Epidemiology of Hairy Cell Leukemia in Los Angeles County

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ABSTRACT

The descriptive epidemiological characteristics of hairy cell leukemia (HCL), a rare chronic lymphoproliferative disorder, were examined by using incidence data collected from 1972 to 1987 by the Cancer Surveillance Program, the population-based cancer registry for Los Angeles County. During the study period, 208 incident cases of histologically confirmed HCL were diagnosed. HCL comprised 2% of all leukemias diagnosed in Los Angeles County during the study period. HCL risk was concentrated in white males; there were few black and Asian patients for analysis. Overall, the age-adjusted incidence rate of HCL for men (2.9/ million population) was 4.8 times greater than that for women (0.6/ million population). Using data from all cancer patients diagnosed during the study period, Jewish men had significantly greater risk of HCL than Protestant men (odds ratio (OR) = 3.0, P < 0.0001); there was no significant variation in risk of HCL by religion for women. For men, the OR was significantly elevated for professional and technical workers (OR = 2.1, P = 0.001); within this category of occupations, risk was significantly elevated for engineers (OR = 3.3, P < 0.0001) and university faculty and school teachers (OR = 4.0, P = 0.0008). HCL patients were more than twice as likely to have multiple primary cancer diagnoses as other cancer patients. Since the majority of the other primary cancer diagnoses occurred prior to (>1 year) or concurrent with (<1 year) the HCL diagnosis, this greater frequency of multiple primaries in HCL patients may be due to impaired immune function.

INTRODUCTION

HCL is a rare, chronic B-cell lymphoproliferative malignancy that is reported to comprise 2% of all leukemias (1). It was first described as a distinct entity in 1958 by Bouroncle et al. (2). Variants of HCL with T-cell features and both T-cell and B-cell features have also been described (3, 4) and the human lymphotropic virus HTLV-II has been detected in several patients with the T-cell phenotype (5, 6). Patients with HCL typically present with nonspecific complaints of fatigue or weakness. Pancytopenia and splenomegaly are present in the majority of patients; lymphadenopathy and hepatomegaly are uncommon (7). HCL is morphologically characterized as a circulating leukemic cell with cytoplasmic projections ("hairy cells") which express the tartrate-resistant isoenzyme of acid phosphatase (8).

Our interest in the descriptive epidemiology of HCL was prompted by our recent study of AIDS-related cancer trends in Los Angeles County men in which we examined cancer risk by marital status under the assumption that the category "never-married" men would include the majority of homosexual men.

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3 The abbreviations used are: HCL, hairy cell leukemia; AIDS, acquired immune deficiency syndrome; CSP, Cancer Surveillance Program; ICDO, International Classification of Diseases for Oncology; OR, odds ratio.
chronic lymphocytic leukemia. For whites and blacks, no There are few black or Asian cases and incidence rates for males cases of histologically confirmed HCL were identified during

For the estimation of incidence rates, we have developed a popula-
tion-at-risk model which is based on the 1970 and 1980 United States
censuses of population (20, 21). To classify the 1980 white population
into Spanish surnamed whites and non-Spanish surnamed whites, data
on the relationship of Spanish surname to the designation of Spanish
origin from the 1980 Public Use Microdata Sample (5% sample) for
Los Angeles County were used (22). Individuals of Spanish origin who
were designated either “whites” or “other races” were allocated to the
Spanish surnamed white ethnicity group on an age-specific, sex-specific
percentage basis. Year-specific population estimates were obtained
individually by racial/ethnic group, 5-year age group, and sex. Intercen-
sual estimates were obtained by interpolation assuming a constant rate
of growth (decline). For the postcensal period, estimates were obtained
by extrapolation assuming the same rate of growth (decline). Age-
adjusted incidence rates per 10^5 population were calculated by direct
standardization, using 5-year age groups with weights derived from the
1970 United States population (20). For the analysis of secular trends,
cases of HCL were classified by year of diagnosis (1972–1975, 1976–

Because census data are not available for religion and because they
cannot be used reliably to produce population denominator figures by
occupation, religion-specific and occupation-specific estimates of risk
were determined by comparing the number of patients with HCL in a
particular religious or occupation category to the total number of pa-
tients with other types of cancer in that particular category on an age-
specific basis (using 5-year age groupings). This approach is essentially
a case-control study using cancer patients with diagnoses other than
HCL as controls. This design is similar to that of a hospital-based case-
control study where controls are patients with diagnoses thought not
to be associated with the risk factors under study. Since we had no
prior hypotheses regarding occupational or religious groups at high risk
of HCL, all other cancer diagnoses were included as controls.

