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Cancers in the TREAT Asia HIV Observational Database (TAHOD): a retrospective analysis of risk factors

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Abstract

Background: This retrospective survey describes types of cancers diagnosed in HIV-infected subjects in Asia, and assesses risk factors for cancer in HIV-infected subjects using contemporaneous HIV-infected controls without cancer.

Methods: TREAT Asia HIV Observational Database (TAHOD) sites retrospectively reviewed clinic medical records to determine cancer diagnoses since 2000. For each diagnosis, the following data were recorded: date, type, stage, method of diagnosis, demographic data, medical history, and HIV-related information. For risk factor analyses, two HIV-infected control subjects without cancer diagnoses were also selected. Cancers were grouped as AIDS-defining cancers (ADCs), and non-ADCs. Non-ADCs were further categorized as being infection related (NADC-IR) and unrelated (NADC-IUR).

Results: A total of 617 patients were included in this study: 215 cancer cases and 402 controls from 13 sites. The majority of cancer cases were male (71%). The mean age (SD) for cases was 39 (10.6), 46 (11.5) and 44 (13.7) for ADCs, NADC-IURs and NADCs-IR, respectively. The majority (66%) of cancers were ADCs (16% Kaposi sarcoma, 40% non-Hodgkin's lymphoma, and 9% cervical cancer). The most common NADCs were lung (6%), breast (5%) and hepatocellular carcinoma and Hodgkin's lymphoma (2% each). There were also three (1.4%) cases of leiomyosarcoma reported in this study. In multivariate analyses, individuals with CD4 counts above 200 cells/mm³ were approximately 80% less likely to be diagnosed with an ADC ($p < 0.001$). Older age (OR: 1.39, $p = 0.001$) and currently not receiving antiretroviral treatment (OR: 0.29, $p = 0.006$) were independent predictors of NADCs overall, and similarly for NADCs-IUR. Lower CD4 cell count and higher CDC stage ($p = 0.041$) were the only independent predictors of NADCs-IR.

Conclusions: The spectrum of cancer diagnoses in the Asia region currently does not appear dissimilar to that observed in non-Asian HIV populations. One interesting finding was the cases of leiomyosarcoma, a smooth-muscle tumour, usually seen in children and young adults with AIDS, yet overall quite rare. Further detailed studies are required to better describe the range of cancers in this region, and to help guide the development of screening programmes.

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Background

HIV infection is associated with an increased risk of a range of cancers, including Kaposi sarcoma (KS), non-Hodgkin's lymphoma (NHL), and cervical cancer [1-3], which are designated as AIDS-defining cancers (ADCs) [4]. Cohort studies of people with HIV have consistently reported an increased risk for non-AIDS-defining cancers (NADCs), such as Hodgkin's disease, and anogenital cancers [1,3,5-10]. However, the epidemiology of cancer in HIV-infected people continues to evolve [11,12], particularly since the introduction of highly active antiretroviral therapy (HAART), which has led to significantly improved survival after HIV diagnosis [13-20].

The widespread use of HAART has resulted in decreases in the incidence of KS and NHL [11,21], although a decline in incidence for other cancers is less evident [11]. Additionally, as patients with HIV are living longer, malignancy is becoming an increasingly prominent cause of death [12,22-25]. Increasingly reported NADCs include lung cancer, liver cancer, anal cancer and leukaemia.

There are limited data on cancer occurrence in HIV-infected patients in Asia. Investigators at the Ramathibodi Hospital at Mahidol University, Bangkok, Thailand, a collaborating site of the Therapeutics Research, Education and AIDS Training in Asia (TREAT Asia) HIV Observational Database (TAHOD), have retrospectively reviewed pathological reports and medical records on malignancies and treatment outcome in Thai HIV-infected patients. Between 1999 and 2003, 3% of more than 1100 HIV-patients were diagnosed with malignancies. More than half (62%) were ADCs, NHL being the most common. NADCs included breast, colorectal and lung cancer.

In this study, treatment of the malignancy was the only significant factor associated with survival, while age, prior AIDS diagnosis and antiretroviral treatment history were not [26]. In India, among all cancers reported at the Tata Memorial Hospital in Mumbai from 2001 to 2005, 251 cases were identified to be in HIV-positive people, and more than half (56%) were NADCs. Among the ADCs, NHL was the most common, and there were no cases of KS. Among the NADCs, head and neck cancers were the most common [27].

Insight into the patterns of cancer occurrence in HIV/AIDS can be inferred from studies of cancer-identifying risk factors in other immune-deficient populations. Such populations include organ transplant recipients who undergo iatrogenic immune suppression post-transplantation. A recent large study of cancer occurrence in Australian kidney transplant recipients found a marked increase in cancer risk at a wide variety of sites. After transplantation, 25 cancer sites occurred at

significantly increased incidence, and risk increased three-fold at 18 of these sites. Most of these cancers were of known or suspected viral aetiology. These data suggest a broader than previously appreciated role of the interaction between the immune system and common viral infections in the aetiology of cancer [28,29].

