Risk of cancer in persons with AIDS in Italy, 1985–1998

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A record linkage was carried out between the Italian Registry of AIDS and 19 Cancer Registries (CRs), which covered 23% of the Italian population, to estimate the overall cancer burden among persons with HIV or AIDS (PWHA) in Italy, according to various characteristics. Observed and expected numbers of cancer and standardised incidence ratios (SIRs) were assessed until 1998 in 12,104 PWHA aged 15–69 years, for a total of 60,421 person-years. Significantly increased SIRs were observed for Kaposi’s sarcoma (KS, 1749-fold higher than the general population), non-Hodgkin’s lymphomas (NHL, 352), and invasive cervical cancer (22). SIR was significantly elevated also for cancer of the anus (34), lung cancer (2.4), brain tumours (4.4), Hodgkin’s disease (16), and leukaemias (5.3). The majority of lung and brain cancers were not histologically confirmed, and the possibility of misclassification with KS or NHL cannot be ruled out. The SIR for all non-AIDS-defining cancers was 2.2 in men and 2.5 in women. Intravenous drug users showed significantly more elevated SIRs for lung cancer (9.4), and brain tumours (6.7) than other transmission categories (SIR = 1.4 and 2.3, respectively). This study confirmed increased SIRs for haemolymphopoietic neoplasms other than NHL in PWHA, although many-fold smaller than for NHL. An association with human papillomavirus-related cancers was also confirmed.

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Since the mid-1990s, cancer incidence in persons with HIV or AIDS (PWHA) has been investigated by a few large population-based linkage studies of AIDS and cancer registries (CRs) in the United States (Goedert et al., 1998), Europe (Franceschi et al., 1998a), and Australia (Grulich et al., 2002). These studies have provided essential information on the frequency and characteristics of cancers in the course of HIV infection.

In comparison with the general population, PWHA show a thousand-fold elevated risk of developing Kaposi’s sarcoma (KS) and a hundred-fold higher risk of non-Hodgkin’s lymphoma (NHL) (IARC, 1996; Dal Maso et al., 2001c). Increases have also been reported for other cancer types, such as squamous carcinomas of the anus, invasive cervical cancer (ICC), skin, conjunctiva, and Hodgkin’s disease (Franceschi et al., 1998a; Frisch et al., 2001; Grulich et al., 2002). Since most of these malignancies are driven by oncogenic viruses, cancer excess in PWHA is likely to be the combined effect of HIV and infections other than HIV (Bosshoff and Weiss, 2002). Excesses of neoplasms, such as cancer of the lung, testis, and liver, have been reported less consistently (IARC, 1996; Frisch et al., 2001). Finally, in all developed countries, the introduction of the highly active antiretroviral therapies (HAART) in the mid-1990s has greatly modified the natural history of AIDS but, except for the decline in KS incidence, the effect of HAART on cancer incidence in PWHA remains unclear (International Collaboration on HIV and Cancer, 2000).

Italy offers an interesting research opportunity with respect to such issues since the AIDS epidemic has grown faster, women constitute a large proportion of PWHA (Dal Maso et al., 1995; Pezzotti et al., 1999; ENAADS, 2000), and validated AIDS surveillance programme covers the whole population while CRs cover nearly a quarter of the population.

We have updated our previous study, including twice as many person-years (Franceschi et al., 1998a). The purpose is to estimate the cancer burden among PWHA in Italy overall and according to time since AIDS and selected characteristics.

MATERIALS AND METHODS

The general design of our record linkage study has been described previously (Franceschi et al., 1998a, b). In brief, notification of AIDS cases from all over Italy to the AIDS Registry (RAIDS) in Rome was initiated on a voluntary basis in 1982 and became mandatory in November 1986. At the end of 2000, a total of 47,503 AIDS cases had been reported (ISS, 2001). A linkage of RAIDS data.
and death certificates in 1992 suggested that under-reporting of AIDS cases in Italy was less than 10% (Conti et al, 1997), that is, one of the lowest percentages of under-reporting in Europe (Ajdacic-Gross et al, 2001).

