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IJC
International Journal of Cancer

Cancer incidence in people with AIDS in Italy

Jerry Polesel[1], Silvia Franceschi[2], Barbara Suligoi[3], Emanuele Crocetti[4], Fabio Falcini[5], Stefano Guzzinati[6], Marina Vercelli[7], Roberto Zanetti[8], Giovanna Tagliabue[9], Antonio Russo[10], Stefano Luminari[11], Fabrizio Stracci[12], Vincenzo De Lisi[13], Stefano Ferretti[14], Lucia Mangone[15], Mario Budroni[16], Rosa Maria Limina[17], Silvano Piffer[18], Diego Serraino[1,19], Francesco Bellù[20], Adriano Giacomin[21], Andrea Donato[22], Anselmo Madeddu[23], Susanna Vitarelli[24], Mario Fusco[25], Roberto Tessandori[26], Rosario Tumino[27], Pierluca Piselli[28] and Luigino Dal Maso[1,29]; for the Cancer and AIDS Registries Linkage (CARL) Study

[1] Epidemiology and Biostatistics Unit, Centro di Riferimento Oncologico IRCCS, Aviano, Pordenone, Italy
[2] International Agency for Research on Cancer, Lyon cedex, France
[3] Epidemiology Unit, Department of Infectious Diseases, National Institute of Health, Rome, Italy
[4] Tuscany Cancer Registry, Unit of Epidemiology, Cancer Prevention and Research Institute, ISPO, Florence, Italy
[5] Department of Medical Oncology, Romagna Cancer Registry, Romagna Cancer Institute (IRST), Meldola, Italy
[6] Registro Tumori del Veneto, Istituto Oncologico Veneto IRCCS, Padua, Italy
[7] Liguria Cancer Registry and Genova University, Istituto Nazionale per la Ricerca sul Cancro IRCCS, Genoa, Italy
[8] Piedmont Cancer Registry, Centro di Prevenzione Oncologica, Torino, Italy
[9] Registro Tumori Lombardia, Provincia di Varese, Istituto Nazionale Tumori, Milan, Italy
[10] Cancer Registry of Milan, Epidemiology Unit, Local Health Authority of Milan, Milan, Italy
[11] Department of Oncology and Hematology, Modena Cancer Registry, University of Modena and Reggio Emilia, Modena, Italy
[12] Department of Surgical Medical and Public Health, Umbria Cancer Registry, University of Perugia, Perugia, Italy
[13] Parma Province Cancer Registry, Azienda Ospedaliera di Parma, Parma, Italy
[14] Ferrara Cancer Registry, Sez. Anatomia Patologica, Dip. Med. Sperimentale & Diagnostica, Ferrara University, Ferrara, Italy
[15] Department of Public Health, Reggio Emilia Cancer Registry, Reggio Emilia, Italy
[16] Cancer Registry of Sassari (ASL1), Sassari, Italy
[17] Brescia Health Unit Cancer Registry, Brescia, Italy
[18] Trento Cancer Registry, Osservatorio Epidemiologico, Trento, Italy
[19] Friuli Venezia Giulia Cancer Registry, Agenzia Regionale di Sanità, Udine, Italy
[20] Alto Adige/Südtirol Cancer Registry, Bolzano, Italy
[21] Prevention Department ASL BI, Epidemiology Unit, Piedmont Cancer Registry, Biella, Italy
[22] Salerno Cancer Registry, Salerno, Italy
[23] Syracuse Province Registry of Pathology (RTP), Syracuse, Italy
[24] Macerata Province Cancer and Mortality Registry, Dip. Medicina Sperimentale e Sanità Pubblica, Camerino University, Camerino, MC, Italy
[25] Campania Cancer Registry, Azienda Sanitaria Locale Napoli 4, Brusciano, NA, Italy

Cancer and AIDS Registries Linkage Study: Mauro Lise, Antonella Zucchetto, Angela De Paoli (Centro di Riferimento Oncologico, Aviano); Teresa Intrieri (Tuscany Cancer Registry); Rosa Vattiato (Romagna Cancer Registry, Meldola); Paola Zambon (Veneto Cancer Registry); Antonella Puppo (Liguria Cancer Registry); Silvia Patriarca (Piedmont Cancer Registry, City of Torino); Andrea Tittarelli (Lombardia Cancer Registry, Varese Province); Mariangela Autelitano (Cancer Registry of Milan); Claudia Cirilli (Modena Cancer Registry); Francesco La Rosa (Umbria Cancer Registry); Paolo Sgargi (Parma Province Cancer Registry); Enza Di Felice (Reggio Emilia Cancer Registry); Rosaria Cesaraccio (Cancer Registry of Sassari); Francesco Donato (Brescia Health Unit Cancer Registry); Silva Franchini (Trento Cancer Registry); Loris Zanier (Friuli Venezia Giulia Cancer Registry); Fabio Vittadello (Alto Adige/Sudtitol Cancer Registry); Pier Carlo Vercellino (Piedmont Cancer Registry, Province of Biella); Gennaro Senatore (Salerno Cancer Registry); Maria Lia Contrino (Syracuse Province Registry of Pathology); Silvia Antonini (Macerata Cancer Registry); Raffaele Palombino (Campania Cancer Registry); Sergio Maspero (Sondrio Cancer Registry); Maria Guglielmina La Rosa (Ragusa Cancer Registry); Laura Camoni, Vincenza Regine (National Institute of Health, Rome).

