Risk of Germ Cell Tumors among Men with HIV/Acquired Immunodeficiency Syndrome

James J. Goedert,1 Mark P. Purdue,2 Timothy S. McNeel,4 Katherine A. McGlynn,3 and Eric A. Engels1, for the HIV/AIDS Cancer Match Study

1Viral Epidemiology Branch, 2Occupational and Environmental Epidemiology Branch, and 3Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland and 4Information Management Services, Inc., Silver Spring, Maryland

Abstract

Background: Men with HIV/acquired immunodeficiency syndrome (AIDS) are reported to be at increased risk for germ cell tumors (GCT), particularly testicular seminoma. We investigated correlates of this association to improve understanding of GCTs. Methods: Testicular and extratesticular seminoma and nonseminoma cases were found by linking population-based cancer and HIV/AIDS registry data for 268,950 men who developed AIDS in 1980 to 2003. Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) were used to compare these cases with the number of cases expected in the demographically matched population. Results: Overall, seminoma risk (161 cases: SIR, 1.9; 95% CI, 1.6-2.2) was increased significantly with HIV/AIDS, whereas nonseminoma risk was not (56 cases: SIR, 1.3; 95% CI, 0.96-1.7). Extratesticular GCT risk also was increased (11 cases: SIR, 2.1; 95% CI, 1.1-3.7). Seminoma risk was elevated regardless of age, race, or HIV/AIDS transmission group. It was highest for disseminated disease (SIR, 4.7; 95% CI, 2.9-7.2) and within 9 months of AIDS onset (SIR, 7.6; 95% CI, 5.8-9.6), but it was unrelated to CD4 count and duration of HIV/AIDS. The excess risk of seminoma declined in more recent calendar periods, and it was no longer elevated (SIR, 1.4; 95% CI, 0.9-1.9) in the highly active antiretroviral treatment era. Conclusions: Men with HIV/AIDS had an increased risk of seminoma, but this risk may have attenuated with improving anti-HIV/AIDS treatments. Although detection bias could partly explain the excess of this cancer, various lines of evidence support a causal relationship. Possible mechanisms underlying this association include impaired tumor immunosurveillance or AIDS-related testicular atrophy.

Introduction

In 1995, Lyter et al. (1) reported a significantly elevated risk of developing testicular germ cell tumor (GCT), particularly seminoma, in a prospective cohort of homosexual men infected with HIV. Similar or higher risks were found in several American, Australian, British, and Italian studies (2-5). The risk may not be limited to the testis, as mediastinal malignant germinoma risk among men with the acquired immunodeficiency syndrome (AIDS) seemed to be increased, based on two studies with very sparse data (1, 2). Remarkably, risk of nonseminoma seems unrelated to HIV/AIDS (1-6).

The increased risk of seminoma among men with HIV/AIDS remains unexplained. Impairment of tumor immunosurveillance by HIV infection has been proposed as a possible underlying mechanism (4). This hypothesis is supported by evidence that the extent of lymphocyte infiltration in stage I seminoma is associated with a reduced risk of disease recurrence (7). Linkage studies in the United States suggested that seminoma risk increased in time relative to an individual’s initial AIDS-defining disease (termed AIDS-relative time), further supporting a role for immune function (2, 6). In Australia, however, there was no association with AIDS-relative time (3). Moreover, among 26 HIV-related seminoma cases in England, median CD4 count was 294 cells/µL, suggesting that immunodeficiency was present but not severe (4).

We examined chronologic, demographic, immunologic, and other data from 268,950 men diagnosed with HIV/AIDS in the United States from 1980 to 2003 to better understand the risk of seminoma and nonseminoma in this population.

Materials and Methods

Populations and Cancer Cases. As reported elsewhere (6, 8, 9), the HIV/AIDS Cancer Match Study used a probabilistic computer algorithm based on name, sex, race, dates of birth and death, and (where available) social security number to link HIV/AIDS and cancer registries in seven states (Colorado, Michigan, New Jersey, Massachusetts, Connecticut, Georgia, and Florida) and five metropolitan areas (San Francisco, Los Angeles, San Diego, Seattle, and New York City).

