Cancer Incidence among an HIV-infected Cohort

C. C. Johnson,1 T. Wilcosky,1 P. Kvale,1 M. Rosen,3 J. Stansell,4 J. Glassroth,5 L. Reichman,6 J. Wallace,7 N. Markowitz,1 J. E. Thompson,2 P. Hopewell,4 and the Pulmonary Complications of HIV Infection Study Group

Malignancies, particularly Kaposi’s sarcoma and non-Hodgkin’s lymphoma (NHL), are associated with human immunodeficiency virus (HIV) infection. Cancer incidence among 1,073 asymptomatic HIV-infected individuals from the Pulmonary Complications of HIV Infection Study cohort, persons from six states followed from 1988 to 1994, was examined. Total cancer incidence was 3.99/100 person-years; for Kaposi’s sarcoma, incidence was 2.64 cases/100 person-years, and for NHL, it was 1.18 cases/100 person-years. Total cancer (n = 156 cases) was higher among nonblacks than among blacks (rate ratio = 2.8, 95% confidence interval 1.3–6.1), with similar results for Kaposi’s sarcoma and NHL. The rate of lung cancer (n = 5) among white, homosexual/bisexual males was 0.18 per 100 person-years, suggesting a high risk of lung cancer. Am J Epidemiol 1997;146:470-5.

Kaposi’s sarcoma, non-Hodgkin’s lymphoma (NHL), and other malignancies are associated with human immunodeficiency virus (HIV) infection (1–14). Few reports analyze the incidence of cancer in HIV-infected populations without a prior acquired immunodeficiency syndrome (AIDS)-defining disease (15–21). We examined the incidence of total cancer, Kaposi’s sarcoma, and NHL among a longitudinally studied, multiracial cohort of HIV-infected homosexual/bisexual (H/B) men and male and female injection drug users.

MATERIALS AND METHODS

The design of the Pulmonary Complications of HIV Infection Study, a cohort of 1,353 individuals from six US sites followed from 1988 through 1994, is described elsewhere (22). Cohort members who met study criteria were recruited by using a variety of methods from the patient and community populations of each site, with the objective of creating a cohort that broadly reflected the demographic aspects of the US AIDS epidemic in 1990 and that contained a range of HIV-mediated immune suppression. If an individual had an AIDS diagnosis by 1986 Centers for Disease Control criteria (23) or preexisting chronic lung disease, he or she was excluded. This paper presents analyses of cancer incidence in the seropositive H/B men and in men and women classified as injection drug users (IDUs) in the cohort who were aged 20 years or over at baseline (n = 1,073). Cancer incidence was ascertained during semiannual study visits and from death certificates and was confirmed by pathology reports.

Incidence rates for all cancers combined (excluding nonmelanoma skin cancer), Kaposi’s sarcoma, and NHL were calculated by age decade, race (black, nonblack), and transmission/sex category (H/B, IDU male, IDU female). The transmission/sex categories were developed because only one transmission category, IDU, included both males and females. Person-years at risk were calculated from study enrollment through the date of diagnosis for the cancer(s) of interest or until the last date of contact that the individual was known to be free of cancer. Crude and adjusted rate ratios were calculated by comparing rates in each category with the rate in a reference category.
Proportional hazards models were used to adjust for each of the above variables as well as for baseline CD4 lymphocyte count (0–199/mm$^3$, 200–499/mm$^3$, and ≥ 500/mm$^3$).

**RESULTS**

The baseline characteristics of the study cohort used in these analyses are displayed in table 1 ($n = 1,073$), and the 167 incident cancers, distributed by transmission risk category, are described in table 2. Cancer was diagnosed in 156 cohort members; eleven had two different primaries. (Multiple occurrences of Kaposi’s sarcoma are not included in this count.) Except for one individual with Kaposi’s sarcoma and cancer of the cecum and another with NHL and rectal cancer, all persons with two primary malignancies had Kaposi’s sarcoma and NHL. Eighty-seven percent of the Kaposi’s sarcoma and 88 percent of the NHL diagnoses were confirmed by tissue biopsy or cytologic stain. Fourteen individuals were presumed to have Kaposi’s sarcoma on the basis of classical skin and/or mucosal lesions without biopsy confirmation, and six people were presumed to have NHL on the basis of characteristic clinical and radiographic findings. Except for the pancreatic tumor, all solid tumors were confirmed by histologic assessment.

