Cancer risk in people living with HIV

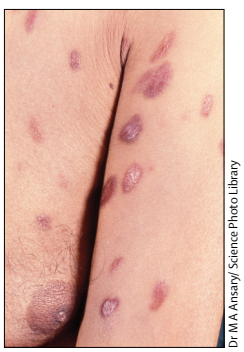
Much has been learned about the risk of malignant diseases in people with HIV from observational and clinical cohort studies, multicohort and meta analyses, and population-based HIV/AIDS and cancer registry-match studies. Specific cancers have been reported either in excess or deficit in people with HIV, relative to the general population, and studies have quantified changes in those risks over time. Most importantly, since 1996, the use of effective antiretroviral therapy (ART) to control HIV infection has led to a striking reduction in HIV-related mortality.[1] However, ART does not fully restore host immune status and, despite the decreases in AIDS-defining cancers—most notably Kaposi's sarcoma and non-Hodgkin lymphoma—the incidence of many cancers, especially those which have viral causes such as Kaposi's sarcoma from human herpesvirus 8 and non-Hodgkin lymphoma from the Epstein-Barr virus, remains high.[2-4] Furthermore, because people living with HIV increasingly reach the age with the highest rates of cancer but still live with compromised host immunity, greater longevity might increase their cumulative exposure to systemic inflammation, oncogenic viral infections, and carcinogens, as well as the accumulation of somatic mutations and epigenetic changes related to carcinogenesis. Because the total burden and predominant types of cancers are likely to change over time, ongoing surveillance of cancer rates in people with HIV is important.

In *The Lancet HIV*, Raúl Hernández-Ramírez and colleagues[5] report an analysis of cancer risk in a cohort of individuals from the USA HIV/AIDS Cancer Match Study, the largest population-based study of malignancies in people with HIV in the world. The investigators used standardised incidence ratios (SIRs) to estimate cancer risk in HIV-infected people compared with the USA general population between 1996 and 2012. In additional analyses, the SIRs were stratified by AIDS diagnosis (AIDS *vs* HIV only), to serve as a proxy of severe immunosuppression to assess its effect on cancer risk. Hernández-Ramírez and colleagues[5] also assessed temporal trends in cancer risks and used calendar time as a surrogate for the effect of ART on cancer incidence.

The greatest excess cancer risk in people with HIV was for AIDS-associated and other virus-related tumours, especially Kaposi's sarcoma (SIR 498·11, 95% CI 477·82–519·03) and non-Hodgkin lymphoma (11·51, 11·14–11·89).[5] Two subtypes of non-Hodgkin lymphoma and Kaposi's sarcoma also showed the largest and most immediate reductions in incidence after the introduction of ART. These results suggest a high sensitivity of these tumours to immunosuppression. The incidences of all human papillomavirus-related tumours were also significantly higher in people living with HIV than in the general population, including cervical cancer (an AIDS-defining malignancy), and cancers of the anus, vulva, vagina, penis, and oropharynx ($p<0·0001$ for all). However, the excess incidence of HPV-related tumours was several-times weaker than those of Kaposi's sarcoma and non-Hodgkin lymphoma, and the decrease in risk of human papillomavirus-related tumours over time was more gradual. An excess risk for liver cancer and Hodgkin's lymphoma, two additional tumours with a viral cause, also gradually declined over time in people living with HIV.

The risks of several virus-unrelated tumours were also greater in people living with HIV, including cancers of the lung, lip, human papillomavirus-unrelated oral cavity or pharynx, larynx, or nasal cavity,[5] which might be a result of high rates of cigarette smoking among people living with HIV.[6] Conversely, several virus-unrelated tumours—cancers of the breast, endometrium, ovary, prostate, colon, rectum, kidneys, brain, and thyroid—had a lower incidence in people living with HIV than in the general population.[5] What causal factors are common to these disparate tumours is not immediately apparent. However, each of these tumours or their major subtypes has been associated with obesity and they are thought to have potential associations with obesity related hormones and inflammation.[7-10] If this theory is correct, the lower incidence among people with HIV might suggest that inflammation is not a major risk factor for these obesity related cancers, given that people living with HIV have high systemic inflammation. Reassuringly, none of the SIRs increased for any cancer during the study period, and SIRs decreased over time for Kaposi's sarcoma, two subtypes of non-Hodgkin lymphoma, and cancers of the anus, liver, and lung.[5] A similar, albeit non-significant, reduction occurred for cervical cancer, Burkitt's lymphoma, and Hodgkin's lymphoma.

