (6.67%; 95% CI: 6.61, 6.73) and the second most common cancer among female PWH (3.27%; 95% CI: 2.91, 3.66; Table S8). Breast cancer incidence was similar or higher among female PWH at younger ages; the incidence curves crossed at age 46, resulting in incidence becoming higher among female beneficiaries without HIV (Figure 2). These patterns were similar when stratified by race/ethnicity (Table S9, Figure S2).

Prostate cancer was the most common NADC among male beneficiaries without HIV (3.97%; 95% CI: 3.91, 4.03) and the third most common cancer among male PWH (2.30%; 95% CI: 2.02, 2.60; Table S8). Prostate cancer incidence was comparable among male beneficiaries with and without HIV below age 50, but incidence became higher for male beneficiaries without HIV at older ages (Table S8, Figure 2). When stratified by race/ethnicity, similar patterns across age were seen among non-Hispanic Black and Hispanic male beneficiaries (Figure S2). The difference in incidence at age 65 by HIV status was highest for non-Hispanic Black male beneficiaries, partly due to a higher prostate cancer incidence among non-Hispanic Black male beneficiaries without HIV (Table S9). For non-Hispanic white male beneficiaries, prostate cancer incidence was comparable at all ages (Table S9, Figure S2).

Head and neck cancer was more common among PWH than those without (Table S8), with consistent results by subtype (Table S10). While head and neck cancer incidence remained higher across all ages among female PWH compared to those without HIV (Figure 3), incidence among male beneficiaries without HIV approached incidence among male PWH by age 65 (Table S8, Figure 3). Head and neck cancer incidence was higher among beneficiaries with HIV at all ages among non-Hispanic white and Hispanic beneficiaries and among all but the oldest ages among non-Hispanic Black beneficiaries (Table S9, Figure S3).
We also observed clear patterns in incidence of several less common NADCS. Colon cancer incidence was higher among both female and male PWH at younger ages; the incidence curves crossed by age 60, resulting in higher incidence among beneficiaries without HIV at older ages (Table S8, Figure 2). This pattern was similar for non-Hispanic white beneficiaries and less pronounced for non-Hispanic Black and Hispanic beneficiaries (Table S9, Figure S2). Liver cancer incidence and anal cancer incidence were modestly higher among beneficiaries with HIV beginning at age 35 (Table S8, Figure 3). Both liver and anal cancers were more common by age 65 among male than female beneficiaries, regardless of HIV status (Table S8, Figure 3). Incidence of anal cancer by age 65 among non-Hispanic white PWH was nearly double the incidence among non-Hispanic Black and Hispanic PWH, while incidence among beneficiaries without HIV was similar across race/ethnicity groups (Table S9, Figure S3).

DISCUSSION

Here, we described incidence of ADCs and select NADCs among adult Medicaid beneficiaries with and without HIV. PWH had a higher incidence of all cancers combined than beneficiaries without HIV. ADCs were more common among PWH at younger ages, while NADCs became more common over 50. We also noted differences in incidence by sex, with male PWH having a higher incidence of ADCs and infection-associated NADCs than female PWH. While incidence of the cancer categories was similar among PWH by race/ethnicity, risk differences across HIV status were largest among Hispanic beneficiaries, largely due to a deficit of cases among Hispanic beneficiaries without HIV. When examining site-specific cancers, a common trend for many NADCs was that incidence was higher among PWH at younger ages but that incidence among beneficiaries without HIV caught up by age 65.

Lung cancer was the most common NADC among male and female PWH. As in prior studies, lung cancer incidence was higher among PWH than among beneficiaries without HIV.\textsuperscript{29,30} Cigarette smoking, the most common cause of lung cancer in the US, is high among PWH and likely to contribute to the
difference in lung cancer incidence. Current smoking prevalence among PWH in the US is estimated to be 47%. Current smoking among Medicaid beneficiaries is lower (28% among men, 26% among women) than among PWH, but higher than their privately insured counterparts (12.5% among men, 10.3% among women). The higher smoking prevalence in our study population may contribute to the observation that lung cancer incidence curves for beneficiaries with and without HIV crossed at older ages for male, non-Hispanic white, and non-Hispanic Black beneficiaries.

Consistent with prior studies, we also observed a higher incidence of infection-associated NADCs, including head and neck, liver, and anal cancers. Smoking, alcohol use, and HPV infection are risk factors for head and neck cancers. Anal and liver cancers are virally mediated by HPV and hepatitis B and C infection, respectively. PWH have a higher prevalence of these co-infections compared to the general population. Additionally, retention in care and access to ART impact the risk of infection-associated cancers among PWH. One prior study found that, although PWH on Medicaid had a high level of retention in HIV care and viral suppression (63%), they were less likely to be retained in care or virally suppressed compared to those with private insurance or Medicare. This may influence the burden of infection-associated cancers in this study population.

