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Cancers in the Australian HIV Observational Database (AHOD)

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Abstract

Objectives—To conduct a within cohort assessment of risk factors for incident AIDS defining cancers (ADC) and non-ADC (NADC) within the Australian HIV Observational Database (AHOD).

Methods—2181 AHOD registrants were linked to the National AIDS Registry/National HIV Database NAR/NHD and the Australian cancer registry to identify those with a notified cancer

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diagnosis. Included in the current analyses were cancers diagnosed after HIV infection. Risk factors for cancers were also assessed using logistic regression methods.

Results—139 cancer cases were diagnosed after HIV infection among 129 patients. More than half the diagnoses (n=68, 60%) were ADC, of which 69% were KS and 31% NHL. Among the NADC, the most common cancers were melanoma (n=10), lung cancer (n=6), and 5 cases each of Hodgkin's lymphoma and anal cancer. Over a total of 21021 person years (PY) of follow-up since HIV diagnosis, the overall crude cancer incidence rate for any cancer was 5.09/1000 PY. The overall rate of cancers decreased from 15.9/1000 PY (95%CI: 9.25-25.40/1000) for CD4 counts below 100 cells/μL to 2.4/1000 PY (95%CI: 1.62-3.39/1000) for CD4 counts above 350 cells/μL. Lower CD4 cell count and prior AIDS diagnoses were significant predictors for both ADC and NADC.

Conclusion—ADC remain the predominant cancers in this population, although NADC rates have increased in the more recent time period. Immune deficiency is a risk factor for both ADC and NADC.

Keywords

HIV/AIDS; cancer; antiretroviral treatment; cohort

Introduction

Historically three cancers in HIV positive patients have been designated as AIDS defining cancers, Kaposi's Sarcoma (KS), non-Hodgkin's lymphoma (NHL) and cervical cancer. The incidence of several other cancers has also been reported to be elevated in HIV positive patients. These include many infection related cancers, such as human papillomavirus (HPV) associated cancers, Hodgkin's lymphoma (HL), and liver and stomach cancer (1-3). The extent to which lifestyle factors such as smoking and alcohol use, or immune deficiency contributes to these increased rates is still under debate (1, 4). Since the introduction of effective combination antiretroviral therapy (cART), the incidence of AIDS-defining malignancies (ADC) has declined, although they remain elevated compared with rates of these cancers in the general population (5-7). It is less certain, if a similar decrease in incidence has occurred post-cART for many of the other non-ADC (NADC) (5, 7).

A large national data linkage study conducted in Australia, linking the national HIV and AIDS registers to the national cancer registry, reported a dramatic decline in KS and NHL from pre to post-cART (5). Large declines in NHL and KS have also been demonstrated in Switzerland (7), Italy (8) and the US since the introduction of cART (2, 9). Among the NADC, HL incidence was elevated in the early cART era (1996-1999) in Australia, although it appears to have declined in more recent years (5). In other countries elevated HL rates in the era of cART have also been reported, yet unlike Australian patterns, incidence rates have remained unchanged between earlier and later cART years (3). Other commonly reported NADC that continue to occur at higher rates in HIV positive patients during cART era are anal cancers (3, 5, 7), and lung cancer (3, 5).

Declining CD4 cell count has an established link with reduced incidence of ADC, in particular KS and NHL (8, 10-13). However, data regarding immunedeficiency and NADCs is conflicting, with some studies reporting an association between CD4 cell count and NADC (14, 15), while others have not (8, 16-18). Infection related NADC in particular have been demonstrated to be associated with immunedeficiency (1, 14). cART is also independently associated with a reduced risk of cancer, in particular ADC (11), yet the impact of HIV therapy on NADC is less is understood.

In Australia there remains limited data assessing associations between cancer risk and HIV related factors; notably CD4 cell count and ART use. The objective of this study was to quantify the rate of incident cancer within the Australian HIV Observational database (AHOD) and to assess risk factors associated with these cancers.

Methods

AHOD is a prospective cohort study of HIV positive patients under routine clinical care. AHOD commenced in 1999, and currently has 27 sites around Australia including HIV tertiary referral centres, HIV specialist general practice clinics and sexual health clinics. Key clinical data are transferred to the coordinating centre, the Kirby Institute, UNSW, on a six monthly basis. These data include patient demographics, HIV disease stage, and antiretroviral treatment history. A detailed description of this cohort has previously been published (19).

