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Cancer Incidence and Risk Among HIV-infected Individuals in Taiwan: Results From a Follow-up Study Combining Two Nationwide Registries

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Abstract

Background: Previous epidemiological studies have reported an increased risk of some cancers in People Living With HIV/AIDS (PLWHA). This study was performed to investigate the epidemiology of cancers in PLWHA in Taiwan.

Methods: Data from Taiwan's National Health Research Database and the HIV/AIDS registry of Taiwan CDC were matched to identify HIV-positive cases from January 2001 to December 2016 who subsequently were diagnosed with cancer. These cases were then compared to general population controls in a 20 to 1 controls to cases ratio. The Incidence Density (ID) and Standardized Incidence Ratio (SIR) were calculated for each cancer.

Results: A total of 1,960 PLWHA with cancer were identified in this study period. For the AIDS-defining cancers, the highest ID per 100,000 person-years was for non-Hodgkin's lymphoma in males (ID=216.17) and cervical cancer in females (ID=480.24). The highest SIR was for Kaposi's sarcoma in males (SIR=252.29, 95%CI=224.49-284.23) and in females (SIR=166.67, 95%CI=53.71-338.94). For the non-AIDS defining cancers, the highest ID per 100,000 person-years was for liver and intrahepatic duct cancer (ID=96.75) in males and bronchus and lung cancer in females (ID=102.55). The highest SIR was for cancer of the anus or anal canal in males (SIR=46.02, 95%CI=36.55-57.2) and in females (SIR=18.75, 95%CI=3.77-54.78). Survival analysis showed that survival was worse in men without HAART and with cancer than in men with HAART and cancer.

Conclusion: PLWHA are at an increased risk of ADCs and NADCs and HAART improves survival. PLWHA should therefore be screened regularly and aggressively for early cancer detection and treatment.

Keywords: Epidemiology • Incidence • Risk • Cancer • HIV

Introduction

With the promotion of widespread HIV screening and improvements in treatment, People Living With HIV/AIDS (PLWHA) are living longer and are susceptible to developing chronic diseases and cancer. Previous cancer epidemiological studies have reported an increased risk of some cancers in PLWHA and different etiologies have been postulated [1-4]. Studies from different parts of the world have reported increased risk of different cancers [1,5-14]. In our previous 11-year study, we used Taiwan's National Health Insurance Research Database (NHIRD) to investigate the epidemiology of cancers in PLWHA [1]. However, because this database is based on claims data, there is the possibility that some cases with uncertain HIV diagnosis were included in the analysis. In this follow-up study, we combined the data from the NHIRD and the HIV/AIDS registry of Taiwan Centers for Disease Control (CDC) to make sure that only confirmed cases of HIV infection were enrolled. We investigated whether PLWHA were at an increased risk of cancers in a 16-year period.

Methods

The NHIRD was used to screen for all cases of HIV infection in Taiwan from January 1, 2001 to December 31, 2016 by using ICD-9-CM and ICD-10-CM codes. Individuals with less than three outpatient visits were excluded to omit false-positives, as the coding was revised in ELISA-positive cases if HIV confirmatory tests came back negative. These cases were then matched to the confirmed HIV-positive cases in the HIV/AIDS registry of Taiwan CDC and a total of 32,402 cases were identified. Cases with incomplete demographic data such as age (n=77) were excluded, as were cases with hemophilia (n=32) and those under 15 years of age (n=306), yielding a total of 31,987 adults HIV-infected cases. Cases were then screened for a subsequent diagnosis of cancer by using ICD-9-CM and ICD-10-CM codes. In accordance to previous studies backdating cancer cases, cases with cancers diagnosed up to 3 years before the first HIV clinic visit were also added to this group.

The general population controls for this study were randomly selected

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from a database linked to the Division of Statistics of the Ministry of Health and Welfare in a roughly 20:1 controls to cases ratio. A total of 592,220 controls were first selected after controlling for age and sex. Hemophilic patients (n=913) and children under 15 years of age (n=797) were then excluded, yielding a total of 590,510 controls (Figure 1).

