Acquired Immunodeficiency Syndrome-Associated Non-Hodgkin’s Lymphomas and Other Malignancies in Patients With Hemophilia


Non-Hodgkin’s lymphoma (NHL) is the most common human immunodeficiency virus (HIV)-associated malignancy in hemophiliacs. We studied the incidence and clinicopathologic features of NHL in 3,041 hemophiliacs followed at 18 US Hemophilia Centers between 1978 and 1989. Of the 1,295 (56.6%) who were HIV(+), 253 (19.5%) developed acquired immunodeficiency syndrome (AIDS), of whom 14 (5.5%) developed NHL. Three NHL occurred in HIV(−) hemophiliacs, for a 36.5-fold greater risk in HIV(+) than HIV(−) hemophiliacs (P < .001). The NHL incidence rate was 29-fold greater than in the US population by Surveillance, Epidemiology, and End Results (SEER) estimates (P < .001). Between 0 and 4 lymphomas have been observed per year between 1978 and 1989. At presentation 13 (92.3%) of the HIV (+) NHL were extranodal. Ten were stage IV, 1 stage II, and 3 stage IE. Ten (71.4%) were high-grade, 3 (21.4%) intermediate-grade, and 1 (7.1%) was a low-grade B-cell lymphoma. Epstein-Barr virus (EBV) DNA was detected in 36% by in situ hybridization, including one central nervous system (CNS) lymphoma. The mean CD4 cell count at NHL diagnosis was 64/mm^3, the mean latency from initial HIV infection was estimated to be 59 months, and the median survival was 7 months. The incidence of basal cell carcinoma in HIV(+) hemophiliacs was 18.3-fold greater than in HIV(−) hemophiliacs (P < .0001) and 11.4-fold greater than in the US population (P < .001). In conclusion, incidence rates of NHL and basal cell carcinoma in HIV(+) hemophiliacs are significantly increased over rates in HIV(−) hemophiliacs and over rates in the US population. Clinicopathologic presentation of NHL in HIV(+) hemophiliacs is similar to that in HIV(+) homosexual men.

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One of the most common malignancies associated with human immunodeficiency virus (HIV) infection is non-Hodgkin’s lymphoma (NHL), initially described in 1982, but not recognized as an acquired immunodeficiency syndrome (AIDS)-defining illness until 1985. Typically, lymphomas associated with HIV infection are aggressive, high-, or intermediate-grade B-cell lymphomas, often with extranodal presentation involving the gastrointestinal tract, central nervous system, bone marrow (BM), and liver. The response to chemotherapy is poor, and the mortality rate is high. Similar to lymphomas occurring in other immunodeficiency states, Epstein-Barr virus (EBV) has been detected in one third to one half of AIDS-associated lymphomas, although whether EBV plays a role in the pathogenesis of these lymphomas remains unknown.

The incidence of NHL in HIV-infected individuals has been increasing since the onset of the AIDS epidemic, with a fourfold increase in homosexual men in San Francisco 1975-78 to 1982-85 by Surveillance, Epidemiology, and End Results (SEER) temporal trends. Centers for Disease Control (CDC) estimates that 3% of reported AIDS-defining illnesses are NHL, a figure that likely underestimates the incidence of NHL because NHL was not an AIDS-defining illness until 1985 and because CDC reporting requires only the first AIDS diagnosis, thus potentially missing 25% of NHL occurring as a second or later AIDS diagnosis. With the treatment advances for HIV infection, including zidovudine and Pneumocystis carinii prophylaxis, and improved life expectancy of AIDS patients, a marked increase in HIV-associated lymphomas has been observed, and projections suggest this trend will continue.

AIDS-associated lymphomas have been studied primarily in homosexual men, with little known about lymphomas in HIV(+) hemophiliacs. NHLs have consistently represented a higher proportion of AIDS-defining illnesses in hemophiliacs than in homosexual men: in 1988, 4.7% versus 1.5%; in 1989, 4.6% versus 1.5%; and, in 1990, 4.6% versus 3.1%, respectively (John Murphy, MD, and Frank de Stefano, MD, Centers for Disease Control, personal communication, August 1988 and August 1990). Further, although there has been a reported doubling in NHL as AIDS-defining illnesses from 1.5% to 3.1% over the last 3 years, this trend has not been reported in hemophiliacs. Although unsubstantiated, potential lymphoma incidence differences between homosexual and hemophilic men might relate to lifestyle and viral or antigenic exposure differences or differences in survival following AIDS diagnosis between these groups. The median survival after AIDS was 0.5 years in hemophiliacs receiving no antiviral therapy, and 2.1 years in those treated with antiviral therapy, barely reaching the minimal 2-year survival on antiretroviral therapy, during which increased lymphoma incidence has been observed.

