Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study

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Summary

Background Monitoring cancer risk among HIV-infected people in the modern antiretroviral therapy (ART) era is essential given their elevated risk for many cancers and prolonged survival with immunosuppression, ART exposure, and ageing. We aimed to examine cancer risk in HIV-infected people in the USA as compared with that in the general population.

Methods We did a registry-linkage study with data from population-based HIV and cancer registries in the USA (the HIV/AIDS Cancer Match Study). We assessed a cohort of HIV-infected people identified in HIV registries in Colorado, Connecticut, Georgia, Maryland, Michigan, New Jersey, New York, Puerto Rico, and Texas from 1996 to 2012. Follow-up started 3 months after either the latest of the beginning of systematic name-based state HIV registration, HIV report date (or AIDS diagnosis, if this was earlier), start of cancer registration, or Jan 1, 1996, and ended at the earliest of either death, end of cancer-registry coverage, or Dec 31, 2012. We identified diagnoses of cancer in this population through linkage with corresponding cancer registries and calculated standardised incidence ratios (SIRs) to measure cancer risk in people with HIV compared with the USA general population, by dividing the observed number of cases in people with HIV by the expected number (estimated by applying general population cancer-incidence rates to person-time in the HIV population based on sex, age, race or ethnic group, calendar year, and registry). We tested SIR differences by AIDS status and over time using Poisson regression.

Findings Among 448 258 people with HIV (who contributed 3 093 033 person-years), 21 294 incident cancers were diagnosed during 1996–2012. In these people, compared with the general population, risk was elevated ($p<0·0001$ for all) for cancer overall (SIR 1·69, 95% CI 1·67–1·72), AIDS-defining cancers (Kaposi's sarcoma [498·11, 477·82–519·03], non-Hodgkin lymphoma [11·51, 11·14–11·89], and cervix [3·24, 2·94–3·56]), most other virus-related cancers (eg, anus [19·06, 18·13–20·03], liver [3·21, 3·02–3·41], and Hodgkin's lymphoma [7·70, 7·20–8·23]), and some virus-unrelated cancers (eg, lung [1·97, 1·89–2·05]), but not for other common cancers. Risk for several cancers was higher after AIDS onset and declined across calendar periods. After multivariable adjustment, SIRs decreased significantly across 1996–2012 for Kaposi's sarcoma, two subtypes of non-Hodgkin lymphoma, and cancer of the anus, liver, and lung, but remained elevated. SIRs did not increase over time for any cancer.

Interpretation For several virus-related cancers and lung cancer, declining risks over time in HIV-infected people probably reflect the expansion of ART since 1996. Additional efforts aimed at cancer prevention and screening in people with HIV are warranted.

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Introduction

HIV-infected people have a higher risk for many cancers than do healthy people, largely as a result of HIV-related immunosuppression, which impairs control of oncogenic viral infections.[1–3] A high prevalence of these infections and other cancer-risk factors (eg, smoking and alcohol use) contribute to the elevated risk.[1–4] Kaposi's sarcoma, some subtypes of non-Hodgkin lymphoma, and cervical cancer are caused by viruses (Kaposi sarcoma-associated herpesvirus, Epstein-Barr virus, and human papillomavirus, respectively) and are among conditions that can mark the onset of AIDS.[3] HIV-infected people have elevated risks for these AIDS-defining cancers and other virus-related non-AIDS-defining cancers, but not for most virus-unrelated non-AIDS-defining cancers.[1–3]

After the introduction of effective antiretroviral therapy (ART) in 1996, the risks for AIDS and death decreased strikingly in HIV-infected people.[3] The incidences of Kaposi's sarcoma and non-Hodgkin lymphomas have also decreased, but remain higher in HIV-infected people than in the general population; trends for other cancers are less clear.[3,5–12] Few recent comprehensive population-based data exist about cancer risks for HIV-infected people.[6,8–10,12]

The risk for some types of cancers might continue to decline as ART regimens improve, treatment is initiated at earlier stages of HIV disease, and access to ART increases.[13] However, treatment might not fully reverse the effect of early immune suppression, and immune dysfunction and chronic inflammation can persist among people receiving ART.[2] HIV-infected people, including those who have not developed AIDS, might therefore still have an elevated risk of cancer. Furthermore, many cancer types have latency periods of

Research in context

Evidence before this study

We searched PubMed for citations published in English during Jan 1, 2000, to Dec 31, 2016, with MeSH terms "cancer", "incidence", and "HIV infections", reviewed personal collections of study reports and reviews, and examined reference lists of reviewed publications to identify publications about cancer risk in people with HIV, compared with the general population or uninfected groups. Specifically, we examined publications that reported risk estimates overall and by AIDS onset, and recent trends covering the era of effective antiretroviral therapy (ART) beginning in 1996. Evidence indicates that HIV-infected people, especially those with AIDS, have an elevated risk for many cancers, especially those from viral causes. Additionally, after the introduction of ART in 1996, the incidence of two AIDS-defining cancers, Kaposi's sarcoma and non-Hodgkin lymphoma, decreased. However, trends for other cancers are less clear, and there is a shortage of recent and comprehensive population-based data about cancer risks for people with HIV.

Added value of this study

The HIV/AIDS Cancer Match (HACM) Study is the largest population-based study of cancer in HIV-infected people. We used data from the study to assess the risk of cancers in a sample of 448 258 people with HIV in the USA during 1996–2012. We found that, compared with the general population, HIV-infected people (including those without AIDS) had a greater risk for various cancers, including AIDS-defining cancers, many other virus-related cancers, and lung cancer. Although the risk for Kaposi's sarcoma, non-Hodgkin lymphoma, and some non-AIDS-defining cancers (anus, liver, and lung) decreased over time, risks generally have remained high.

