Out of the

Division of Infectious Diseases and Tropical Medicine

Trends in AIDS-defining and non-AIDS-defining cancers among patients with AIDS in the city of São Paulo: 1997 - 2012

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Abstract

Background: People with AIDS (PWA) are at increased risk for certain types of cancer. The objective of the present study was to describe three aspects of the cancer epidemiology among PWA: time trends, risk and survival.

Methods: To identify PWA who had cancer, a probabilistic record linkage between the databases "Information System on Disease Notification (SINAN)" (87,109 records) and the "Population-based Cancer Registry of São Paulo" (628,161 cancer cases) was conducted. The trend analyses were based on the annual percent change (APC) and corresponding 95% confidence intervals (95% CI). To assess the risk for cancer the standardized incidence ratio (SIR) and 95% CI were calculated. The survival analyses were conducted by means of Kaplan Meier methods and Cox models.

Results: The database comprised 2,074 cancer cases, diagnosed in 2,000 PWA (seventy-four people had two primary site tumors). The majority were male (1,461; 73.0%), white (1,111; 55.6%) and aged 30-49 years old at cancer diagnosis (1,257; 62.9%). Most cancers (1,057; 51.0%) were non-AIDS defining (NADC). A statistically significant decline in the incidence of AIDS-defining cancers (ADC) was found in males and females (APC_M = -14.1%/year; APC_F = -15.6%/year). Conversely the incidence of NADC has increased since the mid 2000's (APC_M = 7.4%/year) among men. The risks for both ADC (SIR_M = 27.74; SIR_F = 8.71) and NADC (SIR_M = 1.87; SIR_F = 1.44) were significantly elevated. The overall five-year survival in PWA after cancer diagnosis was 49.4% (versus 72.7% in matched non-PWA). The hazard ratios were 2.93 and 2.51 for ADC and NADC, respectively.

Conclusion: Cancer burden among PWA in São Paulo was similar to that described in high-income countries following the introduction of the highly active antiretroviral therapy. Despite the significant reductions in the incidence of ADC, PWA remain at higher risk of developing cancer.

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1. Introduction

The association between human immune deficiency virus (HIV)/ acquired immune deficiency syndrome (AIDS) and cancer has been documented since the initial years of the AIDS epidemic. Kaposi sarcoma (KS) was one of the first signs indicative of immune suppression. In 1982, the first case definition of AIDS, in addition to Kaposi sarcoma, listed certain types of non-Hodgkin lymphoma (NHL) as possibly AIDS-defining conditions. In the same document, the Centers for Disease Control and Prevention (CDC) reported that between June 1981 and September 1982, 593 cases of AIDS had been identified in the United States, of which 37% had Kaposi sarcoma [1]. Only in 1993, was cervical cancer (CC) added to the list of as AIDS-defining conditions. Since then, AIDS-defining cancers (ADC) include Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer [2].

The advent of the highly active antiretroviral therapy changed the course of the AIDS pandemic when it became widely available. Incidence of AIDS-defining illnesses, rates of hospitalization and mortality among HIV-infected people have all dramatically fallen after the introduction of highly active antiretroviral therapy [3, 4]. As a consequence, survival of these individuals significantly improved. Recent studies revealed that the life expectancy in this population is now comparable to that of the general population [5-8].

The incidence of AIDS-defining cancers has followed a similar decreasing pattern. In the United States, between 1980 and 2002, incidence of both Kaposi sarcoma and non-Hodgkin lymphoma significantly declined and the incidence of cervical cancer remained stable throughout the period [9]. On the other hand, incidence of particular non-AIDS-defining cancers, such as anal and liver cancers, has shown opposite upward trends [10, 11].

In assessing the risk of cancer in the HIV-infected population in comparison to the general population, several studies revealed significantly higher rates in the first group. As in other populations with iatrogenic immune suppression, virus-related cancers account for the majority of excessive cases among HIV-infected patients [12].

Concerning survival after cancer diagnosis, a limited number of studies have been conducted worldwide. Survival seems to be impaired in this population, but the disparities may greatly differ according to cancer site/type [13, 14].

Nevertheless, these studies were mainly restricted to high-income countries and cancer burden may differ in other regions for several reasons, including access to antiretroviral therapy and characteristics of the population living with AIDS [9].

2. Rationale and Objectives

The majority of the studies assessing cancer spectrum in the HIV-infected population have been conducted in developed countries, especially the United States and Italy. The disproportional number of studies conducted in these countries was possible due to the co-existing population-based cancer and AIDS registries. Unfortunately, in many countries, population-based registries are nonexistent and therefore epidemiological studies of this nature are not feasible. The city of São Paulo in Brazil, however, has an active population-based cancer registry, and AIDS notification has been mandatory since 1986.

After the case definition for AIDS was released in 1982, the first cases of the syndrome were soon identified in Brazil, with predominance of the city of São Paulo. A case that had occurred in 1980 fulfilled the criteria for AIDS and was retrospectively classified as such. Until the end of the 1980's, the city accounted for almost 40% of all notifications in Brazil, but with the increasing number of cases found in other cities, the proportion dropped to less than 7% in 2013. When considering the entire period (1980-2013), the city concentrated over 12% of all cases diagnosed nationally [15].

In an effort to provide information on cancer among people with AIDS in a middle-income country, the project entitled "São Paulo AIDS-Cancer Linkage Study" was conceived. This is the first population-based study in Brazil describing cancer incidence in this population and one of few to be conducted in a developing nation. As part of this project, the objectives of this thesis were as follows:

1. To assess trends in the incidence of AIDS-defining, non-AIDS-defining and the most frequent cancers among people with AIDS, between 1997 and 2012, stratified by sex and compare those to that of the general population of the same geographical area (city of São Paulo).

2. To compare the risk for cancer among people with AIDS after stratifying for sex, to that in the general population.

3. To describe the five-year overall survival after cancer diagnosis in people with AIDS and contrast this to that of selected controls (without AIDS) from the general population.

Each of the aforementioned objectives originated a separate manuscript; the three of them are part of this thesis, published as:

- ✓ Manuscript one - "Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil" by the "International Journal of STD & AIDS" (January, 2017).
- ✓ Manuscript two - "Risk for cancer among people living with AIDS, 1997-2012: the São Paulo AIDS-cancer linkage study" by the "European Journal of Cancer Prevention" (January, 2017).

The third manuscript entitled "Cancer survival in people with AIDS: A population-based study from São Paulo, Brazil" was submitted on April 25th, 2017 to the International Journal of Cancer and was accepted on September 20th, 2017.

3. Methods

The analyses of the present study are based on residents of São Paulo who had cancer and AIDS. To conduct such a study, the database *Sistema de Informações de Agravos de Notificação* (SINAN)/ Information System on Disease Notification database (87,109 records) and the "Population-based Cancer Registry of São Paulo" (628,161 cancer cases) were linked using a probabilistic method. This design is known as population-based registry linkage study and it is a useful tool to examine cancer burden in people living with HIV/AIDS. It has been employed in other countries, such as Italy, Spain and the United States, among others [9, 10, 13, 14, 16].

Before conducting the probabilistic record linkage, the two databases were standardized using Statistical Package for the Social Sciences (SPSS, version 15), so that all corresponding variables used in the process had the same format, length and coding. For the linkage process, the records were compared based on patient's full name and date of birth using the open source software OpenRecLink (version 2.9). A multi-step procedure was employed and clerical review of matches, based on mother's name and address, was carried out to improve both sensitivity and specificity.

After finalizing the record linkage process for manuscripts one (trends) and two (risk), the following exclusion criteria, which have been used in previous studies, were employed: cancer cases which occurred 60 months or earlier before AIDS diagnosis (n = 86), cases of basal cell skin cancer (n = 173); and *in situ* cancer cases (n = 238). These cases were removed from all analyses. Therefore, for these manuscripts 2,074 cancer cases were assessed in 2,000 people with AIDS (74 patients had two primary site tumors). As for the manuscript on survival, further exclusion criteria allowing for complete follow up of patients were applied, and the final sample comprised 1,314 cancer cases in 1,294 people with AIDS.

Crude rates were calculated by dividing the number of cases by the respective population at risk, according to sex. Age-standardized incidence rates were calculated, based on the world population proposed by SEGI (1960) and modified by DOLL (1976) [17, 18].

3.1. Trends in the incidence

The trend analyses were conducted using Joinpoint software. Joinpoint estimates the annual percent change (APC) and their respective 95% confidence intervals (95% CI) using an exponential distribution. The software identifies shifts in trends, breaking the whole period into subsets and calculating the APC for each resulting period [19]. In the present study, the three-year moving average of the age-standardized incidence rates was used to estimate the APC for AIDS-defining and non-AIDS-defining cancers overall and for the most incident cancer site/type, namely: Kaposi sarcoma, non-Hodgkin lymphoma, anal, lung and colorectal cancers, in men; Kaposi sarcoma, non-Hodgkin lymphoma, cervical, breast and colorectal cancers in women.

3.2. Risk for cancer

The comparison of the risk for cancer across populations (AIDS versus general population) was performed using the standardized incidence ratio (SIR), which is the ratio of expected and observed cases, and respective 95% confidence intervals. To obtain the expected number of cases in the AIDS population during the period of 1997-2012, age-specific rates in the general population, which were provided by the "Population-based Cancer Registry of São Paulo", were considered. The SIRs were calculated according to sex and site/type of cancer. These analyses were conducted using the package Epidemiological tools (Epitools) with the software R.

3.3. Survival after cancer diagnosis

The survival analyses were possible because the "Population-based Cancer Registry of São Paulo" has access to the mortality database of the city of São Paulo (*Programa de Aprimoramento das Informações de Mortalidade no Município de São Paulo - PRO-AIM/* Program for Improvement of Death Information). In these analyses the cases diagnosed between 1997 and 2009 and followed up for at least five years until the outcome of interest (death from any cause) was observed or until the end of the observation period was reached (31st of December 2014) whichever occurred earlier, were included. For those patients who survived beyond this threshold, time was right-censored.

Controls from the general population (without AIDS) were selected to allow for comparison. The survival analyses were conducted using Kaplan Meier methods and Cox proportional hazards models, stratified by matching variables and adjusted for age (in years). These analyses were stratified by cancer site/type and performed using Stata (version 13).

3.4. Ethics

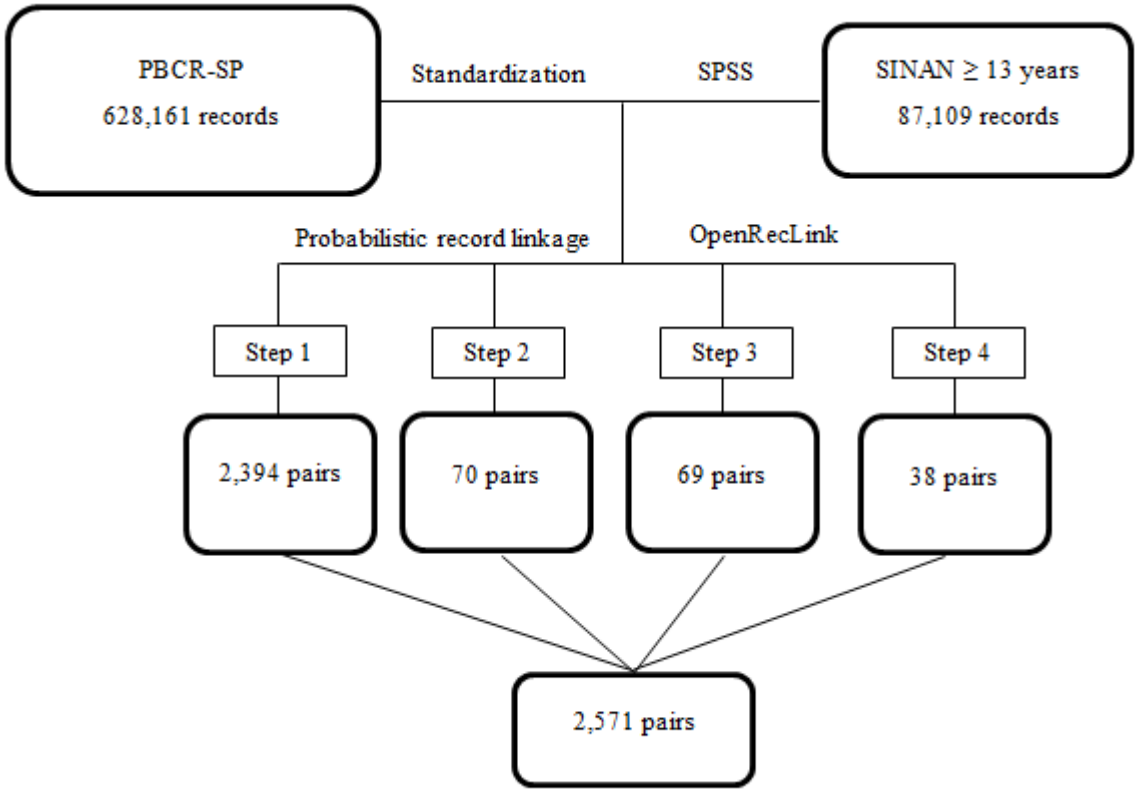
Ethical clearance was obtained from the Ethics Review Board at School Public Health, University of São Paulo (opinion number 686.849), the Municipal Health Secretariat of São Paulo (opinion number 703.467) and the University of Munich (opinion number 233-15) prior to study initiation.

All database management and record linkage were conducted by the main investigator in a password-protected computer which was not connected to any network. After selection of true matches, identification information was deleted to ensure data privacy.

4. Results

A multi-step record linkage process was conducted with the final database containing 2,571 matches (Figure 1). As described in the methods, some cancer cases were removed before further analyses. For this thesis the descriptive analysis comprises 2,074 cancer cases, diagnosed in 2,000 people with AIDS (seventy-four people had two primary site tumors).

Figure 1 - Probabilistic record linkage between the "Population-based Cancer Registry of São Paulo" and Information System on Disease Notification database (SINAN).



The majority were male (1,461; 73.0%), white (1,111; 55.6%) and aged 30-49 years old at cancer diagnosis (1,257; 62.9%). About half of them (974; 48.7%) had five to eleven years of schooling. Heterosexual (674; 33.7%) and homosexual (447; 22.4%) practices were the most frequently stated categories of exposure to HIV.

In the AIDS population, most cancers (1,057 out of 2,074 cancers; 51.0%) were classified as non-AIDS defining, corresponding to 56.7% of cancers in women (n = 320 out of 564). In men, AIDS-defining cancers were slightly more frequent than non-AIDS defining cancers, adding up to 51.2% (n = 773) of all 1,510 cancer cases. The five most incident cancer sites/types among men with AIDS were Kaposi sarcoma (469; 31.1%), non-Hodgkin lymphoma (304; 20.1%), anal cancer (63; 4.2%), colorectal

cancer (59; 3.9%) and lung cancer (54, 3.6%). Cervical cancer (114; 20.2%), non-Hodgkin lymphoma (96; 17.0%), breast cancer (72; 12.8%), Kaposi sarcoma (34; 6.0%) and colorectal cancer (19; 3.4%) were the most frequently found cancer sites/types in women with AIDS.

4.1. Trends in the incidence

The trend analyses in men with AIDS, revealed a statistically significant decline in general for AIDS-defining cancers (APC = -14.1%/year), but also in particular for Kaposi sarcoma (APC = -16.2%/year) and non-Hodgkin lymphoma (APC = -11.9%/year). Conversely, all non-AIDS-defining cancers decreased (APC = -9.7%/year) until the mid-2000's, when a significantly increasing trend could be detected (APC = 7.4%/year). When considering men with AIDS, the incidence of anal and lung cancers have significantly increased (by 24.6% and 15.9%, respectively), whereas the incidence of colorectal cancer remained stable. In the general male population had significant declines in incidence of non-Hodgkin lymphoma (-2.8%/year), colorectal (-1.3%/year), lung (-7.6%/year) and anal (-5.9%/year) cancers.

