Spectrum and Incidence Trends of AIDS- and Non–AIDS-Defining Cancers between 2010 and 2015 in the French Dat'AIDS Cohort

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ABSTRACT

Background: Cancer risk is higher in people living with HIV (PLWH) compared with the general population, and cancers related to age are expected to be most prevalent.

Methods: We determined the spectrum and incidence rates of AIDS-defining cancers (ADC) and non–AIDS-defining cancers (NADC) and of lung, Hodgkin lymphoma (HL), head and neck (HNC), colon–rectum, anal, liver, breast, prostate, and urinary bladder cancers between January 2010 and December 2015 in the French Dat'AIDS cohort. Incidence rates were calculated by year and compared using the χ^2 test for linear trend. Standardized incidence ratios [SIR (95% confidence interval)] were calculated relative to the French general population.

Results: Among 44,642 patients, corresponding to 180,216.4 person-years (PY), 1,440 cancer cases occurred in 1,314 patients. ADC incidence was 191.4 (172.3–212.7)/10^5 PY and declined over time overall and in men, whereas NADC incidence was higher [548.8 (515.6–584.1)/10^5 PY] and did not change. In men, non-Hodgkin lymphoma was the most common cancer, but prostate cancer had the highest incidence among NADCs. Breast cancer was the most common cancer in women. SIRs were higher for cervical cancer [1.93 (1.18–3.14)], HNC in women [2.4 (1.4–4.2)], liver [overall: 3.8 (3.1–4.6); men: 3.2 (2.5–4.0); women: 12.9 (8.3–20.0)], and HL [overall: 13.8 (11.1–17.1); men: 16.2 (12.9–20.4); women: 6.2 (3.22–11.9)] but lower for lung [overall: 0.7 (0.6–0.9); men: 0.7 (0.5–0.8)], prostate [0.6 (0.5–0.7)], and breast cancers [0.6 (0.4–0.7)].

Conclusions: Spectrum of NADCs has changed, with prostate and breast cancers becoming the most common despite their lower SIR.

Impact: These results confirm the need to maintain regular epidemiologic cancer monitoring in order to update screening guidelines.

Introduction

The cancer burden among people living with HIV (PLWH) has changed drastically since the introduction of more potent antiretroviral drugs in 1996, leading to a decreased incidence of AIDS-defining cancers [ADC; that is Kaposi sarcoma, invasive cervical cancer (ICC), and some subtypes of non-Hodgkin Lymphoma (NHL)] in France as in other developed countries, and a substantially shift to more common non-ADCs (NADC; refs. 1–7). Although recent studies monitoring cancer rates over different calendar periods until 2012 in the United States observed a decreased incidence in some NADCs (5), cancer risks remain increased in PLWH compared with the U.S.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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general population (8), even in PLWH with long-term viral suppression (9). Given the increased life expectancy of PLWH, cancers related to age and other age-related risk factors are expected to increase (2) due to the combined effect of aging and HIV on cancer risk in elderly (10).

Incidence rates of breast, colon–rectum, liver, lung, and prostate cancers increased with age in the U.S. cohort of PLWH between 1996 and 2010 (5), and in a modeling study, prostate, lung, and liver cancers are expected to become the most common cancers by 2030 (11). Furthermore, in the general population, considering aging and exposure factors such as smoking and chemicals including cyclophosphamide (12, 13) and radiotherapy (14), a rising incidence of urinary bladder cancer is expected (15). A same evolution might be observed in PLWH considering tobacco consumption in this population in which some subjects are cancer survivors (16).

Epidemiologic monitoring of cancers among PLWH remains relevant to update guidelines of screening. Data on cancer incidence being scarce in France, the last periods studied not exceeding 2009 (1, 17), we aimed to describe the spectrum and incidence trends of ADCs and NADCs in the French Dat'AIDS cohort between 2010 and 2015. Further, we calculated the standardized incidence ratios (SIR) for ICC and NADC categories known to be at increased risk and/or expected to increase in time.

Materials and Methods

Study design

This multicenter analysis was performed using longitudinal data from the French Dat'AIDS cohort (NCT 02898987, ClinicalTrials.gov; ref. 18). In 2010, this cohort represented a collaboration between 17 major French HIV clinical centers that used a common electronic medical record system (NADIS software) for the follow-up of HIV-, hepatitis B virus (HBV)–, and hepatitis C virus (HCV)–infected adults. The data collection was approved by the French National Commission on Informatics and Liberty (CNIL 2001/762876; MR004 2210731v.0), and a written-informed consent was obtained from all patients. This study was conducted in accordance with recognized ethical guidelines and was approved by the scientific committee of the Dat'AIDS cohort. Patient-related data obtained during medical encounters are recorded in a structured database, allowing clinical, epidemiologic, or therapeutic studies. Data quality is ensured by automated checks during data capture, regular controls, annual assessments, and *ad hoc* processes before any scientific analysis is performed.

For this study, we selected patients followed in the cohort between January, 1, 2010, and December, 31, 2015. The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10, World Health Organization, Geneva) codes were used to identify cancer cases (C00 to C95). The ICD-10 codes for every cancer diagnosed during the study period are reported in **Table 1**.

All cancer diagnoses were collected from medical records and were classified as follows: ADCs and non-ADCs. ADCs consisted of Kaposi sarcoma (C46), NHL, and ICC (C53). For NHL incidence, we first considered all NHL cases together (ref. 5; C82–C88, C96), and then, we selected C83 (nonfollicular NHL) and C85 (unspecified NHL). Non-ADCs were subclassified as either virus-related (VR-NADCs) or virus-unrelated (VU-NADCs). VR-NADCs consisted of cancers of the anus, vagina, vulva, penis, and selected oral cavity or pharynx sites for human papilloma virus (HPV) association (C01, C02, C09, C10, C14) as it has been previously defined in other previous head and neck cancer (HNC) studies in which tumor HPV status was not available (19); liver cancer (C22) for hepatitis B and C viruses' association, Hodgkin's lymphoma (HL; C81) for Epstein–Barr virus association; and Merkel cell carcinoma, associated with Merkel cell polyomavirus. VU-NADCs were constituted by all remaining cancers.