Implications of all the available evidence

The decreases in cancer risk in people with HIV over time probably reflect the sustained and widened use of ART. Despite these decreases, however, cancer risks in HIV-infected people have remained elevated during the modern treatment era, indicating that continued cancer control efforts are warranted with additional efforts aimed at cancer prevention and screening.

decades, and the modern ART era is only 20 years old; elevated risks for some cancers might, therefore, emerge over time. Finally, with prolonged survival the HIV population is ageing, and the effect of HIV-related immunosuppression in an ageing population is unclear.[10,14] For these reasons, continued monitoring of cancer risks in this population is vital. In this study, we describe the range of cancer risks among HIV-infected people in the USA during the modern ART era by use of linked data from several population-based HIV and cancer registries.

See Online for appendix

Methods

Study design, participants, and data sources

For the **HIV/AIDS Cancer Match Study** see https://hivmatch.cancer.gov

We used data from the HIV/AIDS Cancer Match (HACM) Study, which examines linked data collected by USA HIV and cancer registries.[15] The study was approved by institutional review boards at participating registries as required, and received exemption from review at the USA National Institutes of Health. Because the study used data collected for public health surveillance, consent of participants was not required.

For this analysis we assessed a cohort of HIV-infected people from HACM identified in HIV registries from Colorado (1996–2007), Connecticut (2005–10), Georgia (2004–12), Maryland (2008–12), Michigan (1996–2010), New Jersey (1996–2012), New York (2001–12), Puerto Rico (2003–12), and Texas (1999–2009). For each registry, follow-up for each cohort member started 3 months after the latest of the beginning of systematic name-based state HIV registration, HIV report date (or AIDS diagnosis if this was earlier), the start of cancer registration, or Jan 1, 1996, and ended at the earliest of death, end of cancer registry coverage, or Dec 31, 2012. The first 3 months of follow-up were excluded to remove prevalent cancers; ie, cancer cases that prompted HIV testing and reporting. Cancer diagnoses were identified through linkage with the corresponding cancer registries (appendix pp 2–3). We assessed individual cancer types and several broad categories, including all cancers, AIDS-defining cancers (Kaposi's sarcoma; AIDS-defining non-Hodgkin lymphomas: diffuse large B-cell lymphoma, Burkitt's lymphoma, unspecified non-Hodgkin lymphoma, and CNS non-Hodgkin lymphoma; and cervical cancer), and non-AIDS-defining cancers, which were subclassified as either virus-related (cancers of the anus, vagina, vulva, penis, and selected oral cavity or pharynx sites [caused by human papillomavirus]; liver cancer [hepatitis B and C viruses]; Hodgkin's lymphoma [Epstein-Barr virus]; and Merkel cell carcinoma [Merkel cell polyomavirus]) or virus-unrelated (remaining cancers).

Statistical analysis

We used standardised incidence ratios (SIRs) to measure cancer risk in people with HIV compared with the USA general population. SIRs were calculated by dividing the observed number of cases in HIV-infected people by the expected number, estimated by applying general population cancer-incidence rates to person-time in the HIV population based on sex, age, race or ethnic group, calendar year, and registry. For Kaposi's sarcoma and CNS non-Hodgkin lymphoma (for which contemporaneous general population rates largely reflect HIV-related cases), expected rates were based on data collected by the Surveillance, Epidemiology, and End

Results (SEER) cancer registries before the AIDS epidemic (1973–79).[15] To calculate SIRs, we counted all cancers (not just first cancers), including multiple cancers of the same type.

In preliminary analyses, we observed that the SIR for a miscellaneous cancers category was significantly raised. We therefore reviewed this category and extracted additional cancer types with at least ten cases for separate assessment (cancers of the extrahepatic bile duct, nasal cavity, accessory sinuses, scrotum, conjunctiva, and thymus, Merkel cell carcinoma, appendageal carcinoma of the skin, sarcomas of the skin, polycythaemia vera, essential thrombocythaemia, and myelodysplastic syndrome), which are included separately in the results.

To assess the association of cancer risk with advancing immunosuppression, we calculated SIRs separately for person-time with AIDS and without AIDS (ie, HIV only). The AIDS onset month was considered the end of the HIV-only period, so some AIDS-defining cancers were counted as occurring in people with HIV only. We compared SIRs for the HIV-only and AIDS periods by use of Poisson regression. These models yielded SIR ratios adjusted for sex or HIV-risk group (men who have sex with men, other males, and females), attained age (<30, 30–39, 40–49, 50–59, and ≥60 years), race or ethnic group (non-Hispanic white, non-Hispanic black, and Hispanic or Latino), calendar year (modelled as one continuous variable, except for Kaposi's sarcoma, diffuse large B-cell lymphoma, and CNS non-Hodgkin lymphoma, which were modelled as separate segments as informed by Joinpoint analysis [version 4.3.1, National Cancer Institute]), registry, and early versus late attained follow-up duration (<10 *vs* ≥10 years after the latest of HIV report or AIDS diagnosis).

We considered calendar trends in cancer risk to reflect increasing use of ART at the population level. To screen for time trends, we first calculated SIRs for four calendar periods (1996–99, 2000–04, 2005–08, and 2009–12) and tested for a trend in SIRs across the periods with unadjusted Poisson models. For selected cancers for which the SIR was elevated overall and the trend across periods was significant, we further assessed trends across individual calendar years. We first used Joinpoint to identify significant changes in SIR trends over calendar time, allowing up to four calendar segments.