In all, 19 independent CRs were active in Italy in the mid-1990s, covering a population of 12.7 million, corresponding to 23% of the total Italian population. They served the regions of Romagna, Friuli-Venezia Giulia, Umbria, and part of Veneto region, the municipality of Turin, the provinces of Genoa, Biella, Varese, Parma, Modena, Ferrara, Macerata, Florence and Prato, Sassari, Trento, Bolzano (Alto Adige), Ragusa, Latina, and part of the province of Naples (Zanetti et al, 2002; Parkin et al, 2002). Cancer Registries varied both in size, ranging from approximately 190 000 to nearly 1.9 million of population covered, and in number of registration years available. Routine indicators of data completeness and quality in Italian CRs were satisfactory (Parkin et al, in press; 1997; Zanetti et al, 2002).

An ‘ad hoc’ software application was developed to perform the record linkage procedure (Dal Maso et al, 2001c). Briefly, records from RAIDS and CRs were linked by last and first name, and by date of birth. Satisfaction of name–date algorithm required: (a) that the records were identical for at least one critical field, and (b) that the other two critical fields, if not identical, differed only in prescribed ways. Since the system operated under procedures that removed all personal identifiers, the staffs of each type of registry were blinded to which persons had been linked.

The present study was restricted to people who: (1) were aged between 15 and 69 years at the time of AIDS diagnosis; (2) reported a legal residence in areas covered by CRs; (3) were diagnosed with cancer in periods deemed complete at both registries (i.e. in most instances through to the end of 1998); and (4) were diagnosed with AIDS after 1985, since no cancer case among PWHA had been reported earlier.

AIDS-defining cancers (i.e. KS, NHL and, since 1993, ICC) are also reported to RAIDS, but only notification of neoplasms to CRs were included in the present analysis for the sake of comparability with non-AIDS defining cancers (NADC). In situ carcinoma of the cervix and other preneoplastic lesions (e.g. behaviour code 0–2) (WHO, 1990) were excluded from the present analysis because of incomplete reporting in CRs.

Cancers at CRs were identified according to International Classification of Disease (ICD), 9th revision (WHO, 1977) and International Classification of Diseases for Oncology (ICDO) (WHO, 1990). Cases were subsequently recoded according to International Classification of Disease, 10th revision (WHO, 1992). Cancers were further subdivided according to whether histological, haematological, or cytological confirmation (henceforth referred to as histological confirmation) was available or diagnosis had been made otherwise (i.e. clinical, instrumental diagnosis, etc.). Cancer Registry coordinators reviewed all records on histological type and site of cancers.

When an AIDS-defining cancer was mentioned in both RAIDS and CR, date of cancer diagnosis was defined as the earliest one. When KS, NHL, or ICC (after 1993) was reported in the CR up to 5 years prior to the date of AIDS diagnosis, the date of AIDS onset was backdated.

Person-years at risk were computed only between 5 years prior to AIDS diagnosis (in order to exclude cancer diagnosis which may have occurred before HIV infection) and date of death or 3.5 years after AIDS diagnosis, whichever occurred earlier, to reduce inaccuracies from losses at follow-up. This interval was left- or right-censored if no complete CR data were available in the corresponding years. Expected numbers of different cancer sites or types were computed in each CR from sex- and age-specific (5 years) incidence rates (Parkin et al, 2002, 1997, 1992) in four periods: early pre-AIDS (from –60 to –25 months), late pre-AIDS (from –24 to –7 months), AIDS period (from –6 to +3 months), and post-AIDS period (from +4 to +42 months). Observed numbers of cancer in PWHA were compared to expected numbers by means of standardised incidence ratios (SIRs). Corresponding 95% confidence intervals (CI) were computed using the Poisson distribution (Breslow and Day, 1987).

RESULTS

Overall, 12,104 AIDS cases (78% men and 22% women) were reported in areas covered by one of the 19 CRs (Table 1) for a total of 60,421 person-years (Table 2). In all, 70% of person-years referred to the periods prior to AIDS diagnosis. The majority of PWHA enrolled in this study were intravenous drug users (IDUs, 62%), and the median age was 33 years. Between 3 years before AIDS diagnosis and 3.5 years thereafter, 170 cancers other than KS, NHL, and ICC were identified (Table 1). Using only cancer information from CRs, the numbers were 525 for KS, 449 for NHL, and 18 for ICC.

Table 2 shows observed and expected numbers and corresponding SIRs for cancer sites or types with at least two cases observed. As expected, high SIRs were found for KS (1749; 95% CI: 1602–2005), NHL (352; 95% CI: 320–386), and, to a lesser extent, ICC (22; 95% CI: 13–35). All ICC were squamous-cell carcinomas.