For HNC incidence, we considered all HNC together (C00 to C14), whereas nasal cavity cancer and middle ear (C30), paranasal sinus cancer (C31), and larynx cancer (C32) were excluded.

Data collection and analysis

The study period began on January, 1, 2010 or on the date of inclusion in the base if after the January, 1, 2010. The end of follow-up was defined as the last medical encounter, or death, or cancer occurrence whichever occurred first, with censoring at December, 31, 2015. Data regarding sex, age, time since HIV diagnosis and study follow-up time, HIV transmission route [heterosexual, men who have sex with men (MSM), intravenous drug use (IVDU), and others], Centers for Disease Control and Prevention (CDC) stage, history of malignant disease, nadir CD4 T-cell count, CD4 and CD8 T-cell counts, CD4:CD8 ratio, HIV-plasma viral load (HIV-pVL), and duration with HIV-pVL $\leq$ 50 copies/mL were collected at the time of cancer diagnosis. For patients without a cancer diagnosis during the study period, the same data were collected at the time of the last available visit. HBV was defined by a positive HBV surface antigen test, and HCV was defined by an HCV antibody positivity. Smoking and alcohol consumption were collected at end of follow-up defined previously. The level of details reported only allowed for categorization as never or past/current. For regulatory reasons, data concerning race and ethnicity were not available.

Definition of incident cancers

For incidence assessment, cases occurring within 30 days of enrollment in the cohort were excluded as were prevalent cancer cases diagnosed before January, 1, 2010. A person with multiple cancer types diagnosed during the study period was included in more than one of the cancer categories (NADCs, VR-NADCs, and VU-NADCs), but only the first cancer was considered for incidence calculation. Recurrences and metastases were also excluded.

Statistical analysis

We considered patients' characteristics at the first cancer case. We described separately patients' characteristics of nine NADCs. For this description, all incident cancer cases of each type were considered.

The patients' characteristics according to cancer occurrence were compared using the nonparametric Mann–Whitney test for comparisons of continuous variables and the χ^2 test for categorical variables. The patients' characteristics according to the cancer categories (NADCs, VR-NADCs, and VU-NADCs) were not statistically compared as some of them presented more than one cancer in the different category during the study period.

The incidence rates were expressed per 100,000 person-years and were calculated separately for each year between 2010 and 2015 and for the entire study period, for all patients and by sex, for ADCs, NADCs, VR-NADCs, and VU-NADCs. The same was done for the three ADCs and for selected VR-NADCs (liver cancer, HL, and anal cancer) and the following VU-NADCs: HNC, urinary bladder cancer, lung cancer, colon and rectum cancer, prostate cancer, and breast cancer. To illustrate trends, we graphically depicted yearly incidence rates for ADCs NADCs, VR-NADCs, VU-NADCs, and by type of the selected cancers, and the χ^2 test for linear trend was performed.

We calculated the SIR using the method of indirect standardization on age and sex, comparing incidence rates in PLWH with those of the 2012 French general population based on the French network of Cancer Registries (FRANCIM), which gathers data from 21 population-based regional French cancer registries covering approximately

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Table 1. Distribution of incident cancer cases overall and by sex between 2010 and 2015 in the French Dat'AIDS cohort.

ICD10 codes	Cancer types	Females	Males	Total
	All cancers	**323**	**1,117**	**1,440**
ADCs		***56***	***279***	***335***
C46	Kaposi sarcoma	10	127	137
C53	Cervix	16		16
C83	Diffuse large B-cell lymphoma	8	48	56
C85	Others lymphoma not specified	22	104	126
NADCs		***267***	***838***	***1,105***
	VR-NADCs	56	229	***285***
C21	Anus	14	43	57
C22	Liver and intrahepatic bile duct	20	76	96
C81	HL	9	73	82
C60	Penis		3	3
C51	Vulva	6		6
	HPV-related oral cavity/pharynx:			
C01	- Base of the tongue	1	4	5
C02	- Tongue, other location not specified		7	7
C09	- Tonsil	3	12	15
C10	- Oropharynx	2	6	8
C14	- Lip, oral cavity, and pharynx locations poorly specified	1	5	6
	VU-NADCs	211	609	***820***
C00	Lip	1	2	3
C07	Parotid	1	1	2
	Non-HPV oral cavity/pharynx:			
C03	- Gum		2	2
C04	- Floor of the mouth	1		1
C05	- Palate		1	1
C06	- Mouth, other location not specified	1	3	4
C11	Rhinopharynx	2	1	3
C12	Pyriform sinus		1	1
C13	Hypopharynx		1	1
C15	Esophagus	1	7	8
C16	Stomach	2	10	12
C18	Colon	3	24	27
C19	Rectosigmoid junction	2	6	8
C20	Rectum	6	5	11
C26	Digestive organs, other locations poorly specified	1	4	5
C23	Gallbladder		1	1
C24	Extrahepatic bile duct		1	1
C25	Pancreas	5	16	21
C30	Nasal cavity and middle ear	1	1	2
C31	Paranasal sinus		2	2
C32	Larynx	1	8	9
C34	Lung and bronchial	22	76	98
C38	Pleura/mediastinum/heart	1	3	4
C41	Bone/joint, other location not specified	2	4	6
C49	Sarcoma/connective tissue	3	2	5
C43	Melanoma	1	15	16
C44	Skin carcinoma	20	77	97
C50	Breast	51	4	55
C56	Ovarian	2		2
C55	Uterus, not specified	4		4
C54	Uterus corpus	3		3
C57	Genital organs, others not specified, females	1		1
C61	Prostate		113	113
C62	Testis		10	10
C63	Genital organs, others not specified, males		3	3
C67	Urinary bladder	2	23	25
C64	Kidney without pelvis	3	24	27
C66	Upper urinary tract	1		1
C68	Urinary organ others not specified		1	1
C69	Eye and ocular annexes	3	1	4
C70	Meninges	1		1