	1996–2012 (n=3 090 033)	1996–99 (n=155 342)	2000–04 (n=756 530)	2005–08 (n=1 071 041)	2009–12 (n=1 107 119)
Sex					
Male	2 196 707 (71%)	114 047 (73%)	546 223 (72%)	763 422 (71%)	773 015 (70%)
Female	893 325 (29%)	41 295 (27%)	210 307 (28%)	307 619 (29%)	334 104 (30%)
Attained age group (years)					
<30	279 425 (9%)	18 337 (12%)	66 529 (9%)	94 737 (9%)	99 822 (9%)
30–39	706 853 (23%)	64 699 (42%)	226 440 (30%)	232 781 (22%)	182 933 (17%)
40–49	1 175 561 (38%)	54 550 (35%)	301 772 (40%)	428 241 (40%)	390 998 (35%)
50–59	697 455 (23%)	14 223 (9%)	127 919 (17%)	242 397 (23%)	312 917 (28%)
≥60	230 739 (7%)	3533 (2%)	33 871 (4%)	72 885 (7%)	120 449 (11%)
Race or ethnic group					
Non-Hispanic white	765 400 (25%)	54 793 (35%)	210 162 (28%)	269 384 (25%)	231 061 (21%)
Non-Hispanic black	1 460 565 (47%)	74 115 (48%)	333 717 (44%)	487 712 (46%)	565 022 (51%)
Hispanic or Latino	864 067 (28%)	26 435 (17%)	212 652 (28%)	313 944 (29%)	311 036 (28%)
HIV-risk group					
MSM	1 006 462 (33%)	52 624 (34%)	244 707 (32%)	355 841 (33%)	353 289 (32%)
Male IDU	455 865 (15%)	30 403 (20%)	129 171 (17%)	153 977 (14%)	142 315 (13%)
MSM or IDU	141 466 (5%)	10 436 (7%)	41 367 (5%)	49 761 (5%)	39 901 (4%)
Male other or unknown	592 915 (19%)	20 584 (13%)	130 978 (17%)	203 843 (19%)	237 510 (21%)
Female IDU	230 618 (7%)	17 363 (11%)	65 706 (9%)	76 567 (7%)	70 981 (6%)
Female other or unknown	662 708 (21%)	23 932 (15%)	144 601 (19%)	231 052 (22%)	263 123 (24%)
AIDS onset					
HIV only	1 114 805 (36%)	66 588 (43%)	235 367 (31%)	384 110 (36%)	428 741 (39%)
AIDS	1 975 228 (64%)	88 755 (57%)	521 164 (69%)	686 931 (64%)	678 378 (61%)
Time since HIV report or AIDS diagnosis (years)					
<10	2 622 217 (85%)	154 787 (>99%)	722 117 (95%)	907 374 (85%)	837 939 (76%)
≥10	467 816 (15%)	555 (<1%)	34 414 (5%)	163 666 (15%)	269 181 (24%)

Data are person-years (%) given according to calendar year period. IDU=injection drug users. MSM=men who have sex with men. Person-years are rounded to the nearest whole number so subtotals across categories may not add up to the total.

Table 1: **Demographic characteristics of person-years contributed by HIV-infected people in the USA**

	Observed cases	SIR (95% CI)
All cancers	21 294	1·69 (1·67–1·72)*
AIDS-defining cancers	6384	13·97 (13·63–14·32)*
Kaposi's sarcoma	2269	498·11 (477·82–519·03)*
AIDS-defining NHLs	3687	11·51 (11·14–11·89)*
DLBCL	2242	10·31 (9·89–10·75)*
Burkitt's lymphoma	435	20·21 (18·35–22·20)*
Unspecified NHL	1010	12·42 (11·66–13·21)*
CNS NHL†	528	152·90 (140·14–166·52)*
Cervix	428	3·24 (2·94–3·56)*
Non-AIDS-defining cancers	14 344	1·21 (1·19–1·23)*
Virus-related non-AIDS-defining cancers	4144	5·39 (5·23–5·55)*
Human papillomavirus-related oral cavity or pharynx	297	1·64 (1·46–1·84)*
Anus	1568	19·06 (18·13–20·03)*
Liver	1104	3·21 (3·02–3·41)*
Merkel cell carcinoma	10	2·58 (1·24–4·74)
Vagina	25	3·55 (2·30–5·24)*
Vulva	151	9·35 (7·91–10·96)*
Penis	114	5·33 (4·39–6·40)*
Hodgkin's lymphoma	875	7·70 (7·20–8·23)*
Virus-unrelated non-AIDS-defining cancers	10 200	0·92 (0·90–0·94)*
Lip	20	2·35 (1·43–3·62)
Salivary gland	33	0·89 (0·62–1·26)
Nasopharynx	31	1·20 (0·82–1·71)
Human papillomavirus-unrelated oral cavity or pharynx	343	2·20 (1·98–2·45)*
Oesophagus	190	1·23 (1·06–1·42)
Stomach	185	0·74 (0·64–0·86)*
Small intestine	54	0·71 (0·53–0·93)
Colon	477	0·61 (0·56–0·67)*
Rectum or rectosigmoid junction	272	0·69 (0·61–0·77)*
Intrahepatic bile duct	21	1·21 (0·75–1·85)
Gallbladder	36	1·34 (0·94–1·85)
Extrahepatic bile duct	20	1·04 (0·64–1·61)
Pancreas	307	1·13 (1·01–1·26)
Nasal cavity	25	2·66 (1·72–3·93)*
(Table 2 continues in next column)		

	Observed cases	SIR (95% CI)
(Continued from previous column)		
Accessory sinuses	17	1·32 (0·77–2·12)
Larynx	347	2·11 (1·89–2·34)*
Lung	2475	1·97 (1·89–2·05)*
Bones and joints	15	0·62 (0·35–1·03)
Soft tissue including heart	99	1·02 (0·83–1·24)
Melanoma	213	0·86 (0·75–0·98)
Appendageal carcinoma of the skin	14	1·68 (0·92–2·81)
Sarcomas of the skin	16	0·79 (0·45–1·28)
Female breast	688	0·63 (0·58–0·68)*
Uterus	83	0·43 (0·34–0·53)*
Ovary	60	0·69 (0·52–0·88)
Prostate	1522	0·48 (0·46–0·51)*
Testis	88	0·86 (0·69–1·06)
Scrotum	20	6·84 (4·18–10·56)*
Urinary bladder	171	0·88 (0·75–1·02)
Kidney or renal pelvis	360	0·74 (0·66–0·82)*
Conjunctiva	21	5·56 (3·44–8·50)*
Brain‡	83	0·57 (0·45–0·70)*
Thyroid	164	0·50 (0·42–0·58)*
Thymus	13	0·89 (0·47–1·52)
Non-AIDS-defining NHLs	510	1·32 (1·20–1·44)*
Myeloma	206	0·89 (0·78–1·02)
Myeloid and monocytic leukaemias	165	1·18 (1·00–1·37)
Polycythaemia vera	79	2·26 (1·79–2·81)*
Essential thrombocythaemia	28	1·02 (0·68–1·47)
Myelodysplastic syndrome	104	2·04 (1·66–2·47)*
Mesothelioma	17	1·15 (0·67–1·84)
Miscellaneous	608	1·77 (1·63–1·92)*
Poorly specified histology at any site	566	2·35 (2·16–2·55)*

