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Cancer incidence and mortality by HIV status in a Georgia prisoner cohort during the HAART era

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ABSTRACT

Objective: Non-AIDS-defining cancers (NADCs) have emerged as significant contributors to cancer mortality and morbidity among persons with HIV. Because NADCs are also associated with many social and behavioral risk factors that underlie HIV, it is difficult to determine the extent to which each of these factors contributes to NADC risk. We examined cancer incidence and mortality among persons with a history of incarceration, because distributions of other cancer risk factors are likely similar between HIV-infected and non-infected prisoners.

Design: Retrospective cohort study.

Participants: Cohort of 22,422 persons incarcerated in Georgia, USA prisons on June 30, 1991, and still alive in 1998.

Outcome measures: Cancer incidence and mortality were assessed between 1998 and 2009, using cancer and death registry data matched to prison administrative records. Age, race and sex-adjusted standardized mortality and incidence ratios, relative to the general population, were calculated for AIDS-defining cancers, viral-associated NADCs, and non-infection-associated NADCs, stratified by HIV status.

Results: There were no significant differences in cancer mortality relative to the general population among those in this cohort, regardless of HIV status. In contrast, cancer incidence was elevated among the HIV-infected. Furthermore, incidence of viral-associated NADCs was significantly higher among HIV-infected vs. those without HIV infection (Ratio of Standardized Incidence Ratios = 6.1, 95% CI: 3.0, 11.7, $p<0.001$).

Conclusions: Among HIV-infected members of this cohort, cancer incidence was elevated relative to the general population, likely related to increased prevalence of oncogenic viral co-infections. Cancer prevention and screening programs within prisons may help to reduce the cancer burden among this high-risk population.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- HIV-infected and uninfected study arms both experienced a history of incarceration and likely have a similar distribution of cancer risk factors.
- The study design and long follow-up period emphasize long-term consequences of viral infection and exposure to alcohol and tobacco.
- Underestimation of associations with HIV-infection is possible as we could not ascertain if those who tested HIV-negative on prison entry later seroconverted to HIV.

INTRODUCTION

In contrast to declining trends in incidence for the two major AIDS-defining cancers (ADCs, Kaposi sarcoma and non-Hodgkin lymphoma), rates for some non-AIDS-defining cancers (NADCs) remain elevated or have increased over time for HIV-infected persons despite widespread access since 1996 to highly active antiretroviral therapy (HAART).[1] Although the causes of temporal increases for some NADCs are complex and multifactorial, an increased prevalence of lifestyle-related risk factors (e.g., tobacco exposure) and the role of prolonged moderate levels of immune suppression among HIV-infected versus uninfected persons likely contribute to increased rates of NADCs.[2-4] Studying cancer among prisoners with and without HIV offers an opportunity to assess the extent to which the heightened risk for malignancies is due to HIV infection itself versus the social and behavioral factors that underlie HIV infection. Regardless of HIV status, incarcerated persons often experience substance abuse, poverty and poor access to medical care prior to incarceration.[5-7] Thus, among inmates, the distribution of important cancer risk factors may be similar between HIV-infected and non-infected persons.

Numerous studies have found two- to three-fold elevated risk for NADCs among HIV-infected people relative to the general population.[8-10] A meta-analysis suggests that the cancer burden differs among those with and without HIV, with the former having excesses of infection-associated malignancies, notably Hodgkin lymphoma (Epstein Barr virus, EBV), anal cancer (human papillomavirus, HPV), and liver cancer (hepatitis B and hepatitis C viruses, HBV and HCV).[8-11] Lung cancer rates are also higher among HIV-infected persons.[12] The reasons why the distribution of NADCs differs between HIV-infected and non-infected individuals are unclear, though some hypotheses exist. The increased prevalence of smoking among HIV-infected persons[13] does not fully account for the observed elevated lung cancer incidence.[12 14] Persistent lung injury from pneumonias, prolonged immunosuppression, oxidative stress, and HAART toxicity may contribute to lung tumorigenesis.[8 11 12] Higher prevalence of co-infection with oncogenic viruses in some subgroups of HIV patients likely plays a role. For example, persistent anal HPV infections are high among HIV-infected men who have sex with men (MSM), contributing to the observed increase in invasive anal cancer in this population.[15] Similarly, liver cancer rates are elevated among HIV-infected persons with a history of injection drug use due

to a high prevalence of chronic HBV and HCV infections. EBV is nearly ubiquitous among all US adults, however among HIV-infected individuals Hodgkin lymphoma is a common NADC, perhaps due to changes in the immune system mediated by HAART.[8 16]

We previously conducted an retrospective cohort study of all-cause mortality in 23,510 incarcerated men and women in the state of Georgia (GA) on June 30, 1991 by linking prison records with the National Death Index (NDI) in 2006.[17] The study was recently updated to include deaths through 2010.[5] While mortality from AIDS, especially in the pre-HAART era, has been substantial in this prisoner population in which 5% is HIV-infected, cancer is a close second to heart disease as a leading cause of death.[5]

The primary goal of the current study was to link the GA prisoner cohort from our previous study to the GA Comprehensive Cancer Registry (GCCR) database in order to ascertain cancer incidence data and to determine and compare cancer incidence patterns in HIV-infected and non-infected cohort members in the HAART era. Specifically, we sought to (1) characterize the distribution of incident cancers and cancer deaths among HIV-infected and uninfected cohort members, (2) compare the distribution of site-specific cancers in this cohort with the general Georgia population using Standardized Incidence Ratios (SIRs) and Standardized Mortality Ratios (SMRs), and (3) compare cancer incidence and mortality rates between the HIV-infected and uninfected cohort members.

METHODS

Study population

As described in our prior studies,[5 17] the initial cohort consisted of all persons incarcerated in Georgia prisons on June 30, 1991. Administrative records containing demographic data and incarceration history were obtained from the Georgia Department of Corrections (GDC) Planning and Strategic Management Section and linked with the NDI through December 31, 2010.[5] For the current analysis, we only considered those participants in the cohort who were alive on January 1, 1998. Between June 30, 1991 and December 31, 1997, a total of 1,088 people died and 22,422 remained alive. Although we had mortality information on the cohort since 1991, cancer incidence data were not available until 1998, which was well

into the HAART era. We also removed from our analytic population 68 persons who did not identify as being "Black" or "White" because we could not generate expected cancer or death counts for them. Therefore, follow-up for study outcomes in the current analysis began on January 1, 1998 and included 22,354 people who were followed until December 31, 2010, cancer incidence or death.

The GDC administrative records contain the result of every HIV test performed during any prison stay. Using data from these records, subjects were classified into two categories, ever HIV-infected or no record of HIV positivity (hereafter referred to as HIV-negative). The latter category includes those with missing HIV test results. Decedents were also classified as being HIV-infected for the entire study period if HIV was listed as the underlying or as a contributory cause of death on the death certificate.

Statistical Analysis

The first aim was to characterize cancer incidence and mortality during 1998-2009 in the cohort of persons in prison on June 30, 1991. To ascertain incident cancer, administrative data on the cohort from the GDC were matched with the GCCR using probabilistic matching algorithms. Invasive cancers were categorized using the International Classification of Diseases for Oncology, *third edition* (ICD-O-3) codes,[18] and only the first cancers were considered. Mortality was assessed through probabilistic matching with GCCR, and, for those with no matches in GCCR, a successive probabilistic matching with the NDI. Mortality data included the date of death and the ICD-9 or ICD-10 codes for the underlying and contributing causes of death.[19 20]

We first calculated the number of person-years of follow-up for the cohort, for both HIV-positive and HIV-negative individuals. We also determined the frequency distributions of descriptive cohort characteristics including: age in 1998, race, sex, educational level, pre-prison employment status, number of prison releases, vital status and cause of death, which were then stratified by HIV status. Finally, we calculated frequency distributions of stage at diagnosis for incident cancers, by HIV status and cancer type. SEER Summary Staging 1977 was used to stage cancers diagnosed between 1998 and 2000, SEER Summary Staging 2000 for cancers

diagnosed between 2001 and 2003, and Collaborative Stage Derived Stage 2000 for cancers diagnosed in 2004 and later.

