Trends and risk of lung cancer among people living with HIV in the USA: a population-based registry linkage study

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See **Comment** page e670

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Summary

Background Lung cancer is a common cancer in people living with HIV, but the risk of cancer in this group has not been investigated for over a decade. We investigated trends in relative and absolute risk of lung cancer among people living with HIV of various age groups in the USA.

Methods In this population-based registry linkage study, we used 2001–16 data from the HIV/AIDS Cancer Match study, which links data from HIV and cancer registries from 13 regions in the USA. We included non-Hispanic White, non-Hispanic Black, and Hispanic individuals living with HIV aged 20–89 years in our study population. Average annual percentage changes in lung cancer rates were estimated with multivariable Poisson regression, and standardised incidence ratios (SIRs) and excess absolute risks were estimated comparing people living with HIV with the general US population. We used non-parametric cumulative incidence curves to estimate the 5-year cumulative incidence of lung cancer and two AIDS-defining cancers (non-Hodgkin lymphoma and Kaposi sarcoma).

Findings There were 3426 lung cancers in 4 310 304 person-years of follow-up in our study population. Age-standardised lung cancer incidence rates in people living with HIV declined by 6% per year (95% CI –7 to –5) during 2001–16, with greater declines in the 20–29 age group (–11%, –16 to 6) than in the older age groups (eg, –3% [–6 to 1] in those aged 70–89 years). During 2013–16, the SIR of lung cancer in people living with HIV was 2·01 (95% CI 1·52 to 2·61) in those aged 40–49 years, and 1·31 (1·12 to 1·52) in those aged 60–69 years, whereas the excess absolute risk among people living with HIV was 11·87 (3·95 to 21·89) per 100 000 person-years for those aged 40–49 years and 48·23 (6·88 to 95·47) per 100 000 person-years for those aged 60–69 years. Beginning in 2011, the 5-year cumulative incidence for lung cancer (1·36%, 95% CI 1·17 to 1·53) surpassed that of Kaposi sarcoma (0·12%, 0·06 to 0·17) and non-Hodgkin lymphoma (0·45%, 0·35 to 0·56) for people living with HIV aged 60–69 years.

Interpretation Between 2001 and 2016, the risk of lung cancer decreased for people living with HIV aged 20–69 years, but remained substantially elevated compared with the general population, probably due to a combination of smoking and immunosuppression. For people living with HIV aged 60 years and older, the risk of lung cancer exceeds that of two of the most common AIDS-defining cancers, highlighting the importance of lung cancer among the growing older population of people living with HIV.

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Introduction

The risk of lung cancer among people living with HIV is 1·5–3 times higher than in the general population.[1,2] Previous work has shown that lung cancer risk is increased with lower CD4 cell counts, greater viral loads, and among individuals with a previous AIDS diagnosis.[1,3] In addition, markers of lung inflammation have been shown to be elevated among individuals with uncontrolled HIV viraemia.[4] Although smoking is more prevalent among people living with HIV than in the general population, some evidence has suggested that HIV is an independent risk factor for lung cancer and possibly interacts with smoking to enhance lung cancer risk among people living with HIV who smoke.[2,5–8]

The antiretroviral therapy (ART) era has resulted in a shift in the cancer burden among people living with HIV from predominantly AIDS-defining cancers (ie, Kaposi sarcoma, some non-Hodgkin lymphomas, and cervical cancer)[9] to predominantly non-AIDS-defining cancers. By 2030, the proportion of people living with HIV who are older than 65 years is expected to double in the USA,[9] introducing greater risks for diseases associated with an ageing population. Lung cancer is the third most common cancer type in people living with HIV, following non-Hodgkin lymphoma and Kaposi sarcoma, and the second largest contributor to death among all cancers.[10] Although lung cancer rates have been declining over time in the USA,[11] such trends have not been investigated among people living with HIV in more than a decade.

As lung cancer is an important cause of morbidity and mortality among people living with HIV, updated estimates of both absolute and relative risk (RR) are

Research in context

Evidence before this study

We searched PubMed for peer-reviewed articles published between Jan 1, 2000, and Dec 31, 2021, with the Medical Subject Headings terms "lung cancer", "incidence", and "HIV", along with personal collections of study reports, reviews, and reference lists of previously identified publications of relevance. Specifically, we examined articles for estimates of the risk of lung cancer among people living with HIV compared with the general population. Incidence of lung cancer has been shown to be 1·5–3 times higher among people living with HIV compared with either the general population or with a comparison group without HIV. The most recent high-quality work that used a US-based HIV surveillance and cancer registry linkage study used data from 1996 to 2012, and found that the relative risk (RR) of lung cancer for people living with HIV in the USA compared with the general population declined over time but remained significantly elevated and was the second most common cancer among people living with HIV. However, these data are now over 10 years old and age-group specific trends were not investigated. Additionally, most publications focused on the RR rather than the absolute risk of lung cancer.

