Cancer as a Cause of Death among People with AIDS in the United States

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(See the article by Puhan et al, on pages 947–956.)

Background. People with human immunodeficiency virus (HIV) infection and AIDS have an elevated risk for cancer. Highly active antiretroviral therapy (HAART), which has been widely available since 1996, has resulted in dramatic decreases in AIDS-related deaths.

Methods. We evaluated cancer as a cause of death in a US registry-based cohort of 83,282 people with AIDS (1980–2006). Causes of death due to AIDS-defining cancers (ADCs) and non-ADCs (NADCs) were assessed. We evaluated mortality rates and the fraction of deaths due to cancer. Poisson regression assessed rates according to calendar year of AIDS onset.

Results. Overall mortality decreased from 302 deaths per 1000 person-years in 1980–1989, to 140 deaths per 1000 person-years in 1990–1995, and to 29 deaths per 1000 person-years in 1996–2006. ADC-related mortality decreased from 2.95 deaths per 1000 person-years in 1980–1989 to 0.65 deaths per 1000 person-years in 1996–2006 (P < .01), but the fraction of ADC-related deaths increased from 1.05% to 2.47% in association with decreases in other AIDS-related deaths. Non-Hodgkin lymphoma was the most common cancer-related cause of death (36% of deaths during 1996–2006). Likewise, NADC-related mortality decreased from 2.21 to 0.84 deaths per 1000 person-years from the period 1980–1989 to the period 1996–2006 (P < .05), but the fraction of NADC-deaths increased to 3.16% during 1996–2006. Lung cancer was the most common NADC cause of death (21% of cancer-related deaths in 1996–2006).

Conclusions. Cancer-related mortality decreased in the HAART era, but because of decreasing mortality due to AIDS, cancers account for a growing fraction of deaths. Improved cancer prevention and treatment, particularly for non-Hodgkin lymphoma and lung cancer, would reduce mortality among people with AIDS.
as continued exposures to environmental and lifestyle cancer risk factors, may change cancer outcomes for persons surviving AIDS in the HAART era.

Large and systematic evaluations of cancer as a cause of death among people with AIDS in the United States are lacking. Furthermore, little is known about how the changing spectrum of cancer risk among people surviving AIDS for many years influences cancer mortality. One US study noted an increase over time in deaths due to NHL and lung cancer, but follow-up stopped in 1999 [10]. Another study from New York City showed no change in overall mortality rates attributable to NADCs during the period 1999–2004 [11]. A recent study from Europe found NADCs to be the most frequent non-AIDS-related cause of death among HIV-infected people but did not provide mortality rates for individual cancers separately [12]. Detailed cancer-specific cause of death information is necessary to accurately describe and monitor the contribution of individual malignancies to the overall mortality experience of people with AIDS.

Evaluating cancer as a cause of death among people with AIDS is complicated, because they often have multiple underlying medical conditions, and mortality attributable to these conditions may change over time. It is necessary to consider both the fraction of deaths due to cancer and cancer mortality rates, because the fraction of deaths due to cancer may increase when overall mortality rates decrease. We conducted a population-based evaluation of cancer-related mortality among people with AIDS to describe trends in cancer-related deaths relative to widespread HAART use.

METHODS

The current analyses used data from the HIV/AIDS Cancer Match Study, a population-based registry linkage study of people with HIV infection or AIDS diagnosed during 1980–2008 in 15 US states and metropolitan regions [4, 5]. Following linkage, only deidentified data were retained for analyses. Institutional review boards at participating sites approved the study.

We constructed a cohort of people with AIDS (excluding people with HIV infection alone) who had been free of cancer as of the time of AIDS onset. AIDS onset was defined using the 1993 Centers for Disease Control and Prevention surveillance case definition [1]. Of 574,242 potentially eligible subjects, we excluded individuals with any cancer reported to the cancer registry, or an ADC reported to the HIV/AIDS registry, before or during the 3 months after AIDS onset (18,107 and 33,374 persons, respectively), so that we could eliminate the possibility that cancer contributed to development of AIDS. Furthermore, 16,073 people with AIDS who were not undergoing follow-up (according to the cancer registries) after month 4 were also excluded, because they contributed no person-time to this analysis. People who received a diagnosis of AIDS before 1980 (n = 11) and children aged <14 years (n = 6546) were also excluded from the study. We also excluded sites that did not routinely obtain underlying causes of death or provide them for the study (10 sites; n = 416,849). These exclusions yielded a cohort of 83,282 adults and adolescents who received a diagnosis of AIDS during 1980–2006 from 5 participating sites (Colorado; Massachusetts; New Jersey; Seattle, Washington; and San Francisco, California).