Person-years was defined as the cumulative years between the first HIV/AIDS clinic visit and death or December 31, 2016. The Incidence Density (ID) of each cancer was calculated by dividing the number of observed cases of cancer by the total person-years at risk for that cancer. The Incidence Density Ratio (IDR) was defined as the ratio of ID of cases with HAART to the ID of cases without HAART. The Standardized Incidence Ratio (SIR) of each cancer was defined as the number of observed cancer cases divided by the expected cancer cases in the general population after adjusting for age, sex and calendar period. Cox proportional hazards regression analysis was performed for survival analysis of PLWHA cancer patients with or without HAART. In patients receiving HAART, the follow-up time began on the day when HAART was first prescribed. Statistical analysis was performed with SAS version 9.4 and statistical significance was set at $p < 0.05$.

Results

A total of 1,960 PLWHA with cancer (males=1755, females=205) were identified in this study period. (Table 1) There were 729 AIDS-Defining Cancers (ADCs) in males and 109 ADCs in females and there were 1,026 Non-AIDS Defining Cancers (NADCs) in males and 96 NADCs in females. For the ADCs in males, the highest ID per 100,000 person-years was for non-Hodgkin's lymphoma (ID=216.17) followed by Kaposi's sarcoma (ID=145.26), while in females, the highest ID per 100,000 person-years was for cervical cancer (ID=480.24) followed by non-Hodgkin's lymphoma (ID=199.32). For the NADCs in males, the highest ID per 100,000 person-years was for liver and intrahepatic duct cancer (ID=96.75), followed by oral cavity cancer (ID=64.14), bronchus and lung cancer (ID=41.41) and anus or anal canal cancer (ID=39.91); while in females, the highest ID per 100,000 person-years was for bronchus and lung cancer (ID=102.55), followed by breast cancer (ID=89.78), liver and intrahepatic duct cancer (ID=76.79) and uterine cancer (ID=63.83).

For the ADCs in males, the highest SIR was for Kaposi's sarcoma

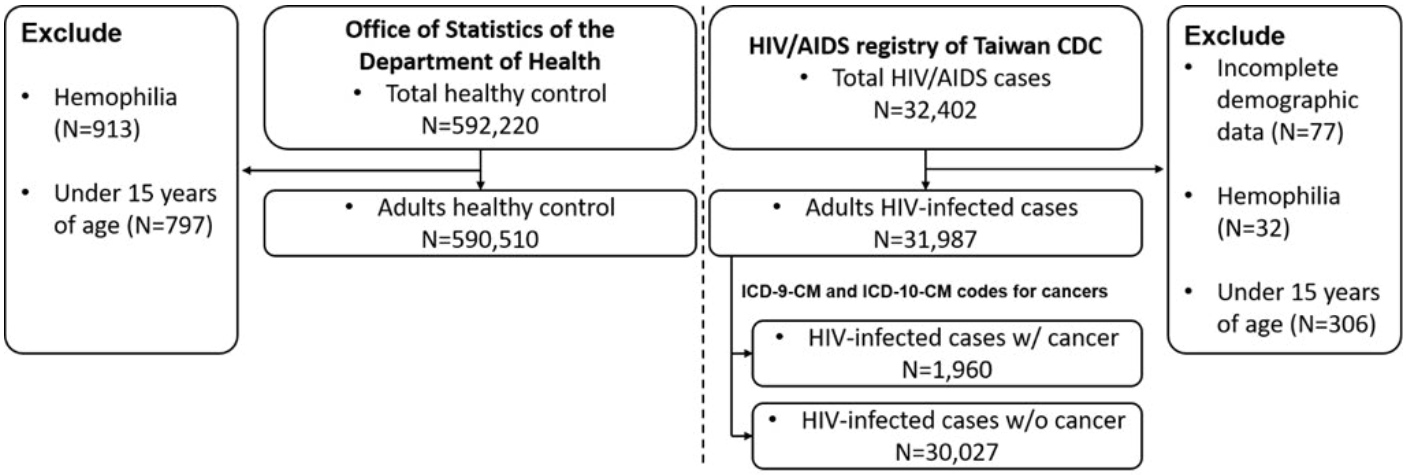

Figure 1. HIV/AIDS population selection flowchart.

Table 1. Incidence density and standardized incidence ratio of AIDS-related and non-AIDS-related cancers in male and female Taiwanese HIV-1/AIDS adult patients enrolled in the National Health Insurance between 2001–2016.