For women with AIDS significant declining trends were found in the incidence of AIDS-defining cancers (APC = -15.6%/year) in general, and for Kaposi sarcoma (APC = -26.7%/year), non-Hodgkin lymphoma (APC = -15.8%/year), cervical cancer (APC = -12.8%/year) and breast cancer (APC = -10.1%/year) in particular. The incidence of colorectal cancer, on the other hand remained stable throughout the study period. Similarly, the decline was statistically significant (APC = -15.8%/year) for all non-AIDS-defining cancers. A similar declining pattern in the general female population was identified for all cancers analyzed.

4.2. Risk for cancer

The overall risk of AIDS-defining cancers and non-AIDS-defining cancers among males with AIDS were significantly higher than among the male general population (SIR_M = 27.74 and 1.87 respectively) than among females with AIDS compared to the female general population (SIR_F = 8.71 and 1.44 respectively). Most virus-related non-AIDS-defining cancers occurred at elevated rates among people with AIDS: anal cancer (SIR_M = 33.02; SIR_F = 11.21), liver cancer (SIR_M = 4.35; SIR_F = 4.84), vulvar and vaginal cancer (SIR_F = 6.78), Hodgkin lymphoma (SIR_M = 5.84; SIR_F = 2.71), among others. Cancers of the trachea and lung (SIR_M = 2.24; SIR_F = 2.60), central nervous system (SIR_M = 1.92; SIR_F = 3.48), and eye in men (SIR_M = 5.28) were also more frequently found in people with AIDS.

In contrast to this, the estimated standardized incidence rates of cancers of the breast, prostate, bladder and esophagus did not differ across populations. Only thyroid cancer occurred at lower rates in both men and women with AIDS in comparison to the general population (SIR_M = 0.50; SIR_F = 0.48).

4.3. Survival after cancer diagnosis

The overall five-year survival in people with AIDS after cancer diagnosis was 49.4% (versus 72.7% in matched people without AIDS) and the hazard ratio was 2.64 (95% CI = 2.39-2.91). More specifically, the hazard ratios were 2.93 for AIDS-defining (95% CI = 2.49-3.45) and 2.51 (95% CI = 2.21-2.84) for non- AIDS-defining cancers.

Among people with AIDS, the poorest survival probabilities were seen for cancers of the trachea and lung (10.5%) and liver (11.1%), as well as for leukemia (14.3%). Conversely, the highest survival probabilities were found for cancers of the thyroid (86.7%), eye (85.7%), vulva and vagina (77.8%) and nonmelanoma skin cancer (70.6%).

With a few exceptions, the type/site-specific analyses revealed a significantly lower survival probability after cancer diagnosis in people with AIDS when compared to the general population.

5. Discussion

This thesis described the cancer spectrum in the era of availability of the highly active antiretroviral therapy among people with AIDS living in São Paulo, the largest city in Brazil and in South America. The incidence of AIDS-defining cancers has shown a pronounced reduction throughout the study period. Nevertheless, people with AIDS remain at higher risk of developing certain malignancies, both AIDS-defining and non-AIDS-defining. For those who developed cancer, the survival probability after diagnosis is generally impaired when compared to that of the general population.

The findings presented by this study are closer to scenarios of industrialized countries, as compared to other low- and middle-income countries, probably due to two aspects: the characteristics of the AIDS epidemic and the access to antiretroviral therapy. In São Paulo, AIDS is still more prevalent in men, with homosexual exposure to HIV representing an important mode of transmission. However, the male to female ratio of newly diagnosed cases has dramatically fallen from 26:1 in 1985 to 2:1 in 2011 [20]. In the United States and Western European countries the HIV-infected populations have similar features, whereas in sub-Saharan Africa, women are disproportionally more affected by AIDS and heterosexual infection is predominant [21]. Furthermore, antiretroviral therapy has been provided free of cost in Brazil to all patients in need since 1996. Brazil was the first developing country to promote such a low barrier policy. Thus, regardless of a patient's economic condition, treatment is universal. More recently, the country updated its treatment guidelines and since the end of 2013 the Brazilian Ministry of Health strongly recommends immediate initiation of antiretroviral therapy regardless of CD4 count [22]. Only a few countries worldwide have adopted a similar measure, despite being the current recommendation of the World Health Organization since 2015 [23].

Cancer burden among people with AIDS in São Paulo was similar to that previously described in other areas located in high-income countries [12, 24, 25]. The majority of virus-related cancers occurred at elevated rates. Apart from cancers of the tongue and penis, the human papilloma virus-related cancers (anus, cervix, tonsil and oropharynx, vulva and vagina) were more frequently found in people with AIDS. Liver cancer, which is related to the hepatitis B and C viruses, as well as cancer of the nasopharynx and Hodgkin lymphoma, both Epstein-Barr-virus-related, also occurred at higher rates. These virus-related cancers accounted for an important share of excessive cases in people with AIDS, as coinfection with oncogenic viruses disproportionally affects this population [24-27]. Tobacco-associated malignancies, especially cancer of the trachea and lung, were also more frequent in this population.

As for survival after cancer diagnosis, the results revealed poorer probabilities among people with AIDS which could be a result of several factors, including faster disease progression, late diagnosis, disparities of treatment uptake in comparison to the general population, lack of specific treatment guidelines for this population and death from other causes [28-31].

Brazil has been an important part of the global history of HIV/AIDS, having developed over the years a national Sexually Transmitted Diseases/AIDS program that is considered by many as an

inspiration for the developing world. This study underscores the effects of the Brazilian policy of universal access to antiretroviral treatment in the incidence of AIDS-defining cancers, but also reveals the need of measures to address emerging non-AIDS-defining cancers, including the intensification of anti-tobacco strategies aimed at this specific population. Since Brazil already offers antiretroviral treatment to all HIV-infected regardless of disease stage, early diagnosis of HIV infection is also an important part of cancer prevention in this population. A recent study revealed that immediate initiation of antiretroviral therapy significantly reduces the risk of cancer [32].

As the life expectancy of HIV-infected people has dramatically improved since the advent of the highly active antiretroviral therapy and is now comparable to that of the general population, the HIV-infected population has dramatically enlarged and aged over the years. Therefore, more people are at risk of developing cancer and the healthcare system should be ready to follow up to offer adapted health care packages for this particular population. Specific prevention and screening strategies might also contribute to the management of cancer in this population and should be investigated further.

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7. Publications

7.1. Manuscript 1 - Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil

Original research article

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Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil

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Abstract

People living with AIDS are at increased risk of developing certain cancers. Since the introduction of the highly active antiretroviral therapy (HAART), the incidence of AIDS-defining cancers (ADCs) has decreased in high-income countries. The objective of this study was to analyse trends in ADCs and non-AIDS-defining cancers (NADCs) in HIV-positive people with a diagnosis of AIDS, in comparison to the general population, in São Paulo, Brazil. A probabilistic record linkage between the 'Population-based Cancer Registry of São Paulo' and the AIDS notification database (SINAN) was conducted. Cancer trends were assessed by annual per cent change (APC). In people with AIDS, 2074 cancers were diagnosed. Among men with AIDS, the most frequent cancer was Kaposi's sarcoma (469; 31.1%), followed by non-Hodgkin lymphoma (NHL; 304; 20.1%). A decline was seen for ADCs (APC = −14.1%). All NADCs have increased (APC = 7.4%/year) significantly since the mid-2000s driven by the significant upward trends of anal (APC = 24.6%/year) and lung cancers (APC = 15.9%/year). In contrast, in men from the general population, decreasing trends were observed for these cancers. For women with AIDS, the most frequent cancer was cervical (114; 20.2%), followed by NHL (96; 17.0%). Significant declining trends were seen for both ADCs (APC = −15.6%/year) and all NADCs (APC = −15.8%/year), a comparable pattern to that found for the general female population. Trends in cancers among people with AIDS in São Paulo showed similar patterns to those found in developed countries. Although ADCs have significantly decreased, probably due to the introduction of HAART, NADCs in men have shown an opposite upward trend.

Keywords

South America, epidemiology, AIDS, HPV, HIV, cancer

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Introduction

Several studies have shown an increased risk for cancer among people living with HIV/AIDS (PLWHA); however, the risks have changed over time. Since the introduction of the highly active antiretroviral therapy (HAART), some countries have documented significant declines in AIDS-defining cancers (ADCs), namely Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL) and cervical cancer (CC). In contrast to this, increasing trends in non-AIDS-defining cancers (NADCs) were found in many recent studies.[1–5] Most of the studies assessing cancer burden in PLWHA have been conducted in developed countries, such as the United States (US), Spain and Italy, where population-based

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cancer and AIDS registries coexist. Unfortunately, in many countries, both at high- and or middle-income levels, such studies are not feasible, due to the lack of population-based registries, or due to the inability of conducting record linkage because of anonymized records, poor database quality or intermittent data collection, among other constraints.

In Brazil, AIDS notification became mandatory in 1986 and cases diagnosed before that time were recorded retrospectively. The state of São Paulo has played a crucial role in the AIDS epidemic, having launched the first AIDS programme in the country, providing treatment free of cost.[6] São Paulo city has the highest percentage (12.6%) of all AIDS cases diagnosed nationally.[7] The city also has a population-based cancer registry, which covers the largest population in Brazil, and has uninterruptedly collected data on cancer incidence since 1997.

The present study analysed the trends in incidence of cancers in residents of São Paulo with HIV between 1997 and 2012, in comparison to the general population.

Methods

A total of 87,109 AIDS cases were diagnosed in HIV-positive persons aged ≥ 13 years in São Paulo from 1980 to 2013.[8] Between 1997 and 2012, the 'Population-based Cancer Registry of São Paulo' (PBCR-SP) registered 628,161 cancers (496,276 invasive) among São Paulo residents.

A probabilistic record linkage was conducted between the PBCR-SP (1997–2012) and the AIDS notification database SINAN (*Sistema de Informações de Agravos de Notificação*/Information System on Disease Notification) (1980–2013) containing AIDS cases. The Brazilian Ministry of Health preferably uses the AIDS case definition of the Centers for Disease Control and Prevention and alternatively the definition of Rio de Janeiro/Caracas.[9] Both registries cover the same territory: the city of São Paulo, which according to the 2010 census, comprises an area of 1521 km^2 and is home to 11,253,503 inhabitants (99.1% urban), corresponding to almost 6% of the Brazilian population. Its current human development index is 0.805.[10]

A probabilistic record linkage was conducted, in a multi-step process, using different blocking strategies. *Soundex*, which is the phonetic algorithm for indexing names by sound, was used in place of names for blocking. The blocking strategies contained a combination of *soundex* of the first name, *soundex* of the last name, decade of birth and sex. Full name and date of birth were used for calculating the weighted scores. Clerical review based on name, date of birth, mother's name and address, when available, was carried out in all steps to improve record linkage sensitivity. This process was conducted using the open source software OpenRecLink (version 2.9). After the identification of true matches, patients were excluded from the analysis if they had a cancer diagnosis 60 months or more prior to their AIDS diagnosis.

Cancers were grouped into two major categories: ADCs (KS, NHL and CC) and NADCs (all other cancers). The annual AIDS population according to gender and age group was estimated as the difference between cumulative cases and cumulative deaths per year.

The crude incidence rates were calculated according to gender, dividing the number of incident cases by the estimated AIDS population in a given year and presented as rates per 100,000 persons. Crude rates were also calculated according to the following age groups: 20–29, 30–39, 40–49, 50–59, 60–69 years. As for the general population, the denominator for rates was the resident population of São Paulo, as provided by the Brazilian Institute of Geography and Statistics.[10] Age-standardized rates (ASRs) by sex were calculated using the direct method based on the world population, as proposed by SEGI and modified by Doll and Waterhouse.[11]

In the descriptive analyses, persons with multiple cancer diagnoses were only included once (considering the first cancer). To assess trends in ADCs, NADCs and most incident cancers (anal, colorectal and lung cancers in men; breast and colorectal cancers in women) in the population with AIDS, the three-year moving average of the ASR was calculated. Subsequently, the annual per cent change (APC) was estimated, as follows: $APC = [\exp(\beta_{year}) - 1] \times 100$, and its respective 95% confidence intervals with exponentially transformed values using the Joinpoint software (version 4.2.0.2). Data from the PBCR-SP were analysed to assess trends in cancer incidence in the general population. The series of the PBCR-SP started in 1997. Since its trends are greatly affected by the AIDS epidemic, no specific trend analysis for the general population was conducted for KS.

To compare risk for cancer within age groups, the ratio between crude age-specific rates of the oldest age group (60–69 years) and the youngest (20–29 years) was calculated. All statistical analyses were stratified by sex.

This research obtained ethical clearance from the Ethics Review Board at the School Public Health, University of São Paulo (686.849), from the Municipal Health Secretariat of São Paulo (703.467) and from the University of Munich (233.15). After record linkage, the database was anonymized to ensure data privacy.

Results

Table 1 displays the main characteristics of all AIDS cases registered in São Paulo from 1980 to 2013.

Table 1. Socio-demographic characteristics of people diagnosed with AIDS, according to gender. São Paulo, 1980–2013.

	Total		Male		Female	
	n	%	n	%	n	%
Race/ethnicity						
White	21,935	25.2	15,360	24.2	6575	27.8
Black	4292	4.9	2715	4.3	1577	6.7
Asian	303	0.3	214	0.3	89	0.4
Pardo[a]	10,079	11.6	6484	10.2	3595	15.2
Indigenous	64	0.1	48	0.1	16	0.1
Unknown	50,436	57.9	38,616	60.9	11,820	49.9
Age at AIDS diagnosis (years)						
13–19	1453	1.7	963	1.5	490	2.1
20–29	22,818	26.2	16,044	25.3	6774	28.6
30–39	34,892	40.1	26,132	41.2	8760	37.0
40–49	18,944	21.7	13,964	22.0	4980	21.0
50–59	6548	7.5	4621	7.3	1927	8.1
60–69	1853	2.1	1258	2.0	595	2.5
≥70	423	0.5	311	0.5	112	0.5
Unknown	178	0.2	144	0.2	34	0.1
HIV exposure category						
Homosexual men	17,589	20.2	17,589	27.7	NA	NA
Bisexual	6001	6.9	5977	9.4	24	0.1
Heterosexual	31,550	36.2	14,832	23.4	16,718	70.6
Intravenous drug user	13,643	15.7	11,256	17.7	2387	10.1
Other	595	0.7	402	0.6	193	0.8
Unknown	17,731	20.4	13,381	21.1	4350	18.4
Total	**87,109**	**100**	**63,437**	**100**	**23,672**	**100**

NA: not applicable.
[a]*Pardo* refers to multiracial persons of African ancestry.
Source: Epidemiological surveillance on STDs/AIDS, Municipal Department of Health, São Paulo, Brazil.

The majority of cases were men (72.8%), aged 20–49 years (88.5%) at AIDS diagnosis. The estimated number of persons living with AIDS increased substantially from 13,895 (of which 76.1% are males) in 1997 to 44,741 (of which 69.0% are males) in 2012. Young males (20–49 years) accounted for over 60% of the AIDS population at risk of cancer (data not shown).

Of all 496,276 invasive cancers diagnosed between 1997 and 2012, 2074 cancers occurred in 2000 persons with AIDS. Seventy-four persons were diagnosed with two primary site tumours, thus, the descriptive statistics shown in Table 2 was based on 2000 persons. The majority were male (1461; 73.0%), white (1111; 55.6%) and aged 30–49 years old at cancer diagnosis (1257; 62.9%). Heterosexual (674; 33.7%) and homosexual (447; 22.4%) practices were the most frequent stated categories of exposure to HIV.

