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Epidemiology of AIDS-Associated Malignances

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Abstract

The evidence for an increased risk of Kaposi's sarcoma and non-Hodgkin's lymphoma in HIV-infected people is consistent and in fact KS and NHL (chiefly immunoblastic, Burkitt's lymphoma, and primary lymphoma of the brain) have, since the early days of the epidemic, been among the so-called «AIDS-defining illnesses». Several additional tumours appear to be associated with HIV infection, albeit with smaller relative and absolute risks. The evidence is strongest for associations of HIV with invasive cervical cancer (ICC), Hodgkin's diseases, anogenital neoplasia, testicular seminoma, paediatric leiomyosarcoma and conjunctival cancer. Since the mid-1990's several epidemiologic studies have led to a better quantification of the burden of malignancies in HIV-infected populations. Different ways of quantifying the higher risk of cancer in persons with AIDS have been tried. Population-based cancer registration data first yielded indirect estimates of HIV-associated cancer, based on surrogate indicators of groups at risk for HIV infection. Cohort studies of HIV-seropositive individuals often provide detailed information of risk-correlates and follow-up but often they were based on too few cancer cases to provide robust RR estimates. The purpose of this review is to summarise and describe the epidemiological findings on malignancies associated with HIV infection and/or AIDS, taking into account the strengths and weaknesses of different study designs.

Keywords

AIDS. Epidemiology. Kaposi's sarcoma. Non-Hodgkin Lymphoma. Invasive cervical cancer.

Introduction

It has long been thought that the immune system plays a vital role in the etiology of cancer[1]. Immunodeficiency, whether congenital, iatrogenic, or due to infections, increases the risk of certain, but not all, types of cancer. The study of cancer in HIV-infected populations offers a unique opportunity to investigate the role of the immune system in controlling the development and dissemination of tumours.

Many cancers have been reported to be increased in people with AIDS and Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) are relatively frequent outcomes of HIV infection[2]. In fact, they have been, since the early times of the epidemic, among the so-called "AIDS-defining illnesses". Several additional tumours appear to be associated with HIV infection, albeit with smaller relative and absolute risks. The evidence is strongest for associations of HIV with invasive cervical cancer (ICC),

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Table 1. *Number of all Kaposi's Sarcoma (KS), non-Hodgkin's lymphoma (NHL), and invasive cervical cancer (ICC) as AIDS-defining illnesses and percentage of all AIDS cases by year. Western Europe, 1988-97*[1]

Year	KS		NHL		I C C	
	N	(%)	N	(%)	N	(%)[2]
1988	1462	13.6	406	3.8	0	
1989	1721	12.2	543	3.9	0	
1990	1869	11.7	588	3.6	0	
1991	2124	11.5	650	3.5	0	
1992	2231	10.9	791	3.9	0	
1993	2136	9.6	812	3.6	64	1.5
1994	2236	8.9	901	3.6	122	2.5
1995	1910	7.9	974	4.0	111	2.3
1996	1540	7.5	836	4.1	97	2.2
1997	900	6.9	647	4.9	76	2.8
Total	18156	9.8	7148	3.9	470	1.4

[1]Data available from Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.
[2]In females

Hodgkin's diseases[3], anogenital neoplasia, testicular seminoma, paediatric leiomyosarcoma and conjunctival cancer[2]. Most other cancers, however, including the carcinomas most common in the general population, do not appear to be increased in HIV infection.

The purpose of this review is to summarise epidemiological findings on malignancies associated with HIV infection and/or AIDS, taking into account the strengths and weaknesses of different study designs.

Kaposis's sarcoma

In northern Europe and in the United States, in the pre-AIDS era, Kaposi's sarcoma (KS) was a very rare cancer. KS has been described in Mediterranean countries as "classic type KS"[4] in sub-Saharan regions as "endemic type KS"[5] and in immunosupressed patients who had organ transplants as "iatrogenic type KS". In the late 1980s, a fourth variant of KS, the so-called "epidemic type KS", was identified through surveillance data and heralded the onset of the AIDS epidemic in the United States (US)[6]. Since then, the high incidence of KS among HIV-infected persons, and its peculiar distribution among particular subpopulations, has stimulated the epidemiological research on this cancer leading, in 1994, to the identification of a new herpes virus (HHV-8) as the potential putative agent of KS. The identification of this virus has added more controversy to the etiology of KS and its relationship with HIV-induced immunosuppression.