The rate for total cancer in the study group was 3.99/100 person-years at risk (156/3,906.7). (This rate was based on follow-up time to the first cancer diagnosis; subsequent cancers were excluded.) For Kaposi’s sarcoma, the rate was 2.64/100 person-years (104/3,939.2), and for NHL, it was 1.18/100 person-years (48/4,051.6). The total cancer rate was 1.02/100 person-years in blacks (9/886.0), 5.06/100 person-years in whites (138/2,727.4), and 3.07/100 person-years in the “other” category (9/293.3). When age, transmission/sex group, baseline CD4 lymphocyte categories and smoking history were adjusted for, there was no difference in rates between the categories white and other ($p = 0.45$), so they were combined for further analyses and designated as “nonblacks.”

Nonblacks showed a high adjusted rate ratio (RR) of 2.8 and a 95% confidence interval of 1.3–6.1 ($p = 0.007$) for all cancers combined compared with black participants (table 3). The adjusted rate ratios demonstrated that each age group had higher rates than did the youngest group, with all but the oldest yielding statistically significant differences. Both male ($p = 0.003$) and female ($p = 0.12$) IDUs were at lower risk of developing cancer than were the H/B males.

Kaposi’s sarcoma (table 4) was more common among nonblacks (RR = 2.4, 95 percent confidence interval 0.95–6.05). All but two of the Kaposi’s sarcoma cases were among the H/B males; the others occurred in female IDUs. Nonblacks had a notably high rate ratio for NHL (RR = 8.9), although the rate for blacks was based on only one case. The rate ratios for the four highest age categories compared with the youngest group were of a much higher magnitude. Although the rate of NHL was slightly higher among female than among male IDUs, there was only one
case in each group, and neither of these groups was statistically different from the H/B category.

There were five cases of primary lung cancer (table 5). Three cases were from San Francisco, California; all were cigarette smokers, white, H/B, and age 50 years or younger. With white H/B men as the denominator, the overall rate for this cancer was 0.18/100 person-years at risk (5/2,819.6).

**DISCUSSION**

In this study, we systematically and actively followed a large cohort of people with HIV infection, but not AIDS, at baseline. The cohort included a substantial number of black and of white individuals and of both H/B men and IDUs. Our data suggest that non-black H/B males are at the highest risk for total cancer, largely reflecting their higher risk for Kaposi’s sarcoma and NHL. We also observed an unusually high rate for lung cancer among the white H/B male group.

The rate for NHL in our H/B group (1.46/100 person-years) was substantially higher than that in a cohort of HIV-positive hemophiliacs without AIDS at baseline (0.15/100 person-years) (16). The lower incidence of NHL among blacks reflects patterns found among the general US population (24). Since the 1940s, NHL incidence and mortality rates have been consistently higher among whites and males. While the incidence and mortality rates have increased over time among all four race-sex groups, there is an apparent protection associated with being black.

The lower incidence of cancer in the IDU group is of interest but must be interpreted with caution because of the relatively small sample of IDUs in the cohort, resulting in rate ratios based on small numbers of cases. Disease progression among HIV-infected IDUs has been found to be slower than that among homosexual men in other settings (25, 26).