Table 3 presents the number of cases and trend analyses of ADCs, NADCs, and most incident cancers in men and women both with AIDS and from the general population; in these analyses all 2074 cancers were considered. Most cancers (51.0%; 1057 out of 2074 cancers) in the AIDS population were classified as NADCs, corresponding to 56.7% cancers in women (n = 320). In men, ADCs were slightly more frequent than NADCs, representing 51.2% (n = 773) of all 1510 male cases. The five most incident cancers among men with AIDS were KS (469; 31.1%), NHL (304; 20.1%), anal cancer (63; 4.2%), colorectal cancer (59; 3.9%) and lung cancer (54, 3.6%). In the general male population, the most frequent cancer sites were prostate (23.4%), colon and rectum (9.5%), lung (7.2%), stomach (6.5%) and skin non-melanoma (6.1%) (data not shown).

In women with AIDS, CC (114; 20.2%), NHL (96; 17.0%), breast cancer (72; 12.8%), KS (34; 6.0%) and colorectal cancer (19; 3.4%) were the most incident cancers. In contrast, among women from the general population, breast (25.6%), colon and rectum (8.9%),

Table 2. Socio-demographic characteristics of 2000 people with AIDS and cancer, according to gender. São Paulo, 1997–2012.

	Total		Male		Female	
	n	%	n	%	n	%
Race/ethnicity						
White	1111	55.6	860	58.9	251	46.6
Black	143	7.2	84	5.7	59	10.9
Asian	14	0.7	10	0.7	4	0.7
Pardo[a]	255	12.8	159	10.9	96	17.8
Unknown	477	23.9	348	23.8	129	23.9
Age at AIDS diagnosis (years)						
13–19	16	0.8	9	0.6	7	1.3
20–29	348	17.4	241	16.5	107	19.9
30–39	733	36.7	534	36.6	199	36.9
40–49	528	26.4	397	27.2	131	24.3
50–59	277	13.9	210	14.4	67	12.4
60–69	82	4.1	55	3.8	27	5.0
≥70	16	0.8	15	1.0	1	0.2
Age at cancer diagnosis (years)						
13–19	8	0.4	6	0.4	2	0.4
20–29	225	11.3	163	11.2	62	11.5
30–39	650	32.5	467	32.0	183	34.0
40–49	607	30.4	438	30.0	169	31.4
50–59	348	17.4	271	18.5	77	14.3
60–69	135	6.8	95	6.5	40	7.4
≥70	27	1.4	21	1.4	6	1.1
HIV exposure category						
Homosexual men	447	22.4	447	30.6	NA	NA
Bisexual	179	9.0	179	12.3	–	–
Heterosexual	674	33.7	313	21.4	361	67.0
Intravenous drug user	145	7.3	105	7.2	40	7.4
Other	10	0.5	4	0.3	6	1.1
Unknown	545	27.3	413	28.3	132	24.5
Total	**2000**	**100**	**1461**	**100**	**539**	**100**

NA: not applicable.
[a]*Pardo* refers to multiracial persons of African ancestry.

thyroid (7.5%), cervix (5.2%) and skin non-melanoma (5.2%) were the most frequent cancer sites (data not shown).

As for the trend analyses in men with AIDS, a statistically significant decline was seen in general for ADCs (APC = −14.1%/year), but also in particular for KS (APC = −16.2%/year) and NHL (APC = −11.9%/year). In contrast to this, all NADCs decreased (APC = −9.7%/year) until the mid-2000s, when it started to increase (APC = 7.4%/year). Incidence of anal and lung cancer have significantly increased by 24.6 and 15.9%, respectively, whereas colorectal cancer remained stable. In the general male population, NHL, colorectal, lung and anal cancers had significant declines in incidence of −2.8, −1.3, −7.6, −5.9%/year, respectively (Figure 1(a) to (d)).

Among women with AIDS, a statistically significant decline was seen in general for ADCs (APC = −15.6%/year), and in particular for KS (APC = −26.7%/year), NHL (APC = −15.8%/year), CC (APC = −12.8%/year) and breast cancer (APC = −10.1%/year) in particular. In contrast to this, the incidence of colorectal cancer remained stable. Additionally, also for all NADCs (APC = −15.8%/year), the decline was significant. Declining trends in all cancers analysed were found for women from the general population.

Table 3. Trends in 2074 cancer cases found among 2000 people with AIDS and cancer and people from general population, according to sex. São Paulo, 1997–2012.

	Persons with AIDS				General population			
	n	APC	95% CI	p	n	APC	95% CI	p
Male[a]								
All AIDS-defining cancers	773	−14.1	−16.6; −11.6	<0.01	NA	NA	NA	NA
Kaposi sarcoma	469	−16.2	−18.8; −13.4	<0.01	NA	NA	NA	NA
Non-Hodgkin lymphoma	304	−11.9	−15.5; −8.2	<0.01	7719	−2.8	−3.5; −2.1	<0.01
All non-AIDS-defining cancers (1997–2005)[b]	361	−9.7	−12.2; −7.1	<0.01	NA	NA	NA	NA
All non-AIDS-defining cancers (2005–2012)	376	7.4	3.6; 11.4	<0.01	NA	NA	NA	NA
Anal cancer[c]	63	24.6	16.0; 33.9	<0.01	616	−5.9	−10.1; −1.5	<0.01
Colorectal cancer	59	−3.9	−11.5; 4.3	0.30	22,565	−1.3	−2.1; −0.5	<0.01
Lung cancer	54	15.9	6.9; 25.7	<0.01	17,082	−7.6	−8.3; −6.9	<0.01
Female[d]								
All AIDS-defining cancers	244	−15.6	−18.8; −12.3	<0.01	NA	NA	NA	NA
Cervical cancer	114	−12.8	−16.3; −9.2	<0.01	14,765	−8.2	−9.1; −7.3	<0.01
Non-Hodgkin lymphoma	96	−15.8	−20.0; −11.4	<0.01	7220	−2.4	−3.0; −1.7	<0.01
Kaposi sarcoma	34	−26.7	−34.7; −17.7	<0.01	NA	NA	NA	NA
All non-AIDS-defining cancers	320	−15.8	−20.0; −11.3	<0.01	NA	NA	NA	NA
Breast cancer	72	−10.1	−19.1; −0.2	<0.01	72,134	−1.8	−2.5; −1.1	<0.01
Colorectal cancer	19	1.9	−10.3; 15.8	0.70	24,975	−1.5	−2.3; −0.7	<0.01

APC: annual per cent change; CI: confidence interval; NA: not applicable.
[a]Cancer cases add up to 1510 in men with AIDS.
[b]Segment provided by Joinpoint.
[c]2002 onwards.
[d]Cancer cases add up to 564 in the women with AIDS.

The analysis of crude rates stratified by age group revealed that the risk for all ADCs (KS, NHL and CC) increased with age (Figure 2(a) and (b)). Risk for all NADCs among persons with AIDS was 38.3-fold in men and 35.6-fold in women, when comparing the oldest (60–69 years) to the youngest age group (20–29 years).

Discussion

This is the first study in Brazil estimating the incidence of cancer in patients with AIDS at a population level. Our results reveal a high and changing cancer burden in this population, as found in similar studies conducted in North America and Europe, as well as a multicentre cohort study performed in Rio de Janeiro (Brazil) and Nashville (US).[2,4,5,12,13]

Although approximately half of cancers identified in our study were classified as ADCs, their incidences have dramatically declined in São Paulo, but remain at high rates when compared to the general population. Declining trends in ADCs have been documented in several studies, with one of the most probable contributors to this being the introduction of HAART in 1996.[2,5] Treatment with HAART, if timely, alters the course of HIV infection by preventing or reversing profound immunosuppression, and thereby, decreasing susceptibility of developing AIDS-defining illnesses, including ADCs.[14,15] Despite efforts to scale up HIV testing and early diagnosis, late entries to HIV care are still very frequent worldwide and could prevent further reduction in ADCs burden.[16,17] A study conducted in Brazil revealed that between 2003 and 2006, 43.6% of persons aged 15 and older diagnosed with AIDS entered HIV care late, either having CD4+ cell counts $\leq$200 cells/mm^3, an AIDS-defining illness at the initial examination or having died within the first 20 days of entry.[18] In these cases, delayed introduction of HAART could be less effective in improving the immune system and its ability to control oncogenic viruses, such as Epstein–Barr virus (risk factor for NHL) and human herpes virus 8 (associated with KS), increasing the overall risk for ADCs.

On the other hand, since 2013, the Brazilian Ministry of Health encourages the immediate initiation of antiretroviral therapy among all individuals diagnosed with HIV infection, regardless of CD4+ cell counts.[19] This measure could lead to further declines in ADCs, by preventing persons diagnosed with HIV only from developing AIDS and its defining illnesses.

Steep reduction (APC = −15.8% in women; −11.9% in men) in NHL in the AIDS population could have

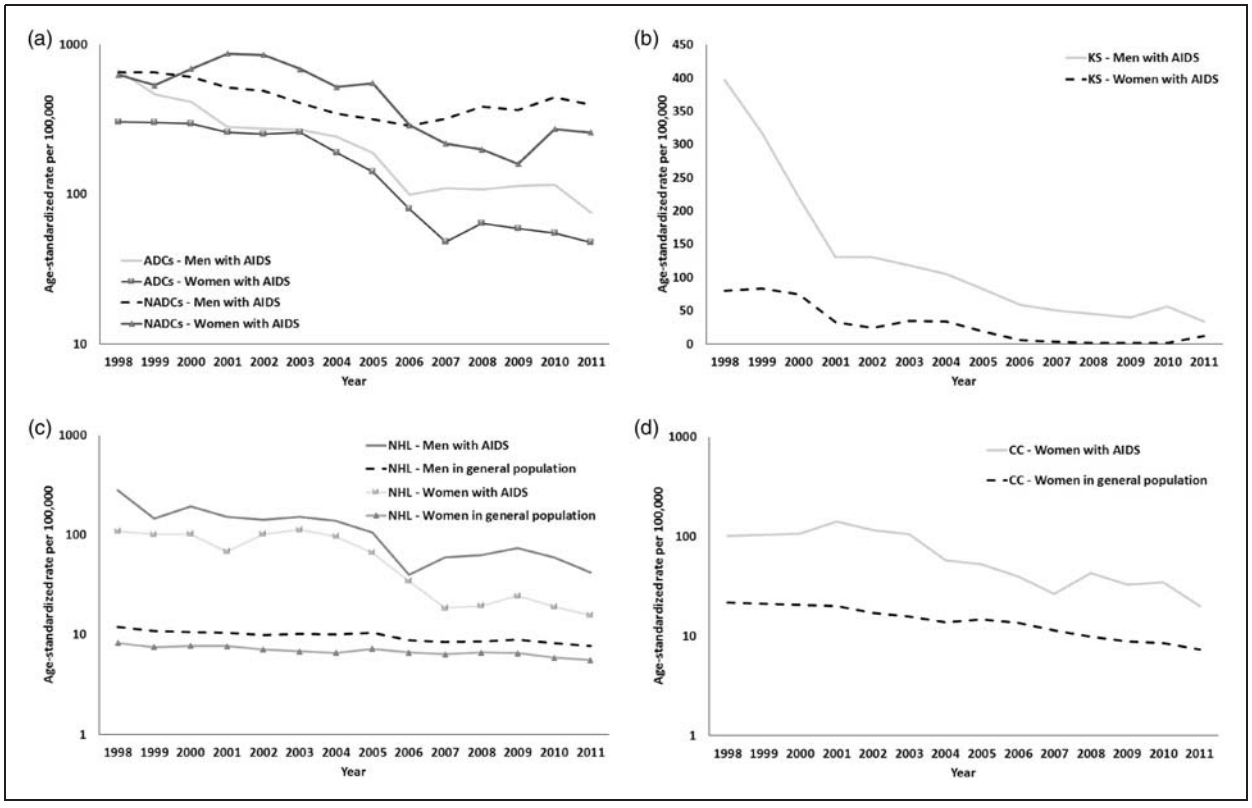

Figure 1. (a) Age standardized incidence rates of AIDS-defining and non-AIDS-defining cancers in the AIDS population according to gender. São Paulo, 1997–2012. Rates are presented based on three-year moving average and displayed on a logarithmic scale. (b) Age standardized incidence rates of Kaposi's sarcoma in the AIDS population according to gender. São Paulo, 1997–2012. Rates are presented based on three-year moving average. (c) Age standardized incidence rates of non-Hodgkin lymphoma in the AIDS population and in the general population according to gender. São Paulo, 1997–2012. Rates are presented based on three-year moving average and displayed on a logarithmic scale. (d) Age standardized incidence rates of cervical cancer in the AIDS population and in the general population. São Paulo, 1997–2012. Rates are presented based on three-year moving average and displayed on a logarithmic scale.

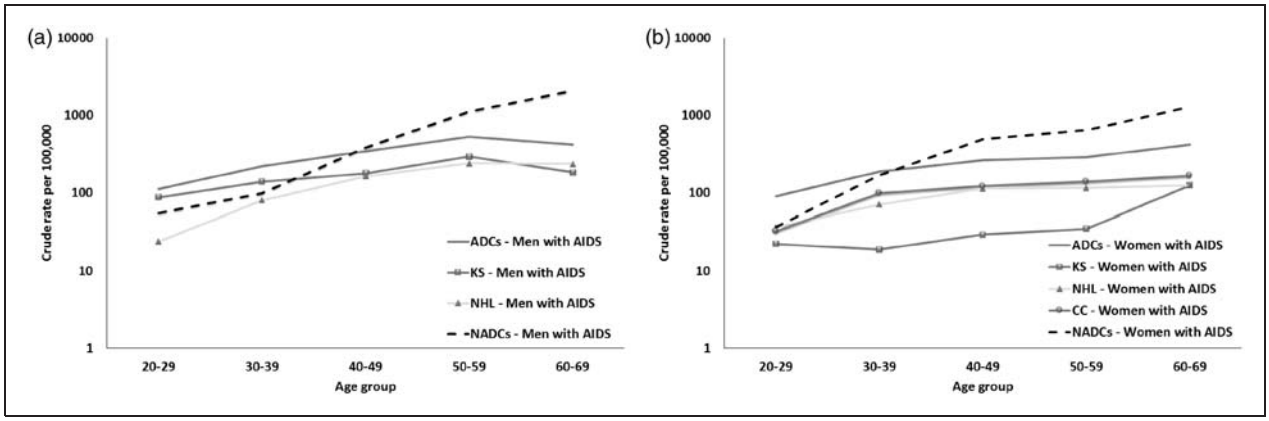

Figure 2. (a) Crude incidence rates for AIDS-defining cancers, non-AIDS-defining cancers, Kaposi's sarcoma and non-Hodgkin lymphoma in men with AIDS according to age group. Sao Paulo, 1997–2012. Rates are displayed on a logarithmic scale. (b) Crude incidence rates for AIDS-defining cancers, non-AIDS-defining cancers, Kaposi's sarcoma, non-Hodgkin lymphoma and cervical cancer in women with AIDS according to age group. Sao Paulo, 1997–2012. Rates are displayed on a logarithmic scale.

contributed to declining trends at the general population level (APC = −2.4% in women; −2.8% in men), as they account for 4% of all cases. Similar declining patterns for CC were identified in women with AIDS and women from the general population. In both cases, the propagation of Pap smear screening may have contributed to this epidemiological pattern as the test can identify cervical lesions before they evolve to CC. In São Paulo, over 90% of female inhabitants belonging to the screening target group reported to have had at least one Pap smear in the last three years.[20]

Conversely, NADCs have become progressively crucial over the years. In both men and women, incidence of NADCs surpassed ADCs in the mid-2000s, but in men, the incidence has been particularly increasing since 2005, driven by lung and anal cancers. Other NADCs, such as female breast and colorectal cancers in the AIDS population follow the pattern of the general population. In São Paulo, coverage of the breast cancer screening programme is about 80%.[20]

The increasing trend in lung cancer among men is not surprising. According to the Brazilian Ministry of Health, the prevalence of smoking among PLWHA ranges from 50 to 70%,[19] which is considerably higher than that of the general population (14.9% in 2013 in São Paulo).[20] Recent data from the US revealed that lung cancer has decreased more rapidly in PLWHA than in the general population, though the authors believe that this might result from a faster decline in smoking prevalence in the first group.[2] In São Paulo there are no data suggesting changes in smoking prevalence in this population. In line with our results, lung cancer in PLWHA in Italy has increased in the post-HAART era when compared to the pre-HAART era.[5] Previous studies have shown that higher incidence of lung cancer in this population is mainly attributable to tobacco smoking rather than other cofactors.[21] There is an ongoing debate on the effectiveness of screening for lung cancer, and until there is enough evidence to adopt it, management of this malignancy must focus on strategies to promote tobacco cessation.