Cancer diagnoses

In 2007, data linkage between the Australian Cancer Database (ACD), and the Australian National HIV Database (NHD) and National AIDS Registry (NAR) was conducted to ascertain incident cancer cases among HIV positive Australians. The linkage procedures between the ACD and the HIV/AIDS registries have been described in detail previously (5). Briefly, the ACD included all incident invasive cancers diagnosed in Australian residents since 1982 (up to 2005), excepting nonmelanoma skin cancer. Date of diagnosis and ICDO-3 and ICD10 codes for tumour topography and morphology were obtained for matched records. Records were linked based on two-by-two name code (first two letters of surname followed by first two letters of first name) sex and date of birth. These are the identifiers that are routinely collected for HIV positive patients in Australia.

The AHOD cohort was subsequently linked to the NHD/NAR records. Records were linked as described above based on two-by-two name code sex and date of birth. AHOD patients provided informed consent. Approval to link AHOD to the HIV/AIDS register was also obtained by all relevant Australian jurisdictional health departments and institutional review boards.

Cancer categorisation

Cancers were determined to have occurred after HIV infection if they satisfied any of the following three criteria. First, the date of cancer diagnosis occurred after HIV diagnosis. Second, in the case where date of HIV diagnosis is unknown, if the cancer diagnosis occurred after enrolment into AHOD. Finally, if participants were receiving cART for at least 1 month prior to date of cancer diagnosis. Cancers were then categorised as ADC if they were either KS, NHL or cervical cancers. All other cancers were categorised as NADC. We also categorised each incident cancer as either infection-related (IR) or non-infection-related (NIR). Included as infection-related cancers were all cancers that have a known infectious cause, as well as those possibly or probably associated with an infectious agent. Examples of these include cancers that are related to Epstein-Barr-Virus (Hodgkin lymphoma, non-Hodgkin lymphoma, nasopharynx), human herpesvirus 8 (HHV-8; KS); HPV (cervix, vagina, penis, anus, oral cavity and pharynx); possibly HPV related (non-melanoma skin cancer, oesophagus, larynx, eye); Hepatitis B and C (liver) and helicobacter pylori (stomach) (1, 20), schistosoma haemotobium (blood fluke) (bladder) (20), and leukaemia, which was similarly elevated in two immune suppressed populations (organ transplant recipients and HIV positive patients)(1), possibly explained by infection with an unknown organism (21).

Statistical analysis

Patient characteristics (age, sex, mode of HIV exposure, CD4 cell count, and HIV viral load, and prior AIDS, antiretroviral treatment (ART)) at the time of diagnosis were described for all cancers overall and by ADC and NADC categories.

For participants with known HIV positive dates, crude incidence rates were calculated from HIV positive diagnosis to the first cancer, and for KS, NHL and NADC. Age standardised rates were calculated by calendar periods (≤1992, 1993-1996, 1997-1999, and ≥2000), and incidence rate ratios were also calculated for calendar periods (reference group ≥2000). Crude rates were also determined for time updated CD4 category cells/μl (<100, 100-199, 200-349, and 350+). All patients were censored on 31st of December 2005 (last date for which cancer diagnoses were available). Person-years (PY) were calculated from first positive date to first cancer diagnosis, death or last follow-up visit.

Risk factors were assessed for NADC and ADC using poisson regression methods. Key a priori covariates assessed were age, CD4 category, HIV viral load, and prior AIDS (all assessed as time updated). Factors with p-value < 0.05 in univariate analyses were then assessed in multivariate analyses using forward stepwise regression methods. All analyses were conducted using STATA version 11 (STATA Corporation, College Station, Texas, USA).

Results

A total of 139 linked cancers (n=129 patients) were identified in the 2181 AHOD registrants. Table 1 lists all cancers types diagnosed, and whether they were infection or non infection related. 88 cancers (63%) were ADC, of which 61 (69%) were KS, and the remaining 27 (31%) were NHL. Among the NADC, the most common cancers were melanoma (n=10), lung cancer (n=6), and 5 cases each of Hodgkin lymphoma and anal cancer. The majority (78%) of all cancers were infection-related.

All but one of the cancers was diagnosed in males. The median age at cancer diagnosis was 43 years (Interquartile range (IQR):37-52), and was slightly lower for ADC (median: 41; IQR: 36-49) compared with NADC (median: 50; IQR: 39-56). Similarly, the median age at cancer diagnosis was lower for IR (median: 43; IQR: 37-51) compared with NIR cancers (median: 49; IQR: 38-57) (Table 2).