Added value of this study

Our study, linking two population-based registries, is to our knowledge the largest study conducted so far to analyse cancer incidence in people living with HIV in the USA, and uses data from 2001 to 2016 analysed across age groups. We found that the RR of lung cancer in people living with HIV compared with the general population has continued to decline since 2001, and was approximately 1·5 during the most recent time period we analysed (2013–16). Our findings show that the youngest age groups of people living with HIV (eg, aged 20–39 years) had greater declines in the RR of lung cancer over time than did the older age groups. However, the largest absolute excess risks continue to be among the oldest age groups (eg, aged 70–89 years). Importantly, based on our most recent data, from 2011 to 2016, we found that the cumulative incidence of lung cancer surpasses that of both non-Hodgkin lymphoma and Kaposi sarcoma for people living with HIV who are older than 50 years.

Implications of all the available evidence

Declines in risk of lung cancer for people living with HIV probably reflect improvements in access to and treatment with combined antiretroviral therapy, especially for the youngest age group (aged 20–39 years). Prevention and detection of lung cancer for people living with HIV should be prioritised for the growing proportion of individuals older than 50 years.

needed overall and across age groups to inform efforts to improve health outcomes in people living with HIV. In this study, we aimed to use data from a population-based study of HIV and cancer registries to describe lung cancer risk in people living with HIV relative to the general population, and the cumulative incidence of lung cancer among people living with HIV in the USA.

Methods

Study design and participants

In this population-based registry linkage study, we used data from the HIV/AIDS Cancer Match (HACM) study, which links data from HIV and cancer registries in the USA.[12] We included includes data from individuals diagnosed with cancer from Jan 1, 2001, to Dec 31, 2016, from 13 regions in the USA, including 11 states (Colorado, Connecticut, Georgia, Louisiana, Massachusetts, Maryland, Michigan, New Jersey, New York, North Carolina, Texas), Washington DC, and Puerto Rico. We included individuals 20 years or older and younger than 90 years in our study population. We included only individuals of non-Hispanic White (ie, White), non-Hispanic Black (ie, Black), and Hispanic race and ethnicity in our analyses due to small sample sizes of people living with HIV of other or unknown race and ethnicity, who represented around 1·5% of the total observed person-time in people living with HIV in our study population and among whom no cases of lung cancer were observed in some years.

The HACM study was approved by institutional review boards at participating registries and was exempt from review at the US National Institutes of Health. Consent of participants was not required for the use of data collected through public health surveillance.

Procedures

HIV registry data captured demographic characteristics and dates of reported HIV, AIDS, and cause of death. We classified risk groups for HIV acquisition on the basis of sex and recorded mode of transmission (eg, people who inject drugs, men who have sex with men [MSM] who do not inject drugs, or other modes of transmission [including MSM who inject drugs] or those with an unknown mode of transmission).

We estimated time since HIV diagnosis and previous AIDS diagnosis using HIV surveillance data for all regions excluding Massachusetts, where those data were unavailable. Years of observation were grouped into four time periods: 2001–04, 2005–08, 2009–12, and 2013–16.

Linked cancer registry data include cancer diagnosis dates, tumour site, morphology, and stage. Using International Classification of Diseases for Oncology, third edition (ICD-O-3) site codes C340–C349, and excluding ICD-O-3 morphology codes 9050–9055, 9140,

and 9590–9992, we classified lung cancer histological subtypes into squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, and other histologies (classified using the Surveillance, Epidemiology, and End Results [SEER] Lung Solid Tumor Rules; appendix p 1).

See Online for appendix

Statistical analysis

We calculated age-standardised incidence rates of lung cancer using the 2010 population of people living with HIV as the standard population and 95% CIs using the Fay and Feuer method.[13] We used Joinpoint to test for any significant changes in trajectory of the age-standardised incidence rates and we did not identify any significant joinpoints, which suggested that the yearly change was constant and that multivariable Poisson regression would be appropriate. To estimate the average annual percentage change in lung cancer incidence rates in people living with HIV, we used a multivariable Poisson regression model to estimate the coefficient for calendar year, adjusted for attained age, sex and HIV risk group, and race and ethnicity with the log person-time as an offset. We used a generalised boosted model to inform the forward selection of covariates for a minimally adjusted model after including the effects of year as a linear term. We also tested for a minimum of a 10% change in the year coefficient to consider additional confounders, including region, time since HIV diagnosis, and previous AIDS diagnosis. We tested for interactions between year and other variables and then estimated stratified average annual percentage changes when the interaction term was significant.

