Risk of Cancer among Hispanics with AIDS Compared with the General Population in Puerto Rico: 1987-2003

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Background: The risk of cancer among Hispanics with Acquired Immune Deficiency Syndrome (AIDS) in the United States and Puerto Rico (PR) has not been well described. The purpose of this study was to determine the risk of AIDS related and non-AIDS related cancers among Hispanics with AIDS in PR.

Methods: A probabilistic record linkage of the PR AIDS Surveillance Program and PR Central Cancer Registry databases was conducted. AIDS cases were grouped according to year of AIDS onset and antiretroviral therapy availability: 1987-1989 (limited availability), 1990-1995 (mono and dual therapy), and 1996-2003 (highly active antiretroviral therapy: HAART). Cancer risk was described using the standardized incidence ratios (SIR).

Results: A total of 612 cancers were identified after 3 months of AIDS diagnosis: 409 (66.7%) AIDS related and 203 (33.1%) non-AIDS related. Although a decreasing trend in the risk of AIDS and non-AIDS related cancers was observed, the risk for both remained higher in the AIDS group compared to the general population in PR. Non-AIDS related cancers with higher risk during the HAART availability were: oropharyngeal, anal, liver, larynx, eye and orbit, Hodgkin lymphoma, and vaginal.

Conclusion: Hispanics with AIDS in PR consistently showed a greater risk of AIDS and non-AIDS related cancers compared to the general population in PR and that has not changed over time. [*P R Health Sci J 2010;3:256-264*]

Key words: Acquired Immune Deficiency Syndrome, Malignancies, Hispanics

Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and cervical cancer are recognized as Acquired Immune Deficiency Syndrome (AIDS) related cancers, and their etiology has been associated with HIV-induced immunosuppression with the potential risk of oncogenic viral co-infection. Human Papilomavirus (HPV), Epstein-Barr virus (EBV), human Herpes virus type 8 (HHV-8), Hepatitis B virus (HBV), and Hepatitis C virus (HCV) are some of the viruses related to human malignancies in people with HIV/AIDS (1-3). Since the advent of highly active antiretroviral therapies (HAART) and the improved immunocompetence of people living with HIV, the incidence of AIDS-related cancers have declined significantly except for cervical cancer, while the incidence of other non-AIDS related cancers have increased significantly (3-5).

Epidemiological studies in the United States (US), Europe, Australia, and Africa have documented standardized incidence ratios (SIR) of AIDS related and non-AIDS related cancers using data from linked Cancer and AIDS registries (4-13). In a population-based registry linkage in New York State, Gallagher et al. (10) reported significant SIR for KS, NHL, invasive cervical cancer, and several non-AIDS related cancers affecting the tongue, mouth, rectum, anus, trachea, bronchus, and lung. In Italy, Dal Maso, Serraino and Franceschi (7) reported a SIR of 302 (95% CI, 253-357) for NHL in AIDS patients. In a linkage of AIDS and cancer registries from 11 US regions, Engels et al. (4) reported important declines in KS and NHL after the introduction of HAART in people with AIDS, no change in cervical cancer, and increased risk of non-AIDS related cancers, particularly Hodgkin lymphoma, anus, liver, and lung cancer. An AIDS-Cancer linkage was also conducted in Africa, where the incidence of all AIDS

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related cancers and some non-AIDS related cancers (Hodgkin lymphoma, conjunctiva, kidney, thyroid, and uterus) were found to be higher among people with AIDS (9). In a more recent prospective cohort study, Patel et al. (5) also reported a reduction in AIDS related malignancies except for cervical cancer, and a significant increase risk of non-AIDS related malignancies in a cohort of adults living with HIV compared to the general population in the US. The most important types of non-AIDS related malignancies were: anal, vaginal, Hodgkin lymphoma, liver, lung, melanoma, oropharyngeal, leukemia, colorectal and renal. These results suggest that the incidence of non-AIDS related cancers has increased more than the incidence of AIDS related cancers, and that the influence of HAART in the development and prognosis of various cancers is still not clear. Biological, environmental and behavioral risk factors must also be explored to better define the long-term cancer risk in people living with HIV/AIDS (14).

Puerto Rico (PR) is one of the top ten US States and territories with the highest cumulative number of AIDS cases, and Puerto Ricans are the second largest group of Hispanics in the US with higher cancer mortality rates (15-16). However, little information is available regarding AIDS related and non-AIDS related malignancies among Hispanics with HIV/AIDS in the US or PR. In one retrospective cohort study in Southern California, Levine et al. (17) reported that from 1982 to 1998 the prevalence of AIDS-related lymphoma decreased significantly in whites but increased in Hispanics. In another study, Fordyce et al. (18) conducted a population-based AIDS-Cancer linkage analysis of women from New York City diagnosed with AIDS between 1981 and 1994, and reported that 47% of all cancer cases were among African Americans, 36% among Hispanics, and 16% among non-Hispanic whites. Mayor et al. (19) conducted a cross-sectional analysis of 3,576 HIV/AIDS patients attending an outpatient clinic in PR from 1992 to 2005. Of these patients, 171 (4.8%) were diagnosed with cancer at some point in their lives: 51.5% AIDS related and 48.5% non-AIDS related cancers. Because no population-based studies have been conducted in PR, the risk of AIDS related and non-AIDS related cancers in PR compared to the general population is still unknown.