There are now several reports of lung cancer in HIV-infected persons (11, 17, 27). Five cases were ascertained in our cohort, all in relatively young, white, H/B male smokers. As reported by Tenholder et al. (27), adenocarcinoma is the predominant cell type.
TABLE 4. Kaposi’s sarcoma and non-Hodgkin’s lymphoma rates per 100 person-years of follow-up, Pulmonary Complications of HIV* Study, 1988-1994

<table>
<thead>
<tr>
<th>Category</th>
<th>Kaposi’s sarcoma</th>
<th>Non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-years at risk</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>886.8</td>
<td>6</td>
</tr>
<tr>
<td>Nonblack</td>
<td>3,052.3</td>
<td>98</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>606.2</td>
<td>12</td>
</tr>
<tr>
<td>30-39</td>
<td>1,981.2</td>
<td>52</td>
</tr>
<tr>
<td>40-49</td>
<td>971.8</td>
<td>29</td>
</tr>
<tr>
<td>50-59</td>
<td>267.9</td>
<td>10</td>
</tr>
<tr>
<td>≥60</td>
<td>42.1</td>
<td>1</td>
</tr>
<tr>
<td>Transmission/sex category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/B*</td>
<td>3,044.7</td>
<td>102</td>
</tr>
<tr>
<td>IDUF*</td>
<td>319.3</td>
<td>2</td>
</tr>
<tr>
<td>IDUM*</td>
<td>575.2</td>
<td>0</td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus; CI, confidence interval; H/B, homosexual/bisexual; IDUF, female injection drug users; IDUM, male injection drug users.
† Cases with multiple occurrences of Kaposi’s sarcoma were counted only at initial diagnosis.
‡ Rate ratio adjusted for other categories in the table and baseline CD4 lymphocyte counts, which were missing for 11 people, one of whom developed cancer.

Our observed rate of 0.18/100 person-years, or 177.3 per 100,000 person-years, among the white H/Bs can be compared with Surveillance, Epidemiology, and End Results data, in which the average annual incidence rate for US white (also defined as white plus Hispanic) males aged 35-44 years in 1973-1974 was 15.9 per 100,000 person-years. In 1987-1988, this rate had dropped to 11.4 per 100,000 person-years (28). Among those aged 45-54 years, the corresponding rates were 78.9 and 73.3 per 100,000 person-years in the two time periods, respectively. These cohort data compared with the Surveillance, Epidemiology, and End Results data are consistent with the hypothesis of an increase in lung cancer associated with HIV infection, and the young ages of the cases in the cohort suggest that infected H/Bs have an unusually high risk. A report of cancer among a San Francisco cohort of men with AIDS did not indicate an excess of lung cancer (14), although there was an apparent increase in bronchogenic cancer among never-married San Francisco-area men aged 25-54 years since the pre-AIDS period (5).

Detection bias may have contributed to an excess of lung cancer because of earlier diagnosis in persons under close medical supervision. However, all five patients died of lung cancer within 2 years of initial diagnosis, suggesting that a material downward shift of age or stage at diagnosis is not an issue.

Cohort members were not systematically ascertainment from defined populations, and therefore, it is unknown whether the study group is representative of HIV-positive individuals in the general population. The observed patterns may reflect unique characteristics of persons with access to the clinic centers in this study. Another limitation of our study is that part of the difference seen between the transmission groups,

TABLE 5. Characteristics of primary lung cancer cases ascertained from 1988 to 1994, Pulmonary Complications of HIV* Study (n = 5)†