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Table 1. Distribution of incident cancer cases overall and by sex between 2010 and 2015 in the French Dat'AIDS cohort. (Cont'd)

ICD10 codes	Cancer types	Females	Males	Total
C71	Brain[a]		10	10
C72	Spinal cord/cranial nerves	1		1
C74	Adrenal		3	3
C73	Thyroid	6	5	11
C75	Other endocrine glands		1	1
C76	Other locations and poorly specified		3	3
C77	Secondary lymph nodes and not specified	5	21	26
C78	Secondary malignant tumor lung/digestive	19	30	49
C79	Secondary malignant tumor other location	23	31	54
	Non–AIDS-defining NHLs:			
C84	- NK/T-cell lymphoma	1	15	16
C82	- Follicular lymphoma		1	1
C96	- Histiocytosis/histiocytic lymphoma	1	1	2
C88	Waldenström macroglobulinemia	1	3	4
C90	Myeloma and plasmacytoma	2	14	16
C91	Lymphoid leukemia	2	2	4
C92	Myeloid leukemia		12	12
C95	Others leukemia with cells not specified		1	1
C94	Others leukemia with cells specified		2	2
C80	Cancer location not specified	2	1	3

Abbreviations: ICD10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; NK/T, lymphocytes natural killer T.
[a]This category does not include central nervous system lymphoma (CNS NHL).

20% of the French general population (20). To calculate the SIR, data were aggregated by sex and age group: (15–19), (20–24), (25–29), (30–34), (35–39), (40–44), (45–49), (50–54), (55–59), (60–64), (65–69), (70–74), (75–79), (80–84), (85–89), and (90–94). The 95% confidence intervals (CI) were calculated using a Poisson distribution. SIRs were calculated globally and separately by sex for the following VU-NADCs: HNC, urinary bladder cancer, lung cancer, prostate cancer, and breast cancer and for selected VR-NADCs (liver cancer and HL). SIR for anal cancer could not be calculated as separate incidence rates for colon, rectum, and anal cancers were not available in the 2012 French general population based on the French network of Cancer Registries FRANCIM. Likewise, for the ADCs, we calculated SIR of ICC only, as Kaposi sarcoma and NHL incidence rates were not available in the French general population.

All analyses were performed with Stata 14·2 software for Windows and SAS software, version 9.4 (SAS Institute Inc.).

Results

We included data from 44,642 PLWH from the Dat'AIDS cohort, representing 180,216.4 person-years (PY) of follow-up; 13,543 were females (30.3%) and 31,099 were males (69.6%). Overall, 1,577 cancer cases were diagnosed, of which 1,440 were incident cancer cases that occurred in 1,314 patients. We did not consider 137 cancer cases that occurred within 30 days of enrollment in the cohort (prevalent cases).

Population description

Subject characteristics are shown in **Table 2**, overall and according to cancer category. Compared with subjects without cancer, those with incident cancers were significantly more likely to be male (77.5% vs. 69.4%), older, HIV infected through IVDU (16.9% vs. 7.9%), HBV and HCV coinfected (7.8% vs. 4.5%; 24.8% vs. 14.8%, respectively), followed for HIV infection for a longer period of time [median (IQR) = 16 (8–23) years vs. 13 (6–21)], and followed in the study for a shorter time (median (IQR) = 2.3 (0.9–3.9) years vs. 5.3 (2.0–5.8)]. They had more frequent AIDS-defining conditions or previous malignant diseases, lower nadir CD4 T count, CD4 T-cell count, CD4:CD8 ratio, shorter time with undetectable HIV-pVL, and higher proportion of patients with detectable HIV-pVL. The proportion of past or current smokers was significantly higher among patients with incident cancer, and the proportion of past or current alcohol consumers was significantly lower.

Subjects' characteristics according to cancer category (ADCs, VR-NADCs, and VU-NADCs) are presented in **Table 2**. Being over 55 years old, having a cancer history, and having a longer time with undetectable HIV-pVL were more frequent among patients with VU-NADCs compared with the two others cancer categories, whereas patients with incident ADCs had shorter time since HIV diagnosis, were more often in MSM-HIV transmission group and less often on ART, and had worse HIV-disease characteristics (lower CD4 T-cell count, CD4:CD8 ratio, and virological control). Finally, the proportion of HBV- and HCV-coinfected patients was higher among patients with VR-NADCs (15% HBV-coinfected and 43.1% HCV-coinfected) than among patients with the two others cancer categories (6.2% and 6.6% of HBV-coinfected and 6.2% and 6.6% of HCV-coinfected). Tobacco and alcohol consumption were similar in the three cancer categories.

Spectrum of cancer cases

Among the 1,440 incident cancer cases, 335 (23.4%) were ADCs and 1,105 (76.6%) were NADCs, of which 285 (25.5%) were VR-NADCs and 820 (74.5%) were VU-NADCs. Spectra of cancer cases, overall and by sex, are reported in **Table 1**. The ten most common cancer types were AIDS-defining NHL ($n = 182$), Kaposi sarcoma ($n = 137$), prostate cancer ($n = 113$), lung cancer ($n = 98$), nonmelanoma skin cancer ($n = 97$), liver cancer ($n = 96$), HL ($n = 82$), anal cancer ($n = 57$), breast cancer ($n = 55$), and HNC ($n = 54$). This distribution differed by sex, AIDS-defining NHL being the most frequent in males and breast cancer being the most frequent in females.