We used Pearson's chi-square test to assess associations of categorical variables and Student's *t*-test for continuous variables.

The second aim was to compare the Georgia prisoner cohort to the Georgia general population with regard to cancer incidence and mortality. Standardized mortality and incidence ratios (SMRs and SIRs, measures of risk relative to the general population) were calculated for all cancer types: ADCs (Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer), infection-associated NADC, and non-infection-associated NADC. Infection-associated NADCs included: HPV-related anal and oropharyngeal cancer, HBV and/or HCV-related liver cancer and EBV-related Hodgkin lymphoma. All other cancers were considered not to be infection-related NADCs. SMRs were adjusted for age (in 5-year intervals), race, sex and year of death. Underlying population mortality rates in Georgia were determined using SEER*Stat software (http://seer.cancer.gov/seerstat) and were used to calculate expected death counts. SIRs were also adjusted for age (in 5-year intervals), race, sex and year of diagnosis. Underlying population cancer incidence rates in Georgia were determined with SEER*Stat and were used to calculate expected count of incident cases. We only considered population rates as recorded in Georgia SEER registries (Atlanta Metropolitan and Rural Georgia in 1998 and 1999, and Atlanta Metro, Rural Georgia, and Greater Georgia from 2000-2009). In order to account for out-migration of the cohort from Georgia, we scaled the number of expected cases to the proportion of the cohort remaining in Georgia each year.

The third aim was to conduct an internal comparison of cancer incidence and mortality by HIV status. SMRs and SIRs were stratified by HIV status and corresponding 95% confidence intervals (95% CIs) were calculated using the Poisson distribution. Both SIRs and SMRs were considered to be statistically significant if their 95% CIs did not include the null-value of 1.0. SIR and SMR ratios were calculated using exact methods. All analyses were conducted on de-identified data using SAS version 9.3 (Cary, NC). P-values <0.05 were considered statistically

significant. This study was approved by the Georgia Department of Public Health and the Emory University Institutional Review Board.

RESULTS

Demographics

Demographic characteristics by HIV status are presented in Table 1. Among 22,354 persons in the cohort remaining alive on January 1, 1998, there were 848 (3.8%) who were classified as ever HIV positive and 21,506 as HIV-negative. HIV-infected incarcerated persons were more likely to be younger, Black, female, less educated and have more releases during the study period. Among HIV-infected people, 37.0% died during the observation period versus 11.4% among HIV-negative people (p<0.0001). HIV infection and cardiovascular disease were the leading cause of death for those ever HIV-infected and HIV-negative, respectively.

Table 1: Selected demographic characteristics of 22,354 inmates incarcerated in a Georgia state prison on June 30, 1991 and followed from January 1, 1998 until December 31, 2010, United States.

Characteristic	HIV-infected (N=848)[a]		HIV-negative (N=21,506)[b]		*p*-value
	N	%	N	%	
Age in 1998 (years)					
20-29	91	10.7	2,547	11.8	
30-39	439	51.8	9,990	46.5	
40-49	274	32.3	6,273	29.2	
≥ 50	44	5.2	2,696	12.5	
Mean (SD)	39 (9)		38 (7)		<0.0001[c]
Race/Ethnicity					<0.0001
Black, non-Hispanic	760	89.6	14,047	65.3	
White, non-Hispanic	88	10.4	7,459	34.7	
Gender					0.038
Male	787	92.8	20,318	94.5	
Female	61	7.2	1,188	5.5	
Education level in 1991					0.014
Less than High school	516	60.9	12,388	57.6	
High school or GED	201	23.7	6,127	28.5	
More than High school	94	11.1	2,214	10.3	
Unknown	37	4.4	777	3.6	
Number of releases during observation period[d]					
0	415	48.9	12,469	58.0	
1	277	32.7	6,077	28.3	

2	100	11.8	2,086	9.7	
3	44	5.2	669	3.1	
≥ 4	12	1.4	205	1.0	
Deceased at study end					<0.0001
Yes	314	37.0	2,457	11.4	
No	534	63.0	19,049	88.6	
Primary cause of death					
HIV infection	221	70.4	0	0	
Cardiovascular diseases	23	7.3	691	28.1	
Cancer	12	3.8	481	19.6	
Liver disease[e]	7	2.2	163	6.6	
Homicide	6	1.9	142	5.8	
Other	45	14.4	980	39.9	

Abbreviations: GED, General Educational Development; HIV, Human Immunodeficiency Virus.
[a] Includes 792 who were HIV-infected and 56 who had HIV infection as a cause of death.
[b] Includes 20,474 who were HIV-negative, 15 who had an indeterminate result and 1,017 unknown.
[c] t-test
[d] Data available through September 2, 2010.
[e] Excludes liver cancer.

Characterizing cancer within the prison cohort during 1998-2009

Cancer incidence among study participants are presented by HIV status and cancer site (Table 2.1). The incidence of all-cancers combined (per 100,000 person-years) was higher (Incidence Rate [IR] = 560.8, 95% CI: 419.5, 735.4) among HIV-infected versus HIV-negative individuals (IR = 303.5, 95% CI: 283.0, 325.1) (Table 2.1). Incidence rates for all ADCs, liver and anal cancer, and Hodgkin's lymphoma were higher among HIV-infected prisoners versus negative. Lung cancer was the most common incident NADC for both HIV-infected and HIV-negative people. Rates of prostate cancer were higher among the HIV-negative. The incidence rate per 100,000 person-years of lung cancer among HIV-infected (91.6, 95% CI: 42.5, 173.9) exceeded that among the HIV-negative group (74.9, 95% CI: 65.0, 85.9) but the 95% confidence intervals for the estimates overlapped (Table 2.1). Stage at diagnosis of incident cancers (Supplementary Tables I-3) did not differ significantly by HIV status.

Table 2.1. Unadjusted cancer incidence, per 100,000 person-years, by site and HIV status.

	HIV-Infected		HIV-Negative	
	N	Incidence per 100,000 PY (95% CI)	N	Incidence per 100,000 PY (95% CI)
All cancers	49	560.8 (419.5, 735.4)	798	303.5 (283.0, 325.1)
ADC	16	183.1 (108.4, 291.0)	29	11.0 (7.5, 15.6)
Non-Hodgkin lymphoma	13	148.8 (82.8, 248.1)	28	10.6 (7.2, 15.2)
Kaposi sarcoma	2	22.9 (3.8, 75.6)	0	--
Cervix	1	11.4 (0.6, 56.4)	1	0.4 (0.02, 1.9)
Viral-related NADC	10	114.5 (58.1, 204.0)	54	20.5 (15.6, 26.6)
Liver	4	45.8 (14.6, 110.4)	25	9.5 (6.3, 13.8)
HPV-related oral[a]	1	11.4 (0.6, 56.4)	18	6.8 (4.2, 10.6)
Anal	2	22.9 (3.8, 75.6)	2	0.8 (0.1, 2.5)
Hodgkin lymphoma	3	34.3 (8.7, 93.5)	8	3.0 (1.4, 5.8)
Penis	0	--	1	0.4 (0.02, 1.9)
Non-viral-related NADC	23	263.2 (170.9, 388.8)	715	271.9 (252.5, 292.4)
Lung and bronchus	8	91.6 (42.5, 173.9)	197	74.9 (65.0, 85.9)
Prostate	1	11.4 (0.6, 56.4)	165	62.7 (53.7, 72.9)
Colorectal	5	57.2 (21.0, 126.9)	82	31.2 (25.0, 38.5)
Kidney and renal pelvis	2	22.9 (3.8, 75.6)	34	12.9 (9.1, 17.9)
Stomach	1	11.4 (0.6, 56.4)	18	6.8 (4.2, 10.6)
Other	6	68.7 (27.8, 142.8)	205	78.0 (67.8, 89.2)

[a] Oropharynx, tonsil, tongue (squamous cell)

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer; PY—Person-Years.