The purpose of this study was to estimate the risk of AIDS related and non-AIDS related cancers among Hispanics with AIDS in PR using the Puerto Rico Central Cancer Registry and the Puerto Rico AIDS Surveillance Program Registry. Both are population-based registries that receive support from the Centers for Disease Control and Prevention. We hypothesized that the risk of all AIDS related cancers and the risk of many non-AIDS related cancers will be higher in the AIDS group compared with the general population in PR. The results of this study will provide the basis for future epidemiological studies to characterize the natural history of specific cancers in HIV infection and other important biological, environmental, and behavioral risk factors.

Methods

Data Sources

Puerto Rico AIDS Surveillance Program

The Puerto Rico AIDS Surveillance Program provides information on the demographic characteristics of individuals with AIDS that permits identification of groups at highest risk of disease. Information on specific exposures or behaviors of AIDS cases have been well documented throughout the surveillance program providing insight into etiology of HIV virus and modes of transmission, permitting early prevention and public health recommendations. Several publications characterizing AIDS in PR have used data from the surveillance program (20-23). The data gathered is analyzed and used to support the Puerto Rico Health Department in the establishment of public policies and to allocate funds for HIV/AIDS services and prevention efforts. AIDS was included as a reportable disease under Bill 81 and Regulation 51 in 1985. In 1987, an island-wide AIDS surveillance system was implemented to carry on the AIDS surveillance activities in PR. A Surveillance specialist conducts active surveillance of AIDS cases in hospitals, immunology clinics, private providers, correctional facilities, and other health care services settings to enhance surveillance activities. In addition, the law requires that every laboratory, hospital and clinic should report to the Health Department within 5 days after processing the sample.

Puerto Rico Central Cancer Registry

The Puerto Rico Central Cancer Registry (PRCCR), the fourth oldest population-based cancer registry in the world, collects information from any facility that diagnoses and/or treats cancer patients in Puerto Rico. In addition, the Puerto Rico Health Department has agreements with other cancer registries in the US so that cancer cases diagnosed outside the island are also captured and registered. From 1973 to 1989, the registry received funds, training and quality control from the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results Program (SEER). In 1997, the PRCCR joined the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries. In 2003 a CDC audit concluded that 95.3% of all cancer cases diagnosed and treated in hospital facilities in PR were appropriately reported to the PRCCR, a result comparable to the US (24). The PRCCR, now under the Puerto Rico Comprehensive Cancer Center at the University of Puerto Rico Medical Sciences Campus, continues to work in collaboration with the CDC Cancer Registries and continues to collect, analyze and disseminate data useful in the prevention, diagnosis and treatment of cancer. The PRCCR monitors the impact of cancer in the population of Puerto Rico and maintains surveillance of new cases and mortality from all cancers.

Linkage and Data Management

The Puerto Rico AIDS Surveillance and PRCCR databases were linked using Link Plus software (Release 2.0, CDC,

Atlanta, GA), a probabilistic record linkage program developed by the CDC's Division of Cancer Prevention and Control in support of the National Program of Cancer Registries. Registry data on name, social security number, sex, date of birth, and date of death were used to conduct the probabilistic record linkage. Authorized personnel from both registries reviewed potential matches to assess their validity and a database with no identifying information was provided to the investigators. The study was approved by the Institutional Committee for the Protection of Human Subjects in Research of the University of Puerto Rico, Río Piedras Campus. Confidential agreements were also signed at both participating registries.

The Puerto Rico AIDS Surveillance Program provided a database on 31,630 patients with AIDS diagnosis. Of these, a total of 3,170 cases were excluded because AIDS was diagnosed in a period that did not conform with the period of complete cancer registration (906 AIDS patients diagnosed before 1987, and 2,264 with AIDS onset after 2003). Therefore, a total of 28,460 patients with AIDS diagnosis during the period from 1987 to 2003 were included in the study.

The PRCCR uses the Surveillance, Epidemiology, and End Results (SEER) Program and the North American Association of Central Cancer Registries (NAACCR) standards for coding cancer data. The third edition of the International Classification of Disease for Oncology (ICD-O-3) was used to code the invasive cancers from 2001 onward. Cancer cases diagnosed before 2001 were converted from the previous coding system (ICD-O-2) to ICD-O-3. Definitions of cancer categories for all cancer types observed in this study were established according to SEER Incidence Site Recode Definition (National Cancer Institute Surveillance Research Program, US National Institutes of Health, Bethesda, Maryland).

Statistical Analyses

AIDS cases were grouped according to the year of AIDS onset and antiretroviral therapy (ART) availability: 1987-1989 (limited or no antiretroviral therapy), 1990-1995 (mono and dual therapy), and 1996-2003 (HAART). A chi square test was used to compare the demographic characteristics between the three groups. For the analysis of cancer risk, first and subsequent malignancies of different types identified in the cancer registry were considered. Prevalent cancer cases that occurred before 3 months after AIDS diagnosis were not included in the analyses for two reasons: 1) in the immediate period after AIDS diagnosis cancer incidence could be inflated because of the intensive clinical evaluation and testing, and 2) to formulate a measure of risk for the post AIDS onset period (4, 12).

Age standardization was performed by the indirect method using the PR population given the small numbers of observations in the AIDS group. Cancer risk was described using the SIR, defined as the observed cancer incidence in people with AIDS divided by the expected incidence based on population rates in PR specific to sex, age group (<15, 15-29, 30-39, 40-49, ≥50 yrs) and calendar year. Individuals who developed AIDS related cancers (KS, NHL and cervical cancer) before 3 months after AIDS diagnosis were excluded from the analyses of risk after 3 months of AIDS diagnosis (4). A SIR value greater than 1.0 indicates that the incidence in people with AIDS is greater than that observed in the general PR population. Exact confidence intervals (95%) were calculated for the SIR based on an assumed Poisson distribution. All analyses were completed using STATA Statistical software (Release 9.2, Stata Corp, College Station, TX).