Incidence trends of ADCs and NADCs between 2010 and 2015

The incidence trends of the ADCs, NADCs, VR-NADCs, and VU-NADCs, overall, by year, and by sex, are reported in **Table 3** and **Fig. 1A–D**.

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Table 2. Patient characteristics at cancer diagnosis between 2010 and 2015 in the French Dat'AIDS cohort.

Characteristics median (IQR), *N* (%)	Whole cohort (*N* = 44,642)	Patients without incident cancer (*N* = 43,328)	Patients with incident cancer (*N* = 1,314)	*P* value[a]	Incident ADCs (*N* = 322)	Incident VU-NADCs (*N* = 752)	Incident VR-NADCs (*N* = 283)
Time since HIV diagnosis (y)	13 (6–21)	13 (6–21)	16 (8–23)	<0.0001	9 (2–18)	17 (10–23)	20 (11–25)
Study follow-up time (y)	5.2 (2.0–5.8)	5.3 (2.0–5.8)	2.3 (0.9–3.9)	<0.0001	1.4 (0.4–2.8)	2.7 (1.3–4.3)	2.5 (1.0. 4.1)
Female	13,543 (30.3)	13,247(30.6)	296 (22.5)	<0.0001	53 (16.5)	195 (25.9)	55 (19.4)
Male	31,099 (69.7)	30,081 (69.4)	1,018 (77.5)		269 (83.5)	557 (74.1)	228 (80.6)
Age	48 (40–55)	48 (40–55)	52 (46–61)	<0.0001	48 (39–55)	56 (48–64)	51 (46–56)
16–25	1,200 (2.7)	1,193 (2.8)	7 (0.5)	<0.0001	6 (1.9)	0	1 (0.4)
25–35	5,515 (12.4)	5,437 (12.6)	78 (5.9)		43 (13.4)	22 (2.9)	14 (4.9)
35–45	11,395 (25.5)	11,164 (25.8)	231 (17.6)		88 (27.3)	99 (13.2)	52 (18.4)
45–55	15,604 (35.0)	15,119 (34.9)	485 (36.9)		111(34.5)	246 (32.7)	143 (50.5)
55–65	7,610 (17.1)	7,278 (16.8)	332 (25.3)		56 (17.4)	226 (30.1)	58 (20.5)
>65	3,316 (7.4)	3,135 (7.2)	181 (13.8)		18 (5.6)	159 (21.1)	15 (5.3)
HIV transmission route				<0.0001			
Heterosexual	18,979 (42.9)	18,514 (43.2)	465 (35.4)		108(33.5)	300 (39.9)	68 (24.0)
MSM	16,986 (38.4)	16,481 (38.4)	505 (38.4)		149(46.3)	270 (35.9)	108 (38.2)
IVDU	3,631 (8.2)	3,409 (7.9)	222 (16.9)		29 (9.0)	109 (14.5)	90 (31.8)
Others	4,623 (10.5)	4,501 (10.5)	122 (9.3)		36 (11.2)	73 (9.7)	17 (6.0)
CDC stage				<0.0001			
A	26,879 (61.0)	26,477 (62.0)	402 (30.6)		10 (3.1)	299 (39.8)	96 (33.9)
B	6,801 (15.4)	6,544 (15.3)	257 (19.6)		1 (0.3)	187 (24.9)	81 (28.6)
C	10,355 (23.5)	9,702 (22.7)	653 (49.8)		310 (96.6)	265 (35.3)	106 (37.5)
Hepatitis C coinfection				<0.0001			
No	37,919 (84.9)	36,931 (85.2)	988 (75.2)		272 (84.5)	584 (77.7)	161 (56.9)
Yes	6,723 (15.1)	6,397 (14.8)	326 (24.8)		50 (15.5)	168 (22.3)	122 (43.1)
Hepatitis B coinfection							
No	39,205 (95.4)	38,068 (95.5)	1,137 (92.2)		271(93.5)	662 (93.2)	233 (85.0)
Yes	1,897 (4.6)	1,801 (4.5)	96 (7.8)	<0.0001	18 (6.2)	47 (6.6)	41 (15.0)
Nadir CD4 T-cell count/mm^3	223 (97–350)	225 (99–353)	150 (50–269)	<0.0001	131 (37–251)	164 (62–280)	124 (42–239)
≥200/mm^3	24,125 (55.2)	23,613 (55.7)	512 (39.5)	<0.0001	112 (36.0)	316 (42.3)	92 (32.6)
<200/mm^3	19,549 (44.8)	18,764 (44.3)	785 (60.5)		199 (64.0)	431 (57.7)	190 (67.4)
CD4 T-cell count/mm^3	601 (413–810)	606 (418–812)	450 (244–648)	<0.0001	285 (128–495)	510 (312–717)	412 (217–609)
≤200/mm^3	3,168 (7.3)	2,914 (6.9)	254 (19.5)	<0.0001	115 (36.5)	94 (12.5)	64 (22.7)
201–500/mm^3	12,587 (28.9)	12,105 (28.7)	482 (36.9)		124 (39.4)	273 (36.4)	103 (36.5)
>500/mm^3	27,778 (63.8)	27,209 (64.4)	569 (43.6)		76 (24.1)	384 (51.1)	115 (40.8)
CD8 T-cell count/mm^3	770 (554–1055)	771 (556–1054)	746 (506–1090)	0.02	798 (538–1271)	730 (500–1030)	725 (470–1034)
≤1,000/mm^3	30,746 (71.1)	29,832 (71.1)	914 (70.5)	0.64	195 (62.7)	544 (72.6)	204 (73.1)
>1,000/mm^3	12,495 (28.9)	12,113 (28.9)	382 (29.5)		116 (37.3)	205 (27.4)	75 (26.9)
CD4:CD8 ratio	0.8 (0.5–1.1)	0.8 (0.5–1.1)	0.6 (0.3–0.9)	<0.0001	0.3 (0.2–0.7)	0.7 (0.40–1.02)	0.6 (0.4–0.9)
<1	28,761 (66.6)	27,743 (66.2)	1,018 (78.6)	<0.0001	280 (90.0)	544 (72.6)	233 (83.5)
≥1	14,454 (33.4)	14,177 (33.8)	277 (21.4)		31 (10.0)	205 (27.4)	46 (16.5)
HIV-pVL copies/mL	20 (20–40)	20 (20–40)	40 (20–68)	<0.0001	93 (26–17093)	40 (20–40)	40 (20–50)
≤50	36,181 (83.1)	35,230 (83.4)	951 (73.0)	<0.0001	142 (45.2)	627 (83.6)	217 (76.9)
>50	7,345 (16.9)	6,994 (16.6)	351 (27.0)		172 (54.8)	123 (16.4)	65 (23.1)
Time follow-up with HIV-pVL <50 copies/mL (y)	2.5 (0.4–6.0)	2.5 (0.4–6.1)	1.5 (0.0–4.6)	<0.0001	0.0 (0.0–1)	2.7 (0.5–6.0)	1.4 (0.1–4.0)
1 y to <2 y	19,656 (45.2)	18,940 (44.9)	716 (55.0)	<0.0001	264 (84.1)	310 (41.3)	164 (58.2)
2 y to <3 y	3,980 (9.1)	3,868 (9.2)	112 (8.6)		8 (2.6)	86 (11.5)	27 (9.6)
3 y to <4 y	3,471 (8.0)	3,377 (8.0)	94 (7.2)		15 (4.8)	60 (8.0)	20 (7.1)
≥4 y	16,419 (37.7)	16,039 (38.0)	380 (29.2)		27 (8.6)	294 (39.2)	71 (25.2)
ART naïve	2,667 (5.0)	2,596 (6.0)	71 (5.4)	0.41	40 (12.4)	26 (3.5)	7 (2.5)
Time exposure to ART (y)	9 (3–17)	9 (3–17)	11 (3–16)	0.37	5 (1–14)	14 (7–17)	14 (6–18)
	21 (6–52)	22 (6–52)	18 (4–42)	<0.0001	10 (3–26)	27 (12–53)	22 (8–43)
History of cancer	2,910 (6.5)	2,724 (6.3)	186 (14.2)	<0.0001	52 (16.2)	199 (26.5)	38 (13.4)
Tobacco consumption							
No	13,095 (41.6)	12,794 (41.9)	301 (30.5)	<0.0001	78 (35.6)	188 (31.7)	46 (21.0)
Past or current	18,396 (58.4)	17,711 (58.1)	685 (69.5)		141(64.4)	404 (68.2)	173 (79.0)
Alcohol consumption							
No	12,138 (41.6)	11,731 (41.5)	407 (45.1)	0.03	88 (46.3)	242 (45.5)	93 (43.7)
Past or current	17,041 (58.4)	16,546 (58.5)	495 (54.9)		102 (53.7)	290 (54.5)	120 (56.3)