Incidence rate

Among the 2181 AHOD patients, 1793 had a recorded date of HIV diagnosis, including 107 of the 129 individuals diagnosed with cancer. Among these patients, there was total of 21021 person years of follow-up since the date of HIV diagnosis, yielding an overall crude cancer incidence rate of 5.09/1000 person years. Table 3 reports the age standardised cancer rates by calendar periods, and incidence rate ratios by KS, NHL and non-AIDS defining cancers. Cancer incidence was greatest during the period 1993 to 1996 for all cancers (5.43/1000 PY 95%CI: 3.54-8.05) and for KS (2.85/1000 PY 95%CI: 1.51-4.83). The rate of NHL was greatest during 1997 to 1999 (1.44/1000 PY 0.54-3.01), while for NADC the rate was the greatest in the most recent calendar period (2.15/1000, PY 95%CI 1.37-3.31). Compared to the latest calendar period (2000 onwards) the only standardised incidence rate ratios which were significantly reduced were for NHL and NADC rates prior to 1992 (Incidence rate ratio (IRR): 0.38 95%CI: 0.09-0.95; and IRR: 0.13, 95%CI 0.03-0.30 respectively).

Crude cancers rates also decreased with increasing CD4 cell count category for all cancers, from 15.9/1000 PY (95%CI: 9.25-25.40/1000 PY) for CD4 counts below 100 cells/μL to

2.0/1000 PY (95%CI: 1.15-3.17/1000 PY) for CD4 counts above 500 cells/μL. Similar decreasing trends were observed for KS, NHL and NADC overall (Figure 1).

Predictors of ADC

In univariate analyses, not receiving ART (p=0.040), lower CD4 cell count category (p<0.001), detectable (>400 copies/ml) HIV viral load (p<0.001), and having a prior AIDS diagnosis (p<0.001) was significantly associated with ADC diagnoses (Table 4). These factors remained significant in multivariate analyses.

Predictors of NADC

In univariate analyses, increasing age, having a prior AIDS diagnosis and low CD4 cell count were significantly associated with an increased risk of an NADC diagnosis (Table 5). In multivariate analyses, the independent risk factors for a NADC diagnosis were increasing age (p<0.001) and having a prior AIDS diagnosis (p=0.004).

Discussion

AIDS-defining cancers were the most common cancers diagnosed in a contemporary cohort of HIV positive Australians. Nonetheless, crude rates of NADC diagnosed appeared to increase in the most recent calendar period. Among the NADC, melanoma and lung cancer were the most common, followed by HL and anal cancer. The rates of cancer decreased as CD4 cell counts increased. This was observed for cancers overall, for ADC and NADC, and for individual cancers such as KS and NHL.

Similar findings have been reported in other studies. In the Swiss HIV Cohort Study (SHCS), the incidence of all ADC and NADC declined in the later cART era. Even NADC that appeared to increase in incidence in the early cART era, began to decline in the later periods, such as anus, liver and nonmelanoma skin cancer. In Australia, while melanoma risk overall has previously been reported as slightly higher in HIV positive patients compared to the general population (22), more recent findings indicate a significantly decreased risk in HIV positive patients compared to the general population in the later cART era (5). Lung cancer remains raised in HIV positive patients, despite a decline in risk from the pre-cART to late cART era (5). This may in large part be due to increased smoking rates among men who have sex with men (the group overwhelmingly represented in the HIV epidemic); they are reported to be two-fold greater than the general population (42% versus 23%)(23). Although also elevated compared to the general population, cancer of the anus remained stable throughout the entire cART era, with little evidence of a decline (5).

More advanced HIV disease defined by either low CD4 cell count or prior AIDS diagnosis, was an independent risk factor for both ADC and NADC in our study. Although some studies have reported no significant association between decreasing CD4 cell count and increased risk of NADC (6, 8, 16-18), this might at least in part be explained by including cancers that are not thought to be infection related. In a previous analysis investigating cancers in the TREAT Asia HIV Observational Database (TAHOD), declining CD4 cell count was significantly associated with an increased of infection related cancers, but not for non-infection-related cancers (14). In the current study, prior AIDS was a significant independent predictor of NADC, although CD4 cell count was not. It is possible that grouping all NADC together may attenuate any CD4 associations that may exist for individual cancers. However, we were underpowered to investigate individual NADC (15). The low risk of NADC by CD4 count, in particular for CD4 counts below 100 cells/μl (Figure 1) may in part be explained due to competing risks, where patients have died due to

other HIV related events. This may also in part explain low rates of NADC pre-1992 (Table 3).