As previous studies of AIDS-associated lymphomas and cancers have included few, if any, hemophiliacs, we studied the incidence and clinicopathologic features of NHL and other malignancies in 3,041 US hemophiliacs enrolled in the Hemophilia Malignancy Study (HMS), to characterize the epidemiology of HIV-associated cancers in hemophiliacs.
MATERIALS AND METHODS

The HMS is a multicenter study of over 3,041 individuals with hemophilia from 18 US Hemophilia Treatment Centers in the 10 Health and Human Services geographic regions. Primary goals of this study are to determine the incidence, risk factors, clinicopathologic, and molecular-biologic characteristics of AIDS-associated malignancy in the hemophilia population. This report summarizes the findings of the Retrospective Study, which is a retrospective review of all past AIDS cases, malignancies, and deaths in HIV(+) and HIV(−) hemophiliacs between January 1, 1978 and December 31, 1989. Data were collected by the nurse coordinator at each center through chart review and data abstraction. These data form the basis for determining the incidence of AIDS, lymphoma, and other cancers in HIV(+) and HIV(−) hemophiliacs. Data entry and management were performed by a Central Coordinating Center. Inconsistencies and missing data were tracked and reviewed with the nurse coordinator by the Pittsburgh project coordinator. Autopsy and pathologic biopsy slides and paraffin blocks from past AIDS or HIV(+) related deaths were collected by each nurse coordinator and sent to the coordinating center, catalogued and coded, and histopathologically classified by independent pathologic review (R.A.J.). All death reports were corroborated by physician report, hospital record, health records, autopsy report, and slides from the autopsy.

Cut slides or paraffin blocks were received from 14 of the patients with lymphomas. Glass slides only were reviewed on the three others. In addition to the usual histochemical stains, hematoxylin/eosin, Periodic acid Schiff, and giemsa stains, immunohistochemistry was performed using an avidin-Biotin detection system (PBC Elite; Vector, Burlingame, CA). The antibodies used were common leukocyte antigen (CLA, CD45), B cell (L-26, CD20), T cell (UCHL-I, CD45R0, and Leu 22 (Becton Dickinson, San Jose, CA) and K-P-1 (a gift from Dr D. Mason, Oxford, England). Dilutions were titrated against known positive biologic controls, one of which was run with each batch, and the negative controls consisted of substitution of a mouse Ig isotype for each antibody.

EBV-DNA was detected in paraffin-embedded tissues after protease digestion using a commercial kit from Digene (Silver Spring, MD) following manufacturer’s directions and using a known positive control processed to paraffin in our own laboratory. A cytomegalovirus (CMV) probe, from the same source, was used as the probe control.

Dates of seroconversion were imputed as the midpoint between the date of the last negative HIV test and the first positive HIV test when both dates were known. These data were only available on 190 subjects. However, 17 had other risk factors or lapes in treatment, and thus only 173 were available for analysis. For the other 1,231 patients who either tested HIV positive, or were presumed positive, the date of seroconversion was estimated to be June 10, 1982 for individuals with hemophilia A, or October 11, 1983 for individuals with hemophilia B. These dates were based on the median date of seroconversion for hemophilia A and B, respectively, for the 173 with known dates of last negative and first positive HIV antibody test.

Cancer incidence in the cohort was compared with the general population, using SEER age-specific rates for all males 1984 to 1988. Age-specific incidence rates for basal cell cancers among males were obtained from the Mayo Clinic registry. Expected numbers of cancers in the HIV(+) and HIV(−) cohorts, respectively, were obtained by applying these rates to the person-years of observation in each cohort. With the exception of a single case of Kaposi’s sarcoma, observed and expected numbers of malignancies are reported for all malignancies in which at least one case was reported.

For each malignancy the number of person-years of observation were calculated separately for the HIV(−) and HIV(+) cohorts. With a single exception, person-years for the HIV(−) cohort were accrued from the time of birth until whichever came first: diagnosis with the cancer, seroconversion, last visit to the hemophilia center, or death. The exception is one of the patients diagnosed with leukemia 2 years after his last visit to a hemophilia center. His person-years of observation are only included until the date of diagnosis of leukemia. Person-years in the HIV(+) cohort were accrued from the date of seroconversion to whichever came first: diagnosis with cancer, last visit to the hemophilia center, or death.

Observed and expected deaths were compared statistically using a test for the ratio of a Poisson variable to its expectation. Chi square analysis was used to compare lymphoma incidence differences and relative risks for cancers and lymphomas between HIV(+) and HIV(−) hemophiliacs. Kaplan-Meier time-limit estimates were constructed for the proportion surviving following first AIDS diagnosis and for the proportion surviving following lymphoma diagnosis.

