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Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe

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ABSTRACT

This investigation highlighted the risk of cancer in 8074 HIV-infected people and in 2875 transplant recipients in Italy and France. Observed and expected numbers of cancer were compared through sex- and age-standardised incidence ratios (SIRs) and 95% confidence

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intervals (CIs). After 15 years of follow-up, the cumulative probability of cancer was 14.7% in transplant recipients and 13.3% in HIV-positives. The SIRs for all cancers were 9.8 in HIV-positives and 2.2 in transplants. Kaposi's sarcoma (SIR = 451 in HIV-positives, 125 in transplants) and non-Hodgkin lymphoma (SIR = 62 and 11.1, respectively) were the most common cancers. A significantly increased SIR for liver cancer also emerged in both groups. The risk of lung cancer was significantly elevated in heart transplant recipients (SIR = 2.8), and of borderline statistical significance in HIV-positive people (95% CI:0.9–2.8). Immune depression entails a two-fold increased overall risk of cancers, mainly related to cancers associated with a viral aetiology.

1. Introduction

The effect of immunosuppression on the occurrence of certain types of cancer was first reported in the early 1970s among people treated with anti-rejection drugs after organ transplantation.[1] Evidence was strengthened in the late 1980s when the same malignancies turned out to be among the commonest manifestations of HIV infection and AIDS.[2] The excess risk seen in immunosuppressed people mainly derives from the increased incidence of non-Hodgkin lymphoma (NHL), Kaposi's sarcoma (KS), non-melanoma skin cancers, and –to a lesser extent – ano-genital cancers, and Hodgkin lymphoma (HL).[2,3] For other cancers found with increased frequency in immunosuppressed people – such as those related to tobacco smoking (e.g. lung), or to organ-specific damage (e.g. kidney dysfunction in renal recipients)[4–7] – the role of immunosuppression has not yet been clarified.

In HIV-infected individuals, KS and NHL occur more frequently when the number of CD4 + cells is greatly reduced (notably below 100/mm^3),[8,9] and in those who had never been treated with highly active antiretroviral therapies (HAART).[6] In transplant recipients, the incidence rates of KS, NHL and of other post-transplant lymphoproliferative disorders (PTLD) increase with type, intensity, and duration of immunosuppressive treatments.[10–12]

The frequency of organ transplants has doubled in the last decade, but few studies have quantified, in southern Europe, the cancer risk of organ transplant recipients.[13–15] To address this question, we carried out a multicentre longitudinal study among transplant recipients and HIV-infected people in Italy and in France.

2. Materials and methods

This study is part of a multicentre longitudinal research conducted in southern Europe on population groups with acquired deficit of the immune system. Data derived from two groups of HIV-infected people (a cohort of seroprevalent individuals from Nice, France (the Dossier Médical Informatique-2 –DMI-2) and an Italian seroincident cohort (the Italian HIV Seroconversion Study -ISS)) and from five groups of transplant recipients in Italy. Some elements of our data had been included in earlier reports in HIV-positive people,[7] and in transplant recipients with regard to KS.[16] Herein, the study group and the range of cancer types considered have been expanded. Table 1 summarises the main characteristics of the study participants.

2.1. The HIV cohorts

The DMI-2 includes epidemiological and clinical information on all HIV-infected individuals who have access to hospital care in France. For the aims of this study, we used the DMI-2 of Provence-Cote d'Azur region, southern France. Between January 1988 and June 2004, information regarding 6072 individuals diagnosed with HIV infection was collected. These people underwent medical examination at enrolment and, on average, every 6 months: they were followed-up for a median time of 3.6 years (interquartile range-IQR: 1.5–7.0).

The ISS is an ongoing multicentre cohort investigation of individuals with a known date of seroconversion, enrolled in 18 clinical centres throughout Italy. These people had a documented HIV-seronegative test, followed by a positive test (with a maximum accepted lag-time between the two tests of 3 years). The midpoint between the two tests was used to estimate the seroconversion time point. Between 1985 and 2005, 2002 individuals were enrolled, and were followed-up for a median time of 8.1 years (IQR: 4.8–11.7).