Key words: AIDS, HAART, cancer incidence, lung cancer, liver cancer

Abbreviations: AIDS: acquired immunodeficiency syndrome; CI: confidence interval; HAART: highly active antiretroviral therapies; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; IR: incidence rates; KS: Kaposi sarcoma; NADC: non-AIDS-defining cancer; NHL: non-Hodgkin lymphoma; PWHA: people with HIV/AIDS; PY: person-years

Grant sponsor: Istituto Superiore di Sanità; **Grant numbers:** 20G.3 and 20G.12; **Grant sponsor:** OncoSuisse; **Grant number:** PC OCS 01355-03-2003

DOI: 10.1002/ijc.25153

History: Received 29 Sep 2009; Accepted 15 Dec 2009; Online 4 Jan 2010

Correspondence to: Jerry Polesel, Epidemiologia e Biostatistica, Centro di Riferimento Oncologico, Via Franco Gallini 2, Aviano, PN 33081, Italy, Tel: +39 0434 659 354, Fax: +39 0434 659 231, E-mail: polesel@cro.it

[26] Sondrio Cancer Registry, Azienda Sanitaria Locale, Sondrio, Italy
[27] Department of Oncology, Azienda Ospedaliera "Civile M.P.Arezzo," Ragusa Cancer Registry and Histopathology Unit, Ragusa, Italy
[28] Department of Epidemiology, INMI "L Spallanzani" IRCCS, Rome, Italy
[29] Institute of Medical Statistics and Biometry "G. A. Maccacaro," University of Milan, Milan, Italy

People with HIV/AIDS (PWHA) have increased risk of some cancers. The introduction of highly active antiretroviral therapies (HAART) has improved their life expectancy, exposing them to the combined consequences of aging and of a prolonged exposure to cancer risk factors. The aim of this study was to estimate incidence rates (IR) in PWHA in Italy, before and after the introduction of HAART, after adjusting for sex and age through direct standardization. An anonymous record linkage between Italian AIDS Registry (21,951 cases) and Cancer Registries (17.3 million, 30% of Italian population) was performed. In PWHA, crude IR, sex- and age-standardized IR and age-specific IR were estimated. The standardized IR for Kaposi sarcoma and non-Hodgkin lymphoma greatly declined in the HAART period. Although the crude IR for all non-AIDS-defining cancers increased in the HAART period, standardized IR did not significantly differ in the 2 periods (352 and 379/100,000, respectively). Increases were seen only for cancer of the liver (IR ratio = 4.6, 95% CI: 1.3–17.0) and lung (IR ratio = 1.8, 95% CI: 1.0–3.2). Age-specific IRs for liver and lung cancers, however, largely overlapped in the 2 periods pointing to the strong influence of the shift in the age distribution of PWHA on the observed upward trends. In conclusion, standardized IRs for non-AIDS-defining cancers have not risen in the HAART period, even if crude IRs of these cancers increased. This scenario calls, however, for the intensification of cancer-prevention strategies, notably smoking cessation and screening programs, in middle-aged HIV-patients.

Individuals who are infected with HIV have an increased risk of cancer.[1–3] Since 1982, Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and—since 1993—invasive cervical cancer have been part of the clinical definition of AIDS.[4] Evidence of a cancer excess among people with HIV/AIDS (PWHA) compared to the general population has accumulated over the years for several other cancers, in particular Hodgkin lymphoma, cancers of the ano-genital tract, liver and lung.[1–3]

HIV infection leads, through immune dysregulation, to increased replication or persistence of oncogenic viruses (in particular, Epstein Barr virus, KS-herpesvirus and human papillomaviruses).[5] Moreover, PWHA have higher prevalence of oncogenic virus infection, compared to the general population.

Although the introduction of highly active antiretroviral therapies (HAART) in 1996 has greatly lowered the risk of KS and NHL in PWHA,[6,7] other cancers have not shown equally favorable trends.[8–11] In addition, improved survival started exposing PWHA to the combined consequences of aging and of the prolonged exposure to cancer risk factors such as oncogenic virus infections and tobacco smoking.

Only a few studies reported population-based estimates of age-adjusted incidence rates (IR) of cancers other than KS and NHL among PWHA.[12,13] This study intends to contribute to the current knowledge showing an update of cancer incidence in a population-based study from a country severely hit by AIDS and where women and injecting-drug users are proportionally more common among AIDS patients than in most other developed countries. A record linkage between the National AIDS Registry and all Italian population-based cancer registries was carried out with the aim to estimate changes in cancer IRs in PWHA in Italy before and after the introduction of HAART, after adjusting for age with direct standardization. On account of the substantial aging of PWHA after HAART availability, special attention was paid to standardize IRs by sex and age and to compare age-specific IRs.

Material and methods

The general design of our record-linkage study has been described previously.[11,14] In brief, the notification of AIDS cases from all over the Country to the National AIDS Registry started in 1982 on a voluntary basis and became mandatory in November 1986. As the end of 2005, a total of 57,531 AIDS cases had been identified[15] of whom 32% had been reported in the HAART period (*i.e.*, after the introduction of HAART, since 1997).