RESULTS

A total of 3,041 patients with hemophilia A or B, cared for at 18 US hemophilia-treatment centers, between January 1, 1978 and December 31, 1989, were enrolled in the study. Of these, 2,420 (79.6%) had been tested for HIV antibody, of whom 1,295 (56.6%) were HIV antibody positive (1,198 or 92.5% Western blot confirmed) and 1,125 (37.0%) were HIV antibody negative. Of the 621 remaining patients, including 576 untested and 45 unknown if tested, a total of 126 were presumed positive because of a diagnosis of severe hemophilia A treated with factor VIII concentrate between 1978 and 1986, the peak period of HIV transmission in hemophiliacs, and because over 90% of this group has become HIV infected. A total of 206 were presumed HIV negative, including 130 never exposed to any blood products and 76 exposed to blood products before 1978 or after 1986, and 289, the remainder, whose risk of HIV infection could not be accurately determined. The reasons given for lack of HIV testing in 576 untested hemophiliacs included: (1) testing was unavailable (before 1985) in 217 (37.7%); (2) patient was too young (birth or exposure after 1986) in 121 (21.0%); (3) patient refused testing for confidentiality reasons in 94 (16.3%); (4) patient had no or little lifetime exposure (not related to young age) in 87 (15.1%); (5) no reason given in 39 (6.8%); and (6) limited follow-up of the patient precluded testing in 18 (3.1%). The median age in those presumed HIV positive was nearly identical to the age of those known HIV(+), while those presumed HIV(−) were much younger than those known HIV(−), reflecting the time of exposure (after 1986) and much lower presumed risk of HIV infection after 1986, related to availability of safer blood products.

Of the 1,295 HIV(+) hemophiliacs, 253 (19.5%) had developed AIDS by December 31, 1989, with the peak frequency in 1988 (1 in 1981, 1 in 1982, 4 in 1983, 7 in 1984, 15 in 1985, 34 in 1986, 47 in 1987, 75 in 1988, 64 in 1989, and 5 unknown). Fourteen (5.5%) developed NHL, 10 (71.4%) as a primary AIDS diagnosis and 4 (28.6%) in patients with a prior diagnosis of AIDS. Three HIV(−) individuals presented with NHL, at a median age of 63.0 years, compared with 31.9 years in HIV(+) patients with NHL. There was a 36.5-fold greater risk of NHL in HIV(+) patients; 14 per 8,549.9 per-
AIDS-ASSOCIATED LYMPHOMAS IN HEMOPHILIACS

The 14 HIV-associated NHL occurred in 13 hemophilia A patients and 1 hemophilia B patient, including 12 with severe disease (<0.01 U/mL factor activity), and 2 with moderate disease (0.01 to 0.04 U/mL) (Table 2). All had been treated with clotting-factor concentrates. Only three had received antiretroviral treatment for HIV infection. One of the latter and one additional HIV(+) patient were also treated with the antiviral acyclovir, one for concomitant oral herpes simplex virus infection. It should be clarified that patient nos. 1, 2, 3, 5, 7, 8, 10, 11, 13, and 14 are truly AIDS-defining, as they were systemic and occurred as a primary AIDS-defining illness: the remaining four, nos. 4, 6, 9, and 12, are HIV-related but not truly AIDS defining by the CDC definition.2 Of the 14 HIV(+) NHL, 10 (71.4%) were high-grade, 3 (21.4%) intermediate-grade, and 1 (7.1%) low-grade by the National Cancer Institute Working Formulation.31 The high-grade NHL included nine diffuse large-cell immunoblastic and one diffuse undifferentiated Burkitt’s lymphomas. The intermediate-grade NHL included two diffuse, large cell noncleaved, and one diffuse, mixed small and large cell lymphoma. The single low-grade NHL was a follicular, small cell cleaved lymphoma.

Ten of the HIV-associated lymphomas (71.4%) were stage IV at presentation; the remaining four included three stage IE and one stage II. All but 1 HIV-associated NHL were extranodal at presentation, including 4 gastrointestinal, 4 intrathoracic (including 3 occurring in the liver and 1 occurring in the spleen with an associated abdominal mass), 2 central nervous system (CNS), and 1 each BM, parotid gland, and subcutaneous skin of the thigh. The single nodal NHL was located in the axilla. Bilaterally: the latter was the only stage II NHL. Ten of 10 tumors (100%) tested showed reactivity with the L-26 B-cell marker, and were unreactive with the UCHL-1 and Leu 22 T-cell markers. Immune phenotype, determined on three, showed IgMk in two and IgMX in one.

EBV was detected in 4 of 11 (36.4%) lymphomas tested by DNA probe, while one CNS lymphoma (no. 2) was EBV(+) by DNA probe and showed c-myc gene rearrangement. The mean latency of the 14 HIV(+) lymphomas was 59.0 months from the date of known or estimated seroconversion (range 20 to 122, median 60.5 months). The median CD4 at NHL diagnosis was 39/mm³, or 41/mm³ in the seven systemic