As for anal cancer in the male population with AIDS, there is a clear increasing trend since 2002, which is contrary to the drop observed in the general population. Similar results have been reported in Italy and the US, though in the US increasing trends in anal cancer in the AIDS population have been identified as driving the upward trend in the general population.[2,5] Anal cancer has been strongly linked to persistent HPV infection and tobacco smoking,[22] and the risk among PLWHA is as high as 37-fold when compared to the general population.[23] A multicentre study in Brazil of 445 HIV-positive men, found a 65.6% prevalence of HPV DNA in anal swabs, with 40.7% detected as oncogenic HPV strains.[24] In an effort towards early detection of anal cancer and its precursor lesions in PLWHA, the Brazilian Ministry of Health has recommended since 2013 annual anal Pap smears for patients who have receptive anal intercourse, HPV infection history, or abnormal vulvar or cervical histology.[19] This strategy could lead to changes in anal cancer burden in the high-risk population in the future.[25]

Our findings are closer to that of industrialized countries, probably due to two aspects: the characteristics of the AIDS epidemic and the access to antiretroviral therapy. In São Paulo, AIDS is still more prevalent in men, with homosexual exposure to HIV representing an important mode of transmission. However, male-to-female ratio of AIDS cases has dramatically fallen from 26:1 in 1985 to 2:1 in 2011.[26] In the US and Western European countries, the populations of PLWHA have similar features, whereas in sub-Saharan Africa, women are disproportionally more affected by AIDS and heterosexual infection is predominant.[27] Concerning antiretroviral therapy, provided in Brazil since 1996, treatment is free of cost to all patients in need. Thus, regardless of a patient's economic condition, treatment is universal.[28]

The analysis of crude rates by age groups highlights that as patients age the risk for cancer increases, but the risk is more pronounced for NADCs. Incidence of NADCs peaks at older ages, a pattern observed for most cancers in the general population. Polesel et al.,[5] when assessing NADCs in PLWHA in Italy, concluded that the strong changes in crude rates were driven by the ageing of the AIDS population.[5]

As for limitations, this study is restricted to the AIDS population and does not examine HIV-only patients. Even though the city of São Paulo occasionally provided notices regarding HIV infection, notification has only recently become mandatory (in June 2014). Thus, data for HIV-only cases for the study period are not precise and was therefore not analysed. Information on clinical data, including CD4+ cell count, viral load and antiretroviral therapy was not assessed because it is not routinely collected by the AIDS registry (SINAN).

The shorter coverage period of the PBCR-SP has limited our analysis to the post-HAART era. It would have been valuable to understand the risk for cancer in this population before HAART became fully available.

Three main sources of cancer underestimation may have occurred in our study. First, this study relies on probabilistic record linkage itself. This method is not error free and might have failed in the identification of some of those PLWHA who had cancer in the study period. To minimize this issue and improve our data matching sensitivity, a multi-step process was carried

out and clerical review was employed. Even so, some degree of underestimation may have occurred. Nevertheless, this strategy has also been employed to estimate cancer incidence in PLWHA in other countries and is the primary source of population-based data.

A second factor that could result in cancer underestimation is outmigration. Residents of São Paulo who were diagnosed with AIDS and outmigrated later could not be captured by our database linkage. There are no data on the percentage of outmigration among AIDS patients, but available information from a report assessing incident cancer cases registered in São Paulo revealed that 4% of deaths were registered outside the municipality (outmigration).[29] If one assumes that the percentage of AIDS cases that moved to other municipalities is similar and that not all of them would develop cancer, then outmigration would not greatly interfere with our findings.

Lastly, PLWHA who are unaware of their status may have been misclassified in our study, and therefore failed to contribute to the cancer burden in persons with AIDS. Nevertheless, this is to be expected in studies, which are based on passive case finding.

Despite the aforementioned constraints, the present study provides valuable population-based information from a developing country. The current body of knowledge is composed mainly of research conducted in developed countries with this study providing aggregated data from a developing country known for its particular plan to fight AIDS. Our findings highlight a marked decrease in ADCs for both genders and a recent increase in NADCs among men, mainly driven by lung and anal cancers. Stratification by gender was important to identify different patterns in cancer trends. This suggests that exposure to risk factors for cancer, such as smoking, varies according to gender and has to be accounted for in explanations of gender differences. In addition, women tend to seek health care more frequently than men do and this might have affected the risk of cancer.[30]

Risk for cancer in persons with AIDS increases dramatically as they age, with a similar pattern seen in the general population. Because PLWHA are living longer and reaching older ages due to advances in disease treatment, cancer in this population will remain an important issue to be addressed. Strategies to promote lifestyle changes to reduce or eliminate modifiable risk factors such as tobacco smoking, as well as screening and early cancer detection are key points for the management of cancer in PLWHA.

Declaration of conflicting interests

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7.2. Manuscript 2 - Risk for cancer among people living with AIDS, 1997-2012: the São Paulo AIDS-cancer linkage study

Risk for cancer among people living with AIDS, 1997–2012: the São Paulo AIDS–cancer linkage study

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Previous studies have reported an increased risk for certain types of cancer in the HIV-infected population. The aim of this study was to assess the risk for cancer in people with AIDS (PWA) in comparison with the general population in São Paulo (Brazil), between 1997 and 2012. A population-based registry linkage study was carried out to assess the risk for cancer, using a standardized incidence ratio (SIR) approach. A total of 480 102 person-years, of which 337 941 (70.4%) person-years were men, were included in the analysis. Around 2074 cancer cases were diagnosed among PWA, of which 51.0% were non-AIDS-defining cancers (NADC). The risk for AIDS-defining cancers and NADC in the male population with AIDS was significantly higher than that in the general population (SIR = 27.74 and 1.87, respectively), as it was in the female population with AIDS compared with the general population (SIR = 8.71 and 1.44, respectively). Most virus-related NADC occurred at elevated rates among PWA: anal cancer (SIR = 33.02 in men and 11.21 in women), liver (SIR = 4.35 in men and 4.84 in women), vulva and vagina (SIR = 6.78 in women) and Hodgkin lymphoma (SIR = 5.84 in men and 2.71 in women). Lung (SIR = 2.24 in men and 2.60 in women) and central nervous system (SIR = 1.92 in men and 3.48 in women) cancers also occurred at increased rates. Cancer burden among PWA in São Paulo was similar to that described in high-income countries such as the USA and Italy following the introduction of the highly active antiretroviral therapy. As coinfection with oncogenic viruses disproportionally affects this population, virus-related cancers accounted for a great share of excessive cases. ***European Journal of Cancer Prevention*** **00:000–000**

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Introduction

Since the beginning of the global AIDS epidemic, cancer and AIDS have been closely linked. Kaposi sarcoma (KS) and certain types of non-Hodgkin lymphoma were among the first illnesses to be recognized as AIDS-defining cancers (ADC) (CDC – Centers for Disease Control and Prevention, 1982). Later in 1993, cervical cancer (CC) was also classified as ADC (CDC – Centers for Disease Control and Prevention, 1992).

The advent of the highly active antiretroviral therapy (HAART) in 1996 has changed the course of the epidemic, by improving immune function and reducing morbidity and mortality among HIV-infected people. The incidence of ADC has decreased, and conversely the proportion of non-AIDS-defining cancers (NADC) among HIV-infected people has increased, surpassing ADC (Engels *et al.*, 2006; Dal Maso *et al.*, 2009).

Previous studies conducted mainly in high-income countries have shown that the increased risk for NADC is largely due to virus-related cancers (Calabresi *et al.*, 2013; de Martel *et al.*, 2015). According to the International Agency for Research on Cancer, HIV infection causes cancer indirectly by promoting immunosuppression and enhancing the effects of oncogenic infections (IARC – International Agency for Research on Cancer, 2012).

In an effort to provide information on cancer risk among people with AIDS (PWA) in a middle-income country, the project entitled 'São Paulo AIDS–Cancer Linkage Study' was conceived. This is the first population-based study in Brazil describing cancer spectrum in PWA. The aim of the present study was to compare the risk for cancer among PWA with that in the general population living in São Paulo.

Methods

In Brazil, notification of AIDS cases is compulsory since 1986, and cases diagnosed before then were retrospectively registered to the SINAN database (Sistema de

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Informações de Agravos de Notificação/Information System on Disease Notification).

The 'Population-based Cancer Registry of São Paulo' (PBCR-SP) covers 11 million inhabitants, residents in the city of São Paulo according to the 2010 census (IBGE – Instituto Brasileiro de Geografia e Estatística, 2016). This registry collects, both actively and passively from all data sources, cancer incidence among São Paulo inhabitants since 1997.

In order to identify PWA who developed cancer, a probabilistic record linkage was performed between the SINAN and the PBCR-SP databases. Both databases used in this study capture the same geographical area (the city of São Paulo) and have high coverage (>90%) (Latorre *et al.*, 2015; SES-SP – Secretaria de Estado da Saúde de São Paulo, 2015).

The study used a multistep strategy using the open source software OpenReclink (version 2.9, Rio de Janeiro, Brazil). Phonetic codes (soundex) of first and last names and date of birth, as well as mother's name and address, when available were used in the process. A clerical review was conducted at each step. Once true matches were identified, registries were anonymized to ensure data privacy.

To be included in the analysis the cases had to be diagnosed with AIDS between 1980 and 2013, be at least 13 years of age at AIDS diagnosis and be a resident of the city of São Paulo. Cancer cases that occurred 5 years or earlier before AIDS diagnosis were excluded from the analysis ($n = 86$), in addition to cases of basal cell skin cancer ($n = 173$) and in-situ lesions ($n = 238$).

Cancer cases were classified and coded according to the International Classification of Diseases for Oncology, third edition (Fritz *et al.*, 2000), and grouped into two major groups – namely, ADC (KS, NHL and CC) and NADC (all other cancers). Cancers were also grouped according to their possible association with viruses (Calabresi *et al.*, 2013; de Martel *et al.*, 2015).

Statistical methods

Crude incidence rates were calculated by dividing the number of cases by the respective population at risk. To compare the risk for cancer in the AIDS population versus the general population, the standardized incidence ratios (SIR), defined as SIR $= \frac{\text{number of observed cases}}{\text{number of expected cases}}$ and their corresponding exact 95% confidence intervals were calculated according to sex and site/type of cancer. To obtain the expected number of cases in the AIDS population during the 1997–2012 period, age-specific incidence rates in the general population were provided by the PBCR-SP for the same period. All statistical analyses were conducted using R (version 3.2.3).

Ethical clearance was obtained from the Ethics Review Board at School Public Health, University of São Paulo (686.849), the Municipal Health Secretariat of São Paulo (703.467) and the University of Munich (233-15) before study initiation.

Results

From 1980 through 2013, 87 109 cases of AIDS in individuals aged 13 years and older have been recorded in the city of São Paulo (DATASUS – Departamento de Informática do SUS, 2016). From 1997 to 2012, 496 276 invasive cancers (excluding basal cell skin cancer and *in situ*) were registered in the city by the PBCR-SP.

The AIDS population at risk comprised a total of 480 102 person-years (PY), which consisted of mostly men [337 941 (70.4%) PY] and patients aged 30–49 years [285 006 (59.4%) PY]. Between 1997 and 2012, there have been 2074 incident cancers cases in 2000 PWA. Seventy-four patients had two primary site tumors (3.7%). Overall, about half of the cancers [1057 (51.0%)] were NADC.

The main characteristics of the 2000 people with AIDS and cancer are shown in Table 1. Most patients were male [1461 (73.0%)] and had acquired HIV through sexual contact [1300 (65.0%)]. Patients who developed ADC were significantly younger than those with NADC (37.5 vs. 45.9 years, respectively; $P < 0.001$). The most frequent cancer in men was KS, accounting for 31.1% ($n = 469$) of all cases, and in women it was CC [114 (20.2%)], as seen in Tables 2 and 3.

In men with AIDS, the risk for ADC overall (SIR = 27.74), KS (SIR = 86.95) and NHL (SIR = 13.53) in particular was significantly increased. NADC overall was also more frequent

Table 1 Characteristics of 2000 people living with AIDS and cancer. São Paulo, 1997–2012

Characteristics	Total	Male	Female
N	2000	1461	539
Age at AIDS-defining cancer onset (median in years)	37.5	37.9	36.6
Age at non-AIDS-defining cancer onset (median in years)	45.9	46.7	44.6
Race/ethnicity [*n* (%)]			
White	1111 (55.6)	860 (58.9)	251 (46.6)
Nonwhite	412 (20.6)	253 (17.3)	159 (29.5)
Unknown	477 (23.9)	348 (23.8)	129 (23.9)
Exposure to HIV [*n* (%)]			
Homosexual or bisexual contact[a]	626 (31.3)	626 (42.8)	NA
Heterosexual contact	674 (33.7)	313 (21.4)	361 (67.0)
Intravenous drug use	145 (7.3)	105 (7.2)	40 (7.4)
Other	10 (0.5)	4 (0.3)	6 (1.1)
Unknown	545 (27.3)	413 (28.3)	132 (24.5)
Period at cancer diagnosis [*n* (%)]			
1997–2001	697 (34.9)	542 (37.1)	155 (28.8)
2002–2006	647 (32.4)	430 (29.4)	217 (40.3)
2007–2012	656 (32.8)	489 (33.5)	167 (31.0)

NA, not applicable.
[a]This category applies to men only.