The Italian network of Cancer Registries (AIRTUM) has been active in Italy since the early 1980s.[16] In the late 1990s, 24 independent Cancer Registries had been established and included a population of 17.3 million (30% of the total Italian population).[11,17] Cancer Registries served the regions of Friuli Venezia Giulia, Romagna, Umbria, part of Veneto region; the municipalities of Milan and Turin; the provinces of Alto Adige/Südtirol, Biella, Ferrara, Florence and Prato, Genoa, Macerata, Modena, Parma, Ragusa, Reggio Emilia, Salerno, Sassari, Sondrio, Syracuse, Trento, Varese; and part of the province of Brescia and Naples.[11] Cancer registries varied both in population size—ranging from ~180,000 to nearly 2.1 million—and in number of registration years available, but the routine indicators of data completeness and quality were considered satisfactory for all registries.[17]

A record linkage between National AIDS Registry and Cancer Registries databases was performed using an *ad hoc* software application previously validated[18] and recently updated.[8] Briefly, records were linked by last and first name, and by date of birth. Satisfaction of name–date algorithm required: (*i*) that the records were identical for at least one critical field and (*ii*) that the other 2 critical fields, if not identical, differed only in prescribed ways. Since the system operated under procedures that removed all personal identifiers, the staff of each registry was blinded to which persons had been linked.[18]

The present study was restricted to 21,951 people with AIDS who: (*i*) were diagnosed with AIDS between 1986 and 2005; (*ii*) reported a legal residence in areas covered by Cancer Registries network; (*iii*) were aged between 16 and 69 years at the time of AIDS diagnosis. Person-years (PY) at risk were computed between 60 months before AIDS diagnosis and the date of cancer incidence, death, 120 months after AIDS diagnosis or 70 years of age whichever occurred earlier. For non-AIDS-defining cancers, reliability of evaluation of cancer risk in PWHA based on cancer experience 5 years before AIDS has been demonstrated.[19] For AIDS-defining cancers (clinical definition triggering AIDS diagnosis) PY were computed starting 4 months after AIDS.

Time intervals were left-censored or right-censored if no complete Cancer Registries data were available in the corresponding years. To obviate the incompleteness of follow-up information in the National AIDS registry, the vital status of PWHA was cross checked with the National Mortality Database.[20]

Observed cases included 839 incident cancers reported to Cancer Registries during the aforementioned PY at risk. Six tumors arisen in patients at age 70 years or older were excluded from the present analysis. Cancers were coded according to International Classification of Disease, 10th revision[21] and were revised for histology type and cancer site by Cancer Registries coordinators. The basis of diagnosis was reported either as microscopic confirmation, including histological, hematological or cytological confirmation, or other, that is, clinical, instrumental diagnosis or death-certificate-only (6.5% in pre-HAART and <1% in the HAART period). When an AIDS-defining cancer was mentioned in both National AIDS Registry and Cancer Registries, date of cancer diagnosis was defined as the earliest one. When an AIDS-defining cancer was reported to a Cancer Registry before the date of AIDS diagnosis in National AIDS Registry, the date of AIDS onset was backdated.

Crude IR, sex- and age-standardized IR and age-specific IR were calculated dividing observed cases by the corresponding PY at risk for 2 calendar periods: the pre-HAART (1986–1996) and the HAART (1997–2004) period. IRs were standardized for gender and age (in 5-year groups) based on the AIDS population in the overall study, using the direct method.[22] IRs were shown for cancer sites/types for which at least 3 cases were detected in each period. Corresponding 95% confidence intervals (CIs) were computed according to the Poisson distribution. Age-specific IRs, standardized by gender on the general population, were also computed among PWHA in 1986–1996 and 1997–2004 in 4 age groups: 25–34 (herein referred to young adults); 35–44 and 45–54 (middle-age people); and 55–69 (old people). For comparison sake, age-specific IRs in the general population from the same areas were also shown.[17] To assess the role of immunodeficiency on cancer incidence, IRs were also computed separately by CD4 level at AIDS diagnosis (<50, ≥50 cells/μl) and interval between first HIV-positive test and AIDS diagnosis (<1, ≥1 year). For these stratified analyses, we have calculated IRs after AIDS (4–120 months) and in the post-HAART period only, because: (*i*) information on CD4 cell referred to the time of AIDS diagnosis and (*ii*) it was not collected before 1996.

Results

A total of 101,669 PY were available, 44% of which from the 1997–2004 period (Table 1). Figure 1 shows the marked shift of study subjects in age-distribution in the HAART period. In the pre-HAART period, the majority of PWHA were aged 25–34 years (58% of PY), whereas those aged 35 years or older predominated (70% of PY) in the HAART period (Fig. 1). Injecting drug users accounted for 64% of PY in 1986–1996, and for 48% in 1997–2004.

KS and NHL IRs greatly decreased in the HAART period (IR ratio = 0.12 and 0.19, respectively). The decline was less marked for NHL than for KS (Table 1), making NHL the most frequent cancer in 1997–2004 (IR = 284/100,000). Central nervous system NHL showed a greater decline in HAART era than systemic NHL. Age-specific IRs of KS and NHL are shown in Figure 2. Incidence curves for KS for 1997–2004 were well below those for 1986–1996 in all age groups, though still much higher than the corresponding curves for the general population. For NHL, IRs in the 2 periods converged at older ages.