Also, the Joinpoint regression model (25) was used to describe changing trends of SIR over time for AIDS related and non-AIDS related cancers. After identifying the best fitting model, the Joinpoint regression estimates the annual percent change (APC) over segments of time where an increase or decrease in the SIR is observed. With this statistical technique, the log of the SIR is modeled as a linear function over time (calendar year); thereby, yielding an annual exponential change of SIR, and identifying the time point where a significant change in the SIR occurs (Joinpoint software, release 3.4.2, National Cancer Institute, National Institutes of Health, Bethesda).

Results

Demographic characteristics of all the Hispanics with AIDS and cancer in PR included in the Puerto Rico AIDS Surveillance and the Puerto Rico Cancer Registry databases from 1987 to 2003 organized by gender, age, and observation period is presented in Table 1. The proportion of men was higher in both registries; however, the difference in gender distribution was much higher in the AIDS registry than the cancer registry. Most AIDS patients were in the age range of 30-49 years (69%), while most of the cancer patients were older than 49 years (84%). The proportion of AIDS cases in PR declined from the period of 1990-1995 to 1996-2003, while the proportion of cancer cases in PR increased during the same time period (Table 1).

A total of 1,351 cases were matched between the AIDS and Cancer databases for the time period from 1987 to 2003, representing 4.7% of the AIDS population in PR. Of these, our study population included 612 cases that were diagnosed with cancer after 3 months of AIDS diagnosis. Their demographic characteristics are included in Table 2. Each time period showed a higher proportion of men; however, comparing gender over time, the proportion of women is higher in the more recent time period (1996-2003) than the proportion of women in the earlier periods. The number of cancers according to ART availability period was 68 during limited or no therapy (1987-1989), 378 during mono-dual therapy (1990-1995), and 166 during HAART era (1996-2003). The highest proportion of cancer diagnosis in AIDS patients (62%) was reported during the period of 1990-1995, and most of these patients (70%) were in the age range of 30-49 years old. Similar to the HIV/AIDS population in PR, injection drug use was the most prevalent

mode of infection, followed by men who have sex with men, and heterosexual contact. Of these three, only the prevalence of heterosexual contact showed an increase over time.

Table 1. Demographic characteristics of AIDS and Cancer patients in Puerto Rico: 1987-2003

Characteristic	Registry Population	
	AIDS	Cancer
Total sample (n, (%))	28460 (100)	153448 (100)
Gender (n, (%))		
Male	21630 (76)	86337 (52.3)
Female	6830 (24)	67111 (43.7)
Age in years (n, (%))		
< 15	414 (1.5)	4804 (16.9)
15-29	12231 (42.9)	7452 (26.2)
30-39	3559 (12.5)	1763 (1.2)
40-49	3516 (2.3)	6200 (4.0)
> 49	13241 (8.6)	128728 (83.9)
Observation period (n, (%))		
1987-1989	3720 (13.1)	21085 (13.7)
1990-1995	13844 (48.6)	52280 (34.1)
1996-2003	10896 (38.3)	80083 (52.2)

The number of cancer cases and SIR of AIDS related and non-AIDS related cancers are shown in Table 3. Of all the cancer cases reported during the period from 1987 to 2003, 70% were AIDS related and 33% non-AIDS related cancers. Overall, the percent of AIDS defining cancers has decreased over time from 72% in 1987-1989 to 58% in 1996-2003. Most of this decrease is due to the lower percent of Kaposi sarcoma in the HAART era than the pre HAART eras. In contrast, the percent of non-AIDS defining cancers has increased over time, from 28% in 1987-1989 to 42% in 1996-2003.

A significantly higher risk of all AIDS related cancers was observed for Hispanics with AIDS in PR compared to the general population in PR; but the risk has decreased over time. Figure 1a shows a non significant increasing trend from 1987 to 1993 in all AIDS related cancers, and a significant decreasing trend from 1993 to 2003. The patterns for specific histological subtypes of NHL are also presented in Table 3. The risk of all subtypes was higher in Hispanics with AIDS in PR compared to the general population in PR in all time periods evaluated, and for each subtype the SIR was lowest in the 1996-2003 time period, except for Immunoblastic NHL that increased from 1990-1995 to 1996-2003.

Of all non-AIDS related cancer types, 16 showed a significantly higher risk in at least one of the three time periods evaluated (Table 3). Compared to the earlier period in 1987-1989, the HAART era (1996-2003) showed higher SIRs for cancer of the oral cavity and pharynx cancer, anus, liver, vagina and vulva, and eye and orbit. The SIR for urinary bladder cancer was higher in the earlier period (1987-1989) but no longer significant for the later periods. The SIR for larynx cancer was high in all time periods, but only significant in the HAART era. Hodgkin lymphoma and cancers of unknown primary sites were the only non-AIDS defining cancers with a significantly higher risk in all three time periods and no apparent change over time. In contrast, the SIR for colon cancer was lowest in the HAART era and the incidence was no longer higher for Hispanics with AIDS compared to the general population in PR. The risk for all non-AIDS defining cancers combined was higher in Hispanics with AIDS compared to the general population in PR for all three time periods, but similar to all AIDS related cancers, the risk has decreased over time. Figure 1b shows a non significant increasing trend from 1987 to 1998 in all non-AIDS related cancers, and a significant decreasing trend from 1998 to 2003.