SIR=standardised incidence ratio. NHL=non-Hodgkin lymphoma. DLBCL=diffuse large B-cell lymphoma. *p<0·0001. †CNS NHL is defined based on site rather than histology, so this category overlaps with other AIDS-defining NHL subtypes, and the total of the subcategories is greater than for AIDS-defining NHL overall. ‡This category does not include CNS NHL.

***Table 2*: Standardised incidence ratios for cancer in HIV-infected people, 1996–2012**

Incorporating the interval parameterisation identified in Joinpoint, we then used Poisson regression to characterise calendar trends adjusted for sex or HIV-risk group, attained age, race or ethnic group, registry, and attained follow-up duration.

If individuals move out of cancer registry areas, SIRs might be underestimated, especially with extended time after HIV registration. In a sensitivity analysis to address this possible bias, we recalculated SIRs after decreasing the expected cancer counts by 27% for the late follow-up period defined above (appendix p 1). Participating registries provided data for varying calendar intervals, which might have affected overall calendar trends, so in another sensitivity analysis we recalculated trends excluding one registry at a time. We did all statistical analyses, except the Joinpoint analysis, with SAS (version 9.3). We present values with

	SIR (95% CI)		Adjusted SIR ratio (AIDS *vs* HIV only)*	
	HIV only	AIDS	Ratio (95% CI)	p value
All cancers	1·24 (1·20–1·28)	1·88 (1·85–1·91)	1·83 (1·77–1·89)	<0·0001
AIDS-defining cancers	6·99 (6·58–7·43)	17·34 (16·88–17·81)	3·15 (2·94–3·37)	<0·0001
Kaposi's sarcoma	276·91 (248·96–307·13)	585·77 (559·79–612·63)	3·21 (2·86–3·60)	<0·0001
AIDS-defining NHLs	5·90 (5·43–6·40)	14·01 (13·52–14·51)	3·12 (2·85–3·42)	<0·0001
DLBCL	5·05 (4·53–5·62)	12·64 (12·08–13·22)	3·32 (2·94–3·73)	<0·0001
Burkitt's lymphoma	17·49 (14·52–20·88)	21·51 (19·19–24·03)	1·63 (1·31–2·03)	<0·0001
Unspecified NHL	4·92 (4·09–5·87)	15·74 (14·72–16·81)	4·27 (3·52–5·17)	<0·0001
CNS NHL	30·44 (20·82–42·97)	206·50 (188·73–225·50)	10·09 (7·02–14·48)	<0·0001
Cervix	2·04 (1·66–2·48)	3·94 (3·53–4·39)	2·20 (1·74–2·76)	<0·0001
Non-AIDS-defining cancers	0·99 (0·96–1·02)	1·30 (1·27–1·32)	1·45 (1·39–1·51)	<0·0001
Virus-related non-AIDS-defining cancers	3·25 (3·02–3·50)	6·27 (6·06–6·49)	2·21 (2·03–2·40)	<0·0001
Human papillomavirus-related oral cavity or pharynx	1·15 (0·88–1·48)	1·84 (1·61–2·09)	1·76 (1·32–2·36)	0·0001
Anus	7·41 (6·39–8·56)	24·17 (22·92–25·48)	3·49 (2·98–4·08)	<0·0001
Liver	2·81 (2·48–3·17)	3·36 (3·14–3·59)	1·25 (1·08–1·44)	0·0029
Merkel cell carcinoma	1·84 (0·22–6·63)	2·87 (1·24–5·65)	1·56 (0·33–7·35)	0·5734†
Vagina	0·84 (0·10–3·02)	4·95 (3·14–7·43)	6·76 (1·58–28·91)	0·0100
Vulva	4·00 (2·54–6·00)	12·30 (10·26–14·62)	3·22 (2·04–5·08)	<0·0001
Penis	1·94 (0·97–3·48)	6·54 (5·34–7·93)	3·67 (1·94–6·92)	<0·0001
Hodgkin's lymphoma	4·64 (4·00–5·35)	9·42 (8·72–10·15)	2·12 (1·80–2·51)	<0·0001
Virus-unrelated non-AIDS-defining cancers	0·84 (0·81–0·87)	0·95 (0·93–0·97)	1·25 (1·20–1·31)	<0·0001
Lip	0·76 (0·09–2·75)	3·05 (1·81–4·83)	4·30 (0·96–19·27)	0·0568
Salivary gland	0·52 (0·19–1·14)	1·06 (0·70–1·55)	2·27 (0·92–5·58)	0·0745
Nasopharynx	1·29 (0·62–2·38)	1·17 (0·72–1·78)	0·90 (0·43–1·92)	0·7903†
Human papillomavirus-unrelated oral cavity or pharynx	1·35 (1·03–1·74)	2·54 (2·26–2·86)	2·20 (1·65–2·92)	<0·0001
Oesophagus	0·79 (0·55–1·10)	1·40 (1·19–1·64)	2·20 (1·51–3·21)	<0·0001
Stomach	0·69 (0·51–0·92)	0·76 (0·64–0·90)	1·18 (0·84–1·66)	0·3275
Small intestine	0·83 (0·50–1·30)	0·66 (0·46–0·92)	0·85 (0·48–1·53)	0·5931
Colon	0·68 (0·58–0·80)	0·58 (0·52–0·65)	0·95 (0·78–1·16)	0·5943
Rectum or rectosigmoid junction	0·60 (0·46–0·75)	0·72 (0·63–0·83)	1·40 (1·02–1·92)	0·0360‡
Intrahepatic bile duct	1·20 (0·44–2·61)	1·21 (0·68–2·00)	1·01 (0·39–2·61)	0·9800†
Gallbladder	1·03 (0·44–2·02)	1·47 (0·97–2·12)	1·39 (0·61–3·18)	0·4367
Extrahepatic bile duct	0·54 (0·11–1·59)	1·24 (0·72–1·99)	2·29 (0·67–7·80)	0·1865†
Pancreas	0·98 (0·77–1·22)	1·19 (1·04–1·36)	1·26 (0·96–1·65)	0·0953
Nasal cavity	1·41 (0·38–3·60)	3·21 (1·98–4·90)	2·61 (0·87–7·80)	0·0861
Accessory sinuses	1·58 (0·58–3·44)	1·22 (0·61–2·18)	0·77 (0·28–2·08)	0·6057†
Larynx	1·71 (1·35–2·13)	2·26 (2·00–2·54)	1·51 (1·17–1·96)	0·0019
Lung	1·57 (1·45–1·71)	2·13 (2·03–2·22)	1·51 (1·37–1·66)	<0·0001
Bones and joints	0·82 (0·33–1·68)	0·52 (0·22–1·02)	0·73 (0·25–2·10)	0·5603
Soft tissue including heart	0·77 (0·50–1·14)	1·14 (0·90–1·44)	1·70 (1·06–2·73)	0·0272
Melanoma	0·87 (0·68–1·09)	0·85 (0·72–1·01)	1·07 (0·80–1·44)	0·6575
Appendageal carcinoma of the skin	0·00 (0·00–1·42)	2·44 (1·33–4·09)	..	..
Sarcomas of the skin	0·56 (0·15–1·42)	0·92 (0·48–1·61)	1·66 (0·54–5·14)	0·3808†
Female breast	0·67 (0·59–0·76)	0·60 (0·55–0·66)	0·95 (0·81–1·11)	0·4958
Uterus	0·38 (0·25–0·57)	0·45 (0·34–0·58)	1·27 (0·78–2·06)	0·3316
Ovary	0·59 (0·35–0·93)	0·74 (0·53–1·00)	1·35 (0·77–2·38)	0·2956
Prostate	0·55 (0·50–0·60)	0·46 (0·43–0·49)	0·91 (0·81–1·02)	0·1131