2.2. The cohorts of transplant recipients

In total, 2875 Italian residents who underwent solid organ transplantation in the North (Milan, Padua, Pavia, and Udine) or Centre (Rome) of the country were included. Of these, 1829 received renal transplant, 724 received heart (n = 682) or lung (n = 42) transplant, and 322 liver transplant. Because of the small number of lung transplant recipients, data on heart and lung transplant recipients were combined. Transplant recipients were followed up for a median of 6.5 years (IQR: 3.0–11.6).

To avoid inclusion of prevalent cases of cancer and for consistency with previous investigations,[4,7,14] the following were excluded from this analysis: individuals with history of any cancer; individuals who developed cancer within 30 days after transplant or after enrolment in the HIV cohorts; individuals of both groups who had died within 30 days after transplant or after enrolment in the HIV cohorts. Accordingly, 91 HIV-infected people (including four cases of prevalent cancers) and 218 transplant recipients (including 55 cases of prevalent cancers) were excluded.

Table 1 – Characteristics of HIV-positive people and transplant recipients

Characteristics	HIV-positive persons				Transplant recipients					
	DMI-2, France		ISS, Italy		Kidney		Heart/Lung		Liver	
	No.	Person-years	No.	Person-years	No.	Person-years	No.	Person-years	No.	Person-years
Sex										
Women	1739	8556	592	5117	634	5653	130	827	96	451
Men	4333	19,127	1410	11,600	1195	10,543	594	4143	226	1057
Age at enrolment (years)										
<35	3855	19,282	1618	14,193	609	7057	106	872	31	170
35–49	1803	7054	317	2073	751	6562	215	1573	118	546
⩾50	414	1347	67	451	469	2577	403	2525	173	792
Calendar period at enrolment										
<1991	1921	10,656	1147	11,690	730	10,371	188	2092	0	0
1991–1995	2441	12,432	505	3841	374	3193	203	1643	82	515
⩾1996	1710	4595	350	1186	725	2632	333	1235	240	993
Overall	6072	27,683	2002	16,717	1829	16,196	724	4970	322	1508
Median (interquartile range) years of follow-up	3.6 (1.5, 7.0)		8.2 (4.8, 11.7)		7.3 (3.4, 13.7)		6.2 (2.4, 10.4)		5.2 (1.9, 6.9)	

HIV, human immunodeficiency virus; DMI-2: Dossier Médical Informatique-2; ISS: Italian HIV Seroconversion Study.

Follow-up visits were scheduled at least every 6 months for HIV-infected people, and at various intervals – in accordance with immunosuppressive protocols – in transplant recipients. Person-years (PYs) at risk for cancer were computed from 30 days after enrolment (i.e. the date of transplant, or the date of enrolment in the HIV-cohorts) to the date of last follow-up visit, or to the date of cancer diagnosis, or to the date of death.

Observed cancers were the incident cases diagnosed in the cohorts during the study period. Cancer diagnoses were recorded during the follow-up visits, histologically confirmed and coded according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10).[17] To avoid follow-up losses, information on cancer and on vital status was actively elicited either from clinical records, cancer registries (when available), the national AIDS registries, or the census bureau of the town of residence. Multiple primary cancers were separately considered in the statistical analysis. Non-melanoma skin cancers, *in-situ* and pre-neoplastic lesions were not included in the present analysis as i) information on basal cell carcinoma was not recorded, and ii) the report of squamous cell carcinoma might not have been complete.

2.3. *Statistical analysis*

The number of observed incident cancer cases was compared to the expected number. This was computed from sex- and age-specific incidence rates from Italian and French population-based cancer registries.[18] Standardised incidence ratios (SIRs) were computed dividing the number of observed cases by the number of expected ones. Ninety five percent confidence intervals (CIs) of SIRs were determined using the Poisson distribution.[19] In order to evaluate the influence of immunosuppression, the SIRs for the most frequent cancers (i.e. ⩾10 observed cases in either group) and for all cancers were separately assessed – among HIV-infected individuals – by use of HAART (no/yes). For individuals ever exposed to HAART (defined as prescription of at least three antiretroviral drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor), PYs under HAART were computed since the start of therapy to cancer diagnosis, death, or last follow-up visit. Among transplant recipients, the SIRs for the most frequent cancers, and for all cancers combined, were separately computed in three time periods after transplantation (i.e. < =17 months; 18–89 months; > = 90 months).