Crude IR of non-AIDS-defining cancers (NADC) increased by 73% in the HAART period, but age-standardized IRs did not substantially change (IR = 352/100,000 in 1986–1996, 379 in 1997–2004; IR ratio = 1.08, 95% CI: 0.87, 1.34; Table 1). IRs increased for liver cancer (from 5.7 in 1986–1996 to 26.4/100,000 in 1997–2004, IR ratio = 4.61; 95% CI: 1.25, 16.95) and lung cancer (from 36.9 to 65.1/100,000, IR ratio = 1.76; 95% CI: 0.98, 3.17). Conversely, the IR for leukemia declined from 21.5 to 4.9/100,000 (IR ratio = 0.23; 95% CI: 0.06, 0.87; Table 1). No change emerged for Hodgkin lymphoma (IR ratio = 0.82; 95% CI: 0.52, 1.29), and no substantial difference in incidence was found between mixed cellularity and other subtypes. IRs of other common cancer types (*i.e.*, colon-rectum, female breast and skin) did not changed significantly between periods.

PWHA with CD4 levels <50 cells/μl at AIDS diagnosis showed higher IRs for Kaposi sarcoma in comparison with higher levels (371 and 189/100,000, respectively; Table 2).

Table 1. Incidence rates (IR, per 100,000), corresponding to 95% confidence intervals (CI), and incidence rates ratios of Kaposi sarcoma, non-Hodgkin lymphoma, invasive cervical cancer and selected non-AIDS-defining cancers in people with HIV/AIDS by period (Italy, 1986–2004)

	1986–1996			1997–2004			
ICD10; Cancer site or type	*N*	Crude IR	IR (95% CI)[1]	*N*	Crude IR	IR (95% CI)[1]	IR Ratio (95% CI)[1]
Person-years			56,643			45,026	
C46; Kaposi sarcoma[2]	165	1,859	2,131 (1,818–2,482)	56	216	250 (189–325)	0.12 (0.08–0.18)
C82–C85, C96; Non-Hodgkin lymphoma[2]	136	1,480	1,483 (1,244–1,754)	91	343	284 (228–348)	0.19 (0.14–0.26)
Central nervous system	33	359	338 (233–475)	11	41.4	46.6 (23.1–83.8)	0.14 (0.06–0.30)
Other Non-Hodgkin lymphoma	103	1,121	1,137 (928–1,380)	80	301	236 (188–294)	0.21 (0.15–0.28)
C53; Invasive cervical cancer[2]	1	10.7	37.8 (0.0–216)	7	25.9	78.9 (31.3–163)	2.09 (0.25–17.37)
C00–C14, C30–C32; Head and neck	6	10.6	14.1 (5.1–30.9)	11	24.4	16.3 (8.0–29.2)	1.16 (0.45–2.94)
C16; Stomach	6	10.6	13.6 (4.9–29.7)	6	13.3	9.8 (3.5–21.4)	0.72 (0.22–2.38)
C18–C20; Colorectum	7	12.4	18.4 (7.3–38.1)	16	35.5	24.6 (13.9–40.0)	1.33 (0.54–3.30)
C21; Anus	6	10.6	14.5 (5.2–31.7)	11	24.4	19.8 (9.8–35.5)	1.37 (0.47–3.96)
C22; Liver	3	5.3	5.7 (1.1–16.9)	16	35.5	26.4 (15.0–42.9)	4.61 (1.25–16.95)
C34; Lung	17	30.0	36.9 (21.4–59.2)	42	93.4	65.1 (46.9–88.0)	1.76 (0.98–3.17)
C43; Melanoma	3	5.3	6.5 (1.2–19.4)	3	6.7	4.4 (0.8–13.1)	0.68 (0.14–3.39)
C44; Skin non melanoma	18	31.8	49.4 (29.2–78.2)	28	62.3	46.2 (30.7–66.8)	0.94 (0.50–1.73)
C50; Female breast	3	24.1	34.1 (6.4–101)	5	42.2	25.9 (8.2–60.8)	0.76 (0.18–3.19)
C51–C52–C54–C57; Female genital organs	4	31.1	40.7 (10.6–105)	4	36.2	21.9 (5.7–56.6)	0.54 (0.13–2.21)
C70–C72; Brain and central nervous system	8	14.1	15.1 (6.4–29.8)	8	17.8	14.5 (6.2–28.7)	0.96 (0.35–2.69)
C81; Hodgkin lymphoma	47	83.1	84.1 (61.8–112)	37	82.4	69.0 (48.5–95.1)	0.82 (0.52–1.29)
C81.2; Mixed cellularity	19	33.6	32.8 (19.7–51.3)	16	35.7	28.7 (13.3–46.6)	0.87 (0.43–1.77)
C81.0–1, C81.3–9; Other subtypes	28	49.5	51.2 (34.0–74.1)	21	46.8	40.2 (24.8–61.5)	0.78 (0.43–1.10)
C90; Myeloma	3	5.3	7.2 (1.3–21.2)	4	8.9	8.0 (2.1–20.8)	1.12 (0.22–5.79)
C91–C95; Leukemia	11	19.4	21.5 (10.7–38.6)	3	6.7	4.9 (0.9–14.5)	0.23 (0.06–0.87)
Total non-AIDS-defining cancers	162	287	352 (299–410)	221	496	379 (330–432)	1.08 (0.87–1.34)

[1]Standardized for gender and age according to people with HIV/AIDS. [2]Person-years and incidence rates were calculated from 4 to 120 months after AIDS diagnosis.

According to level of immunodeficiency, no IR difference emerged for other cancers. IRs of NADS were 375 and 350/100,000 for CD4 cell count $<$ and $\geq$50, respectively. On the other hand, IR increased with interval between first HIV-positive test and AIDS diagnosis for NHL (IRs from 149 to 378/100,000 in PWHA whose interval was $<$1 and $>=$1 year, respectively) and for NADC (from 246 to 454/100,000, respectively; Table 2).