HIV-infected study participants (N=12) experienced few cancer deaths (Table 2.2). Lung cancer was the most common cause of cancer death among this group (N=5) (Table 2.2). There was a single infection-associated NADC death: one participant died of hepatocellular carcinoma. Among HIV-negative participants, there were 481 cancer-related deaths. Lung (N=195), colorectal (N=43) and hepatocellular cancer (N=28) predominated. Mortality rates for all causes of cancer deaths (Table 2.2) did not differ significantly by HIV status.

Table 2.2. Unadjusted all-cause and cancer mortality rates, per 100,000 person-years, by site and HIV status.

	HIV-Infected		HIV-Negative	
	N	**Incidence per 100,000 PY (95% CI)**	**N**	**Incidence per 100,000 PY (95% CI)**
All-cause mortality	314	3560.1 (3182.4, 3970.7)	2457	926.5 (890.5, 963.7)
All cancers	12	136.1 (73.7, 231.3)	481	181.4 (165.7, 198.2)
ADC	0	--	12	4.5 (2.5, 7.7)
Non-Hodgkin lymphoma	0	--	12	4.5 (2.5, 7.7)
Kaposi sarcoma	0	--	0	--
Cervix	0	--	0	--
Viral-related NADC	1	11.3 (0.6, 55.9)	35	13.2 (9.3, 18.2)
Liver	1	11.3 (0.6, 55.9)	28	10.6, 15.1)
HPV-related oral[a]	0	--	5	1.9 (0.7, 4.2)
Anal	0	--	2	0.8 (0.1, 2.5)
Hodgkin lymphoma	0	--	0	--
Penis	0	--	0	--
Non-viral-related NADC	11	124.7 (65.6, 216.8)	434	163.7 (148.8, 179.6)
Lung and bronchus	5	56.7 (20.8, 125.7)	195	73.5 (63.7, 84.4)
Prostate	0	--	21	7.9 (5.0, 11.9)
Colorectal	2	22.7 (3.8, 74.9)	43	16.2 (11.9, 21.6)
Kidney and renal pelvis	0	--	15	5.7 (3.3, 9.1)
Stomach	0	--	16	6.0 (3.6, 9.6)
Other	4	45.4 (14.4, 109.4)	124	46.8, 55.6)

[a] Oropharynx, tonsil, tongue (squamous cell)

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer; PY—Person-Years.

Comparing the prisoner cohort to the Georgia general population: an external comparison

Among the HIV-infected individuals, SIRs (a measure of relative risk, adjusted to the general population) were significantly greater than 1.0 for all cancers combined and for ADC, viral associated NADC, and lung cancer (Table 3.1). Only the SIR for lung cancer (1.5, 95% CI: 1.3, 1.7) was significantly higher than 1.0 for HIV-negative individuals.

Table 3.1: Standardized incidence ratios* in a prisoner cohort, by sub-types of cancers and HIV status.

	HIV-infected			HIV-negative				
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	SIR Ratio (95%CI)	*p*
All cancers	49	26	2.0 (1.5, 2.6)	798	928	0.9 (0.8, 0.9)	2.3 (1.7, 3.0)	<0.001
ADC	16	2	8.0 (4.6, 13.0)	29	53	0.6 (0.4, 0.8)	14.6 (7.8, 26.8)	<0.001
NADC	33	24	1.4 (0.9, 1.9)	769	916	0.8 (0.8, 0.9)	1.6 (1.1, 2.3)	0.009
Viral-associated	10	2	6.3 (3.0, 11.5)	54	53	1.0 (0.8, 1.3)	6.1 (3.0, 11.7)	<0.001
Non-viral-associated	23	23	1.0 (0.6, 1.5)	715	863	0.8 (0.8, 0.9)	1.2 (0.8, 1.8)	0.37
Lung and bronchus	8	3	2.7 (1.2, 5.3)	197	134	1.5 (1.3, 1.7)	1.8 (0.8, 3.5)	0.12
Colorectal	5	3	1.7 (0.5, 3.9)	82	98	0.8 (0.7, 1.04)	2.0 (0.7, 4.6)	0.16

Abbreviations: SIR – Standardized Incidence Ratio; ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.
*SIRs adjusted for age (in 5-year intervals), race, sex and year of diagnosis.

Table 3.2: Standardized mortality ratios* in a prisoner cohort, by sub-types of cancers and HIV status.

	HIV-infected			HIV-negative				
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	SMR Ratio (95%CI)	*p*
All causes	314	55	5.7 (5.1, 6.4)	2,457	1,863	1.3 (1.3, 1.4)	4.3 (3.8, 4.9)	<0.001
All cancers	12	10	1.2 (0.6, 2.1)	481	394	1.2 (1.1, 1.3)	1.0 (0.5, 1.7)	0.99
ADC	0	0.3	--	12	13	0.9 (0.5, 1.6)	--	--
NADC	12	10	1.2 (0.6, 2.1)	469	381	1.2 (1.1, 1.4)	1.1 (0.6, 1.8)	0.81
Viral-associated	1	0.7	1.4 (0.04, 8.0)	35	23	1.5 (1.1, 2.1)	0.9 (0.05, 4.9)	1.00
Non-viral-associated	11	9	1.2 (0.6, 2.2)	434	358	1.2 (1.1, 1.3)	1.01 (0.5, 1.8)	0.94
Lung and bronchus	5	3	1.7 (0.5, 3.9)	195	121	1.6 (1.4, 1.9)	1.03 (0.4, 2.3)	0.89
Colorectal	2	1	2.0 (0.2, 7.2)	43	40	1.1 (0.8, 1.5)	1.9 (0.3, 6.5)	0.40

Abbreviations: SMR – Standardized Mortality Ratio; ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

*SMRs were adjusted for age (in 5-year intervals), race, sex and year of death.

Notes for Tables 3.1 and 3.2: 95% confidence intervals for SIR and SMR were estimated using exact methods based on the Poisson distribution. Exact methods used to compare two SIRs and two SMRs.

Brownlee, K. Statistical theory and methodology in science and engineering. Second edition. New York: John Wiley; 1965. p. 184.

WHO. Statistical Methods in Cancer Research - Volume II - The Design and Analysis of Cohort Studies: Comparison of standardized mortality ratios. http://www.iarc.fr/en/publications/pdfs-online/stat/sp82/SP82_vol2-3.pdf

All-cancer mortality was elevated for both prisoner groups (compared to the general population) although the SMR was only statistically significant for HIV-negative individuals (SMRs for both groups = 1.2) (Table 3.2). The SMR for non-infection-related NADCs in HIV-infected individuals was 1.4 but the 95% confidence interval was wide and included 1.0. No ADC deaths were observed among those HIV-infected during the study period. HIV-negative individuals had significantly higher all-cause mortality and cancer mortality, except from ADC, as compared to the reference population.

An indirect, internal comparison of cancer incidence and mortality ratios by HIV status

SIR ratios (Table 3.1) for all cancers combined (2.3, 95% CI: 1.7, 3.0) and viral associated NADCs (6.1, 95% CI: 3.0, 11.7) were both significantly elevated (p<0.001 for each) among HIV

positive vs. negative individuals. Confidence intervals for the SIRs for non-viral associated ADCs between the HIV-infected and -negative overlapped.

Table 3.2 illustrates that all-cause mortality was higher among HIV-infected vs. negative participants (SMR ratio = 4.3, 95% CI: 3.8, 4.9, $p<0.001$). However, the SMRs for all cancers, and cancers by type, did not significantly differ.