For breast, prostate, and colon cancers—NADCs common in the general population with population-level screening—we found that incidence was similar or higher among PWH at younger ages than beneficiaries without HIV but lower at older ages. Our findings for older beneficiaries are consistent with most prior studies. However, one prior study reported lower incidence of these cancers at younger ages among PWH compared to the general population. More work is needed to understand the factors that may influence burden of these cancers among Medicaid beneficiaries with and without HIV and how these factors differ relative to the general population.

One previous study used competing event methodology to estimate incidence of eight cancer types by HIV status, in the North American AIDS Cohort Collaboration on Research and Design
Considering the overlapping calendar periods, we saw higher incidences in PWH of non-Hodgkin’s and Hodgkin’s lymphoma, Kaposi’s sarcoma, and liver cancer; similar incidences of lung, colon, and anal cancer; and lower incidence of oropharyngeal cancer. Among those without HIV, we saw higher incidence of liver cancer; comparable incidence of lung and colon cancer; and lower incidence of oropharyngeal cancer. The lower incidence of oropharyngeal cancer may be explained by a higher proportion of female participants in our sample (in NAACORD, 86% of PWH and 93% of those without HIV were male). In the general US population, lifetime incidence of oropharyngeal cancer among men is double that of women. It is possible that the higher incidence of liver cancer is due to greater alcohol use or hepatitis C infection among Medicaid beneficiaries, which we can investigate in future work.

Limitations of our analysis include that we had no information on beneficiaries prior to enrollment in Medicaid or before the start of our data in 2001. We could be failing to exclude individuals with prior cancers or missing individuals with HIV if there was no record of those conditions in the first six months of eligibility. Our study period only covered the 2001-2015 period; we will examine more recent data in future work. Our study sample also only included adults under the age of 65. Additionally, our definition of HIV did not consider viral suppression or immune function (due to lack of these data in Medicaid) and only considered baseline HIV status. While we saw in preliminary analyses that most new HIV diagnoses in the first eligibility period occurred within six months, there were 103,812 beneficiaries who had a diagnosis of HIV post-baseline. Nevertheless, given the time from HIV seroconversion to development of cancer and the median follow-up of 13 months, it is unlikely that cancer would have developed and been observed except in a small proportion of PWH. Furthermore, our combined outcomes for all cancers and NADCs include only those cancers in Table S1. While we accounted for most common cancers in the US, our list does not include other, rarer cancers like soft tissue cancers. We also did not look specifically at non-infection-related NADCs. However, to estimate incidence of non-infection-related NADCs, one can subtract the risk of infection-related NADCs from the risk of all NADCs.
Our analyses were purely descriptive, and the risks and risk differences should be interpreted as such. We partly controlled for differences in socioeconomic status and healthcare by using Medicaid data and for sex and race/ethnicity by stratification. In future causal analyses, researchers will need to consider these characteristics as well as other potential confounders, such as geographic region, comorbidities, or substance use disorders, and differential loss-to-follow-up.

Our study is the first to compare incidence of a broad range of cancers by HIV status within a nationwide sample of Medicaid beneficiaries. Our sample size enabled us to evaluate cancer incidence overall and by sex and race/ethnicity sub-groups. We saw a high incidence of cancer among Medicaid beneficiaries. As in prior studies, we observed a high incidence of ADCs and some NADCs among PWH across all ages. We also saw meaningful differences in the incidence of common NADCs across ages between beneficiaries with and without HIV. That these differences remained in our Medicaid sample, which partially controlled for social determinants of health like access to healthcare, indicates that further analyses are needed to explore other possible drivers, such as cancer screening, behavioral differences, or biological mechanisms. While there exists little evidence on whether cancer prevention guidelines should differ for PWH, the differences in cancer incidence we observed here highlight the importance of access to integrated care for low income PWH, to allow for receipt of routine cancer screening, monitoring for potentially carcinogenic infections, interventions to reduce cancer-related behaviors such as smoking, and other cancer prevention services.
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FIGURE LEGENDS

Figure 1. Cumulative incidence of AIDS-defining cancers, non-AIDS-defining cancers, and death by HIV status (A) overall and among (B) female beneficiaries, (C) male beneficiaries, (D) non-Hispanic Black beneficiaries, (E) non-Hispanic white beneficiaries, and (F) Hispanic beneficiaries.

Figure 2. Cumulative incidence of NADCs that are common in the general US population by sex. Note that the range of the y-axes differ, to highlight the observed trends by HIV status.

Figure 3. Cumulative incidence of select NADCs by sex. Note that the range of the y-axes differ, to highlight the observed trends by HIV status.