Age-adjusted ORs were estimated by using the Mantel Haenszel
method and 95% confidence limits were calculated by using the Corn-
field method (23). To evaluate proportional risk by religion, Protestants
were used (arbitrarily) as the baseline comparison group. For risk
estimates by occupation, the base-line comparison group was comprised
of all patients in the remaining occupation categories. All P values
reported are two sided.

RESULTS

Average annual age-adjusted incidence rates of HCL for men
and women residing in Los Angeles County are presented in
Table 1 for the years 1972 through 1987. Overall, 208 incident
cases of histologically confirmed HCL were identified during
the study period. HCL risk is concentrated in white males.
There are few black or Asian cases and incidence rates for males
overall are nearly 5 times greater than those for females.

Incidence rates for other major categories of leukemia in men
and women aged 20 and older are provided in Table 1 as a
point of reference for the HCL rates. The pattern of occurrence
of HCL by sex and race/ethnicity does not resemble the patterns
of these more common leukemias. For all races and ethnicities
combined, the male:female rate ratios range from 1.5 for acute
nonlymphocytic and acute lymphocytic leukemia to 1.9 for
chronic lymphocytic leukemia. For whites and blacks, no
male:female rate ratio is greater than 1.9.

During the study period, there were 10,605 persons who were
diagnosed with some form of leukemia in Los Angeles County.
Overall, HCL comprised 2.0% of these diagnoses. For adult
males (aged 20 and older), 3.9% (166 of 4303) of all leukemias
were HCL, whereas, for adult women, the figure was 1.2% (42
of 3556).

Male and female age-specific incidence rates of HCL for all
racial/ethnic groups combined are shown in Fig. 1. A male
excess is present in all age categories except the 20- to 24-year-
old age group. Average annual age-adjusted incidence rates by
calendar period of diagnosis and sex are shown in Table 2. The
rates prior to 1976 are lower than later rates. After 1976, there
is no trend in rates for either males or females. Over all time
periods, the male:female excess has remained constant.

Overall, 91.6% (152 of 166) of male HCL patients had known
marital status. Of these, 12 had never been married. For all
other male cancer patients aged 20 and older, marital status
was recorded for 95.1%. Never-married men had lower risk of
HCL than ever-married men; however, this result was not
statistically significant (OR = 0.6, P = 0.11).

Because of the few blacks or Asians with HCL, assessment
of risk by religious preference was restricted to white patients.
Data on religion were available for 73.4% of white males and
78.1% of white females diagnosed with cancer during the time
period of interest and for 75.3% (119 of 158) of white males
and 90.0% (36 of 40) of white females with HCL (Table 3).
Based on all cancers diagnosed in Los Angeles County white
men with known religious preference during the years 1972–
1987, Jewish men had three times greater risk of HCL than did
Protestant men (P < 0.0001). For men with other religious
preferences, the risks were not appreciably different from that
of Protestant men. For white women, the risk of HCL was
similar in all religious preference categories.

Information on occupation at the time of diagnosis was
available on 75.9% of white males with HCL (120 of 158,
including 11.4% who were retired) and 84.8% of all white males
with cancer (including 27.8% who were retired). The ORs for
broad census classifications of occupations were estimated rel-
etive to other nonretired men with known occupation at the
time of diagnosis (Table 4). The OR for the category, profes-
sional and technical workers, was significantly elevated (OR =
2.1, P = 0.001). No other broad category of occupation was
significantly elevated. Within these broad categories, only four
subgroups had more than three HCL patients: engineers (in-
cluding aeronautical, chemical, electrical and electronic, indus-
trial, and mechanical engineers); university faculty and school
teachers; writers, artists and entertainers; and mechanics. Sig-
nificantly elevated ORs were observed for engineers (OR = 3.3,
P < 0.0001) and university faculty and school teachers (OR =
4.0, P = 0.0008); results for mechanics (OR = 2.0, P = 0.09)
and writers, artists and entertainers (OR = 2.0, P = 0.53) were
not statistically significant. Similar results were obtained for all
occupational categories evaluated when the analyses were re-
stricted to white males aged 20 to 64.