Our objective was to undertake a retrospective survey of cancer diagnoses in HIV-infected subjects at the clinical sites in Asia that currently participate in the TREAT Asia HIV Observational Database (TAHOD). The specific aims of this study were to describe the range of cancers diagnosed in HIV-infected subjects in Asia, and to determine risk factors for cancer in HIV-infected subjects in Asia compared with contemporaneous HIV-infected subjects without cancer.

Methods

TAHOD commenced in 2003 and is a collaborative observational cohort study including 17 participating clinical sites in the Asia and Pacific region. A detailed description of this collaboration has been published previously [30]. TAHOD sites that maintained patient visit records from 2000 onwards were invited to participate in this retrospective case-control study. Individual TAHOD sites determined their capacity to review their entire clinic records for cases, or whether they restrict the review to TAHOD only patients.

In total, 13 of the 17 TAHOD sites were able to participate. Eight of the sites reviewed all clinic patient records regardless of whether patients were enrolled in the TAHOD study ($n = 7$ records from 2000; $n = 1$ record from 2004), totalling an estimated 12,000 patients. Four sites limited record reviews to patients within the TAHOD study ($n = 3$) or those participating in clinical trials ($n = 1$), approaching more than 800 patient records. In total, an estimated 13,000 patient records were reviewed to ascertain cancer cases. One site was not able to recruit controls.

Ethical approval for TAHOD was obtained from the University of New South Wales, Sydney, Australia, and for individual clinical sites from their local institutional review boards, as required. Unless required by a site's local ethics, written consent was not a requirement of sites in TAHOD because data are collected in an anonymous form. All TAHOD study procedures were developed in accordance with the revised 1975 Helsinki Declaration

Selection of cases

Contributing sites were required to review all medical records from 1 January 2000 (or later, if relevant) to 1 January 2008 to ascertain cases of cancer diagnosed. Only the first cancer diagnosed was considered for each case.

To standardize ascertainment and reporting across the sites, a half-day, face-to-face investigator training session was conducted. The facilitators of this training session were cancer epidemiologists from the National Centre in HIV Epidemiology and Clinical Research (NCHECR), and the Lowy Cancer Research Centre, University of New South Wales. The training included issues of determining morphology (histological classification of the cancer tissue, site and staging of the cancer, as well as establishing a date of diagnosis). The training also included describing the sources and hierarchy of information for a cancer diagnosis (e.g., pathology, biopsy, or cytology report, laboratory data, imaging, treatment details, autopsy report).

Participating sites were advised to report all pathological diagnoses of invasive/malignant, *in situ* or unknown/uncertain neoplasms. In the absence of histologic or cytologic confirmation, sites were advised to report a case based on a clinical diagnosis made by a recognized medical practitioner.

Selection of controls

For each case, two contemporaneous cancer-free, HIV-positive controls were selected from a complete list of patients attending the respective clinic on the day or corresponding week that the cancer case was first diagnosed. If both daily and weekly patient lists were available, then sites randomly selected two controls from the daily patient list. Instructions were provided to the sites to ensure a standardized approach for the selection of cases and control. The selection of controls was determined using the RANDBETWEEN function in Excel.

Data collection

Data were entered into an Access database developed at the NCHECR. The data were then forwarded to the NCHECR for case review and confirmation. The following data were obtained from patient medical records and reported for both cases and controls: date of birth (or age); sex; mode of HIV exposure (patient self-report); date of first positive HIV test; ethnicity; hepatitis B (HBV) and hepatitis C (HCV) status (defined as HBV surface antigen positive and HCV antibody positive, respectively); AIDS-defining illness diagnosed prior to case diagnosis; CDC stage; CD4 cell count at diagnosis; smoking and alcohol use (patient self-report); antiretroviral treatment history; and date of death (if known).

Case data included: date of diagnosis; site; morphology; method of diagnosis (e.g., pathology, cytology, radiology, laboratory data, clinical diagnosis, death certificate); stage; node; and class scheme. All measures (excluding death, patient demographics and cancer treatment) were recorded at the time of the cancer

diagnosis for the case, or at the time of the corresponding clinic visit for the control.

Case validation

Cancer cases were reviewed by a medical cancer epidemiologist at NCHECR, and clarification was sought from the sites as needed.