DISCUSSION

In this exploratory, observational study of a cohort incarcerated two decades ago, we found that incident cancers were common among both the HIV-infected and non-infected members of the cohort imprisoned on June 30, 1991. During the HAART era, rates of viral associated NADCs were about 6 times higher than expected among HIV-infected persons relative to the general population, highlighting a higher prevalence of oncogenic viral co-infections and perhaps poorer overall health status. Regarding cancer mortality, there were few cancer deaths among HIV-infected subjects hampering our ability to draw strong conclusions regarding differences by HIV status among people with a history of incarceration. Nonetheless, there was a suggestion that liver cancer deaths may be elevated in this population. Similar to studies of HIV-infected persons in the general population, HIV-infected persons with a history of incarceration are at elevated risk for some cancers, which warrant public health interventions.

The pattern of incident cancers among HIV-infected persons in our study differs somewhat from among HIV-infected people observed previously.. Similar to a large nationally representative study, we found that non-Hodgkin lymphoma was the most common ADC.[21] However, among HIV-infected persons with a history of incarceration we noted lung, colon and liver cancers as the most common NADCs versus lung, anal and prostate cancers in the general HIV population. Reasons for fewer anal cancers diagnosed in the cohort are unclear—whether participants have lower risk verus undisclosed risk and thus less frequent screening. The paucity of prostate cancers may stem from this being a relatively young population. Nonetheless, the elevated SIRs among HIV-infected persons in our study for ADCs and NADCs (particularly viral associated NADCs) are important areas for prevention and future research. Importantly, the

only SIR that was elevated for both groups regardless of HIV status was for lung cancer, highlighting that incarceration may be a more important risk factor for lung cancer in this group than HIV alone.

Relative to the general population, all-cause mortality, but not cancer mortality, was significantly elevated among HIV-infected versus negative subjects with a history of incarceration. Perhaps this reflects an even playing field between the HIV-infected and negative cancer patients with regards to mortality. Conversely, the follow-up period may have been insufficient for incident cancers to have progressed into fatal disease. Our analyses of cancer mortality were likely underpowered due to the small number of observed cancer deaths among HIV-infected persons with a history of incarceration, although the point estimates for all cancers combined (SMR=1.2) suggested an increased risk of cancer death. Two recent studies suggest that cancer treatment rates are lower among people with HIV/AIDS, which likely contributes to this disparity.[22 23] Elevated all-cause mortality among HIV-infected persons relative to the general population may be due in part to inadequate control of HIV-related disease, underscoring the need for programs that retain HIV-infected persons in the HIV care system after release.[24-26]

Although most prison systems lack adequate resources to expand cancer screening and prevention programs, courts have ruled that they cannot have deliberate indifference to previously existing or newly diagnosed medical conditions. HIV viral suppression – which is associated with increased survival time and a decreased risk of some ADCs and NADCs – should be a focus for HIV-infected prisoners.[27 28] Additionally, treatment and screening for HBV and HCV, which decrease the risk of hepatocellular carcinoma, are important components of correctional healthcare systems. Finally, smoking is associated with a number of cancers and tobacco cessation reduces the risk of lung and other tobacco-associated malignancies. A prison record may hinder employment and thus health insurance, resulting in decreased access to healthcare. Lack of insurance[29 30] and diminished lifetime earning power,[31] estimated 10%-30% less among people with a history of incarceration,[32 33] may increase risk of several cancer types as well as adversely impact treatment and survival. In addition, exposure to known carcinogens is high among prisoners: 65.7% and 85.4% are smokers and alcohol users, respectively, and risk

of cancer is higher than age, gender, race, socioeconomic controls; only when further adjusting for smoking does the risk of cancer become equivalent to the non-incarcerated.[34]

This study has several strengths. Persons in the HIV-infected and uninfected arms had some characteristics in common, most notably incarceration. HIV-infected subjects were more likely to be Black and less educated, factors associated with poorer overall, HIV and cancer-specific survival; on the other hand they were younger and more likely female, factors that are normally protective. Nonetheless, if they were not matched by socioeconomic status in 1991, releasees in both arms had to contend with similar barriers to health care. Additionally, by studying a cohort formed by taking a cross-section of persons dwelling in prison, rather than a cohort of releasees, we de-emphasize immediate deaths, including cancer deaths. Instead, the methodology highlights long-term sequelae of exposure to toxins such as alcohol and tobacco, and viruses such as HBV and HCV.[35]

Our study also has limitations, such as possible ascertainment bias. We did not have access to HIV status apart from the prison records and death data. Some persons classified as HIV-negative based on prison entry testing may have later seroconverted to HIV, therefore underestimating observed associations with HIV-infection. Causes of mortality were obtained from prisoners' and releasees' death certificates, which are filled out either by physicians or county coroners. Unlike many other states, Georgia does not mandate autopsy for deaths in custody, which could potentially introduce misclassification of cause of death although any such misclassification would be independent of HIV-infection. We were also unable to obtain information on smoking status, HAART adherence, cancer treatment, and markers of HIV severity (e.g. CD4 count, viral load). Finally, because we defined our cohort based on incarceration in 1991 but began follow-up in 1998, survival bias may have been introduced.

In conclusion, this descriptive study found elevated cancer incidence among HIV-infected persons with a history of incarceration relative to the general population. These results underscore the need for cancer prevention and control programs within prisons and to ensure releasees also have access to a medical home with follow-up appointments and regular cancer screening. Longer study of this cohort is warranted to assess whether an excess of cancer mortality will eventually be observed and if that will differ by HIV status. Expanding such

registry-linkage studies to other states with larger incarcerated HIV populations will further inform correctional and public health policy in the United States.

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COMPETING INTERESTS

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DATA SHARING STATEMENT

No additional data are available.

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Table I. Distribution of cancer stage at diagnosis by HIV status.

	HIV-positive (%)		HIV-negative (%)		
Stage at diagnosis	**N**	**%**	**N**	**%**	***p*-value**[a]
In situ	0	0	1	0.1	0.60
Localized	15	30.6	286	35.8	
Regional	8	16.3	181	22.7	
Distant	20	40.8	257	32.3	
Unknown	6	12.2	73	9.1	

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

Table II. Distribution of cancer at diagnosis by cancer type, among HIV-positive.

	ADC		Viral-associated NADC		Non-viral-associated NADC		
Stage at diagnosis	**N**	**%**	**N**	**%**	**N**	**%**	***p*-value**
In situ	0	0	0	0	0	0	0.32
Localized	7	43.8	1	10.0	7	30.4	
Regional	1	6.3	4	40.0	3	13.0	
Distant	6	37.5	4	40.0	10	43.5	
Unknown	2	12.5	1	10.0	3	13.0	

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

Table III. Distribution of cancer at diagnosis by cancer type, among HIV-negative.

	ADC		Viral-associated NADC		Non-viral-associated NADC		
Stage at diagnosis	**N**	**%**	**N**	**%**	**N**	**%**	***p*-value**
In situ	0	0	0	0	1	0.1	<0.0001
Localized	4	13.8	8	14.8	274	38.3	
Regional	3	10.3	26	48.1	152	21.3	
Distant	17	58.6	13	24.1	227	31.7	
Unknown	5	17.2	7	13.0	61	8.5	

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

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A retrospective cohort study of cancer incidence and mortality by HIV status in a Georgia, USA prisoner cohort during the HAART era

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ABSTRACT

Objective: Non-AIDS-defining cancers (NADCs) have emerged as significant contributors to cancer mortality and morbidity among persons living with HIV (PLWH). Because NADCs are also associated with many social and behavioral risk factors that underlie HIV, determining the extent to which each of these factors contributes to NADC risk is difficult. We examined cancer incidence and mortality among persons with a history of incarceration, because distributions of other cancer risk factors are likely similar between prisoners living with HIV and non-infected prisoners.