The frequency of other malignancies in HCL patients was
examined; 30 (14.4%) of these patients had another primary
cancer diagnosis that occurred within the study period com-
pared with 6.7% of all patients diagnosed with cancer during
the study period. Women were more likely than men to have
another primary cancer diagnosis (21.4 versus 12.6%); this
contrasts with results for all cancer patients showing men and
women equally likely to have multiple primary cancer diag-
noses. For HCL patients, the other primary cancer diagnoses
included a wide variety of solid tumors; no lymphomas or
leukemias were included. The most frequently occurring cancer
sites were colon (5 men and 1 woman), breast (4 women), and
**Table 1** Average annual age-adjusted incidence rates of hairy cell leukemia and of other leukemias per million population aged 20 and older, Los Angeles County, 1972–1987, by sex and ethnicity

<table>
<thead>
<tr>
<th>Type of leukemia</th>
<th>Racial/ethnic group</th>
<th>Males</th>
<th>Females</th>
<th>Male/female rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whites</td>
<td>Non-Spanish surnamed</td>
<td>3.5 (134)*</td>
<td>0.8 (36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spanish surnamed</td>
<td>3.4 (22)</td>
<td>0.4 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blacks</td>
<td>0.7 (4)</td>
<td>0.3 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians/other</td>
<td>1.5 (6)</td>
<td>0.3 (2)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td></td>
<td>2.9 (166)</td>
<td>0.6 (42)</td>
</tr>
<tr>
<td>Acute non-lymphocytic</td>
<td>Whites</td>
<td>Non-Spanish surnamed</td>
<td>31.0 (1140)</td>
<td>20.1 (1037)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spanish surnamed</td>
<td>23.9 (173)</td>
<td>18.3 (159)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blacks</td>
<td>21.3 (99)</td>
<td>20.3 (138)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians/other</td>
<td>18.2 (69)</td>
<td>10.8 (57)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td></td>
<td>28.5 (1481)</td>
<td>19.3 (1391)</td>
</tr>
<tr>
<td>Acute lymphocytic</td>
<td>Whites</td>
<td>Non-Spanish surnamed</td>
<td>3.9 (149)</td>
<td>2.6 (126)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spanish surnamed</td>
<td>6.2 (69)</td>
<td>4.3 (49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blacks</td>
<td>2.3 (14)</td>
<td>1.9 (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians/other</td>
<td>3.6 (18)</td>
<td>0.9 (5)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td></td>
<td>4.0 (250)</td>
<td>2.7 (195)</td>
</tr>
<tr>
<td>Chronic myelogenous</td>
<td>Whites</td>
<td>Non-Spanish surnamed</td>
<td>14.7 (544)</td>
<td>8.2 (424)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spanish surnamed</td>
<td>18.1 (132)</td>
<td>9.9 (89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blacks</td>
<td>14.6 (75)</td>
<td>10.7 (74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians/other</td>
<td>6.9 (28)</td>
<td>2.9 (16)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td></td>
<td>14.5 (779)</td>
<td>8.4 (602)</td>
</tr>
<tr>
<td>Chronic lymphocytic</td>
<td>Whites</td>
<td>Non-Spanish surnamed</td>
<td>30.8 (1131)</td>
<td>15.8 (892)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spanish surnamed</td>
<td>13.8 (75)</td>
<td>7.5 (50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blacks</td>
<td>24.8 (110)</td>
<td>14.4 (90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians/other</td>
<td>3.8 (11)</td>
<td>1.0 (4)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td></td>
<td>26.8 (1327)</td>
<td>14.0 (1036)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of cases.

**Fig. 1.** Age-specific incidence rates of hairy cell leukemia per million population by sex, Los Angeles County, 1972–1987.