Surveillance data from population-based AIDS registries, collecting the presenting form of the disease, have been the principal data source to describe both the magnitude and distribution of HIV-associated KS (HIV-KS). Information for KS in 17 western European countries, updated to June 1998, was made available by the European Non-Aggregate AIDS Data Set (ENAIDS)[7]. Between 1988 and 1997, a total of 18,156 AIDS cases had KS as an AIDS-defining illness 10% (Table 1). As a percentage of AIDS-defining illnesses, KS decreased throughout the following period, from 13.6% in 1988 to 7% in 1997. Moreover, surveillance data has consistently shown that KS is more common among homosexual and bisexual men and also among women who reported sexual exposure to bisexual men HIV[8-11].

Record linkage between AIDS and cancer registration databases is an alternative methodology for examining associations between HIV infection and the overall incidence of cancer[12-15]. Reynolds *et al.*[12] linked 1,454 cases of KS in the California Tumour Registry with all AIDS cases diagnosed in San Francisco since 1980. The relative risk was 716, comparing AIDS patients and the general population. Goedert *et al.*[13] matched 98,336 people with AIDS and 1,125,098 with cancer, in seven regions of the US and in Puerto Rico. The relative risk for KS after AIDS diagnosis was 1,000 at the time of AIDS diagnosis and 310 between 4 and 27 months after diagnosis. In Europe, Franceschi *et al.*[14] matched the Italian registry of AIDS and 13 Cancer Registries, covering a population of about 8 million. The relative risk for KS after AIDS diagnosis was 1,300.

The high prevalence of HIV-related Kaposi's sarcoma (AIDS-KS) among homosexual and bisexual men compared to other HIV risk groups whose acquisition of HIV was by non-sexual routes, suggested that a sexually-transmitted infectious agent could be responsible for KS[16]. Although some studies have identified specific sexual behaviours associated with KS[17,18], other studies could not confirm this association[19-22].

In 1994, sequences of a novel herpesvirus, Kaposi's sarcoma-associated herpesvirus (KSHV), or human herpesvirus 8 (HHV-8), were identified in AIDS-KS tissue[23]. HHV-8 DNA sequences initially discovered in AIDS-KS lesions have subsequently been detected in all epidemiological forms and histological stages of KS[23,24]. Several studies have found a correlation between the risk of developing AIDS-KS and infection with HHV-8. Moreover, homo-

sexual and bisexual men are the risk group with the highest prevalence of HHV-8 and intravenous drug users (IVDUs) are the risk category with the lowest prevalence[25-27].

KS unrelated to HIV infection (Classic KS) is more common in Mediterranean areas of Europe, such as Greece and Italy, than in northern European countries or the US, as well as in those of Jewish descent[4,28] and parts of sub-Saharan Africa (African endemic KS)[29,30]. Accordingly, HHV-8 infection is uncommon in the US and the UK, with a reported prevalence between 0 to 5%[4,31,32], but is more prevalent in Italy, Greece and Israel[27,32-34]. In Italy, the seroprevalence of HHV-8 correlates with the incidence of KS in different regions with up to 25% of blood donors testing positive in the south, where classic KS is more common, compared to 7% in the north[33-35]. In Africa, prevalence rates of over 50% have been reported[36-39]. In Spain a recent seroprevalence study has shown a higher HHV-8 prevalence in all risk groups than in northern Europe, in particular among homosexual men (86.7%). Interestingly, HIV+ female IVDUs have a higher HHV-8 prevalence than those HIV-, suggesting that in this group of women (30% of whom are involved in sex trade for drugs) heterosexual transmission may be the main route of HHV-8 acquisition[40].