Data analysis

All cancers (excluding *in situ* neoplasms) were categorized into the following groups based on published reports (29-31): ADCs (KS, NHL and cervical cancer); NADCs infection-unrelated (NADCs-IUR); and NADCs infection-related (possible/probable) (NADCs-IR). NADCs-IR included: hepatocellular carcinoma, Hodgkin's lymphoma, leiomyosarcoma, and cancers of the anus, bladder, larynx, nasopharynx, oral cavity, penis, stomach, tongue and tonsils [29,31,32]. Key baseline demographic, HIV disease stage and health status were also summarized. Baseline was defined as the date on which the cases were first diagnosed with cancer, and for the controls, the date on which the control attended the clinic (on the day of, or within one week of the matched cases diagnosis date).

Statistical analysis

Conditional logistic regression methods were used to determine factors associated with ADCs and NADCs. The following baseline demographic and clinical factors were assessed as covariates: age; mode of HIV exposure; ethnicity; prior AIDS; CDC stage; CD4 cell count (within one year prior to case diagnosis); HBV and HCV status; antiretroviral treatment history; and smoking and alcohol use.

A sensitivity analysis for the NADC-IR endpoint was also conducted, excluding bladder, larynx and oral cavity cancers, less than 20% of which had been attributed to infections. All covariates with $p < 0.100$ in univariate analyses were assessed in the multivariate models. The final model included only covariates with $p < 0.05$. Forward stepwise methods were used. The site that was unable to identify controls was excluded from risk factor analyses. Analyses were conducted using Stata V10.0 (Texas, USA) and SAS V9.1 (Carey, NC, USA) statistical packages.

Results

A total of 617 patients were included in this study, including 215 cancer cases and 402 controls from 13 sites (nine cancer cases were from the site that did not recruit controls). The majority (65%) of cancer cases were ADCs ($n = 141$); of these, 62% were NHL, 24% were KS, and 14% were cervical cancers (Table 1). The

Table 1 Cancer diagnosis categorized by AIDS and non-AIDS defining, and summarised by sex

	Male	Female	Total
AIDS defining cancers (ADCs)			
Cervix	0	20	20
Kaposi sarcoma	32	2	34
NHL – Burkitt's	8	1	9
NHL – DLBL	20	4	24
NHL – Other	34	12	46
NHL – primary of brain	7	1	8
<i>Subtotal</i>	101	40	141
Non-AIDS defining cancers (NADCs)			
<i>NADC-IUR</i>			
Acute lymphocytic leukaemia	1	0	1
Acute promyelocytic leukaemia	1	0	1
BCC	1	0	1
Breast	0	10	10
Cancer of unknown primary	2	1	3
Colon	2	0	2
Endometrial	0	2	2
Facial sinus tumour - NOS	1	0	1
Kidney	1	0	1
Lung	11	1	12
Multiple myeloma	2	0	2
Oesophagus	2	0	2
Pancreas	1	0	1
Plasmacytoma	2	0	2
Rectum	2	1	3
Sarcoma – NOS	0	1	1
Thyroid	3	0	3
<i>Subtotal</i>	32	16	48
<i>NADC-IR</i>			
Anus	2	0	2
Bladder	1	0	1
Hepatocellular carcinoma	4	1	5
Hodgkin's lymphoma – NOS	1	0	1
Hodgkin's lymphoma – depletion type	1	0	1
Hodgkin's lymphoma – mixed cellularity	1	2	3
Larynx	1	0	1
Leiomyosarcoma – EBV associated	0	2	2
Leiomyosarcoma – smooth muscle tumour	0	1	1
Nasopharynx	1	0	1
Oral cavity	1	0	1
Penile	2	0	2
Stomach	2	0	2
Tongue	2	0	2
Tonsil	1	0	1
<i>Subtotal</i>	20	6	26
Grand total	153	62	215

DLBL: diffuse large B cell lymphoma; EBV: Epstein-Barr virus; NOS: Not otherwise specified

majority of KS cases were from Hong Kong (29%), Malaysia (18%), Philippines (15%), Bali (12%) and Taiwan (12%). One case was from Thailand, and there were no cases of KS reported from the India or Singapore sites (data not shown). Almost all KS cases were among men (32 of 34), of whom only 41% reported homosexual contact as mode of HIV exposure. Among NHL cases, 60% were among males, and 19% reported male homosexual contact as mode of HIV exposure.

Among the NADCs, 48 (22% of total cancers) were NADCs-IUR, and 26 (12% of total cancers) were NADCs-IR (probable/possible). Lung (25%) and breast cancer (21%) were the most common NADCs-IUR. Hepatocellular carcinoma (HCC) and Hodgkin's lymphoma were the most common NADCs-IR (19% each), followed by leiomyosarcoma (12%).

Patient demographics are summarized in Table 2. The majority of cancer cases were male (71%), and the mean age (SD) for the cases was 39 years (10.6) for ADCs, 46 (11.5) for NADCs-IUR and 44 (13.7) for NADCs-IR. The rate of current smoking was greater among the NADC-IR (15%), compared with 9% and 10% among the ADC and NADC-IUR groups, and 12% among the controls. Homosexual contact as mode of HIV transmission was reported by 19% of those with ADCs, compared with 6% among those with NADCs-IUR, 15% among those with NADCs-IR, and 11% among the controls. When cases of KS were excluded from the ADC group, only 13% reported homosexual exposure as mode of HIV transmission.