[a]Mann–Whitney test in case of continuous variables and χ^2 test for categorical data.

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Table 3. Global incidence rates overall and by sex of ADCs and selected NADCs in the French Dat'AIDS cohort between 2010 and 2015.

	Overall		Men		Women	
	N[a]	Incidence/100,000 PY (95% CI)	*N*[a]	Incidence/100,000 PY (95% CI)	*N*[a]	Incidence/100,000 PY (95% CI)
ADCs	345	191.4 (172.3–212.7)	289	232.9 (207.6–261.4)	56	99.7 (76.8–129.6)
Kaposi sarcoma	137	76.0 (64.3–89.9)	127	102.4 (86.0–121.8)	10	17.8 (9.6–33.1)
NHL	191	106.0 (92.0–122.1)	160	129.0 (110.5–150.6)	31	55.2 (38.8–78.5)
NHL (ICD-10: C83 and C85)	169	93.8 (80.7–109.0)	141	113.7 (96.4–134.1)	28	49.9 (34.4–72.2)
ICC					16	28.5 (17.5–46.5)
NADCs	989	548.8 (515.6–584.1)	746	601.3 (559.7–646.0)	234	432.8 (381.6–490.7)
Lung cancer	98	54.4 (44.6–66.3)	76	61.3 (48.9–76.7)	22	39.2 (25.8–59.5)
Liver cancer	96	53.3 (43.6–65.1)	76	61.3 (48.9–76.7)	20	35.6 (23.0–55.2)
HL	82	45.5 (36.6–56.5)	73	58.8 (46.8–74.0)	9	16.0 (8.3–30.8)
HNC	54	30.0 (23.0–39.1)	42	33.9 (25.0–45.8)	12	21.4 (12.1–37.6)
Anus cancer	57	31.6 (24.4–41.0)	43	34.7 (25.7–46.7)	14	24.9 (14.8–42.1)
Colon and rectum cancer	45	25.0 (18.6–33.4)	35	28.2 (20.3–39.3)	10	17.8 (9.6–33.1)
Anus/colon/rectum cancer[b]	96	53.3 (43.6–65.1)	74	59.6 (47.5–74.9)		39.2 (25.8–59.5)
Urinary bladder cancer	25	13.9 (9.4–20.5)	23	18.5 (12.3–27.9)	2	3.6 (0.9–14.2)
Breast cancer					51	90.8 (69.0–119.5)
Prostate cancer			113	91.1 (75.7–109.5)		

[a]Only first cases in each category were considered for analysis.
[b]SIR calculated aggregating colon, rectum, and anal cancer cases as they were grouped in the general population.