(Table 3 continues on next page)

	SIR (95% CI)		Adjusted SIR ratio (AIDS *vs* HIV only)*	
	HIV only	AIDS	Ratio (95% CI)	p value
(Continued from previous page)				
Testis	0·88 (0·61–1·22)	0·85 (0·64–1·12)	0·99 (0·63–1·54)	0·9529
Scrotum	5·86 (1·90–13·69)	7·24 (4·05–11·94)	1·23 (0·45–3·40)	0·6833†
Urinary bladder	0·81 (0·59–1·09)	0·90 (0·75–1·08)	1·24 (0·87–1·78)	0·2353
Kidney or renal pelvis	0·80 (0·67–0·96)	0·71 (0·62–0·80)	0·90 (0·71–1·13)	0·3576
Conjunctiva	1·88 (0·23–6·79)	7·00 (4·22–10·94)	3·72 (0·87–15·99)	0·0770†
Brain§	0·48 (0·30–0·72)	0·61 (0·46–0·78)	1·32 (0·80–2·19)	0·2735
Thyroid	0·55 (0·42–0·70)	0·47 (0·38–0·57)	0·85 (0·61–1·19)	0·3540
Thymus	0·42 (0·05–1·53)	1·11 (0·55–1·99)	2·62 (0·58–11·83)	0·2098†
Non-AIDS-defining NHLs	1·14 (0·95–1·35)	1·39 (1·26–1·54)	1·44 (1·18–1·77)	0·0004
Myeloma	1·08 (0·84–1·36)	0·82 (0·69–0·97)	0·83 (0·61–1·12)	0·2173
Myeloid and monocytic leukaemias	0·78 (0·54–1·08)	1·37 (1·14–1·62)	1·97 (1·34–2·89)	0·0006
Polycythaemia vera	1·97 (1·22–3·02)	2·38 (1·81–3·08)	1·40 (0·83–2·35)	0·2114
Essential thrombocythaemia	0·55 (0·18–1·29)	1·24 (0·79–1·86)	2·24 (0·85–5·88)	0·1029†
Myelodysplastic syndrome	0·86 (0·46–1·48)	2·53 (2·03–3·10)	3·51 (1·94–6·34)	<0·0001
Mesothelioma	0·70 (0·14–2·04)	1·33 (0·73–2·23)	1·91 (0·55–6·64)	0·3097†
Miscellaneous	1·53 (1·30–1·79)	1·87 (1·70–2·06)	1·32 (1·09–1·59)	0·0038
Poorly specified histology at any site	1·49 (1·22–1·81)	2·69 (2·45–2·95)	2·21 (1·77–2·75)	<0·0001

DLBCL=diffuse large B-cell lymphoma. NHL=non-Hodgkin lymphoma. SIR=standardised incidence ratio. *Unless otherwise indicated, SIR ratios are from models adjusted for sex or HIV-risk group (men who have sex with men, other males, and females), attained age (<30, 30–39, 40–49, 50–59, ≥60 years), race or ethnic group (non-Hispanic white, non-Hispanic black, and Hispanic or Latino), calendar year (modelled as one continuous variable, except for Kaposi's sarcoma, DLBCL, and CNS NHL, which were modelled as separate segments as informed by Joinpoint analysis [see Methods]), registry, and attained follow-up duration (<10 years *vs* ≥10 years after the latest of HIV report or AIDS diagnosis). †SIR ratio (95% CI) and p value from unadjusted model, as adjusted model did not converge. ‡SIR ratio (95% CI) and p value for rectal cancer only, as adjusted model for rectosigmoid junction cancer did not converge. §Does not include CNS NHL.