Table 1. Age-Adjusted Lymphoma Rates in HIV(+) and HIV(−) Hemophilic Men

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Person-yrs</th>
<th>Expected</th>
<th>Observed</th>
<th>Person-yrs</th>
<th>Expected</th>
<th>Observed</th>
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<tr>
<td>0-9</td>
<td>991.2</td>
<td>.01</td>
<td>0</td>
<td>26,289.7</td>
<td>.23</td>
<td>0</td>
</tr>
<tr>
<td>10-19</td>
<td>2381.4</td>
<td>.04</td>
<td>4</td>
<td>18,246.9</td>
<td>.32</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>2,627.7</td>
<td>.08</td>
<td>3</td>
<td>11,217.8</td>
<td>.34</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>1,861.7</td>
<td>.13</td>
<td>3</td>
<td>5,672.8</td>
<td>.49</td>
<td>1</td>
</tr>
<tr>
<td>40-49</td>
<td>623.7</td>
<td>.10</td>
<td>2</td>
<td>2,908.4</td>
<td>.45</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>238.2</td>
<td>.06</td>
<td>0</td>
<td>1,458.1</td>
<td>.39</td>
<td>0</td>
</tr>
<tr>
<td>60-69</td>
<td>83.2</td>
<td>.04</td>
<td>2</td>
<td>553.3</td>
<td>.26</td>
<td>0</td>
</tr>
<tr>
<td>70-79</td>
<td>15.6</td>
<td>.01</td>
<td>0</td>
<td>127.9</td>
<td>.10</td>
<td>1</td>
</tr>
<tr>
<td>≥80</td>
<td>7.3</td>
<td>.01</td>
<td>0</td>
<td>14.7</td>
<td>.02</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>8,549.9</td>
<td>.48</td>
<td>14*</td>
<td>66,789.4</td>
<td>2.60</td>
<td>3</td>
</tr>
</tbody>
</table>

* The observed to expected ratio in HIV(+) hemophiliacs is 14/0.48 or 29.12 and for HIV(−) hemophiliacs is 3/2.60 or 1.15.
Table 2. Clinicopathologic Characteristics of Lymphomas in Hemophiliacs

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Hemophilia Type/Severity</th>
<th>CD4 at DX No./mm³</th>
<th>AIDS DX 1° or 2°</th>
<th>Latency*</th>
<th>Site</th>
<th>Grade</th>
<th>Histopathology</th>
<th>DNA Probes</th>
<th>Treatment</th>
<th>Survival†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>38</td>
<td>A, Severe</td>
<td>9</td>
<td>1°</td>
<td>46</td>
<td>CNS</td>
<td>High</td>
<td>Diffuse large cell immunoblastic, plasmacytoid</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2.</td>
<td>12</td>
<td>A, Severe</td>
<td>20</td>
<td>1°</td>
<td>76</td>
<td>Liver</td>
<td>Intermediate</td>
<td>Diffuse large cell non-cleaved</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td>42</td>
<td>A, Severe</td>
<td>269</td>
<td>1°</td>
<td>122</td>
<td>Parotid</td>
<td>High</td>
<td>Diffuse large cell immunoblastic</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4.</td>
<td>18</td>
<td>A, Severe</td>
<td>ND</td>
<td>2°</td>
<td>88</td>
<td>CNS</td>
<td>High</td>
<td>Diffuse large cell immunoblastic, plasmacytoid</td>
<td>-</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>5.</td>
<td>23</td>
<td>B, Severe</td>
<td>ND</td>
<td>1°</td>
<td>23</td>
<td>GI</td>
<td>High</td>
<td>Diffuse large cell immunoblastic, plasmacytoid</td>
<td>+</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>6.</td>
<td>44</td>
<td>A, Severe</td>
<td>ND</td>
<td>2°</td>
<td>51</td>
<td>Liver</td>
<td>High</td>
<td>Diffuse large cell immunoblastic</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7.</td>
<td>15</td>
<td>A, Severe</td>
<td>41</td>
<td>1°</td>
<td>27</td>
<td>GI</td>
<td>High</td>
<td>Diffuse large cell immunoblastic</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8.</td>
<td>17</td>
<td>A, Severe</td>
<td>37</td>
<td>1°</td>
<td>66</td>
<td>BM</td>
<td>High</td>
<td>Burkitt's</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>9.</td>
<td>34</td>
<td>A, Severe</td>
<td>74</td>
<td>2°</td>
<td>37</td>
<td>LN</td>
<td>Intermediate</td>
<td>Diffuse mixed, small &amp; large cell</td>
<td>ND</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>10.</td>
<td>21</td>
<td>A, Severe</td>
<td>41</td>
<td>1°</td>
<td>69</td>
<td>Skin</td>
<td>High</td>
<td>Diffuse large cell immunoblastic, pleomorphic</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>11.</td>
<td>34</td>
<td>A, Severe</td>
<td>ND</td>
<td>1°</td>
<td>20</td>
<td>Abdominal mass/spleen</td>
<td>High</td>
<td>Diffuse large cell immunoblastic</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12.</td>
<td>60</td>
<td>A, Moderate</td>
<td>ND</td>
<td>2°</td>
<td>64</td>
<td>GI</td>
<td>High</td>
<td>Diffuse large cell immunoblastic</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>13.</td>
<td>29</td>
<td>A, Moderate</td>
<td>ND</td>
<td>1°</td>
<td>57</td>
<td>GI</td>
<td>Intermediate</td>
<td>Diffuse large cell, non-cleaved</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14.</td>
<td>60</td>
<td>A, Severe</td>
<td>21</td>
<td>1°</td>
<td>79</td>
<td>Liver</td>
<td>Low</td>
<td>Follicular small cell cleaved</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