Table 2 Number of expected and observed cases, standardized incidence ratio and 95% confidence interval of cancers among men with AIDS, according to cancer type/site. São Paulo, 1997–2012

Cancer types/sites (ICD-10 code)	Observed	Expected[a]	SIR	95% CI
All AIDS-defining cancers	*773*	*27.86*	*27.74*	*25.85–29.77*
Kaposi sarcoma (C46)	*469*	*5.39*	*86.95*	*79.42–95.18*
Non-Hodgkin lymphoma (C82–C85; C96)	*304*	*22.47*	*13.53*	*12.09–15.14*
All non-AIDS-defining cancers[b]	*737*	*394.79*	*1.87*	*1.74–2.01*
Lip, mouth and pharynx (C00–C14)	*68*	*35.87*	*1.90*	*1.49–2.40*
Tongue (C01–C02)	14	9.13	1.53	0.91–2.59
Tonsil and oropharynx (C09–C10)	*14*	*4.73*	*2.96*	*1.75–4.99*
Nasopharynx (C11)	*6*	*1.79*	*3.34*	*1.50–7.44*
Esophagus (C15)	13	13.94	0.93	0.54–1.61
Stomach (C16)	*37*	*25.81*	*1.43*	*1.04–1.98*
Small intestine (C17)	*6*	*1.85*	*3.24*	*1.45–7.20*
Colon-rectum (C18–C20)	*59*	*36.93*	*1.60*	*1.24–2.06*
Anus and anal canal (C21)	*63*	*1.91*	*33.02*	*25.80–42.27*
Liver (C22)	*18*	*4.14*	*4.35*	*2.74–6.91*
Gall bladder and biliary tract (C23–C24)	4	1.97	2.03	0.76–5.42
Pancreas (C25)	*12*	*6.07*	*1.98*	*1.12–3.48*
Nasal cavity (C30–C31)	2	1.39	1.44	0.36–5.75
Larynx (C32)	*22*	*12.96*	*1.70*	*1.12–2.58*
Lung (C33–C34)	*54*	*24.15*	*2.24*	*1.71–2.92*
Mediastinum (C37–C38)	3	1.02	2.93	0.95–9.09
Bone (C40–C41)	2	4.40	0.46	0.11–1.82
Melanoma (C43)	6	10.42	0.58	0.26–1.28
Skin nonmelanoma (C44)[c]	*49*	*17.80*	*2.75*	*2.08–3.64*
Connective tissue (C49)	11	6.38	1.72	0.95–3.11
Breast (C50)	3	2.30	1.30	0.42–4.04
Penis (C60)	6	3.39	1.77	0.80–3.94
Prostate (C61)	49	48.88	1.00	0.76–1.33
Testis (C62)	17	15.59	1.09	0.68–1.75
Kidney (C64–C66; C68)	15	11.19	1.34	0.81–2.22
Bladder (C67)	9	12.14	0.74	0.39–1.42
Eye (C69)	*9*	*1.70*	*5.28*	*2.75–10.15*
Central nervous system (C70–C72)	*27*	*14.04*	*1.92*	*1.32–2.80*
Thyroid (C73)	*10*	*20.17*	*0.50*	*0.27–0.92*
Hodgkin lymphoma (C81)	*49*	*8.39*	*5.84*	*4.42–7.73*
Multiple myeloma (C90)	8	4.51	1.77	0.89–3.55
Leukemia (C91–C95)	*21*	*13.34*	*1.57*	*1.03–2.41*

Statistically significant results are presented in italics.
[a]Number of expected cases rounded to nearest hundredth.
[b]Including 85 cases of ill-defined primary site.
[c]Excluding basal cell carcinoma.

Table 3 Number of expected and observed cases, standardized incidence ratio and 95% confidence interval of cancers among women with AIDS, according to cancer type/site. São Paulo, 1997–2012

Cancer type/site (ICD-10 code)	Observed	Expected[a]	SIR	95% CI
All AIDS-defining cancers	*244*	*28.02*	*8.71*	*7.68–9.87*
Kaposi sarcoma (C46)	*34*	*0.22*	*156.69*	*111.96–219.29*
Cervix (C53)	*114*	*20.97*	*5.44*	*4.52–6.53*
Non-Hodgkin lymphoma (C82–C85; C96)	*96*	*6.83*	*14.06*	*11.51–17.18*
All non-AIDS-defining cancers[b]	*320*	*222.16*	*1.44*	*1.29–1.61*
Lip, mouth and pharynx (C00–C14)	*13*	*5.06*	*2.57*	*1.49–4.42*
Tongue (C01–C02)	1	1.01	0.99	0.14–7.04
Tonsil and oropharynx (C09–C10)	*5*	*0.67*	*7.51*	*3.13–18.04*
Nasopharynx (C11)	*2*	*0.35*	*5.65*	*1.41–22.60*
Esophagus (C15)	2	1.18	1.69	0.42–6.76
Stomach (C16)	*15*	*6.81*	*2.20*	*1.33–3.66*
Colon-rectum (C18–C20)	19	15.51	1.23	0.78–1.92
Anus and anal canal (C21)	*10*	*0.89*	*11.21*	*6.03–20.83*
Liver (C22)	*4*	*0.83*	*4.84*	*1.82–12.90*
Gall bladder and biliary tract (C23–C24)	*4*	*1.21*	*3.32*	*1.24–8.84*
Pancreas (C25)	2	2.11	0.95	0.24–3.78
Larynx (C32)	3	1.06	2.82	0.91–8.76
Lung (C33–C34)	*17*	*6.54*	*2.60*	*1.62–4.18*
Bone (C40–C41)	3	1.43	2.10	0.68–6.52
Melanoma (C43)	2	4.60	0.43	0.11–1.74
Skin nonmelanoma (C44)[c]	*17*	*5.53*	*3.08*	*1.91–4.95*
Connective tissue (C49)	2	2.59	0.77	0.19–3.09
Breast (C50)	72	76.20	0.94	0.75–1.19
Vulva and vagina (C51–C52)	*14*	*2.06*	*6.78*	*4.02–11.45*
Uterus (C54–C55)	*13*	*6.63*	*1.96*	*1.14–3.38*
Ovary (C56)	*16*	*8.42*	*1.90*	*1.16–3.10*
Kidney (C64–C66; C68)	3	2.55	1.18	0.38–3.65
Bladder (C67)	5	2.26	2.22	0.92–5.32
Eye (C69)	2	0.66	3.04	0.76–12.15
Central nervous system (C70–C72)	*16*	*4.60*	*3.48*	*2.13–5.68*
Thyroid (C73)	*18*	*37.50*	*0.48*	*0.30–0.76*
Adrenal and other endocrine glands (C74–C75)	2	0.58	3.45	0.86–13.78
Hodgkin lymphoma (C81)	*9*	*3.32*	*2.71*	*1.41–5.21*
Multiple myeloma (C90)	3	1.62	1.85	0.60–5.74
Leukemia (C91–C95)	5	4.40	1.14	0.47–2.73

Statistically significant results are presented in italics.
[a]Number of expected cases rounded to nearest hundredth.
[b]Including 29 cases of ill-defined primary site.
[c]Excluding basal cell carcinoma.

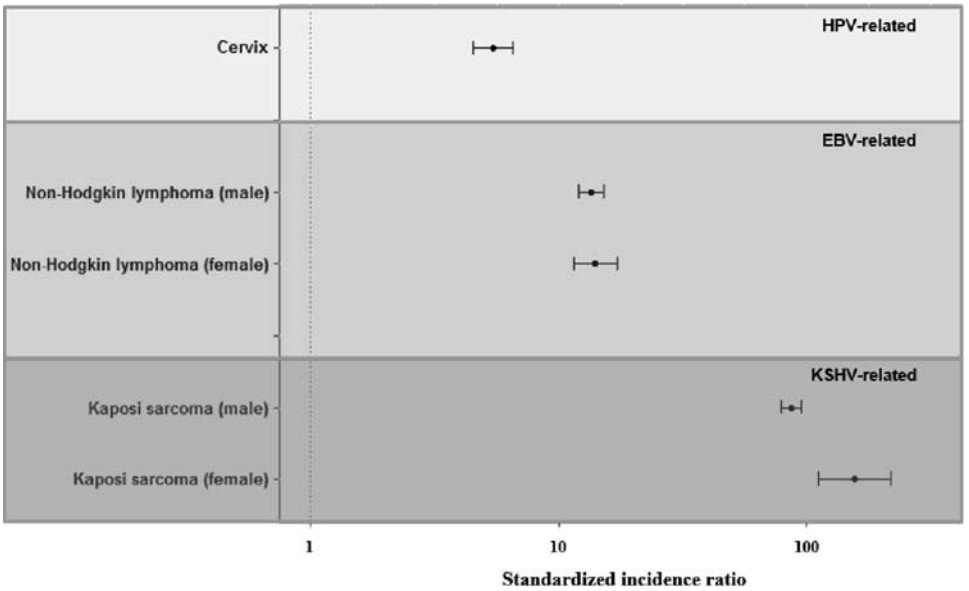
in PWA when compared with the general population (SIR = 1.87). The incidence of virus-related cancers was significantly elevated in men with AIDS, with the highest risk seen for anal cancer (SIR = 33.02), followed by Hodgkin lymphoma (SIR = 5.84). The risk for cancer in women with AIDS showed a similar pattern to that seen in men; there was a significant increase in ADC overall (SIR = 8.71), KS (SIR = 156.69), NHL (SIR = 14.06) and CC (SIR = 5.44) in particular. NADC also occurred at higher rates in female patients with AIDS (SIR = 1.44), most notably for anal cancer (SIR = 11.21), tonsil and oropharynx (SIR = 7.51), vulva and vagina (SIR = 6.78), nasopharynx (SIR = 5.65) and liver (SIR = 4.84) (Table 3 and Figs 1 and 2).

Discussion

The present study identified an increased risk for cancer among PWA in the city of São Paulo. All ADC and most virus-related NADC occurred at higher rates in this population. The manifestation of ADC occurred on average 8 years earlier than that of NADC.

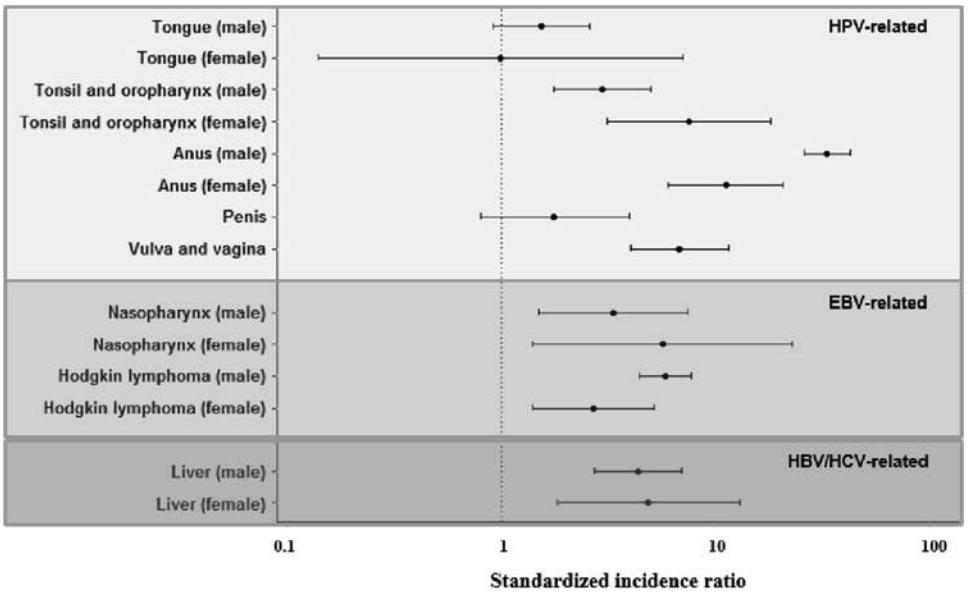
As expected, KS had the highest risk and was the most frequent cancer overall in PWA in São Paulo. In the pre-HAART era, when the incidence of KS peaked, SIR levels greatly surpassed 1000 (Dal Maso *et al.*, 2001). With the introduction of HAART, the incidence of KS among HIV-infected people dramatically decreased, but the risk remains substantially higher when compared with the general population (Engels *et al.*, 2006). In São Paulo, the risk for KS was about 100-fold, not as low as has been reported in Uganda (Mbulaiteye *et al.*, 2006), but not as high as in some European countries (Galceran *et al.*, 2007; Polesel *et al.*, 2010).

Fig. 1



Standardized incidence ratio of AIDS-defining cancers, according to possible oncogenic virus. São Paulo, 1997–2012. Standardized incidence ratio and respective confidence intervals are displayed on a log scale. EBV, Epstein–Barr virus; HPV, human papilloma virus; KSHV, Kaposi's sarcoma-associated herpesvirus.

Fig. 2



Standardized incidence ratio of virus-related non-AIDS-defining cancers, according to possible oncogenic virus. São Paulo, 1997–2012. Standardized incidence ratio and respective confidence intervals are displayed on a log scale. EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papilloma virus.

Epstein–Barr virus is significantly more frequently involved in the oncogenesis of NHL, Hodgkin lymphoma and nasopharyngeal carcinoma. In the present study, all these cancers were found to affect PWA, as seen in previous studies (Shiels *et al.*, 2009). Rates of NHL among PWA in São Paulo were ~13-fold that in the general population, considerably lower than that reported in the USA and Europe (Galceran *et al.*, 2007; Polesel *et al.*, 2010).

Currently, there are consistent data attributing excess cancer cases among HIV-infected people to oncogenic viruses such as human papilloma virus (HPV), Epstein–Barr virus, hepatitis B virus (HBV) and hepatitis C virus (HCV) (Calabresi *et al.*, 2013; de Martel *et al.*, 2015).

The infection with oncogenic HPV strains is associated with the development of cancers of the cervix, anus, vulva, vagina, penis, tongue, tonsil and oropharynx. Association with tobacco smoking, in many cases, further increases the risk for cancer (Cogliano *et al.*, 2005). With the exception of cancers of the tongue and penis, all cancer sites associated with HPV infection occurred at increased rates among PWA.

In the present study, anal cancer presented the highest risk among NADCs in both sexes. Apart from a study conducted in Uganda, which did not find an increased risk for anal cancer among PWA, studies have found SIRs ranging from 18 to 75 (Shiels *et al.*, 2009). It is estimated that HPV-infection accounts for as many as 93% of all anal squamous cell cancers (Gillison *et al.*, 2008). In Brazil, among men who have sex with men with HIV/AIDS, the prevalence of coinfection was found to be 40.7% (Guimaraes *et al.*, 2011). In the present study, most but not all men with AIDS who had this malignancy reported being men who have sex with men. Women with AIDS are also more likely to be affected by high-risk HPV anal infection compared with HIV-uninfected women. In a cohort of 863 HIV-infected women in Rio de Janeiro, 51% had anal infection with high-risk carcinogenic HPV and 31% had abnormal anal cytology (Cambou *et al.*, 2015).

Cervical cancer and cancers of the vulva, vagina and uterus were more frequent among women with AIDS. Although uterus presented a higher risk in women with AIDS, it is possible that a part of these cases could have been misclassified and were actually CC, especially cases of advanced disease (Loos *et al.*, 2004). CC, vulvar and vaginal cancers are all HPV-associated and high-risk HPV types are frequently found in the anogenital area of HIV-infected women (Castilho *et al.*, 2015). São Paulo has a CC screening program based on Pap smear for women aged 25–64 years, whose coverage surpasses 90% (CEInfo – Coordenação de Epidemiologia e Informação, 2010). Among HIV-infected women, current national guidelines recommend annual Pap smear screening, regardless of age. Although there is no information on screening uptake in this population, in the present study, about 40% of women were diagnosed with CC 1 year or later after AIDS diagnosis, suggesting that adjustments to current practice may be needed (Franceschi and Jaffe, 2007).

Among PWA, the overall risk for head and neck malignancies was elevated, particularly for tonsillar and oropharyngeal cancers, two HPV-related cancer sites. Oral infection with HPV, although not as frequent as in the anogenital area, seems to be higher among HIV-infected people than in uninfected individuals (Matos *et al.*, 2015). The recent introduction of the HPV vaccine for young girls and boys (9–13 years) and for HIV-infected patients (9–26 years) will likely contribute to a future reduction in the burden of HPV-related cancers in these cohorts, but not in older patients.

The incidence of liver cancer among PWA was approximately four-fold higher than that in the general population, in accordance with previous research (Shiels *et al.*, 2009). In São Paulo, viral hepatitis accounted for ~6% of all deaths among PWA (Domingues and Waldman, 2014). Since 1998 the city offers HBV vaccination free of charge; nevertheless, its coverage in adults (15–64 years-old) was only 15.3% in 2014 (SMS-SP – Secretaria Municipal de Saúde de São Paulo, 2014). In 2015, daclatasvir, sofosbuvir and simeprevir were added as options to treat HCV and could raise rates of cure to over 90% (MS – Ministério da Saúde. Secretaria de Vigilância em Saúde, 2015). The vaccination against HBV and the treatment for HCV will likely contribute to a future reduction in the incidence of hepatitis-associated liver cancer in this population.

Concerning gastric cancer, existing data are conflicting (Shiels *et al.*, 2009). In São Paulo, an excess of cases was found among PWA. Infection with *Helicobacter pylori* is a known risk factor for noncardia gastric cancer (EUROGAST Study Group, 1993), but coinfection among HIV-infected people seems to be low (Fialho *et al.*, 2011). Therefore, other exposures such as smoking and alcohol consumption could have contributed to this risk pattern.