The cumulative probabilities of developing cancer after transplant or, in the ISS, after HIV seroconversion, were estimated according to Kaplan–Meyer. The Log-rank test was used to compare the probabilities of cancer development within subgroups.[20]

3. Results

In total, 10,949 people (8074 HIV-infected individuals and 2875 transplant recipients) were included and followed up for 67,074 PYs (Table 1). HIV-infected people (median age: 31.3 years, IQR: 26.7–37.1) were younger than transplant recipients (median age: 45.5 years, interquartile range: 34.5–53.5). Women represented 28.8% of HIV-positive individuals and 29.9% of transplant recipients. With regard to period of study enrolment, 25.5% of HIV-infected people were enrolled after the introduction of HAART, while 41.5% of transplant recipients were transplanted after 1995, when the new generation anti-rejection drugs (e.g. tacrolimus, mycophenolate mofetil, sirolimus, anti-CD25) became available (Table 1).

During follow-up, 625 cases of cancer were diagnosed in HIV-infected people and 222 in transplant recipients. The cumulative probabilities of developing any type of cancer (excluding non-melanoma skin cancers) after transplantation or HIV seroconversion are illustrated in Fig. 1. At 3 years,

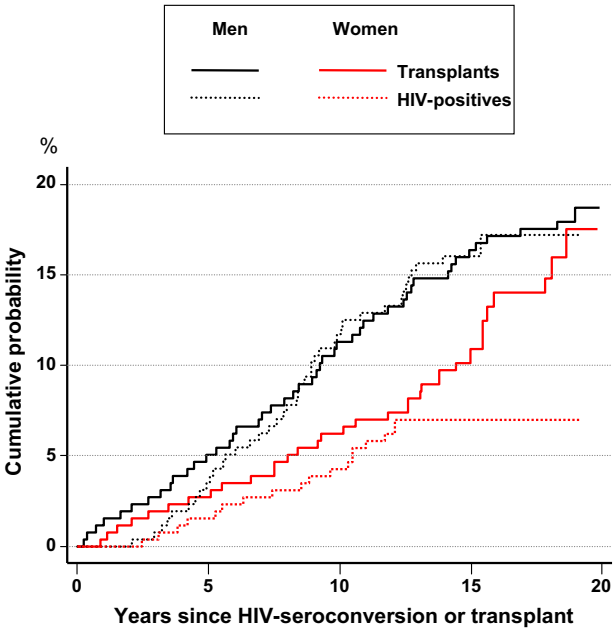

Fig. 1 – Cumulative probability of developing all cancers in HIV-infected persons and in transplant recipients, by sex.

cancers were more frequently diagnosed in transplant recipients (2.5%, 95% CI:2.0%–3.2%) than in HIV-positives (0.8%, 95% CI:0.5%–1.3%). After 5 years, 3.1% of HIV-positives and 4.4% of transplants had cancer, and the cumulative probabilities at 15 years of follow-up were similar in the two groups, 13.3% in HIV-positives (95% CI:11.2%–15.9%) and 14.7% in transplant recipients (95% CI:12.7%–17.0%). Men developed cancer more frequently than women ($p = 0.02$ in HIV-positives; and $p < 0.01$ in transplants) (Fig. 1). With regard to cancer type (data not shown), the commonest types were – at 15 years of follow-up – KS (6.1% in HIV-positives and 2.1% in transplants) and NHL (5.4% in HIV-positives and 3.2% in transplants).

SIRs for cancer sites or types with at least three observed cases in either one of the two study groups are shown in Table 2. The SIR for all cancer sites was 9.8 (95% CI: 9.0–10.6) in HIV-infected individuals and 2.2 (95% CI: 1.9–2.5) in transplant recipients. After the exclusion of KS and NHL, the SIRs for all cancers became similar (1.9 in HIV-infected people and 1.4 in transplant recipients) (Table 2).

Significantly increased risks were seen, in both groups, for KS (SIR = 451 in HIV-infected people and 125 in transplant recipients), NHL (SIR = 62 and 11), and liver cancer (SIR = 9.4 and 3.2) (Table 2). SIRs for cancer of the lung were 1.7 (95 CI: 0.9–2.8) among HIV-positive individuals and 1.6 (95% CI: 1.1–2.3) in transplant recipients. Among HIV-infected people only, significantly elevated SIRs were found also for anal and cervical cancers and HL (Table 2).