Among all men diagnosed with AIDS ages 15 to 92 years, the current study evaluated the risk of invasive seminoma (International Classification of Diseases for Oncology, third edition M9060-9064) and nonseminomatous GCT (International Classification of Diseases for Oncology, third edition M9065, 9070-9085, 9100-9103; ref. 10). In a sensitivity analysis, codes M9063 (spermatocytic seminoma) and M9064 (germ cell not otherwise specified) were excluded. Separate analyses were done for cancers arising in the testis (International Classification of Diseases for Oncology, third edition C620-629) and for extratesticular tumors (all other sites). Hispanic and missing/other race men (n = 37 cases) were excluded due to limited population-based incidence data for comparison.

Statistical Analyses. Detailed statistical methods were reported elsewhere (6, 8, 9). Briefly, time at risk was calculated from the start to the end of complete cancer.
registration in each area, no earlier than 60 months before
nor later than 120 months after AIDS onset (defined as month zero for each individual), and censored at death if earlier than 120 months after AIDS. As the measure of risk, we used the standardized incidence ratio (SIR), which is the ratio of observed to expected cancer cases derived from contemporaneous, race-, age-, and registry-specific population-based incidence rates. We calculated 95% confidence intervals (95% CI) assuming a Poisson distribution of the observed cancers (11). CI excluding unity (e.g., two-sided \( P = 0.05 \)) was considered statistically significant. A two-sided score test was used to assess trends with time and CD4 count (2, 6). Testing for trend in risk by calendar year was limited to the 2 years (months +4 to +27) after AIDS onset. Risk assessments for CD4 count (at AIDS onset) and stage by calendar year were limited to the 5 years (months +4 to +60) after AIDS onset. Alternative restrictions on the time intervals yielded similar results (not presented). All trend and subgroup analyses were defined a priori.

**Results**

For matching done in 2003 to 2005, there were 268,950 men with AIDS (56% white, 44% black) who were followed for 2,100,317 person-years (mean, 7.8 years). Like the U.S. AIDS population, they had a median age of 38 years. AIDS onset occurred before 1990 in 22%, during 1990 to 1995 in 47%, and in 1996 to 2003 in 31%.

There were 217 testicular GCT cases with AIDS compared with 129 cases expected (SIR, 1.7; 95% CI, 1.5-1.9; Table 1). Men with AIDS had an elevated risk for testicular seminoma (161 cases; SIR, 1.9). Their risk for extratesticular nonseminoma was markedly elevated (56 cases; SIR, 1.3; 95% CI, 0.96-1.7). Extratesticular GCT was diagnosed in 11 men with AIDS (SIR, 2.1; 95% CI, 1.1-3.7), including 8 with seminoma (germinoma) histology (SIR, 2.5; 95% CI, 1.1-5.0) and 3 with other germ cell histologies (SIR, 1.4; 95% CI, 0.3-4.1). Exclusion of cases of spermatocytic seminoma or germ cell not otherwise specified histologies had minimal effect on these risk estimates, although the SIR for extratesticular germinoma was no longer statistically significant (footnote in Table 1).

As shown in Table 2, testicular seminoma risk was higher for disseminated disease (SIR, 4.7) than for regional (SIR, 2.0) or localized (SIR, 1.6) disease. Seminoma risk was elevated before age 35 (SIR, 2.1) and at or after age 35 (SIR, 1.8) and in whites (SIR, 1.9) and blacks (SIR, 1.8). Seminoma risk was unrelated to CD4 count measured at AIDS onset based on sparse data. Seminoma risk was elevated significantly in men who had sex with men (SIR, 2.0), who accounted for 73% of the cases, and in transfusion- and hemophilia-associated AIDS (SIR, 9.8). Nonseminoma risk did not differ from that in the general population for any demographic or HIV transmission category (data not shown).

Seminoma risk was markedly increased (SIR, 7.6; 95% CI, 5.8-9.6) near the time of AIDS onset. The risk was less elevated up to 2 years before (SIR, 1.7) and after (SIR, 2.1) AIDS onset. It also was not elevated more than 2 years before or after AIDS onset (Table 3), but these data are very sparse and could underestimate the true risk by 15% or more due to migration into or out of the registry area (9).