	Male(N=30,131)			Female(N=1,856)			Total(N=31,987)		
	Person-years=208,871.2			Person-years=16,214.1			Person-years=225,085.3		
Cancer	**Cases**	**ID[a]**	**SIR (95%CI)**	**Cases**	**ID[a]**	**SIR (95%CI)**	**Cases**	**ID[a]**	**SIR (95%CI)**
Total	1755	840.23		205	1264.33		1960	870.78	
AIDS-related	729	349.02		109	672.25		838	372.3	
Kaposl's sarcoma	293	145.26	252.59 (224.49-283.23)*	5	31.97	166.67 (53.71-388.94)*	298	132.39	250.42 (222.79-280.53)*
Non-Hodgkin's lymphoma	436	216.17	23.84 (21.65-26.18)*	31	199.32	25.83 (17.55-36.67)*	467	207.48	23.96 (21.84-26.24)*
Cervix				73	480.24	8.7 (6.82-10.94)*			
Non AIDS-related	1026	491.21		96	592.08		1122	498.48	
Lip	6	2.74	5 (1.83-10.88)*	0	-	-	6	2.67	5.0 (1.83-10.88)*
Oral cavity	130	64.14	2.83 (2.37-3.36)*	<3	6.38	1.52 (0.02-8.43)	131	58.2	2.81 (2.35-3.34)*
Oropharynx and hypopharynx	35	17.24	2.08 (1.45-2.89)*	<3	12.77	13.33 (1.5-48.14)*	37	16.44	2.18 (1.53-3)*
Nasopharynx	70	32.5	2.46 (1.92-3.1)*	<3	6.38	1.02 (0.01-5.68)	71	31.54	2.46 (1.92-3.1)*
Esophagus	10	4.57	0.72 (0.34-1.31)	0	-	-	10	4.44	0.71 (0.34-1.31)
Stomach	33	16.26	2.69 (1.85-3.78)*	4	25.54	4.12 (1.11-10.56)*	37	16.44	2.8 (1.97-3.85)*
Small intestine	10	4.92	4.05 (1.94-7.45)*	0	-	-	10	4.44	3.92 (1.88-7.21)*
Colon	56	27.6	1.57 (1-192.05)*	8	51.17	2.85 (1.23-5.61)*	64	28.43	1.67 (1.28-2.13)*
Rectum or rectosigmoid junction	51	25.12	7.53 (5.61-9.91)*	<3	12.77	2.82 (0.32-10.17)	53	23.55	7.09 (5.31-9.27)*
Anus or anal canal	81	39.91	46.02 (36.55-57.2)*	3	19.15	18.75 (3.77-54.78)*	84	37.32	43.75 (34.9-54.17)*
Liver and intrahepatic duct	196	96.75	2.71 (2.35-3.12)*	12	76.79	3.73 (1.92-6.51)*	208	92.41	2.76 (2.39-3.16)*
Pancreas	22	10.83	3.17 (1.99-4.81)*	3	19.15	4.92 (0.99-14.37)	25	11.11	3.32 (2.15-4.89)*
Larynx	10	4.57	1.72 (0.82-3.17)	0	-	-	10	4.44	1.72 (0.82-3.17)
Bronchus and lung	84	41.41	2.49 (1.98-3.08)*	16	102.55	5.08 (2.9-8.25)*	100	44.43	2.71 (2.2-3.29)*
Melanoma	3	1.48	2.04 (0.41-5.96)	0	-	-	3	1.33	1.9 (0.38-5.55)

Non-melanoma skin	42	20.69	5.16 (3.72-6.97)*	0	-	-	42	18.66	4.74 (3.41-6.4)*
Breast	0	-	-	14	89.78	1 (0.55-1.68)	14	6.22	0.97 (0.53-1.63)
Uterus	-	-	-	10	63.83	2.51 (1.2-4.61)*	-	-	-
Ovary	-	-	-	<3	6.38	0.46 (0.01-2.55)	-	-	-
Prostate	14	6.89	0.86 (0.47-1.45)	-	-	-	-	-	-
Testis	21	10.34	2.26 (1.4-3.45)*	-	-	-	-	-	-
Kidney and renal pelvis	20	9.85	2 (1.22-3.09)*	<3	6.38	1.2 (0.02-6.7)	21	9.33	1.94 (1.2-2.96)*
Brain	28	13.79	2.58 (1.72-3.73)*	5	31.95	7.14 (2.3-16.67)*	33	14.66	2.86 (1.97-4.02)*
Thyroid	11	5.41	0.83 (0.42-1.49)	5	31.96	1.31 (0.42-3.05)	16	7.11	0.94 (0.54-1.53)
Hodgkin's lymphoma	17	8.37	6.07 (3.53-9.72)*	0	-	-	17	7.55	5.82 (3.39-9.32)*
Multiple myeloma	18	8.86	8.87 (5.25-14.01)*	3	19.17	14.29 (2.87-41.74)*	21	9.33	9.38 (5.8-14.33)*
Leukemia	37	18.23	3.94 (2.77-5.43)*	3	19.17	3.8 (0.76-11.1)	40	17.77	3.93 (2.81-5.35)*
Bladder	21	10.34	1.61 (1.00-2.46)	0	-	-	21	9.33	1.52 (0.94-2.32)

