ORIGINAL ARTICLE

HIV and Cancer in Germany

Manfred Hensel, Armin Goetzenich, Thomas Lutz, Albrecht Stoehr, Arend Moll, Jürgen Rockstroh, Nicola Hanhoff, Hans Jäger, Franz Mosthaf

SUMMARY

Background: Cancer is now the leading cause of death in persons with HIV. In this study, we gathered current epidemiological data on Aids-defining (AD) and non-Aids-defining (NAD) malignancies among HIV-positive patients in Germany.

Methods: From 2000 to 2007, all 35 specialized HIV outpatient clinics and 189 HIV ambulatory care centers in Germany were contacted and asked to fill out a structured questionnaire on the incidence of malignancies in HIV-positive patients during multiple periods of observation.

Results: 552 evaluable data sets were reported. 253 (45.8%) of the reported malignancies were AD. Among the 299 cases (54.2%) of NAD malignancies, there were 214 solid tumors, including 71 anal carcinomas (23.7% of all NAD malignancies), and 85 hematopoietic malignancies, including 29 cases of Hodgkin`s lymphoma (9.7% of all NAD malignancies). The high percentage of NAD malignancy remained constant throughout the entire period of the study. Only a single case of primary cerebral lymphoma was reported after 2001. The number of patients with Hodgkin`s lymphoma rose steadily from 2000 to 2007.

Conclusion: The spectrum of HIV-associated malignancies has changed since the early days of the HIV epidemic. In Germany, NAD malignancies have become more common than AD malignancies. In particular, anal carcinoma and Hodgkin's lymphoma are much more common among persons with HIV than in the general population. Persons with HIV need more intensive preventive care for cancer than non-infected persons do.

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Mannheimer Onkologie Praxis: Prof. Dr. med. Hensel

Deutsche Arbeitsgemeinschaft niedergelassener Ärzte in der Versorgung HIV-Infizierter e.V. (DAGNAE) Berlin: Goetzenich, Hanhoff, Dr. med. Jäger

Infektiologikum Frankfurt/Main: Dr. med. Lutz

ifi-Medizin GmbH, Asklepios Klinik St. Georg, Hamburg: Dr. med. Stoehr

Praxiszentrum Kaiserdamm, Berlin: Dr. med. Moll

Med. Universitätsklinik I, Bonn: Prof. Dr. med. Rockstroh

Gemeinschaftspraxis für Hämatologie, Onkologie und Infektiologie Karlsruhe: Dr. med. Mosthaf

Kerngruppe HIV und Onkologie der DAGNAE: Prof. Dr. med. Hensel, Dr. med. Mosthaf

The association between human immunodeficiency virus (HIV) / acquired immune deficiency syndrome (Aids) and cancer has been known since the early 1980s (e1). Particularly Kaposi sarcoma, invasive cervical carcinoma, and non-Hodgkin's lymphoma (NHL) have been found more frequently in HIV-infected and immune-deficient patients. The introduction of combined antiretroviral therapy (cART) in 1996 was followed by dramatic changes in the morbidity and mortality of HIV infection and especially in the spectrum of malignancies observed in HIV-infected patients. The incidence of Aids-defining (AD) malignancies has steadily declined, while the incidence of other malignancies, such as Hodgkin's lymphoma, invasive anal carcinoma, lung cancer, skin cancer, and hepatocellular carcinoma presents new challenges to those responsible for the treatment of these patients (1). Today malignant diseases are the commonest cause of death (2) and one of the most frequent reasons for hospitalization (3) in HIV-positive patients. The longer survival time as a result of cART only partially explains the growing incidence of non-Aids-defining (NAD) malignancies. The pathogenesis of these tumors is highly varied: some are associated with oncogenic viruses (e.g., Hodgkin's lymphoma and anal carcinoma), while others are influenced by environmental factors such as smoking and sunlight (e.g., lung cancer and skin cancer). The frequency of NAD malignancies has been described with increasing clarity in recent years, but the precise associations remain unclear (3–8). Ground-breaking investigations into the treatment of HIV-associated lymphomas have been conducted in Germany in the past few years (9–12), yet hardly any data exist on the epidemiology of HIV-associated cancers in Germany (13–15).

