Cancer risk among the HIV-infected elderly in the United States

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Objective: HIV-infected people and elderly people have higher cancer risk, but the combined effects of aging and HIV are not well described. We aimed to evaluate the magnitude of cancer risk in the HIV-infected elderly population.

Design: We conducted a case-cohort study including a 5% sample of U.S. Medicare enrollees and all cancer cases aged at least 65 in linked cancer registries.

Methods: HIV was identified through Medicare claims. Among the HIV-infected, absolute cancer risk was calculated accounting for the competing risk of death. Associations between HIV and cancer were estimated with weighted Cox regression adjusting for demographic characteristics.

Results: Among 469 954 people in the 5% sample, 0.08% had an HIV diagnosis. Overall, 825 776 cancer cases were identified in cancer registries. Over 5 years, 10.1% of the HIV-infected elderly developed cancer, the most common diagnoses comprising lung (5-year cumulative incidence=2.2%), prostate (2.7%, among men), and colorectal cancer (0.9%), and non-Hodgkin lymphoma (0.8%). HIV was strongly associated with incidence of Kaposi sarcoma [adjusted hazard ratio (aHR)=94.4, 95% confidence interval (95%CI)=54.6–163], anal cancer (aHR=34.2, 95%CI=23.9–49.0) and Hodgkin lymphoma (aHR=6.3, 95%CI=2.8–14.3). HIV was also associated with incidence of liver cancer, non-Hodgkin lymphoma and lung cancer (aHR=3.4, 2.6, and 1.6, respectively).

Conclusion: In the elderly, HIV infection is associated with higher risk for many cancers, although some associations were weaker than expected, perhaps reflecting effects of non-HIV pathways on cancer development. Due to the effects of HIV and aging, the HIV-infected elderly have a sizeable absolute risk, highlighting a need for cancer prevention.

Introduction

HIV-infected individuals have elevated risk for a number of cancers [1,2]. In the general population, risk of most cancers increases with age, including cancers frequently diagnosed in HIV-infected people, for example non-Hodgkin lymphoma (NHL), lung cancer, and liver cancer [3]. Understanding the magnitude of cancer risk in the HIV-infected elderly can inform screening or prevention programs. As effective antiretroviral treatment has greatly prolonged life expectancy, the proportion of the HIV population in older age groups has increased and will

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likely continue increasing in the future. Because of these changes, obtaining robust data on cancer risk in the HIV-infected elderly is particularly important [4].

Because a small proportion of the current HIV population is older than 65 [5,6], examining the relationship between HIV and cancer in the elderly has been difficult. We used a linkage between data from cancer registries in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute and Medicare claims (SEER-Medicare) to estimate absolute cancer risk among people aged 65 and older with an HIV diagnosis and evaluate the association between HIV and cancer in this age group [7].

Methods

SEER-Medicare links 17 SEER cancer registries covering approximately 28% of the U.S. population with claims from Medicare, the U.S. government health insurance program for people aged at least 65 [7,8]. SEER cancer registry areas covered approximately 9.4 million Medicare enrollees during 2004–2011. SEER-Medicare includes Medicare claims for all linked SEER cancer cases, and for a random 5% sample of the entire Medicare population living in SEER areas, referred to hereafter as the 5% subcohort.

To evaluate the relationship between HIV and cancer, we conducted a case–cohort study [9], including the 5% subcohort and 100% of cancer cases within SEER-Medicare during 2004–2011. Follow-up started at the latest of: age 65; January 1, 2004; residence in a SEER area; start of cancer registry coverage; beginning of Medicare coverage for inpatient and provider care outside of a health maintenance organization; and first Medicare claim. Time in a health maintenance organization was excluded, because Medicare does not routinely receive individual claims under such coverage. Follow-up ended at the earliest of: death, migration out of a SEER area, first discontinuation of the specified Medicare coverage, or December 31, 2011. For analyses of the incidence of each cancer type, follow-up ended at the first diagnosis of that cancer type, but not for other cancer types.

HIV diagnosis was based on a claim in Medicare for International Classification for Diseases, version 9 codes 042.X-044.X or V08. HIV diagnoses were defined as the presence of one hospital HIV claim or two outpatient/provider HIV claims at least 30 days apart within the follow-up defined above. HIV exposure was time-varying, with individuals categorized as HIV-uninfected until they met our HIV diagnosis definition.