For **Joinpoint** see https://surveillance.cancer.gov/joinpoint/

To compare risks between people living with HIV and the general population, we used standardised incidence ratios (SIRs) for the included registry areas. SIRs were calculated by dividing the observed number of lung cancer diagnoses in people living with HIV by the expected number, estimated by applying general population cancer incidence rates (which were provided in the HACM study) to person-time in the HIV population based on sex, attained age, race and ethnic group, calendar year, and registry. To assess calendar trends of SIRs over the four specified time periods, we used Poisson regression adjusting for age group, sex and HIV risk group, and race and ethnicity with the log of the expected number of lung cancer diagnoses (based on the general population) as an offset. We estimated the excess absolute risk of lung cancer by calculating the difference between the observed and the expected cancer rates as estimated from the general population.

As information on cigarette smoking was not available in the HACM study, we conducted bias factor analyses to estimate the RR between smoking and lung cancer that would be needed for the true SIR to be null after accounting for smoking (ie, $SIR_{true}=1$) under various prevalence rates of smoking in the general population (A; 20%, 25%, and 30%) and people living with HIV (B; 40%, 60%, and 80%) using the following bias factor equation:[14]

$$\frac{SIR_{true}}{SIR_{observed}} = \frac{(1-A) + (RR * A)}{(1-B) + (RR * B)}$$

We used prevalence estimates of smoking in the general population based on data data from US National Health and Nutrition Examination Survey (NHANES) 1999–2016.[15]

We calculated non-parametric cumulative incidence curves for lung cancer by treating death from causes other than lung cancer as a competing event. Point-wise estimates at 5 years of follow-up in three separate models using time origins of 2001, 2006, and 2011 were calculated for each age group. We included weights in our models to account for left truncation and right censoring due to registries entering and leaving the study at various points. To contextualise the risk of lung cancer in people living with HIV, we estimated cumulative incidence of AIDS-defining cancers (ie, Kaposi sarcoma and non-Hodgkin lymphoma) using the same approach.

All analyses were conducted using R (version 4.1.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, but did review a final version of the manuscript before submission.

Results

We observed a total of 4 310 304 person-years of follow-up among our study population of people living with HIV in the USA between Jan 1, 2001, and Dec 31, 2016 (incidence rate 79·4 per 100 000 person-years). The proportion of the study population aged 50 years and older nearly doubled, from around 21·5% of the total person-time observed in 2001–04 to over 41·6% in 2013–16 (table 1). Over time, there was a decrease in the proportion of people who inject drugs of male and female sex, and an increase in the proportion of MSM. By 2013–16, 49·2% of the study population had been living with HIV for at least 10 years, and there was a 15% decrease in the proportion of people living with HIV with a previous AIDS diagnosis compared with 2001–04.

Over the course of follow-up, there were 3426 lung cancer diagnoses observed in people living with HIV. The most common histological subtype was adenocarcinoma (accounting for 1368 [40%] of all 3426 lung cancers), followed by squamous cell carcinoma (853 [25%]), small cell carcinoma (313 [9%]), and large cell carcinomas (87 [3%]). On the basis of the total expected counts for each histological group, these proportions were similar to what would be expected in the general population, in which 43% of lung cancers would be adenocarcinoma and 21% would be squamous cell

	2001–04 (n=743 220)	2005–08 (n=1 171 773)	2009–12 (n=1 583 882)	2013–16 (n=811 428)
Age group, years				
20–39	284 608 (38·3%)	356 772 (30·4%)	425 480 (26·9%)	235 996 (29·1%)
40–49	299 321 (40·3%)	474 044 (40·5%)	567 403 (35·8%)	237 153 (29·2%)
50–59	126 515 (17·0%)	263 486 (22·5%)	433 146 (27·3%)	238 148 (29·3%)
60–69	27 181 (3·7%)	64 188 (5·5%)	131 154 (8·3%)	82 998 (10·2%)
70–89	5596 (0·8%)	13 284 (1·1%)	26 699 (1·7%)	17 133 (2·1%)
Sex and HIV risk group				
Male, other or unknown	170 790 (23·0%)	278 085 (23·7%)	383 217 (24·2%)	182 494 (22·5%)
Female, other or unknown	144 548 (19·4%)	251 947 (21·5%)	353 794 (22·3%)	172 893 (21·3%)
Male PWID	125 451 (16·9%)	161 431 (13·8%)	174 802 (11·0%)	73 602 (9·1%)
Female PWID	63 902 (8·6%)	81 726 (7·0%)	90 845 (5·7%)	37 853 (4·7%)
MSM	238 530 (32·1%)	398 584 (34·0%)	581 224 (36·7%)	344 585 (42·5%)
Race and ethnicity				
Hispanic	187 475 (25·2%)	310 383 (26·5%)	399 103 (25·2%)	208 350 (25·7%)
Non-Hispanic Black	350 350 (47·1%)	556 115 (47·5%)	781 135 (49·3%)	377 419 (46·5%)
Non-Hispanic White	205 394 (27·6%)	305 275 (26·1%)	403 644 (25·5%)	225 660 (27·8%)
Time since HIV diagnosis, years*				
≤5	260 425/743 220 (35·0%)	316 903/1 152 575 (27·5%)	337 306/1 525 326 (22·1%)	155 886/732 363 (21·3%)
>5 to 10	226 406/743 220 (30·5%)	335 074/1 152 575 (29·1%)	416 349/1 525 326 (27·3%)	187 354/732 363 (25·6%)
>10 to 15	108 513/743 220 (14·6%)	226 730/1 152 575 (19·7%)	315 264/1 525 326 (20·7%)	166 042/732 363 (22·7%)
>15	17 332/743 220 (2·3%)	101 486/1 152 575 (8·8%)	272 829/1 525 326 (17·9%)	194 167/732 363 (26·5%)
Missing	130 544/743 220 (17·6%)	172 382/1 152 575 (15·0%)	183 578/1 525 326 (12·0%)	28 914/732 363 (3·9%)
Previous AIDS diagnosis*				
No	262 460/743 219 (35·3%)	446 698/1 152 575 (38·8%)	632 278/1 525 327 (41·5%)	330 237/732 363 (45·1%)
Yes	480 759/743 219 (64·7%)	705 877/1 152 575 (61·2%)	893 049/1 525 327 (58·5%)	402 126/732 363 (54·9%)