Design: Registry-based retrospective cohort study.

Participants: Cohort of 22,422 persons incarcerated in Georgia, USA prisons on June 30, 1991, and still alive in 1998.

Outcome measures: Cancer incidence and mortality were assessed between 1998 and 2009, using cancer and death registry data matched to prison administrative records. Age, race and sex-adjusted standardized mortality and incidence ratios, relative to the general population, were calculated for AIDS-defining cancers, viral-associated NADCs, and non-infection-associated NADCs, stratified by HIV status.

Results: There were no significant differences in cancer mortality relative to the general population in the cohort, regardless of HIV status. In contrast, cancer incidence was elevated among the PLWH. Furthermore, incidence of viral-associated NADCs was significantly higher among PLWH vs. those without HIV infection (ratio of standardized incidence ratios = 6.1, 95% CI: 3.0, 11.7, $p<0.001$).

Conclusions: Among PLWH with a history of incarceration, cancer incidence was elevated relative to the general population, likely related to increased prevalence of oncogenic viral co-infections. Cancer prevention and screening programs within prisons may help to reduce the cancer burden in this high-risk population.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- PLWH and HIV-uninfected members of the cohort both experienced a history of incarceration and likely have a similar distribution of cancer risk factors.
- The study design and long follow-up period emphasize long-term consequences of viral infection and exposure to alcohol and tobacco.
- Underestimation of associations with HIV-infection is possible as we could not ascertain if those who tested HIV-negative on prison entry later seroconverted to HIV.

INTRODUCTION

In contrast to declining trends in incidence for the two major AIDS-defining cancers (ADCs, Kaposi sarcoma and non-Hodgkin lymphoma), rates for some non-AIDS-defining cancers (NADCs) remain elevated or have increased over time for persons living with HIV (PLWH) despite widespread access since 1996 to highly active antiretroviral therapy (HAART).[1] Although the causes of temporal increases for some NADCs are complex and multifactorial, an increased prevalence of lifestyle-related risk factors (e.g., tobacco exposure) and the role of prolonged moderate levels of immune suppression among PLWH versus uninfected persons likely contribute to increased rates of NADCs.[2-4] Studying cancer among prisoners with and without HIV offers an opportunity to assess the extent to which the heightened risk for malignancies is due to HIV infection itself versus the social and behavioral factors that underlie HIV infection. Regardless of HIV status, incarcerated persons often experience substance abuse, poverty and poor access to medical care prior to incarceration.[5-7] Thus, among inmates, the distribution of important cancer risk factors may be similar between PLWH and non-infected persons.

Numerous studies have found two- to three-fold elevated risk for NADCs among PLWH relative to the general population.[8-10] A meta-analysis suggests that the cancer burden differs among those with and without HIV, with the former having excesses of infection-associated malignancies, notably Hodgkin lymphoma (Epstein Barr virus, EBV), anal cancer (human papillomavirus, HPV), and liver cancer (hepatitis B and hepatitis C viruses, HBV and HCV).[8-11] Lung cancer rates are also higher among PLWH.[12] The reasons why the distribution of NADCs differs between PLWH and non-infected individuals are unclear, though some hypotheses exist. The increased prevalence of smoking among PLWH[13] does not fully account for the observed elevated lung cancer incidence.[12,14] Persistent lung injury from pneumonias, prolonged immunosuppression, oxidative stress, and HAART toxicity may contribute to lung tumorigenesis.[10-12] Higher prevalence of co-infection with oncogenic viruses in some subgroups of HIV patients likely plays a role. For example, persistent anal HPV infections are high among men living with HIV who have sex with men, contributing to the observed increase in invasive anal cancer in this population.[15] Similarly, liver cancer rates are elevated among PLWH with a history of injection drug use due to a high prevalence of chronic HBV and HCV infections. EBV is

nearly ubiquitous among all US adults, however among PLWH, Hodgkin lymphoma is a common NADC, perhaps due to changes in the immune system mediated by HAART.[10,16]

We previously conducted an retrospective cohort study of all-cause mortality in 23,510 incarcerated men and women in the state of Georgia (GA) on June 30, 1991 by linking prison records with the National Death Index (NDI) in 2006.[17] The study was recently updated to include deaths through 2010 and found 5% of the population were HIV infected and overall cancer was a close second to heart disease as a leading cause of death among all prisoners regardless of HIV status.[6]

The primary goal of the current study was to link the GA prisoner cohort from our previous study to the GA Comprehensive Cancer Registry (GCCR) database in order to ascertain cancer incidence data and to determine and compare cancer incidence patterns in PLWH and non-infected cohort members in the HAART era. Specifically, we sought to (1) characterize the distribution of incident cancers and cancer deaths among PLWH and uninfected cohort members, (2) compare the distribution of site-specific cancers in this cohort with the general Georgia population using Standardized Incidence Ratios (SIRs) and Standardized Mortality Ratios (SMRs), and (3) compare cancer incidence and mortality rates between the PLWH in the cohort and uninfected cohort members.

METHODS

Study population

As described in our prior studies,[6,17] the initial cohort consisted of all persons incarcerated in Georgia prisons on June 30, 1991. Administrative records containing demographic data and incarceration history were obtained from the Georgia Department of Corrections (GDC) Planning and Strategic Management Section and linked with the NDI through December 31, 2010.[6] Participants could be either in prison, in the general population, or alternating between both during the observational period.[17] For the current analysis, we only considered those participants in the cohort who were alive on January 1, 1998. Between June 30, 1991 and December 31, 1997, a total of 1,088 people died and 22,422 remained alive. Although we had mortality information on the cohort since 1991, cancer incidence data were

not available until 1998, which was well into the HAART era. We defined cause of death as the primary cause of death on the death certificate. We also removed from our analytic population 68 persons who did not identify as being "Black" or "White" because we could not generate expected cancer or death counts for them. Therefore, follow-up for study outcomes in the current analysis began on January 1, 1998 and included 22,354 people who were followed until December 31, 2010, cancer incidence or death.

The GDC administrative records contain the result of every HIV test performed during any prison stay. Using data from these records, subjects were classified into two categories, ever HIV-infected or no record of HIV positivity (hereafter referred to as HIV-negative). The latter category includes those with missing HIV test results. Decedents were also classified as being persons who had lived with HIV for the entire study period if HIV was listed as the underlying or as a contributory cause of death on the death certificate. ADC assumes an HIV-infected status; when discussing these cancers in the HIV-negative population, we mean cancers of the same type as those that qualify as ADC.

Statistical Analysis

The first aim was to characterize cancer incidence and mortality during 1998-2009 in the cohort of persons in prison on June 30, 1991. To ascertain incident cancer, administrative data on the cohort from the GDC were matched with the GCCR using probabilistic matching algorithms. Invasive cancers were categorized using the International Classification of Diseases for Oncology, *third edition* (ICD-O-3) codes,[18] and only the first cancers were considered. Mortality was assessed through probabilistic matching with GCCR, and, for those with no matches in GCCR, a successive probabilistic matching with the NDI. Mortality data included the date of death and the ICD-9 or ICD-10 codes for the underlying and contributing causes of death.[19,20]

We first calculated the number of person-years of follow-up for the cohort, for both PLWH and HIV-negative individuals. We also determined the frequency distributions of descriptive cohort characteristics including: age in 1998, race, sex, educational level, pre-prison employment status, number of prison releases, vital status and cause of death, which were

then stratified by HIV status. Finally, we calculated frequency distributions of stage at diagnosis for incident cancers, by HIV status and cancer type. SEER Summary Staging 1977 was used to stage cancers diagnosed between 1998 and 2000, SEER Summary Staging 2000 for cancers diagnosed between 2001 and 2003, and Collaborative Stage Derived Stage 2000 for cancers diagnosed in 2004 and later.