The SIRs are provided for males and females separately in Table 4. The risk of AIDS related cancers was significantly higher for both males and females in all time periods evaluated compared to the general population in PR, and the risk also appears to decline over time. For men, non-AIDS defining cancers with a high SIRs during the period of mono-dual therapy and HAART availability were: oral cavity and pharynx, anus, liver, eye and orbit, and Hodgkin lymphoma; and in females: lung and bronchus, and vagina and vulva. Non-AIDS defining cancers with high SIR only in the HAART availability period were: larynx and myeloma in males, and eye and orbit in females.

Discussion

This is the first population-based study to report the risk of AIDS and non-AIDS related cancers among Hispanics with AIDS in PR compared to the general population in PR. The major findings of the study are two-fold: 1) the risk of all AIDS related cancers was higher in the AIDS group compared to the general population in PR for all time periods evaluated; however, the risk has declined over time, and 2) the risk of several non-AIDS related cancers (i.e., oral cavity and pharynx, anus, liver, larynx, vagina and vulva, eye and orbit, and Hodgkin lymphoma) was higher in our AIDS group compared to the general population in PR even in the period of HAART availability, but the combined risk of all non-AIDS related cancers also has declined over time.

The decline in the risk of AIDS related cancers such as KS and NHL observed in Hispanics with AIDS in PR is consistent with previous reports in the US and Europe (2, 4-5, 26) and it has been attributed in part to the availability of ART. However, the excessively high risk of KS and NHL compared to the general population indicates that these two AIDS related cancers are still an important clinical problem. Also noteworthy is the fact that among AIDS patients in PR the risk for KS during the HAART availability period was 277.8 (95% CI, 202.6-371.7) and 39.6 (95% CI, 28.2-54.1) for NHL, and the risk for these two cancers among AIDS patients in the US was 3640 (95% CI, 3330-3980) and 22.6 (95% CI, 20.8-24.6), respectively (4). There are two important differences in the AIDS population

Table 2. Demographic characteristics of patients with AIDS in Puerto Rico who developed cancer after 3 months of AIDS diagnosis: 1987-2003.

Characteristic	Total Sample	AIDS diagnosis year						
		1987-89		1990-95		1996-2003		P-value
		Males	Females	Males	Females	Males	Females	
Total Sample (n, (%))	612 (100)	54 (79)	14 (21)	309 (82)	69 (18)	123 (74)	43 (27)	0.08
Age at AIDS in years (n, (%))								<0.001
< 15	3 (0.5)	0 (0)	1 (7.1)	1 (0.3)	1 (1.5)	0 (0)	0 (0)	
15-29	113 (18.5)	17 (31.5)	4 (28.6)	57 (18.5)	19 (27.5)	11 (8.9)	5 (11.6)	
30-39	267 (43.6)	24 (44.4)	8 (57.1)	145 (46.9)	30 (43.5)	46 (37.4)	14 (35.6)	
40-49	150 (24.5)	8 (14.8)	1 (7.1)	73 (23.6)	17 (24.6)	36 (29.3)	15 (34.9)	
> 49	79 (12.9)	5 (9.3)	0 (0)	33 (10.7)	2 (2.9)	30 (24.4)	9 (20.9)	
Mode of HIV exposure (n, (%))								<0.001
MSM	191 (31.2)	18 (33.3)	-	138 (44.7)	-	35 (28.5)	-	
IDU	195 (31.9)	26 (48.2)	9 (64.3)	92 (29.8)	20 (39.0)	38 (30.9)	10 (21.3)	
MSM + IDU	55 (9.0)	5 (9.3)	-	32 (10.4)	-	17 (13.8)	-	
Hemophilia	1 (0.2)	1 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Heterosexual contact	146 (23.9)	2 (3.7)	4 (28.6)	35 (11.3)	44 (63.8)	33 (26.8)	28 (68.1)	
Transfusion	3 (0.5)	1 (1.9)	0 (0)	0 (0)	1 (1.5)	0 (0)	1 (2.3)	
Pediatric	3 (0.5)	0 (0)	1 (7.1)	1 (0.3)	1 (1.5)	0 (0)	0 (0)	
Other/unknown	18 (2.9)	1 (1.9)	0 (0)	11 (3.6)	3 (4.4)	0 (0)	3 (7.0)	

MSM= men who have sex with men, IDU= injecting drug use

and the general population in the US and PR. One being the principal mode of HIV infection which is injection drug use in PR and men who have sex with men in the US, and the other is the high prevalence of HCV infection in PR (6.3%) compared to the US (0.9-3.9%) (27). The difference in the mode of HIV transmission and the prevalence of HCV co-infection in PR could explain the increased risk of liver cancer and less impact on anal cancer in PR (fewer cases, wider confidence intervals) compared to other reports in the US (4-5). However, the potential association between injection drug use and HCV co-infection with the risk of KS and NHL needs evaluation. Other potential factors linked to KS and NHL in the AIDS population that also requires further evaluation is the co-infection with HHV-8 and low CD4 cell count before initiation with HAART as previously suggested (26, 28-29).