Data are number of person-years rounded to the nearest whole number (%). PWID=people who inject drugs. MSM=men who have sex with men. *Numbers for HIV-related factors excluded Massachusetts.

Table 1: **Descriptive characteristics of person-years contributed by the study population of people living with HIV in the USA, over time**

carcinoma given the population distribution. There was a marked decrease in lung cancer over time, with an age-standardised incidence rate of 124·4 per 100 000 person-years in 2001–04 and 58·3 per 100 000 person-years in 2013–16 (table 2), corresponding to a 6% (95% CI –7 to –5) decline per year from 2001 to 2016. Similar declines per calendar year increase were observed across all histological subtypes (table 3). Compared with men living with HIV in the other or unknown risk group, women who inject drugs and men who inject drugs had significantly elevated lung cancer risk, and MSM and women in the other or unknown risk groups had significantly lower lung cancer risk. Lung cancer risk increased with age and was similar among Black people living with HIV and lower among Hispanic people living with HIV than in White people living with HIV (table 3). Findings were similar to the overall lung cancer group when looking at histological subtypes, with some evidence that RRs associated with age and risk group vary by histological subtype (table 3).

Among individuals aged 20–39 years, the average annual percentage change in lung cancer incidence rate was –11% (95% CI –16 to –6) compared with an average annual percentage change of –5% (–7 to –4) for individuals aged 50–59 years. We noted that the average annual percentage change did not reach statistical significance for individuals aged older than 70 years (–3%, –6 to 1; appendix p 1). In our adjusted model, we found a greater average annual percentage change among Hispanic people living with HIV (–9%, –11 to –7) than in non-Hispanic White (–4%, –6 to –3) and non-Hispanic Black people living with HIV (–6%, –7 to –5).

The overall SIR for people living with HIV compared with the general population declined from 2·46 (95% CI 2·27–2·65) in 2001–04 to 1·48 (1·36–1·61) in 2013–16. SIRs were the largest for younger age groups, among whom the greatest declines in SIRs over time were observed. Compared with the general population, lung cancer rates among people aged 20–39 years living with HIV were significantly higher in 2001–04 (SIR 5·17, 3·64–7·12), but not significantly elevated during 2013–16 (1·57, 0·51–3·67). Among individuals aged 40–49 years, the SIR was 3·14 (2·74–3·59) in 2001–04 and 2·01 (1·52–2·61) in 2013–16 (figure 1). In addition, rates of lung cancer among people living with HIV aged 50–59 years (SIR 1·61, 1·41–1·82) and 60–69 years (1·31, 1·12–1·52) were significantly elevated in 2013–16, but were not significantly higher among people living with

	2001–04	2005–08	2009–12	2013–16
20–39	13·0 (10·9–15·1)	7·9 (6·4–9·3)	5·2 (4·1–6·3)	2·1 (1·2–3·1)
40–49	73·2 (68·2–78·1)	56·8 (53·3–60·2)	42·0 (39·2–44·7)	23·6 (20·5–26·8)
50–59	210·3 (197·4–223·1)	162·1 (154·2–169·9)	126·1 (120·7–131·4)	103·3 (96·7–109·9)
60–69	401·0 (362·6–439·4)	325·6 (303·1–348·1)	261·5 (247·4–275·6)	206·0 (190·3–221·8)
70–89	464·7 (373·5–555·8)	429·1 (372·3–485·9)	344·6 (308·7–380·5)	350·2 (305·0–395·4)
Overall*	124·4 (114·5–135·0)	97·9 (91·8–104·3)	76·1 (71·9–80·4)	58·3 (53·4–63·5)

Data are incidence rate (95% CI). *Age-standardised using the age distribution of people living with HIV in 2010.