Deaths among people with AIDS occurring ≥4 months after AIDS onset were then evaluated. HIV/AIDS registries obtain vital status information via routine linkage to state and national mortality files. Matching of AIDS records to multiple sources increases the likelihood of HIV/AIDS registries detecting deaths among people who may have migrated out of their catchment area [13, 14]. Underlying cause of death (hereafter referred to as the cause of death) is the medical condition that initiated the train of events leading directly to death and was ascertained by interpreting the multiple causes of death listed on death certificates [15]. Causes of death were coded using codes from the International Classification of Diseases, 9th Revision (during 1979–1998) [16], and International Classification of Diseases, 10th Revision (from 1999 onward) [17]. On the basis of information regarding contributory causes, the final (underlying) cause of death was determined at each study site. To limit underascertainment of specific causes of death among people with AIDS diagnosed most recently, deaths and follow-up times were censored 2 years prior to the last month and calendar year of death recorded in each individual registry.

On the basis of International Classification of Diseases codes for causes of death, we classified deaths with specified causes as cancer related (ADC or NADC), AIDS related (excluding ADCs), and other, non–cancer related, non-AIDS related. We classified subjects according to calendar period of AIDS onset: 1980–1989 (no or limited availability of antiretroviral therapy), 1990–1995 (monotherapy and/or dual therapy), and 1996–2006 (HAART). We calculated mortality rates per 1000 person-years with exact 95% confidence intervals (CIs). Person-years were calculated from the start of the fourth month after AIDS onset to the end of the risk period (which was the first of death, end of cancer registry coverage, or censoring as defined above). We used Poisson regression to assess trends in rates across the 3 calendar periods, and P values <.05 were considered to be statistically significant.

RESULTS

Among 83,282 people with AIDS included in the study, most were male (81.3%). With regards to race or ethnicity, almost one-half (49.4%) of all subjects were non-Hispanic white and 33.4% were non-Hispanic black. Most subjects were aged 30–39 years (47.3%) or 40–49 years (28.6%) at the time of AIDS
onset, and most experienced onset of AIDS during 1990–1995 (51.2%) or 1996–2006 (30.6%).

Overall mortality rates decreased markedly over time, from 302 to 140 to 29 deaths per 1000 person-years for persons who had onset of AIDS during 1980–1989, 1990–1995, and 1996–2006, respectively (Table 1). Cause of death was specified for 93%, 85%, and 93% of these cases, respectively. Remaining analyses focus on deaths with a specified cause.

Mortality rates for cancer overall, ADC, and NADC decreased significantly across the calendar periods of AIDS onset ($P < .05$ for all comparisons) (Table 1). For ADC, mortality rates decreased 78% (2.95 and 0.65 deaths per 1000 person-years in 1980–1989 and 1996–2006, respectively). Likewise, for NADC, mortality rates decreased 62% across the same intervals (2.21 and 0.84 deaths per 1000 person-years). Nonetheless, cancer-associated deaths represented an increasing fraction of deaths over time, due to steep decreases in deaths due to the remaining causes (particularly for AIDS-related deaths, which showed a 95% decrease, as well as other non–cancer-related, non–AIDS-related deaths, which showed a 79% decrease over time) (Table 1).

Among ADCs, KS mortality rates exhibited a 11-fold decrease and NHL exhibited a 4-fold decrease over time. There was little change in the fraction of deaths with KS as the cause, but with the sharp decreases in other causes, the fraction of deaths caused by NHL increased over time. Despite decreases in NHL mortality rates, NHL remained the most common cancer-related cause of death in the HAART era (36% during 1996–2006). Cervical cancer was a much rarer cause of death, and mortality rates did not change significantly.

Among NADCs, lung cancer was the most common cause of death (22% of all cancer-related deaths during the HAART era) followed by liver cancer and Hodgkin lymphoma (Table 1). Mortality rates for lung cancer decreased almost 3-fold over calendar periods, and mortality rates for Hodgkin lymphoma and liver cancer also decreased steeply. Mortality rates for anal cancer did not exhibit a significant trend. Mortality from the remaining NADCs significantly decreased 56% over time, but individual cancer types were too uncommon to analyze separately. The proportion of all deaths attributable to lung cancer, liver cancer, and the remaining group of other NADCs increased over time, as a result of the dramatic decreases in other causes of death.

