Survival After Cancer in Italian Persons With AIDS, 1986–2005: A Population-Based Estimation

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Background: Cancer survival in persons with AIDS (PWA) after introduction of antiretroviral therapies remains poorly characterized. The aim is to provide population-based estimates of cancer survival, overall and for the most important cancer types in PWA, and a comparison with persons without AIDS (non-PWA) affected by the same cancer.

Methods: PWA with cancer at AIDS diagnosis or thereafter were individually matched with non-PWA by type of cancer, sex, age, year of diagnosis, area of living, and, for lymphomas, histological subtype. Five-year observed survival and hazard ratios (HRs) of death in PWA versus non-PWA with 95% confidence intervals (CIs) were estimated.

Results: We included 2262 Italian PWA and 4602 non-PWA with cancer diagnosed during 1986–2005. Between 1986 and 1995, and 1996 and 2005, 5-year survival for all cancers in PWA improved from 12% to 41% and the corresponding HR versus non-PWA decreased from 5.1 (95% CI: 4.3 to 6.1) to 2.9 (95% CI: 2.6 to 3.3). During 1996–2005, HRs were 2.0 (95% CI: 1.4 to 2.9) for Kaposi sarcoma, 3.4 (95% CI: 2.9 to 4.1) for non-Hodgkin lymphoma, and 2.4 (95% CI: 1.4 to 4.0) for cervical cancer. HRs were 2.5 (95% CI: 2.1 to 3.1) for all non–AIDS-defining cancers, 5.9 (95% CI: 3.1 to 11.2) for Hodgkin lymphoma, and 7.3 (95% CI: 2.8 to 19.2) for nonmelanoma skin cancer. A ≤3-fold survival difference was found for cancers of the stomach, liver, anus, lung, brain, and the most aggressive lymphoma subtypes.

Conclusions: The persisting, although narrowing, gap in cancer survival between PWA and non-PWA indicates the necessity of enhancing therapeutic approaches, so that PWA can be provided the

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Cancer and AIDS Registries Linkage Study members are listed in the Appendix.

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same chances of survival observed in the general population, and improving cancer prevention and screening.

Key Words: survival, AIDS patients, cancer, hazard ratio

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INTRODUCTION

HIV increases cancer risk, primarily by immunosuppression.[1] Evidence was considered sufficient to establish that HIV infection is causally linked to the occurrence of Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and carcinoma of the cervix, anus, and conjunctiva. Moreover, a positive association has been observed between HIV infection and cancers of the liver, vulva, vagina, penis, and skin (nonmelanoma).[1]

The life expectancy of people with HIV or AIDS has dramatically increased in high-resource countries during the antiretroviral therapy (ART) era,[2] although it remains still lower than that of the general population.[3–5]

Cancer continues to be an important cause of mortality in persons with AIDS (PWA) in high-resource countries during the ART era.[4,6,7] It was estimated that NHL and KS represented 15%–18% of all deaths with several 100-fold higher risks of death than in the general population.[8,9] In addition, non–AIDS-defining cancers (ie, cancers other than KS, NHL, and invasive cervical cancer—ICC) caused approximately 10%–15% of all deaths in PWA,[8–13] with a 7-fold higher risk of death than that of the general population.[14]

The survival of PWA after a diagnosis of cancer, especially KS and NHL, has been explored by several clinical-based investigations.[15–20] However, population-based studies on cancer survival in PWA are few[21,22] and so are the comparisons of cancer survival with the general population (thereafter referred to as non-PWA).[23]

In Italy, a high-quality nationwide AIDS Registry has been active since the beginning of the epidemic,[24] along with a network of cancer registries covering up to one-third of the population in the same period.[25] Taking advantage of these opportunities, we carried out a record linkage investigation to provide population-based information on cancer survival in PWA.

Our study aim was to compare the survival for several cancers in PWA with that of sex- and age-matched patients with closely similar cancer types in the general population without AIDS.

MATERIALS AND METHODS

Subjects

The general design of our record linkage study has been previously described.[26,27] In brief, reporting of AIDS cases to the Italian AIDS Registry started in 1982 on a voluntary basis and became mandatory in November 1986. At the end of 2005, a total of 57,531 AIDS cases had been reported nationwide and HIV-positive patients without AIDS diagnosis had not been included.[24] The AIDS Registry has been recording information on sociodemographic characteristics, $CD4^+$ cell count (since 1990), time at first HIV-positive test (since 1996), and ART before AIDS diagnosis (since 1999). A network of cancer registries has been active in Italy since the early 1980s.[28] During the late 1990s, 24 population-based cancer registries had been established, including 17.3 million inhabitants (30% of the total Italian population). They varied both in size (between 180,000 and 2 million) and in duration of activity. Routine indicators of data completeness and quality of Italian cancer registries were deemed to be satisfactory.[25] Record linkage between the AIDS Registry and each cancer registry was performed using an updated version of a validated software.[29,30]

The present study was restricted to patients who had been diagnosed with cancer at or after AIDS between 1986 and 2005 (ie, cancers diagnosed in HIV patients before the AIDS diagnosis have been excluded) and who reported a "legal residence" in areas covered by a cancer registry. Further restrictions required that PWA had a cancer diagnosis (1) between 16 and 74 years of age and (2) in years in which complete registry data were available. We excluded cancer cases diagnosed only on the basis of death certificate or autopsy (2.0% in PWA and 0.7% in non-PWA).[28,31] Multiple primary tumors were included in the site-specific survival analyses, but only the first or, in the case of synchronous diagnoses, the most severe malignancy was considered for the estimation of all-cause observed survival.[32] Cancer prognosis was based on 5-year relative survival in Italy.[28]