HIV-positive individuals who had been treated with HAART showed a three-fold lower risk for all cancers than those who had never been treated (SIR = 4.1 and 12.4, respectively). Such decrease was completely attributable to the reduction of SIRs for KS and for NHL. Conversely, HAART did not affect the SIRs for liver cancer, cervical cancer, HL and all cancers combined except KS and NHL (Table 3).

According to type of transplanted organ, significantly elevated SIRs were seen for lung cancer in recipients of heart transplant (2.8), and for head and neck cancers in recipients of liver transplant (5.5) (Table 4). In respect to time since transplant, the SIR for KS peaked up in the first 17 months after transplant (SIR = 378) and tended to decline thereafter (SIR = 52 after 90 months), while the SIRs for other cancer types or for all cancers combined did not significantly change overtime (Table 4).

SIRs for all cancers combined and for the commonest cancer sites were further evaluated in individuals below or over age 40 (data not shown in tables). In both groups, SIRs for all cancers combined were higher in individuals under 40 years than in older ones. Higher SIRs for KS and NHL were consistently seen among HIV-positive individuals than in transplant recipients in each of the age groups considered. With regard to gender, SIRs for KS were non-significantly higher in women than in men in both HIV-positive individuals and transplant recipients (data not shown in tables).

4. Discussion

This epidemiological investigation allowed the comparison of cancer risk on a large number of HIV-positive individuals and transplant recipients from southern Europe. It also provided the possibility of assessing the severity of immunosuppression on cancer risks. Our study results highlighted that, after 15 years of immunosuppression, approximately 15% of individuals develops cancer. Moreover, it confirmed the prominent role of oncogenic viruses in the onset of cancers that follow HIV infection or organ transplantation and put in evidence some interesting differences in SIRs according to type of transplanted organ.

The 2.2-fold increased risk for all types of post-transplant cancers was in agreement with SIRs reported in the Unites States (2.0), Japan (2.8), Australia and New Zealand (3.3).[21–23] It was well comparable with SIRs from Nordic countries, when the lack of non-melanoma skin cancers from our present analysis was taken into account.[4,24] The SIR for all cancers combined in HIV-positive people by far exceeded the SIR registered in transplant recipients. However, when KS and NHL were excluded from the analysis, the SIRs for all other cancer types were of similar magnitude overall (i.e. 1.8 in HIV-positives and 1.4 in transplants) and according to age and sex.

Novel findings regarding specific cancer types that emerged from this investigation include liver and lung cancers. The suggestion that transplant recipients may have an increased risk for liver cancer was recently documented in Australia and New Zealand,[23] but it was not previously seen in northern Europe,[4] in the United States,[25] or in Japan.[22] With regard to the elevated risk of liver cancer in Italian kidney transplant recipients, it should be noted that, in Italy, the prevalence of infection with HBV and/or with HCV among dialysis patients is high[26] and that HCV infection in the recipient is not generally considered a contraindication for organ transplant.

We noted elevated risks of similar magnitude for lung cancer in HIV-positive people and in transplant recipients. Our SIR for all transplants combined (i.e. 1.6) was very close to SIRs recorded in northern Europe,[4] in the United States,[25] and in Australia/New Zealand kidney transplants.[23] However,

Table 2 – Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) for cancer in HIV-positive people and in transplant recipients