Cancers were identified through SEER cancer registries. We included cancers with an incidence among HIV-uninfected individuals that was high enough to expect at least 10 HIV-infected cases under the null hypothesis of no HIV-cancer association. We also included Kaposi sarcoma, which is rare in the general population, but one of the most common cancers in the HIV population. For NHL, analyses were also done separately for AIDS-defining subtypes.

We conducted a case–cohort study wherein sampling weights were applied to create an analytic population representative of the entire Medicare population [9,10]. Using the resulting weighted person-time, we calculated cancer incidence rates among HIV-infected and HIV-uninfected people. Among the HIV-infected, the 5-year cumulative incidence of cancer was estimated accounting for the competing risk of death [11,12], both overall and by sex.

We estimated the association between HIV and cancer incidence with weighted Cox regression. Hazard ratios (aHRs) were adjusted for sex, age, race and calendar year. For colorectal, breast, and prostate cancers, analyses were also done by cancer stage at diagnosis.

Results

In the 5% subcohort, there were 469 954 people aged 65 years or older with Medicare during 2004–2011. In the subcohort, 41 604 people had a cancer diagnosis, which (as expected) comprised 5% of the 825 776 cancer cases among all Medicare enrollees aged 65 years or older both within and outside the subcohort. In total, our study population thus included 1 254 126 Medicare enrollees (469 954 in the subcohort, including 41 604 with cancer, plus 784 172 cancer cases outside the subcohort; Supplementary Figure). The most frequently diagnosed cancers were lung ($N = 145\,775$), prostate ($N = 142\,940$), breast ($N = 93\,919$), and colorectal cancers ($N = 93\,555$).

In the subcohort, 0.08% of people had an HIV diagnosis ($N = 361$). For these people, the median time between the start of follow-up and HIV diagnosis was 6 months (interquartile range = 3–23 months). Compared with people without an HIV diagnosis, HIV-infected individuals were more frequently male (73 vs. 42%) and of black race (36 vs. 9%). HIV-infected people were younger at the start of follow-up (median of 66 vs. 70 years), but were more likely to die during follow-up (28 vs. 23%).