A larger proportion of ADC cases were of Chinese (34%) or Indian (31%) ethnicity, compared with NADC cases (21% and 31% NADC-IUR, and 31% and 15% for NADC-IR). A larger proportion of people with NADCs-IR were HCV positive (11%) compared with 4% among both ADC cases and NADC-IR cases, and 5% in the controls. A greater proportion of ADC cases had a prior AIDS diagnosis (49%) than NADC cases (31% NADC-IUR and 42% NADC-IR). Mean (SD) CD4 count was lower for ADC cases (176 cells/mm³: SD 195) compared with NADC cases and controls (non-infection-related cancers: 307 cells/mm³: SD 244; infection-related cancers: 257 cells/mm³: SD 211) and controls (309 cells/mm³: SD 242). Among the NHL cases, mean CD4 counts was highest for Burkitt's (210 cells/mm³: SD 119), lower for diffuse large B cell lymphoma (154 cells/mm³: 153) and other types (145 cells/mm³: SD 127), and lowest for primary NHL of the brain (77 cells/mm³: SD 105).

Predictors of ADCs

In univariate analyses, homosexual contact as the mode of HIV exposure ($p = 0.004$), CDC stage C ($p = 0.035$)

Table 2 Patient demographics at time of cancer case diagnosis for cases and controls

	ADC		NADC-IUR		NADC-IR		Controls		Total
Total	141		48		26		402		617
Male	101	71.6	32	66.7	20	76.9	279	69.4	432
Female	40	28.4	16	33.3	6	22.2	123	30.6	185
Mean age (SD)	39.0	(10.6)	45.7	(11.5)	44.4	(13.7)	38.8	(11.0)	39.6 (11.2)
Homosexual	27	19.1	3	6.3	4	15.4	43	10.7	77
Heterosexual	92	65.2	42	87.5	18	69.2	308	76.6	460
IDU	4	2.8	0	0.0	0	0.0	19	4.7	23
Other	18	12.8	3	6.3	4	15.4	32	8.0	57
Smoking									
Never	76	53.9	25	52.1	7	26.9	197	49.0	305
Ever	29	20.6	11	22.9	10	38.5	67	16.7	117
Current	13	9.2	5	10.4	4	15.4	47	11.7	69
Missing	23	16.3	7	14.6	5	19.2	91	22.6	126
Alcohol									
Never	77	54.6	29	60.4	8	30.8	218	54.2	332
Ever	25	17.7	8	16.7	6	23.1	59	14.7	98
Current	16	11.3	2	4.2	4	15.4	34	8.5	56
Missing	23	16.3	9	18.8	8	30.8	91	22.6	131
Caucasian	2	1.4	2	4.2	0	0.0	3	0.7	7
Chinese	48	34.0	10	20.8	8	30.8	119	29.6	185
Indian	44	31.2	15	31.3	4	15.4	132	32.8	195
Malay	4	2.8	0	0.0	0	0.0	9	2.2	13
Filipino	6	4.3	1	2.1	1	3.8	12	3.0	20
Thai	18	12.8	17	35.4	10	38.5	82	20.4	127
Indonesian	6	4.3	1	2.1	0	0.0	14	3.5	21
Vietnamese	1	0.7	0	0.0	0	0.0	0	0.0	1
Other	12	8.5	2	4.2	3	11.5	31	7.7	48
HBVS negative	73	51.8	24	50.0	16	61.5	232	57.7	345
HBVS positive	6	4.3	4	8.3	4	15.4	18	4.5	32
Missing	62	44.0	20	41.7	6	23.1	152	37.8	240
HCV negative	59	41.8	18	37.5	14	53.8	182	45.3	273
HCV positive	5	3.5	2	4.2	3	11.5	18	4.5	28
Missing	77	54.6	28	58.3	9	34.6	202	50.2	316
No prior AIDS	46	32.6	23	47.9	13	50.0	175	43.5	257
Prior AIDS	69	48.9	15	31.3	11	42.3	186	46.3	281
Missing	26	18.4	10	20.8	2	7.7	41	10.2	79
CDC A	35	24.8	15	31.3	4	15.3	109	27.1	163
CDC B	13	9.2	4	8.3	12	46.2	89	22.1	118
CDC C	89	63.1	22	45.8	9	34.6	190	47.3	310
Missing	4	2.8	7	14.6	1	3.8	14	3.5	26

Table 2 Patient demographics at time of cancer case diagnosis for cases and controls (Continued)