The combination of NADC showed a SIR of 2.3 (95% CI: 2.0–2.7). Significantly elevated SIRs were seen for cancer of the anus (34; 95% CI: 12–74), lung (2.4; 95% CI: 1.5–3.7), brain (4.4; 95% CI: 2.2–8.0), Hodgkin’s disease (HD) (16; 95% CI: 12–22), and leukaemias (5.3; 95% CI: 2.8–9.2). In respect to time of cancer diagnosis, all sites and types showed the highest SIR in the AIDS period and a compensatory fall in SIR after AIDS. Risk excess before AIDS was seen for ICC and cancer of the anus, and for HD and leukaemias.

Anal cancers (six cases) included five squamous-cell carcinomas and one cloacogenic carcinoma.

Only 12 out of 22 lung cancers were histologically confirmed, including five squamous-cell carcinoma, two adenocarcinoma, and one each of five other histologies. In four out of 10 nonhistologically confirmed lung cancer cases, lung lesions of infectious origin, such as pneumocystis carinii pneumonia, were reported at RAIDS. None of the 11 brain cancers were histologically confirmed, eight had occurred in the AIDS period, and three had a concurrent diagnosis of cerebral toxoplasmosis or HIV encephalopathy at RAIDS. The proportions of histologically confirmed cancers among PWHA (79%) were similar to the proportion in the general population of the same CRs (80%). Restricting the analysis to cancers with histological confirmation, the SIR was 1.7 (95% CI: 1.4–2.1) for the combination of all NADC. The greater reduction in SIR, after the exclusion of unconfirmed cases, was noted for cancer of the lung (SIR = 1.3) and brain (SIR = 0.0) (not shown).

Among 45 HDs, the histological type was mixed cellularity in 19 subjects and nodular sclerosis in 13. The other HDs were of lymphocytic predominance (one), lymphocytic depletion (three), and unspecified type (nine).

The cancer sites or types that showed a significant excess in PWHA were observed in more than 10 individuals were re-examined in separate strata of gender, age, and HIV-exposure category (Table 3). Standardised incidence ratios were higher in women than in men for KS (2717 vs 1696, respectively), NHL (538 vs 321), and cancer of the lung (8.7 vs 2.2). For the combination of all NADS, no difference emerged between genders (SIR = 2.2 and 2.5 in men and women, respectively). The age distribution varied by cancer type: median age was 37 years for KS (range: 19–68), 33 years for NHL (21–68), 35 years for ICC (37–48), 42 years for anal cancer (34–55), 39 years for lung cancer (23–68), 50 years for non-melanomatous skin cancer (36–69), 31 years for brain cancer (28–58), 32 years for HD (19–43), and 32 years for leukaemias (21–67). Standardised incidence ratios tended to be higher in the

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15–34-year age group than in the 35–69-year age group for all cancer sites, except for KS and cancers of the cervix uteri and anus. Standardised incidence ratios were also higher among IDUs than other HIV exposure category for all cancer types except for KS and leukaemias. Standardised incidence ratio for KS and anal cancer was particularly high among homosexual and bisexual men (6066 and 56, respectively).

The risk of NADCs in PWHA at or after AIDS diagnosis (patients who were likely to take advantage of HAART) did not diminish between pre-HAART (SIR = 2.8) and post-HAART period (SIR = 5.7). Moreover, no statistically significant change emerged for any specific cancer site or type of NADCs (data not shown).

DISCUSSION

Cancers of the anus, brain, lung, HD, and leukaemias, in addition to AIDS-defining cancers (KS, NHL, and ICC), have been found in our study to be significantly increased in PWHA. As in previous reports (Andrieu et al., 1993; Serraino et al., 1993), the most common subtype of HD in PWHA was mixed cellularity type. Nodular sclerosis type (i.e. the commonest HD type in the general population of an age comparable to PWHA) was relatively rare. Besides being more aggressive and more frequently involving bone marrow, HD in PWHA seems to be associated with EBV more often than in the general population (Tirelli et al., 2000).