[a]Incidence density per 100,000 person-years
*The SIR is significant
<3 Numbers of cases less than three

(SIR=252.29, 95%CI=224.49-283.23) followed by non-Hodgkin's lymphoma (SIR=23.84, 95%CI=21.65-26.18); while in females the highest SIR was also for Kaposi's sarcoma (SIR=166.67, 95%CI=53.71-388.94) followed by cervical cancer (SIR=31.47, 95%CI=24.66-39.56).

For the NADCs in males, increased SIRs were found for lip cancer, oral cavity cancer, oropharyngeal and hypopharyngeal cancer, nasopharyngeal cancer, stomach cancer, small intestine cancer, colon cancer, rectum and rectosigmoid junction cancer, anus or anal canal cancer, liver and intrahepatic duct cancer, pancreatic cancer, bronchus and lung cancer, non-melanoma skin cancer, testicular cancer, kidney and renal pelvis cancer, brain cancer, Hodgkin's lymphoma, multiple myeloma, leukemia and bladder cancer. The highest SIR was for cancer of the anus or anal canal (SIR=46.02, 95%CI=36.55-57.2), followed by multiple myeloma (SIR=8.87, 95%CI=5.25-14.01), cancer of the rectum or rectosigmoid junction (SIR=7.53, 95%CI=5.61-9.91) and Hodgkin's lymphoma (SIR=6.07, 95%CI=3.53-9.72).

For the NADCs in females, increased SIRs were found for oropharyngeal and hypopharyngeal cancer, stomach cancer, small intestine cancer, colon cancer, anus or anal canal cancer, liver and intrahepatic duct cancer, bronchus and lung cancer, uterine cancer, brain cancer and multiple myeloma. The highest SIR was for anus or anal canal cancer (SIR=18.75, 95%CI=3.77-54.78), followed by multiple myeloma (SIR=14.29, 95%CI=2.87-41.74), oropharyngeal and hypopharyngeal cancer (SIR=13.33, 95%CI=1.5-48.14) and brain cancer (SIR=7.14, 95%CI=2.3-16.67).

PLWHA in this cohort were then categorized as either receiving or not receiving Highly Active Antiretroviral Therapy (HAART). (Table 2) The IDR of cases with HAART to cases without HAART was increased in the ADCs, including Kaposi's sarcoma (IDR=2.79, 95%CI 1.82-4.31), non-Hodgkin's lymphoma (IDR=1.44, 95%CI 1.12=1.84) and cervical cancer (IDR=2.16, 95%CI 1.04-4.48). The IDRs were not statistically different in the NADCs.

Survival analysis showed that survival was worse in men without HAART and with cancer than in men with HAART and cancer (Figure 2).

Discussion

This population-based study showed that PLWHA had an increased risk of many cancers when compared to the non-HIV population. It also showed that the IDR of HAART cases to non-HAART cases was increased in the ADCs. In Taiwan, before 2016, HAART was started in PLWHA only if CD4 counts were below 200 cells/μl. Only after 2016 did the Taiwan CDC start to recommend initiation of HAART regardless of CD4 count. This may explain why in our study HAART patients were at a higher risk of cancer than non-HAART patients. Many of the patients who were given HAART were in a more advanced HIV disease stage (WHO stage 3 or 4) and were therefore at a higher risk of cancer. However, once HAART was started, these cancer patients had better survival than those without HAART. Studies have shown that long-term HIV suppression with HAART reduced ADC and NADC risks compared with the unsuppressed or early suppressed patients, indicating that reducing HIV-induced immunodeficiency with HAART may be a potent cancer prevention strategy [15,16], but these cancer risks were still higher than those in uninfected patients [17]. Fortunately, for some cancers such as Kaposi sarcoma and non-Hodgkin lymphoma, survival rates in PLWHA are improving and are nearing those in the general population [18].