The age-specific IRs for NADC in PWHA, were higher than the corresponding curve in the general population below 45 years of age in pre-HAART period and below 55 years of age in HAART period (Fig. 3). Conversely, among PWHA aged 55 years or older no difference in IRs emerged in comparison with the general population. Age-specific IRs of NADC among injecting drug users showed similar pattern as all PWHA. Conversely, PWHA infected by sexual contacts (*i.e.*, men having sex with men and

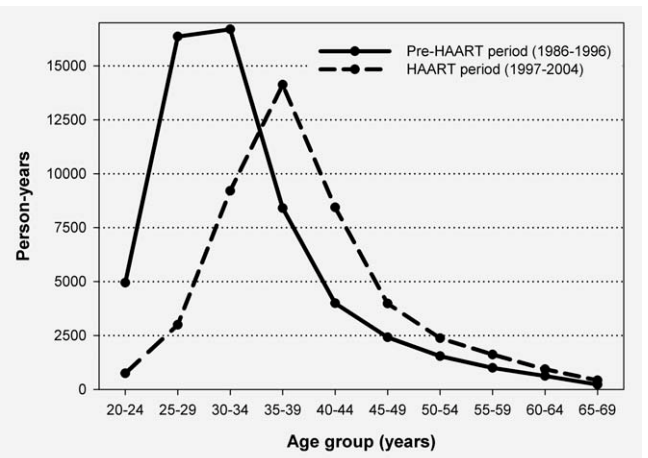

Figure 1. Distribution of person-years of observation by age group and period (Italy, 1986–2004).

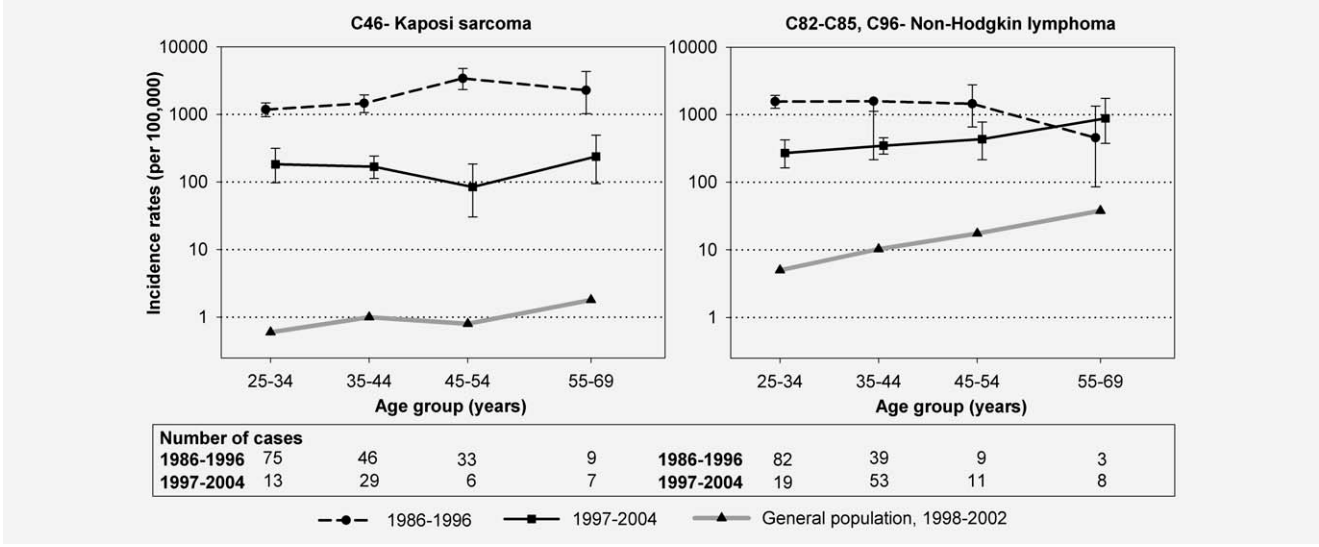

Figure 2. Age-specific incidence rates for Kaposi sarcoma and non-Hodgkin lymphoma in people with HIV/AIDS and general population by period. Person-years and incidence rates were calculated from 4 to 120 months after AIDS diagnosis. Vertical bars represent 95% confidence intervals (Italy, 1986–2004).

Table 2. Incidence rates (IR, per 100,000), and corresponding 95% confidence intervals (CI)[1] of Kaposi sarcoma, non-Hodgkin lymphoma, invasive cervical cancer and selected non-AIDS-defining cancers in people with HIV/AIDS by CD4 cells count at enrollment and time since first HIV-positive test (Italy, 1997–2004)