Other cancers whose SIRs were found to be consistently elevated in PWHA are those associated with HPV infection (IARC, 1995). In contrast to KS and NHL, ICC has been an AIDS defining disease only since 1993 (Ancelle Park, 1993). We were, therefore, able to observe some ICC cases prior to AIDS and noticed that, although SIR peaked in the AIDS period as for all other sites and types, some excess was present years before AIDS. A similar time pattern was found for anal cancer, whose overall SIR (34) was well comparable to the one seen for ICC. Three additional cases of cancer of the vulva, penis, and uterus (not otherwise specified) further support the possibility that HIV-induced immune impairment facilitates the persistence of HPV infection (Palefsky et al., 1999; Ahdieh et al., 2000): progression into pre-malignant (Sun et al., 1997) and, ultimately, in the lack of early detection, invasive cancer. As suggested also by studies where preinvasive lesions of the cervix and anogenital tract were included (Frisch et al., 2000), the control of HPV infections seems to be impaired in HIV-positive women and men years before a diagnosis of AIDS. Early events in HPV carcinogenesis are probably affected to a greater extent than late ones (i.e. invasiveness). The SIR for cancer of the cervix and anus was marginally greater but not restricted to specific HIV exposure categories (i.e. IDUs and homosexual and bisexual men, respectively).

Histological confirmation was available for almost all HDs (43 out of 45), myelomas (three out of three), and leukaemias (10 out of 13) in our study. A misdiagnosis of NHL as other haemolymphopoietic neoplasms cannot be totally ruled out because the classification of haemolymphopoietic neoplasms in PWHA is especially difficult (Carbone, 2002). Some leukaemias might be leukemoid transformations of AIDS-related NHL. The SIR for lymphoid leukaemia was not significantly greater than the one for myeloid leukaemia, in agreement with the findings by Frisch et al. (2001) in the United States.
### Table 2: Observed (Obs) and expected (Exp) numbers of cancers in person HIV or with AIDS, SIR, and corresponding 95% CI by time of diagnosis and overall. Italy, 1985–1998

| ICD10, cancer type or site | 60–25 months before AIDS | 24–7 months before AIDS | 6 months before to 3 months after AIDS | 4–42 months after AIDS | Total |
|---------------------------|--------------------------|-------------------------|-------------------------------------|-----------------------|-------|
|                           | Obs | SIR (95% CI) | Obs | SIR (95% CI) | Obs | SIR (95% CI) | Obs | SIR (95% CI) | Obs | SIR (95% CI) | Person years |
| C46, KS                   | 27,882 | 14,652 | 406 | 6667 (6034–7348) | 119 | 497 (412–595) | 525 | 0.30 1749 (1602–1905) |
| C82–C85, NHL              | 322 | 1229 (1098–1371) | 24 | 8.1 (2.1–21.1) | 5 | 5.2 (0.5–19.0) | 18 | 0.82 21.8 (12.9–34.6) |
| C53, ICC                  | 1 | 3.0 (0.0–17.5) | 1 | 1.1 (0.0–6.2) | 1 | 1.6 (0.0–9.4) | 1 | 1.3 (0.0–7.5) | 1 | 1.3 21.8 (12.9–34.6) |
| C16, Stomach              | 2 | 9.6 (0.9–35.4) | 4 | 8.1 (2.1–21.1) | 2 | 5.2 (0.5–19.0) | 5 | 2.18 21.8 (12.9–34.6) |
| C18, Colon                | 1 | 1.7 (0.0–100) | 2 | 6.5 (0.6–23.9) | 2 | 51.5 (49–189.2) | 6 | 0.18 33.6 (12.1–73.6) |
| C20, Rectum               | 1 | 44.4 (8.4–131.4) | 0 | 0 — | 1 | 3.7 (0.0–21.0) | 1 | 3.0 (0.0–17.3) | 2 | 1.95 1.0 (0.1–3.8) |
| C21, Anus                  | 0 | 0 — | 1 | 4.3 (0.0–24.6) | 2 | 6.9 (0.7–25.5) | 3 | 1.5 1.9 (0.4–5.6) |
| C22, Liver                 | 0 | 0 — | 1 | 5.5 (0.0–31.4) | 1 | 4.4 (0.0–25.1) | 2 | 1.27 1.6 (0.1–5.8) |
| C25, Pancreas              | 0 | 0 — | 1 | 3.7 (0.0–21.0) | 1 | 3.0 (0.0–17.3) | 2 | 1.95 1.0 (0.1–3.8) |
| C32, Larynx                | 0 | 0 — | 1 | 4.3 (1.1–112) | 0 | 0 — | 0 | 0 — | 4 | 3.73 1.1 (0.3–2.8) |
| C33–C34, Trachea and lung | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C43, Melanoma              | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C44, Skin                  | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C50, Breastb               | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C56, Ovary                 | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C61, Prostate              | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C62, Testis                | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C64, Kidney                | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C67, Bladder               | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C70–C72, Brain             | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C81, Hodgkin’s disease     | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C91–C95, Leukaemia, all    | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C91, Leukaemia, lymphoid   | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| C92, Leukaemia, myeloid    | 0 | 0 — | 1 | 1.1 (0.0–6.1) | 2 | 3.9 (0.4–14.3) | 0 | 0 — | 3 | 3.72 0.8 (0.2–2.4) |
| All non-AIDS defining cancers | 18 | 0.6 (0.3–0.9) | 39 | 2.0 (1.4–2.8) | 68 | 6.6 (5.1–8.4) | 45 | 3.3 (2.4–4.5) | 170 | 74.8 2.3 (2.0–2.7) |