***Table 3*: Standardised incidence ratios for cancer in HIV-infected people by AIDS status**

95% CIs, but because we made multiple comparisons, we used a conservative two-sided p value of 0·001 to determine significance.

Role of the funding source

The funder of the study reviewed and approved the final submitted report but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the aggregate data in the study and had final responsibility for the decision to submit for publication.

Results

448 258 HIV-infected people contributed 3 090 033 person-years of follow-up (table 1). Across calendar periods during 1996–2012, the contribution by women and older age groups increased, while the contribution from non-Hispanic whites and injection drug users decreased. The proportion of follow-up time of at least 10 years after an HIV report or AIDS diagnosis increased from <1% (1996–99) to 24% (2009–12).

21 294 cases of cancer were diagnosed during 1996–2012 (incidence: 689 per 100 000 person-years), of which 6384 (30%) were AIDS-defining cancers, 14 344 (67%) were non-AIDS-defining cancers, and 566 (3%) were poorly specified (table 2). Overall, cancer risk was 69% higher among HIV-infected people than in the general population (SIR 1·69, 95% CI 1·67–1·72). Risks were also elevated in the HIV-infected population for AIDS-defining cancers and for non-AIDS-defining cancers, driven by the elevation for virus-related non-AIDS-defining cancers; the risk for virus-unrelated non-AIDS-defining cancers was slightly decreased (table 2).

The most common individual cancer types were AIDS-defining non-Hodgkin lymphomas, lung cancer, Kaposi's sarcoma, anal cancer, prostate cancer, liver cancer, and Hodgkin's lymphoma (table 2). Risks were elevated (p<0·0001) for almost all virus-related cancers, except for Merkel cell carcinoma (p=0·0133), and elevated for each subtype of AIDS-defining non-Hodgkin lymphoma, cancers of the (human papillomavirus-unrelated) oral cavity or pharynx, nasal cavity, larynx, lung, scrotum, and conjunctiva, as well as non-AIDS-defining non-Hodgkin lymphomas, polycythaemia vera, myelodysplastic syndrome, and miscellaneous cancers. By contrast, risks were significantly decreased for cancers of the stomach, colon, rectum or rectosigmoid junction, female breast, uterus, prostate, kidney or renal pelvis, brain, and thyroid (table 2). Correcting SIRs for potential out-migration

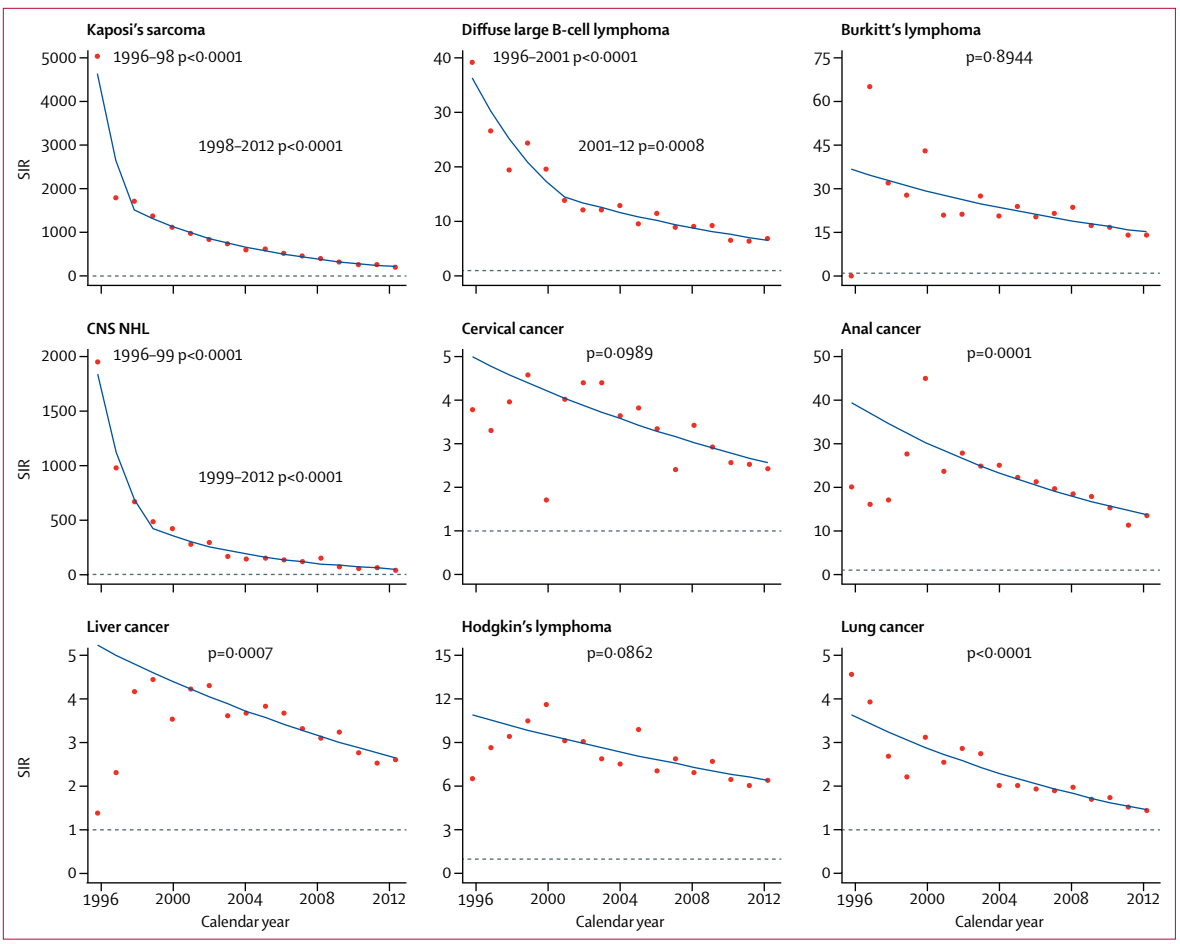

***Figure*: Calendar trends in standardised incidence ratios for selected cancers in HIV-infected people in the USA**
Dots denote observed standardised incidence ratios (SIRs) and lines denote fitted crude trends characterised by Joinpoint. Horizontal lines indicate an SIR of 1. p values are tests of trends from Poisson models adjusted for sex or HIV-risk group (men who have sex with men, other males, and females), attained age (<30, 30–39, 40–49, 50–59, ≥60 years), race or ethnic group (non-Hispanic white, non-Hispanic black, and Hispanic or Latino), registry, and attained follow-up duration (<10 years *vs* ≥10 years after the latest of HIV report or AIDS diagnosis). NHL=non-Hodgkin lymphoma.