<table>
<thead>
<tr>
<th>Center</th>
<th>Race</th>
<th>Transmission category</th>
<th>Study enrollment date</th>
<th>Smoker</th>
<th>CD4 lymphocyte count</th>
<th>Body mass index</th>
<th>Date of cancer diagnosis</th>
<th>Histology</th>
<th>Age at diagnosis (years)</th>
<th>CD4 lymphocyte count at diagnosis</th>
<th>Date of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>San Francisco</td>
<td>White</td>
<td>H/B*</td>
<td>2/89</td>
<td>Yes</td>
<td>197</td>
<td>25.8</td>
<td>9/90</td>
<td>Adenocarcinoma</td>
<td>35</td>
<td>221</td>
<td>11/90</td>
</tr>
<tr>
<td>San Francisco</td>
<td>White</td>
<td>H/B</td>
<td>5/89</td>
<td>Yes</td>
<td>127</td>
<td>23.8</td>
<td>2/90</td>
<td>Adenocarcinoma</td>
<td>43</td>
<td>117</td>
<td>12/91</td>
</tr>
<tr>
<td>San Francisco</td>
<td>White</td>
<td>H/B</td>
<td>8/89</td>
<td>Yes</td>
<td>262</td>
<td>21.8</td>
<td>8/91</td>
<td>Adenocarcinoma</td>
<td>40</td>
<td>151</td>
<td>6/92</td>
</tr>
<tr>
<td>Chicago</td>
<td>White</td>
<td>H/B</td>
<td>1/89</td>
<td>Yes</td>
<td>1,026</td>
<td>31.9</td>
<td>11/92</td>
<td>Squamous cell carcinoma†</td>
<td>47</td>
<td>868</td>
<td>6/93</td>
</tr>
<tr>
<td>New York</td>
<td>White</td>
<td>H/B</td>
<td>12/89</td>
<td>Yes</td>
<td>129</td>
<td>19.5</td>
<td>9/91</td>
<td>Adenocarcinoma</td>
<td>50</td>
<td>85</td>
<td>12/91</td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus; H/B, homosexual/bisexual.
† Characteristics refer to baseline unless otherwise indicated.
‡ Biopsy report stated poorly differentiated carcinoma suggestive of poorly differentiated squamous cell carcinoma, stage IIIA, non-small cell lung cancer.

Am J Epidemiol Vol. 146, No. 6, 1997
irrespective of sample size concerns, may be attributable to differential follow-up and consequent diagnosis of malignancies. The overall 60-month retention of this study cohort was 84 percent, but with a lower retention among the IDU group (75 percent) than among the H/B category (86 percent). However, the cancer rate among IDUs lost to follow-up would need to be extremely high to account for the difference across transmission groups, and cohort members who developed serious illnesses would presumably seek the medical care that was readily available at the study clinics.

In summary, this is the first large cohort of HIV-seropositive individuals in which cancer rates were compared between two HIV transmission categories. The rate of Kaposi’s sarcoma was higher in H/BS, and Kaposi’s sarcoma and NHL rates were lower in blacks. The finding of five lung cancer cases among fairly young men was striking.

ACKNOWLEDGMENTS

Supported by contracts 1-HR-6029, 6030, 6031, 6032, 6033, 6034, and 6035 with the National Heart, Lung, and Blood Institute and jointly sponsored by the National Institute of Allergy and Infectious Disease, National Institutes of Health.

The authors thank Lynn Barylski for collecting extra information for these analyses. The assistance of Susan McGuinness in the preparation of the manuscript was greatly appreciated. The members of the Pulmonary Complications of HIV Infection Study Group are as follows: Clinical Centers—University of California, San Francisco, San Francisco, CA—Dr. Philip C. Hopewell (Principal Investigator, Steering Committee Chairman), Dr. John Stansell, Joan Turner, Dr. Dennis Osmond, and Cynthia Merrifield; Northwestern University, Chicago, IL—Dr. Jeffrey Glassroth (Principal Investigator, Steering Committee Vice Chairman), Melinda Mossar, and Dr. Robert Hirschtick; Beth Israel Medical Center, New York, NY—Dr. Mark J. Rosen (Principal Investigator), Lori Meiselman, Kim K. Manghis, and Dr. Roslyn F. Schneider; University of Medicine and Dentistry of New Jersey, New Jersey Medical School, University Hospital, Newark, NJ—Dr. Lee B. Reichman (Principal Investigator), Dr. Bonita Mangura, and Sandra Barnes; University of California, Los Angeles, Los Angeles, CA—Dr. Jeanne M. Wallace (Principal Investigator), Barbara Richer, Dr. Janet Au, Anne Coulson, and Virjilio Clemente; Henry Ford Hospital, Detroit, MI—Dr. Paul A. Kvale (Principal Investigator), Dr. Norman Markowitz, Dr. Louis D. Saralovatz, Dr. Christine Johnson, Joanne Huitsing, and AnnaMarie Krystoforski.

REFERENCES