Several studies have already described increased rates of lung cancer among HIV-infected people, as seen in this study. Some pieces of evidence indicate that the excess risk for lung cancer in this population is mainly due to increased smoking, rather than HIV-associated immunosuppression or pulmonary disease (Clifford *et al.*, 2012).

In line with the results from a study conducted in Uganda (Mbulaiteye *et al.*, 2006), the risk for eye cancer was increased in men with AIDS. Exposure to sunlight is a known risk factor for this malignancy. In São Paulo, the ultraviolet irradiation is frequently high even during winter and can reach extreme levels in the summer (de Paula Correa and Ceballos, 2010). In addition to sunlight, there is growing evidence that HPV is also involved in the oncogenesis of eye cancer (Carreira *et al.*, 2013).

Moreover, in accordance with previous studies, PWA developed nonmelanoma skin cancer at higher rates (Shiels *et al.*, 2009). Exposure to sunlight and skin phototype are known risk factors for these malignancies. Among HIV-infected people, immune suppression seems to be associated with the occurrence of squamous cell carcinoma, and recent research suggests that HPV

might also contribute to its oncogenesis (Silverberg *et al.*, 2013).

Although elevated rates of brain tumors have been identified in both sexes, results should be interpreted with caution, because only 23.3% of cases were microscopically confirmed. Cases of primary central nervous system lymphomas or other HIV-related malignancies could have been misclassified as brain tumors, resulting in inflated SIRs.

A causal hypothesis could not be developed for the increased rates of certain cancers, such as small intestine, colon-rectum and gall bladder among PWA. These significant findings were restricted to sex and were not consistent with previous studies (Shiels *et al.*, 2009). These correlations have to be reconfirmed through future studies, and potentially explanatory models need to be investigated.

The estimated SIR of several cancer sites, such as breast, prostate, bladder and esophagus did not differ from 1 : 1, in agreement with other investigations (Shiels *et al.*, 2009).

This study has limitations inherent to its design. As an ecological study, this study has low analytical capacity, being essentially descriptive. The record linkage itself could be a source of error if it fails in identifying some patients with both AIDS and cancer, resulting in underestimation of SIR. To keep this error minimal, a multistep process and clerical review were used in each step. These strategies have already been proven effective when linking the PBCR-SP and the mortality system to complete patients' follow-up, as a part of the registry's routine (Peres *et al.*, 2014). As the AIDS database was conceived primarily for administrative purposes, detailed information on patients' clinical conditions were not available. The analyses were restricted to PWA and did not include HIV-only patients.

This study also has strengths. It is one of the first population-based studies in South America assessing the risk of cancer among PWA. As the largest city in Brazil, São Paulo accounts for more cases of AIDS compared with any other city (12.6% of all cases) in the country. Almost 500 000 PY were included in the analysis, and the number of cancer cases allowed for stratification by sex. Although the catchment area of this study has been restricted to São Paulo, it is possible that similar patterns could be identified in other capitals or large cities in Brazil with comparable population profiles. These results provide useful information to local health authorities that can be used to plan and adapt current health policies, such as early detection and routine vaccination aimed at HIV-infected people.

The present study revealed a similar pattern for the risk for cancer among PWA as has been described in other countries (Shiels *et al.*, 2009). As coinfection with oncogenic viruses disproportionally affects these individuals, virus-related NADC accounted for an important share of excessive cases. Modifiable risk factors, such as tobacco smoking and alcohol consumption, might have also contributed to this scenario. A fraction of these cases could have been prevented if exposure to these risk factors were reduced.

Since 2013, the Brazilian Ministry of Health recommends the initiation of HAART immediately after diagnosis, regardless of CD4 count (MS – Ministério da Saúde. Secretaria de Vigilância em Saúde, 2013). Early initiation of HAART could also contribute to reduce cancer risk among HIV-infected people, in particular those associated with known viruses. However, the success of this strategy depends on the ability of the health system to diagnose HIV-infected patients in time.

Primary prevention, including strategies to encourage smoking cessation and reduce alcohol consumption, vaccination against potentially oncogenic viruses such as HPV and HBV, and effective treatment of chronic infections including HAART, are important tools in the management of cancer among HIV-infected people. Early cancer detection through screening and timely treatment could further contribute to reduced morbidity and mortality in this population. Although the current Brazilian guidelines for the management of HIV address some of these issues, cancer will remain a major concern with the growth and ageing of the HIV-infected population.

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Conflicts of interest

There are no conflicts of interest.

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8. Conclusion

In this session, the main conclusions of the study are presented according to the objectives stated in Session 2 (Rationale and Objectives).

8.1. There was a significant declining trend in the incidence of AIDS-defining cancers in men and women. However, an upward trend in non-AIDS-defining cancers starting in the mid 2000´s has been identified in men with AIDS, driven by lung and anal cancers.

8.2. The overall risk of cancer was significantly higher in people with AIDS when compared to the general population. Most virus-related cancers occurred at significantly higher rates in this population.

8.3. The five-year overall survival after cancer diagnosis was significantly lower in people with AIDS than that of matched controls from the general population.

9. Annex

Manuscript 3 - Cancer survival in people with AIDS: a population-based study from São Paulo, Brazil

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Cancer survival in people with AIDS: A population-based study from São Paulo, Brazil

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Cancer Epidemiology

Cancer survival among people with AIDS (PWA) has been described in developed countries, but there is lack of data from developing countries. The aim of this study was to evaluate survival after cancer diagnosis in PWA and compare it with people without AIDS (non-PWA) in São Paulo, Brazil. A probabilistic record linkage was carried out between the databases of the Population-based Cancer Registry of São Paulo (PBCR-SP) and the AIDS registry of SP (SINAN) to identify PWA who developed cancer. For comparison, non-PWA were frequency matched from the PBCR-SP by cancer site/type, sex, age, and period. Hazard ratio (HR) stratified by matching variables was estimated using a Cox proportional hazards model. A total of 1,294 PWA (20 patients with two primary site tumors) were included in the site/type-specific analyses. AIDS-defining cancers (ADC) comprised 51.9% of cases assessed. The all-cancer 5-year overall survival in PWA was 49.4% versus 72.7% in non-PWA (HR = 2.64; 95%CI = 2.39–2.91). Survival was impaired in PWA for both ADC (HR = 2.93; 95%CI = 2.49–3.45) and non-ADC (HR = 2.51; 95%CI = 2.21–2.84), including bladder (HR = 8.11; 95% CI = 2.09–31.52), lung (HR = 2.93; 95%CI = 1.97–4.36) and anal cancer (HR = 2.53; 95%CI = 1.63–3.94). These disparities were seen mainly in the first year after cancer diagnosis. The overall survival was significantly lower in PWA in comparison with non-PWA in São Paulo, as seen in high-income countries. Efforts to enhance early diagnosis and ensure proper cancer treatment in PWA should be emphasized.

Introduction

The introduction of the highly active antiretroviral therapy (HAART) has greatly improved life expectancy among HIV-infected individuals, turning the infection into a chronic condition and consequently enlarging the HIV-infected population.[1,2]

Key words: HIV/AIDS, medical record linkage, epidemiology, survival, cancer

Abbreviations: ADC: AIDS-defining cancer; CC: cervical cancer; CI: confidence interval; DCO: death certificate only; HAART: highly active antiretroviral therapy; HL: Hodgkin lymphoma; HR: hazard ratio; KS: Kaposi sarcoma; NADC: non-AIDS-defining cancer; NHL: non-Hodgkin lymphoma; NMSC: non-melanoma skin cancers; PBCR-SP: Population-Based Cancer Registry of São Paulo; PWA: people with AIDS

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People with AIDS (PWA) are at increased risk for several types of cancers, both AIDS-defining (ADC), such as Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and cervical cancer (CC) and non-AIDS-defining (NADC) such as lung, anal and Hodgkin lymphoma (HL).[3–6] Impaired immune response, co-infections with potentially oncogenic viruses, such as the human papilloma virus, hepatitis B and C viruses and higher frequency of exposure to tobacco smoking are some of the known factors associated with an increased risk for cancer.[5]

Increasing trends in cancer-related mortality in PWA have been reported in Brazil[7] and other countries.[8] In the city of São Paulo (Brazil), the proportion of cancer-related deaths in PWA has increased from 6.2% in the pre-HAART era (1991–1996) to 10.1% in the late post-HAART era (2000–2006) and is likely to reach even higher proportions as this population is living longer and reaching older ages.[8,9] Nevertheless, survival after cancer diagnosis at a population level has been less explored, especially in low- and middle-income countries.[10,11] São Paulo is the largest city in South America and one of the largest worldwide, home to over 12 million inhabitants.[12] Brazil was the first developing country to provide universal

What's new?

While increasing trends in cancer-related mortality in people with AIDS have been widely reported, survival after cancer diagnosis remains less explored. This is the first population-based study in Brazil and one of the few conducted in developing countries assessing cancer survival in people with AIDS. The large sample size allowed stratification by cancer type/site and analysis of 22 non-AIDS-defining cancers. The results revealed an impaired 5-year overall survival after cancer diagnosis in people with AIDS in comparison to the general population, suggesting that national guidelines for the prevention, early diagnosis and management of cancer among HIV-infected people may be beneficial.

treatment when HAART became available in 1996 and has developed over the years an internationally recognized AIDS program.[13] In 2013, the country expanded HAART to all HIV-infected people regardless of CD4 count. These unique features make São Paulo a place of interest to study AIDS-related malignancies in this particular population.[14]

The existence of a population-based cancer registry in São Paulo and the mandatory notification of AIDS since the first years of the epidemic enable the conduction of a population-based study. Its objective was to describe the 5-year overall survival after cancer diagnosis in PWA and compared this to that of selected controls from the general population in São Paulo.

Methods

A probabilistic record linkage was conducted to identify patients with AIDS who were diagnosed with cancer. To summarize briefly this procedure, the database of the "Population-based Cancer Registry of São Paulo" (PBCR-SP) which contains 628,161 cancer cases diagnosed from 1997 to 2012 was linked to the *Sistema de Informação de Agravos de Notificação*/Information System on Disease Notification database (SINAN) which comprises 87,109 records of people diagnosed with AIDS from 1980 through 2013. Both databases have high coverage and comprehend the same geographical area, namely the city of São Paulo.[15,16] Therefore, our study is restricted to São Paulo residents only.

In the linkage process, the records were compared based on patient's full name and date of birth using the open source software OpenRecLink (version 2.9). A multi-step procedure was employed and clerical review of matches, based on mother's name and address, was carried out to improve both sensitivity and specificity. After true matches had been identified all personal identifiers were removed from the database to ensure data privacy.

Exclusion criteria were the following: *in situ* cancers, cancers reported by death certificate only (DCO), cancers diagnosed before AIDS and cancers diagnosed from 2010 onwards leading to incomplete follow up (considering 31st December, 2014 as the end of the observation period), patients aged 75 years and older and patients with two primary non-melanoma skin cancers (NMSC), in that case only the earliest tumor was considered.

Selection of subjects

The record linkage procedure identified 2,571 cancers in PWA. However, 1,257 cases were excluded from the survival analyses as follows: 238 *in situ* cancers; 281 cancers reported by DCO, 394 cancers diagnosed before AIDS; 323 cancers diagnosed from 2010 onwards; 15 patients aged 75 years and older and six patients with two primary NMSC.

To compare survival probabilities between PWA and people from the general population without AIDS (non-PWA), a control group has been randomly selected following the approach described in a previous study.[11] Our study considered as non-PWA all subjects who could not be matched during the record linkage procedure. A random matching in a 4:1 (non-PWA:PWA) ratio was conducted for all cancer types/sites, with the exception of non-Hodgkin lymphoma (2:1), due to the insufficient cases in the general population. Matching by cancer site, histology (third revision of the International Classification of Diseases for Oncology, ICD-O-3), age Group (10-year age bands), sex and period at cancer diagnosis (1997–2000, 2001–2004 and 2005–2009) was prioritized, and when not possible fewer matching variables were used until the matching procedure was possible. In the case of KS, all matching attempts had failed because KS in non-PWA is a rare condition in São Paulo; hence, a 1:1 ratio for controls was used, respecting the same age range (15–74 years).

Patients with two primary tumors were included only once in the combined analyses (all-cancer, all-ADC and all-NADC). In this case, the first tumor or the one with the poorest prognosis was considered.

Statistical methods

The PBCR-SP conducts routine record linkage with the official mortality database of São Paulo, ensuring updated vital status of cancer patients. For PWA, information on death was also available in the AIDS data set.

Patients included in the analyses were followed up for 5 years, until the outcome of interest (death from any cause) was observed or the end of the observation period was reached (31st December, 2014), whichever occurred earlier. For those patients who survived beyond this threshold, time was right-censored.

Kaplan–Meier survival curves were estimated. To compare the risk for death according to AIDS status (PWA *vs.* non-PWA), the estimated hazard ratios (HR) and the respective 95% confidence intervals (95%CI) were calculated by means of the Cox proportional hazards model, stratified by

Table 1. Characteristics of people with AIDS and cancer and of controls from the general population. São Paulo, 1997–2009

	People with AIDS						People without AIDS[1]	
	Total		ADC		NADC			
	N	%	*N*	%	*N*	%	*N*	%
Sex								
Male	951	73.5	517	77.0	434	69.7	1,988	61.3
Female	343	26.5	154	23.0	189	30.3	1,252	34.2
Age at cancer diagnosis (years)								
15–19	4	0.3	3	0.5	1	0.2	8	0.2
20–29	157	12.1	119	17.7	38	6.1	243	7.5
30–39	441	34.1	286	42.6	155	24.9	959	29.6
40–49	383	29.6	172	25.6	211	33.9	1,052	32.5
50–59	221	17.1	75	11.2	146	23.4	666	20.6
60–69	73	5.6	14	2.1	59	9.5	256	7.9
70–74	15	1.2	2	0.3	13	2.1	56	1.7
Age at AIDS diagnosis (years)								
15–19	12	0.9	9	1.3	3	0.5	–	–
20–29	239	18.5	157	23.4	82	13.2	–	–
30–39	494	38.2	279	41.6	215	34.5	–	–
40–49	335	25.9	152	22.7	183	29.4	–	–
50–59	165	12.8	64	9.5	101	16.2	–	–
60–69	46	3.6	9	1.3	37	5.9	–	–
70–74	3	0.2	1	0.2	2	0.3	–	–
Exposure to HIV								
Homosexual men	306	23.7	198	29.5	108	17.3	–	–
Bisexual men	140	10.8	74	11.0	66	10.6	–	–
Heterosexual	432	33.4	198	29.5	234	37.6	–	–
Intravenous drug use	113	8.7	43	6.4	70	11.2	–	–
Other	5	0.4	4	0.6	1	0.2	–	–
Unknown	298	23.0	154	23.0	144	23.1	–	–
Year of cancer diagnosis								
1997–2000	443	34.2	302	45.0	141	22.6	937	28.9
2001–2004	351	27.1	182	27.1	169	27.1	918	28.3
2005–2009	500	38.6	187	27.9	313	50.2	1,385	42.8
Period of AIDS diagnosis								
Pre-HAART (before 1996)	217	16.8	92	13.7	125	20.1	–	–
HAART (1996 onwards)	1,077	83.2	579	86.3	498	79.9	–	–
Total	1,294	100	671	100	623	100	3,240	100

[1]Excluding cases of Kaposi sarcoma for which no matching strategy was employed.
Sources: Population-based Cancer Registry of São Paulo and *Sistema de Informação de Agravos de Notificação* (SINAN).