In the study reported here we set out to update and extend the DAGNAE study group's data on the epidemiology of AD and NAD malignancies in the HIV-positive population in Germany in the years 2000 to 2003 and to describe the trends in these illnesses over the past decade. Our findings provide the basis for an urgently required updated recommendation for tumor screening in HIV-positive individuals.

Patients and methods

In the year 2000 the HIV and Oncology Core Group of the German Study Group of Physicians in Private Practice Treating HIV-Infected Patients (*Deutsche Arbeitsgemeinschaft niedergelassener Ärzte in der Versorgung*

TABLE 1

Questionnaire (with fictive data)

Name code (analogous to Robert Koch Institute registration form)	Sex	Stage of HIV infection at diagnosis of malignancy	Malignancy type at first diagnosis	TNM or Ann Arbor stage (not applicable for acute leukoses)	Treatment for malignancy	Treatment response (complete remission, partial remission, no change, progression, not yet assessable)
Example 1: L6K3	M	C3	Aggressive B-cell Non-Hodgkin's lymphoma (immunoblastoma), diagnosed 01/07	III B	6 x R-CHOP 01/07–05/07	Complete remission
Example 2: G7M3	F	B2	Colon cancer, diagnosed 03/07	pT3 pN1(6/20) cM0	OP 08/07, 4 x FolFOx4 protocol, since 09/07	Not yet assessable

HIV-Infizierter, DAGNAE) cooperated with the Association of Hematologists and Oncologists in Primary Care in Germany (*Berufsverband der niedergelassenen Hämatologen und Onkologen*, BNHO) to initiate a project whose goal was to create a database of HIV-associated malignancies. An easy-to-use structured questionnaire was designed and sent to all members of DAGNAE and all specialized HIV outpatient clinics in Germany (n = 35) at the following time points: in 2002 for the incidence period 2000 to 2001, in 2003 for 2002, in 2006 for 2005, and in 2008 for 2007. The questionnaire was also available to the HIV physicians and DAGNAE members on the DAGNAE website and in the quarterly newsletter. The membership of DAGNAE embraces 189 HIV ambulatory care centers with a total of 235 regular members of the study group.

The questionnaire was kept simple to increase the chance of a high response rate *(Table 1)*. It asked for information on all newly diagnosed AD and NAD hematological neoplasms and solid tumors. The details requested were date of diagnosis, tumor stage, tumor treatment, and response to treatment. The United States Centers for Disease Control (CDC) stage of HIV and (from 2002 onwards) the patient's sex were also recorded.

All statistical analyses were carried out using SPSS software (release 16.0; SPSS Inc., Chicago, Illinois). Predominantly descriptive statistical methods were employed (mean, median, range, standard deviation). Relationships between individual variables were evaluated by means of the chi-square test. The results of the statistical tests were considered significant when the two-sided p-value did not exceed 5%.

Results

Completed questionnaires were returned by 111 centers (27.3% of them outpatient clinics, 72.7% ambulatory care centers). The overall response rate was thus 49.6%. A total of 552 evaluable sets of data on 542 patients were recorded during the observation period. Ten patients were represented by two data sets each because two different malignancies occurred at different times. The sex of 367 patients was recorded; 89% were male. The majority of patients showed advanced HIV disease (CDC stage C3) and thus had full-blown Aids. However, the proportion of patients with stage C3 disease decreased during the observation period, falling from 58% in 2000 to 36.8% in 2007.