	CD4 cell count at AIDS[2]				Time since first HIV-positive test[3]			
	<50 cells/μl		≥50 cells/μl		<1 year		≥1 year	
ICD10; Cancer site or type	*N*	IR (95% CI)	*N*	IR (95% CI)	*N*	IR (95% CI)	*N*	IR (95% CI)
Person-years	10,377		15,668		6,779		13,618	
C46; Kaposi sarcoma	25	371 (240–549)	31	189 (129–269)	18	251 (149–398)	22	264 (165–400)
C82–C85, C96; Non-Hodgkin lymphoma	32	289 (197–409)	54	279 (210–365)	15	149 (83.2–247)	58	378 (287–489)
C53; Invasive cervical cancer	2	44.2 (4.2–163)	5	110 (34.7–259)	1	45.0 (0.0–258)	3	74.7 (14.1–221)
C18–C20; Colorectum	3	22.9 (4.3–67.7)	7	29.1 (11.5–60.2)	3	21.4 (4.0–63.4)	7	44.1 (17.4–91.4)
C21; Anus	3	19.6 (3.7–57.9)	6	32.8 (11.8–71.8)	1	6.4 (0.0–36.7)	5	23.1 (7.3–54.3)
C22; Liver	2	11.6 (1.1–42.5)	4	14.7 (3.8–38.2)	1	8.7 (0.0–49.6)	2	8.3 (0.8–30.4)
C34; Lung	10	64.9 (30.9–120)	14	63.9 (34.8–108)	6	48.5 (17.4–106)	13	107 (56.5–183)
C44; Skin non melanoma	7	50.8 (20.1–105)	11	47.2 (25.1–81.0)	3	16.4 (3.1–48.4)	10	43.3 (20.6–79.9)
C81; Hodgkin lymphoma	9	75.7 (34.3–144)	11	54.3 (26.9–97.4)	4	52.3 (13.6–135)	12	71.6 (36.8–126)
Total non-AIDS-defining cancers	46	375 (275–501)	77	350 (276–438)	29	246 (164–353)	69	454 (353–574)

[1]Standardized for gender and age according to people with HIV/AIDS. Person-years and incidence rates were calculated from 4 to 120 months after AIDS diagnosis. [2]1,114 person-years (4.1%) and 6 cancer cases (4.7%) were excluded because of missing values. [3]6,762 person-years (24.9%) and 31 cancer cases (24.0%) were excluded because of missing values.

heterosexuals) showed an excess of NADC only in young adults in 1986–1996 and in middle-age people in the HAART period (Fig. 3).

Figure 4 shows age-specific IRs by period for the 4 most frequent types of NADC in PWHA and in the general population. Only in 1997–2004 were cases of liver cancer reported in middle aged PWHA and age-specific IRs were well above the corresponding IRs in the general population. Age-specific IRs for lung cancer in PWHA did not significantly increase between the pre-HAART and HAART period but in 1997–2004 they became significantly higher than in the general population in the middle-age groups. Age-specific IRs for non-melanomas skin cancer in PWHA were similar in the 2 periods, and they were significantly higher than in the general population in PWHA aged 45-54 years in the HAART period. No case of Hodgkin lymphoma were found in people aged ≥45 years in 1986–1996. In HAART period, IRs for Hodgkin lymphoma in PWHA were significantly higher than in the general population in all age groups considered. In HAART period, IRs for Hodgkin lymphoma in PWHA were