**Table 2** Average annual age-adjusted incidence rates of hairy cell leukemia per million population, Los Angeles County, by sex and year of diagnosis, for all racial and ethnic groups combined

<table>
<thead>
<tr>
<th>Year category</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972–1975</td>
<td>1.4 (19)*</td>
<td>0.3 (5)</td>
</tr>
<tr>
<td>1976–1978</td>
<td>3.5 (34)</td>
<td>0.8 (10)</td>
</tr>
<tr>
<td>1979–1981</td>
<td>3.0 (30)</td>
<td>0.5 (6)</td>
</tr>
<tr>
<td>1982–1984</td>
<td>3.8 (39)</td>
<td>0.7 (10)</td>
</tr>
<tr>
<td>1985–1987</td>
<td>3.9 (44)</td>
<td>0.8 (11)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of cases.

**Table 3** Age-adjusted OR and 95% confidence limits (CL) for hairy cell leukemia by religion and sex, for whites (non-Spanish surnamed and Spanish surnamed) with stated religious preference

<table>
<thead>
<tr>
<th>Religion</th>
<th>OR</th>
<th>95% CL</th>
<th>N</th>
<th>OR</th>
<th>95% CL</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protestant</td>
<td>1.0*</td>
<td></td>
<td></td>
<td>1.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catholic</td>
<td>1.1</td>
<td>0.7, 1.7</td>
<td>32</td>
<td>1.2</td>
<td>0.6, 2.6</td>
<td>13</td>
</tr>
<tr>
<td>Other Christian</td>
<td>1.5</td>
<td>0.5, 4.2</td>
<td>4</td>
<td>0.8</td>
<td>0.1, 5.9</td>
<td>1</td>
</tr>
<tr>
<td>Jewish</td>
<td>3.0</td>
<td>1.9, 4.8</td>
<td>30</td>
<td>1.3</td>
<td>0.5, 3.4</td>
<td>5</td>
</tr>
<tr>
<td>No religion</td>
<td>1.5</td>
<td>0.8, 2.9</td>
<td>11</td>
<td>0.9</td>
<td>0.2, 4.0</td>
<td>2</td>
</tr>
</tbody>
</table>

* Reference group.

**Table 4** Age-adjusted OR and 95% confidence limits (CL) for hairy cell leukemia by occupation at diagnosis, for white males (non-Spanish surnamed and Spanish surnamed) with known occupation

<table>
<thead>
<tr>
<th>Occupation</th>
<th>OR</th>
<th>95% CL</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional and technical workers</td>
<td>2.1</td>
<td>1.3, 3.0</td>
<td>35</td>
</tr>
<tr>
<td>Engineers</td>
<td>3.3</td>
<td>2.1, 5.6</td>
<td>17</td>
</tr>
<tr>
<td>University faculty and school teachers</td>
<td>4.0</td>
<td>1.9, 8.3</td>
<td>7</td>
</tr>
<tr>
<td>Writers, artists and entertainers</td>
<td>1.5</td>
<td>0.6, 3.7</td>
<td>5</td>
</tr>
<tr>
<td>Managers and administrators</td>
<td>0.8</td>
<td>0.5, 1.4</td>
<td>17</td>
</tr>
<tr>
<td>Sales workers</td>
<td>0.6</td>
<td>0.2, 1.4</td>
<td>5</td>
</tr>
<tr>
<td>Clerical workers</td>
<td>1.4</td>
<td>0.7, 2.9</td>
<td>8</td>
</tr>
<tr>
<td>Craftsmen</td>
<td>0.8</td>
<td>0.5, 1.3</td>
<td>18</td>
</tr>
<tr>
<td>Mechanics</td>
<td>2.0</td>
<td>1.0, 4.0</td>
<td>8</td>
</tr>
<tr>
<td>Operators, except transportation</td>
<td>0.7</td>
<td>0.3, 1.4</td>
<td>5</td>
</tr>
<tr>
<td>Transportation operatives</td>
<td>1.1</td>
<td>0.5, 2.7</td>
<td>5</td>
</tr>
<tr>
<td>Laborers, except farm</td>
<td>1.1</td>
<td>0.5, 2.6</td>
<td>5</td>
</tr>
<tr>
<td>Service workers, except household</td>
<td>0.5</td>
<td>0.2, 1.4</td>
<td>4</td>
</tr>
</tbody>
</table>

* Each occupation category is compared with a reference group of all other occupation categories combined.