(ie, individuals moving out of registry areas) did not substantially affect the estimates (appendix p 4).

Compared with people with HIV only, those with AIDS had significantly higher SIRs for grouped AIDS-defining cancers, virus-related non-AIDS-defining cancers, and virus-unrelated non-AIDS-defining cancers (table 3). This pattern was also present for each individual AIDS-defining cancer and virus-related non-AIDS-defining cancer, except liver and vaginal cancers, and Merkel cell carcinoma. SIRs were also higher for people with AIDS compared with those with HIV only for the following virus-unrelated non-AIDS-defining cancers: cancers of the (human papillomavirus-unrelated) oral cavity or pharynx, oesophagus, and lung, non-AIDS-defining non-Hodgkin lymphomas, myeloid and monocytic leukaemias, and myelodysplastic syndrome.

SIRs did not increase across calendar periods for any cancer (appendix pp 5–6). Moreover, SIRs decreased significantly for many cancer types, including some for which risk was elevated overall (grouped AIDS-defining cancers, Kaposi's sarcoma, each AIDS-defining non-Hodgkin lymphoma, grouped virus-related non-AIDS-defining cancers, cancers of the anus, liver, and lung, non-AIDS-defining non-Hodgkin lymphomas, and miscellaneous cancers), grouped virus-unrelated non-AIDS-defining cancers and myeloma; decreasing trends bordering on significance were also observed for cervical cancer and Hodgkin's lymphoma. Despite these decreases, SIRs remained elevated during the most recent period of analysis from 2009 to 2012, with 95% CIs excluding 1·00, for several cancer types (appendix pp 5–6).

For most cancers selected for detailed calendar trend analysis, SIRs appeared to decrease steadily over time (figure). For Kaposi's sarcoma, diffuse large B-cell lymphoma, and CNS non-Hodgkin lymphoma, moderating changes in slope were identified; ie, steep early decreases became attenuated after 1998, 2001, and 1999, respectively. For anal cancer, liver cancer, and Hodgkin's lymphoma, there was a suggestive increase in

the earliest years of the analysis, but Joinpoint identified only a single decreasing trend for these cancers across 1996–2012. After multivariable adjustment, calendar trends in SIRs significantly decreased for Kaposi's sarcoma, diffuse large B-cell lymphoma, CNS non-Hodgkin lymphoma, and cancers of the anus, liver, and lung. Adjusted calendar trends were not significant for Burkitt's lymphoma, cervical cancer, or Hodgkin's lymphoma. In a sensitivity analysis, exclusion of one registry at a time did not change the trends appreciably (data not shown).

Discussion

During 1996–2012, HIV-infected people in the USA, including those who had not developed AIDS, had elevated risks for many cancer types, especially those with viral causes. There was a decrease in risk during this period for several virus-related cancers and lung cancer, presumably resulting, at least partly, from improved efficacy, earlier use, and wider access to ART over time.[12,13] Although risk remained elevated for several cancers even in the most recent years of the analysis (2009–12), we did not observe increasing trends in SIRs for any cancer. The elevated risk for many cancers, especially after AIDS onset, highlights the continuing contribution of immunosuppression to cancer risk in this population.

A decline in risk for AIDS-defining cancers, especially Kaposi's sarcoma and non-Hodgkin lymphoma, has been well established in the ART era in the USA and other high-income countries.[3,5,6,8,10–12] Trends for Kaposi's sarcoma and non-Hodgkin lymphoma (mainly diffuse large B-cell lymphoma and CNS non-Hodgkin lymphoma) have steeply decreased,[3,5,6,8,10–12,15–17] but we observed that they have moderated in recent years. The trend for Burkitt's lymphoma has been less clear,[15–17] and, in this study, after accounting for demographic changes, the decrease between 1996 and 2012 was not significant. Furthermore, our finding that the difference in risk between people with HIV only and those with AIDS was much smaller for Burkitt's lymphoma than for Kaposi's sarcoma and other AIDS-defining non-Hodgkin lymphomas confirms findings from a previous analysis of the HACM Study.[17] These observations for Burkitt's lymphoma, along with evidence that Epstein-Barr virus is less frequently detected in AIDS-related Burkitt's lymphoma tumour cells than in other subtypes of non-Hodgkin lymphoma,[16] suggest a complex causal relation with immunosuppression.[18]

Some data suggest that the risk of cervical cancer in HIV-infected women might also be decreasing.[3,8,10] Although SIRs for cervical cancer appeared to decrease over time in our analysis, this trend was not significant after multivariable adjustments. We also noted that risk of cervical cancer was most highly elevated in women with a previous AIDS diagnosis, consistent with a causal role for long-term immunosuppression. An AIDS diagnosis could also be a marker for an absence of appropriate medical care and inadequate screening for cervical cancer.[19]

The elevated risks for virus-related non-AIDS-defining cancers, particularly after an AIDS diagnosis, highlight the biological relevance of immunosuppression for these cancers as well. In previous studies,[1–3,5–7,9,10,12,20–22] risk for each virus-related non-AIDS-defining cancer was also elevated, and risk for Hodgkin's lymphoma and some cancers related to human papillomavirus increased in relation to AIDS onset. Consistent with findings from some studies[9,12] we noted decreasing trends in risk relative to the general population for anal and liver cancers, but other studies showed null or increasing trends.[5–7,9,10,12] These discrepancies among studies might partly be explained by differences in the included calendar years, since our plots suggest an increasing trend for these cancers in the earliest years, followed by a more recent decrease.