SIR=Standardized Incidence Ratios; CI=Confidence Intervals; KS=Kaposi’s Sarcoma; NHL=Non-Hodgkin Lymphoma; ICC=Invasive Cervical Cancer; *For KS and NHL: from AIDS to 3 months after. +Females only. It includes neoplasms excluding KS, NHL and ICC plus one of each: lip, nasopharynx, digestive organs, not otherwise specified; nasal cavity, mediastinum, connective tissue, retroperitoneum, vulva, corpus uteri, uterus, not otherwise specified; penis, endocrine glands; and unknown primary site.
lymphocyte to the early (E) oncoprotein six antigen is associated with persistence of HPV infection (Tindle, 2002).

Nonmelanomatous skin cancer showed a three-fold excess in PWHA in our previous report (Franceschi et al., 1998a), whereas a somewhat lower SIR (1.5; 95% CI: 0.8–2.5) emerged from our present update. Misclassification with K5 seems unlikely, since all nonmelanomatous skin cancers in PWHA were histologically confirmed (seven squamous-cell and seven basal-cell carcinomas). The report of nonmelanomatous skin cancer to CRs is, however, incomplete (Levi et al., 1995; Parkin et al., 1997) and the corresponding SIR must be interpreted cautiously. No data on C21: anus

Table 3 Observed cases (Obs) of selected cancers, SIR and corresponding 95% CI among people with HIV or AIDS by gender, age group, and HIV exposure category, Italy, 1985–1998