We used Pearson's chi-square test to assess associations of categorical variables and Student's *t*-test for continuous variables.

The second aim was to compare the Georgia prisoner cohort to the Georgia general population with regard to cancer incidence and mortality. Standardized mortality and incidence ratios (SMRs and SIRs, measures of risk relative to the general population) were calculated for all cancer types: ADCs (Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer), infection-associated NADC, and non-infection-associated NADC. Infection-associated NADCs included a subset of NADCs with a known infectious cause: HPV-related anal and oropharyngeal cancer, HBV and/or HCV-related liver cancer and EBV-related Hodgkin lymphoma.[9,21] All other cancers were considered not to be infection-related NADCs. SMRs were adjusted for age (in 5-year intervals), race, sex and year of death. Underlying population mortality rates in Georgia were determined using SEER*Stat software (http://seer.cancer.gov/seerstat) and were used to calculate expected death counts. SIRs were also adjusted for age (in 5-year intervals), race, sex and year of diagnosis. Underlying population cancer incidence rates in Georgia were determined with SEER*Stat and were used to calculate expected count of incident cases. We only considered population rates as recorded in Georgia SEER registries (Atlanta Metropolitan and Rural Georgia in 1998 and 1999, and Atlanta Metro, Rural Georgia, and Greater Georgia from 2000-2009). In order to account for out-migration of the cohort from Georgia, we scaled the number of expected cases to the proportion of the cohort remaining in Georgia each year.

The third aim was to conduct an internal comparison of cancer incidence and mortality by HIV status. SMRs and SIRs were stratified by HIV status and corresponding 95% confidence intervals (95% CIs) were calculated using the Poisson distribution. Both SIRs and SMRs were

considered to be statistically significant if their 95% CIs did not include the null-value of 1.0. SIR and SMR ratios and their 95% CIs were calculated using exact methods.[22,23] All analyses were conducted on de-identified data using SAS version 9.3 (Cary, NC). P-values <0.05 were considered statistically significant. This study was approved by the Georgia Department of Public Health and the Emory University Institutional Review Board.

RESULTS

Demographics

Demographic characteristics by HIV status are presented in Table 1. Among 22,354 persons in the cohort remaining alive on January 1, 1998, there were 848 (3.8%) who were classified as PLWHand 21,506 as HIV-negative. Incarcerated PLWH were more likely to be younger, Black, female, less educated and have more releases during the study period. Among PLWH, 37.0% died during the observation period versus 11.4% among HIV-negative people (p<0.0001). HIV infection and cardiovascular disease were the leading cause of death for PLWH and those HIV-negative, respectively.

Table 1: Selected demographic characteristics of 22,354 inmates incarcerated in a Georgia state prison on June 30, 1991 and followed from January 1, 1998 until December 31, 2010, United States.

Characteristic	HIV-infected (N=848)[a]		HIV-negative (N=21,506)[b]		*p*-value
	N	%	N	%	
Age in 1998 (years)					
20-29	91	10.7	2,547	11.8	
30-39	439	51.8	9,990	46.5	
40-49	274	32.3	6,273	29.2	
≥ 50	44	5.2	2,696	12.5	
Mean (SD)	39 (9)		38 (7)		<0.0001[c]
Race/Ethnicity					<0.0001
Black, non-Hispanic	760	89.6	14,047	65.3	
White, non-Hispanic	88	10.4	7,459	34.7	
Gender					0.038
Male	787	92.8	20,318	94.5	
Female	61	7.2	1,188	5.5	
Education level in 1991					0.014[d]
Less than High school	516	60.9	12,388	57.6	
High school or GED	201	23.7	6,127	28.5	
More than High school	94	11.1	2,214	10.3	

Unknown	37	4.4	777	3.6	
Number of releases during observation period[e]					
0	415	48.9	12,469	58.0	
1	277	32.7	6,077	28.3	
2	100	11.8	2,086	9.7	
3	44	5.2	669	3.1	
≥ 4	12	1.4	205	1.0	
Deceased at study end					<0.0001
Yes	314	37.0	2,457	11.4	
No	534	63.0	19,049	88.6	
Primary cause of death					
HIV infection	221	70.4	0	0	
Cardiovascular diseases	23	7.3	691	28.1	
Cancer	12	3.8	481	19.6	
Liver disease[f]	7	2.2	163	6.6	
Homicide	6	1.9	142	5.8	
Other	45	14.4	980	39.9	

Abbreviations: GED, General Educational Development; HIV, Human Immunodeficiency Virus.
[a] Includes 792 who were HIV-infected and 56 who had HIV infection as a cause of death.
[b] Includes 20,474 who were HIV-negative, 15 who had an indeterminate result and 1,017 unknown.
[c] t-test
[d] Calculation excludes those with Unknown education level. The *p*-value including those with Unknown status is 0.02.
[e] Data available through September 2, 2010.
[f] Excludes liver cancer.

Characterizing cancer within the prison cohort during 1998-2009

Cancer incidence among study participants are presented by HIV status and cancer site (Table 2.1). The incidence of all-cancers combined (per 100,000 person-years) was higher (Incidence Rate [IR] = 560.8, 95% CI: 419.5, 735.4) among PLWH versus HIV-negative individuals (IR = 303.5, 95% CI: 283.0, 325.1) (Table 2.1). Incidence rates for all ADCs, liver and anal cancer, and Hodgkin's lymphoma were higher among PLWH versus negative subjects. Lung cancer was the most common incident NADC for both PLWH and HIV-negative people. Rates of prostate cancer were higher among the HIV-negative, a finding that has been previously observed.[24,25] The incidence rate per 100,000 person-years of lung cancer among PLWH (91.6, 95% CI: 42.5, 173.9) exceeded that among the HIV-negative group (74.9, 95% CI: 65.0, 85.9) but the 95%

confidence intervals for the estimates overlapped (Table 2.1). Stage at diagnosis of incident cancers (Supplementary Tables I-3) did not differ significantly by HIV status.

Table 2.1. Unadjusted cancer incidence, per 100,000 person-years, by site and HIV status.

	HIV-Infected		HIV-Negative	
	N	Incidence per 100,000 PY (95% CI)	N	Incidence per 100,000 PY (95% CI)
All cancers	49	560.8 (419.5, 735.4)	798	303.5 (283.0, 325.1)
ADC	16	183.1 (108.4, 291.0)	29	11.0 (7.5, 15.6)
Non-Hodgkin lymphoma	13	148.8 (82.8, 248.1)	28	10.6 (7.2, 15.2)
Kaposi sarcoma	2	22.9 (3.8, 75.6)	0	--
Cervix	1	11.4 (0.6, 56.4)	1	0.4 (0.02, 1.9)
Viral-related NADC	10	114.5 (58.1, 204.0)	54	20.5 (15.6, 26.6)
Liver	4	45.8 (14.6, 110.4)	25	9.5 (6.3, 13.8)
HPV-related oral[a]	1	11.4 (0.6, 56.4)	18	6.8 (4.2, 10.6)
Anal	2	22.9 (3.8, 75.6)	2	0.8 (0.1, 2.5)
Hodgkin lymphoma	3	34.3 (8.7, 93.5)	8	3.0 (1.4, 5.8)
Penis	0	--	1	0.4 (0.02, 1.9)
Non-viral-related NADC	23	263.2 (170.9, 388.8)	715	271.9 (252.5, 292.4)
Lung and bronchus	8	91.6 (42.5, 173.9)	197	74.9 (65.0, 85.9)
Prostate	1	11.4 (0.6, 56.4)	165	62.7 (53.7, 72.9)
Colorectal	5	57.2 (21.0, 126.9)	82	31.2 (25.0, 38.5)
Kidney and renal pelvis	2	22.9 (3.8, 75.6)	34	12.9 (9.1, 17.9)
Stomach	1	11.4 (0.6, 56.4)	18	6.8 (4.2, 10.6)
Other	6	68.7 (27.8, 142.8)	205	78.0 (67.8, 89.2)

[a] Oropharynx, tonsil, tongue (squamous cell)

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer; PY—Person-Years.