CD4 cells/mm ³									
<= 100	44	31.2	6	12.5	6	23.1	64	15.9	120
101-200	25	17.7	8	16.7	5	19.2	40	10.0	78
201-350	13	9.2	6	12.5	6	23.1	73	18.2	98
>= 351	16	11.3	10	20.8	5	19.2	102	25.4	133
Missing	43	30.5	18	37.5	4	15.4	123	30.6	188
Mean CD4 (SD)	176	(194.8)	307	(243.6)	257	(211.4)	309	(241.9)	275 (236.5)
ART									
Never	26	18.4	16	33.3	5	19.2	73	18.2	120
Ever	12	8.5	6	12.5	5	19.2	19	4.7	42
Current	90	63.8	24	50.0	14	53.8	294	73.1	422
Missing	13	9.2	2	4.2	2	7.7	16	4.0	33

ART: antiretroviral treatment; IDU: Injecting drug user

and CD4 cell count <100 cells/mm³ ($p < 0.001$) were associated with ADCs. In multivariate analyses, mode of HIV exposure and CD4 cell count remained as independent predictors of ADCs. Patients who reported heterosexual contact or injecting drug use as the mode of HIV exposure were at decreased risk of cancer compared with homosexual exposure (Odds Ratio (OR) 0.35, $p = 0.005$ and OR: 0.17, $p = 0.013$, respectively), and individuals with CD4 counts above 200 cells/mm³ were approximately 80% less likely to be diagnosed with an ADC ($p < 0.001$). After adjustment for these independent predictors, CDC stage was borderline significant ($p = 0.058$) (Table 3).

We also underwent a sensitivity analysis removing the KS cases and their controls from the logistic regression. Although the risks remained broadly similar for each of the exposure groups, overall, exposure category was no longer significant, and CD4 cell count remained the only independent risk factor for ADCs (data not shown).

Predictors of NADCs

Increasing age, a history of smoking status and not receiving antiretroviral treatment were significantly associated with increased NADC risk overall in univariate analyses ($p < 0.001$; $p = 0.024$; $p < 0.001$, respectively). Declining CD4 cell count was borderline significant ($p = 0.056$). Older age (OR: 1.39, $p = 0.001$) and currently receiving antiretroviral treatment (OR: 0.29, $p = 0.006$) remained as the only independent predictors of NADCs overall in the multivariate model.

After adjustment for these predictors, CD4 cell count and smoking status were no longer significantly associated with NADCs ($p = 0.419$ and 0.296 , respectively) (Table 4). We also adjusted CD4 cell count for age and

smoking covariates independently, and CD4 cell count remained non-significant ($p = 0.398$ and $p = 0.090$, respectively). In the regression analyses limited to the NADCs-IUR, increasing age and non-receipt of antiretroviral treatment were significant predictors in both univariate ($p = 0.001$ and $p = 0.002$) and multivariate analyses ($p = 0.005$ and $p = 0.008$) (Table 5).

Due to the small numbers, covariates assessed for association with NADCs-IR were limited to factors that were significant in univariate analyses for either the ADC or NADC overall endpoints. These included age, CDC stage, CD4 cell count, smoking status and antiretroviral treatment. As HCC was one of the most common NADCs-IR, and all five cases were either HBV surface antigen ($n = 4$) or HCV core antibody positive ($n = 3$), we also assessed coinfection with HBV or HCV. In univariate analyses, increasing age ($p = 0.023$), increasing CDC stage ($p = 0.032$), CD4 category >200 cells/mm³ ($p = 0.041$), and ever smoking ($p = 0.020$) were associated with NADCs-IR (Table 6). CD4 cell count and CDC stage remained significant in the multivariate analyses ($p = 0.041$ each). In the sensitivity analysis excluding bladder, larynx and oral cavity cancers ($n = 3$), the results remained largely unchanged (data not shown).

Discussion

In this retrospective case-control study, more than half (66%) the cancer cases identified were ADCs. The remaining cancers were either NADCs-IUR (22%) or NADCs-IR (12%). NHL was the most commonly reported ADC overall, as well as among men, while cervical cancer was the most common among women. Lung and breast cancers were the most commonly