An individual matching of cancer cases was conducted to improve comparability between PWA and non-PWA. Non-PWA were defined as cancer patients who were not found in the AIDS registry. For each cancer case in PWA, 5 patients were randomly selected among non-PWA in the anonymous database of Italian cancer registries by means of an automated procedure.[33] A different matching ratio had to be used for KS (1:1) and NHL (1:2), on account of the rarity of these malignancies in non-PWA of the same age as PWA.[34–36]

Matching criteria included the following: cancer type (*International Classification of Diseases, 10th Revision*, 3 digits), histological type (International Classification of Diseases for Oncology, third edition- ICDO-3 for NHL, HL, ICC, and nonmelanoma skin), sex, age at cancer diagnosis (in 5-year groups), period of diagnosis (1986–1990, 1991–1995, 1996–2000, and 2001–2005), and area (North, Center, South and Islands).[28] When no controls were found in the exact matching category (mainly in the case of KS), a less stringent matching criteria was used, which allowed the extraction from the nearest categories of area of living, period, or age.

The Italian Cancer and AIDS Registries Linkage study was approved by the institutional review boards of the Centro di Riferimento Oncologico (Aviano) and of all participating registries.

Statistical Methods

For each person, time at risk in days was calculated from cancer diagnosis to death or December 31, 2009,[28] whichever occurred earlier. The Kaplan–Meier method was

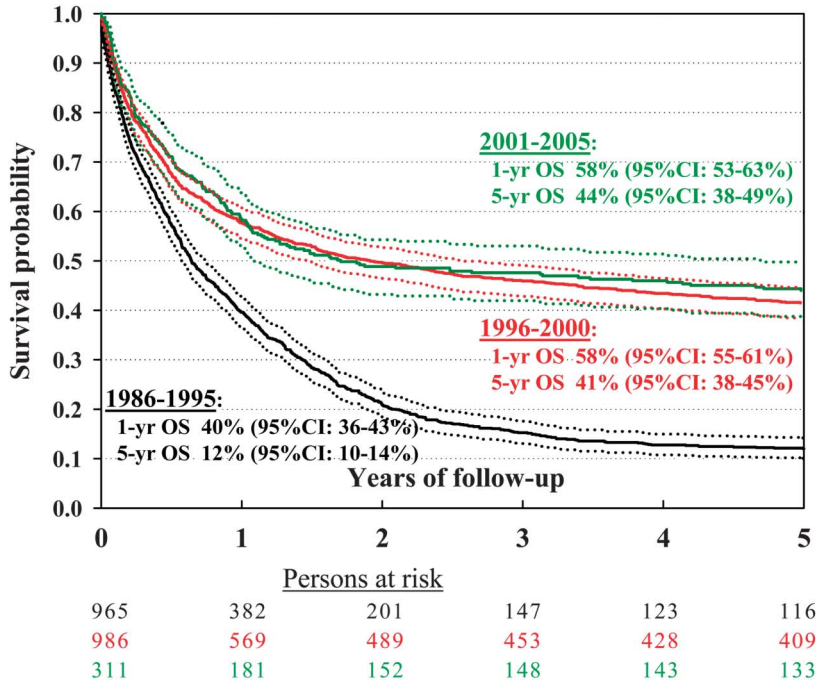

FIGURE 1. Number of cancer cases and observed survival (OS) after cancer in PWA (patients aged 16–74 years, in Italy) by period, during 1986–2005. Dotted lines represent 95% CIs.

used to generate observed 5-year survival curves for all cancers and individual malignancies among PWA during 1986–1995 (pre-ART era); 1996–2000 or 2001–2005. We used Cox models to estimate hazard ratios (HRs) of death after 5 years from cancer diagnosis in PWA compared with non-PWA and the corresponding 95% confidence intervals (CIs) for all cancer types for which 5 or more cases were observed among PWA during either 1986–1995 or 1996–2005 (ART period). To distinguish differences in short-term and long-term survival[37], we also computed 1-year and 5-year survivals conditioned on being alive at 1 year since diagnosis. The proportional hazard assumption was assessed through the log(−log (survival)) plots and including interactions with follow-up time. No violation of this assumption was observed. The Wald test was used to assess the heterogeneity of HRs by different PWA characteristics.

All analyses were conditioned on individual matching and additionally adjusted for age at cancer diagnosis in years as a continuous variable.