Also consistent with previous reports (4) was the significantly higher risk of cervical cancer observed in the group of Hispanic females with AIDS in PR compared to the general population in PR, and that has not changed over time. The risk of cervical cancer in PR in the period of limited therapy, dual-mono therapy, and HAART availability [SIR (95% CI)] was 46.5 (9.6-135.8), 67.7 (43.4-100.8), and 28.7 (14.8-50.2), respectively; and the risk in the US [SIR (95% CI)] was 7.7 (3.7-14.1), 4.2 (2.9-5.8), and 5.3 (3.6-7.6), respectively (4). Because the risk of cervical cancer is not clearly associated with immunosuppression, some investigators have questioned its inclusion among the AIDS-related cancers (9). However, there is evidence supporting a strong association between cervical cancer and HPV infection in women with HIV/AIDS (9, 30-31), and HPV infection has been associated with low CD4 counts in women living with HIV (30). Therefore, it is possible that the association between cervical cancer and immunosuppression is indirect rather than direct. Moreover, Mangclaviraj et al. (32) observed a significant association between low CD4 count and low income with cervical abnormalities in women living with HIV infection in Bangkok. Whether the high risk of cervical cancer among Hispanic women with AIDS in PR could be explained by factors such as HPV infection, low CD4 count, or low income; remains unknown.

The increased risk of breast cancer in women living with HIV/AIDS in PR, particularly during the pre-HAART period compared to the general population in PR has not been observed in other studies. For example, in a meta-analysis of the incidence of non-AIDS cancers, Shiels et al. (33) found that the risk of breast cancer is lower during pre-HAART and HAART era compared to the general population (SIR [95% CI]: 0.43 [0.31-0.59], 0.64 [0.50-0.82]) and suggested that hormonal changes associated with HIV infection might provide a protective effect. It is possible that other factors such as environmental exposures, socioeconomic level, opportunities for clinical screening, and lifestyle behaviors could provide an explanation for this discrepancy and thus be a source of further investigation. Also, the increased rate of heterosexual HIV transmission over the years could explain the observed increase of cancer among women with AIDS in PR.

The decreasing trend in all AIDS related cancers (KS, NHL and cervical) in PR starting in the period where only mono and dual ART were available (1993) suggests that these therapies

Table 3. Risk of cancer among people with AIDS (>3 months after AIDS diagnosis) in Puerto Rico compared with the general population in Puerto Rico: 1987-2003.