| 31.9 ± 4.2 | 39/mm³ |
| (mean)     | (median) |
| 58.9 ± 7.5 | (mean) |

| HIV (−) |          |                          |                  |                  |          |      |       |                |            |           |           |
|---------|----------|--------------------------|------------------|------------------|----------|      |       |                |            |           |           |
| 15.    | 33       | A, Severe                | —                | —                | CNS      | Intermediate | Diffuse large cell, cleaved | +          | -         | -         | +         | -         | 1         |
| 16.    | 75       | A, Mild                  | —                | —                | LN       | Low   | Follicular small cell | +          | -         | -         | +         | -         | 36        |
| 17.    | 81       | B, Mild                  | —                | —                | BM       | Low   | Follicular mixed, small & large cell | +          | -         | +         | -         | 10        |

| 63.0 ± 15.1 | (mean) |

EBV is Epstein-Barr virus DNA in-situ; LMP is latent membrane protein, immunologic; CH = chemotherapy; IR = irradiation; AV = antiviral therapy.

* Latency indicates time in months from known or imputed seroconversion to the development of the lymphoma.
† Survival is indicated in months.
‡ Zidovudine.
§ Tissue unavailable or insufficient for pathology review. Diagnosis given is that of local pathologists.
|| Acyclovir.
NHL. The median survival for the 14 lymphomas in HIV(+)
hemophiliacs was 7 months; by contrast, the median survival
after AIDS diagnosis in this cohort (n = 253) was 16 months
(Fig 1). The longest survivals in HIV-associated NHL, 80
and 50 months, occurred in patients receiving both chemotherapya
tand antiretroviral treatment: these were also among
the younger patients developing lymphoma (age 23 and 15
years, respectively). The three CNS lymphomas (2 of which
were HIV(+)) showed a median survival of 1 month.

The three HIV(−) lymphomas (Table 2) occurred in a 33-
year-old patient with severe hemophilia A in 1978, likely
before exposure to HIV, and in 2 older patients with mild
hemophilia, 1 a 75-year-old with mild hemophilia A, treated
only with cryoprecipitate, and the other an 81-year-old with
mild hemophilia B, never treated with blood products.
The former was a high-grade lymphoma of the CNS, and the latter
2, 1 intermediate-grade diffuse lymphocytic poorly differ-
entiated lymphomas, stage II, presenting in axillary lymph
nodes and the other a low-grade nodular mixed small- and
large-cell lymphoma, stage IV, presenting in the BM. All three
were L-26 positive, B-cell tumors. All three were EBV negative
by DNA probe. The median survival in HIV(−) NHL was
10 months. None of these three were known to be farmers
or had a history of chemical exposure.

Basal cell carcinoma was the next most common malign-
nancy occurring in hemophilic men (Table 3). There was an
18.3-fold greater incidence of basal cell carcinoma in HIV(+),
7 per 8534.1 person-years, (82.0 per 100,000 person-years),
compared with HIV(−) hemophiliacs, 3 in 66,777.0 person-
years (4.0 per 100,000 person-years), P < .0001. The mean
age at which basal cell carcinoma occurred in HIV(+) men
was 40 years, as compared with 55 years in HIV(−) hemophiliic
men. When compared with the US population incidence
dates per as per Mayo Clinic estimates,17 (Christopher
Chute, MD, MPH, Mayo Clinic, personal communication,
November 1991), there was an 11.4-fold greater incidence in
basal cell carcinoma in HIV(+) hemophiliacs (P < .001).
The age-adjusted basal-cell carcinoma incidence was signif-
ificantly lower in HIV(−) hemophiliacs than the US population
(P < .01). The incidence rates of all other observed cancers
were not significantly different from expected using SEER
estimates (P > .05)18: the only exception was the significantly
lower incidence of lung carcinoma in HIV(−) hemophiliacs
than in the US population (P < .001) (Table 4).

Two cancers were diagnosed at autopsy. These occult can-
cers included one hepatocellular carcinoma and one prostatic
carcinoma. The incidence of hepatocellular carcinoma was
less than 1% among hemophiliacs overall, and not signifi-
cantly different between HIV(+) and HIV(−), with 1 per
8554.8 person-years compared with one per 66,789.4 person-
years, respectively. The only case of Kaposi’s sarcoma oc-
curred in an HIV(+) hemophilic man who was also homo-
sexual. Overall, cancers occurred a mean 13 years earlier in
HIV(+) than HIV(−) hemophiliacs.

A total of 226 deaths occurred in this cohort through De-
CEMBER 31, 1989. Data were obtained by medical records in
174 (77.0%), by physician in 52 (23.0%), by family or next
of kin in 38 (18.6%), and/or by death certificate in 42 (18.6%).
The three leading causes of death were AIDS in 121 (56%),
bleeding in 43 (19%), and liver disease in 22 (10%). Autopsies
were obtained in 18 (8%) with the detection of two occult
malignancies (11%), as noted above.