This study has important strengths, including the large number of reported cancer cases and extensive



Dr M A Ansary/ Science Photo Library

Lancet HIV 2017

Published Online
August 10, 2017
http://dx.doi.org/10.1016/S2352-3018(17)30147-9

See Online/Articles
http://dx.doi.org/10.1016/S2352-3018(17)30125-X

person-years of observation that encompassed most of the ART era, and the use of population-based registry data from eight USA states and Puerto Rico. However, registry-based studies such as this are not without limitations and the authors were forthright in reporting them. Foremost, there is an absence of information about many individual-level characteristics, including tobacco and alcohol use, viral co-infections, use and duration of ART, CD4 cell count, and HIV RNA viral loads. Other types of studies, such as observational and clinical cohort studies, are better equipped to address the effect of specific cancer-risk factors.

Results from the current study are important for public health surveillance of cancer risks in people with HIV, and an essential ongoing effort is needed to inform clinical programmes and interventions at local, state, and national levels. Epidemiological investigations that exploit high quality HIV/AIDS and cancer registries, with their large population-based data sets and established methodology, are especially useful for this purpose. These data are fundamental to setting cancer-screening priorities and treatment guidelines for individuals living with HIV. Therefore, studies such as this from Hernández-Ramírez and colleagues will continue to be on the frontline to detect emerging trends in the spectrum of cancer risk in people living with HIV, and must be maintained as a public health resource.

Nancy A Hessol, Howard D Strickler
Departments of Clinical Pharmacy and of Medicine, University of California, San Francisco, CA, USA (NAH); Albert Einstein College of Medicine, Bronx, NY, USA (HDS)
nancy.hessol@ucsf.edu

We declare no competing interests.

1 Centers for Disease Control and Prevention. HIV mortality through 2014. https://www.cdc.gov/hiv/pdf/library/slidesets/cdc-hiv-mortality.pdf (accessed June 27, 2017).
2 Park LS, Tate JP, Sigel K, et al. Time trends in cancer incidence in persons living with HIV/AIDS in the antiretroviral therapy era: 1997–2012. *AIDS* 2016; **30:** 1795–806.
3 de Martel C, Shiels MS, Franceschi S, et al. Cancers attributable to infections among adults with HIV in the United States. *AIDS* 2015; **29:** 2173–81.
4 Robbins HA, Pfeiffer RM, Shiels MS, Li J, Hall HI, Engels EA. Excess cancers among HIV-infected people in the United States. *J Natl Cancer Inst* 2015; **107:** 1–8.
5 Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV* 2017; published online Aug 10. http://dx.doi.org/10.1016/S2352-3018(17)30125-X.
6 Lifson AR, Lando HA. Smoking and HIV: prevalence, health risks, and cessation strategies. *Curr HIV/AIDS Rep* 2012; **9:** 223–30.
7 Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer* 2015; **15:** 484–98.
8 Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *Lancet* 2014; **384:** 755–65.
9 Sergentanis TN, Tsivgoulis G, Perlepe C, et al. Obesity and risk for brain/CNS tumors, gliomas, and meningiomas: a meta-analysis. *PLoS One* 2015; **10:** e0136974.
10 Little RB, Madden MH, Thompson RC, Olson JJ, Larocca RV, Pan E, et al. Anthropometric factors in relation to risk of glioma. *Cancer Causes Control* 2013; **24:** 1025–31.