Table 3 Factors associated with ADC

	Controls	Cases	OR	95% CI	p-value	p-overall	OR	95% CI	p-value	p-overall
Total	264	134								
Age per 5 years	39.2 (10.9)	38.5 (9.9)	0.969	0.871 1.079	0.57					
Male	179	96								
Female	85	38	0.77	0.44 1.32	0.340					
Homosexual	26	25								
Heterosexual	202	89	0.35	0.18 0.72	0.004	0.005	0.35	0.16 0.73	0.005	0.007
IDU	17	4	0.18	0.05 0.67	0.010		0.17	0.04 0.69	0.013	
Other	19	16	1.05	0.44 2.51	0.911		1.14	0.44 2.96	0.784	
Chinese	82	41								
Indian	94	44	0.24	0.03 2.08	0.196	0.328				
Other	88	49	1.25	0.55 2.83	0.590					
No prior AIDS	106	45								
Prior AIDS	124	63	1.31	0.81 2.13	0.273	0.247				
Missing	34	26	4.25	1.52 11.89	0.006					
CDC A	62	25								
CDC B	54	11	0.59	0.24 1.48	0.263	0.002	0.57	0.21 1.52	0.258	0.058
CDC C	137	94	2.18	1.06 4.51	0.035		1.73	0.76 3.94	0.191	
Missing	11	4	1.26	0.31 5.10	0.746		0.75	0.16 3.57	0.713	
CD4 cells/mm³										
<= 100	47	42								
101-200	26	24	0.84	0.41 1.72	0.637	<0.001	0.73	0.34 1.55	0.412	<0.001
201-350	51	13	0.20	0.09 0.45	<0.001		0.16	0.06 0.38	<0.001	
>= 351	60	14	0.20	0.09 0.43	<0.001		0.21	0.09 0.46	<0.001	
Missing	80	41	0.60	0.30 1.17	0.133		0.54	0.27 1.09	0.085	
Smoking										
Never	125	70								
Ever	83	41	0.86	0.50 1.48	0.583	0.357				
Missing	56	23	0.60	0.30 1.21	0.155					
Alcohol										
Never	141	71								
Ever	67	40	1.22	0.70 2.13	0.475	0.271				
Missing	56	23	0.64	0.31 1.31	0.218					
HBVS positive	149	70								
HBVS negative	9	5	1.21	0.36 4.00	0.758	0.558				
Missing	106	59	1.34	0.78 2.28	0.288					
HCV positive	117	55								
HCV negative	12	5	0.93	0.31 2.75	0.890					
Missing	135	74	1.39	0.79 2.45	0.255					

Table 3 Factors associated with ADC (Continued)

ART							
Never	48	26					
Ever/not current	14	12	1.58	0.66	3.78	0.304	0.126
Current	186	83	0.80	0.47	1.37	0.420	
Missing	16	13	1.86	0.67	5.18	0.235	

ART: antiretroviral treatment; IDU: Injecting drug user

Table 4 Factors associated with NADC (all)

	Controls	Cases	OR	95% CI	p-value	p-overall	OR	95% CI	p-value	p-overall		
Total	138	73										
Age per 5 years	38.0 (11.0)	45.0 (12.2)	1.41	1.19	1.66	<0.001	1.39	1.15	1.68	0.001		
Male	100	51										
Female	38	22	1.07	0.52	2.21	0.853						
Homosexual	17	7	1.00									
Heterosexual	106	59	1.51	0.46	4.92	0.494	0.926					
IDU	2	0	0.00	0.00		0.992						
Other	13	7	1.45	0.31	6.76	0.635						
Chinese	37	17										
Indian*	38	19	-	-	-	-						
Other	63	37	1.71	0.41	7.05	0.458						
No prior AIDS	69	35										
Prior AIDS	62	26	0.98	0.52	1.83	0.946	0.787					
Missing	7	12	9.15	1.88	44.61	0.006						
CDC A	44	17										
CDC B	34	14	1.13	0.45	2.85	0.799	0.179					
CDC C	56	33	1.70	0.74	3.91	0.214						
Missing	4	9	7.04	1.69	29.25	0.007						
CD4 cells/mm ³												
<= 100	17	12	1.00									
101-200	14	13	1.12	0.38	3.34	0.839	0.056	1.08	0.27	4.38	0.915	0.419
201-350	22	12	0.55	0.17	1.78	0.316		0.91	0.24	3.41	0.888	
>= 351	42	15	0.37	0.13	1.09	0.072		0.57	0.17	1.94	0.368	
Missing	43	21	0.64	0.25	1.67	0.366		0.78	0.25	2.45	0.667	
Smoking												
Never	72	31	1.00									
Ever	31	29	2.32	1.13	4.76	0.022	0.024	1.68	0.72	3.93	0.231	0.296
Missing	35	13	0.75	0.29	1.92	0.548		0.69	0.20	2.36	0.559	
Alcohol												
Never	77	36	1.00									
Ever	26	19	1.61	0.77	3.37	0.210	0.405					
Missing	35	18	0.95	0.41	2.19	0.900						

Table 5 Factors associated with NADC-IUR (Continued)

Alcohol												
Never	56	29	0.95	0.35	2.62	0.922	0.991					
Ever	18	9	0.94	0.31	2.88	0.916						
Missing	17	9										
HBVS negative												
HBVS positive	7	4	1.31	0.33	5.24	0.707	0.713					
Missing	33	19	1.43	0.59	3.44	0.430						
HCV negative												
HCV positive	3	2	1.33	0.11	15.73	0.820	0.535					
Missing	47	27	1.76	0.65	4.75	0.263						
ART												
Never	16	16										
Ever/not current	5	6	1.00	0.23	4.28	0.999	0.002	0.81	0.17	3.86	0.788	0.008
Current	70	23	0.23	0.09	0.62	0.004		0.26	0.09	0.74	0.012	
Missing	0	2	--	--	--	--		--	--	--	--	