Table 2: **Incidence rates per 100 000 person-years for lung cancer in people living with HIV in the USA, by age group, over time**

	Lung	Squamous cell carcinoma	Adenocarcinoma	Small cell carcinoma	Large cell carcinoma
Calendar year* (per year increase)	0·94 (0·94–0·95)	0·96 (0·94–0·97)	0·97 (0·96–0·98)	0·94 (0·91–0·97)	0·86 (0·81–0·90)
Age group, years					
20–39	0·05 (0·04–0·07)	0·02 (0·01–0·03)	0·04 (0·03–0·06)	0·04 (0·02–0·08)	0·05 (0·01–0·15)
40–49	0·35 (0·32–0·38)	0·27 (0·22–0·33)	0·36 (0·31–0·41)	0·24 (0·17–0·33)	0·31 (0·18–0·53)
50–59	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
60–69	2·09 (1·92–2·27)	2·41 (2·05–2·84)	1·88 (1·64–2·16)	2·53 (1·93–3·29)	2·03 (1·16–3·44)
70–89	3·04 (2·64–3·49)	4·39 (3·44–5·53)	2·35 (1·84–2·97)	3·10 (1·92–4·77)	2·00 (0·6–5·00)
Sex and HIV risk group					
Male, other or unknown	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female, other or unknown	0·89 (0·80–0·99)	0·68 (0·55–0·84)	1·08 (0·92–1·27)	1·33 (0·94–1·89)	1·23 (0·68–2·23)
Male PWID	1·26 (1·15–1·39)	1·17 (0·97–1·41)	1·43 (1·22–1·67)	1·41 (0·99–2·01)	1·01 (0·52–1·90)
Female PWID	1·62 (1·44–1·83)	1·10 (0·84–1·43)	1·92 (1·59–2·31)	2·57 (1·73–3·80)	1·54 (0·70–3·14)
MSM	0·63 (0·57–0·70)	0·48 (0·39–0·59)	0·79 (0·67–0·93)	0·97 (0·69–1·35)	0·52 (0·26–0·99)
Race and ethnicity					
Hispanic	0·46 (0·41–0·52)	0·43 (0·34–0·54)	0·55 (0·46–0·66)	0·43 (0·30–0·62)	0·22 (0·08–0·51)
Non-Hispanic Black	1·07 (0·99–1·17)	0·90 (0·76–1·06)	1·23 (1·07–1·40)	0·83 (0·64–1·09)	1·02 (0·62–1·73)
Non-Hispanic White	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

Data are relative risk (95% CI), from multivariable Poisson regression. Other histologies included in the lung cancer category: carcinoma not otherwise specified (NOS; 8010), bronchioloalveolar carcinoma (8253), adenosquamous carcinoma (8560), giant cell and spindle cell carcinoma (8031), carcinoid tumour NOS (8240), sarcoma NOS (8800/3), solid carcinoma NOS (8230), and spindle cell sarcoma (8801). PWID=people who inject drugs. MSM=men who have sex with men. *Calendar year of cancer diagnosis.

Table 3: **Risk of lung cancer and histological subtypes among people living with HIV in the USA, 2001–16**

HIV aged 70 years and older (1·24, 0·94–1·59; appendix p 3). When 2013–16 data were analysed by HIV risk group, lung cancer rates among people living with HIV were elevated most strongly among women who inject drugs (SIR 3·27, 2·45–4·28), with the smallest elevation observed among MSM (1·13, 0·96–1·32), who had a non-significant elevated risk compared with the general population (appendix p 3).

In contrast to findings regarding the SIRs, the largest excess absolute risks were among individuals aged 60–69 years and 70–89 years, although all excess absolute risks for those who were 70–89 years had 95% CIs that crossed 0 during 2013–16 (appendix p 3). Although excess absolute risks have also declined over time for most age groups, excess absolute risks for people living with HIV aged 70 years and older increased from an excess of 18·05 (95% CI –74·25 to 128·81) per 100 000 person-years in 2009–12 to 66·95 (–46·98 to 209·81) per 100 000 person-years in 2013–16, although neither excess was significant (figure 1).

According to NHANES data, during the time periods of our study, the estimated prevalence of smoking was 26% in the general population and 47% among people living with HIV. Our bias factor analyses found that in all scenarios, the elevated risk observed in people living with HIV who were 70 years and older could be plausibly explained by confounding due to smoking prevalence (appendix p 4). For example, given a prevalence of smoking of 25% in the general population and 40% in people living with HIV, an RR of 2·45 for the effect of smoking on lung cancer could explain the observed SIR of 1·16 in people living with HIV aged 70 years or older. However, no RRs could be estimated that would explain the elevated risks observed among 20–39-year-olds and 40–49-year-olds in scenarios in which smoking prevalence was 40% in people living with HIV.