There were 653 cancer cases among HIV-infected people, including 55 AIDS-defining and 598 non-AIDS-defining cancers. Among HIV-infected individuals, 10.1% were diagnosed with cancer over the course of 5 years of follow-up [95% confidence interval (CI) = 8.7–11.5%, Fig. 1]. The most common cancer was lung cancer (5-year cumulative incidence = 2.2%), followed by prostate cancer (1.9%), colorectal cancer (0.9%), NHL (0.8%), and anal cancer (0.6%) (Fig. 1).
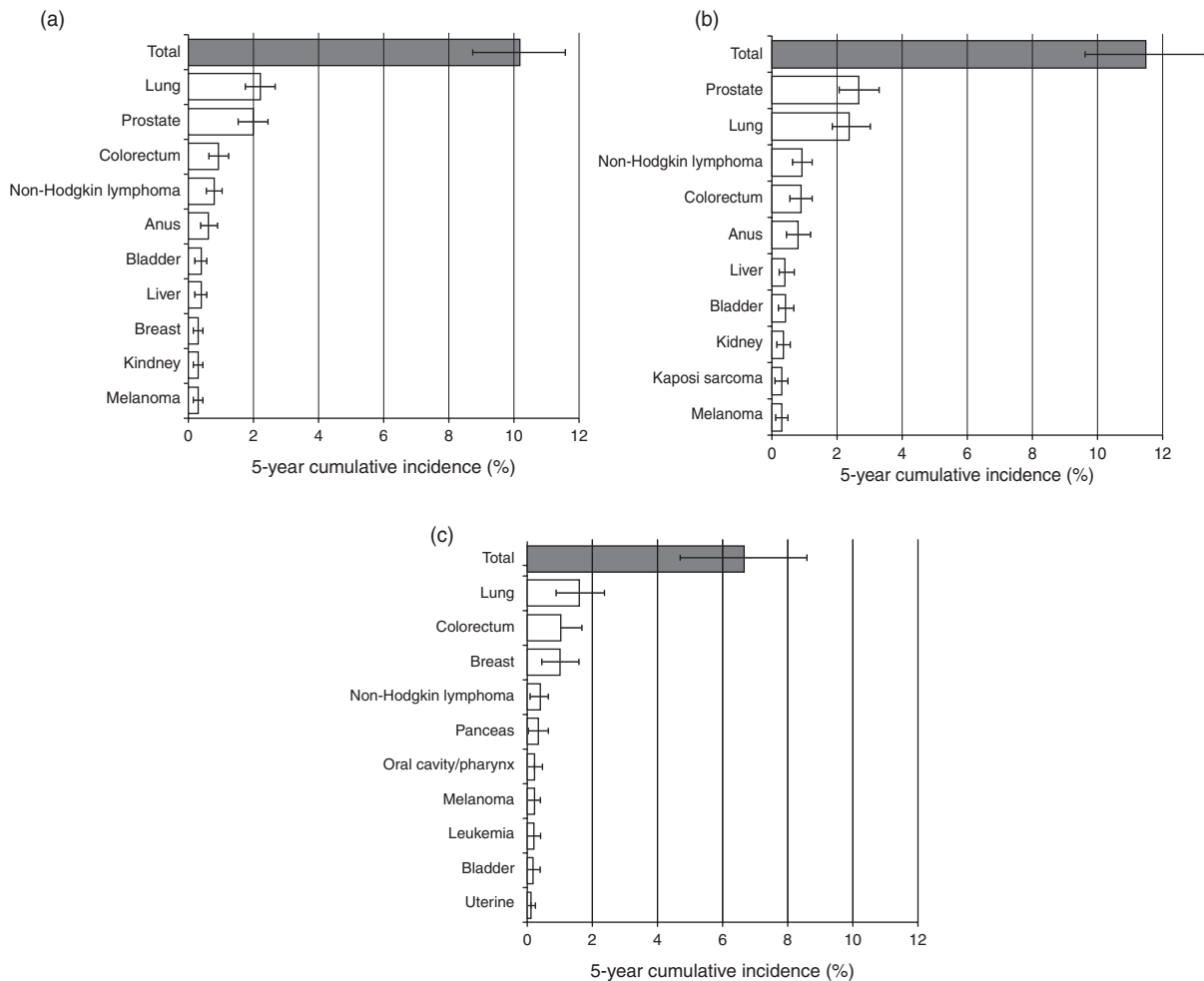
Fig. 1. Cumulative incidence of cancer by type among elderly HIV-infected adults. Among Medicare recipients age 65 and older, 5-year cumulative incidence estimates are shown for all HIV-infected individuals (a), HIV-infected men (b), and HIV-infected women (c) after accounting for the competing risk of death. Included are the estimates for total cancer, as well as the ten most frequently diagnosed cancer types in each population. Error bars represent 95% confidence intervals calculated using jackknife resampling.

Among HIV-infected men, 11.5% (95%CI = 9.6–13.3%) were diagnosed with cancer over 5 years, whereas 6.7% (95%CI = 4.7–8.6%) of HIV-infected women were diagnosed with cancer over 5 years (Fig. 1). The most frequent cancers among men were prostate cancer (5-year cumulative incidence = 2.7%), lung cancer (2.4%), NHL (0.9%), colorectal cancer (0.9%), and anal cancer (0.8%). Among women, the most frequent cancers were lung cancer (5-year cumulative incidence = 1.6%), colorectal cancer (1.0%), breast cancer (1.0%), NHL (0.4%), and pancreatic cancer (0.3%).

Cancer incidence was approximately 50% higher in HIV-infected compared with HIV-uninfected individuals (aHR = 1.52, 95%CI = 1.32–1.75; Table 1). HIV was most strongly associated with Kaposi sarcoma (aHR = 94.4, 95%CI = 54.6–163). HIV was also associated with elevated incidence of anal cancer (aHR = 34.2), Hodgkin lymphoma (aHR = 6.30), liver cancer

(aHR = 3.35), NHL (aHR = 2.55), oral cavity/pharyngeal cancer (aHR = 1.79), and lung cancer (aHR = 1.61; Table 1). HIV was inversely associated with prostate cancer (aHR = 0.78, 95%CI = 0.63–0.98).

For NHL, associations were strongest for the AIDS-defining subtypes, which comprised 65% of NHLs in HIV-infected people. Central nervous system lymphoma was most strongly associated with HIV (aHR = 15.3, 95%CI = 6.81–34.6). Incidence was also elevated for diffuse large B-cell lymphoma (aHR = 5.61) and Burkitt lymphoma (aHR = 18.8; Table 1). Other specified lymphomas were not associated with HIV (aHR = 0.74, 0.74, 95%CI = 0.40–1.35), though they made up 20% of NHL cases among HIV-infected people.

