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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.

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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/mm³),^{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 ex-

panded. 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.

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