Cancer site or type (ICD-10)[a]	HIV-positive persons[b]			Transplant recipients[b]		
	Cases	SIR	(95% CI)	Cases	SIR	(95% CI)
Head and neck (C 00–14 and 30, 32)	10	1.2	(0.6–2.1)	12	1.5	(0.8–2.6)
Oesophagus (C 15)	0	0.0	(0.0–1.7)	3	2.0	(0.4–5.9)
Stomach (C 16)	4	1.8	(0.5–4.5)	11	1.6	(0.8–2.9)
Colon (C 18)	1	0.3	(0.0–1.6)	11	1.4	(0.7–2.6)
Anus (C 21)	5	33	(11–76)	0	0.0	(0.0–10.8)
Liver (C 22)	11	9.4	(4.7–16.9)	10	3.2	(1.5–5.8)
Pancreas (C 25)	2	2.3	(0.3–8.3)	5	2.0	(0.7–4.7)
Lung (C 34)	14	1.7	(0.9–2.8)	33	1.6	(1.1–2.3)
Melanoma of skin (C 43)	2	1.2	(0.1–4.2)	3	1.4	(0.3–4.0)
Kaposi's sarcoma (C 46)	317	451	(403–504)	39	125	(89–170)
Breast, female (C 50)	5	0.8	(0.3–1.9)	8	0.9	(0.4–1.8)
Cervix uteri (C 53)	22	14.6	(9.1–22)	3	3.3	(0.7–9.7)
Uteri, corpus (C 54)	0	0.0	(0.0–6.8)	3	2.1	(0.4–6.1)
Ovary (C 56)	0	0.0	(0.0–4.3)	3	2.8	(0.6–8.3)
Kidney (C 64)	0	0.0	(0.0–1.7)	9	2.7	(1.2–5.1)
Bladder (C 67)	2	0.7	(0.1–2.4)	4	0.5	(0.1–1.2)
Brain (C 71)	3	1.7	(0.4–5.1)	3	1.5	(0.3–4.2)
Hodgkin lymphoma (C 81)	18	10.8	(6.4–17.0)	0	0.0	(0.0–3.4)
Non-Hodgkin Lymphoma (C 82-85 and 96)	201	62	(54–71)	42	11.1	(8.0–15.0)
Leukaemia (C 91-95)	3	1.7	(0.4–5.1)	2	0.9	(0.1–3.2)
Multiple myeloma (C 90)	0	0.0	(0.0–7.6)	3	3.0	(0.6–8.6)
All cancers[c,d]	625	9.8	(9.0–10.6)	222	2.2	(1.9–2.5)
All cancers except KS and NHL	107	1.9	(1.5–2.3)	141	1.4	(1.2–1.7)

a ICD-10, *International Classification of Disease*, Tenth Revision; HIV, human immunodeficiency virus.
b It includes cancer sites or types with at least three cases observed in one of the two groups.
c The following cancers were also diagnosed (n. of cases): HIV-positive persons: small intestine (1); prostate (1); bone (1); adrenal glands (1); testis (1). Transplant recipients: small intestine (1); mesothelioma (2); thyroid (2); prostate (2); gallbladder (1); seminoma (1); other and unspecified cancers (2); connective and soft tissues (2); uterus not otherwise specified (2).
d Ten HIV-positive persons and six transplant recipients had two or more cancers.

Table 3 – Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) for cancers with ⩾10 observed cases in HIV-positive persons, according to use of highly active antiretroviral therapies (HAART)

Cancer site or type	HAART use					
	No			Yes		
	Cases	SIR	(95% CI)	Cases	SIR	(95% CI)
Head and neck	7	1.3	(0.5–2.6)	3	1.0	(0.2–2.8)
Liver	7	9.1	(3.7–18.7)	4	10.2	(2.8–26.1)
Lung	7	1.3	(0.5–2.7)	7	2.4	(1.0–5.0)
Kaposi's sarcoma	298	548	(487–614)	19	120	(72–187)
Cervix uteri	17	15.7	(9.1–25)	5	11.8	(3.8–27.5)
Hodgkin lymphoma	15	11.1	(6.2–18.3)	3	9.4	(2.0–27.6)
Non-Hodgkin Lymphoma	171	72	(61–83)	30	35	(24–50)
All cancers	543	12.4	(11.3–13.4)	82	4.1	(3.3–5.1)
All cancers except KS and NHL	74	1.8	(1.4–2.3)	33	1.7	(1.2–2.4)

this stratified analysis indicated that the SIR for lung cancer was significantly elevated only among recipients of heart transplant, and no excess risk was seen among recipients of kidney or liver transplants. With regard to HIV-infected individuals, the study findings confirmed that HIV-positive people are at increased risk for lung cancer and that HAART treatment does not influence such risk.[6] Since smokers could have been over represented in both heart transplant recipients (because smoking-related conditions lead to heart transplant) and in individuals with HIV infection, it is difficult to disentangle the role of immunosuppression in lung cancer onset. Moreover, factors other than smoking and immunosuppression may be involved in lung cancer occurrence.[27]

Infection with human papillomaviruses (HPV) is highly prevalent in the context of immunosuppression, particularly among HIV-infected women. Scant data, however, are available on the risk of invasive cervical cancer in transplant recipients. In the United States, only one out of several studies reported a nearly six-fold excess of invasive cervical cancer in transplanted women.[25] In northern Europe, a nearly