Prostate cancer incidence of both localized/regional and distant stage cases appeared decreased among HIV-infected people, though the association was only

Table 1. Associations between HIV diagnosis and cancer among elderly adults in the United States.

Cancer type	Total N	Incidence rate[a]		Adjusted hazard ratio[b] (95% CI)
		HIV+	HIV−	
Total	825 776	2690	1950	1.52 (1.32–1.75)
AIDS-defining cancers				
Non-Hodgkin lymphoma	50 708	241	120	2.55 (1.91–3.39)
Diffuse large B-cell lymphoma	13 257	129	31.3	5.61 (3.87–8.13)
Burkitt lymphoma	300	13.4	0.68	18.8 (5.96–59.2)
Other specified lymphoma	30 764	49.1	72.8	0.74 (0.40–1.35)
Unspecified lymphoma	6387	49.1	15.1	5.19 (2.96–9.10)
Central nervous system lymphoma[c]	788	13.4	1.86	15.3 (6.81–34.6)
Kaposi sarcoma	384	80.3	0.83	94.4 (54.6–163)
Non-AIDS-defining cancers				
Prostate[d]	142 940	758	803	0.78 (0.63–0.98)
Localized/regional prostate[e]	127 329	687	715	0.74 (0.59–0.94)
Distant prostate	6792	29.6	38.4	0.79 (0.32–1.92)
Lung	145 775	607	345	1.61 (1.31–1.98)
Colorectum	93 555	227	221	1.15 (0.86–1.55)
Localized colorectum	39 166	85	89	1.00 (0.63–1.57)
Regional colorectum	31 258	97.9	73.8	1.70 (1.12–2.58)
Distant colorectum	16 600	31.2	39.2	0.83 (0.39–1.77)
Breast[d]	93 919	226	359	0.64 (0.37–1.11)
Localized breast	61 885	166	237	0.73 (0.39–1.37)
Regional breast	22 586	45.2	86.3	0.49 (0.15–1.55)
Distant breast	6224	15.1	23.8	0.57 (0.08–4.07)
Anus	2299	143	5.37	34.2 (23.9–49.0)
Bladder	51 282	103	121	0.80 (0.52–1.23)
Liver	10 304	103	24.3	3.35 (2.21–5.07)
Melanoma	28 794	80.3	68.1	1.37 (0.84–2.23)
Kidney	25 816	71.4	61.1	0.91 (0.55–1.51)
Oral cavity/pharynx	15 549	71.4	36.8	1.79 (1.11–2.90)
Pancreas	28 433	66.9	67.3	1.13 (0.69–1.86)
Leukemia	17 440	53.5	41.3	1.44 (0.81–2.58)
Uterus[d]	18 909	45.2	72.3	0.56 (0.18–1.76)
Stomach	15 375	44.6	36.4	1.27 (0.73–2.23)
Myeloma	13 211	31.2	31.3	0.84 (0.42–1.71)
Ovary[d]	11 330	30.2	43.3	0.82 (0.20–3.36)
Hodgkin lymphoma	1797	26.8	4.24	6.30 (2.79–14.3)
Myelodysplastic syndrome	14 036	26.8	33.2	0.98 (0.43–2.20)

A total of 7103 colorectal cancer, 3338 breast cancer, and 8819 prostate cancer cases were unstaged and are not included in the stage-specific results.
[a]Incidence rates are presented per 100 000 person-years.
[b]Hazard ratios were adjusted for age, sex, race, and calendar year at the start of follow-up.
[c]Central nervous system lymphomas overlap with the other lymphoma subtype categories, because they are defined by the topographic site whereas all other lymphoma subtypes are defined by histology.
[d]Analyses for cancer of the breast, ovary and the uterus were done only among women. Analyses for prostate cancer were done only among men.
[e]SEER historic staging categorizes localized and regional stage prostate cancer together.

significant for localized/regional prostate cancer (aHR = 0.74, 95%CI = 0.59–0.94; Table 1). HIV was not associated with breast cancer incidence at any stage. Incidence of localized and distant colorectal cancer was the same in individuals with and without HIV, whereas incidence of regional stage colorectal cancer was elevated among HIV-infected people (aHR = 1.70, 95%CI = 1.12–2.58).