To evaluate the quality of mortality information in both HIV/AIDS and cancer registries, we conducted an additional analysis of the 389 people with NHL listed as the cause by the HIV/AIDS registry. Of those 389 persons who died of NHL, 278 (72%) had a prior incident NHL recorded in the cancer registry, and the cancer registry indicated that 141 (36%) of them died with NHL as the cause of death. As another example, of the 179 people with AIDS who died with lung cancer listed as the cause of death, 127 (71%) had an incident lung cancer recorded in the cancer registry, and 103 (58%) had lung cancer listed as a cause of death in the cancer registry.

**DISCUSSION**

In this population-based assessment of causes of death among people with AIDS, we demonstrated dramatic decreases in overall mortality, which reflected decreasing mortality attributable to AIDS, cancer, and other causes. Across calendar periods of AIDS onset, the decreases in mortality due to ADC (specifically KS and NHL) and other AIDS-related conditions (opportunist infections) can likely be attributed to immune restoration associated with widespread HAART use, and have been demonstrated in other studies in the United States and elsewhere [7, 11, 18, 19]. Prior studies have not specifically evaluated mortality due to individual ADCs and NADCs as reported by death certificates or have not provided rates for these causes of death.

Despite decreases in ADC mortality, NHL remained the most common cancer-related cause of death. Although the incidence of NHL among people with AIDS has decreased and survival following NHL diagnosis has improved in the HAART era, a large fraction of people with AIDS-associated NHL still die of malignancy [5, 9, 20, 21]. For example, in a recent European analysis of patients with AIDS-related NHL, 34% had died by 1 year after diagnosis and 45% by 5 years after diagnosis [22]. Major adverse prognostic factors included a diagnosis of central nervous system NHL, advanced immunodeficiency, and prior receipt of HAART (presumably reflecting incomplete adherence or development of drug-resistant HIV) [22].

Treatment options for AIDS NHL are complicated by late presentation [23]. For patients with AIDS-related NHL, a recent phase 2 trial demonstrated the safe addition of rituximab (a chimeric monoclonal B–cell antibody) to concurrent infusional chemotherapy, resulting in complete remission for 73% of patients evaluated [24]. Another recent study found that NHL tumor subtype was an independent predictor of outcome, emphasizing the heterogeneity of AIDS NHLs and the need for additional clinical studies that evaluate treatments for individual histologic subtypes of NHL [25, 26]. Finally, improved HAART regimens could also have a major impact on NHL mortality, both by decreasing NHL incidence and increasing survival among people with AIDS who develop NHL.

We also demonstrated notable decreases in mortality due to NADCs. Because the incidence of these malignancies has not fallen over time in a corresponding manner [5, 20], the decrease in mortality may reflect improvements in cancer prognosis, perhaps due to earlier detection, better access to cancer care, or more effective use of cancer therapy in conjunction with HAART. Among people with AIDS who died in the HAART era, lung cancer was the most frequent NADC cause of death,
### Table 1. Causes of Death among People with AIDS in the United States, 1980–2006 (n = 83,282)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No. (%) of deaths, according to calendar year of AIDS onset&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of deaths per 1000 person-years (95% CI), according to calendar year of AIDS onset&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths reported to HIV/AIDS registry</td>
<td>13,924</td>
<td>26,847</td>
<td>2491</td>
</tr>
<tr>
<td>Nonmissing cause of death</td>
<td>12,903 (100)</td>
<td>22,713 (100)</td>
<td>2311 (100)</td>
</tr>
<tr>
<td>Cancer cause of death</td>
<td>238 (1.84)</td>
<td>666 (2.93)</td>
<td>130 (5.63)</td>
</tr>
<tr>
<td>AIDS-defining cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>136 (1.05)</td>
<td>317 (1.40)</td>
<td>57 (2.47)</td>
</tr>
<tr>
<td>KS</td>
<td>41 (0.32)</td>
<td>63 (0.28)</td>
<td>7 (0.30)</td>
</tr>
<tr>
<td>NHL</td>
<td>92 (0.71)</td>
<td>250 (1.10)</td>
<td>47 (2.03)</td>
</tr>
<tr>
<td>Cervical cancer&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3 (0.23)</td>
<td>4 (0.13)</td>
<td>3 (0.50)</td>
</tr>
<tr>
<td>Non–AIDS-defining cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>102 (0.79)</td>
<td>349 (1.54)</td>
<td>73 (3.16)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>40 (0.31)</td>
<td>111 (0.49)</td>
<td>28 (1.21)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>6 (0.06)</td>
<td>19 (0.08)</td>
<td>5 (0.22)</td>
</tr>
<tr>
<td>Other non-AIDS-defining cancers</td>
<td>47 (0.33)</td>
<td>190 (0.84)</td>
<td>39 (1.69)</td>
</tr>
<tr>
<td>AIDS-related (excluding AIDS-defining cancer)</td>
<td>9566 (74.14)</td>
<td>17,301 (76.17)</td>
<td>951 (41.15)</td>
</tr>
<tr>
<td>Other non-cancer, non-AIDS-related</td>
<td>3099 (24.02)</td>
<td>4746 (20.90)</td>
<td>1230 (53.22)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; HIV, human immunodeficiency virus; KS, Kaposi sarcoma; ICD-9, International Classification of Diseases, 9th Revision; ICD-10, International Classification of Diseases, 10th Revision; NHL, non-Hodgkin lymphoma.


