Determinants of Second Primary Cancer Type in Survivors of Virus-Related and Non-Virus-Related Cancer Living With HIV in the French Dat’AIDS Cohort

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Abstract

Objectives: People who survive after primary cancer are at an increased risk for subsequent primary cancers. We aimed to investigate the possible determinants of second primary cancer (SPC) in HIV-positive cancer survivors.

Methods: This was a multicenter retrospective study using longitudinal data from the French Dat’AIDS cohort. Subjects who developed at least 2 primary cancers were selected. Cancer cases were identified using ICD10 codes and distributed in 3 cancer categories: AIDS-defining cancer (ADC), virus-related non-ADC (VR-NADC), and virus-unrelated-NADC (VU-NADC). The possible determinants considered were the first primary cancer category, sex, age, HIV transmission route, duration of HIV infection follow-up, duration of ART exposure, nadir CD4+ T cell count, and hepatitis C and hepatitis B serostatus.

Results: Among the 44642 patients in the Dat’AIDS cohort, 4855 were diagnosed with cancer between 1 December 1983 and 31 December 2015, of whom 444 (9.1%) developed at least 2 primary cancers: 130 ADCs, 85 VR-NADCs, and 229 VU-NADCs. A longer delay between the first primary cancer and the SPC was associated with an increased risk of occurrence of a VR-NADC rather than a secondary ADC. Having had a first primary VU-NADC, an older age, and a longer delay between the HIV diagnosis and the first primary cancer as well as between the first primary cancer and the SPC were associated with an increased risk of VU-NADC rather than ADC.

Conclusion: SPCs are now a major concern in HIV-positive cancer survivors justifying the development of monitoring strategies after a first cancer.

Keywords

secondary primary cancer, cancer survivors, HIV, AIDS, associated factors

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Introduction

Previous studies highlighted that many factors contributed to the occurrence of second primary cancer (SPC) in cancer survivors, including the type of the first primary cancer, age, primary cancer treatments, environmental and lifestyle exposures, and genetic susceptibility. Furthermore, for different cancer types that shared the same hormonal, genetic, or lifestyle factors, a clustering of SPCs was also identified.

People living with HIV (PLWH) have a substantially elevated risk of developing Kaposi sarcoma (KS), certain types of high-grade non-Hodgkin lymphoma (NHL), and invasive cervical cancer (ICC), all of which are considered AIDS-defining cancers (ADCs) and have an elevated risk for some other cancers. Given the increased life expectancy of PLWH, a steady increase in the incidence of SPC has been reported in this population in the USA and in France. Furthermore, the pattern of SPC could change over time as previously reported for the secondary cancers associated with KS. To date, data remains limited.

We investigated the possible determinants of the SPC category (ADC vs virus-related non-ADC (VR-NADC) and virus-unrelated-NADC [VU-NADC]) including the first primary cancer category and demographic and epidemiological characteristics related to HIV infection.

Methods

This multicenter retrospective study was performed using longitudinal data from the French Dat’AIDS cohort (NCT 02898987, ClinicalTrials.gov) that represented a collaboration between 17 major French HIV clinical centers that used a common electronic medical record system (NADIS®) 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) in 2001 with the number 2001/762876 and methodology of reference (MR):MR004 2210731v.0., and all patients signed an informed consent form before being included in this database. Patient-related data obtained during medical encounters are recorded in a structured database, allowing clinical, epidemiological, or therapeutic studies. For this study, the database was censored on 31 December 2015.

Data Collection

Data collected from the database were sex, birth date, HIV transmission route (heterosexual, men who have sex with men (MSM), intravenous drug user (IVDU), others), year of HIV diagnosis (according to the following periods: 1983–1989; 1990–1995; 1996–2001; 2002–2007; >2007), date of anti-retroviral therapy (ART) initiation, and date of each cancer event. ART exposure was assessed according to whether it was initiated before or after the ART era (≤1996 and >1996). Hepatitis B and hepatitis C serological status was defined as follows: Hepatitis B virus (HBV) infection by a positive HBV surface antigen test and hepatitis C infection (HCV) by HCV antibody positivity. The HIV viral load could not be considered in the associated factors analysis as HIV VL measurement was implemented in 1996 in France. Likewise, the CD4 cell count at the time of HIV diagnosis and at the time of the diagnosis of the first cancer was not available, but we were able to consider the CD4 count nadir.

Study Population

We selected subjects who presented at least 2 primary cancers after HIV diagnosis. The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD10, World Health Organization, Geneva) codes were used to identify cancer cases (ICD codes C00 to C95). No delay between the 2 cancer diagnoses was defined, except for cancer cases identified with the same ICD code in the same patient, for which the delay had to be longer than 5 years. Cases of metastatic primary malignancies, secondary lymph nodes, and primary cancer relapse defined as the same cancer type occurring within 5 years were excluded.