Of note, across every AIDS-relative time interval, seminoma SIR declined with more recent calendar year of AIDS onset (Table 3). Considering all cases in all intervals, SIR fell from 3.3 to 1.7 to 1.4 with AIDS onset in 1980 to 1989, 1990 to 1995, and 1996 to 2003, respectively. For the time interval with the most complete prospective follow-up (+4 to +27 months after AIDS onset), the change in SIR with calendar time was marginally significant (\( P_{trend} = 0.056; \) Table 3). During the +4 to +60 months after AIDS onset, SIR declined over time for all stages of seminoma. As shown in Table 4, from AIDS onset in 1980 to 1989 to 1996 to 2003, seminoma local stage SIR declined from 1.9 to 1.2, for regional stage SIR declined from 3.1 to 1.1, and for distant stage it declined from 3.8 to 0.

### Discussion

Compared with the general population, we found that men with AIDS had an ~90% higher risk of seminoma but no significant difference in risk of nonseminoma. Seminoma risk was highest with AIDS onset during the 1980s, when little or no

<table>
<thead>
<tr>
<th>GCT site and histology*</th>
<th>GCT cases observed</th>
<th>GCT cases expected</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All testicular GCT</td>
<td>217</td>
<td>129.1</td>
<td>1.7 (1.5-1.9)</td>
</tr>
<tr>
<td>Testis seminoma</td>
<td>161</td>
<td>85.0</td>
<td>1.9 (1.6-2.2)</td>
</tr>
<tr>
<td>Testis nonseminoma</td>
<td>56</td>
<td>44.1</td>
<td>1.3 (0.96-1.7)</td>
</tr>
<tr>
<td>Extratestis seminoma</td>
<td>8</td>
<td>3.1</td>
<td>2.5 (1.1-5.0)</td>
</tr>
<tr>
<td>Extratestis other GCT</td>
<td>3</td>
<td>2.1</td>
<td>1.4 (0.3-4.1)</td>
</tr>
</tbody>
</table>

*With exclusion of spermatocytic seminoma (M9063) and germ cell not otherwise specified (M9064) histologies, there were 155 testis seminoma observed and 82.3 expected (SIR, 1.88; 95% CI, 1.60-2.20), 56 testis nonseminoma observed and 44.1 expected (SIR, 1.27; 95% CI, 0.96-1.65), 4 extratestis seminoma observed and 1.2 expected (SIR, 3.29; 95% CI, 0.90-8.41), and 3 extratestis other GCT observed and 1.9 expected (SIR, 1.56; 95% CI 0.32-4.55).
no antiretroviral therapy was available, and it was less elevated during the early 1990s, when single and dual nucleoside reverse transcriptase therapy was widely used. With AIDS onset during the highly active antiretroviral therapy (HAART) era (8, 9), starting in 1996, seminoma risk did not differ from that in the general population. However, this attenuation of the elevated risk with improving anti-HIV therapy was not mirrored by associations with CD4 count or AIDS-relative time. Although risk was not related to these measures of immune function, the trends in seminoma risk could still be related to other changes in the AIDS population. Seminoma risk was increased with transfusion- and hemonucleoside reverse transcriptase inhibitors (1990-1995), and availability of HAART combinations (1996-2003).

In AIDS, testicular atrophy is thought to be due to the general debilitating effects of the disease rather than due to specific immune, hormonal, or infectious disorders or treatments (16, 17, 21). Improving anti-HIV treatments was associated with a decreased prevalence of spermatogenic arrest, which declined from 48% among men who died of AIDS in 1981 to 1987 to 28% among AIDS decedents in 1988 to 1995 (18). Two (29%) of seven AIDS decedents in the HAART era also had spermatogenic arrest (18). It is possible that testicular dysgenesis in men with HIV/AIDS predisposed them to developing testicular GCT and that effective HIV treatments have prevented this precursor condition.

