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Changing temporal trends in non-AIDS cancer mortality among people diagnosed with AIDS: San Francisco, California, 1996–2013

Nancy A. Hessol[a,*], Danning Ma[b], Susan Scheer[c], Ling C. Hsu[c], Sandra K. Schwarcz[c]

[a] Departments of Clinical Pharmacy and of Medicine, University of California, 3333 California Street, Suite 420, San Francisco, CA, 94143-0613, USA
[b] Department of Clinical Pharmacy, University of California, 3333 California Street, San Francisco, CA, 94143-0613, USA
[c] San Francisco Department of Public Health, 25 Van Ness Avenue, Suite 500, San Francisco, CA, 94102-6012, USA

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ABSTRACT

Background: Antiretroviral therapy (ART) has reduced AIDS-defining cancer (ADC) mortality, but its effect on non-AIDS-defining cancer (NADC) mortality is unclear. To help inform cancer prevention and screening, we evaluated trends in NADC mortality among people with AIDS (PWA) in the ART era.

Methods: This retrospective cohort study analyzed AIDS surveillance data, including causes of death from death certificates, for PWA in San Francisco who died in 1996–2013. Proportional mortality ratios (PMRs), and year, age, race, sex-adjusted standardized mortality ratios (SMRs) were calculated for 1996–1999, 2000–2005, and 2006–2013, corresponding to advances in ART.

Results: The study included 5822 deceased PWA of whom 90% were male and 68% were aged 35–54 at time of death. Over time, the PMRs significantly decreased for ADCs (2.6%, 1.4%, 1.2%) and increased for NADCs (4.3%, 7.0%, 12.3%). For all years combined (1996–2013) and compared to the California population, significantly elevated SMRs were observed for these cancers: all NADCs combined (2.1), anal (58.4), Hodgkin lymphoma (10.5), liver (5.2), lung/larynx (3.0), rectal (5.2), and tongue (4.7). Over time, the SMRs for liver cancer (SMR 19.8, 11.2, 5.0) significantly decreased while the SMRs remained significantly elevated over population levels for anal (SMR 123, 48.2, 45.5), liver (SMR 19.8, 11.2, 5.0), and lung/larynx cancer (SMR 5.3, 4.7, 3.6).

Conclusion: A decline in ADC PMRs and increase in NADC PMRs represent a shift in the cancer burden, likely due to ART use. Moreover, given their elevated SMRs, anal, liver, and lung/larynx cancer remain targets for improved cancer prevention, screening, and treatment.

1. Introduction

The use of effective antiretroviral therapy (ART) to control HIV infection has led to a dramatic reduction in HIV-related mortality, extending life expectancy among persons with HIV/AIDS to ages at which cancer incidence rapidly rises [1–7]. The combination of older age, immune perturbation, and prolonged exposure to carcinogens and oncogenic viral infections puts ART-treated adults at a heightened risk of cancer and cancer-related mortality [8,9].

From the beginning of the AIDS epidemic, the cancers commonly reported as underlying and contributory causes of death among people with AIDS (PWA) were two AIDS-defining cancers (ADCs) – non-Hodgkin lymphoma (NHL) and Kaposi sarcoma (KS) [10,11]. Now, with the widespread use of effective ART, non-AIDS-defining cancers (NADCs) have become increasingly more common as a cause of death among PWA [12,13]. Although the use of ART has resulted in a decreased number of ADC deaths and increased life expectancy among PWA [6], the impact of ART on NADC mortality is less well known [13]. There are only a few recently published studies that have compared cancer-related morality in the United States (US) among PWA to that of the general population, particularly for NADCs, and even fewer studies that have assessed temporal trends in cancer mortality [12,13].

In this investigation, we evaluated the changing impact of ART on NADC mortality by examining temporal trends in NADC-related causes of death among San Francisco PWA from 1996 to 2013. We hypothesized that the proportion of ADC deaths would decrease as the proportion of NADC deaths increase over time commensurate with the increased use and potency of ART. We also hypothesized that the standardized mortality ratios (SMRs) for certain NADCs would be elevated above population levels as a result of longer life expectancies among PWA and contributory factors such as immune dysfunction, and prolonged exposure to cancer causing agents and viral infections.

* Corresponding author.
E-mail address: Nancy.Hessol@ucsf.edu (N.A. Hessol).

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2. Methods

2.1. Study population

We conducted a population-based retrospective cohort study of cancer-related mortality among PWA in San Francisco. In San Francisco, HIV/AIDS surveillance has been conducted through active and passive methods and, as of December 31, 2015, 15,995 people were reported living with HIV [14]. For this investigation we included all people diagnosed with AIDS (infected with HIV and have either a CD4+ T-cell count < 200 cells/μL, a CD4+ T-cell percentage of total lymphocytes of < 15%, or one of the AIDS-defining illnesses) [15] who were aged > 15 years and who died from January 01, 1996 through December 31, 2013. The study excluded individuals with an HIV diagnosis who did not develop AIDS since name-based reporting of HIV infection began in 2006 and thus was not available for the entire study time period. Also excluded were children < 15 years of age due to their low risk of cancer-related mortality.