RESULTS

Among 21,951 PWA (78% men) who had been reported between 1986 and 2005 in Italian areas covered by a cancer registry, 2262 were diagnosed with one or more cancer type. The total number of cancers among PWA was 2337, in which 1042 were KS, 938 NHL, 67 ICC, and 290 were non–AIDS-

TABLE 1. HR of Death and 95% CIs at 5 years from cancer diagnosis in PWA* Versus Non-PWA† During 1986–1995

	PWA			Non-PWA			
Cancer Type‡	Cases	Deaths	Survival (%)	Cases	Deaths	Survival (%)	HR§ (95% CI)
All patients	965	850	12	1667	563	66	5.1 (4.3 to 6.1)
KS	520	447	14	520	107	79	5.1 (3.4 to 7.6)
NHL	377	348	8	754	319	58	4.6 (3.7 to 5.7)
Invasive cervical cancer	15	6	60	75	11	85	5.6 (1.5 to 21.9)
All non–AIDS-defining cancers	72	67	7	360	151	58	7.6 (5.1 to 11.3)
Colon–rectum	6	6	0	30	20	33	6.3 (1.8 to 22.9)
Lung	9	9	0	45	30	33	2.5 (1.0 to 5.9)
Brain	5	5	0	25	15	40	24.4 (2.7 to 220)
HL	19	16	16	95	15	84	11.6 (4.6 to 29.4)

*Patients aged 16–74 years, in Italy.
†Matched by type (1:1 for KS, 1:2 for NHL, 1:5 for other cancers), histology (for NHL, ICC, skin, and HL), sex, age, period of diagnosis, and area in Italy.
‡Only cancer types with ≥5 cases have been shown.
§Estimates from the Cox proportional hazard model conditioned on matching variables and adjusted for age at diagnosis in years.

defining cancers (see **Table, Supplemental Digital Content 1,** http://links.lww.com/QAI/A524).

The relative contribution of non–AIDS-defining cancers to all cancers increased from 7.3% during 1986–1995 to 27.6% during 2001–2005 (see **Figure, Supplemental Digital Content 2a,** http://links.lww.com/QAI/A524) and so did the proportion of diffuse large B-cell lymphoma (35.6%–45.9% of all lymphomas) and HL (4.8%–10.3% of all lymphomas) (see **Figure, Supplemental Digital Content 2b,** http://links.lww.com/QAI/A524).

The majority (55%) of KS among PWA occurred among men having sex with men, whereas approximately 50% of NHL and other cancers were diagnosed among injecting drug users. For KS and, to a lesser extent, NHL, the age distribution of cancer cases in PWA differed from that in non-PWA. For all other cancers, the distribution of matching variables did not differ between PWA and non-PWA (see **Table, Supplemental Digital Content 3,** http://links.lww.com/QAI/A524).

Figure 1 shows observed all-cancer survival in PWA in 3 periods. Five-year survival was low in the pre-ART period (12%; 95% CI: 10% to 14%) with a median survival of 7.7 months, but it improved during 1996–2000 (41%; 95% CI: 38% to 45%) and 2001–2005 (44%; 95% CI: 38% to 49%).

Table 1 shows 5-year survival for all cancers, AIDS-defining cancers, all non–AIDS-defining cancers, and the most frequent non–AIDS-defining cancers in PWA during 1986–1995 and the corresponding HRs of death in PWA versus non-PWA. Only 12% of the PWA with cancer survived 5 years or more, compared with 66% of matched non-PWA (HR of death = 5.1; 95% CI: 4.3 to 6.1). An HR of approximately 5 was found for KS, NHL, and ICC, whereas it was 7.6 (95% CI: 5.1 to 11.3) for all non–AIDS-defining cancers.

TABLE 2. HR of Death and 95% CIs at 5 years from cancer diagnosis in PWA* Versus Non-PWA† During 1996–2005

	PWA			Non-PWA			
Cancer Type‡	**Cases**	**Deaths**	**Survival (%)**	**Cases**	**Deaths**	**Survival (%)**	**HR§ (95% CI)**
All patients	1297	751	42	2935	1042	65	2.9 (2.6 to 3.3)
KS	522	202	61	522	121	77	2.0 (1.4 to 2.9)
NHL	561	418	25	1122	402	64	3.4 (2.9 to 4.1)
NHL, CNS (all histologies)	47	43	9	94	67	29	3.1 (1.6 to 6.2)
NHL, DLBC and immunoblastic	264	187	29	528	180	66	3.0 (2.3 to 3.8)
NHL, Burkitt	39	29	26	78	43	45	1.2 (0.7 to 2.2)
NHL, follicular and SLL/CLL	11	8	27	22	2	91	27.4 (1.1 to 757)
NHL, T cell	13	8	38	26	3	88	20.9 (1.6 to 268)
NHL, other specified histology	7	5	29	14	5	64	15.6 (1.3 to 186)
NHL, NOS	180	138	23	360	102	72	5.3 (3.8 to 7.5)
Invasive cervical cancer	52	23	56	260	54	79	2.4 (1.4 to 4.0)
Squamous	30	18	40	150	31	79	4.3 (2.2 to 8.4)
Other and NOS	22	5	77	110	23	79	0.9 (0.4 to 2.5)
All non–AIDS-defining cancers	218	153	30	1090	496	55	2.5 (2.1 to 3.1)
Head and neck	8	7	13	40	18	55	5.2 (1.7 to 16.1)
Stomach	8	7	13	40	25	38	2.5 (0.9 to 6.8)
Colon–rectum	14	10	29	70	22	69	3.9 (1.6 to 9.3)
Anus	10	7	30	50	24	52	2.2 (0.8 to 5.9)
Liver	13	12	8	65	50	23	1.9 (0.9 to 4.2)
Lung	46	40	13	230	199	13	1.6 (1.1 to 2.3)
Skin, nonmelanoma	28	11	61	140	10	93	7.3 (2.8 to 19.2)
Squamous	13	9	31	65	4	94	21.2 (4.5 to 98.9)
Basal	10	2	80	50	3	94	4.9 (0.7 to 35.2)
NOS	5	0	100	25	3	88	0 (—)
Brain	7	6	14	35	23	34	2.1 (0.7 to 5.7)
HL	36	21	42	180	25	86	5.9 (3.1 to 11.2)
HL, mixed cell	17	7	59	85	14	84	2.7 (1.0 to 7.3)
HL, nodular sclerosis	9	7	22	45	5	89	19.9 (3.6 to 109)
HL, NOS	10	7	30	50	6	88	8.8 (2.5 to 30.9)
Leukemias	6	6	0	30	13	57	6.5 (1.7 to 24.2)
Other non–AIDS-defining cancers	42	26	38	210	87	59	2.4 (1.5 to 3.9)