In our study, cART use was significantly protective against ADC risk, although this was not the case for NADC. Likewise in the Swiss HIV Cohort Study there was a significantly lower risk of ADC in cART users (HR 0.26, 95%CI: 0.20-0.33) compared with non-cART users (11). In the Chelsea and Westminster cohort, cART use was associated with an increased risk of NADC (15). We may not have seen a significant association between cART use and risk of NADC due to relatively low numbers of NADC in our analysis. Alternatively, CD4 count was time updated in our analysis, which may have taken into account any effect of cART use.

Unsurprisingly, ageing was significantly associated with all cancers; NADC in particular. As result of effective cART, patients are now living longer, and are therefore at increased risk of many age associated comorbidities including non-AIDS cancers. In the Swiss and Italian studies, the increased incidence of NADC in the era of cART was largely explained by ageing of HIV positive patients (7, 8). Increasing age was also associated with an increased risk of NADC in Asia (24).

There are some limitations to this study. First, we were limited by the number of events in this cohort. Our event rate is similar to that reported in other studies, but overall these are small numbers, and we were therefore unable to assess the risk of individual cancers. For instance, we identified only four cases of anal cancer which is now the most common non-AIDS defining cancer among the predominantly gay male population of HIV-positive Australians (5). Longer follow-up and larger numbers in the cohort are required. Second, linkage was based on two-by-two name code, date of birth and sex, which may affect the sensitivity of the linkage and cancer ascertainment. A pilot study previously conducted by our group, linking NSW AHOD patients to the state births deaths and marriages registry using two by two name code, date of birth, and sex, demonstrated a very high sensitivity of 99.8% and a specificity of 81% (unpublished data). If similar rates apply to our current linkage study, then this would result in an under-ascertainment of true cancers. Finally, we were unable to assess behavioural risk factors for cancer such as smoking and alcohol use.

In summary, we found both ADC and NADC are strongly associated with immunedeficiency. Further, there appears to be some evidence of increasing numbers of NADC most likely due to ageing. Longer follow-up will be required to investigate individual or rarer cancers in the future.

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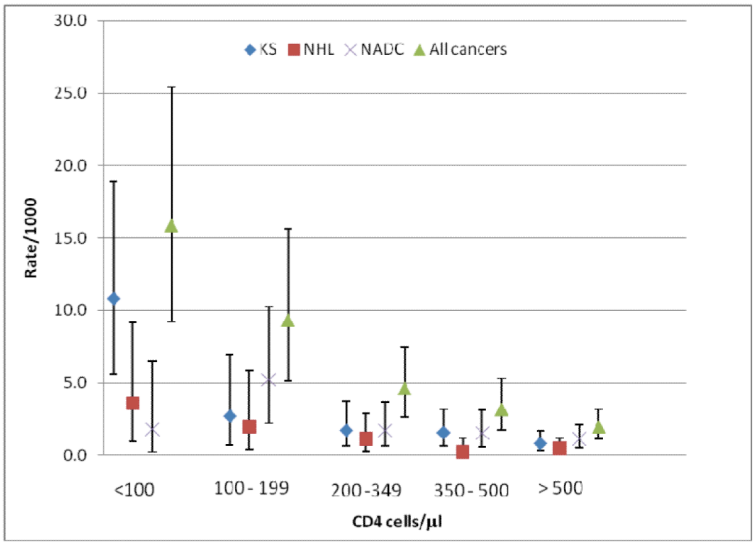

Figure 1.
Crude cancer rates by CD4 count

Table 1

Incident cancers diagnosed by infection 406 related status

Infection related*	N	Not infection related	N
KS	61	Bone	1
NHL	27	Brain	1
HL	5	Lung	6
Anus	5	Colon	1
Lip	3	Mesothelioma	1
Liver	1	Oesophagus	2
Tongue	1	Kidney	2
Salivary	1	Melanoma	10
Gallbladder	1	Prostate	3
Stomach	2	Testis	3
Leukemia	1	Unknown	1
Total (%)	108 (78)	Total (%)	31 (22)

Table 2

CD4 cell count and age at time of cancer diagnosis[1]

	N	Mean	STD	median	Lower Quartile	Upper quartile
CD4 cells/μl						
All cancers	102	339	308	260	130	480
ADC	58	260	249	218	26	537
NADC	44	444	348	343	195	573
IR	75	294	282	232	33	460
NIR	27	466	347	390	190	610
Age (years)						
All cancers	139	45	10.8	43	37	52
ADC	88	43	9.7	41.4	35.8	48.9
NADC	51	48	11.5	50.3	39.2	54.6
IR	109	44	9.9	42.7	36.6	50.6
NIR	30	48	11.9	49.1	38.0	57.6

[1] CD4 cell measure closest to cancer diagnosis date within 1 year (prior) of diagnosis