**DISCUSSION**

NHL is over 36 times more common in HIV(+) than
HIV(−) hemophilic men. Although only 10 of the 14 HIV(+)
hemophilia patients with NHL were truly AIDS-defining by
the CDC definition,2 for purposes of this discussion, we have
included all NHL in HIV(+) hemophiliacs. The lymphoma
incidence among AIDS cases is 5.5%, which is similar to the
proportion in San Francisco AIDS cases (7%)23 and to the
proportion of AIDS-associated lymphoma reported to the
CDC (3%).20 Compared with the US population by SEER
rates, the observed age-adjusted incidence rates of NHL in
HIV(+) hemophiliacs is 29-fold greater. This figure is some-
what lower than the 60-fold risk estimated by Beral et al21 in
a CDC study of primarily homosexual men or the 100-fold
risk estimated by Rakhlin et al22 from the San Francisco SEER
registry. However, unlike the CDC and SEER registry data,
the source of our data was the comprehensive medical records
from hemophilia treatment centers, which contain both in-
patient and outpatient outcome information, as well as the
results of HIV testing. Seroconversion data were available,
thereby providing an estimate of whether observed NHL were
HIV-related or unrelated. With this method, there was a ten-
dency to be more conservative, as seen in one patient (no.
15) who developed NHL in 1978, 4 years before the 1982
imputed seroconversion date; thus, his lymphoma was des-
dignated HIV-unrelated, although his severe hemophilia A
and chronic factor-concentrate exposure put him at great risk for
early HIV infection. However, if we were to assume his lymph-
oma was HIV-related, we would have to make two assump-
tions, each of which alone is unlikely. First, we would
have to assume he became infected at least 2 years earlier
than the other hemophiliacs in the United States, and spe-
cifically other hemophiliacs in his state of residence, Penn-
sylvania, where the earliest seroconversions in hemophiliacs
occurred in 1978 and 1979.10 This seems very unlikely. We

**Table 3. Age-Adjusted Basal Cell Carcinoma Rates in HIV(+) and HIV(−) Hemophilic Men**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Person-</th>
<th>Expected</th>
<th>Observed</th>
<th>Person-</th>
<th>Expected</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>991.2</td>
<td>.00</td>
<td>0</td>
<td>26,289.7</td>
<td>.00</td>
<td>0</td>
</tr>
<tr>
<td>10-19</td>
<td>513.8</td>
<td>.06</td>
<td>0</td>
<td>18,246.9</td>
<td>.40</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>5,628.8</td>
<td>.36</td>
<td>0</td>
<td>11,271.8</td>
<td>1.44</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>1,582.1</td>
<td>.89</td>
<td>2</td>
<td>5,966.8</td>
<td>3.36</td>
<td>1</td>
</tr>
<tr>
<td>40-49</td>
<td>616.3</td>
<td>.83</td>
<td>1</td>
<td>2,901.0</td>
<td>3.91</td>
<td>1</td>
</tr>
<tr>
<td>50-59</td>
<td>228.1</td>
<td>.64</td>
<td>3</td>
<td>1,457.3</td>
<td>4.03</td>
<td>0</td>
</tr>
<tr>
<td>60-69</td>
<td>81.0</td>
<td>.38</td>
<td>1</td>
<td>553.3</td>
<td>2.60</td>
<td>0</td>
</tr>
<tr>
<td>70-79</td>
<td>15.6</td>
<td>.12</td>
<td>0</td>
<td>127.9</td>
<td>0.97</td>
<td>1</td>
</tr>
<tr>
<td>&gt;80</td>
<td>7.3</td>
<td>.18</td>
<td>0</td>
<td>14.7</td>
<td>.23</td>
<td>0</td>
</tr>
<tr>
<td>8,534.1</td>
<td>3.46</td>
<td>*</td>
<td>7</td>
<td>66,777.0</td>
<td>16.94</td>
<td>3</td>
</tr>
</tbody>
</table>

* The observed to expected ratio for basal cell carcinoma in HIV(+) hemophiliacs is 7/3.46 or 2.03 and for basal cell carcinoma in HIV(−) hemophiliacs is 3/16.94 or 0.18.
would also have to assume that the incubation period, between initial HIV seroconversion and development of lymphoma, occurred at the extreme minimum duration of infection, 2 years.\textsuperscript{13} This also seems very unlikely, and thus we believe that his lymphoma occurred as an incidental HIV(\texttext{-}) lymphoma, rather than an HIV-related lymphoma. If our assumptions are incorrect, at worst this would suggest the 29-fold risk of lymphoma in HIV(\texttext{+}) hemophiliacs may be an underestimate. Alternatively, another patient (no. 6) developed NHL at age 15, within the HIV-related time frame and 27 months after seroconversion, but his greater than 6-year survival is distinctly unusual for HIV-related NHL. Thus, given his known HIV infection and date of development of NHL, we believe his lymphoma was an HIV-related lymphoma.

Although Rabkin et al noted in their study of hemophiliacs\textsuperscript{22} that the risk of NHL increases with age, our data show a similar risk throughout all age groups. Further, as so few of the patients had received antiretroviral therapy before the development of NHL, it is unlikely that antiretroviral therapy played a major role in the development of NHL in this study group.