<sup>c</sup> P value was determined using Poisson regression.

<sup>d</sup> Analysis was restricted to women. Percentage reflects frequency of cervical cancer as a cause of death among deaths with a nonmissing cause. Among women, there were 1316 deaths (6082 person-years) during 1980–1989, 2910 deaths (34,168 person-years) during 1990–1995, and 602 deaths (20,847 person-years) during 1996–2006.

<sup>e</sup> These entries include anal cancer deaths (7 deaths with ICD-9 code 154.3 and 4 deaths with ICD-10 code C21.0) and rectal cancer deaths (4 deaths with ICD-9 code 154.1 and 1 death with ICD-10 code C20). Rectal cancers can be misclassified anal cancers, especially in people with AIDS.
underscoring the importance of this malignancy. HIV-infected people have an elevated risk for lung cancer owing to an excess of smoking [27, 28]. In addition, other factors such as frequent pulmonary infections or inflammation may also contribute in synergy with tobacco [29]. Although we observed declining mortality rates due to lung cancer, survival among HIV-infected lung cancer patients remains poor [9, 30], emphasizing a need to encourage smoking cessation in people with AIDS. Data from lung cancer treatment trials limited to the HIV-infected population are lacking. For those with early stage cancer, surgical resection is an option, but optimum radiation and chemotherapy protocols are unknown.

Liver cancer mortality rates decreased significantly across calendar periods in our study, but with decreases in other causes, the fraction of deaths due to liver cancer increased in the HAART era. The overall burden of liver cancer deaths may continue to rise in people with AIDS as the combined effects of alcohol use and coinfection with hepatitis B or C viruses manifests as liver disease [31].

The decrease in mortality from other causes led to an increase in the fraction of all deaths due to cancer (both ADC and NADC). We note the importance of considering both mortality rates and the fraction of all deaths attributable to a specific cause, since they yield complementary information. In an additional analysis of NHL and lung cancer deaths (which were the most common cancer-related causes of death in our study), we found that most had had that cancer reported to the cancer registry. However, the lack of perfect concordance between information on the cause of death in the HIV/AIDS and cancer diagnoses in the cancer registries suggests that some death certificate diagnoses could have been inaccurate.

A strength of this study is our use of data from population-based HIV/AIDS registries to capture and classify all deaths among people with AIDS. Although information on cause of death was available from only 5 of our study sites, the demographic characteristics of our cohort of people with AIDS were generally similar to the overall population of persons with AIDS in the United States. Cause of death was specified for the majority of included subjects, but a limitation is that this information was missing for some (between 7% and 15%, depending on the calendar period). We note that it takes multiple years for cause of death information to be verified, and completeness increases over time. Furthermore, as people’s understanding of HIV disease and deaths in this population evolved over time, the attribution of death to a given cause likely changed in parallel (eg, HIV disease is now considered less limiting, so attribution to other causes may have increased over time). Nonetheless, the overall decreases we note in mortality rates are consistent with what has been reported by other studies. It should also be noted that we lacked individual data on HAART use. However, our results accurately reflect overall the population-level effects of HAART use on mortality. Our goal was to evaluate cancer-related causes of death, so we did not separately evaluate other causes of death. Other studies suggest that cardiovascular disease and substance abuse contribute substantially to this category and should be a focus of prevention programs [7, 11]. Finally, we evaluated only people with AIDS and did not consider people with less advanced HIV infection. Although we did not include data on this group, one would expect lower mortality rates among HIV-infected people without AIDS.

In summary, our findings demonstrate that cancer mortality among people with AIDS has decreased in the HAART era, but with concomitant decreases in other causes of death, cancers now account for a growing fraction of deaths. As HIV-infected people continue to live longer following an AIDS diagnosis and as they age, cancer may increase as a cause of mortality. In particular, improved prevention and treatment of NHL and lung cancer, the 2 most common cancer-related causes of death, would be expected to favorably impact survival among HIV-infected people.

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