Definition of Cancer Cases

Cancer cases were classified into 3 categories: ADCs, that is, KS (ICD10: C46), NHL (ICD10: C82-C85), and ICC
(ICD10:C53), VR-NADCs, and VU-NADCs. VR-NADCs consisted of cancers associated with human papilloma virus (HPV), that is, cancers of anus, vagina, vulva, penis, and selected oral cavity or pharynx sites (ICD10: C01, C02, C09, C10, and C14); hepatitis B and C viruses (liver cancer [ICD10: C22]); Epstein–Barr virus (Hodgkin’s lymphoma [ICD10:C81]); and Merkel cell polyomavirus (Merkel cell carcinoma). VU-NADCs were constituted by all remaining cancers.

**Statistical Analysis**

We first compared the sociodemographic and HIV-related characteristics according to the category of the second primary cancer. The delays of first ART and first cancer event were also compared.

Table 1. Patients’ Characteristics by Second Primary Cancer Category in the French Dat’AIDS Cohort.

| Characteristic                          | SPC ADCs, N = 130 | SPC VR-NADCs, N = 85 | SPC VU-NADCs, N = 229 | Total, N = 444 | P      |
|----------------------------------------|-------------------|----------------------|------------------------|----------------|--------|
| Delay between the HIV diagnosis and the first primary cancer (y) | 3.6 (1.0–10)      | 5.9 (6.6–12.1)       | 8 (3.2–14)             | 6.5 (9.5–13)   | .0001  |
| Gender                                 |                   |                      |                        |                |        |
| Women                                  | 15 (11.5)         | 15 (17.6)            | 45 (19.6)              | 75 (16.9)      | .14    |
| Men                                    | 115 (88.5)        | 70 (82.3)            | 184 (80.3)             | 369 (83.1)     |        |
| Age at first cancer event (y)          | 43 (36–49)        | 42 (35–50)           | 50 (40–59)             | 46 (38–54)     | <.0001 |
| HIV transmission route                  |                   |                      |                        |                |        |
| Heterosexual                           | 37 (28.5)         | 20 (23.5)            | 72 (31.4)              | 129 (29.0)     | .10    |
| IVDU                                    | 10 (7.7)          | 13 (15.3)            | 35 (15.3)              | 58 (13.1)      |        |
| Other/unknown                          | 19 (14.6)         | 10 (11.8)            | 16 (7.0)               | 45 (10.1)      |        |
| MSM                                    | 64 (49.2)         | 42 (49.4)            | 106 (46.3)             | 212 (47.7)     |        |
| Period of HIV diagnosis                |                   |                      |                        |                |        |
| 1983–1989                              | 37 (28.5)         | 28 (32.9)            | 68 (29.7)              | 133 (29.9)     | .03    |
| 1990–1995                              | 32 (24.6)         | 24 (28.2)            | 74 (32.3)              | 130 (29.3)     |        |
| 1996–2001                              | 18 (13.8)         | 19 (22.3)            | 43 (18.8)              | 80 (18.0)      |        |
| 2002–2007                              | 20 (15.4)         | 10 (11.8)            | 27 (11.8)              | 57 (12.8)      |        |
| 2008–2015                              | 23 (17.7)         | 4 (4.7)              | 17 (7.4)               | 44 (9.9)       |        |
| Nadir CD4/mm³                           |                   |                      |                        |                |        |
| Nadir CD4 > 500                        | 3 (3.0)           | 1 (1.5)              | 8 (4.0)                | 12 (3.3)       | .05    |
| 200 ≥ Nadir CD4 ≤ 500                  | 16 (15.8)         | 7 (10.4)             | 50 (25.0)              | 73 (19.8)      |        |
| Nadir CD4 < 200                        | 82 (81.2)         | 59 (88.1)            | 142 (71.0)             | 283 (76.9)     |        |
| HBs antigenemia                         |                   |                      |                        |                |        |
| Positive                               | 9 (8.0)           | 12 (16.2)            | 14 (6.9)               | 35 (9.0)       | .05    |
| Negative                               | 103 (92.0)        | 62 (83.8)            | 188 (93.1)             | 353 (91.0)     |        |
| HCV antibodies                          |                   |                      |                        |                |        |
| Negative                               | 115 (88.5)        | 65 (76.5)            | 193 (84.3)             | 373 (84.0)     | .06    |
| Positive                               | 15 (11.5)         | 20 (23.5)            | 36 (15.7)              | 71 (16.0)      |        |
| First primary cancer category           |                   |                      |                        |                |        |
| ADCs                                   | 95 (73.1)         | 57 (67.1)            | 117 (51.1)             | 269 (60.6)     | <.0001 |
| VR-NADCs                               | 13 (10.0)         | 13 (15.3)            | 25 (10.9)              | 51 (11.5)      |        |
| VU-NADCs                               | 22 (16.9)         | 15 (17.6)            | 87 (38.0)              | 124 (27.9)     |        |
| First cancer occurrence according to ART period |                   |                      |                        |                |        |
| During ART era (>1996)                  | 96 (73.8)         | 65 (76.5)            | 184 (80.3)             | 345 (77.7)     | .35    |
| Before ART era (≤1996)                  | 34 (26.2)         | 20 (23.5)            | 45 (19.6)              | 99 (22.3)      |        |
| First cancer occurrence according to ART initiation | 113 (86.9) | 78 (91.8)            | 209 (91.3)             | 400 (90.1)     | .35    |
| After                                  | 17 (13.1)         | 7 (8.2)              | 20 (8.7)               | 44 (9.9)       |        |
| Before                                 | 1 (0–4)           | 2 (0–9)              | 5 (0–11)               | 3 (0–9)        | <.0001 |
| Delay between first ART and first cancer event (y) | 1 (0–6)   | 6 (3–11)             | 4 (2–10)               | 4 (1–9)        | <.0001 |