Risks were also elevated in HIV-infected people compared with those in the general population for lung cancer and several other virus-unrelated AIDS-defining cancers. Among HIV-infected people in our study, lung cancer was second only to AIDS-defining non-Hodgkin lymphomas in incidence. The elevated risk of lung cancer has been previously documented, and is partly, although not entirely, accounted for by a high prevalence of smoking among HIV-infected people.[1–4,23] The more pronounced risk for lung cancer among people with AIDS and the decrease in SIRs over time (which is consistent with findings from other studies[5,9,10] and with widened access to effective ART) both support a contribution from immunosuppression.[23] HIV-related chronic pulmonary inflammation, abnormal immune activation, and repeated lung infections might also play a role.[20,23,24] Smoking probably contributes to the elevated risk observed for cancers of the oral cavity or pharynx, nasal cavity, and larynx.[25] We also noted elevated risks for scrotal cancer, conjunctival cancer, polycythaemia vera, and myelodysplastic syndrome. Scrotal cancer, like other anogenital cancers, might be caused by human papillomavirus, as suggested by reported detection of this virus in some tumours.[26] An elevated risk of conjunctival cancer has been noted previously, especially in people with HIV in Africa, although an infectious agent has not been clearly identified.[27,28] Risks for polycythaemia vera and myelodysplastic syndrome are elevated among immunosuppressed transplantation recipients,[29] although they do not have known viral causes.

Most virus-unrelated non-AIDS-defining cancers did not have elevated risks, consistent with findings from previous studies in the ART era.[1–3,5,6,10,12,22] Indeed, risks for some of these cancers were actually decreased compared with the risks in the general population. These deficits confirmed previous observations for breast and prostate cancers, and identified new deficits for other cancers with previously inconclusive results (eg, uterine and colorectal cancers) or modest elevations (eg, stomach and kidney or renal pelvis cancers).[1–3,5,6,10,12,22] We considered that the deficits might

reflect under-ascertainment of cancers, specifically from out-migration (eg, people moving from registry areas). However, these deficits persisted after we allowed for 27% out-migration at least 10 years after the HIV report or AIDS diagnosis, even though out-migration to such an extent seems unlikely. The deficits might have biological explanations (eg, hormonal or metabolic abnormalities),[1] which could be assessed in future studies.

Limitations of our study include the absence of individual-level data about ART use and HIV disease markers (ie, CD4 cell count and HIV viral load). Instead, we used calendar year as a population-level measure of ART use (with more recent calendar years associated with more effective ART, wider use, and earlier initiation), and AIDS onset as an indicator of ever having had advanced immune suppression. Changes in the prevalence of oncogenic viral infections and other cancer risk factors (eg, smoking and alcohol use) over time might have potentially affected our results, but the absence of data for these factors precluded us from assessing them as confounders for the patterns we observed. Finally, we assessed many cancers, so some findings could be due to chance. However, we used a stringent threshold ($p<0\cdot001$) to identify cancers for which risk differed significantly from the general population, and to test differences in risk by AIDS status and over time.

A major strength of our study was its population-based design. The study covered eight states and Puerto Rico across a calendar period of 17 years during the ART era. The study population comprised all people with known HIV infection living in these areas, including all HIV-risk groups and ages. The approximate similarity between the distribution of the demographic characteristics of our population and the USA HIV population[14] upholds the representativeness of our sample and the generalisability of our results. Moreover, cancers were ascertained using linked data from cancer registries, which have greater validity than other data sources.[22] HACM is the largest study of cancer in HIV-infected people, which enabled the examination of a range of individual cancers, including subtypes of non-Hodgkin lymphoma and rare cancers. Furthermore, since ageing and other changes in the demographic characteristics of the HIV population could have affected time trends in the SIRs, we adjusted the calendar trends by use of multivariable regression. Finally, in the sensitivity analysis, we observed similar trends when excluding one registry area at a time, which suggested that the observed overall trends were not disproportionally affected by one registry or the varying calendar intervals by registry.

Additional efforts aimed at cancer prevention and screening in HIV-infected people are warranted. Although SIRs did not increase for any cancer, and have decreased over time for several cancers, SIRs were still elevated in HIV-infected people in the most recent period of our analysis.[3,8–10,12] Because the HIV population is ageing and growing in size,[3,14] the burden of cancer might increase in this population even in the absence of increasing incidence rates.[11] Early diagnosis of HIV infection, prompt and sustained ART after diagnosis, and reduction of non-HIV cancer risk factors are crucial for cancer prevention.[2,4,30] With further improvement of ART and expansion of ART use, reductions in the risk of Kaposi's sarcoma, AIDS-defining non-Hodgkin lymphomas, and potentially other cancers can be expected. Because ART does not completely restore immunological health,[2] close monitoring of cancer risk factors and assessment of symptoms possibly related to cancer is needed, even in virally suppressed patients. Efforts should aim to optimise cessation of smoking and alcohol, and treatment of infections with hepatitis C and B.[30] Screening for cervical cancer, and possibly for anal, liver, and lung cancers, is appropriate for high-risk populations.[30]

In conclusion, cancer risk has decreased in HIV-infected people in the USA, but remains elevated for a range of cancers, notably for AIDS-defining cancers, many other virus-related cancers, and lung cancer. Sustained and widened access to ART has probably contributed to the decreases in cancer risk, but improvements are needed to reduce the cancer burden further.

Contributors

RUH-R and EAE wrote the first draft of the report. RUH-R did the statistical analysis. MSS and EAE, who are principal investigators in the HIV/AIDS Cancer Match Study, acquired the data, obtained funding, and supervised the study. All authors contributed to the study design and the interpretation of the data, critically reviewed the manuscript for important intellectual content, and approved the final version of the report.

Declaration of interests

We declare no competing interests.

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