Study participants living with HIV experienced few cancer deaths (N=12;Table 2.2). Lung cancer was the most common cause of cancer death among this group (N=5) (Table 2.2). There was a single infection-associated NADC death: one participant died of hepatocellular carcinoma. Among HIV-negative participants, there were 481 cancer-related deaths. Lung (N=195), colorectal (N=43) and hepatocellular cancer (N=28) predominated. Mortality rates for all causes of cancer deaths (Table 2.2) did not differ significantly by HIV status.

Table 2.2. Unadjusted all-cause and cancer mortality rates, per 100,000 person-years, by site and HIV status.

	HIV-Infected		HIV-Negative	
	N	**Incidence per 100,000 PY (95% CI)**	**N**	**Incidence per 100,000 PY (95% CI)**
All-cause mortality	314	3560.1 (3182.4, 3970.7)	2457	926.5 (890.5, 963.7)
All cancers	12	136.1 (73.7, 231.3)	481	181.4 (165.7, 198.2)
ADC	0	--	12	4.5 (2.5, 7.7)
Non-Hodgkin lymphoma	0	--	12	4.5 (2.5, 7.7)
Kaposi sarcoma	0	--	0	--
Cervix	0	--	0	--
Viral-related NADC	1	11.3 (0.6, 55.9)	35	13.2 (9.3, 18.2)
Liver	1	11.3 (0.6, 55.9)	28	10.6, 15.1)
HPV-related oral[a]	0	--	5	1.9 (0.7, 4.2)
Anal	0	--	2	0.8 (0.1, 2.5)
Hodgkin lymphoma	0	--	0	--
Penis	0	--	0	--
Non-viral-related NADC	11	124.7 (65.6, 216.8)	434	163.7 (148.8, 179.6)
Lung and bronchus	5	56.7 (20.8, 125.7)	195	73.5 (63.7, 84.4)
Prostate	0	--	21	7.9 (5.0, 11.9)
Colorectal	2	22.7 (3.8, 74.9)	43	16.2 (11.9, 21.6)
Kidney and renal pelvis	0	--	15	5.7 (3.3, 9.1)
Stomach	0	--	16	6.0 (3.6, 9.6)
Other	4	45.4 (14.4, 109.4)	124	46.8, 55.6)

[a] Oropharynx, tonsil, tongue (squamous cell)

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer; PY—Person-Years.

Comparing the prisoner cohort to the Georgia general population: an external comparison

Among PLWH in the cohort, SIRs (a measure of relative risk, adjusted to the general population) were significantly greater than 1.0 for all cancers combined and for ADC, viral associated NADC, and lung cancer (Table 3.1). Only the SIR for lung cancer (1.5, 95% CI: 1.3, 1.7) was significantly higher than 1.0 for HIV-negative individuals.

Table 3.1: Standardized incidence ratios* in a prisoner cohort, by sub-types of cancers and HIV status.

	HIV-infected			HIV-negative				
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	SIR Ratio (95%CI)	*P***
All cancers	49	26	2.0 (1.5, 2.6)	798	928	0.9 (0.8, 0.9)	2.3 (1.7, 3.0)	<0.001
ADC	16	2	8.0 (4.6, 13.0)	29	53	0.6 (0.4, 0.8)	14.6 (7.8, 26.8)	<0.001
NADC	33	24	1.4 (0.9, 1.9)	769	916	0.8 (0.8, 0.9)	1.6 (1.1, 2.3)	0.009
Viral-associated	10	2	6.3 (3.0, 11.5)	54	53	1.0 (0.8, 1.3)	6.1 (3.0, 11.7)	<0.001
Non-viral-associated	23	23	1.0 (0.6, 1.5)	715	863	0.8 (0.8, 0.9)	1.2 (0.8, 1.8)	0.37
Lung and bronchus	8	3	2.7 (1.2, 5.3)	197	134	1.5 (1.3, 1.7)	1.8 (0.8, 3.5)	0.12
Colorectal	5	3	1.7 (0.5, 3.9)	82	98	0.8 (0.7, 1.04)	2.0 (0.7, 4.6)	0.16

Abbreviations: SIR – Standardized Incidence Ratio; ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.
*SIRs adjusted for age (in 5-year intervals), race, sex and year of diagnosis.
**p value is for SIR ratio difference.

Table 3.2: Standardized mortality ratios* in a prisoner cohort, by sub-types of cancers and HIV status.

	HIV-infected			HIV-negative				
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	SMR Ratio (95%CI)	*P***
All causes	314	55	5.7 (5.1, 6.4)	2,457	1,863	1.3 (1.3, 1.4)	4.3 (3.8, 4.9)	<0.001
All cancers	12	10	1.2 (0.6, 2.1)	481	394	1.2 (1.1, 1.3)	1.0 (0.5, 1.7)	0.99
ADC	0	0.3	--	12	13	0.9 (0.5, 1.6)	--	--
NADC	12	10	1.2 (0.6, 2.1)	469	381	1.2 (1.1, 1.4)	1.1 (0.6, 1.8)	0.81
Viral-associated	1	0.7	1.4 (0.04, 8.0)	35	23	1.5 (1.1, 2.1)	0.9 (0.05, 4.9)	1.00
Non-viral-associated	11	9	1.2 (0.6, 2.2)	434	358	1.2 (1.1, 1.3)	1.01 (0.5, 1.8)	0.94
Lung and bronchus	5	3	1.7 (0.5, 3.9)	195	121	1.6 (1.4, 1.9)	1.03 (0.4, 2.3)	0.89
Colorectal	2	1	2.0 (0.2, 7.2)	43	40	1.1 (0.8, 1.5)	1.9 (0.3, 6.5)	0.40

Abbreviations: SMR – Standardized Mortality Ratio; ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

*SMRs were adjusted for age (in 5-year intervals), race, sex and year of death.

**p value is for SMR ratio difference.

Notes for Tables 3.1 and 3.2: 95% confidence intervals for SIR and SMR were estimated using exact methods based on the Poisson distribution. Exact methods used to compare two SIRs and two SMRs.

Brownlee, K. Statistical theory and methodology in science and engineering. Second edition. New York: John Wiley; 1965. p. 184.

WHO. Statistical Methods in Cancer Research - Volume II - The Design and Analysis of Cohort Studies: Comparison of standardized mortality ratios. http://www.iarc.fr/en/publications/pdfs-online/stat/sp82/SP82_vol2-3.pdf

All-cancer mortality was elevated for both prisoner groups (compared to the general population) although the SMR was only statistically significant for HIV-negative individuals (SMRs for both groups = 1.2) (Table 3.2). The SMR for non-infection-related NADCs in PLWH was 1.4 but the 95% confidence interval was wide and included 1.0. No ADC deaths were observed among PLWH during the study period. HIV-negative individuals had significantly higher all-cause mortality and cancer mortality, except from ADC, as compared to the reference population.

An indirect, internal comparison of cancer incidence and mortality ratios by HIV status

SIR ratios (Table 3.1) for all cancers combined (2.3, 95% CI: 1.7, 3.0) and viral associated NADCs (6.1, 95% CI: 3.0, 11.7) were both significantly elevated (p<0.001 for each) among PLWH vs. negative individuals. Confidence intervals for the SIRs for non-viral associated ADCs between the PLWH and HIV-negative overlapped.

Table 3.2 illustrates that all-cause mortality was higher among PLWH vs. negative participants (SMR ratio = 4.3, 95% CI: 3.8, 4.9, p<0.001). However, the SMRs for all cancers, and cancers by type, did not significantly differ.