MSM: men who have sex with men; ADCs: AIDS-defining cancers; VR-NADCs: virus-related non-AIDS-defining cancers; VU-NADCs: virus-unrelated non-AIDS-defining cancers; ART: antiretroviral treatment; HCV: hepatitis C virus; HB: hepatitis B.

* Nadir CD4 available for 360 patients (SPC ADCs category: n = 111; SPC VR-NADCs category: n = 67; SPC VU-NADCs category: n = 200).
cancer category. For this analysis, we used the nonparametric Mann–Whitney test for comparisons of continuous variables and the chi-squared test for categorical data. The following potential correlates were considered in the analyses: (1) sociodemographic characteristics, including sex and age; (2) HIV-related variables, including HIV transmission route (heterosexual, men who have sex with men [MSM]), intravenous drug user (IVDU) (others/unknown), and duration of HIV infection follow-up; (3) the nadir CD4+ T cell count; and (4) co-infection with hepatitis C and hepatitis B. Continuous variables were standardized when entered in the regression models.

Univariate analysis enabled us to identify the major correlates, which were considered candidates for inclusion in the multivariate models if $P$ was <0.20. Multinomial logistic regression was then performed using a stepwise procedure according to a $P$ value at entry of 0.20 and a $P$ value to remain of 0.10. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata/SE software (version 14.2; Stata Corp LP).

### Results

Among the 44642 PLWH included in the Dat’AIDS cohort, 4855 were diagnosed with cancer between 1 December 1983 and 31 December 2015, of whom 444 (9.1%) developed at least 2 primary cancers. At the time of the censoring, 55.4% of the patients were alive, 35.1% had died, and 9.5% had been lost to follow-up. The distribution of SPCs and subsequent cancer events are presented in Figure 1. The characteristics of patients are reported in Table 1. The results of the univariate analysis of factors associated with the occurrence of VR- and VU-NADC vs an ADC as a second primary cancer are reported in Table 2.

Most of the study population were men (83.1%) of which 47.8% were MSM, 16.0% were HCV coinfected, and 9.1% were women. The odds ratios and $P$ values for the factors considered in the analysis are presented in Table 2.

**Table 2.** Univariate Analysis of Factors Associated With the Occurrence of a Virus-Related and Unrelated Non-AIDS-Defining Cancer vs an AIDS-Defining Cancer as a Second Primary Cancer in the French Dat’AIDS Cohort.