Cancer type	No. cases (%)			SIR (95% CI)		
	1987-1989	1990-1995	1996-2003	1987-1989	1990-1995	1996-2003
AIDS related						
Kaposi sarcoma	31 (45.6)	164 (43.2)	45 (27.3)	350.4* (238.1-497.4)	303.7* (259.0-353.9)	277.8* (202.6-371.7)
Non-Hodgkin lymphoma	15 (22.1)	76 (20.0)	39 (23.6)	77.0* (43.1-127.0)	70.8* (55.8-88.6)	39.6* (28.2-54.1)
Burkitt NHL	1 (1.5)	11 (2.9)	3 (1.8)	163.2* (4.1-909.0)	199.1* (99.4-356.2)	59.1* (12.2-172.8)
Diffuse large B cell NHL	7 (10.3)	38 (10.0)	21 (12.7)	114.9* (46.2-236.7)	93.0* (65.8-127.6)	60.4* (37.4-92.4)
Immunoblastic NHL	3 (4.4)	8 (2.1)	5 (3.0)	575.9* (118.8-1683.1)	127.0* (54.8-250.2)	238.4* (77.4-556.4)
Other NHL	6 (8.8)	18 (4.7)	6 (3.6)	184.4* (67.7-401.4)	95.7* (56.7-151.3)	45.5* (16.7-99.1)
Cervix Uteri	3 (4.4)	24 (6.3)	12 (7.3)	46.5* (9.6-135.8)	67.7* (43.4-100.8)	28.7* (14.8-50.2)
All AIDS related cancers	49 (72.1)	264 (69.5)	96 (58.2)	96.5* (71.4-127.5)	101.9* (90.0-114.9)	47.7* (38.7-58.3)
Non-AIDS related						
Oral cavity and pharynx	0 (0.0)	7 (1.8)	9 (5.5)	0.0 (0.0-14.3)	6.7* (2.7-13.8)	9.8* (4.5-18.5)
Esophagus	0 (0.0)	1 (0.3)	0 (0.0)	0.0 (0.0-30.8)	2.1 (0.5-11.9)	0.0 (0.0-9.2)
Stomach	1 (1.5)	3 (0.8)	1 (0.6)	4.2 (0.1-23.4)	3.1 (0.6-9.0)	1.2 (0.0-6.6)
Colon and rectum	3 (4.4)	10 (2.6)	3 (1.8)	6.2* (1.3-18.0)	4.2* (2.0-7.8)	1.0 (0.2-2.9)
Anus	0 (0.0)	10 (2.6)	2 (1.2)	0.0 (0.0-215.0)	119.7* (57.4-220.2)	19.4* (2.4-70.2)
Liver	0 (0.0)	2 (0.5)	7 (4.2)	0.0 (0.0-55.6)	5.6 (0.7-20.3)	14.9* (6.0-30.7)
Gallbladder	0 (0.0)	1 (0.3)	0 (0.0)	0.0 (0.0-150.4)	9.5 (0.2-53.0)	0.0 (0.0-48.4)
Pancreas	0 (0.0)	2 (0.5)	1 (0.6)	0.0 (0.0-42.0)	4.7 (0.6-17.1)	2.7 (0.1-14.9)
Other digestive organs	0 (0.0)	2 (0.5)	0 (0.0)	0.0 (0.0-336.8)	67.1* (8.1-242.3)	0.0 (0.0-107.3)
Nose, nasal cavity and middle ear	0 (0.0)	1 (0.3)	1 (0.6)	0.0 (0.0-272.8)	18.0 (0.5-100.1)	21.2 (0.5-118.1)
Larynx	1 (1.5)	2 (0.5)	3 (1.8)	14.5 (0.4-80.8)	6.4 (0.8-23.3)	9.1* (1.9-26.5)
Lung and bronchus	1 (1.5)	16 (4.2)	4 (2.4)	3.7 (0.1-20.7)	12.9* (7.4-21.0)	3.1 (0.9-8.0)
Soft tissue including heart	0 (0.0)	1 (0.3)	1 (0.6)	0.0 (0.0-80.6)	6.7 (0.2-37.2)	6.5 (0.2-36.0)
Melanoma of the skin	0 (0.0)	0 (0.0)	1 (0.6)	0.0 (0.0-77.7)	0.0 (0.0-18.4)	4.6 (0.1-25.4)
Other non-epithelial skin	0 (0.0)	4 (1.1)	0 (0.0)	0.0 (0.0-179.0)	56.4* (15.4-144.3)	0.0 (0.0-46.8)
Breast	0 (0.0)	6 (1.6)	3 (1.8)	0.0 (0.0-14.3)	4.3* (1.6-9.3)	1.4 (0.3-4.1)
Uterus	0 (0.0)	2 (0.5)	1 (0.6)	0.0 (0.0-102.9)	8.3 (1.0-30.1)	2.5 (0.1-14.2)
Vagina and vulva	0 (0.0)	2 (0.5)	2 (1.2)	0.0 (0.0-533.5)	42.5* (5.1-152.5)	33.9* (4.1-122.5)
Prostate	1 (1.5)	7 (1.8)	3 (1.8)	1.4 (0.0-7.8)	1.1 (0.5-2.3)	0.5 (0.1-1.4)
Penis	0 (0.0)	1 (0.3)	1 (0.6)	0.0 (0.0-56.6)	3.9 (0.1-21.8)	5.3 (0.1-29.3)
Urinary bladder	2 (2.9)	1 (0.3)	0 (0.0)	15.6* (1.9-56.2)	1.8 (0.0-9.9)	0.0 (0.0-5.8)
Kidney and renal pelvis	1 (1.5)	1 (0.3)	1 (0.6)	15.5 (0.4-86.4)	2.9 (0.1-16.0)	2.5 (0.1-13.8)
Eye and orbit	0 (0.0)	10 (2.6)	4 (2.4)	0.0 (0.0-339.4)	144.5* (69.3-265.7)	75.7* (20.6-193.8)
Brain	1 (1.5)	2 (0.5)	0 (0.0)	10.2 (0.3-56.6)	5.2 (0.6-18.7)	0.0 (0.0-10.4)
Thyroid	0 (0.0)	0 (0.0)	1 (0.6)	0.0 (0.0-36.9)	0.0 (0.0-6.2)	1.2 (0.0-6.9)
Hodgkin lymphoma	4 (5.9)	4 (1.1)	5 (3.0)	46.7* (12.7-119.6)	11.6* (3.2-29.7)	19.4* (6.3-45.3)
Myeloma	0 (0.0)	1 (0.3)	1 (0.6)	0.0 (0.0-55.1)	3.9 (0.1-22.0)	3.9 (0.1-21.8)
Lymphocytic leukemia	0 (0.0)	2 (0.5)	0 (0.0)	0.0 (0.0-94.0)	11.9* (1.4-43.1)	0.0 (0.0-29.4)
Myeloid and monocytic leukemia	1 (1.5)	0 (0.0)	0 (0.0)	11.3 (0.3-63.1)	0.0 (0.0-10.8)	0.0 (0.0-13.3)
Other leukemia	1 (1.5)	1 (0.3)	1 (0.6)	59.2* (1.5-329.6)	11.5 (0.3-64.2)	7.8 (0.2-43.2)
Renal cell carcinoma	0 (0.0)	1 (0.3)	1 (0.6)	0.0 (0.0-101.5)	4.4 (0.1-24.4)	3.7 (0.1-20.8)
Unknown primary site	2 (2.9)	13 (3.4)	13 (7.9)	14.2* (1.7-51.1)	19.6* (10.4-33.5)	16.8* (8.9-28.7)
All non-AIDS related cancers	19 (27.9)	115 (30.3)	69 (41.8)	4.4* (2.7-6.9)	5.5* (4.5-6.6)	3.1* (2.4-3.9)

NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio; CI, confidence interval; CNS, central nervous system. *P < 0.05
Note: Cancers with no reported cases in the period between 1987 and 2003 were excluded from the table (CNS NHL, Small intestine, Trachea, Bones & Joints, Ovary, Testes, Mesothelioma, and Testis seminoma)

have a positive influential effect. For non-AIDS related cancers the decreasing trend started after HAART availability (1998). However, during this period the risk remained significantly higher for non-AIDS related cancers such as Hodgkin lymphoma, anus, liver, oropharyngeal, and larynx in Hispanics with AIDS in PR compared to the general population in PR as well as in people with AIDS in US compared with the general population in the US (4-5). However, different from the US (4), cancer of the vagina and vulva in females and eye and orbit cancer in both males and females were among the non-AIDS related cancers with a significant higher risk in Hispanics with AIDS in PR compared to the general population in PR. Also, only men with AIDS in PR had a significantly higher risk of Hodgkin lymphoma compared with the general population

in PR in all the time periods evaluated. Different from other studies (33), the risk of Hodgkin lymphoma in females with AIDS was not significantly higher than the general population in PR. It is important to highlight that Hodgkin lymphoma, liver, vaginal, anus, oropharyngeal, and eye and orbit have all been related to oncogenic viral infections such as hepatitis (HBV and HCV), HPV, and HHV-8 infection (33-36). Other factors such as injection drug use, alcohol abuse, smoking, and inadequate diet have also been related to many of these non-AIDS related cancers (33, 37). Therefore, to develop effective

Table 4. Risk of cancer among males and females with AIDS in Puerto Rico compared with the general population in Puerto Rico: 1987-2003.