*Patients aged 16–74 years, in Italy.
†Matched by type (1:1 for KS, 1:2 for NHL, 1:5 for other cancers), histology (for NHL, ICC, skin, and HL), sex, age, period of diagnosis, and area in Italy.
‡Only cancer types with ≥5 cases have been shown.
§Estimates from the Cox proportional hazard model conditioned on matching variables and adjusted for age at diagnosis in years.
NOS, not otherwise specified; CNS, central nervous system; DLBC, diffuse large B-cell; SLL/CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

All-cancer 5-year survival in PWA in the ART period was 42% (Table 2), with a nearly 3-fold higher risk of death than non-PWA (HR = 2.9, 95% CI: 2.6 to 3.3). Five-year overall survival was 61% for KS and 56% for ICC, although it remained significantly worse than in non-PWA (HR = 2.0, 95% CI: 1.4 to 2.9; and 2.4, 95% CI: 1.4 to 4.0, respectively). Five-year survival in PWA was 25% after any NHL (HR versus non-PWA = 3.4; 95% CI: 2.9 to 4.1) and 29% after diffuse large B-cell lymphoma (HR = 3.0; 95% CI: 2.3 to 3.8), the most common NHL subtype. However, HRs varied substantially by NHL subtype, ranging between 1.2 for Burkitt lymphoma and 27.4 for follicular or small lymphocytic lymphoma.

HR in the ART era was 2.5 (95% CI: 2.1 to 3.1) for all non–AIDS-defining cancers. The magnitude of HRs for the worst prognosis cancer types, ie, lung (1.6, 95% CI: 1.1 to 2.3), liver (1.9; 95% CI: 0.9 to 4.2), and brain (2.1; 95% CI: 0.7 to 5.7), was lower than that recorded for other non–AIDS-defining neoplasms, like cancer of the colon–rectum (3.9; 95% CI: 1.6 to 9.3), nonmelanoma skin cancer (7.3, 95% CI: 2.8 to 19.2), and leukemias (6.5, 95% CI: 1.7 to 24.2). The HR for all types of HL combined was 5.9 (95% CI: 3.1 to 11.2), but it was 19.9 (95% CI: 3.6 to 109) for the nodular sclerosis subtype (5-year survival of 22%). Notably, and at variance with non-PWA, a poor outcome emerged for PWA with squamous-cell carcinoma of the skin (5-year survival of 31%). The exclusion of patients with nonmelanoma skin cancers, or multiple primaries, did not substantially modify the risk of death for PWA versus non-PWA (HR = 3.0 and 2.8, respectively, data not shown).

In the ART era (1996–2005), survival curves after cancer were consistently lower in PWA than in non-PWA for all the most frequent cancer types (ie, KS, NHL, ICC, nonmelanoma skin cancer, and HL) except for lung cancer in which the difference diminished with time since diagnosis (see **Figure, Supplemental Digital Content 4,** http://links.lww.com/QAI/A524).

Table 3 shows that HRs in PWA versus non-PWA after 1 year (3.1; 95% CI: 2.7 to 3.6) tended to be higher, though nonstatistically significant, than HRs after 5 years conditioned to be alive 1 year after cancer (2.4; 95% CI: 1.9 to 3.1). This pattern was consistent in AIDS-defining and non–AIDS-defining cancers, with the exception of HL (HR = 10.5 and 3.3, respectively).

In the ART era, no significant differences in HR for type-specific cancers or all cancers combined were found between men and women, age groups, and calendar periods (Table 4). However, being an injecting drug user vs. other categories, having a history of HIV positivity lasting one or more years vs. less than one year, and ART use before AIDS vs. no use were all associated to significantly greater HRs. The difference in HRs by transmission category was mainly driven by worse survival for KS in injecting drug users compared with other groups, whereas the unfavorable influence of other characteristics on 5-year survival tended to be found consistently in each AIDS-defining cancer and in the combination of non–AIDS-defining cancers.