The etiology of cancers in HIV-infected patients is complex. A combination of traditional risk factors such as age [19] and alcohol and smoking [20,21] viruses [2] and HIV-associated metabolic changes [22], immunosuppression and inflammation [5] may be related with oncogenesis. HIV infection is a risk factor for cancers associated with viral infections [22,23]. It has been hypothesized that HIV infection suppresses immune function and thereby allows oncoviruses to infect and survive in the host and hinder the surveillance of emerging tumors. Other forms of immunosuppression have also been reported to increase the risk of these cancers [24].

Some viruses known to be associated with cancer include Human Papillomaviruses (HPV) with cervical, anal, penile, vulvar, oropharyngeal and laryngeal cancer; hepatitis B and C viruses with liver cancer; Epstein–Barr virus with Hodgkin's lymphoma, Burkitt's lymphoma and nasopharyngeal carcinoma; Kaposi's sarcoma-associated herpesvirus with Kaposi's sarcoma; human T-cell lymphotropic virus-1 with adult T-cell leukemia and lymphoma; and Merkel cell polyomavirus with Merkel cell carcinoma [2]. Other viruses with a less clear but probable association with cancer include BK polyoma virus with bladder cancer [25] and HPV with prostate cancer [26]. Infection with the bacterium Helicobacter pylori is associated with gastric cancer [27].

In this study, the highest SIR for NADCs was for cancer of the anus or anal canal in both males and females. Previous studies have reported that the rates of anal cancer in HIV-infected patients have continued to increase despite of antiretroviral therapy [28-30]. The incidence of anal cancer in men-having-sex-with men has been estimated to be 80 times higher than in men in the general population [31]. Strickler HD, et al. reported that in PLWHA the risks of HPV replication and pre-cancerous intraepithelial neoplasia development increased with lower CD4 levels [32]. Guiguet M, et al. also reported that the risk of anal cancer in HIV patients increased if the CD4 count was <200 cells/mm^3 and the viral load was >100,000 copies/mL, suggesting that immunosuppression may play a role in the pathogenesis of anal cancer [33]. Bushara O, et al. proposed that in HIV-infected patients, chronic inflammation may upregulate the expression of the inhibitory receptor Programmed Death 1 (PD-1) on T cells, leading to the exhaustion of CD8+ T lymphocytes, which in turn may attenuate the cytotoxic response against the formation of anal precancerous and cancerous lesions [34]. In addition, the cumulative effect of genetic alterations on the host cell genome and transcriptome, such as alterations in cell cycle regulatory genes, DNA damage repair genes, tumor suppressor genes and apoptosis-related genes are also believed to play a role in anal carcinogenesis [35].

The SIR for multiple myeloma was also high in both males and females. The overall SIR (9.38) was higher than that reported by previous studies

Table 2. Incidence density and Incidence density ratio of AIDS-related and non-AIDS-related cancers with and without HAART in male and female Taiwanese HIV-1/AIDS adult patients enrolled in the National Health Insurance between 2001–2016.