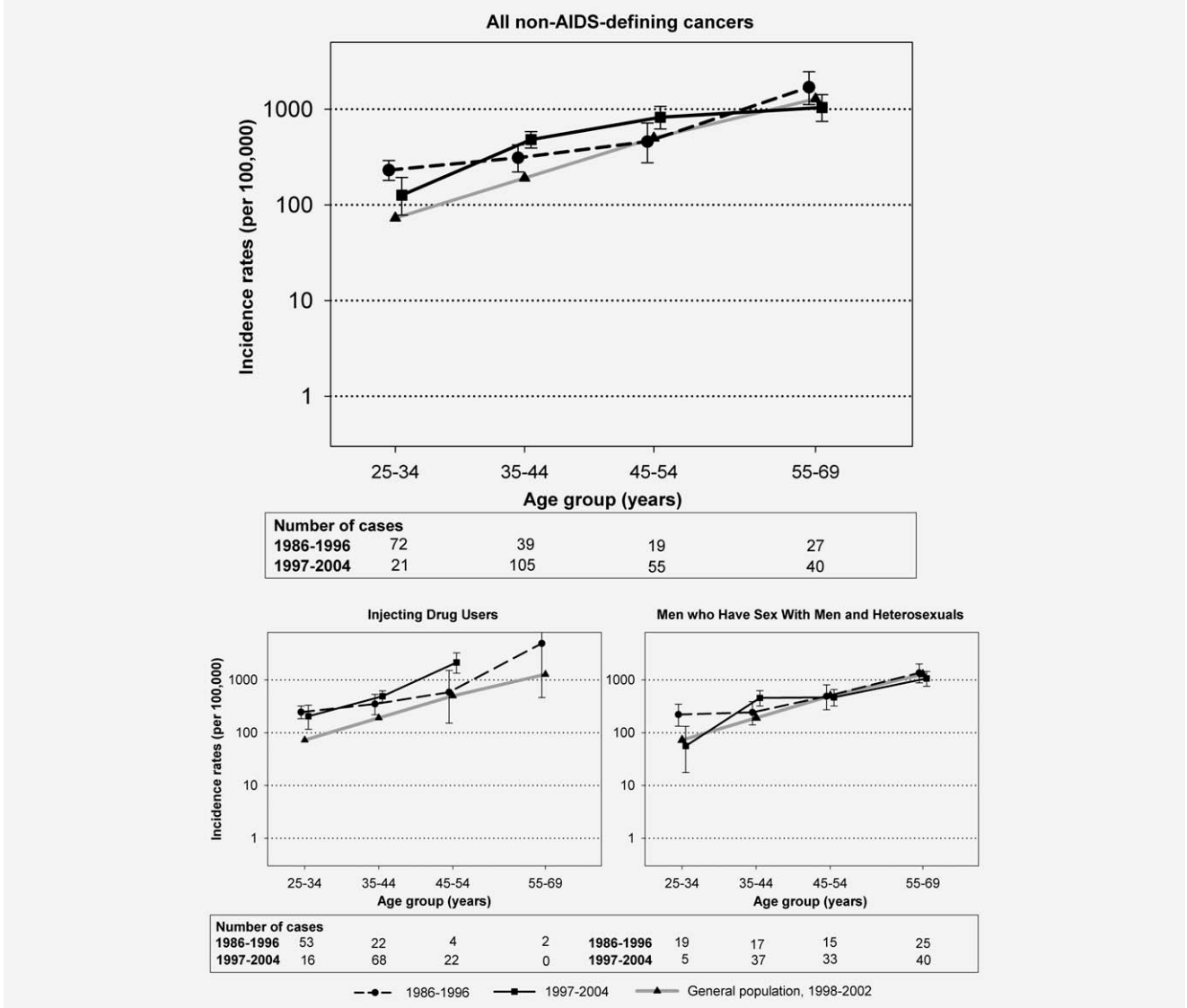

Figure 3. Age-specific incidence rates for non-AIDS-defining cancers in people with HIV/AIDS and in the general population by period, overall and by HIV transmission category (Injecting drug users *vs*. Sexual intercourses). Person-years and incidence rates were calculated from 60 months before to 120 months after AIDS diagnosis. Vertical bars represent 95% confidence intervals (Italy, 1986–2004).

significantly higher than in the general population in all age groups considered.

Discussion

The present study showed the strong influence of aging on changes in the crude IRs of cancers other than KS and NHL among PWHA after the introduction of HAART. After adjustment for age, through direct standardization, IRs showed that the majority of NADCs have not increased between the pre-HAART and the HAART period. With respect to the few cancer types for which we did show a significant increase (*i.e.*, liver and lung), full allowance for the effect of age is very difficult as nearly all the few NADCs in the pre-HAART period involved young adults whereas after 1996, the vast majority of NADCs arose in middle age. Age-specific IRs for liver cancer in 1986–1996 and 1997–2004, for instance, can only be compared among PWHA younger than 35 years of age and, due to small number of cases, no significant difference was detectable. The high IRs that were seen after 1996 greatly exceeded the corresponding rates in the general population, and mainly involved middle age PWHA. They represented, therefore, a new phenomenon made possible by the improved survival followed by HAART use.

Our present study confirmed the decrease in IRs of KS and, to a lesser extent, NHL already reported by many studies in high-income countries.[10–13,23–25] Investigations on HAART users showed that the KS and NHL occurrence halved in the first 6 months of treatment, and remained low up to 10 years since starting HAART.[6,7] The assessment of IRs of invasive cervical cancer was especially hampered by

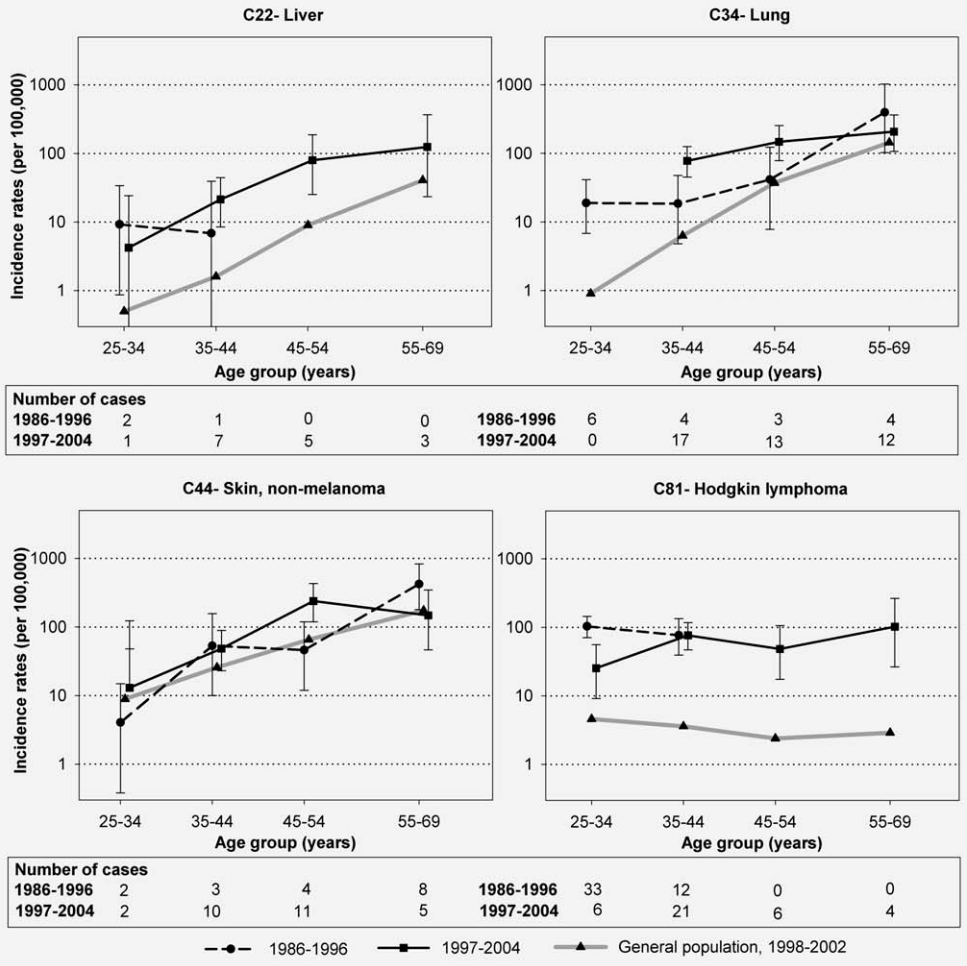

Figure 4. Age-specific incidence rates for cancer of the liver, lung, skin non-melanoma and Hodgkin lymphoma in people with HIV/AIDS and general population by period. Person-years and incidence rates were calculated from 60 months before to 120 months after AIDS diagnosis. Vertical bars represent 95% confidence intervals (Italy, 1986–2004).