	SIR (95% CI)					
	Males			Females		
Cancer Type	**1987-1989**	**1990-1995**	**1996-2003**	**1987-1989**	**1990-1995**	**1996-2003**
AIDS Related						
Kaposi sarcoma	178.3* (116.5-261.3)	183.4* (155.4-214.9)	192.6* (138.8-260.4)	2594.5* (842.4-6054.6)	783.0* (404.6-1367.8)	270.3* (55.7-790.0)
Non-Hodgkin lymphoma	57.5* (29.7-100.5)	55.6* (42.6-71.3)	31.7* (21.1-49.9)	131.6* (27.1-384.6)	90.6* (49.5-152.0)	53.0* (26.4-94.8)
Cervix Uteri	NA	NA	NA	46.5* (9.6-135.8)	67.7* (43.4-100.8)	28.7* (14.8-50.2)
Non-AIDS Related						
Oral cavity and pharynx	~	4.8* (1.9-9.8)	6.8* (2.9-13.4)	~	~	10.6 (0.3-58.8)
Esophagus	~	1.6 (0.0-8.8)	~	~	~	~
Stomach	3.6 (0.1-20.0)	2.8 (0.6-8.2)	1.2 (0.0-6.7)	~	~	~
Colon and rectum	6.4* (1.3-18.7)	4.2* (1.9-8.1)	1.2 (0.2-3.4)	~	2.5 (0.1-13.9)	~
Anus	~	195.3* (93.6-359.1)	33.3* (4.0-120.4)	~	~	~
Liver	~	4.7 (0.6-17.1)	13.2* (5.3-27.2)	~	~	~
Gallbladder	~	19.8 (0.5-110.4)	~	~	~	~
Pancreas	~	4.6 (0.6-16.6)	3.1 (0.1-17.4)	~	~	~
Other digestive organs	~	34.0 (0.9-189.5)	~	~	229.1* (5.8-1276.2)	~
Nose, nasal cavity and middle ear	~	~	23.9 (0.6-133.3)	~	119.5* (3.0-666.0)	~
Larynx	9.1 (0.2-50.7)	4.2 (0.5-15.3)	6.3* (1.3-18.3)	~	~	~
Lung and bronchus	2.9 (0.1-16.2)	8.9* (4.9-15.0)	1.4 (0.2-5.2)	**	16.7* (2.0-60.4)	10.2* (1.2-36.7)
Soft tissue including heart	~	~	~	~	41.2 (1.0-229.3)	~
Melanoma of the skin	~	~	5.6 (0.1-30.9)	~	~	~
Other non-epithelial skin	~	65.6* (17.9-167.8)	~	~	~	~
Female breast	NA	NA	NA	~	4.3* (1.6-9.3)	1.4 (0.3-4.1)
Vagina and vulva	NA	NA	NA	~	42.5* (5.1-152.5)	33.9* (4.1-122.5)
Prostate	1.4 (0.0-7.8)	1.1 (0.5-2.3)	0.5 (0.1-1.4)	NA	NA	NA
Penis	~	3.9 (0.1-21.8)	5.3 (0.1-29.3)	NA	NA	NA
Urinary bladder	5.7 (0.1-31.7)	1.4 (0.0-7.6)	~	110.3*(2.8-614.5)	~	~
Kidney and renal pelvis	~	2.6 (0.1-14.3)	2.4 (0.1-13.6)	137.2* (3.5-764.7)	~	~
Eye and orbit	~	117.2* (56.2-215.6)	36.6* (4.4-132.2)	~	~	220.5* (26.7-796.5)
Brain	~	2.8 (0.1-15.6)	~	76.6* (1.9-426.9)	15.0 (0.4-83.3)	~
Thyroid	~	~	3.8 (0.1-21.4)	~	~	~
Hodgkin lymphoma	57.5* (15.7-147.3)	11.8* (3.2-30.3)	21.2* (6.9-49.6)	~	~	~
Myeloma	~	4.0 (0.1-22.1)	4.4 (0.1-24.6)	~	~	~
Lymphocytic leukemia	~	13.2* (1.6-47.8)	~	~	~	~
Myeloid and monocytic leukemia	11.6 (0.3-64.7)	~	~	~	~	~
Other leukemia	61.8* (1.6-344.3)	11.3 (0.3-62.8)	9.1 (0.2-50.7)	~	~	~
Renal cell carcinoma	~	3.5 (0.1-19.7)	3.6 (0.1-20.0)	~	~	~
Unknown primary site	13.6* (1.6-49.1)	17.6* (8.8-31.6)	10.4* (4.2-21.5)	0.0 (0.0-218.5)	18.6* (2.3-67.3)	35.4* (13.0-77.1)
All non-AIDS related cancers	4.2* (2.4-6.8)	5.0* (4.1-6.1)	2.8* (2.1-3.6)	4.7 (1.0-13.8)	5.3* (3.2-8.3)	3.2* (1.9-5.1)

NHL, non-Hodgkin lymphoma; SIR, standardized incidence ratio; CI, confidence interval; CNS, central nervous system. *P < 0.05
~No SIR provided because there were no reported cases during the specific time period.
Note: Cancers with no reported cases in the period between 1987 and 2003 were excluded from the table (CNS NHL, Small intestine, Trachea, Bones & Joints, Ovary, Testes, Mesothelioma, and Testis seminoma)

cancer prevention strategies for Hispanic men and women with HIV/AIDS, future studies must explore the effect of multiple risk factors in the development of non-AIDS related cancers such as gender, viral co-infections, smoking, hormone contraceptives, dietary and physical activity behavior, adherence and chronic use of HAART, number of sexual partners, and socio-economic status.