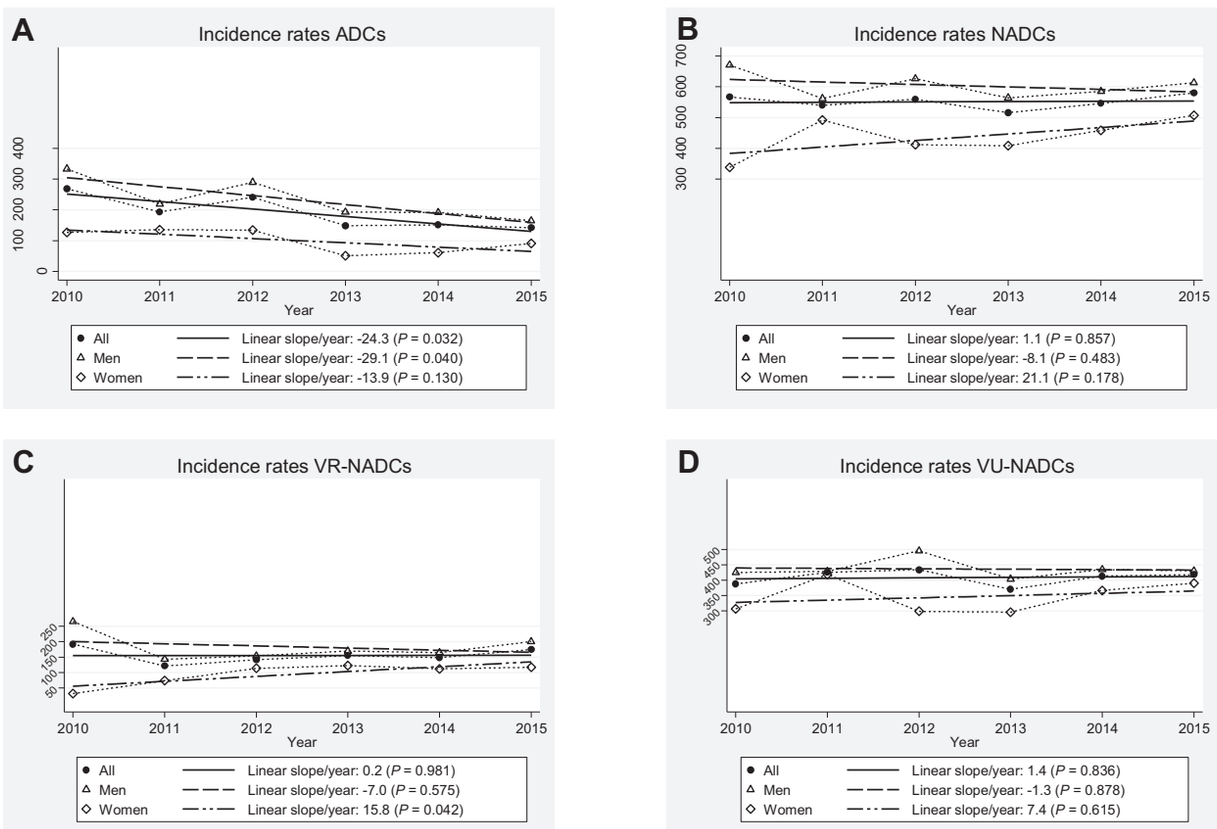

Figure 1.
Incidence rates, overall and by sex, of (**A**) ADCs, (**B**) NADCs, (**C**) VR-NADCs, and (**D**) VU-NADCs in the French Dat'AIDS cohort between 2010 and 2015.

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Table 4. SIR[a] overall and by sex of ICC and selected NADCs in the French Dat'AIDS cohort between 2010 and 2015.

	Overall SIR (95% CI)	Men SIR (95% CI)	Women SIR (95% CI)
ICC			1.93 (1.18–3.14)
Lung cancer	0.7 (0.6–0.9)	0.7 (0.5–0.8)	1.4 (0.9–2.0)
Liver cancer	3.8 (3.1–4.6)	3.2 (2.5–4.0)	12.9 (8.31–20.0)
HL cancer	13.8 (11.1–17.1)	16.2 (12.9–20.4)	6.2 (3.2–11.9)
Head and neck cancer	1.1 (0.9–1.5)	1.0 (0.7–1.3)	2.4 (1.4–4.2)
Urinary bladder cancer	0.9 (0.6–1.4)	0.9 (0.6–1.4)	1.3 (0.3–5.3)
Breast cancer			0.6 (0.4–0.7
Prostate cancer		0.6 (0.5–0.7)	

[a]SIR using the method of indirect standardization on age and sex.

The ADCs' incidence over the 2010–2015 period declined significantly (**Fig. 1A**) from 268.5 (216.0–333.8)/10^5 PY in 2010 to 142.0 (101.9–197.7)/10^5 PY in 2015 ($P = 0.03$). This decline was also observed in males ($P = 0.04$) but not in females.

Among ADCs, only the Kaposi sarcoma incidence rate decreased significantly overall and in men (Supplementary Fig. S1A). However, for AIDS-defining NHL (C83, C85), the incidence rate was 126.0 (91.7–173.1) in 2010 and 77.1 (49.2–120.8) in 2015, but the difference did not reach the significance ($P = 0.08$; Supplementary Fig. S1C). For ICC, incidence rate was 28.5 (17.5–46.5) and did not change significantly over the study period ($P = 0.24$).

No trend was evidenced for the incidence of NADCs over the 2010–2015 period (**Fig. 1B**), as for the nine selected NADCs, overall and for both sexes (Supplementary Fig. S2).

The overall VR-NADCs' incidence decreased significantly over the 2010–2015 period in women only ($P = 0.042$). No trend was evidenced for the incidence of VU-NADCs over the 2010–2015 period (Supplementary Fig. S1D).