| ICD10–cancer type or site | Gender | 15–34 | 35–69 | IDU | Other |
|---------------------------|--------|-------|-------|-----|-------|
|                           | Men    | Women |       |     |       |
| C46: K5                   |        |       |       |     |       |
| Obs                       | 483    | 1696  | 42    | 271 |       |
| (1548 –1854)              |        |       | (1597 –3675) | |       |
| SIR (95% CI)              | 228    | 1218  |       | 297 | 2628  |
| (1065 –1387)              |       | (2337 –2945) | | | |
| C82–C85: NHL              |        |       |       |     |       |
| Obs                       | 350    | 321   | 99    | 538 |       |
| (288 –356)                |        | (437 –655) | | |       |
| SIR (95% CI)              | 268    | 417   |       | 181 | 286   |
| (369 –470)                |       | (246 –331) | | | |
| C53: ICC                  |        |       |       |     |       |
| Obs                       | —      | —     | 18    | 21.8|       |
| (12.9 –34.6)              |        |       |       | |       |
| SIR (95% CI)              | 8      | 23.4  |       | 10  | 20.7  |
| (100 –46.4)               |       | (9,9 –38.2) | | | |
| C211: anus                 |        |       |       |     |       |
| Obs                       | 5      | 35.1  | 1     | 27.6|       |
| (11.1 –82.5)              |        | (0.0 –158.3) | | |       |
| SIR (95% CI)              | 6      | 19.4  |       | 16  | 18.1  |
| (0.0 –179.3)              |       | (10.8 –80.2) | | | |
| C33, C34: trachea and lung|        |       |       |     |       |
| Obs                       | 19     | 2.2   | 3     | 8.7 |       |
| (1.3 –3.4)                |        | (1.6 –25.9) | | |       |
| SIR (95% CI)              | 6      | 19.4  |       | 16  | 18.1  |
| (7.0 –42.4)               |       | (10.8 –80.2) | | | |
| C44: skin                 |        |       |       |     |       |
| Obs                       | 13     | 1.7   | 1     | 0.7 |       |
| (0.9 –2.8)                |        |       |       | |       |
| SIR (95% CI)              | 0      | 0     |       | 14  | 1.9   |
| (0.0 –2.0)                |       | (1.0 –3.1) | | | |
| C70–C72: brain            |        |       |       |     |       |
| Obs                       | 8      | 3.8   | 3     | 8.5 |       |
| (1.6 –7.4)                |        | (1.6 –25.3) | | |       |
| SIR (95% CI)              | 6      | 6.4   |       | 5   | 3.2   |
| (2.3 –14.1)               |       | (1.0 –7.6) | | | |
| C81: Hodgkin’s disease    |        |       |       |     |       |
| Obs                       | 36     | 16.7  | 9     | 14.6|       |
| (11.7 –23.1)              |        | (6.6 –27.9) | | |       |
| SIR (95% CI)              | 33     | 17.9  |       | 12  | 12.9  |
| (12.3 –25.2)              |       | (6.7 –22.7) | | | |
| C91–C95: leukaemias       |        |       |       |     |       |
| Obs                       | 12     | 5.7   | 1     | 2.9 |       |
| (2.9 –10.1)               |        | (0.0 –16.7) | | |       |
| SIR (95% CI)              | 8      | 8.4   |       | 5   | 3.4   |
| (3.6 –16.7)               |       | (1.1 –7.9) | | | |
| All non-AIDS defining Cancers | 135  | 2.2   | 35 | 2.5 | 74 | 4.6 |
| (1.9 –2.7)               |       | (1.7 –3.4) | | | (3.6 –5.8) |
| SIR (95% CI)              | 4.6    | 16   | 35   | 16 | 87 | 3.6 |
| (2.0 –4.9)               |       | (1.3 –2.0) | | | (1.3 –2.1) |

SIR=Standardized Incidence Ratios; CI=Confidence Intervals; KS=Kaposi’s Sarcoma; NHL=Non-Hodgkin Lymphoma; ICC=Invasive Cervical Cancer. IDU=Intravenous drug user.

with other authors (Frisch et al., 2001; Gallagher et al., 2001; Grulich et al., 2002). It is possible that, until recently, PWHA have not survived long enough to allow the carcinogenic effect of hepatitis viruses to manifest (Deuffic et al., 1999).

Standardised incidence ratios were above unity for a few additional cancer types (i.e. stomach, rectum, and ovary), but corresponding CI were broad, due to the relatively small number of cases observed.

No reduction in the SIR of NADCs emerged in Italy after the introduction of HAART. Our present study is based, however, on too short a period after HAART to allow any conclusion.

The validity of cohorts defined by AIDS diagnosis, as in record linkage studies, to estimate risks of NADCs before AIDS has been questioned (Goedert et al., 1998; International Collaboration on HIV and Cancer, 2000). Li et al. (2002), however, have recently demonstrated that in Australia one cohort based on AIDS diagnosis and two based on HIV diagnosis provided consistent SIRs for the 10 commonest NADCs.

Since a large number of NADCs occurs before AIDS, the major strength of such methodology is represented by the access to a large number of person-years of observation both before and after AIDS (Franceschi et al., 1998b; Goedert et al., 1998). The number of PWHA and of cancer diagnoses may be underestimated on account of incompleteness of reporting to either AIDS or CRs or of missed linkages. However, the completeness of RAIDS and Italian CRs had been shown to be satisfactory and the linkage procedures we used had been validated (Conti et al., 1997; Adajic-Gross et al., 2001; Dal Maso et al., 2001a). The problem of migration of PWHA out of CR areas should be less severe in Italy than elsewhere, as population mobility is comparatively low and HIV and cancer treatments are available free of charge in all Italian regions (Franceschi et al., 1998b). As already reported (Biggar et al., 1996), SIRs for all cancer sites or types are exaggerated in the
months immediately before and after AIDS by an increased medical surveillance and some cancers would have been otherwise found later. Our present SIRs in the post-AIDS period are therefore underestimate and this hampers the evaluation of trends in cancer risk by immune status. Cancer excesses were also found, however, prior to AIDS diagnosis, for ICC, cancer of the anus, and HD.

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**APPENDIX**

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