We estimated a 5-year cumulative incidence of lung cancer of 0·02% (95% CI 0·01–0·03) for people living with HIV aged 20–39 years using a time of origin of 2011, which increased with each age group to 1·65% (1·19–2·08) for those aged 70 years and older (figure 2; appendix p 5). Although the 5-year cumulative incidence of either Kaposi sarcoma or non-Hodgkin lymphoma was greater than that of lung cancer in individuals who were younger than 50 years, the cumulative incidence of lung cancer for people aged 50–59 years living with HIV (0·62%, 95% CI 0·56–0·68) was equivalent to non-Hodgkin lymphoma (0·56%, 0·50–0·62) and greater than Kaposi sarcoma (0·14%, 0·11–0·17). The 5-year cumulative incidence of lung cancer in people aged 60–69 years living with HIV at time of origin of 2011 was 1·36% (95% CI 1·17–1·53), which is notably greater than non-Hodgkin lymphoma (0·45%, 0·35–0·56) and Kaposi sarcoma (0·12%, 0·06–0·17). For additional comparisons, we calculated the cumulative incidences using time of origins of 2001 and 2006, separately (appendix p 5). We note that although the 5-year cumulative incidence of lung cancer for people living with HIV aged 60–69 years declined across the time period, with a cumulative incidence of 1·93% (1·03–2·79) with an origin of 2001, there have also been considerable declines in that of non-Hodgkin lymphoma with an estimated 5-year cumulative incidence based on the 2001 origin of 1·31% (1·01–1·59), and of Kaposi sarcoma (0·23%, 0·11–0·35).

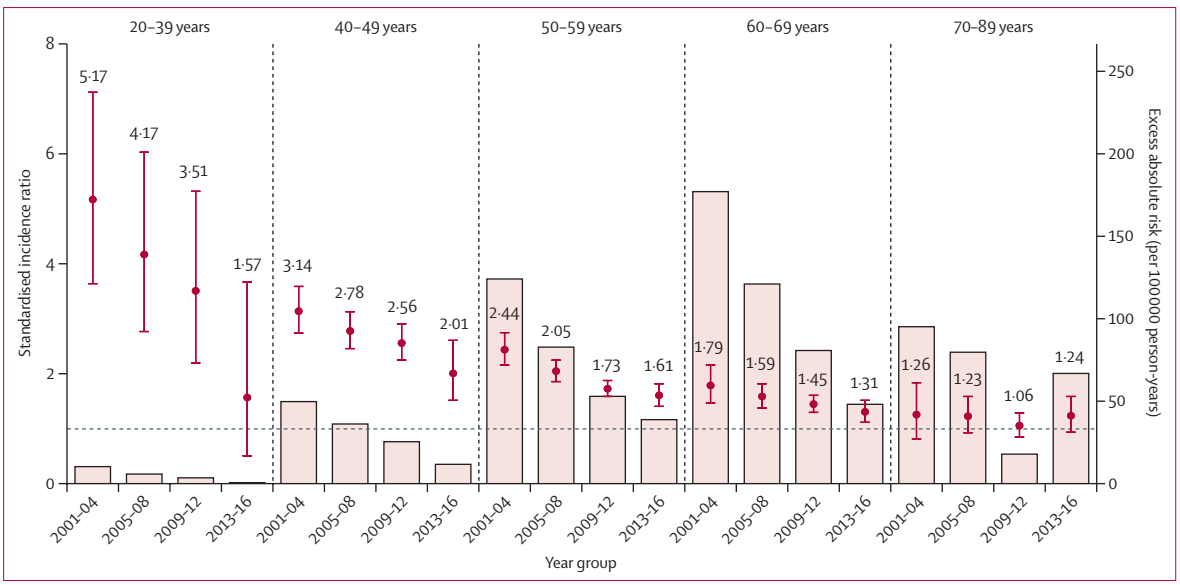

Figure 1: **Standardised incidence ratio and excess absolute risk for lung cancer over time for people living with HIV in the USA compared with the general population, by age group**

Standardised incidence ratios are shown by the red dots and accompanying error bars showing 95% CIs, with the scale on the left y-axis; the dashed horizontal line shows the standardised incidence ratio of 1 (ie, same incidence as in the general population). Excess absolute risk (per 100 000 person-years) are shown by the pink bars, with the scale on the right y-axis.