In addition to a high prevalence of testicular dysgenesis with AIDS, it may be that tumor-infiltrating lymphocytes are deficient with untreated HIV infection. Tumor-infiltrating lymphocytes correlate directly with better seminoma prognosis (4, 7, 24, 25). For men with HIV/AIDS, we found that seminoma risk was significantly higher for disseminated than for earlier stages. This finding indicates a shift toward metastatic behavior of seminomas among men with HIV/AIDS. We speculate that a deficit of tumor-infiltrating lymphocytes in untreated HIV infection accounts for this shift and may also increase the risk of seminoma and perhaps extratesticular germinoma as well. We further speculate that recovery of tumor-infiltrating lymphocyte activity with improving anti-HIV treatments might account for the attenuation of seminoma risk during the 1990s.

Our findings are subject to bias. AIDS-associated seminoma risk was markedly increased for diagnosis within a few months of AIDS onset, pointing to an effect of screening.

### Table 3. SIR of testicular seminoma among men with AIDS, by AIDS-relative time and calendar year of AIDS onset

<table>
<thead>
<tr>
<th>AIDS-relative time interval (mo)*</th>
<th>Obs.</th>
<th>SIR</th>
<th>Obs.</th>
<th>SIR</th>
<th>Obs.</th>
<th>SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>−60 to −25</td>
<td>7</td>
<td>1.3</td>
<td>9</td>
<td>0.7</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>−24 to −7</td>
<td>12</td>
<td>3.7</td>
<td>9</td>
<td>1.2</td>
<td>6</td>
<td>1.2</td>
</tr>
<tr>
<td>−6 to +3</td>
<td>20</td>
<td>10.4</td>
<td>30</td>
<td>7.0</td>
<td>15</td>
<td>6.3</td>
</tr>
<tr>
<td>+4 to +27</td>
<td>10</td>
<td>3.4</td>
<td>15</td>
<td>2.0</td>
<td>5</td>
<td>1.3</td>
</tr>
<tr>
<td>+28 to +60</td>
<td>2</td>
<td>1.4</td>
<td>6</td>
<td>0.9</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>+61 to +120</td>
<td>2</td>
<td>1.7</td>
<td>6</td>
<td>1.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All AIDS-relative time intervals:</td>
<td>53</td>
<td>3.3</td>
<td>75</td>
<td>1.7</td>
<td>33</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Abbreviation: Obs., number of seminoma cases observed.

<table>
<thead>
<tr>
<th>*</th>
<th>95% CI for SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2.5-4.3)</td>
<td>(1.3-2.1)</td>
</tr>
</tbody>
</table>

### Table 4. SIR of testicular seminoma during 4 to 60 mo after AIDS onset, by stage and calendar year of AIDS onset

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs.</td>
<td>Exp.</td>
<td>SIR</td>
</tr>
<tr>
<td>Localized</td>
<td>6</td>
<td>3.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Regional</td>
<td>2</td>
<td>0.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Distant</td>
<td>1</td>
<td>0.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>0.2</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Abbreviation: Exp., number of seminoma cases expected.

| * | Excludes one registry where stage data were not obtained.
contrast to seminoma, nonseminoma may be less affected by screening bias because nonseminoma may be less indolent and thus less likely to be diagnosed incidentally (26). However, an accelerated diagnosis of indolent seminoma at AIDS onset would not account for the continuing excess that we observed during the 2 years after AIDS onset. Moreover, the stronger risk observed for disseminated testicular cancer is incompatible with screening bias. Finally, if screening bias was substantial, the increased intensity and frequency of monitoring of HIV/AIDS patients during the 1990s and into the HAART era should have increased, rather than decreased, the apparent risk of seminoma.

In summary, our analysis of ~40% of the non-Hispanic U.S. population with AIDS revealed that testicular seminoma risk was increased significantly, whereas nonseminoma risk was not. The increased risk was no longer apparent in recent years, perhaps because of overall clinical and immunologic improvement with HAART. Follow-up data from large populations of men with HIV/AIDS may help to clarify these associations with testicular cancer.

Acknowledgments

We thank the staff members of the above-mentioned registries who collected the data, prepared data files for the matches, and facilitated the record linkages; Phil Virgo (Computer Sciences Corp., Rockville, MD) for doing the record linkages; Norma Kim, Emily Moser, and Christopher McClure (RTI International, Rockville, MD) for study management; and Dr. Robert Biggar for helpful discussions and review of the manuscript.

References


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