Longitudinal data to assess the natural history of HHV-8 and the risk of KS development is scarce. Data from the San Francisco Men's Study[41] showed that the 10 year probability of KS was 49.6 % and that baseline HHV-8 seropositivity, even adjusted by CD4 counts and number of sexual partners, was independently associated with KS. An Italian study[42] following 366 individuals with known date of HIV seroconversion, found that the actual rate of KS development among HIV and HHV-8 co-infected individuals was 30% at 10 years after HIV seroconversion, the titres of HHV-8 being a predictive factor for KS development. Sitas *et al.*[43] also reported HHV-8 titretation as a risk factor for KS, independent of HIV sero-status. A retrospective follow-up of 1,458 homosexual men from the Amsterdam cohort study[44] found an incidence rate of HHV-8 of 3.6/100 person-years, with previous HIV infection being one independent determinant for HHV-8 seroconversion.

Moreover, a cross-sectional study among 330 HHV-8, positive individuals did not find any correlation between HHV-8 titres and either CD4 or HIV viral load[40]. Although acquiring HHV-8 after HIV infection has been reported to lead to a higher risk of developing KS[45], the specific role of immunosupression on HHV-8 infection and KS development deserves further attention.

Although other routes of transmission have been suggested, there is enough epidemiological evidence that HHV-8 may be transmitted mainly sexually. Nevertheless, the specific mechanisms of transmission remain unclear. Data from the Amsterdam Cohort Study[44] have also identified that orogenital insertive sex and orogenital receptive sex with more than 5 partners in the last 6 months were associated to HHV-8 seroconversion. Moreover, data from an European case-control study, including 265 HHV-8 positive and 137 HHV-8 negative individuals, showed that homosexual men involved in it had an increased risk of being infected by HHV-8 (data not published). Interestingly, a recent study performed among 27 HHV-8 infected homosexual men showed that HHV-8 DNA was present in 30% of oropharingeal samples as compared with 1% of anal and genital samples and that the median long titre of HHV-8 in the oral cavity was 2.5 times higher than that from other sites[46]. This study adds biological plausibility to the potential transmission of HHV-8 through saliva.

In summary, from the currently available descriptive epidemiological data it is now clear that HHV-8 is not a ubiquitous virus, that its distribution reflects that of KS and is consistent with sexual transmission being the main route of acquisition. Nevertheless, some descriptive epidemiological findings will need further clarification. Despite the high prevalence of HHV-8 among homosexual men, only a very small fraction will eventually develop KS, this fraction being even smaller among other transmission groups. Regardless of the HHV-8 prevalence, KS has a clear male preponderance in all groups and the dramatic decrease in HIV-associated KS occurrence after the introduction of the HAART in 1996[47,48] adds some questions about the role of HIV itself in KS development. Finally, sensitive and specific serological tests are needed to better interpret the magnitude and distribution of HHV-8 infection in relationship to KS and longitudinal studies, including specific behavioural data, will help to identify its specific mechanisms of transmission.

Non-Hodgkin's lymphoma

NHL in HIV-infected patients is a heterogeneous disease resulting from a complex and sequential interaction of several factors, i.e.: chronic antigenic stimulation of B-lymphocytes, deregulation of cytokines (IL-4, IL-6, Il-10, Il-12, TNF and others) and co-stimulatory networks, infection by oncogenic viruses (Epstein-Barr, HHV-8 and others), and oncogene rearrangements in B-lymphocytes (C-MYC, BCL-6, BCL-2, TCL-1, P53 and others). These interactions are probably different in the distinct subtypes of HIV-related NHL. In Burkitt's lymphoma C-MYC rearrangement, P53 mutations and Epstein-Barr virus infection are the key events. In large-cell immunoblastic NHL the main events are BCL-6 and C-MYC rearrangements, whereas in primary-effusion lymphomas, HHV-8 virus has a direct etiologic role. Up to now there is no evidence for a direct role of HIV in lymphomagenesis.

NHL accounts for approximately 4% of cancer cases and 4% of cancer deaths in the general population non-infected with HIV[49]. Ever after accounting for the effect of HIV, the incidence of NHL has continued to increase more rapidly than most other tumours.