[2] ADC=AIDS defining cancer; NADC=Non-AIDS defining cancer

[3] IR=Infection related

Table 3

Age standardised rates and incidence rate ratios

	Observed events	Person Years	Age standardised rates	‘95%	CI	Standardised incidence rate ratio	‘ 95%	CI
KS								
<1992	3	1561	1.36	0.16	4.62	0.84	0.09	3.38
1993 - 1996	19	4598	2.85	1.51	4.83	1.76	0.78	3.88
1997 - 1999	12	5197	2.05	1.06	3.78	1.27	0.55	3.01
≥2000	18	9914	1.62	0.92	2.62	Ref		
NHL								
<1992	1	1557	0.28	0.07	0.66	0.38	0.09	0.95
1993 - 1996	5	4616	0.56	0.05	1.90	0.76	0.06	3.28
1997 - 1999	4	5231	1.44	0.54	3.01	1.98	0.58	6.44
≥2000	13	10089	0.73	0.28	1.43	Ref		
NADC								
<1992	1	1559	0.28	0.07	0.66	0.13	0.03	0.30
1993 - 1996	7	4598	1.99	0.90	3.71	0.93	0.36	2.02
1997 - 1999	7	5226	1.21	0.42	2.50	0.56	0.17	1.33
≥2000	24	10058	2.15	1.37	3.31	Ref		
All cancers								
<1992	5	1560	1.91	0.40	5.61	0.47	0.09	1.47
1993 - 1996	31	4579	5.43	3.54	8.05	1.33	0.77	2.24
1997 - 1999	23	5151	5.20	3.46	7.62	1.28	0.75	2.13
≥2000	48	9731	4.07	2.94	5.59	Ref		

[1]KS, NHL and NADC does not add up to All cancers, as patients may have more than once cancer, therefore counted twice

Table 4

Risk factors for all incident AIDS defining cancers (ADC)

	Univariate					Multivariate				
	IRR	**95 %**	**CI**	**p-value**	**p-trend**	**IRR**	**95 %**	**CI**	**p-value**	**p-trend**
Total										
Age per five years	1.06	0.95	1.20	0.292		1.14	1.01	1.29	0.039	
CD4 cells/μl										
≥ 350	1.00					1.00				
200-349	2.20	1.01	4.81	0.047	<0.001	1.77	0.80	3.90	0.158	0.001
100-199	3.66	1.52	8.83	0.004		2.37	0.96	5.89	0.063	
<100	10.61	5.30	21.24	<0.001		5.08	2.35	11.01	<0.001	
Missing	8.91	4.76	16.68	<0.001		4.32	1.95	9.57	<0.001	
No/off ART	1.00					1.00				
On ART	0.61	0.38	0.98	0.040		0.45	0.28	0.74	0.002	
no prior AIDS	1.0					1.00				
Prior AIDS	4.32	2.71	6.89	<0.001		3.98	2.39	6.62	<0.001	
HIV Viral load (copies/mL)										
> 400	1.00					1.00				
≤ 400	0.25	0.12	0.52	<0.001		0.35	0.16	0.77	0.009	0.007
Missing	1.88	1.14	3.09	0.013	<0.001	1.36	0.70	2.66	0.366	

[1]All covariates were time updated

Table 5

Risk factors for all incident non-AIDS defining cancers (NADC)

	Univariate					Multivariate				
	IRR	**95 %**	**CI**	**p-value**	**p-trend**	**IRR**	**95 %**	**CI**	**p-value**	**p-trend**
Age per 5 years[1]	1.31	1.14	1.52	0.000		1.30	1.13	1.51	<0.001	
no prior AIDS	1.00					1.00				
Prior AIDS	2.83	1.47	5.45	0.002		2.63	1.37	5.06	0.004	
CD4 cells/μl[2]										
≥350	1.00					1.00[1]				
200-349	1.33	0.53	3.38	0.544	0.027	1.18	0.46	3.00	0.731	0.087
100-199	4.09	1.76	9.48	0.001		3.49	1.48	8.22	0.004	
<100	1.41	0.33	6.12	0.644		1.17	0.26	5.24	0.833	
Missing	2.45	0.97	6.21	0.059		2.38	0.94	6.04	0.068	
HIV Viral load (copies/mL)										
>400	1.00									
≤400	1.35	0.62	2.93	0.443	0.443					
Missing	1.69	0.72	3.98	0.230						
No/off ART										
On ART	1.76	0.81	3.84	0.153						

[1] All covariates were time updated

[2] CD4 cell count adjusted for independent risk factors Age and prior AIDS diagnosis