Discussion

During 2001–16, lung cancer rates among people living with HIV declined over time but was 48% higher than the general population in 2013–16. Lung cancer rates declined most rapidly among individuals aged 20–49 years, and risks were also most elevated in these age groups relative to the general population. Although smoking probably contributed to the elevated RR, other factors including immunosuppression could also play a role, particularly among young people living with HIV. Despite declines in RRs over time, lung cancer is an important cancer among older people living with HIV as the cumulative incidence of lung cancer among people living with HIV aged 50 years and older surpasses that of both non-Hodgkin lymphoma and Kaposi sarcoma.

Lung cancer is estimated to have been the second most common cancer among people living with HIV in the USA in 2020 and is expected to increase to represent 15% of all cancers in this population by 2030.[9] We found that the highest risk of lung cancer in people living with HIV occurs among those aged 60 years and older, exceeding that of the most common AIDS-defining cancers—non-Hodgkin lymphoma and Kaposi sarcoma. Despite the elevated risk among younger age groups (ie, aged 20–49 years) of people living with HIV compared with the general population, the greatest excess risks on the absolute scale are among older age groups of people living with HIV (ie, those aged ≥60 years). This finding is particularly important as older individuals comprise an increasing proportion of people living with HIV and are reaching ages associated with the highest risk of lung cancer. Although the higher prevalence of smoking in people living with HIV than in the general population could explain the observed increased risk in lung cancer in the older age groups, we emphasise the public health importance of this additional burden when considering strategies to mitigate the effect of lung cancer in this population.

Cigarette smoking causes 90% of lung cancers in the general population[16] and probably contributes strongly to elevated rates of lung cancer among people living with HIV, and is the primary risk factor for cancer in the modern era, particularly among people who inject drugs.[6,15,17] For context, estimates for the RR of lung cancer in people who smoke versus those who have never smoked range between 16 and 115 for men and 8 and 121 for women depending on cancer subtype.[18,19] The most recent estimates of smoking status in the USA based on the NHANES for 1999–2016 reported that 47% of survey participants with HIV were current smokers compared with 26% of survey participants without HIV, with similar declines in smoking prevalence over time.[15] Although smoking cessation programmes tailored to people living with HIV are merited to bridge the remaining gap in smoking prevalence, more research on the effects of HIV as an independent and synergistic risk factor are also needed.[20,21] Our bias analysis showed that differences in smoking prevalence could plausibly explain many of the elevated SIRs observed, although it is likely that improvements in immunosuppression have also contributed to the decrease in SIR over time, particularly among younger people living with HIV for whom the association between smoking and lung cancer is known to be weaker.[18]

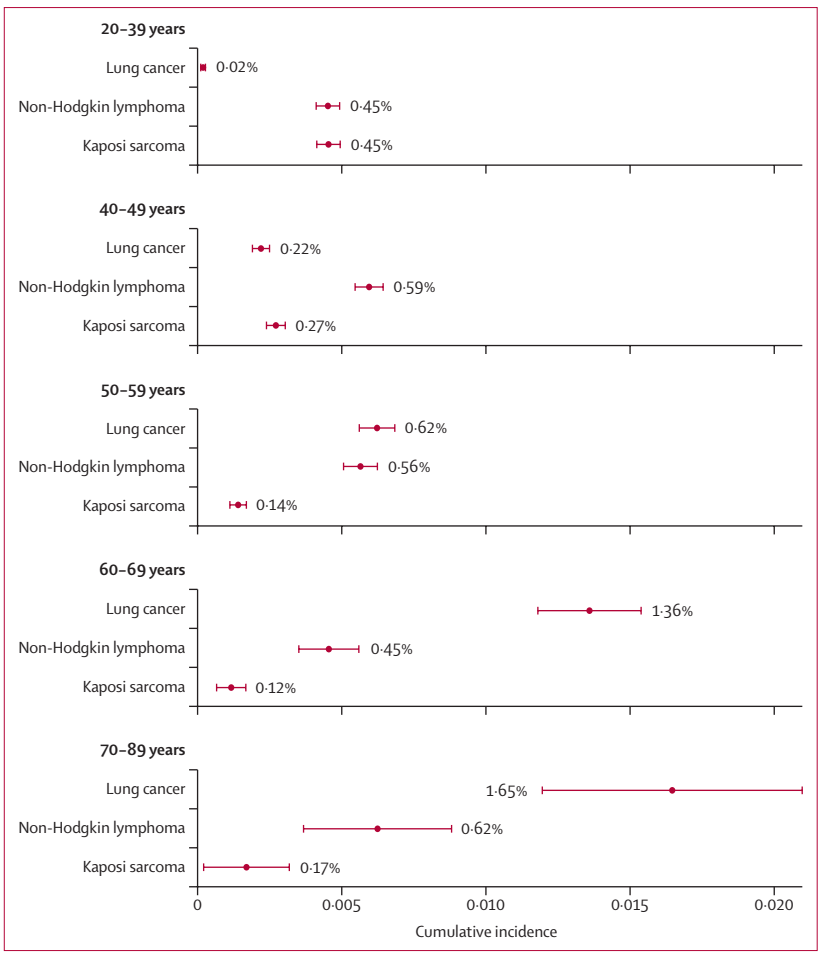

Figure 2: **5-year cumulative incidences of lung cancer in people living with HIV in the USA starting in 2011, by age group**
Error bars show 95% CIs.