	Male			Female			Total		
	With HAART (N=21,490)	Without HAART (N=8,641)		With HAART (N=1,333)	Without HAART (N=523)		With HAART (N=22,823)	Without HAART (N=9,164)	
	Person-years= 170,540.4	Person-years= 38,330.8		Person-years= 12,949.9	Person-years= 3,264.2		Person-years= 183,490.3	Person-years= 41,595.0	
Cancer	ID[a] (Cases)	ID[a] (Cases)	IDR (95%CI)	ID[a] (Cases)	ID[a] (Cases)	IDR (95%CI)	ID[a] (Cases)	ID[a] (Cases)	IDR (95%CI)
Total	832.06 (1419)	688.74 (264)	1.21 (1.05-1.39)*	1312.75 (170)	673.98 (22)	1.95 (1.25-3.06)*	909.58 (1669)	694.8 (289)	1.31 (1.16-1.48)*
AIDS-related	378.8 (646)	216.54 (83)	1.75 (1.38-2.23)*	741.32 (96)	398.26 (13)	1.86 (1.03-3.35)*	404.38 (742)	230.8 (96)	1.75 (1.4-2.18)*
Kaposl's sarcoma	164.86 (270)	60.64 (23)	2.72 (1.77-4.18)*	40.24 (5)	0	-(-)	156.07 (275)	55.9 (23)	2.79 (1.82-4.31)*
Non-Hodgkin's lymphoma	229.54 (376)	158.36 (60)	1.45 (1.11-1.9)*	210.73 (26)	155.54 (5)	1.35 (0.52-3.53)	228.23 (402)	158.14 (65)	1.44 (1.12-1.84)*
Cervix	-(-)	-(-)	-(-)	541.12 (65)	250.91 (8)	2.16 (1.04-4.48)*	36.67 (65)	19.45 (8)	1.89 (0.91-3.94)
Non AIDS-related	453.27 (773)	472.21 (181)	0.96 (0.82-1.13)	571.43 (74)	275.72 (9)	2.07 (1.04-4.14)*	505.2 (927)	464 (193)	1.09 (0.93-1.28)
Lip	3.63 (6)	0	-(-)	0	0	-(-)	3.38 (6)	0	-(-)
Oral cavity	61.89 (102)	73.94 (28)	0.84 (0.56-1.27)	X	X	X	58.11 (103)	68.15 (28)	0.85 (0.57-1.28)
Oropharynx and hypopharynx	17.56 (29)	15.82 (6)	1.11 (0.46-2.66)	X	X	X	16.89 (30)	17.01 (7)	0.99 (0.44-2.25)
Nasopharynx	35.17 (58)	31.64 (12)	1.11 (0.59-2.08)	X	X	X	33.27 (59)	29.17 (12)	1.14 (0.61-2.14)
Esophagus	4.24 (7)	7.91 (3)	0.54 (0.14-2.08)	0	0	-(-)	3.94 (7)	7.29 (3)	0.54 (0.14-2.08)
Stomach	16.35 (27)	15.82 (6)	1.03 (0.43-2.48)	32.13 (4)	0	-(-)	17.46 (31)	14.59 (6)	1.2 (0.5-2.89)
Small intestine	4.24 (7)	7.91 (3)	0.54 (0.14-2.08)	0	0	-(-)	3.94 (7)	7.29 (3)	0.54 (0.14-2.08)
Colon	27.27 (45)	29.02 (11)	0.94 (0.48-1.84)	64.41 (8)	0	-(-)	29.87 (53)	26.75 (11)	1.12 (0.58-2.14)