ART: antiretroviral treatment; IDU: Injecting drug user

reported NADCs overall, and hepatocellular carcinoma was the most common NADC-IR. Factors associated with ADCs were immunodeficiency and lower CD4 cell count, while among NADCs overall and for NADCs-IUR, factors were older age and not currently receiving antiretroviral treatment. CDC stage C and lower CD4 cell count were significantly associated with NADCs-IR.

A novel finding in our study was the reporting of KS cases. KS has been thought to be relatively rare in some countries of Asia, largely attributed to the low prevalence of human herpes virus (HHV8) known to cause KS [33,34]. KS cases were largely reported from the Hong Kong site, and from Malaysia, the Philippines and Taiwan. In the Thai study, KS was reported in only 5% of ADCs [26], and no cases of KS were observed in the Mumbai study [27]. Almost all the KS cases in our study were among men (94%), of whom only 41% reported homosexual contact as the mode of HIV transmission. In western countries, KS occurs predominately among homosexual men [21]. We believe that our findings may reflect underreporting of male-to-male sex as a primary or concomitant risk factor for HIV infection in Asian countries.

The increased incidence of NADCs has been extensively reported in the literature [5,8,35-37]. Specific NADCs that have been reported to be higher in HIV-positive people than in HIV-negative people include Hodgkin's lymphoma, lung cancer, hepatocellular carcinoma [38], anal, vaginal, oropharyngeal, colorectal cancers, melanoma and leukemia [39], and cancer of the lips and testis [7].

Even in developing countries, where HAART is largely unavailable, the incidence of NADCs has increased. In India, there has been an increase in anal cancer, Hodgkin's lymphoma, testicular and colon cancers, and head and neck cancers [27]. In our study, lung and breast cancers were the most commonly reported NADCs, as well as head and neck cancers. Although lung cancer has been identified as one of several NADCs at increased incidence in HIV-infected patients, for breast cancer, the evidence of increasing incidence is still equivocal [31,35,40,41]. In the Thai study, the prevalence of breast cancer was 3%, and 10% of all NADCs, a little lower than our 14% of NADCs [26]. Head and neck cancers have been reported as the most common NADC in one Indian study [27].

Among the NADCs-IR, HCC was the most frequently reported. HCC is a commonly reported NADC in the literature, and is likely to remain important in HIV-infected populations, particularly in the context of coinfection with HBV and HCV [22]. In our study, all five cases were either HCV or HBV positive. Although we did not find a statistically significant association of HCV or HBV coinfection and NADCs-IR, this may be explained by low numbers, but may also likely be due to the inclusion of other cancers in this analysis, whose primary risk is not HBV or HCV infection.

Also of particular interest were the three cases of leiomyosarcoma reported, all in women. Leiomyosarcoma, smooth-muscle tumours, are usually seen in children and young adults with AIDS [42], yet overall are quite rare.

Table 6 Factors associated with NADC-IR

	Controls	Cases	OR	95%	CI	p-value	p-overall	OR	95%	CI	p-value	p-overall
Age per 5 years			1.43	1.05	1.94	0.023						
HCV core antibody												
Negative	32	16										
Positive	2	4	1.64	0.30	8.94	0.566	0.206					
Missing	13	6	0.82	0.23	2.89	0.756						
HBV surface antigen												
Negative	24	14	3.26	0.55	19.25	0.192	0.454					
Positive	3	3	1.03	0.25	4.21	0.972						
Missing	20	9										
CDC A	23	3										
CDC B	7	10	9.29	1.74	49.63	0.009	0.032	32.72	2.22	481.07	0.011	0.041
CDC C	16	11	5.96	1.11	32.13	0.038		12.14	0.84	175.11	0.067	
Missing	1	2	13.50	0.81	223.93	0.069		22.30	0.54	913.42	0.101	
CD4 cells/mm³												
<= 100	2	6										
101-200	5	5	0.26	0.02	2.85	0.271	0.021	0.79	0.04	14.43	0.876	0.041
201-350	10	6	0.05	0.00	0.94	0.045		0.03	0.00	2.15	0.108	
>= 351	19	5	0.03	0.00	0.44	0.011		0.01	0.00	0.48	0.022	
Missing	11	4	0.05	0.00	0.89	0.041		0.04	0.00	1.38	0.075	
ART												
Never	9	5	0.65	0.13	3.16	0.595						
Ever	38	19	-	-	-	-						
Missing	0	2										
Smoking												
Never	22	6										
Ever	8	14	6.06	1.52	24.21	0.011	0.020					
Missing	17	6	0.95	0.20	4.66	0.953						

ART: antiretroviral treatment

Epstein-Barr virus has been associated with this tumour, and only sporadic case reports have been published [43].