DISCUSSION

In this exploratory pilot study of a cohort incarcerated two decades ago, we found that incident cancers were common among both PLWH and non-infected members of the cohort imprisoned on June 30, 1991. During the HAART era, rates of viral associated NADCs were about 6 times higher than expected among PLWH relative to the general population, highlighting a higher prevalence of oncogenic viral co-infections and perhaps poorer overall health status. Regarding cancer mortality, there were few cancer deaths among the PLWH in the cohort hampering our ability to draw strong conclusions regarding differences by HIV status among people with a history of incarceration. Nonetheless, there was a suggestion that liver cancer deaths may be elevated in this population. Though we did not have data on the prevalence of HBV and HCV infection in this population, as Georgia prisons do not conduct routine screening for these viruses, previous studies of incarcerated populations have found that seroprevalence of these infections is high.[26,27] Similar to studies of PLWH in the general population, PLWH with a history of incarceration are at elevated risk for some cancers, which warrant public health interventions.

The pattern of incident cancers among PLWH in our study differs somewhat from among PLWH observed previously. Similar to a large nationally representative study, we found that non-Hodgkin lymphoma was the most common ADC.[28] However, among PLWH with a history of incarceration we noted lung, colon and liver cancers as the most common NADCs versus lung, anal and prostate cancers in the general HIV population.[1,3] Reasons for fewer anal cancers diagnosed in the cohort are unclear—whether participants have lower risk verus risk

undisclosed to their healthcare providers and thus less frequent screening. The paucity of prostate cancers may stem from this being a relatively young population. Nonetheless, the elevated SIRs among PLWH in our study for ADCs and NADCs (particularly viral associated NADCs) are important areas for prevention and future research.

Relative to the general population, all-cause mortality, but not cancer mortality, was significantly elevated among PLWH versus HIV-negative subjects with a history of incarceration. Perhaps this reflects an even playing field between PLWH and HIV-negative cancer patients with regards to mortality. Conversely, the follow-up period may have been insufficient for incident cancers to have progressed into fatal disease. It is also possible that HIV-related mortality presented a competing risk for this group, thus attenuating the rate of cancer mortality. Our analyses of cancer mortality were likely underpowered due to the small number of observed cancer deaths among PLWH with a history of incarceration, although the point estimates for all cancers combined (SMR=1.2) suggested an increased risk of cancer death. Two recent studies suggest that cancer treatment rates are lower among people with HIV/AIDS, which likely contributes to this disparity.[29,30] Elevated all-cause mortality among PLWH relative to the general population may be due in part to inadequate control of HIV-related disease, underscoring the need for programs that retain PLWH in the HIV care system after release.[31-33]

Although most prison systems lack adequate resources to expand cancer screening and prevention programs, courts have ruled that they cannot have deliberate indifference to previously existing or newly diagnosed medical conditions. HIV viral suppression – which is associated with increased survival time and a decreased risk of some ADCs and NADCs – should be a focus for prisoners living with HIV.[34,35] Additionally, treatment and screening for HBV and HCV, which decrease the risk of hepatocellular carcinoma, are important components of correctional healthcare systems. Finally, smoking is associated with a number of cancers and tobacco cessation reduces the risk of lung and other tobacco-associated malignancies. A prison record may hinder employment and thus health insurance, resulting in decreased access to healthcare. Lack of insurance[36,37] and diminished lifetime earning power,[38] estimated 10%-30% less among people with a history of incarceration,[39,40] may increase risk of several cancer types as well as adversely impact treatment and survival. In addition, exposure to known carcinogens

is high among prisoners: 65.7% and 85.4% are smokers and alcohol users, respectively, and risk of cancer is higher than age, gender, race, socioeconomic controls; only when further adjusting for smoking does the risk of cancer become equivalent to the non-incarcerated.[41]

This study has several strengths. Persons in the HIV-infected and uninfected arms had some characteristics in common, most notably incarceration. PLWH were more likely to be Black and less educated, factors associated with poorer overall, HIV and cancer-specific survival; on the other hand they were younger and more likely female, factors that are normally protective. Nonetheless, if they were not matched by socioeconomic status in 1991, releasees in both arms had to contend with similar barriers to health care. Additionally, by studying a cohort formed by taking a cross-section of persons dwelling in prison, rather than a cohort of releasees, we de-emphasize immediate deaths, including cancer deaths. Instead, the methodology highlights long-term sequelae of exposure to toxins such as alcohol and tobacco, and viruses such as HBV and HCV.[6]

Our study also has limitations, such as possible ascertainment bias. We did not have access to HIV status apart from the prison records and death data. Some persons classified as HIV-negative based on prison entry testing may have later seroconverted to HIV, therefore underestimating observed associations with HIV-infection. Causes of mortality were obtained from prisoners' and releasees' death certificates, which are filled out either by physicians or county coroners. Unlike many other states, Georgia does not mandate autopsy for deaths in custody, which could potentially introduce misclassification of cause of death although any such misclassification would be independent of HIV-infection. We were also unable to obtain information on smoking status, HAART adherence, cancer treatment, and markers of HIV severity (e.g. CD4 count, viral load). Finally, because we defined our cohort based on incarceration in 1991 but began follow-up in 1998, survival bias may have been introduced. All of these factors may reduce generalizability.

In conclusion, this descriptive study found elevated cancer incidence among PLWH with a history of incarceration relative to the general population. These results underscore the need for cancer prevention and control programs within prisons and to ensure releasees also have access to a medical home with follow-up appointments and regular cancer screening. Longer

study of this cohort is warranted to assess whether an excess of cancer mortality will eventually be observed and if that will differ by HIV status. Expanding such registry-linkage studies to other states with larger incarcerated HIV populations will further inform correctional and public health policy in the United States.

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CONTRIBUTORSHIP STATEMENT

ACS, PJM, KW and EPS conceived and planned the study. MZ, LCM and KE performed the stastical analyses. MZ, ACS, LCM, DC, JB and EPS contributed to writing the paper and prepared the manuscript. KE, JB and PJM made critical edits to the manuscript. All authors reviewed and approved the final version.

COMPETING INTERESTS

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DATA SHARING STATEMENT

No additional data are available.

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Table I. Distribution of cancer stage at diagnosis by HIV status.

	HIV-positive (%)		HIV-negative (%)		
Stage at diagnosis	**N**	**%**	**N**	**%**	***p*-value**[a]
In situ	0	0	1	0.1	0.60
Localized	15	30.6	286	35.8	
Regional	8	16.3	181	22.7	
Distant	20	40.8	257	32.3	
Unknown	6	12.2	73	9.1	

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

Table II. Distribution of cancer at diagnosis by cancer type, among HIV-positive.

	ADC		Viral-associated NADC		Non-viral-associated NADC		
Stage at diagnosis	**N**	**%**	**N**	**%**	**N**	**%**	***p*-value**
In situ	0	0	0	0	0	0	0.32
Localized	7	43.8	1	10.0	7	30.4	
Regional	1	6.3	4	40.0	3	13.0	
Distant	6	37.5	4	40.0	10	43.5	
Unknown	2	12.5	1	10.0	3	13.0	

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

Table III. Distribution of cancer at diagnosis by cancer type, among HIV-negative.

	ADC		Viral-associated NADC		Non-viral-associated NADC		
Stage at diagnosis	**N**	**%**	**N**	**%**	**N**	**%**	***p*-value**
In situ	0	0	0	0	1	0.1	<0.0001
Localized	4	13.8	8	14.8	274	38.3	
Regional	3	10.3	26	48.1	152	21.3	
Distant	17	58.6	13	24.1	227	31.7	
Unknown	5	17.2	7	13.0	61	8.5	

Abbreviations: ADC – AIDS-Defining Cancer; NADC – Non-AIDS-Defining Cancer.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Relevant page(s) in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7

Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-8
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			Relevant page(s) in manuscript
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.