Rectum or rectosigmoid junction	25.44 (42)	23.73 (9)	1.07 (0.52-2.23)	X	X	X	24.78 (44)	21.87 (9)	1.13 (0.54-2.34)
Anus or anal canal	43.63 (72)	23.73 (9)	1.84 (0.92-3.67)	24.09 (3)	0	-(-)	42.26 (75)	21.88 (9)	1.93 (0.97-3.86)
Liver and intrahepatic duct	93.49 (154)	110.94 (42)	0.84 (0.61-1.17)	72.47 (9)	93.49 (3)	0.78 (0.21-2.89)	92.01 (163)	109.57 (45)	0.84 (0.61-1.17)
Pancreas	12.71 (21)	2.64 (<3)	4.81 (0.65-35.52)	0	0	-(-)	12.95 (23)	4.86 (<3)	2.66 (0.63-11.36)
Larynx	5.45 (9)	2.64 (<3)	2.06 (0.26-16.12)	0	0	-(-)	2.43 (9)	2.43 (<3)	1 (0.13-7.85)
Bronchus and lung	44.87 (74)	26.38 (10)	1.7 (0.87-3.32)	104.95 (13)	93.34 (3)	1.12 (0.32-3.9)	49.06 (87)	31.61 (13)	1.55 (0.86-2.8)
Melanoma	5.27 (<3)	0.61 (<3)	8.64 (0.79-94.63)	0	0	-(-)	0.56 (<3)	4.86 (<3)	0.12 (0.01-1.31)
Non-melanoma skin	21.81 (36)	15.82 (6)	1.38 (0.58-3.25)	0	0	-(-)	20.28 (36)	14.59 (6)	1.39 (0.59-3.29)
Breast	-(-)	-(-)	-(-)	96.79 (12)	62.58 (<3)	1.55 (0.35-6.89)	6.76 (12)	4.86 (<3)	1.39 (0.31-6.17)
Uterus	-(-)	-(-)	-(-)	72.28 (9)	31.1 (<3)	2.32 (0.3-18.17)	5.07 (9)	2.43 (<3)	2.09 (0.27-16.44)
Ovary	-(-)	-(-)	-(-)	X	X	X	2.43 (<3)	0	-(-)
Prostate	7.27 (12)	5.27 (<3)	1.38 (0.31-6.11)	-(-)	-(-)	-(-)	4.86 (12)	4.86 (<3)	1 (0.23-4.44)
Testis	10.3 (17)	10.34 (4)	1 (0.33-3)	-(-)	-(-)	-(-)	9.57 (17)	9.72 (4)	0.98 (0.33-2.94)
Kidney and renal pelvis	8.48 (14)	15.83 (6)	0.54 (0.21-1.4)	-(-)	-(-)	-(-)	8.44 (15)	14.59 (6)	0.58 (0.23-1.49)
Brain	15.75 (26)	5.27 (<3)	2.99 (0.72-12.55)	40.21 (5)	0	-(-)	17.46 (31)	4.86 (<3)	3.59 (0.86-15.03)
Thyroid	4.84 (8)	7.91 (3)	0.61 (0.16-2.32)	40.23 (5)	0	-(-)	7.32 (13)	7.29 (3)	1 (0.29-3.49)
Hodgkin's lymphoma	9.08 (15)	5.27 (<3)	1.72 (0.39-7.46)	0	0	-(-)	8.44 (15)	4.86 (<3)	1.74 (0.4-7.54)
Multiple myeloma	7.87 (13)	13.18 (5)	0.6 (0.21-1.7)	24.12 (3)	0	-(-)	9.01 (16)	12.15 (5)	0.74 (0.27-2.01)
Leukemia	18.17 (30)	18.47 (7)	0.98 (0.43-2.23)	24.13 (3)	0	-(-)	18.59 (33)	17.03 (7)	1.09 (0.48-2.48)
Bladder	11.51 (19)	5.27 (<3)	2.18 (0.51-9.3)	0	0	-(-)	10.7 (19)	4.86 (<3)	2.2 (0.52-9.39)