Discussion

Total cancer burden was high among the HIV-infected U.S. elderly, with one out of 10 people getting cancer over 5 years. This reflected an elevated risk for many HIV-associated cancers and a high frequency of cancers

that are common among older adults but unassociated with HIV. The resulting cancer distribution reflects both HIV and aging effects. Overall, cancer risk was 50% higher in HIV-infected people than in HIV-uninfected people.

The most frequently diagnosed cancers were those associated with aging: lung, prostate, colorectal, and breast cancers, and NHL. Lung cancer and NHL risks are likely impacted by both HIV and age-related processes [13–16]. Lung cancer was the most common cancer, and it is a common cause of death in HIV-infected people [17,18]. These observations point to the potential importance of smoking cessation. Given the high incidence of lung cancer overall, current smokers in the elderly HIV population might particularly benefit

from lung cancer screening with low-dose computed tomography [19].

As in other studies, HIV was associated with higher incidence of many virus-related cancers, such as Kaposi sarcoma related to human herpesvirus-8, lymphomas related to Epstein−Barr virus, anal cancer related to human papillomavirus, and liver cancer related to hepatitis C and B viruses [1]. These associations provide further evidence that elevated cancer risk is at least partly because HIV-infected individuals have poor immunologic control of oncogenic viruses. However, some associations were weaker than those identified in younger people. In our study, Kaposi sarcoma incidence was about 100 times higher and NHL incidence was 2−3 times higher in HIV-infected people compared with HIV-uninfected people. By comparison, in studies of younger HIV-infected populations, Kaposi sarcoma incidence is 200−800 times higher and NHL incidence is 6−17 times higher than in the general population [6,20,21]. This lower relative increase could reflect more widespread HIV treatment, viral suppression, and immune reconstitution compared with younger HIV populations [21,22], which may result in better control of oncogenic viruses and, for Kaposi sarcoma, possible regression of tumors before they reach a clinically detectable stage [23]. Associations could also be weaker because of larger contributions of HIV-unrelated causal pathways in the elderly. For instance, our NHL associations were more similar to findings in younger HIV populations when evaluated by NHL subtype [20,24], but the HIV-associated subtypes (diffuse large B-cell lymphoma, Burkitt lymphoma, and central nervous system lymphoma) made up a smaller portion of the NHL burden in our population.

Even though they contributed substantially to the cancer burden in our HIV population, overall incidence of breast and colorectal cancer was not associated with HIV, and prostate cancer incidence appeared lower. Reduced risk was suggested for distant stage prostate cancer, arguing against a deficit of prostate cancer screening in HIV-infected men. As screening detects cancers early, reduced screening typically manifests as a reduced risk of only localized cancer, sometimes accompanied by an increase in regional/distant stage cancer. Importantly, prostate cancer screening through prostate-specific antigen testing is not generally recommended, due to a lack of survival benefit [19]. However, for breast and colorectal cancer, current recommendations support screening up to age 75 [19]. Because these cancers are common in the older HIV population, and risk was largely similar to risk observed in HIV-uninfected adults, our findings support adherence to these guidelines for HIV-infected people.

Our study has several strengths. Using an efficient case-cohort design, we were able to leverage the SEER-Medicare database to study a large, population-based sample of elderly HIV-infected adults and calculate absolute risk. This sample also provided a comparable HIV-uninfected population. Reliable cancer diagnoses were provided by SEER cancer registries, which apply rigorous data quality standards for case ascertainment.

Our study is limited by missing information. We did not have claims information for individuals before age 65, so we did not know how long individuals had been HIV diagnosed. Medication claims were only available after 2006, when prescription benefits were introduced, and so we could not systematically assess antiretroviral use, which influences risk for HIV-associated cancers. We also lacked information on other cancer risk factors, such as tobacco use or human papillomavirus infection.