DISCUSSION

This population-based study showed that cancer survival in PWA substantially improved in the ART era, in Italy. The 5-year all-cancer survival for those diagnosed during 2001–2005 (44%) was higher than the 1-year survival recorded in the pre-ART period (40%). Moreover, the gap in all-cancer survival between PWA and non-PWA decreased from 5-fold in the pre-ART period to 3-fold

TABLE 3. HR of Death in PWA* Versus Non-PWA According to Time Since Cancer Diagnosis During 1996–2005

	At 1 yr After Diagnosis			At 5 yrs After Diagnosis, Conditioned to be Alive After 1 yr		
Cancer Type†	**Cases**	**Deaths**	**HR‡ (95% CI)**	**Cases**	**Deaths**	**HR‡ (95% CI)**
All patients	1297	547	3.1 (2.7 to 3.6)	750	204	2.4 (1.9 to 3.1)
KS	522	125	2.0 (1.3 to 3.1)	397	77	2.0 (1.1 to 3.6)
NHL	561	341	3.5 (2.9 to 4.2)	220	77	3.3 (2.2 to 4.9)
Invasive cervical cancer	52	9	2.8 (1.2 to 6.6)	43	14	2.2 (1.1 to 4.3)
All non–AIDS-defining cancers	218	105	2.7 (2.1 to 3.4)	113	48	2.3 (1.6 to 3.4)
Head and neck	8	2	2.6 (0.4 to 18.4)	6	5	7.6 (1.8 to 32.7)
Stomach	8	5	3.6 (1.1 to 12.1)	3	2	1.2 (0.2 to 6.9)
Colon–rectum	14	6	4.6 (1.5 to 14.4)	8	4	3.1 (0.8 to 12.1)
Anus	10	4	2.4 (0.7 to 8.5)	6	3	2.1 (0.4 to 10.2)
Liver	13	7	1.7 (0.7 to 4.4)	6	5	2.5 (0.5 to 13.1)
Lung	46	33	1.8 (1.2 to 2.8)	13	7	0.9 (0.3 to 2.4)
Skin, nonmelanoma	28	3	5.0 (1.0 to 25.0)	25	8	9.0 (2.6 to 31.0)
Brain	7	5	2.2 (0.7 to 6.8)	2	1	1.0 (0.1 to 12.9)
HL	36	13	10.5 (4.0 to 27.7)	23	8	3.3 (1.3 to 8.5)
Leukemias	6	6	6.7 (1.8 to 25.6)	—	—	—
Other non–AIDS-defining cancers	42	21	3.0 (1.7 to 5.2)	21	5	1.2 (0.4 to 3.2)

*Patients aged 16–74 years, in Italy.
†Only cancer types with ≥5 cases have been shown.
‡Estimates from the Cox proportional hazard model conditioned on matching variables and adjusted for age at diagnosis in years.

TABLE 4. HR* of Death and 95% CIs at 5 years from cancer diagnosis in PWA† Versus Non-PWA According to Selected Characteristics‡ During 1996–2005

			Cancer Type							
	All Patients		KS		NHL		Invasive Cervical Cancer		All Non–AIDS-Defining Cancers	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Sex										
Men	1057	2.9 (2.5 to 3.4)	478	2.1 (1.4 to 3.1)	447	3.4 (2.8 to 4.1)	—	—	178	2.5 (2.0 to 3.2)
Women	240	2.8 (2.2 to 3.6)	44	1.5 (0.5 to 4.2)	114	3.7 (2.5 to 5.4)	52	2.4 (1.4 to 4.0)	40	2.5 (1.5 to 4.2)
Age group (yrs)										
16–39	677	3.0 (2.5 to 3.6)	268	1.5 (0.8 to 2.6)	307	3.4 (2.7 to 4.3)	40	2.0 (1.1 to 3.7)	83	3.2 (2.3 to 4.6)
40–74	620	2.8 (2.3 to 3.3)	254	2.4 (1.5 to 3.8)	254	3.4 (2.6 to 4.3)	12	3.6 (1.3 to 9.7)	135	2.2 (1.7 to 2.9)
Period of cancer diagnosis										
1996–2000	986	2.9 (2.5 to 3.3)	420	2.2 (1.4 to 3.2)	430	3.3 (2.7 to 4.0)	44	2.0 (1.1 to 3.6)	126	2.7 (2.1 to 3.5)
2001–2005	311	2.9 (2.3 to 3.7)	102	1.3 (0.6 to 3.1)	131	4.0 (2.8 to 5.8)	8	4.4 (1.4 to 13.8)	92	2.3 (1.7 to 3.3)
Transmission category										
Injecting drug users	461	3.7 (3.0 to 4.7)§	104	3.4 (1.3 to 8.7)§	240	4.0 (3.1 to 5.2)	32	2.8 (1.5 to 5.4)	97	3.4 (2.5 to 4.7)
Men who have sex with men	429	2.5 (1.9 to 3.2)	275	1.8 (1.1 to 3.0)	128	3.4 (2.4 to 5.0)	—	—	52	2.4 (1.5 to 3.6)
Heterosexuals/other	407	2.3 (1.9 to 2.8)	143	1.7 (0.9 to 3.2)	193	2.7 (2.0 to 3.6)	20	1.8 (0.8 to 4.2)	69	1.9 (1.3 to 2.7)
CD4 at AIDS diagnosis (cells/mL)										
<100	618	3.1 (2.6 to 3.7)	276	2.3 (1.4 to 3.7)	238	4.2 (3.2 to 5.6)	16	4.1 (1.7 to 9.6)	117	2.3 (1.7 to 3.0)
≥100	625	2.6 (2.2 to 3.2)	229	1.6 (0.9 to 2.8)	296	2.8 (2.2 to 3.5)	35	1.7 (0.9 to 3.3)	90	3.2 (2.3 to 4.5)
Years since first HIV positivity										
<1	466	2.0 (1.6 to 2.6)§	265	1.6 (1.0 to 2.5)§	170	2.9 (2.1 to 4.0)	9	1.4 (0.4 to 5.1)	33	1.1 (0.7 to 2.0)§
≥1	831	3.3 (2.8 to 3.8)	257	2.9 (1.6 to 5.3)	391	3.6 (3.0 to 4.5)	43	2.6 (1.5 to 4.6)	185	3.0 (2.4 to 3.8)
ART before AIDS‖										
Yes	197	3.1 (2.3 to 4.2)§	59	1.2 (0.4 to 3.7)	106	3.3 (2.2 to 4.8)	12	4.0 (1.5 to 10.4)	24	3.7 (2.0 to 7.0)
No	318	1.8 (1.4 to 2.4)	160	1.0 (0.5 to 1.8)	120	2.4 (1.7 to 3.5)	6	1.7 (0.4 to 6.7)	41	1.5 (0.9 to 2.4)
Missing	165	3.0 (2.2 to 4.0)	27	1.8 (0.5 to 6.5)	48	3.0 (1.7 to 5.3)	6	4.7 (1.2 to 18.9)	104	3.1 (2.2 to 4.2)