Two hundred fifty-three (45.8%) of the registered malignancies were AD tumors: 132 Kaposi sarcomas, 109 aggressive B-cell lymphomas, and 12 invasive cervical carcinomas. The aggressive B-cell lymphomas included 28 Burkitt lymphomas, 30 diffuse large-cell B-cell lymphomas, 9 cases of Castleman disease, and 8 primary cerebral lymphomas, among others *(Figure 1)*.

The 299 (54.2%) NAD malignancies were made up of 214 solid tumors *(Figure 2)*, including 71 anal carcinomas (23.7% of all NAD malignancies), and 85 hemoblastoses, including 29 Hodgkin's lymphomas (9.7% of all NAD malignancies). The high proportion of NAD malignancies remained constant throughout the observation period *(Table 2)*.

On closer inspection of the AD and NAD malignancies over the course of the observation period, most subtypes showed no change in relative frequency. Exceptions were primary cerebral lymphoma and Hodgkin's lymphoma: Only one case of primary cerebral lymphoma (out of eight in total) was registered after 2001. The number of patients with Hodgkin's lymphoma rose continuously from 3 in 2000 to 8 in 2007.

Discussion

At the beginning of the Aids pandemic in the 1980s, the patients exhibited high rates of Kaposi sarcoma, invasive cervical carcinoma, and non-Hodgkin's lymphoma. Before 1995, all other malignancies together made up less than one third of all cancers in HIV patients (16). This was taken into consideration in the definition of the stages of Aids: the three typical malignancies

were termed "Aids-defining" and the presence of any of them led to assignment of the patient to the highest clinical category, stage C, in the CDC classification of HIV infection.

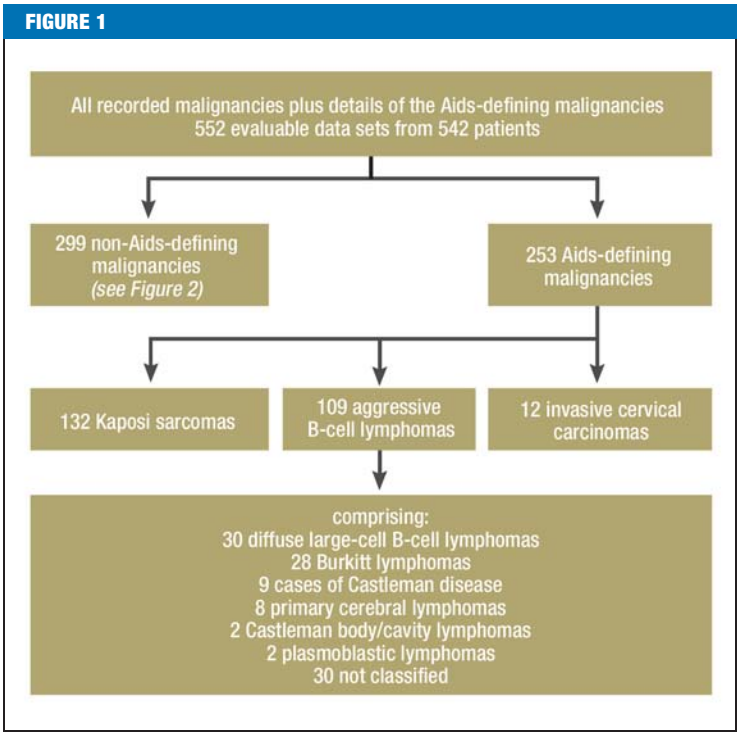
The most important finding of the present study is the observation that NAD malignancies outnumber AD malignancies in Aids patients in Germany. The incidence of HIV-associated malignancies remained stable in our cohort of patients from 2000 to 2007. Although Kaposi sarcoma (132 cases during the observation period) was still the most frequent cancer entity in HIV-infected persons, ahead of the aggressive lymphomas (109 cases), there were conspicuous numbers of anal carcinomas, skin tumors, bronchial carcinomas, and Hodgkin's lymphomas. Other classical cancers of the non-immune-suppressed were also observed, e.g., gastroesophageal carcinoma (8 patients), breast cancer (7 patients), and urothelial carcinoma (6 patients).