Excess risk

The SIRs comparing the incidence rate by sex and age with the French general population are reported in **Table 4**.

With respect to the French general population, no significant difference was observed for the incidence of urinary bladder cancer. A significantly higher incidence was detected for liver cancer [SIR (95% CI): overall: 3.8 (3.1–4.6); men: 3.2 (2.5–4.0); women: 12.9 (8.3–20.0)], HL [SIR (95% CI): overall: 13.8 (11.1–17.1); men: 16.2 (12.9–20.4); women: 6.2 (3.2–11.9)], and HNC among women only [SIR (95% CI): 2.4 (1.4–4.2)]. A significantly lower incidence was detected for lung cancer overall and in men [SIR (95% CI): overall: 0.7 (0.6–0.9); men: 0.7 (0.5–0.8)], for breast cancer [SIR (95% CI) = 0.6 (0.4–0.7)], and for prostate cancer [SIR (95% CI) = 0.6 (0.5–0.7)].

Subjects' characteristics for each cancer are reported in Supplementary Table S1. Of note, HIV transmission route through IVDU was overrepresented among subjects with liver cancer (58.3%) as were HCV (75%) and HBV coinfection (25%), and MSM was overrepresented in anal cancer (56.1%) and HL (58.5%).

Discussion

This study, carried out in 17 large French HIV clinical centers, confirmed the persistence of a downward trend in the incidence of ADCs but not in NADCs between 2010 and 2015, with a significant difference in risk levels compared with the French population depending on the type of NADCs studied. Furthermore, the spectrum analysis of NADCs highlighted that prostate cancer and breast cancer were the most frequent.

The global incidence trends for ADCs and NADCs observed in this study may be related to the high rate of patients with control viremia and with CD4 cell count higher than 500/mm^3 in our cohort. These trends are consistent with studies performed on previous calendar periods (2, 8), as were the trends of the three types of ADCs (7, 8, 21–23). Earlier therapeutic management initiated at higher CD4 levels and long-term HIV-pVL suppression should at least partially explain the incidence trend for Kaposi sarcoma, and in a lesser extent for NHL (9, 24). Concerning ICC, no significant linear trend in incidence rate was observed between 2010 and 2015, and the risk remained higher compared with the French general population. Higher ICC risk was also reported in three American studies covering different time periods, from 1996 to 2012 (8), 1996 to 2010 (25), and during 20 years until 2015 (26). The persistence of higher risk observed in our study may be partly explained by (i) the low cervical HPV clearance rate in women living with HIV (WLWH; ref. 27); (ii) a delay in HIV testing leading to late HIV diagnosis (28, 29); (iii) an insufficient access to ICC screening, despite a recent French study showing most adequate access in WLWH than in the French general population (30); and (iv) a past or persistent severe immunosuppression (23), which concerned 5 of our 16 patients (35%). Our data confirm the need to maintain differentiated recommendations for ICC screening in HIV-positive women, particularly in those with strong immunosuppression or low nadir CD4.

We did not evaluate factors associated with the incidence of specific cancer categories, but in our study, patients diagnosed with ADCs were more likely to be ART-naïve than those diagnosed with VU-NADCs or VR-NADCs. This result is consistent with a previous study that found a strong association between HIV viral suppression and a reduction of ADCs' incidence, whereas this association was found to be weaker for VR-NADCs and absent for VU-NADCs (9).

In this study, two main results are reported for the first time at our knowledge: a lower lung cancer risk overall and in men, and a higher HNC risk in women, both with respect to the French general population.

Previously, a decline in lung cancer risk in PLWH was observed between 1996 and 2012 in the U.S. HIV/AIDS Cancer Match Study, but the risk remained increased in the last period of this study (8). This decline was attributed to the expansion of antiretroviral therapies (ART) since 1996 and differential smoking cessation rates (8). In our cohort, data on tobacco consumption were not enough to further analyze if this trend was related with a high level of smoking cessation. In a study performed using the French cohort hospital database of PLWH (ANRS CO4-FHDH), the SIR for lung cancer between 2005 and 2009 was 2.8 (2.5–3.1), but 0.9 (0.6–1.3) in patients on ART for at least 2 years with a CD4 T-cell count higher than 500 cells/mm^3 (17) that concern 64% of our cohort. In our study, associated factors with specific cancer risk were not investigated. However, recent data highlighted the key role of the immune system in cancer protection (31), and among cancer immunity effector cells, $CD8^+$ T cells were identified as having a major role (32). Thus, in the study conducted by Le cornet and colleagues on healthy individuals, significant inverse associations were observed between relative $CD8^+$ counts and risks of lung and breast cancer, whereas a significant positive association was observed between relative counts of $FOXP3^+$ regulatory T cells and lung cancer risk (31). $CD8^+$ T-cell counts are elevated during HIV infection and do not normalize despite long-term ART with sustained undetectable HIV viral load (33). So, further studies are needed to

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assess if there is a relationship between CD8 T-cell count, CD8 T-cell subtypes, and cancer risk in PLWH.

The three major causes of HNC cancer in the general population are HPV infection, tobacco, and alcohol use (34, 35), and these factors are widely spread among PLWH. Thus, in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), the SIRs between 1996 and 2009 of both HPV-related and HPV-unrelated HNC cancers were 3-fold higher in HIV-infected individuals than in the U.S. general population (19). We could not further explore the relationship between tobacco exposure, alcohol consumption, and HNC risk in our study. Likewise, we could not confirm whether the higher risk of HNC observed for WLWH compared with those of the French general population was related to an increase in HPV-related cases, as HPV-tumor status was not collected in our study.