NHL is the second most common malignancy associated with HIV infection and includes immunoblastic and Burkitt lymphoma, primary brain lymphoma (PBL), as well as the novel clinicopatho-

Table 2. *Prevalence of HHV8 antibodies in several Spanish subpopulations[40].*

	Positive/tested	Percentage of positive
Children	0/100	
Blood donors	40/613	6.5
HIV negative		
IVDU	15/128	11.7
Heterosexual	24/148	16.2
Homosexual	42/150	28.0
HIV positive		
IVDU	29/254	11.4
Heterosexual	23/125	18.4
Homosexual	157/181	86.7

logic entities such as primary effusion lymphoma or plasmablastic lymphoma of the oral cavity[2,23].

In contrast to the variation in risk for KS, there are relatively small differences in the frequency of NHL by HIV exposure groups in developed countries and the AIDS cases with NHL as AIDS-defining illness is consistently between 2 and 5% in western Europe and in the US[2]. This suggests that environmental co-factors for AIDS-NHL are unlikely to be as important as for KS[23].

Information for all NHLs as AIDS-defining illness in 17 western European countries was made available by ENAADS. Between 1988 and 1997, a total of 7,148 AIDS cases had NHL as the AIDS-defining illness (3.9%). As a percentage of AIDS-defining illnesses, NHL increased from 3.6% in 1994 to 4.9% in 1997 (Table 1) ENAADS[7].

Biggar *et al.*[50], linked 83,434 AIDS cases reported to AIDS registries in 7 regions in the US. The RR was 283 for NHL and it nearly doubled between semesters 2 and 4 after diagnosis of AIDS. The relative risk for NHL in Goedert *et al.*[13] was 325 in proximity to AIDS. In Europe, the record linkage carried out by Franceschi *et al.*[51] allowed to estimate a RR of 228 for NHL between 1 year prior to and 3.5 years after AIDS. In Australia, 778 cancers cases were identified in 3,616 people with AIDS[52]. Relative risk was 18 after allowance for differential survival in AIDS patients. The largest prospective study, the Multicentre AIDS Study (MACS), had 2,876 HIV-seronegative participants and 2,746 seropositive ones[53]. After 11-years follow-up, RRs in HIV-seropositive individuals compared to the US general population were approximately 170 for NHL. Between 1984 and 1993, Lyer *et al.*[54] examined the incidence of NHL in 430 HIV-seropositive homosexual men. The annual incidence was 0.6%, 83-fold higher than population rates.

The effect of HAART on incidence of NHL is less consistent in the above-described studies. The NHL incidence reported at MACS has risen about 20% per year[55], even though only 1 (13%) of 8 NHL cases in the nested case-control studies had used HAART. This rate did not differ statistically from the rate reported by controls without NHL (34%). Conversely, among 6,587 participants of ACTG[56], NHL incidence declined 26% in 1996-97 compared to 1992-95. From 1993 to 1996, the San Francisco City Clinic Cohort study[47] showed relatively constant incidence rates of NHL (about 1.5/100 person-year). The prevalence of HAART in this population had reached 50% by 1996. The ASD study[57] showed an incidence for all NHLs of 17/1,000 person-years of observation in persons that had used antiretroviral therapy and 7/1,000 in persons without therapy, with a statistically significant decrease only for PBL.

In spite of the weak effect of HAART on the incidence of NHL, it seems evident that the prognosis of NHL (especially that of large-cell or immunoblastic) has improved in the HAART era, suggesting a direct or indirect role of antiretroviral therapy against NHL. This effect has been observed in several studies based on historical comparison of uniformly treated patients[58] or in AIDS surveillance registries[59].

Invasive cervical cancer

Invasive cervical cancer (ICC) is caused by the persistent infection of certain types of Human Papillomavirus (HPV). HPV characteristics such as type, viral load and time since infection together with the immune status of the subject have been shown to influence the rate of progression from infection to cervical neoplasia. The natural history of HPV cervical infection is that women persistently infected with HPV are at high risk of developing high-grade cervical lesions[60]. Many women in the general population have HPV infections at some point in time, but few will have it in a persistent manner. The addition of HIV infection to an already existent HPV infection may be a contributory factor to induce chronic infection and ICC development. This aspect is supported by the strong link between severely impaired cell-mediated immunity and HPV-induced carcinomas in non HIV-immune suppressed patients[61].