The lack of an increase in the rate of NHL since 1984 in HIV(\texttext{+}) hemophiliacs is distinctly different from that observed in homosexual men.\textsuperscript{13,24} If factors, such as prior antiretroviral therapy or survival greater than 2 years with immunodeficiency, play a role in the development of lymphoma as proposed by Pluda et al,\textsuperscript{13} then the small proportion of lymphoma patients receiving antiretroviral treatment and the short survival (16 months) after an AIDS diagnosis in this group may explain the lack of increase in the rate of development of NHL in this population. However, it should be noted that the study of Pluda et al\textsuperscript{13} may be limited by the small number of cases and, in scope, with primarily CNS lymphomas. Despite this, there are clear lifestyle and antigenic exposure differences between hemophiliacs and homosexual men; whether these factors account for any potential differences in rates of development of lymphomas between hemophiliac and homosexual men remains unknown.

Lymphomas were primarily intermediate- or high-grade in the HIV(\texttext{+}) hemophiliacs, although we also noted one low-grade lymphoma, similar to that described by McGrath et al.\textsuperscript{27} Unlike Rabkin et al\textsuperscript{24} who found no cases of CNS lymphoma, we observed three CNS lymphomas and, as noted by others,\textsuperscript{5} these lymphomas were associated with an extremely short survival. The mean CD\textsubscript{4} at presentation of NHL was extremely low, similar to patients previously reported,\textsuperscript{5,24} including those treated with antiretroviral therapy,\textsuperscript{26} but lower than a series reported by Levine et al.\textsuperscript{27} Although CD\textsubscript{4} level has been related to the site of tumor presentation and histology in nonhemophilic patients, it is possible that CD\textsubscript{4} number in hemophilia patients at NHL presentation may reflect not only the result of underlying HIV infection with the quantitative decrease in CD\textsubscript{4}, but also may be related to the chronic immunosuppression associated with chronic foreign protein and antigenic exposure with chronic blood transfusion.\textsuperscript{28-31} For instance, it is well known that depressed CD\textsubscript{4} number and natural killer activity occurs in hemophiliacs and other transfusion recipients, even in the absence of HIV infection.\textsuperscript{28,31}

Using DNA probes, only one third of the HIV-associated NHL had detectable EBV. This technique is relatively insensitive under the best conditions. EBV PCR or EBV probes with greater expression\textsuperscript{32} may improve detection of EBV in lymphoma tissue, provide a basis for comparison with tumors in homosexual men, and potentially clarify the role of this virus in HIV-related lymphomagenesis. The Prospective Study of lymphomas in the Hemophilia Malignancy Study, currently underway, is addressing this question.
Unlike findings in homosexual men, there appeared to be no association of NHL development and the occurrence of opportunistic malignancies or viral infections: none of our 14 HIV(+) patients with NHL experienced a second malignancy nor any acute viral infection at the onset of NHL.

Of the 3 lymphomas developing in HIV(−) hemophiliacs, 2 occurred in the midwestern United States. However, none of the latter HIV(−) hemophiliacs were farmers nor was there any history of herbicide exposure, a suspected risk factor for NHL nor any acute viral infection at the onset of NHL. Therefore, we believe that these findings suggest a significantly increased risk of basal cell cancers in association with HIV infection in the hemophilia population. Moreover, this finding suggests that the immunosuppression associated with HIV plays a role in the earlier predisposition to development of basal cell cancers in HIV(+) hemophiliacs. By comparison, studies of other immunosuppressed patients, including congenital immunodeficiency disorders and acquired immunodeficiency, for example, associated with transplantation have shown increased incidence of lymphomas but no increase in basal cell cancers. It is important to recognize that this study is a retrospective study and that incidence figures may underestimate the malignancy incidence, and specifically the low incidence of basal cell cancers in HIV(−) hemophiliacs. However, it is also likely that basal cell cancers in HIV(+) hemophiliacs are underestimated. Longer follow-up in our Prospective Study will be necessary to verify this hypothesis.

The single case of Kaposi's sarcoma occurred in a hemophiliac who was also homosexual. It is likely related to his homosexual behavior, given the much greater incidence of this tumor in that risk group. Kaposi's sarcoma has been reported only rarely as an AIDS-defining illness in hemophiliacs, mostly in homosexual hemophiliacs (John Murphy, MD, Centers for Disease Control, personal communication, August 1990). Some investigators have postulated that the occurrence of Kaposi's sarcoma in HIV(+) individuals is related to the effects of growth factors, cytokines, viral infections and elaborated factors, or sexually transmitted diseases. Findings in our study continue to support the concept that patients with hemophilia were either not exposed or not susceptible to whatever agent or factors cause Kaposi's sarcoma. By comparison, although there has been some increase in the incidence of Kaposi's sarcoma in transplant recipients, there has been no such increase noted in congenital immunodeficiency states.

The incidence of hepatocellular carcinoma, which has been associated with chronic hepatitis B and C infections, was not increased in HIV(+) or HIV(−) hemophiliacs. Despite the high proportion of hemophiliacs with chronic hepatitis B and chronic hepatitis C infection, there appears to be no increase in the frequency of this tumor. This is in concordance with findings of a survey by Colombo et al and is similar to the lack of any increase in hepatocellular cancer in either transplant recipients or congenital immunodeficiency states. With the increasing duration of HIV immunosuppression and improving survival in HIV(+) hemophiliacs treated with antiretroviral drugs, the incidence of hepatocellular cancer, given their chronic hepatitis B and C exposure, could potentially increase.