It is worthy of note however that HPV infection and tobacco smoking interacted with each other, tobacco exposure enhancing HPV16-E6 and -E7 oncogene transcription (36) and overexpression of HPV16-E7 oncoprotein contributing to oral cancer progression (37). These interactions could be modulated according to time of oral HPV infection and life course smoking trajectories which could modify the HNC risk (38). Unfortunately, history related to HPV infection and tobacco exposure was not available in our study. Anyway, all these data stress the need to reinforce smoking cessation and to investigate HPV tumor status of HNC in PLWH. The potential role of therapeutic HPV vaccines in reducing the burden of such cancers, including in those with HPV infection history, should be evaluated (39).

This study also confirms the persistence of a higher risk for HL and liver cancer compared with the French general population.

Concerning HL, the trend is consistent with reports conducted on previous periods in the United States (5, 8). It is noteworthy that 32% of patients with HL in our study had a CD4 T-cell count >500/mm^3, stressing that CD4 cell recovery is not sufficient to control the excess risk for HL as previously reported (17). The SIR difference according to sex observed in our study is consistent with a previous report that showed a reduced risk for HL in WLWH compared with MSM living with HIV (40). Unfortunately, in this study, SIR was not calculated according to the HIV transmission group, but 58.5% of patients with HL were MSM.

Increased liver cancer incidence was attributed to the high prevalence and long-term exposure to HBV and HCV in PLWH, which represented 4.6% and 15.1%, respectively, of the subjects in our cohort and were overrepresented among patients with liver cancer (25.3% and 75.0%, respectively). However, we did not calculated SIR of liver cancer according to HCV or HBV coinfection.

In our study, we could not calculate SIR for anal cancer separately, but no significant linear trend was observed for anal cancer incidence between 2010 and 2015 in both sexes. As previously reported, MSM HIV transmission group was overrepresented among patients with anal cancer. In the HIV/AIDS Cancer Match study conducted between 1996 and 2012, anal cancer incidence remained markedly elevated among HIV-positive MSM as well as in older individuals and people with AIDS (41). But of note in our study, 14 anal cancer cases were diagnosed among females, which is in line with the French HIV guidelines that recommend anal cancer screening in WLWH with history of HPV infection or ICC (42).

The decrease in ADCs' incidence confirms that spectrum of cancers that occur among PLWH has changed since the ART era (22). But this study also highlighted a change in the spectrum of NADCs among PLWH. Indeed, prostate cancer and breast cancer were the most frequently observed cancers, with rates higher than observed in previous studies: 10.91% of all cancers cases in men and 17.78% of all cancers cases in women, respectively. In the ONCOVIH French study performed in 2006, prostate cancer represented 1.8% of all cancers cases, and the most frequent NADCs were anal and lung cancer in men and breast cancer in women (43). The most common cancer type observed between 1996 and 2012 in the United States was AIDS-defining NHLs, prostate and breast cancers representing 7.1% and 3.2% of all cancer cases, respectively (8).

This high number of cases observed despite incidence rates that did not change between 2010 and 2015 might be driven by aging within the cohort (2). However, as we did not estimate age-standardized incidence, we could not explore this hypothesis. The lower SIR compared with general population observed for these two cancers in our study has already been reported in PLWH and remains unexplained (44).

Up to 2015, we did not observe a higher risk of urinary bladder cancer compared with the French general population, and its incidence did not significantly change between 2010 and 2015. Thus, urinary bladder cancer screening does not need specific recommendations for PLWH others than those established for the general population (45).

Our study has several limitations. First, the incidence rates observed in our cohort could not be considered representative of all PLWH in France. However, the 17 centers contributing to the Dat'AIDS cohort between 2010 and 2015 were distributed throughout the country (overseas territory included). Second, the regional territories covered by the FRANCIM and the Dat'AIDS cohort do not match, which might have had an impact on SIRs calculation, as in France, cancer incidence differs according to region (46).

Furthermore, an underreporting of cancer cases might have decreased incidence rates and SIR in the DAT'AIDS cohort as this cohort was not designed to register cancer cases in PLWH. However, data of this cohort are collected from an electronic medical record, in which the medical staff are also responsible for data entry, thereby ensuring data quality and completeness. We did not check the histologic report for each cancer case, and thus we cannot exclude misclassifications of high-grade lesions into cancer codes. However, a return to the medical report was done for all prostate cancer cases and for all cancers encoded as metastasis and secondary cancers without specification of a primary origin. We also used data from 2012 for the general population to calculate SIRs over the 2010–2015 period, and we did not have specific data concerning anal cancer in the FRANCIM cohort. Moreover, absence of significant changes in incidence of NADCs may also be a result of the short period of observation. The lack of data regarding history of cumulative bacterial pneumonia, a factor reported to be associated with lung cancer risk (47), nor history related to HPV infection, sociodemographic characteristics (e.g., education level, ethnic origin), and precise consumption behaviors (e.g., tobacco, alcohol, and drug consumption), prevented us from being able to adjust and explain cancer incidence rates. Furthers studies should take in to account all these factors in the study of cancer risk and incidence and should analyze the impact of smoking cessation in lung cancer risk especially.

In conclusion, we showed that, in a recent large cohort of PLWH who were mostly on ART with a controlled HIV viral load, the NADCs' incidence did not significantly change between 2010 and 2015 and remain higher than that of ADCs. Clinicians have to be aware of the persistence of a high risk of ICC in WLWH in these last recent years despite specific screening recommendations. We also showed the growing importance of prostate cancer and breast cancer in PLWH,

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albeit with a lower risk compared with the French general population. Clinicians have to be aware of these new trends and perform screening recommendations established for the general population for these two cancer types.

The lower risk for lung cancer compared with the French general population observed both overall and in men should be further investigated. The higher risk for HNC in women stresses the need to reinforce tobacco cessation and HPV vaccine campaigns. Our results argue to maintain regular epidemiologic monitoring of cancers in PLWH.

Authors' Disclosures

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Authors' Contributions

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