In summary, NAD malignancies occur two to three times more frequently in HIV-infected patients than in the general population, with a wide spectrum of variation depending on sex and tumor type (8). There are several reasons for this. A decisive part is played by the prolonged survival of HIV patients due to cART. Only since the introduction of cART do the large majority of HIV patients live long enough to fall victim to NAD malignancies. Another possible reason for the persisting elevated risk of cancer among HIV-infected persons is the higher prevalence of traditional risk factors such as smoking (45% to 50%), high alcohol consumption (10% to 15%), and coinfection with oncogenic viruses, including human papilloma virus (HPV) (e2) and hepatitis B and C (2, 8). Furthermore, the immune deficiency associated with HIV infection may contribute to the elevated cancer risk. It is feasible that the weakness of the immune system leads to a general reduction in the immune monitoring for malignant cells. Another possibility is that the immune system has a reduced capacity for suppression of oncogenic viruses and that this results in an increased risk of cancer (17, e2). This seems to have a particularly important role in the pathogenesis of the HIV-associated lymphomas, where chronic antigen stimulation and cytokine dysregulation are involved in addition to polyclonal B-cell stimulation and proliferation owing to the infection of T-lymphocytes with HIV (e3). Moreover, gamma herpesviruses play an important part as cofactors: the Epstein-Barr virus (EBV) genome is found in around 50% of all HIV-associated lymphomas (e4–e6).

The present study represents the largest set of data on the incidence of cancers in HIV-positive persons yet collected in Germany. The findings on the relative incidence of AD and NAD malignancies confirm recent observations from other countries (16, 18, 19). One of the largest databases of HIV-infected individuals in the world comes from California. Silberberg et al. showed that there, too, NAD malignancies occur more frequently than AD tumors (19). In a recent retrospective cohort study by this group of researchers, the cancer rate of 20 277 HIV-infected persons was compared with that of 202 313 "matched" people without HIV from the same region of California. The cohort of HIV-infected persons contained 609 NAD and 502 AD malignancies (20). The ratio of NAD to AD malignancies was thus 1.21, comparable with the NAD:AD ratio of 1.18 in our study. In the Californian study the incidence of AD malignancies was 34.7 times greater in HIV-infected than in non-infected persons. Among the NAD malignancies, the potentially infection-associated tumors (cancers of the vagina, vulva, penis, and anus; squamous epithelial carcinomas of the oral cavity and the pharynx; hepatitis B- and C-associated liver cancers; stomach cancer; Hodgkin's lymphoma) were 9.2 times as common as in non-HIV-infected people. The non-infection-associated malignancies, however, were only 1.3 times more frequent.

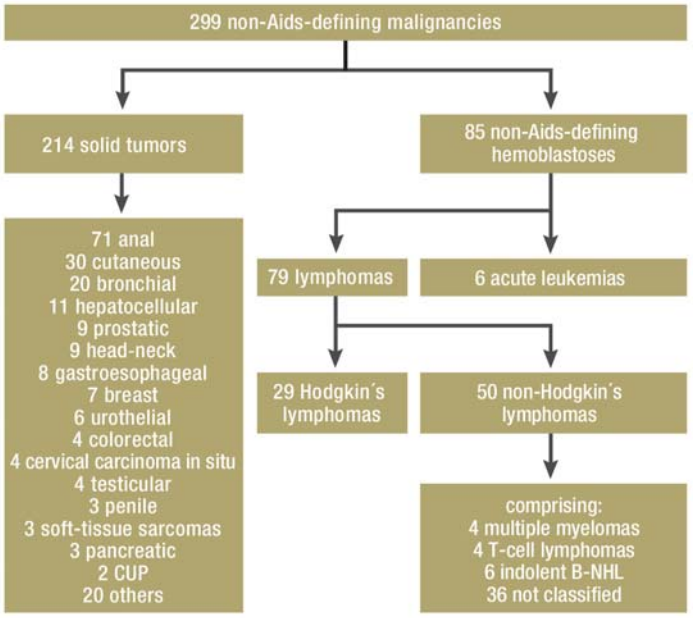
Data from cancer registries in Colorado, Florida, and New Jersey show that NAD malignancies made up only 31.4% of all cancers in HIV patients in the period 1991 to 1995, but 58% between 1996 and 2002 (16). The incidence of Kaposi sarcoma and NHL sank with time, but was still higher than in the general population in the latter period. The incidence of Hodgkin's lymphoma and hepatocellular carcinoma was higher in the period 1996 to 2002 than in 1991 to 1995 (16). This agrees with our finding of a continuous increase in the incidence of Hodgkin's lymphoma during the observation period. Investigation of a French cohort comprising nearly 80 000 HIV-infected persons showed 32 times higher incidence of Hodgkin's lymphoma in men and 14 times higher incidence in women (1). Interestingly, a