Table 4 – Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) for cancers with ⩾10 observed cases in transplant recipients, according to type of transplant and time since transplant

Cancer site or type	Type of transplant						Time since transplantation (months)					
	Kidney		Liver		Heart		⩽17		18–89		⩾90	
	Cases	SIR (95% CI)	Cases	SIR (95% CI)	Cases	SIR (95% CI)	Cases	SIR (95% CI)	Cases	SIR (95% CI)	Cases	SIR (95% CI)
Head and neck	6	1.4 (0.5–3.1)	4	5.5 (1.5–14.0)	2	0.6 (0.1–2.3)	2	1.8 (0.2–6.4)	6	1.5 (0.6–3.4)	4	1.3 (0.4–3.3)
Liver	6	4.0 (1.5–8.7)	0	0.0 (0.0–10.9)	4	2.9 (0.8–7.4)	0	0.0 (0.0–7.7)	4	2.7 (0.7–7.0)	6	4.6 (1.7–10.0)
Lung	8	0.8 (0.4–1.6)	1	0.5 (0.0–3.1)	24	2.8 (1.8–4.2)	4	1.5 (0.4–4.0)	22	2.3 (1.4–3.5)	7	0.9 (0.3–1.8)
KS	23	114 (72–171)	5	253 (82–589)	11	121 (60–217)	18	378 (224–598)	15	100 (55–164)	6	52 (19–114)
NHL	15	6.7 (3.8–11.0)	5	16.4 (5.3–38.2)	22	17.9 (11.2–27)	5	9.3 (3.0–22)	19	10.5 (6.3–16.4)	18	12.6 (7.5–20)
All cancers	104	1.9 (1.5–2.3)	23	2.7 (1.7–4.0)	95	2.6 (2.1–3.2)	37	2.7 (1.9–3.7)	100	2.1 (1.7–2.5)	85	2.2 (1.7–2.7)
All cancers except KS and NHL	66	1.2 (0.9–1.6)	13	1.5 (0.8–2.6)	62	1.7 (1.3–2.2)	14	1.0 (0.6–1.8)	66	1.4 (1.1–1.8)	61	1.6 (1.2–2.0)

KS: Kaposi's sarcoma; NHL: Non-Hodgkin lymphoma.

nine-fold increase seen in 1995 in women who underwent kidney transplant [28] was not confirmed by subsequent investigations.[4,29] We found a three-fold increased risk of cervical cancer in transplanted women, but the confidence interval was too broad to allow a firm interpretation.

Although not new, some other findings of this comparison are worth noting. Epstein–Barr virus plays a key role in the occurrence of both NHL and HL related to immunosuppression, but HL has been rarely diagnosed in transplant recipients. In case-series of transplant recipients HL has often been classified as PTLD, and elevated risks have been rarely demonstrated.[23] Our observation that the degree of immunosuppression does not seem to affect the risk of HL in HIV-infected people is at variance with other investigations conducted in Europe[6,30] and in the United States.[31] These studies showed a positive association between HAART use and risk of HL, suggesting that increasing risk of HL could reflect immune-modulating effects of antiretroviral therapy.[31]

Some limitations of our study should be born in mind. The number of expected cases of cancers was drawn from rates registered in the general populations of Italy and France in the early years of the AIDS epidemic (i.e. 1988–1992), when AIDS-associated cancers had a negligible impact on the general population. However, we acknowledge that over a long study period, the referent population used in the study might have influenced the SIRs. For some cancer types, the external validity of SIRs was limited because the number of expected cases was low and the study had insufficient power. Individual data on immunosuppressive drugs were not available for most of the transplant recipients included in this study, and we were not able to assess the potential association between type of treatment and cancer risk. In addition, we lacked information on important risk factors other than immunosuppression (e.g. smoking, presence of chronic infection with viruses other than HIV). Finally, the inclusion of different types of transplants provided novel information but made our findings not immediately comparable with previous studies that were generally restricted to renal transplants.

In conclusion, in southern Europe organ transplantation entails a two-fold increased overall risk of cancers (other than skin cancers), mainly related to cancers associated with a viral aetiology. The cancer pattern of transplant recipients resembled the one seen in HIV-positive individuals, except for the substantially greater burden of KS and NHL in HIV-positive individuals who had not used HAART.

Conflict of interest statement

None declared.

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