Although ICC has been included among AIDS-defining conditions since January 1993, the role of HIV in ICC development still remains controversial (CDC 1992). It is generally accepted that HIV-positive women are more likely to be infected by HPV[62-64]. The co-infection seems to be more common than would be expected by both infections being sexually transmitted. The effect of HIV is probably explained

by the reactivation of latent HPV infections due to loss of immune competence[62]. There has, however, been a lack of consistent changes in ICC incidence with HIV prevalence rates, not only in high resource settings, but also in African countries[2,13,65-67]. Conversely, an association between HIV and ICC has also been described in several studies. Among women with AIDS reported to the Italian AIDS-Registry between 1993 and 1995, the frequency of ICC as AIDS-defining disease was nearly 3 times higher among intravenous drugs users than those infected by heterosexual contact[68]. In Italy the linkage of the National AIDS Registry and the populations cancer registries showed a RR of 15 for ICC for women with AIDS[14]. The joint Italian-French follow-up study of HIV-positive women also showed a 13-fold increase in rates of ICC for HIV-positive women. In Spain, the Catalonian AIDS surveillance system detected 58 cases of ICC among 823 HIV positive women. This represented a 18-fold increased risk of ICC in AIDS patients as compared to the general population[69]. Frutcher *et al.* 1998 reported that HIV-positive women in New York had a 3-fold increase in ICC as compared to HIV-negative women. Independent predictors were symptoms-duration and lack of papanicolau smear. Similarly, Chin *et al.*[70] in the US reported an increased risk of ICC among black and Hispanic women in the Sentinel Hospital Surveillance System.

A full evaluation of HIV as co-factor for ICC development requires data on several aspects related to the natural history of ICC. It is necessary to report on previous history of papanicolau smears and also on cervical cancer treatment. This information is rarely expressed in the published reports. In high-resource settings, women with low-grade lesions that are detected to be HIV-positive may undergo drastic surgical treatment. Women with previous conization, history of previous cervical biopsies or previous cervical laser therapy may have their risk for ICC reduced (Maiman & Palefsky 1st National AIDS Malignancy Conference). Survival in AIDS patients is strongly linked to treatment[71,72]. It is likely that HIV-positive women in poor countries with no access to medical care die before they have time to develop cervical cancer or to have the medical attention necessary to be diagnosed[73]. Studies on cancer incidence rates in HIV-endemic countries should take into account HIV survival rates while evaluating ICC trends.

The controversy as to whether HIV promotes HPV infection and its adverse clinical consequences needs detailed information on therapeutic as well as preventive practices before it can be concluded that HIV does not affect the women's risk to develop ICC. Meanwhile, the scientific community should ensure that HIV-infected patients are attentively followed up for potential cervical damage and make all possible efforts to guarantee the best available treatment for HIV, irrespective of country of residency.

Findings on other cancers came only from clinical series in which there was no suggestion of significant decrease for ICC[57], or any neoplasm other than KS during HAART[48].

HIV infection and other cancers

In western countries, individuals with HIV infection have an overall cancer risk (excluding KS and NHL) that is approximately 2-fold higher than that registered in the general population of the same age and gender[13,14]. For a few neoplasms like Hodgkin's disease, anal cancer, hepatocellular carcinoma, lung cancer, non-melanoma skin cancer, and some other cancers, there have been reports of associations with HIV infection.