the restriction to the post-AIDS period. Out of the recorded 44 invasive cervical cancers, only 8 had occurred 4 months or more after AIDS diagnosis. Anal cancer, that is also associated with human papillomavirus infection,[26] was also rare in PWHA largely due to the small fraction in Italy of men having sex with men.[11,15]

In agreement with previous studies,[9,25,27–29] we found that lung cancer incidence was increased in PWHA compared to general population in both periods. However, the difference became statistically significant only after 1996. No substantial decrease in the disease was expected in the HAART period as low CD4 cell count does not seem clearly associated with lung cancer risk.[8,9,29] Although an excess of lung cancer risk was also reported among transplant-recipients[1,25] and seemed to persist among PWHA after attempts to adjust for smoking habits,[9] the association between intensity and duration of tobacco smoking with lung cancer is so strong[30] that a confounding effect from tobacco smoking, is extremely difficult to rule out.

Liver cancer is increasingly reported among PWHA,[2,10,13] and, together with lung cancer, is one of the rising causes of cancer-related death.[31] Hepatitis B and/or C virus infection is the strongest risk factors for liver cancer and is substantially more frequent among PWHA than in the general population. Although HAART may have hepatotoxic effects, a recent investigation from the Swiss HIV Cohort Study did not support a direct association between HAART and liver cancer risk.[32] HAART-improved survival, however, is certainly allowing PWHA to experience more often the long-term complications of HBV and HCV infection.[33]

Hodgkin lymphoma incidence remained stable after HAART introduction in our study, in agreement with some previous works[12,24,34] but at variance with some reports where standardized incidence ratios before and after HAART were compared.[10,13,35] The age-standardized and age-specific IRs, that we have used in the present study to compare incidence of Hodgkin lymphoma in the pre-HAART and in the HAART period, avoid some of the dangers of relying upon standardized

incidence ratios. Using standardized incidence ratios, age is taken into account in the comparison of cancer risk between PWHA and the general population but the changes in age distribution of the AIDS population across periods are not considered. This problem is aggravated by the difference in the age distribution of Hodgkin lymphoma sub-types. The bi-modal age distribution of Hodgkin lymphoma seen in the general population in our study and elsewhere chiefly derives from the age distribution of nodular sclerosis subtype.[36] In contrast, mixed cellularity, which is the most frequently detected subtype in PWHA, does not show a decline after 35 years of age.[36] Figure 4 clearly shows that Hodgkin incidence among PWHA did not decrease with age as it did in the general population. An accurate comparison of the Hodgkin lymphoma incidence in PWHA and the general population would, therefore, require larger numbers of Hodgkin lymphomas in individual histological subtypes than those available in our present study.

Systematic reporting of HIV infections is limited to few areas in Italy[15] and, therefore, in the present study we had to rely on the linkage of AIDS cases with cancer registries. AIDS, however, which once was an irreversible stage of HIV progression, after the introduction of HAART became a much rarer and largely reversible condition.[37] The use in our present study of an extended period of observation (60 months before and 120 months after AIDS diagnosis) should have helped, however, to reduce the bias associated with delay of AIDS diagnosis and improvement of prognosis after the introduction of HAART.

Survival bias (*i.e.*, PWHA with cancer have to survive long enough to develop AIDS to be included in the present analysis) may also have affected our results. The exclusion of person-years prior to AIDS diagnosis would prevent this type of bias. However, it would also lead to the loss of a large amount of information before/at AIDS, especially in the pre-HAART period, and to other types of bias due to the change in the meaning of AIDS diagnosis in the HAART period.[37] Mathematical models may be applied to adjust PY and observed cases,[19,38] but they would require many questionable assumptions. No such models have been validated yet. The only formal comparison of the methodological approaches used in AIDS and cancer linkage studies demonstrated that cancer risk in PWHA may be reliably estimated based on cancer experience 5 years before AIDS.[19]

Strengths of the present study included the number of AIDS cases and person-years available, both before and after the introduction of HAART. Completeness and good quality of AIDS and cancer registration in Italy have been shown[17,39] and so has the accuracy of our linkage procedures.[18] Vital status of the PWHA is not always updated in the National AIDS registry but record-linkage with National Mortality Database[20] helped distinguishing deaths from losses to follow-up.

In conclusion, we have shown that, using appropriate tools to account for the changes in the age distribution of PWHA, concerns about increases in cancer risk and possible new cancer causes (including the possible carcinogenicity of HAART) should not be overemphasized, and that the downward trends in KS and NHL predominate on the overall cancer trends in the HAART period. In absolute terms, however, the number of NADC is rising due to the increasing longevity of PWHA; therefore, an intensification of cancer prevention, notably smoking cessation and screening programs, is needed.

Acknowledgement

The authors are deeply grateful to Mr. T. Perdrix-Thomas for editorial assistance.

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