[a] Incidence density per 100,000 person-years

* The IDR is significant

<3 Numbers of cases less than three

X Cannot be shown as case numbers less than three

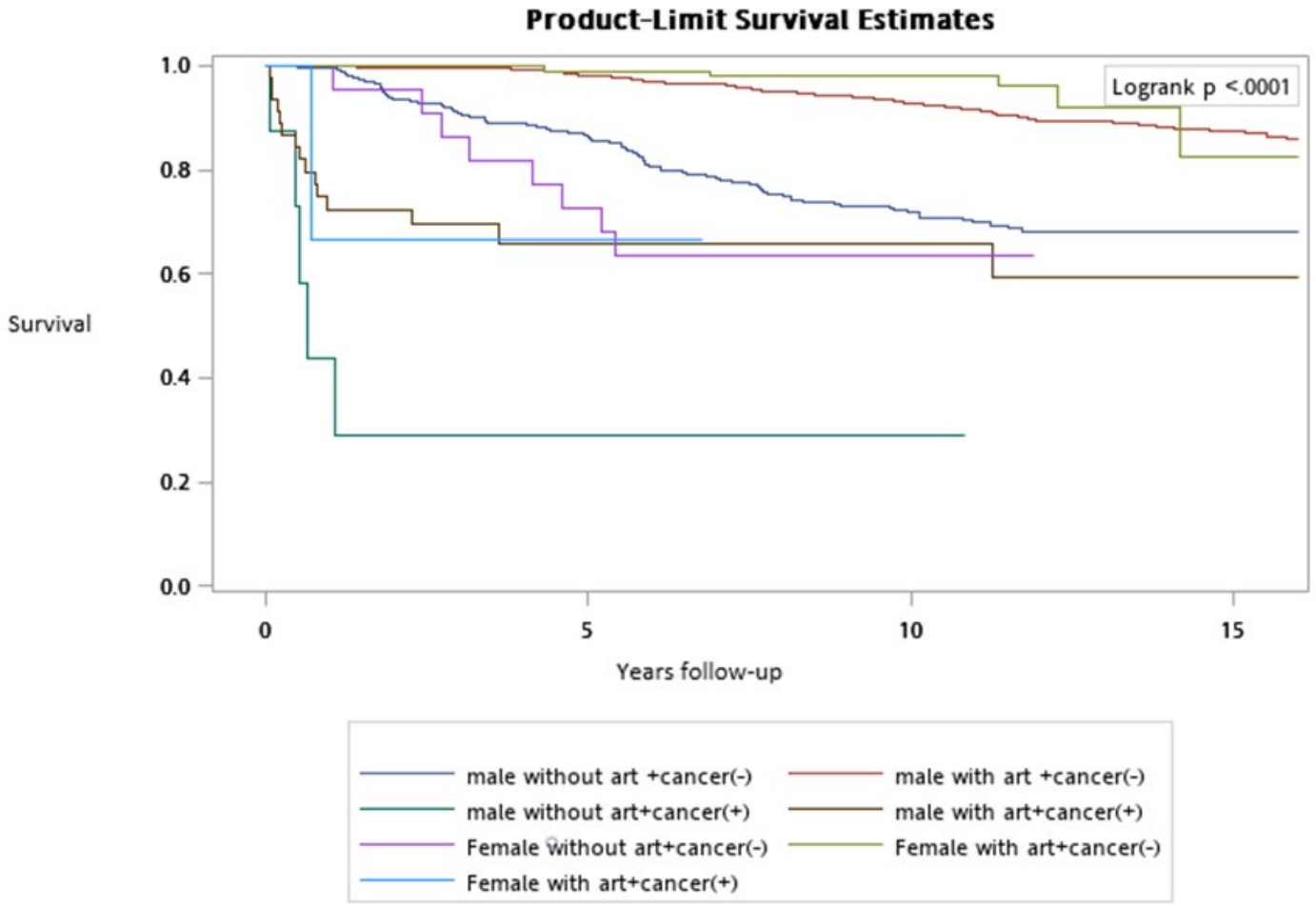

Figure 2. Survival curves of male and female Taiwanese HIV-1/AIDS patients with or without antiretroviral therapy (art) and cancer.

(SIR between 2.20 and 5.00) [36-43]. Gori, et al. reported three mechanisms that could be implicated in the development of multiple myeloma in PLWHA: 1) the production of a paraprotein (such as immunoglobulin) may serve as trigger to HIV viral antigens such as HIV-p24 and p55; 2) HIV-induced T-cell depletion or dysfunction may provoke B-cell activation, which in turn may result in increased immunoglobulin secretion, expression of activation markers and risk of malignant transformation; and 3) the expansion of T follicular regulatory cells seen in HIV may lead to altered regulation of B cells. This immunological dysregulation may lead to B cell abnormalities and result in lymphoid malignancies such as multiple myeloma [44].

Incidences of Cancers in PLWHA may vary among countries due to socioeconomic or structural barriers to cancer screening. Blair Spence, et al. even suggested the assessment of current cancer screening guidelines and the development of more aggressive and targeted implementation strategies in PLWHA [45].

In previous studies using the NHIRD, the HIV diagnoses could not be confirmed. In this study, we matched the NHIRD cases with those of the HIV/AIDS registry of Taiwan CDC to identify HIV-positive cases. This decreased the number of false-positive HIV cases in this cohort. The cancer cases were not linked to the population-based Taiwan Cancer Registry to confirm the cancer diagnoses because it only records cases from hospitals with a minimum of 50 beds capacity and therefore some cases may not have been registered.

Cases with cancers diagnosed up to 3 years before the first HIV clinic visit were included in this study because HIV diagnosis is often late. Previous studies backdated cases up to 5 years [37]. In this 16-year follow-up study, we used the same study design as in our previous 11-year study [1] and we also backdated cases 3 years for comparative purposes. In both studies, Kaposi's sarcoma had the highest SIR for ADCs in both males and females. In the previous study, the SIR for NADCs was highest for anus or anal cancer in males and for brain cancer in females, whereas in this study, the SIR was highest for anus or anal canal cancer in both males and females.

Conclusion

In conclusion, PLWHA are at an increased risk of ADCs and NADCs and HAART improves survival in these cancer patients. PLWHA should therefore be screened regularly and aggressively for early cancer detection and treatment.

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None.

Conflict of Interest

The authors declare no conflicts of interest.

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