matching variables and adjusted for age (in years). These estimates were provided according to cancer type/site. Cancers were also grouped into AIDS-defining (KS, NHL and CC) and non-AIDS-defining (all other). To describe early and late risk, as presented by other studies, the HRs for 1- and 5-year survival (conditional on surviving the first year) were estimated.[11,17] In addition, the survival analyses were also stratified by sex and age group (<40 years *vs.* ≥40 years), separately to allow for comparison to a previous study.[11] The proportional hazard assumption was graphically assessed based on plots of the log(-log(survival probability)) *vs.* log (time) and all models met this criterion. This graph shows

Table 2. Hazard ratio of death and corresponding 95% confidence intervals at 5-years after cancer diagnosis by cancer type. São Paulo, 1997–2009

	People with AIDS			People without AIDS			
Cancer type/site	Cases	Deaths	Survival (%)	Cases	Deaths	Survival (%)	HR (95% CI)[1,2]
All[3]	1,294	655	49.4	3,610	986	72.7	2.64 (2.39–2.91)
ADC[3]	671	333	50.4	1,118	257	77.0	2.93 (2.49–3.45)
KS	373	162	56.6	373	46	87.7	3.66 (2.59–5.19)
NHL	228	146	36.0	456	142	68.9	3.02 (2.43–3.76)
CC	73	28	61.6	292	70	76.0	2.02 (1.34–3.04)
NADC[3]	623	322	48.3	2,492	729	70.7	2.51 (2.21–2.84)
Head and neck	63	44	30.2	252	114	54.8	1.78 (1.28–2.48)
Esophagus	6	3	50.0	24	16	33.3	0.57 (0.11–2.89)
Stomach	26	19	26.9	104	52	50.0	1.90 (1.16–3.14)
Colon-rectum	32	22	31.3	128	44	65.6	3.46 (1.99–5.99)
Anus	43	23	46.5	172	48	72.1	2.53 (1.63–3.94)
Liver	9	8	11.1	36	22	38.9	3.43 (1.40–8.39)
Gallbladder	6	4	33.3	24	16	33.3	0.74 (0.28–1.93)
Lung	38	34	10.5	152	99	34.9	2.93 (1.97–4.36)
NMSC	126	37	70.6	504	33	93.5	5.39 (3.53–8.22)
Breast	40	15	62.5	160	31	80.6	2.72 (1.53–4.83)
Vulva and vagina	9	2	77.8	36	5	86.1	1.94 (0.50-7.51)
Ovary	6	2	66.7	24	6	75.0	1.23 (0.19–7.88)
Prostate	23	9	60.9	92	14	84.8	6.07 (2.39–15.45)
Testis	9	4	55.6	36	4	88.9	3.45 (0.96–12.32)
Kidney	9	6	33.3	36	12	66.7	5.14 (1.63–16.24)
Bladder	9	6	33.3	36	5	86.1	8.11 (2.09–31.52)
Eye	7	1	85.7	28	1	96.4	4.93 (0.49–49.64)
CNS	17	14	17.6	68	48	29.4	3.08 (1.64–5.80)
Thyroid	15	2	86.7	60	2	96.7	3.79 (0.60–24.01)
HL	36	17	52.8	144	30	79.2	2.75 (1.61–4.69)
Multiple myeloma	7	4	42.9	28	8	71.4	4.05 (1.27–12.89)
Leukemia	14	12	14.3	56	33	41.1	2.90 (1.52–5.54)
Other	90	41	54.4	360	99	72.5	1.77 (1.29–2.44)

[1]HR stratified by matching variables and adjusted for age (in years) at cancer diagnosis.
[2]Matched by cancer type (1:1 for KS, 1:2 for NHL, 1:4 for other cancers), sex, age and period of diagnosis.
[3]People with two primary site cancers were included only once in the analysis.
Sources: Population-based Cancer Registry of São Paulo and *Sistema de Informação de Agravos de Notificação* (SINAN).

the hazards over time and when curves are parallel, the assumption of proportionally is not violated.[18]

The statistical analyses were carried out in Stata (version 13) using anonymized records. This research is part of the "São Paulo AIDS-Cancer Linkage Study" and obtained ethical clearance from all institutions concerned: the School of Public Health (686.849), Municipal Health Secretariat of São Paulo (703.467) and the University of Munich (233–15).

Results

A total of 1,294 PWA were included in the cancer type/site-specific survival analysis, of which 20 (1.5%) PWA had two primary site tumors. These 20 PWA were considered only once in the all-cancer and respective all-ADC and all-NADC analyses.

The descriptive analysis was based on 1,294 patients (Table 1). The majority of PWA were male (951; 73.5%) and aged 30–49 years at cancer diagnosis (824; 63.7%). Sexual contact was the main mode of exposure to HIV (878; 67.9%). There was a slight predominance of ADC in relation to NADC in the period as a whole, but the ADC:NADC ratio shifted from 2.1:1 (1997–2000) to 0.6:1 (2005–2009), highlighting that NADC are already more frequent than ADC among PWA in São Paulo. Over 40% of ADC were

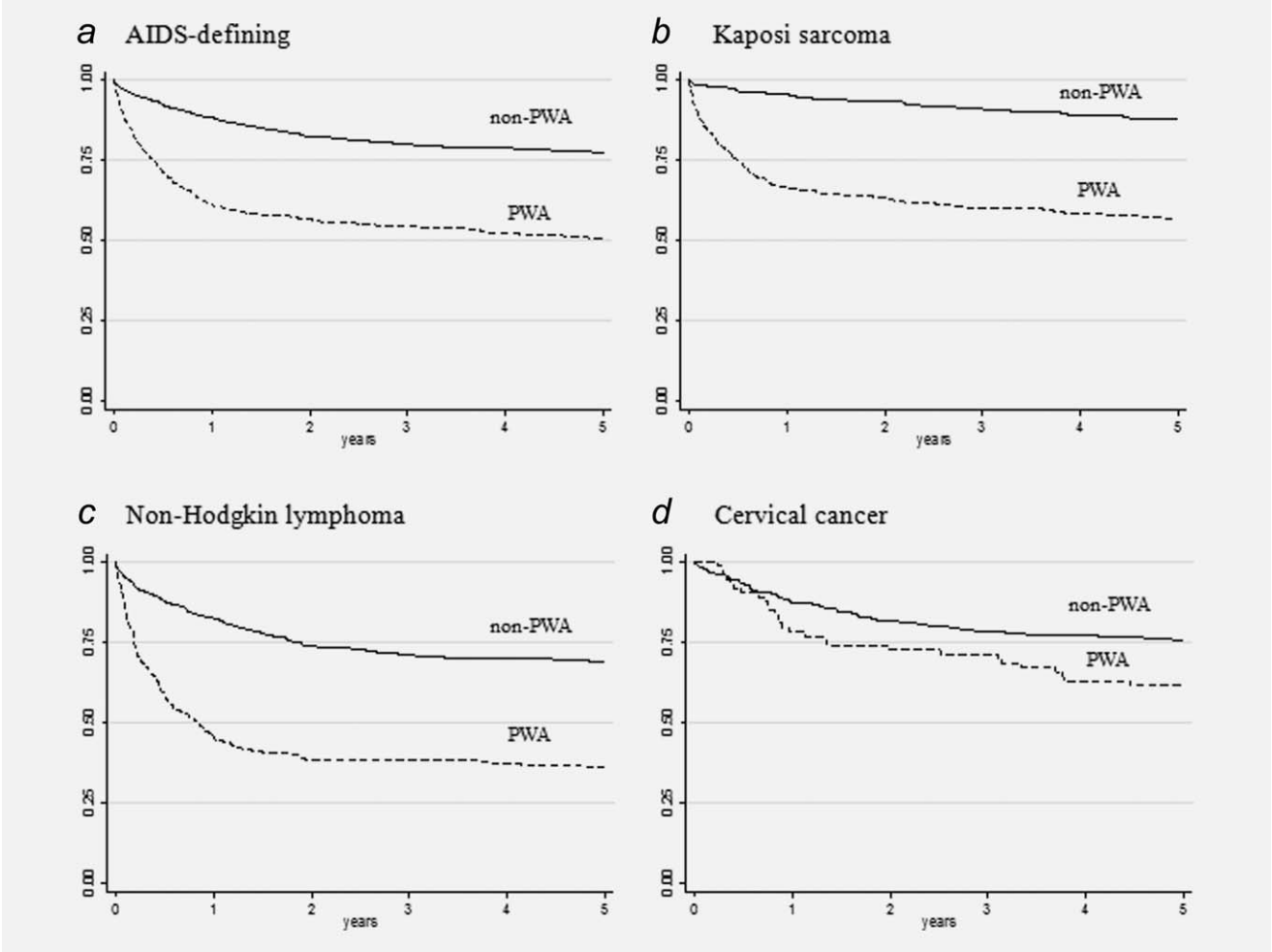

Figure 1. Five-year overall survival after diagnosis of AIDS-defining cancers by AIDS status. São Paulo, 1997–2009.
Note: Matched by cancer type (1:1 for KS, 1:2 for NHL, 1:4 for cervical cancer), sex, age and period of diagnosis.

diagnosed between 1997 and 2000, whereas, half of NADC in the 2005–2009 period. Concerning the period of AIDS diagnosis, most patients (1,077; 83.2%) had been diagnosed in the post-HAART period.

Among ADC cases, 373 were KS (28.4%). As for NADC, the most frequent cancer was NMSC, including basal cell carcinoma (126; 9.6%), followed by head and neck (63; 4.8%). All type/site-specific percentages were calculated based on 1,314 records.

The all-cancer 5-year overall survival among PWA was 49.4% (*vs.* 72.7% in matched non-PWA) and the death HR (PWA *vs.* non-PWA) was 2.64 (95%CI = 2.39–2.91). The death HRs were further 2.93 for ADC (95%CI = 2.49–3.45) and 2.51 (95%CI = 2.21–2.84) for NADC. The type/site-specific analyses revealed that for the majority of malignancies assessed, PWA died more frequently. The highest HRs were found for cancers of the bladder (HR = 8.11; 95%CI = 2.09–31.52), prostate (HR = 6.07; 95%CI = 2.39–15.45) and NMSC (HR = 5.39; 95%CI = 3.53–8.22). Survival did not differ according to AIDS status for cancers of the esophagus, ovary and thyroid (Table 2).

In PWA, the poorest survival was observed for lung cancer (10.5%), followed by liver cancer (11.1%) and leukemia (14.3%). Conversely, the highest survival probabilities were seen for cancers of the thyroid (86.7%), eye (85.7%), vulva and vagina (77.8%) and NMSC (70.6%). The survival curves for ADC and selected NADC can be found in Figures 1 and 2, respectively.

The results of the 1- and 5-year survival (conditional on surviving the first year) analyses after cancer diagnosis are shown in Table 3. For lung cancer (HR = 3.20; 95%CI = 2.10–4.89), leukemia (HR = 4.00; 95%CI = 2.04–7.83) NHL (HR = 3.73; 95%CI = 2.90–4.80), among others, the survival gap was restricted to the first year after diagnosis. However, for anal, breast and prostate cancers, risk differences emerged after the first year of diagnosis. For head and neck cancer, NMSC and CC survival disparities could be observed throughout the entire period.

In the stratified analyses by age group and sex no differences were found when comparing groups. Although not statistically significant, the HRs for most cancers assessed tended to be higher in younger (<40 years) than in older patients (≥40 years) (Table 4).

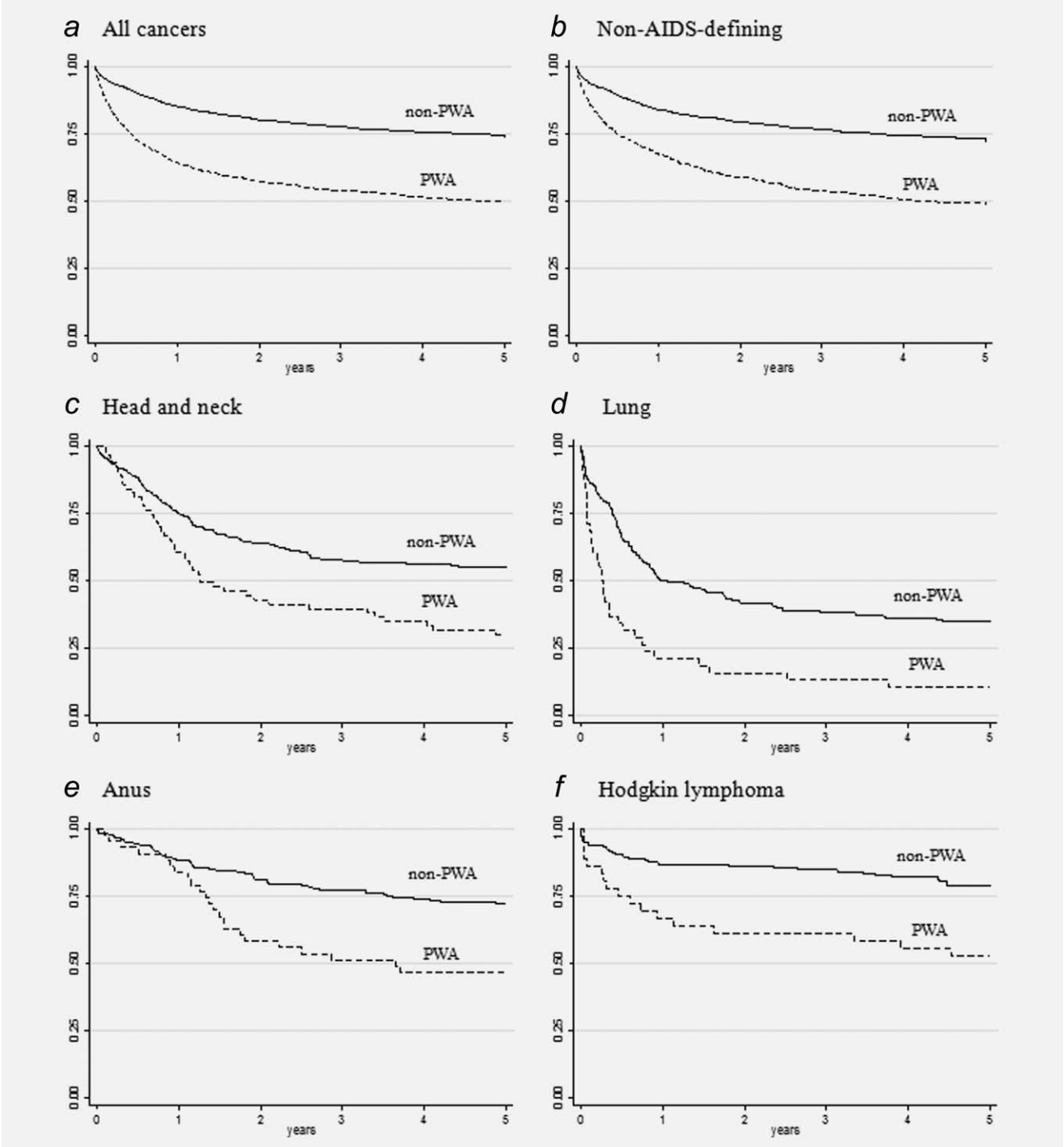

Figure 2. Five-year overall survival after diagnosis of selected non-AIDS-defining cancers by AIDS status. São Paulo, 1997–2009. *Note*: Matched by cancer type (1:1 for KS, 1:2 for NHL, 1:4 for other cancers), sex, age and period of diagnosis.