Hodgkin's disease

Cohort studies and case-control studies indicate that the incidence of Hodgkin's disease is increased slightly above that expected in the HIV-infected population. In Australia[52], the risk for HD after allowance for differential survival in AIDS patients was 18.3%. Linkage studies of AIDS and Cancer Registries also show an increase in the relative risk (RR) for Hodgkin's disease in HIV-infected individuals. It was 8.8% in the linkage study from San Francisco, 8.5% in the above-mentioned study from Australia[52], ? in the US and Puerto Rico[13], and 8.9% in Italy[14]. In some of these studies the incidence of HD increased significantly around the time of AIDS diagnosis, suggesting that the probability of HD is proportional to the degree of immunosuppression. All this evidence points out that an association between HD and HIV infection seems to be well established, although with a RR much lower than that for NHL. The two largest series of HD patients with HIV infection were reported from Italy[3] and Spain[74] and the risk factor in the majority of patients in both series was intravenous drug abuse.

Anal cancer

The occurrence of anal cancer has been strongly associated with HPV infection, particularly types 16 and 18[61], and there is evidence that such HPV types are found more frequently in HIV-positive than in HIV-negative homosexuals[75]. Furthermore, it has been shown that homosexual men with a history of receptive anal intercourse are at a higher risk of developing anal cancer than men in the general population[76].

Homosexual men were at increased risk of anal cancer even before the AIDS epidemic. Reports from Europe and the US showed that significant increases in the incidence of anal cancer started decades before the emergence of the AIDS epidemic[77-79]. Such increases were more apparent in urban than in rural areas and, with the lack of information on sexual orientation, among unmarried men than in married men, suggesting that relevant behavioural and environmental changes had occurred before the spread of HIV infection.

Most studies showing a positive association between HIV infection and anal cancer risk were carried out in metropolitan areas of the US (i.e., San Francisco and New York City). A linkage study of AIDS and cancer registries showed that anal cancer was 14 to 27-fold more common among HIV-

infected individuals (depending upon time from AIDS diagnosis) than in the general population[80]. Studies from Italy[14] and Africa[30] have failed to demonstrate such a positive association, or an increase in incidence rates of such neoplasm following the AIDS epidemic[81]. They had, however, low statistical significance, chiefly on account of relatively low proportions of homosexual and bisexual men among HIV-infected individuals.

In summary, the rise in incidence rates of anal cancer preceded the AIDS epidemic, and anal cancer is more common in population groups at risk for AIDS (i.e., homosexual men) even in the absence of HIV infection. It is difficult, therefore, to attribute to HIV a specific causal role in anal cancer onset.

Hepatocellular carcinoma

Rising trends of hepatocellular carcinoma in the first years of the AIDS epidemic led to the hypothesis that HIV infection might increase the risk of developing such neoplasm[82]. An increased frequency of hepatocellular carcinoma among individuals with HIV infection may be expected since such cancer is primarily caused by infection with hepatitis B virus (HBV) and/or with hepatitis C virus (HCV) –two sexually transmitted agents– and an increased risk has been reported among immunosuppressed transplant recipients before the introduction of blood screening for HBV and HCV[83]. However, later observations did not support a rise in hepatocellular carcinoma incidence as a consequence of HIV infection[84], nor was such evidence demonstrated in Africa[30].

In a linkage study between AIDS and Cancer Registries in the US, Goedert *et al.*[13] found, in the interval between 5 years prior to and 27 months after AIDS, a non-significant RR for hepatocellular carcinoma over 10.

Lung cancer

Some clinical reports suggested that lung cancer might be more frequent among HIV-positive individuals[85,86], and a small increase in lung cancer was noted in 1994 among unmarried men in the US[87]. Recent linkage studies[14,13,52] seem now to substantiate previous observations with a statistically significant 2-fold higher risk in all studies.

Miscellany

Many case reports and case-series suggest that various cancers might be increased among HIV-infected individuals[88,89]. These cancers include squamous cell carcinoma of the conjunctiva, a rare cancer for which the evidence of an association with HIV infection is very strong, but coming exclusively from African data[66], and leiomyosarcoma in children, an extremely rare tumour apparently linked to EBV infection. Case reports in HIV-infected children suggested that it occurs at higher rates than in the general population of the same age[2,90]. Testicular cancer[13,53], non-melanoma skin cancers[14] and cancer of the penis have also been reported to occur with an increased frequency in HIV-infected individuals.

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