*Estimates from the Cox proportional hazard model conditioned on matching variables and adjusted for age at diagnosis in years.
†Patients aged 16–74 years, in Italy.
‡Numbers of cases and controls may not sum to these totals because of missing values.
§*P* value for heterogeneity <0.05, missing values not included in the heterogeneity test.
‖Not systematically collected before 1999.

thereafter. The number of non–AIDS-defining malignancies proportionally increased among PWA, and improvement in their survival as compared with non-PWA was larger (from 7.6- to 2.5-fold difference) than for AIDS-defining cancers, although the difference in survival for the worst prognosis cancers was less than 2-fold. Cancer survival among PWA tended, however, to be worse among injecting drug users than in other HIV transmission categories and in PWA who had a history of HIV positivity lasting one or more years or who had been already using ART before AIDS diagnosis.

These findings are in substantial agreement with previous evidence from population-based study of cancer survival in PWA[22,23,38] and with several clinical-based studies.[19,20,39] It should be noted, however, that survival estimates in clinical series tended to be more favorable than survival in population-based series.

The proportion of KS among all cancers in PWA decreased from 52% in the pre-ART period to 31% in the ART period, and the corresponding survival gap compared with non-PWA diminished from 5.1 to 2.0. The risk of dying after NHL in PWA as compared with non-PWA decreased from 4.6 before 1996 to 3.4 in the ART period, in agreement with findings from the United States.[17,19,23] However, the survival gap in the ART period varied substantially by NHL subtype. Although no difference was found with regard to Burkitt lymphoma, more than 20-fold difference emerged for some better prognosis subtypes, which are common in non-PWA but very rarely detected in PWA, ie, follicular, small lymphocytic (chronic lymphoid leukemias), or T-cell lymphoma. Despite a clear reduction in the survival gap, the 2-fold higher risk of dying after ICC compared with non-PWA provides evidence that participation rates and quality of cervical cancer screening in HIV-infected women in Italy need improvement.[40]

The assessment of survival after individual non–AIDS-defining cancers is, as elsewhere,[23] hampered by the small number of cases. Lung cancer was by far the most frequent

non–AIDS-defining cancer in Italy. In the ART period, it was associated with a poor 5-year survival (13%) in our study and in previous reports.[21,23,38,41] The increase in the risk of dying after lung cancer in PWA versus non-PWA was concentrated in the first year after cancer diagnosis pointing to the possibility of later stage diseases or less effective treatment protocols in PWA.[39,42] An approximately 2-fold lower survival in PWA versus non-PWA was also found for bad prognosis neoplasms (stomach, liver, brain) and for anal cancer.[16,23]

HL is one of the cancer types showing the largest survival difference between PWA and non-PWA in our study (HR = 5.9), notably in histological subtypes other than mixed-cell HL. Population-based studies showed less favorable HL survival than recent clinical-based studies[43] that endorsed the possibility to use similarly aggressive chemotherapy regimens in PWA and in non-PWA.[44] The largest survival gap between PWA and non-PWA was found for nonmelanoma skin cancer, especially squamous-cell carcinoma, which was reported to be a more strongly associated HIV infection than basal-cell carcinoma.[45] It is unclear whether skin cancer in PWA is more aggressive than in non-PWA, as it is in organ transplant recipients.[46] Differences in cancer survival between PWA and non-PWA may be explained by later diagnosis and less adequate treatment because of comorbidities that affect range of cancer treatment options in addition to overall survival per se.[3,47]

The most important strength of this population-based national record linkage study, including a 20-year period across the introduction of ART, is reliance on population-based survival in unselected and well-matched PWA and non-PWA. Completeness and good quality of AIDS reporting and cancer registration in Italy have been shown[25,48] and so has the accuracy of our linkage procedures.[29,30] In addition, the similarly active follow-up of PWA and non-PWA through death certificates and cancer registry data[4,28] provides reassurance on the accuracy and good comparability of our findings. Our study is the first population-based survival analysis in which PWA and non-PWA were individually matched using a strict criteria, including, when relevant, histological subtype that greatly differs in terms of prognosis.[22,23] Finally, we applied rigorous criteria for dealing with multiple cancers in PWA (6.5% of all cancers) and in non-PWA (5.5%).[32]