Discussion

The aim of our study was to compare survival after cancer in PWA and non-PWA. The results revealed that in São Paulo all-cancer 5-year overall survival was significantly lower in PWA than in non-PWA with the same cancer type/site, sex and age (49.4% *vs*. 72.7%), as reported in previous studies using population-based data.[10,11]

Despite ADC being somewhat more frequent in the period as a whole, NADC had already become more incident in 2005–2009, reflecting the changing AIDS epidemic since the advent of HAART, a well-documented phenomenon in high-income countries.[19] Studies which compared cancer survival before and after HAART revealed that the gap between HIV-infected and their uninfected counterparts narrowed, but still

Table 3. Hazard ratio of death and corresponding 95% confidence intervals at 1 and 5 years (conditional on surviving the first year) after cancer diagnosis by cancer type. São Paulo, 1997–2009

	1-Year survival			5-Year survival (conditional on surviving the 1st year)		
Cancer type/site	Cases	Deaths	HR (95% CI)[1]	Cases	Deaths	HR (95% CI)[1,2]
All[3]	1,294	464	2.90 (2.58–3.26)	830	191	2.18 (1.82–2.60)
ADC[3]	671	261	3.77 (3.09–4.60)	410	72	1.66 (1.21–2.27)
KS	373	124	6.67 (3.88–11.47)	249	38	1.73 (1.02–2.96)
NHL	228	124	3.73 (2.90–4.80)	104	22	1.33 (0.83–2.13)
CC	73	16	1.92 (1.16–3.16)	57	12	2.24 (1.18–4.24)
NADC[3]	623	203	2.49 (2.14–2.90)	420	119	2.53 (2.05–3.13)
Head and neck	63	25	1.79 (1.20–2.67)	38	19	1.74 (1.04–2.92)
Esophagus	6	1	0.31 (0.02–3.80)	5	2	*
Stomach	26	16	1.99 (1.17–3.38)	10	3	1.61 (0.51–5.04)
Colon-rectum	32	16	4.62 (2.20–9.71)	16	6	2.01 (0.81–4.97)
Anus	43	7	1.43 (0.66–3.09)	36	16	4.04 (2.18–7.49)
Liver	9	6	3.89 (1.23–12.23)	3	2	3.46 (0.32–37.81)
Gallbladder	6	3	0.77 (0.25–2.35)	3	1	*
Lung	38	30	3.20 (2.10–4.89)	8	4	1.47 (0.51–4.22)
NMSC	126	14	11.57 (4.84–27.65)	112	23	4.18 (2.55–6.84)
Breast	40	4	2.73 (0.93–7.98)	36	11	2.87 (1.40–5.90)
Vulva and vagina	9	1	2.35 (0.25–22.03)	8	1	1.57 (0.31–8.08)
Ovary	6	2	3.05 (0.57–16.37)	4	–	*
Prostate	23	3	5.32 (0.81–35.17)	20	6	6.39 (2.24–18.22)
Testis	9	3	3.66 (0.85–15.82)	6	1	2.42 (0.38–15.46)
Kidney	9	2	1.75 (0.31–9.83)	7	4	24.14 (2.48–234.61)
Bladder	9	4	15.18 (1.36–169.47)	5	2	4.21 (0.88–20.17)
Eye	7	1	4.93 (0.49–49.64)	6	–	*
CNS	17	11	3.67 (1.84–7.29)	6	3	1.96 (0.64–5.98)
Thyroid	15	1	*	14	1	1.83 (0.15–23.12)
HL	36	12	3.00 (1.55–5.81)	24	5	2.40 (0.87–6.64)
Multiple myeloma	7	4	4.12 (1.26–13.46)	3	–	*
Leukemia	14	11	4.00 (2.04–7.83)	3	1	0.63 (0.08–4.87)
Other	90	28	1.71 (1.16–2.51)	62	13	1.92 (1.06–3.48)

[1]HR stratified by matching variables and adjusted for age (in years) at cancer diagnosis.
[2]Matched by cancer type (1:1 for KS, 1:2 for NHL, 1:4 for other cancers), sex, age and period of diagnosis.
[3]People with two primary site cancers were included only once in the analysis.
*HR not available due to insufficient number of events among cases or controls.
Sources: Population-based Cancer Registry of São Paulo and *Sistema de Informação de Agravos de Notificação* (SINAN).

remained significant for most cancers, as seen in São Paulo.[10,11]

In the type/site-specific analyses, the probability of survival was impaired in PWA for all ADC and most NADC, in accordance with previous findings using a similar approach.[11] The lowest survival probabilities were found for cancers of the lung, liver and central nervous system (CNS), malignancies with generally poor prognosis. Survival after lung cancer has been described earlier.[10,11,20–24] While some studies reported comparable survival rates between the two populations[10,20,21] our study identified poorer outcomes among PWA.[11,22–24] These discrepancies may arise from the diversity of strategies used for the selection of controls and also the HR adjustments. Unlike other studies,[10,11,24] in São Paulo, PWA had greater risk of death of anal cancer (HR = 2.53), but this gap appeared only after the first year of diagnosis.

In contrast to non-PWA, survival for leukemia ranked among the least favorable in PWA (14.3%). In a study conducted in Italy, all six patients with leukemia had already died by the end of the first year of follow up, the poorest

Table 4. Hazard ratio of death and corresponding 95% confidence intervals at 5 years, by cancer type, sex and age group. São Paulo, 1997–2009

	Sex				Age group			
	Men		Women		<40 years		≥40 years	
Cancer type/site	*n*	HR (95% CI)[1,2]	*n*	HR (95% CI)[1,2]	*n*	HR (95% CI)[1,2]	*n*	HR (95% CI)[1,2]
All[3]	951	2.60 (2.31–2.92)	343	2.66 (2.22–3.20)	602	3.19 (2.71–3.76)	692	2.41 (2.13–2.73)
ADC[3]	517	3.30 (2.69–4.06)	154	2.23 (1.68–2.95)	408	3.02 (2.42–3.76)	263	2.89 (2.26–3.71)
KS	346	4.07 (2.78–5.97)	27	1.44 (0.56–3.69)	241	4.07 (2.38–6.96)	132	3.52 (2.16–5.75)
NHL	174	2.88 (2.27–3.67)	54	3.63 (2.17–6.08)	121	3.17 (2.34–4.30)	107	2.99 (2.16–4.14)
CC	NA	NA	73	1.96 (1.18–3.26)	48	2.20 (1.09–4.42)	25	2.19 (1.09–4.42)
NADC[3]	434	2.3 (1.99–2.68)	189	3.02 (2.37–3.84)	194	3.41 (2.68–4.33)	429	2.28 (1.97–2.64)
Head and neck	56	1.56 (1.11–2.20)	7	10.72 (2.66–43.96)	13	2.28 (0.99–5.27)	50	1.65 (1.16–2.36)
Stomach	14	1.53 (0.79–2.97)	12	2.76 (1.31–5.79)	9	1.95 (0.85–4.49)	17	1.88 (1.01–3.49)
Colon-rectum	21	3.60 (1.89–6.88)	11	2.79 (1.04–7.50)	10	6.48 (1.89–22.18)	22	2.82 (1.48–5.37)
Anus	39	1.91 (1.02–3.60)	4	2.23 (0.53–9.33)	11	8.04 (2.27–28.49)	32	2.04 (1.26–3.29)
Lung	29	3.09 (1.97–4.85)	9	2.66 (1.09–6.50)	8	3.53 (1.36–9.13)	30	2.77 (1.76–4.36)
NMSC	99	5.20 (3.15–8.60)	27	6.18 (2.77–13.76)	36	7.98 (3.17–20.06)	90	4.77 (2.97–7.68)
Breast	1	*	39	2.56 (1.43–4.58)	16	2.22 (0.92–5.38)	24	3.25 (1.47–7.20)
CNS	10	1.94 (0.84–4.47)	7	6.92 (2.15–22.22)	9	10.23 (3.33–31.40)	8	1.64 (0.68–3.94)
HL	29	3.53 (1.93–6.45)	7	1.48 (0.10–21.22)	15	2.99 (0.97–9.20)	21	3.63 (1.76–7.48)
Leukemia	9	1.96 (0.88–4.38)	5	9.10 (2.22–37.35)	8	2.80 (1.23–6.37)	6	3.60 (1.20–10.81)

Abbreviation: NA, not applicable.
[1]HR stratified by matching variables and adjusted for age (in years) at cancer diagnosis.
[2]Matched by cancer type (1:1 for KS, 1:2 for NHL, 1:4 for other cancers), sex, age and period of diagnosis.
[3]People with two primary site cancers were included only once in the analysis.
*HR not available due to insufficient number of events among cases or controls.
Sources: Population-based Cancer Registry of São Paulo and *Sistema de Informação de Agravos de Notificação* (SINAN).

survival among all cancers assessed and significantly worse in PWA when compared to non-PWA.[11] Our study could not conduct analysis according to leukemia subtype due to insufficient number of cases, but it could be possible that the impaired survival reflected the predominance of acute subtypes, for which prognosis is less favorable.

Wide gaps in survival according to AIDS status were seen for tumors which are not particularly aggressive in the general population, namely bladder cancer (HR = 8.11), prostate cancer (HR = 6.07) and NMSC (HR = 5.39). Prostate cancer does not seem to have more severe presentation in HIV-infected people,[25,26] but Riedel *et al.* observed advanced disease more frequently in this population.[27] As for NMSC, our results are in line with a previous study, where this malignancy showed one the greatest survival gaps in Italian patients.[11] Evidences indicate NMSC tends to present in more aggressive forms in HIV-infected people,[28] but elevated HR is likely to be a result of death from other causes, as NMSC is rarely fatal.

The 1-year overall survival analyses revealed that for several cancers, including KS, NHL, lung cancer and leukemia, the survival gap was restricted to the first year after diagnosis, in agreement with a previous report.[11] Findings from the US revealed that HIV-infected patients were more frequently diagnosed with distant disease.[29] The diagnosis of cancer in this population can be challenging. Some signs and symptoms might be initially mistaken by other morbidities that commonly affect the HIV-infected, delaying diagnosis. In an HIV specialty clinic, lung cancer was diagnosed at advanced stage (III and IV) in 88% of HIV-infected patients as opposed to 66% of HIV-uninfected controls.[21]

Suneja *et al.* compared treatment uptake in HIV-infected (88.5% PWA) and HIV-uninfected patients with cancer in the US. HIV-infected patients were less likely to undergo treatment for cancer. The main predictors for the lack of treatment among the HIV-infected included distant and unknown stages, intravenous drug use as exposure to HIV and older age (45–64 years).[29] Another study conducted in the US found discrepancies in the type of treatment for prostate cancer and HL in HIV-infected when compared to HIV-uninfected people.[24]

The inexistence of national guidelines for the diagnosis and management of malignancies in HIV-infected people in Brazil could also be associated with low survival rates for these patients.[30] A barrier to the establishment of these guidelines is that less information on treatment efficacy is available for NADC in the HIV-infected population because HIV infection is often an exclusion criterion in randomized controlled trials.[31]

A study assessing death records of PWA in São Paulo revealed that over 90% of all deaths in the post-HAART era were still associated with infectious and parasitic agents, especially tuberculosis (>20%). The same study also identified assault as one of the leading underlying causes of death among PWA in low-income areas of the city.[9]

Non-adherence to HIV treatment, including routine medical appointments and use of HAART, could have led to poorer outcomes. Despite the existence of a healthcare system free of cost, patients could face barriers to seek care and follow medical treatment.[32] In São Paulo, HIV disproportionally affects vulnerable populations, including sex workers, drug users, street dwellers and imprisoned people, conditions that could negatively impact adherence to HIV treatment.[33]

The strengths of our study are the matching process, which included histological groups among other variables: the number of assessed cancer sites and its representativeness. Matching was an effective tool to ensure comparability of PWA and non-PWA, as it was shown in previous research.[11] Due to the number of cancer cases in PWA our study was able to include, in addition to ADCs, 22 NADCs in the type/site-specific analyses. Survival for some of these cancers has been poorly documented previously.[10,11,23]

This is the first population-based study estimating survival after cancer among PWA in Brazil and one of the few in developing countries. We employed a multi-step record linkage procedure and clerical review, although time-consuming, to improve the sensitivity and specificity of this method.[6,34]

Our study has also limitations. It was not possible to include clinical staging of the cases in the analyses, because this information was available for a small fraction of cases. Another constraint is that our study was restricted to PWA diagnosed with cancer in the post-HAART era. As the time series of the PBCR-SP begins only in 1997, it was not possible to analyze a longer period and compare survival across periods as previously done in other countries.[10,11] Because reporting of HIV infection without AIDS was not mandatory until 2013 in Brazil, some of the controls from the general population could be HIV-infected, but since the prevalence of HIV infection in the country is low (0.6% in adults) this would not greatly affect our results.[35] Information on antiretroviral regimen and CD4 count were also not available because they are not routinely collected by the AIDS registry (SINAN).

Since there is no information on smoking status in the databases used in our study, it was not possible to control the analysis for this variable. Smoking is strongly associated with the incidence of cancer as well as early mortality and it is more frequent among HIV-infected people than in the general population.[36]

Lastly, the insufficient number of events in some type/site-specific analyses resulted in large confidence intervals, but since cancer is a rare event, this would not be unexpected.

Our study revealed that there is a significant survival gap between PWA and non-PWA with cancer even after the introduction of HAART. A number of factors could have contributed to unfavorable outcomes in PWA, such as disparities in cancer diagnosis, differences in treatment uptake across populations, lack of specific treatment guidelines for the HIV-infected population and death from other causes including external causes, among others.[21,29,37]

As in the developed world, an important share of these cancers is related to life style, especially tobacco smoking and is preventable.[6] Although, Brazil has effectively implemented strategies to control tobacco at a population level,[38] it seems to have been less successful in reaching the HIV-infected people. Therefore, approaches targeted at this specific population for preventing cancer, by reducing or eliminating the exposure to key risk factors should be strengthened. The assessment and the implementation of specific screening guidelines for this population as an attempt to ensure early cancer diagnosis should be also considered. As proposed by Goedert *et al.*, physical examination of HIV-infected patients during routine appointments could be a tool to detect some malignancies.[39] In addition to that, efforts to ensure proper cancer treatment in this population should also be emphasized.

In this scenario, patients and healthcare providers would greatly benefit from the development of national guidelines for the prevention, early diagnosis and management of cancer among HIV-infected people.

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Curriculum Vitae

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Wichtige Publikationen

Tanaka LF, Latorre MRDO, Gutierrez EB, Heumann C, Herbinger KH, Froeschl G. Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil. Int J STD AIDS. 2017.

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List of publications

1) **Tanaka LF**, Latorre MRDO, Gutierrez EB, Heumann C, Herbinger KH, Froeschl G. Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil. Int J STD AIDS. 2017;28(12):1190-8.

2) **Tanaka LF**, Latorre MRDO, Gutierrez EB, Froeschl G, Heumann C, Herbinger KH. Risk for cancer among people living with AIDS, 1997-2012: the São Paulo AIDS-cancer linkage study. Eur J Cancer Prev. 2017

3) Peres SV, Latorre MRDO, **Tanaka LF**, Michels FAS, Teixeira MLP, Coeli CM, Almeida MF. Melhora na qualidade e completitude da base de dados do Registro de Câncer de Base Populacional do município de São Paulo: uso das técnicas de *linkage.* Rev Bras Epidemiol. 2016;19:753-65.

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Statement on pre-release and contribution

Parts of this thesis have been already published in the form of manuscripts:

1) Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil. Int J STD AIDS. 2017;28(12):1190-8.

2) Risk for cancer among people living with AIDS, 1997-2012: the São Paulo AIDS-cancer linkage study. Eur J Cancer Prev. 2017 (published ahead of print)

The remaining part of thesis, on survival entitled "Cancer survival in people with AIDS: A population-based study from São Paulo, Brazil" was submitted on April 25th, 2017 to the International Journal of Cancer and was accepted on September 20th, 2017.

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Affidavit

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I hereby declare, that the submitted thesis entitled

Trends in AIDS-defining and non-AIDS-defining cancers among patients with AIDS in the city of São Paulo: 1997 - 2012

is the result of my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

The submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

I further declare that the electronic version of the submitted thesis is congruent with the printed version both in content and format.

Nuremberg, 28th April 2017

Place, Date

Signature of PhD Candidate