FIGURE 1



Malignancies in HIV patients from 111 German centers in the years 2000–2002, 2005, and 2007

FIGURE 2



Non-Aids-defining malignancies; CUP, cancer of unknown primary; NHL, non-Hodgkin's lymphoma

recent report from the Swiss HIV cohort study, in which 14 606 HIV-infected persons are being followed up for 20 years, showed that the risk of contracting Hodgkin's lymphoma has not increased in recent years in Switzerland. Moreover, there was no indication that the risk of Hodgkin's lymphoma increases with improving immune status (21).

Diffuse large-cell non-Hodgkin's lymphoma, which are assigned to the AD malignancies, occur preferentially in patients with strongly depressed CD4 cell counts. In contrast, Burkitt lymphoma and Hodgkin's lymphoma typically occur in patients with medium to high numbers of CD4 cells. This leads to the supposition that there are distinct etiological mechanisms resulting in lymphoma. It has been proposed that precisely Burkitt and Hodgkin's lymphomas can arise from chronic antigen stimulation, cytokine dysregulation, and the association with oncogenic viruses such as EBV or HHV-8 (22).

We witnessed only one case of primary cerebral lymphoma after 2001. Primary cerebral lymphomas were previously typically diagnosed in HIV patients with severe immune suppression. Since the introduction of cART, however, the incidence of this rare subgroup of lymphoma has decreased greatly (23).

A recent case control study from Italy compared clinical manifestations and outcome between HIV-positive and HIV-negative patients with colorectal carcinoma (CRC). Relative to the HIV-negative patients, the HIV-positive individuals showed lower performance status, less favorable Dukes stage, poorer grading, and shorter survival (24). In particular, the HIV-positive patients had a median age of 48 years at the time of CRC diagnosis, while three quarters of the HIV-negative patients were over 65 when CRC was detected. The majority of HIV-positive patients developed CRC very early in the course of their HIV disease; only few patients (5/27) developed another AD malignancy earlier. Because of this age difference the authors recommend that screening colonoscopy of HIV-positive patients should begin at the age of 45 years.

Anal carcinoma was the most frequent of the NAD malignancies in the present study (71 cases, 24%). The relative risk for anal carcinomas is estimated to be 30 to 60 times higher for HIV-positive patients than for the general population (13). This may be related to the greatly increased risk of anal HPV infections in HIV-positive patients. The persisting HPV infection gives rise to anal intraepithelial neoplasia, from which anal carcinoma may develop. In agreement with other groups, we recommend specific screening for anal carcinoma at least annually (25).