In conclusion, the absolute risk of cancer in the U.S. HIV-infected elderly is sizeable, reflecting effects of both HIV and aging. HIV infection in the elderly is associated with higher risk for many cancers previously identified as HIV-associated. However, the relative elevation is lower for some of these cancers, likely due in part to contributions of HIV-unrelated causes of cancer in the elderly population. In fact, the most frequently identified cancers were those related to aging. These patterns highlight a clear need for cancer prevention in this age group and the importance of screening, particularly for lung, colorectal, and breast cancers, for which accepted screening modalities are available.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. **Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis.** *Lancet* 2007; **370**:59–67.
2. Shiels MS, Cole SR, Kirk GD, Poole C. **a meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals.** *J Acquir Immune Defic Syndr* 2009; **52**:611–622.
3. Howlander N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, *et al. SEER Cancer Statistics Review, 1975–2012.* Bethesda, MD: National Cancer Institute; 2015, http://seer. cancer.gov/csr/1975_2012/. [Accessed 1 November 2015].
4. Centers for Disease Control and Prevention. HIV Surveillance Report, 2013. http://www.cdc.gov/hiv/library/reports/surveillance/. [Accessed 1 November 2015]
5. Kitahata MM, Rodriguez B, Haubrich R, Boswell S, Mathews WC, Lederman MM, *et al.* **Cohort profile: the Centers for AIDS Research Network of Integrated Clinical Systems.** *Int J Epidemiol* 2008; **37**:948–955.
6. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, *et al.* **Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003.** *Ann Intern Med* 2008; **148**:728–736.
7. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. **Use of surveillance, epidemiology, and end results-Medicare data to conduct case-control studies of cancer among the US elderly.** *Am J Epidemiol* 2011; **174**:860–870.
8. National Cancer Institute. SEER-Medicare Linked Database. In: Applied Research: Cancer Control and Population Sciences. Bethesda, MD: National Cancer Institute. http://appliedresearch.cancer.gov/seermedicare/. [Accessed 1 November 2015]
9. Borgan O, Samuelsen SO. **A review of cohort sampling designs for Cox's regression model: potentials in epidemiology.** *Norsk Epidemiologi* 2003; **13**:239–248.
10. Yanik EL, Katki HA, Silverberg MJ, Manos MM, Engels EA, Chaturvedi AK. **Leukoplakia, oral cavity cancer risk, and cancer survival in the U.S. elderly.** *Cancer Prev Res (Phila)* 2015; **8**:857–863.
11. Lin G, So Y, Johnston G. *Analyzing survival data with competing risks using SAS Software. In: SAS Global Forum 2012 Conference.* Cary, NC: SAS Institute Inc; 2012.
12. Korn EL, Graubard BI. *Analysis of health surveys.* 1st ed. New York: Wiley-Interscience; 1999.
13. Kirk GD, Merlo C, O'Driscoll P, Mehta SH, Galai N, Vlahov D, *et al.* **HIV infection is associated with an increased risk for lung cancer, independent of smoking.** *Clin Infect Dis* 2007; **45**:103–110.
14. Hjalgrim H, Engels EA. **Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence.** *J Intern Med* 2008; **264**:537–548.
15. American Cancer Society. *Cancer Facts and Figures 2014.* Atlanta, GA: American Cancer Society; 2014.
16. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. **Elevated incidence of lung cancer among HIV-infected individuals.** *J Clin Oncol* 2006; **24**:1383–1388.
17. Vandenhende MA, Roussillon C, Henard S, Morlat P, Oksenhendler E, Aumaitre H, *et al.* **Cancer-related causes of death among HIV-infected patients in France in 2010: evolution since 2000.** *PLoS One* 2015; **10**:e0129550.
18. Simard EP, Engels EA. **Cancer as a cause of death among people with AIDS in the United States.** *Clin Infect Dis* 2010; **51**:957–962.
19. US Preventive Services Task Force. Published Recommendations. http://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations. [Accessed 1 November 2015].
20. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, *et al.* **Cancer risk in people infected with human immunodeficiency virus in the United States.** *Int J Cancer* 2008; **123**:187–194.
21. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, *et al.* **Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy.** *J Natl Cancer Inst* 2005; **97**:425–432.
22. Yanik EL, Napravnik S, Cole SR, Achenbach CJ, Gopal S, Olshan A, *et al.* **Incidence and timing of cancer in HIV-infected individuals following initiation of combination antiretroviral therapy.** *Clin Infect Dis* 2013; **57**:756–764.
23. Uldrick TS, Whitby D. **Update on KSHV epidemiology, Kaposi sarcoma pathogenesis, and treatment of Kaposi sarcoma.** *Cancer Lett* 2011; **305**:150–162.
24. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. **Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study.** *AIDS* 2014; **28**:2313–2318.