Our study has also some limitations. As in all population-based cancer studies, it is almost impossible to separate cancer-specific mortality from overall mortality. Therefore, HRs in our study merely inform on the risk of dying of PWA after cancer compared with non-PWA. Two major possible confounding factors included stage differences and differences in treatment between PWA and non-PWA. This information is not routinely collected by cancer registries, and, in particular, treatment approaches to cancer have changed significantly over this period and may have differed between PWA and non-PWA. Moreover, as in most population-based survival studies,[28] information on other correlates of survival (eg, tobacco or injecting drug use)[4] were not available. In addition, variations in case-mix across periods, sexes, or other characteristics should be kept in mind when comparing survival estimates because of the concomitant differences in cancer prognosis, eg, KS versus lung cancers.[28] The restriction to PWA, rather than people living with HIV, can be considered another weakness of our study. PWA has become a rather ill-defined group in the ART era[49] because, even in countries such as Italy in which AIDS definition is based on AIDS-defining diseases rather than CD4 count, people with HIV can benefit from immune reconstitution at any time in their infection history. Cancer survival in PWA is likely to provide a less favorable picture of cancer outcome than survival in people living with HIV. Restriction to PWA, however, had no impact on survival analyses of AIDS-defining cancers because their detection determines an AIDS diagnosis. Conversely, some HIV-infected patients would have certainly died from a non–AIDS-defining cancer before progressing to AIDS. Although the impact of this bias on our findings is uncertain, it is unlikely to be large.

In conclusion, our population-based study demonstrates still persistent differences in cancer survival between PWA and non-PWA in the ART era, thus indicating a need to enhance the therapeutic approach to offer PWA the same chances of survival observed in the general population.[50]

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REFERENCES

1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100B. A Review of human carcinogenesis. *IARC Monogr Eval Carcinog Risks Hum.* 2012;100(pt B):1–441.
2. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372:293–299.
3. Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA*. 2008;300:51–59.
4. Serraino D, Zucchetto A, Suligoi B, et al. Survival after AIDS diagnosis in Italy, 1999–2006: a population-based study. *J Acquir Immune Defic Syndr*. 2009;51:99–102.
5. Harrison KMD, Song R, Zhang X. Life expectancy after HIV diagnosis based on national HIV surveillance data from 25 states, United States. *J Acquir Immune Defic Syndr*. 2010;53:124–130.
6. Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study. *AIDS*. 2010;24:1537–1548.
7. Helleberg M, Kronborg G, Larsen CS, et al. Causes of death among Danish HIV patients compared with population controls in the period 1995–2008. *Infection*. 2012;40:627–634.
8. Serraino D, De Paoli A, Zucchetto A, et al. The impact of Kaposi sarcoma and non-Hodgkin lymphoma on mortality of people with AIDS in the highly active antiretroviral therapies era. *Cancer Epidemiol*. 2010;34:257–261.
9. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis*. 2010;50:1387–1396.
10. Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. *Clin Infect Dis*. 2010;51:957–962.
11. Marin B, Thiébaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS*. 2009;23:1743–1753.