| Factor                                      | Odds Ratio, VR-NADCs vs ADCs | P value | Odds Ratio, VU-NADCs vs ADCs | P value |
|---------------------------------------------|------------------------------|--------|------------------------------|--------|
| Delay between the HIV diagnosis and the first primary cancer (y) | 1.29 (.96–1.73) | .09    | 1.63 (1.29–2.07) | <.0001 |
| Gender                                      |                              |        |                              |        |
| Women                                       | 1.64 (.76–3.57) | .21    | 1.88 (1.00–3.52) | .05    |
| Men                                         |                              |        |                              |        |
| Age at first cancer event (y)               | .82 (.61–1.12)  | .21    | 1.65 (1.30–2.08) | <.0001 |
| HIV transmission route                      |                              |        |                              |        |
| Heterosexual                                | .82 (.42–1.61)  | .57    | 1.18 (.71–1.94)  | .53    |
| IVDU                                        | 1.98 (.80–4.93) | .14    | 2.11 (.98–4.56) | .06    |
| Other/unknown                               | .80 (.34–1.89)  | .61    | .51 (.24–1.06)  | .07    |
| MSM                                         |                              |        |                              |        |
| Period of HIV diagnosis                     |                              |        |                              |        |
| 1983–1989                                   | 4.35 (1.35–14.02) | .01    | 2.49 (1.18–5.23) | .02    |
| 1990–1995                                   | 4.31 (1.31–14.12) | .02    | 3.13 (1.48–6.63) | .003   |
| 1996–2001                                   | 6.07 (1.75–21.02) | .004   | 3.23 (1.40–7.44) | .01    |
| 2002–2007                                   | 2.88 (1.78–10.60) | .11    | 1.83 (1.78–4.29) | .17    |
| 2008–2015                                   |                              |        |                              |        |
| Nadir CD4/mm³                                |                              |        |                              |        |
| Nadir CD4 > 500                             | .46 (.05–4.57)  | .51    | 1.54 (1.40–5.97) | .53    |
| 200 ≥ nadir CD4≤ 500                        | .61 (.24–1.57)  | .30    | 1.81 (.97–3.37) | .06    |
| Nadir CD4 < 200                              |                              |        |                              |        |
| HBs antigenemia                             |                              |        |                              |        |
| Positive                                    | 2.22 (.88–5.56) | .09    | .85 (.36–2.04)  | .72    |
| Negative                                    |                              |        |                              |        |
| HCV antibodies                              |                              |        |                              |        |
| Negative                                    |                              |        |                              |        |
| Positive                                    | 2.36 (1.13–4.92) | .02    | 1.43 (.75–2.73) | .28    |
| First primary cancer category               |                              |        |                              |        |
| ADCs                                        |                              |        |                              |        |
| VR-NADCs                                    | 1.67 (.72–3.85) | .23    | 1.56 (.76–3.22) | .23    |
| VU-NADCs                                    | 1.14 (.55–2.37) | .73    | 3.21 (1.87–5.51) | <.0001 |
HBV-coinfected (Table 1). The median follow-up time between the first primary cancer event and the last available data was 9 years (IQR: 4–15) (data not shown). The category of the first primary cancer was ADC in 269 patients, VR-NADC in 51, and VU-NADC in 124 patients. The median age at the first cancer event was 46. The category of SPC NADCs was 70.7% and 29.3% of SPC ADCs with a median age of 51 (IQR: 44–60) (data not shown). The median delay between the first and second primary cancer category was significantly shorter for SPC ADC and also differed significantly according to the first cancer category: 6 years (IQR: 1–10) after a first ADC, 2 years (IQR: 1–5) after a first VR-NADC, and 2 years (IQR: 1–6) after a first VU-NADC (P < .0001) (data not shown). Most subjects were HIV-diagnosed before the ART era (62.6%), 90.1% initiated ART before the first cancer event, and 76.9% had a nadir CD4 count less than 200/mm³.

**Multivariate Analysis**

The results are reported in Table 3. A longer delay between the first primary cancer and the SPC was associated with an increased risk of occurrence of VR-NADC rather than a secondary ADC. Having had a first primary VU-NADC, an older age, and a longer delay between the HIV diagnosis and the first primary cancer as well as between the first primary cancer and the SPC were associated with an increased risk of VU-NADC rather than ADC.

**Discussion**

In this population of cancer survivors living with HIV who developed at least two primary cancers, most were HIV-diagnosed before the ART era and had a nadir CD4 count less than 200/mm³. In these patients, ADC was the most common category of first primary cancer, but VU-NADC was the most common category of SPC, regardless of the category of the first primary cancer. In our cohort, we had more cases of SPC NADCs than SPC ADCs. These results are in line with another cohort study, which presented as well more cases of SPC NADCs compared with SPC ADCs. Our study showed that the category of the first primary cancer, the delay between the HIV diagnosis and the first primary cancer, the age at the first cancer, and the follow-up time after the first cancer event were associated with the SPC category among cancer survivors living with HIV, whereas HIV transmission route, the duration of ART exposure, CD4 count nadir, and HCV and HBV serostatus showed no such association. Due to the small sample sizes in some cancer subgroups in our cohort, this analysis was carried out after grouping cancers by category and not for each specific type of cancer. Furthermore, other potential HIV-related associated factors, such as the HIV-VL and CD4 cell count, could not be considered in this analysis. The potential for the underreporting of cancer cases cannot be excluded as this study was carried out within a cohort and not a cancer registry, without the standardization of the collection of cancer diagnoses. Therefore, we are not able to conclude that the factors associated with the category of SPC among PLWH are now a major concern in this population. Moreover, further studies are needed and deserve to be reported insofar as they could prove useful for the development of patient monitoring strategies after a first cancer. The knowledge of excess risk of each SPC type for this population should allow to define appropriate screening procedures. Furthermore, this study highlights the need to take into account the possibility of previous cancer cases in this population and to distinguish them from those without such cases to avoid overestimating the cancer risk in this population.5

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