A limitation of this study is the small number of cases observed for many types of cancers and its effect on the stability of the SIR. A wide range of confidence intervals not reliable for comparative analyses are the result of this small number of cases (less than 5). For example, during HAART availability period the SIR for KS was higher in females (270.3) than in males (192.6). However, KS is more prevalent in males; therefore, more cases and narrower SIR confidence intervals for males (138.8-260.4) than females (55.7-790.0). Given the wide confidence intervals in the SIR for many types of cancers presented in this study, the clinical significance of these reported SIR should be interpreted with caution.

In conclusion, although a decreasing trend in the risk in all AIDS related cancers and non-AIDS related cancers has been observed among Hispanics with AIDS in PR, the risk remains significantly greater compared to the general population in PR, and that has not changed over time. It is possible that the increased life expectancy for people living with HIV/AIDS using HAART may help explain the unchanged cancer risk and potential increase in the risk of non-AIDS related cancers in the future. Clinicians and investigators must be aware of these risks and evaluate the effectiveness of early screening and other preventive strategies to reduce the cancer burden in this population.

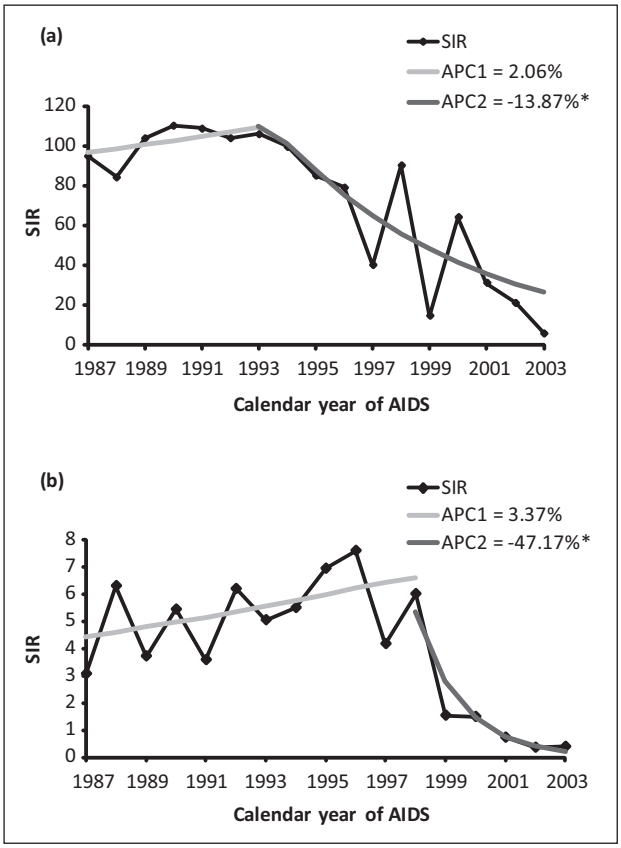

Figure 1. Risk of all AIDS related cancers (a) and all non-AIDS related cancers (b) in AIDS patients in Puerto Rico by calendar year from 1987 to 2003 using the Joinpoint regression model (APC, annual percent change; * P < 0.05)

Resumen

El riesgo de cáncer entre hispanos con el Síndrome de Inmunodeficiencia Adquirida (SIDA) en los Estados Unidos y Puerto Rico (PR) no se ha descrito claramente. El propósito de este estudio fue determinar el riesgo de cáncer relacionado y no relacionado con SIDA entre hispanos con SIDA en PR. Un pareo probabilístico se condujo entre los bancos de datos del Programa de Vigilancia de SIDA de PR y el Registro Central de Cáncer de PR. Los casos de SIDA fueron agrupados de acuerdo al año de diagnostico de SIDA y disponibilidad de terapia antirretroviral: 1987-1989 (disponibilidad limitada), 1990-1995 (terapias sencillas o duales), y 1996-2003 (terapias altamente activas, HAART). El riesgo de cáncer se describió utilizando la tasa de incidencia estandarizada (SIR). De un total de 612 casos de pacientes con SIDA, diagnosticados con cáncer luego de 3 meses del diagnóstico de SIDA, 409 (66.7%) fueron cánceres relacionados con SIDA y 203 (33.1%) no relacionados con SIDA. Aunque se observó una tendencia descendente en estas dos clasificaciones, el riesgo continuó siendo mayor en pacientes con SIDA comparados con la población general en PR. Durante la disponibilidad de HAART, los cánceres no relacionados con SIDA con mayor riesgo fueron: oro-faríngeo, ano, hígado, laringe, ojo y órbita, linfoma Hodgkin y vagina. Los hispanos con SIDA en PR muestran consistentemente mayor riesgo de cáncer relacionado y no relacionado con SIDA que la población general en PR, aspecto que no ha cambiado con el tiempo.

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