In addition to smoking, immunosuppression and pulmonary inflammation are likely to play a role in the development of lung cancer among people living with HIV. Lower CD4/CD8 ratios have been associated with higher incidence of lung cancer,[22] even independent of the association with episodes of bacterial pneumonia.[3] A study conducted in France in people living with HIV also has shown a decline of lung cancer over time and elevated risk compared with the general population, but a less elevated SIR for people living with HIV who had CD4 cell recovery and were on combination ART.[22] Previous AIDS diagnosis, a marker of previous severe immunosuppression, was shown to be associated with an increased risk of lung cancer both in an earlier study[1] and in our study. The decrease in SIR for people living with HIV over time could be due to greater access to more effective ART, improving the overall health of this population and decreasing progression to immunosuppression and risk of pulmonary infections.

Mechanisms that have previously been attributed to both direct oncogenic effects of HIV[23] and indirect result of immunosuppression,[14,24] or risk of pulmonary infections and inflammation,[3,25,26] might have become less relevant in over the past 15 years as fewer people living with HIV are progressing to AIDS and have severe immunosuppression. Rates of lung cancer have declined as much as 11% per year in people living with HIV aged 20–39 years between 2001 and 2016, but these declines have been less dramatic in older age groups and non-significant for those aged 70 years and older. In combination with declining SIRs over time in younger people living with HIV, this evidence supports a role of HIV viraemia or immunocompromised status in lung cancer risk—unless smoking prevalence has disproportionately declined in younger people living with HIV (we are unaware of data to support that possibility).

As in the general US population, most lung cancers in people living with HIV are not diagnosed until advanced stages.[27] These factors have resulted in lung cancer contributing substantially to mortality in people living with HIV. The US Preventative Services Task Force (USPSTF) has provided some recom-mendations for the use of low-dose CT for adults aged 50–80 years with a 20 pack-year smoking history who are current smokers or had quit within the previous 15 years.[28] However, more research specifically on the use of low-dose CT among people living with HIV is needed to identify populations with an increased risk of death from lung cancer and additional factors that might be clinically relevant. Previous studies have suggested an interaction between HIV infection and smoking.[5,23,24] If true, it could merit more tailored USPSTF guidelines for lung cancer screening with low-dose CT in people living with HIV who are younger than 50 years or have a less severe smoking history.[29,30] However, work on the benefits of low-dose CT in people living with HIV in the USA found that similar mortality reductions to the general population can be achieved by following the Centres for Medicare and Medicaid Services criteria (ie, age 55–77 years, 30 pack-years of smoking, and current smoker or ex-smoker who had quit within 15 years of screening).[31]

Although the primary strength of our study is the linkage of two population-based registries, representing the largest study conducted so far that has analysed cancer incidence in people living with HIV, it is still subject to limitations in the extent to which variables were captured in either of those data sources. As neither HIV surveillance nor cancer registries capture smoking and smoking-related information, we were limited in our ability to adjust for or stratify by smoking history in calculating our estimates. Similarly, information related to socioeconomic status, which could be relevant to both risk of HIV and lung cancer, were unavailable for our analyses. Although we emphasise the descriptive nature of our study and the importance of these estimates overall for people living with HIV, future work to estimate

the effects of smoking and other factors in this population merit investigation.

Using large, national surveillance and registry data in the USA, we have shown an overall decrease in age-standardised incidence rates of lung cancer in people living with HIV between 2001 and 2016, and a decline in the relative excess risk of lung cancer compared with the general population. The reduction in risk for lung cancer in people living with HIV is most pronounced among those younger than 50 years, who show substantial decreases in relative excess risk compared with the general population. However, for the increasing proportion of people living with HIV who are living beyond the age of 50 years, the absolute risk of lung cancer has surpassed that of common AIDS-defining cancers and is a considerable excess risk and public health burden. Strategies for prevention and early detection are necessary to reduce the disparities in lung cancer risk for people living with HIV.

Contributors

CBH and MSS were responsible for the conceptualisation of this study, investigation, and, along with RMP, determined the use of methodology. MSS provided supervision. MSS, QL, and CBH had access to and verified the data. CBH performed the formal analyses, created visualisations, and wrote the original draft and revised versions. M-JH and QL provided project administration. SG and BQ provided resources. All authors contributed to reviewing and editing of manuscript drafts and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data used in this study cannot be shared publicly due to the terms of the US National Cancer Institute's (NCI's) data use agreements with the cancer and HIV surveillance systems.

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