Factors associated with ADCs and NADCs

Immune suppression and exposure category were independently associated with ADCs in our study, similar to what has been reported in the literature [3,39]. The risk of an ADC decreased by approximately 80% with CD4 cell counts >200 cells/mm³, while patients who reported homosexual contact as the mode of HIV infection had an almost three-fold increased risk of an ADC compared with those who reported heterosexual contact, and six-fold increased risk compared with those who reported injecting drug use.

However, the exposure category effect we observed is largely explained by a greater proportion of KS

cases reporting homosexual contact. In the sensitivity analyses where KS cases were excluded, the homosexual exposure effect was removed, and immunodeficiency remained the only significant factor. A substantial proportion of patients in this study were diagnosed with HIV at the time of the cancer diagnosis, with more than a quarter of cancers diagnosed within one month of HIV diagnosis (28% and 26% of ADCs and NADCs, respectively). Late diagnosis may reflect particular marginalized groups, such as men who have sex with men, and their reluctance to seek medical care.

Older age and having never received antiretroviral treatment, but not CD4 count, were associated with being diagnosed with any NADC, both overall and for NADC-IUR, similar to other studies [3,37]. Longer

duration of HIV infection and a history of opportunistic infections have also been reported [35].

In our study, immune suppression (CDC stage and lower CD4 cell count) was associated with NADCs-IR. Several studies examining CD4 and NADCs during the HAART era have not found an association with CD4 [3,7,37]. However, these studies did not restrict their analysis to NADCs that are currently thought to be infection related. More recent data have shown several NADCs in HIV-positive patients to be increasing, similar to the risk seen in transplantation recipients, suggesting a link between immune suppression and increased risk of a specific NADC [29].

Smoking was not associated with NADCs-IUR, despite lung cancer being the most commonly cancer reported in this group, and yet a mild association was observed for NADCs-IR. We believe the lack of association with the NADC-IUR group is due largely to the inclusion of cancers where smoking is not a primary risk factor. The association with smoking and NADCs-IR on the other hand may reflect risk behaviour, where people who may engage in unprotected sex or drug use, which lead to viral coinfections, may also be more likely to smoke.

There are some limitations to this study. First, this is a retrospective survey of cancer cases and controls, and subject to selection bias and concerns regarding complete ascertainment of cases. Most sites reviewed all patient records for case ascertainment since 2000, while some sites reviewed more recent time periods or restricted review to TAHOD patients. Furthermore, there may be variation between TAHOD sites in the level of cancer screening, despite sites being primarily urban referral centres. Care must be taken in generalizing our results to Asian patients in other types of clinical centres or geographic locales.

Second, our division between NADCs-IUR and NADCs-IR may be debated. Included in our list of NADCs-IR were cancers where only a small proportion ($\leq 20\%$) were attributed to infections (including bladder, larynx and oral cavity). However, we did conduct a predictor analysis for NADCs overall, as well as dividing cases by relationship to infection, and our results were consistent with what has been shown previously in the literature. Finally, we did not have enough NADC cases to examine patient characteristics and factors associated with individual cancers potentially masking risk factors for specific cancers, such as that demonstrated by smoking and lung cancer. Nor did we collect any other behavioural data beyond smoking and alcohol use.

Conclusions

In conclusion, the spectrum of cancer diagnoses in the Asia region currently does not appear dissimilar to that observed in non-Asian HIV populations. Key findings in

our study include the much more commonly diagnosed KS than expected, as KS has been widely thought to be rare in Asia. This may reflect a common misreporting of HIV exposure among men in Asia. Second, we identified three cases of leiomyosarcoma, a rare and uncommonly reported malignancy, with links to Epstein-Barr virus.

Third, this is the first study to our knowledge to have examined both infection-related and infection-unrelated NADCs in the Asia region. Given the diversity in prevalence and infectious agents between countries within this region, further detailed studies are required to better describe the range of cancers in this region. To this end, new diagnoses of cancers have been prospectively reported in TAHOD since 2008. These studies will help guide where screening programmes are needed.

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Authors' contributions

The TAHOD Steering Committee was responsible for the overall design of the TAHOD Retrospective Cancer Study. KP, ML and AG designed the current study concept. KP conducted the statistical analyses and drafted the manuscript. All members of the writing committee (KP, EH, NK, SK, JC, YC, TM, FJ, PL, SS, SP, RD, CL, AG and ML) discussed the analysis plan, contributed to interpretation of the analysis results and commented on drafts of the manuscript. All authors approved the final manuscript draft for journal submission.

Competing interests

The authors declare that they have no competing interests.

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