Of all cancers in HIV(−) hemophiliacs, lymphomas were the only cancer similar in incidence to the US population, with the remaining cancer incidence much lower than US population by SEER rates. The incidence of both basal cell cancer and lung cancer in HIV(−) hemophiliacs were significantly lower than the US population. We are not aware of sun exposure or cigarette exposure data in this population, but these might be of help in understanding the above figures. One could postulate that hemophiliacs, in general, because of the morbidity and disability of their disease, and periodic requirements for braces, casts, and immobilization, likely work or spend less time outdoors or in the sun. Life expectancy before the 1970s and the introduction of clotting factor concentrates was lower than the general population and therefore could have contributed to lower cancer incidence, but our study spans the years from 1978 through 1989, a time during which longevity in this population approached that of the normal population, at least before AIDS.

In summary, the risk of NHL in HIV(+) hemophiliacs is greatly increased over that in HIV(−) hemophiliacs and in the general US population. No increase in the rate of lymphomas has been observed since 1984, distinctly different from the findings in homosexual men. This may relate to: (1) lack of further HIV exposure or re-exposure through newer, safer blood products; (2) decrease in the total number of hemophiliacs who are HIV(+) and who have AIDS; (3) shorter survival after AIDS diagnosis; and/or (4) lifestyle differences including that monogamy is typical, and sexually transmitted diseases and parenteral drug use are rare. Basal cell carcinomas also appear to be significantly increased in HIV(+) as compared with HIV(−) hemophiliacs, and occur at an earlier age. It is likely that the observed rates of lymphoma and cancers in this group are conservative for several reasons. First, in this series there was an 11% occult malignancy rate noted at autopsy. Moreover, in autopsy series of patients with AIDS, as many as 20% have been found to have NHL, 40% of which were not detected antemortem. Thus, it is likely that a significant number of NHL may have been missed. Finally, the risk factors associated with the development of these cancers are unknown, but the subject of our ongoing Prospective Study.

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APPENDIX: PARTICIPATING HEMOPHILIA MALIGNANCY STUDY INVESTIGATORS

The participants in the Hemophilia Malignancy Study are as follows: Participating Institutions and Investigators: Eastern Hemophilia Treatment Centers: Worcester Memorial Hospital, Worcester, MA, D. Brettler, MD; Brigham & Women's Hospital, Boston, MA, B. Ewenstein, MD, H. Mahoney West, PNP; Mt Sinai School of Medicine, New York, NY, L. Aledort, MD, J. McCarthy, RN; Cornell, New York Hospital, New York, NY, M. Hilgartner, MD, M. Cahill-Bordas, RN; University of Pittsburgh School of Medicine, Pittsburgh, PA, W. Ragni, MD, M. Kratofil, RN; Hemophilia Treatment Center, Allentown, PA, L. Barron, MD, A. Odenwelder, RN; University of North Carolina, Chapel Hill, C. McMillan, MD, A. Schlaudecker, RN.

Midwestern Hemophilia Treatment Centers included: Great Lakes Hemophilia Foundation, Wauwatosa, WI, J. C. Gill, MD, P. Timmons, RN; Northwestern University, Chicago, IL, D. Green, MD, J. Deutsche, RN; Gulf States Hemophilia Center, Houston, TX, W. K. Hoots, MD, M. Cantini, RN; University of Texas School of Medicine Hemophilia Center, North Texas Group, Dallas, G. Buchanan, MD, C. Woźniak, RN and A. Johnson, RN; University of Pennsylvania Medical Center, Omaha, J. Goldsmith, MD, J. McCarthy, RN; Children's Hospital, Los Angeles, CA, N. Sanders, MD, K. Belle, PhD, Project Statistician, L. Kingsley, DrPH, Project Epidemiologist, and M. Ragni, MD, Project Director.

Pathologists participating in the Hemophilia Malignancy Study included: Great Lakes Hemophilia Foundation, Wauwatosa, WI, J. C. Gill, MD, P. Timmons, RN; Northwestern University, Chicago, IL, D. Green, MD, J. Deutsche, RN; Gulf States Hemophilia Center, Houston, TX, W. K. Hoots, MD, M. Cantini, RN; University of Texas School of Medicine Hemophilia Center, North Texas Group, Dallas, G. Buchanan, MD, C. Woźniak, RN and A. Johnson, RN; University of Pennsylvania Medical Center, Omaha, J. Goldsmith, MD, J. McCarthy, RN; Children's Hospital, Los Angeles, CA, N. Sanders, MD, K. Belle, PhD, Project Statistician, L. Kingsley, DrPH, Project Epidemiologist, and M. Ragni, MD, Project Director.

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Acquired immunodeficiency syndrome-associated non-Hodgkin's lymphomas and other malignancies in patients with hemophilia

MV Ragni, SH Belle, RA Jaffe, SL Duerstein, DC Bass, CW McMillan, EW Lovrien, LM Aledort, CT Kisker and SP Stabler