Our study has some limitations, for example the retrospective design. No doubt some of the malignancies that occurred in the incidence periods went undocumented, almost certainly leading to underestimation of case numbers. We can thus assume that the absolute incidence of cancer was underestimated. However, this probably had no influence on the calculation of relative frequency, which was our primary concern, and most likely also had no impact on the development of cancer frequency at the different time points. Furthermore, the composition of the centers that contributed patients to the study differed somewhat from that of all centers contacted (15.6% of the centers contacted were hospital outpatient clinics, compared with 27.3% of the contributing centers). This difference, too, likely had no decisive influence on the above-mentioned goals of the study.

TABLE 2

Proportions of Aids-defining and non-Aids-defining malignancies during the observation period (differences between years not significant: chi-square test p = 0.2)

Year*	n	Aids-defining (%)	Non-Aids-defining (%)
2000	81	42	58
2001	104	53.8	46.2
2002	133	47.4	52.6
2005	128	39.8	60.2
2007	106	46.2	53.8

* year of cancer diagnosis

Conclusion and recommendation for cancer screening in HIV-positive patients

Alongside advances in antiretroviral therapy and the development of curative treatment strategies, the

TABLE 3

Recommendations for cancer screening

Problem	Patients/age	Procedure	Evidence of benefit	Interval	Remarks
Cervical carcinoma	Women ≥ 20 years	Gynecological genital examination, swab, and cytology	Cervical carcinoma mortality ↓	1 year	
Breast cancer	Women 50–69 years	Mammography	Breast cancer mortality ↓	2 years	
Anal carcinoma	Men and women with receptive anal intercourse	Inspection of anus and genitals, digital rectal examination (DRE), on conspicuous findings: high-resolution anoscopy and proctoscopy	Unknown, but recommended by some experts; swab with cytology insufficiently validated	1 year	Not yet recommended for HIV-negative patients in Germany
Skin cancer	Men and women ≥ 35 years	Skin cancer screening	Controversial		
Colorectal carcinoma	Men and women ≥ 45 years	Colonoscopy (secondarily: examination of stool for occult blood)	Colorectal carcinoma mortality ↓ in HIV-negative patients	5–10 years	Recommended only from age 55 years for HIV-negative patients in Germany
Prostate cancer	Men > 45 years	DRE ± PSA test	Controversial	1 year	Only DRE recommended for HIV-negative patients in Germany

Cancer screening procedures that are generally recommended and funded by the statutory health insurers in Germany (source: AOK 2009). Adapted for HIV-positive patients by the authors, taking account of the November 2009 guidelines of the European Aids Clinical Society.

growing life expectancy of HIV-infected individuals means that an increasingly important role will be played by the prevention and treatment of HIV-associated comorbidity, particularly cancer. Tumor screening and cancer prevention should be intensified and performed in painstaking manner *(Table 3)*. In this respect, special attention should be paid to anal carcinoma.

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Conflict of interest statement
Dr. Lutz: Consultancy (advisory board) and lectures for Roche Pharma AG, MSD, Abbott, Gilead Sciences, and Boehringer-Ingelheim.
Prof. Rockstroh: Consultancy (advisory board) and lectures for Abbott, BMS, Boehringer-Ingelheim, Gilead, GSK, MSD, Novartis, Pfizer, Roche, Schering-Plough, Tibotec, and Vertex.
Dr. Mosthaf: Consultancy (advisory board) and lectures for Abbott, BMS, Boehringer-Ingelheim, Gilead, Roche, and ViiV.
The remaining authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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KEY MESSAGES

- Malignancies are increasingly responsible for morbidity and mortality in HIV-infected persons.
- The so-called non-Aids-defining malignancies have now come to the fore.
- Particularly anal carcinoma and Hodgkin's lymphoma show a pronounced increase in relative incidence.
- The HIV-associated malignancies occur earlier and have a more aggressive course.
- A general recommendation for intensified cancer screening seems warranted.

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Corresponding author
Prof. Dr. med. Manfred Hensel
Mannheimer Onkologie Praxis
Q 5, 14–22, 68161 Mannheim, Germany
hensel@mannheimer-onkologie-praxis.de

For eReferences please refer to:
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