12. Puhan MA, Van Natta ML, Palella FJ, et al. Excess mortality in patients with AIDS in the era of highly active antiretroviral therapy: temporal changes and risk factors. *Clin Infect Dis.* 2010;51:947–956.
13. Lewden C, May T, Rosenthal E, et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: the "Mortalité 2000 and 2005" Survey (ANRS EN19 and Mortavic). *J Acquir Immune Defic Syndr*. 2008;48:590–598.
14. Zucchetto A, Suligoi B, De Paoli A, et al. Excess mortality for non-AIDS-defining cancers among people with AIDS. *Clin Infect Dis.* 2010;51:1099–1101.
15. Brau N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.–Canadian multicenter study. *J Hepatol.* 2007;47:527–537.
16. Oehler-Jänne C, Huguet F, Provencher S, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. *J Clin Oncol.* 2008;26:2550–2557.
17. Norden AD, Drappatz J, Wen PY, et al. Survival among patients with primary central nervous system lymphoma, 1973–2004. *J Neurooncol.* 2011;101:487–493.
18. Gramenzi A, Tedeschi S, Cantarini MC, et al. Outcome of hepatocellular carcinoma in human immunodeficiency virus-infected patients. *Dig Liver Dis.* 2013;45:516–522.
19. Chao C, Xu L, Abrams D, et al. Survival of non-Hodgkin lymphoma patients with and without HIV infection in the era of combined antiretroviral therapy. *AIDS*. 2010;24:1765–1770.
20. Spagnuolo V, Travi G, Galli L, et al. Clinical, virologic, and immunologic outcomes in lymphoma survivors and in cancer-free, HIV-1-infected patients: a matched cohort study. *Cancer*. 2013;119:2710–2719.
21. Rengan R, Mitra N, Liao K, et al. Effect of HIV on survival in patients with non-small-cell lung cancer in the era of highly active antiretroviral therapy: a population-based study. *Lancet Oncol.* 2012;13:1203–1209.
22. Gopal S, Patel MR, Yanik EL, et al. Temporal Trends in presentation and survival for HIV-associated lymphoma in the antiretroviral therapy era. *J Natl Cancer Inst.* 2013;105:1221–1229.
23. Biggar RJ, Engels E, Ly S, et al. Survival after cancer diagnosis in persons with AIDS. *J Acquir Immune Defic Syndr*. 2005;39:293–299.
24. Centro Operativo AIDS. Aggiornamento dei casi di AIDS notificati in Italia e delle nuove diagnosi di infezione da HIV. Dicembre 2007. *Notiziario dell'Istituto Superiore di Sanità.* 2008;21(suppl 1):3–23.
25. Curado MP, Edwards B, Shin HR, et al, eds. *Cancer Incidence in Five Continents, Vol. IX*. Lyon: International Agency for Research on Cancer; 2007.
26. Polesel J, Franceschi S, Suligoi B, et al. Cancer incidence in people with AIDS in Italy. *Int J Cancer.* 2010;127:1437–1445.
27. Franceschi S, Dal Maso L, Arniani S, et al. Risk of cancer other than Kaposi's sarcoma and non-Hodgkin's lymphoma in persons with AIDS in Italy. Cancer and AIDS Registry Linkage Study. *Br J Cancer.* 1998; 78:966–970.
28. AIRTUM Working Group. Italian cancer figures report. Survival of cancer patients in Italy. *Epidemiol Prev.* 2011;35(suppl 3):1–200. Available at: http://www.registri-tumori.it/cms/Rapp2011. Accessed May 30, 2014.
29. Dal Maso L, Braga C, Franceschi S. Methodology used for "software for automated linkage in Italy" (SALI). *J Biomed Inform.* 2001;34:387–395. [Description of upgraded version of SALI software at http://www.registri-tumori.it/PDF/AIRTUM2009HANDBOOK/Chapter_Appendix2.pdf].
30. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst.* 2005; 97:425–432.
31. De Angelis R, Francisci S, Baili P, et al. The EUROCARE-4 database on cancer survival in Europe: data standardisation, quality control and methods of statistical analysis. *Eur J Cancer.* 2009;45:909–930.
32. Rosso S, De Angelis R, Ciccolallo L, et al. Multiple tumours in survival estimates. *Eur J Cancer.* 2009;45:1080–1094.
33. Dal Maso L. *Legame tra l'immunodeficienza HIV-correlata e l'insorgenza di tumori: aspetti di metodologia statistica*. Ph.D. Thesis. Milan University: Italy; 2012. Available at: http://air.unimi.it/bitstream/2434/168454/4/phd_unimi_R08222.pdf.
34. Dal Maso L, Rezza G, Zambon P, et al. Non-Hodgkin lymphoma among young adults with and without AIDS in Italy. *Int J Cancer.* 2001;93:430–435.
35. Dal Maso L, Polesel J, Ascoli V, et al. Cancer and AIDS registry linkage study. Classic Kaposi's sarcoma in Italy, 1985-1998. *Br J Cancer.* 2005; 92:188–193.
36. Shiels M, Pfeiffer RM, Hall HI, et al. Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980-2007. *JAMA*. 2011;305: 1450–1459.
37. Montlahuc C, Guiguet M, Abgrall S, et al. Impact of late presentation on the risk of death among HIV-infected people in France (2003-2009). *J Acquir Immune Defic Syndr.* 2013;64:197–203.
38. Sigel K, Crothers K, Dubrow R, et al. Prognosis in HIV-infected patients with non-small cell lung cancer. *Br J Cancer.* 2013;109:1974–1980.
39. Acherbach CJ, Cole SR, Kitahara MM, et al. Mortality after cancer diagnosis in HIV-infected individuals treated with antiretroviral therapy. *AIDS*. 2011;25:691–700.
40. Dal Maso L, Franceschi S, Lise M, et al. Self-reported history of Pap-smears in HIV-positive women in Northern Italy: a cross-sectional study. *BMC Cancer*. 2010;10:310.
41. Pakkala S, Chen Z, Rimland D, et al. Human immunodeficiency virus-associated lung cancer in the era of highly active antiretroviral therapy. *Cancer*. 2012;118:164–1672.
42. Suneja G, Shiels MS, Melville SK, et al. Disparities in the treatment and outcomes of lung cancer among HIV-infected individuals. *AIDS*. 2013; 27:459–468.
43. Montoto S, Shaw K, Okosun J, et al. HIV status does not influence outcome in patients with classical Hodgkin lymphoma treated with chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine in the highly active antiretroviral therapy era. *J Clin Oncol.* 2012;30:4111–4116.
44. Martis N, Mounier N. Hodgkin lymphoma in patients with HIV infection: a review. *Curr Hematol Malig Rep.* 2012;7:228–234.
45. Silverberg MJ, Leyden W, Warton EM, et al. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. *J Natl Cancer Inst.* 2013;105:350–360.
46. Ulrich C, Kanitakis J, Stockfleth E, et al. Skin cancer in organ transplant recipients-Where do we stand today? *Am J Transpl.* 2008;8:2192–2198.
47. Antiretroviral Therapy Cohort Collaboration. Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal. *Clin Infect Dis.* 2009;48:1138–1151.
48. Conti S, Farchi G, Galletti A, et al. La notifica della mortalità per AIDS in Italia (1992): qualità della certificazione e sottonotificata. *Giornale Italiano Dell'AIDS.* 1997;8:12–16.
49. Kaldor JM, Delpech V, Guy RJ. AIDS case reporting: do we still need it? *Lancet*. 2008;373:181–183.
50. Spano JP, Costagliola D, Katlama C, et al. AIDS-related malignancies: state of the art and therapeutic challenges. *J Clin Oncol*. 2008;26: 4834–4842.

APPENDIX

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