2.2. Dependent and independent variables

Data on the date of AIDS diagnosis, demographic characteristics, HIV mode of transmission, country of origin, current address, and prescription of ART among PWA were ascertained through the San Francisco Department of Public Health (SFDPH) HIV/AIDS registry. Race was categorized as African American, Hispanic, Other (including multi-race), or White and age was categorized into 10-year age groups. We defined an individual as residing in an impoverished neighborhood at diagnosis if they lived in a census tract where > 20% of persons aged 18 years of older had a median annual household income that was below the U.S. poverty level [16]. All independent variables used in these analyses were obtained at the time of diagnosis except for age, which was calculated as of the date of death.

Information on underlying and contributory causes of death was obtained from computer matches with the National Death Index (NDI), which included deaths through December 2013. For each decedent, underlying and contributory causes of death were classified as AIDS-defining cancer (ADC; KS, NHL, and invasive cervical cancer), cancers that meet the U.S. Centers for Disease Control and Prevention HIV stage 3 disease case definitions [10], non-AIDS-defining cancer (NADC), HIV/AIDS related non-cancer, or other. The frequencies of all underlying cancer causes of death were examined and those cancers that occurred in four or more persons were selected for cause-specific analyses.

2.3. Statistical analysis

To explore temporal changes, we divided time into three calendar periods, which corresponded to the improvements in ART: 1996–1999 (early years of effective ART), 2000–2005 (following FDA approval of lopinavir/ritonavir—Kaletra® and tenofovir disoproxil fumarate—Viread®), and 2006–2013 (following FDA approval of multi-class combination medication). We analyzed changes in the distribution of socio-demographic, risk, survival, and treatment characteristics of our study population over the three time periods using the Maentel-Hanzel chi-square test for trends.

We also examined the number of underlying causes of deaths due to ADCs, NADCs, HIV/AIDS related non-cancers, and other conditions in each time period. The causes of death information on the death certificates [17] was summarized and coded using the International Classification of Diseases [18,19]. A single underlying cause of death was identified from all reported conditions that began the chain of events that resulted in death using the NDI Automated Classification of Medical Entities computer program [20]. All coded conditions (including the underlying and contributory causes of death) listed on the death certificate were included in our multiple cause of death category.

Furthermore, we calculated proportional mortality ratios (PMRs) by calendar period for underlying and multiple causes of death. PMRs were expressed as a ratio of the number of deaths from a specific cause over the total number of deaths from all causes. We used chi-squared or Fisher's exact test to measure changes in PMRs across the three time periods. The PMR analyses were stratified by sex at birth. There were 181 transgender females (male to female) in our study sample and we categorized them by their sex at birth (male) because sex specific cancers such as prostate cancer are more closely associated with anatomy than gender identity. There were no transgender males (female to male) in our study sample. Given the relatively low number of females in our study (n = 499), we only reported female PMRs for all ADCs and all NADCs combined without a breakdown of specific cancer types.

Year-, age-, race-, and sex-adjusted SMRs with 95% Poisson confidence intervals were calculated for specific underlying NADC causes of death for all years combined (1996–2013) and then stratified by the three periods: 1996–1999, 2000–2005, and 2006–2013. The SMRs were calculated as the ratio of observed to expected number of deaths. The California population was our standard population for both number alive and cause-specific deaths [21,22]. The expected deaths were calculated by multiplying the death rates of the California population by the total number of participants in the study population at the corresponding year, age, race, and sex group and summing up all the values for each group (using indirect standardization). Changes in the SMRs across the three time periods were measured using Poisson regression using a log of the expected counts as an offset. All analyses were performed using SAS® [23].

3. Results

3.1. Population characteristics

The study sample included 5822 deceased PWA of whom 90% were male, 68% were aged 35–54 at time of death, 63% were White, and 59% were men who have sex with men (MSM). The distribution of socio-demographic, risk, and clinical characteristics of the study population changed significantly from 1996 to 2013 (Table 1). There were increases in the proportions of females, decedents aged 45 to 94 years, persons who survived more than eight years post-AIDS diagnosis, non-Whites, MSM-PWID (MSM who also inject drugs), persons with non-U.S. country of origin, residents of impoverished neighborhoods and those who were prescribed ART.

3.2. Overall distribution of deaths

The number of deaths in which an ADC was the underlying cause primarily decreased between the first two time periods and then remained relatively stable between 2000 and 2005 and 2006–2013 ($p = 0.002$; Fig. 1). Meanwhile, the number of deaths from a NADC as the underlying cause increased over the three time periods from 93 to 132 to 222 ($p < 0.001$). The number of deaths due to AIDS other than cancer decreased over the three time periods while deaths from non-AIDS-related underlying causes increased significantly.

3.3. Proportional mortality ratios—underlying causes of death

When stratified by sex, the PMRs for underlying causes of death for both ADCs and NADCs in females did not change significantly over time largely due to the small sample size ($p = 0.59$ and 0.51, respectively; Table 2). Among males, the PMRs for ADCs significantly decreased for all ADCs combined ($p = 0.004$) and for NHL ($p < 0.001$), but not for KS ($p = 0.67$; Table 2). In men, the PMRs significantly increased for certain NADCs, specifically, colon ($p = 0.01$), liver ($p = 0.005$), lung/larynx cancer ($p < 0.001$), pancreas ($p = 0.005$) and prostate ($p = 0.008$) while the PMRs for anal cancer had a borderline significant increase ($p = 0.06$).