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prostate (3 men). One male patient was diagnosed with Kaposi's sarcoma after his HCL diagnosis; this patient, who was in his seventies when diagnosed, has previously been reported in the literature (24). Eight (27%) of the other primary malignancies were diagnosed at least 1 year prior to the HCL diagnosis; 12 (40%) were “concurrent” diagnoses occurring within 12 months of the HCL diagnosis; and 10 (33%) were diagnosed at least 1 year after the patient had been diagnosed with HCL.

**DISCUSSION**

Case reports linking leukemia to the AIDS epidemic have appeared in the literature (25–27). This population-based study of the epidemiological features of HCL was initially motivated by our observation that five never-married men, aged 18 to 54, had been diagnosed with HCL during the period 1983–1985, while no cases of HCL in such men had occurred prior to 1983 (9). Although we found no indication of an association between AIDS and the more frequent types of leukemia in this earlier study, the observed increase in HCL in never-married men suggested a possible link of this cancer with the AIDS epidemic. Since 1985, however, no further cases of HCL in never-married men in this age range have been ascertained by the CSP; moreover, the risk of HCL in never-married men overall appears to be lower than that of ever-married men.

Our population-based data provide the first estimates of the incidence of HCL in a defined population. Our data confirm the descriptive characteristics observed in case-series reports in the literature: a marked excess of HCL in males, median age of diagnosis in the mid-fifties, and a 2% relative incidence in comparison with other types of leukemia. There is no evidence of a secular increase in HCL over the time period studied. The initial increase in incidence rates which is evident after 1975 likely reflects a lack of recognition of HCL by pathologists in the early 1970s.

Compared to Protestant men, Jewish men had significantly greater risk of HCL, but no similar elevation in risk was observed for Jewish women. A number of studies, summarized by Linet (28), have reported elevated risks of all leukemias in Jews compared to non-Jews. Haenszel (29) examined results of several mortality studies in Jewish populations, noting that the male:female ratios of mortality from leukemia appeared to be closer to 1 in Jews than in non-Jews. In an earlier study, we examined patterns of cancer risk by religion in Los Angeles County and found that, compared with the major subgroup of Protestant religions, Jews had significantly greater risk of lymphomas (particularly non-Hodgkin's types) and, although the risk of all leukemias was elevated for Jewish males, the excess was only 20% (30). In this earlier study, we noted that Jewish men had lower risks of lung, larynx, esophageal, oral, prostate, and rectal cancer than the Protestant comparison group. When we eliminated patients with these cancers from the control group, the risk of HCL in Jewish men remained significantly elevated (OR = 2.4, P = 0.0003).

Our results showing a significantly elevated risk for professional and technical workers may represent a social class effect since risk was elevated for three different groups within this broad classification. It is unlikely that engineers, university professors, and writers, artists, and entertainers who share similar occupational exposures. However, the significantly increased risk for engineers and the number affected (17 or 16.7% of those with known occupation) may reflect some occupationally related etiological exposure. In fact, three of the five cases of HCL diagnosed in never-married young men (aged 20–54) during the period 1983–1985 were engineers.

Several exposures have been proposed in the literature as possible etiological factors for HCL. Oleske et al. (31) compared histories of cases from a HCL treatment center with those of population-based controls, and found significantly elevated risks associated with farm birthplace, history of anemia, migraine headaches and infectious mononucleosis, routine use of aspirin, and exposure to organic chemicals in the workplace. Marginal associations were observed with farming and woodworking occupations. Chronic benzene exposure has been anecdotally linked with HCL (32, 33). Stewart and Keating (34) reported a greater frequency of prior occupational, accidental, or therapeutic radiation exposure in HCL patients than in patients with solid tumors.

HCL patients appear to have a greater risk of multiple primary cancers than other cancer patients. This may reflect both lower median age than cancer patients overall (mid-fifties versus late sixties) or the greater likelihood of survival. However, neither of these explanations would account for the large percentage of other malignancies that were diagnosed prior to (27%) or concurrent with (40%) the HCL diagnosis in Los Angeles County patients. A more plausible explanation is that patients who develop HCL may have impaired immune function. There have been reports in the literature of decreased natural killer cell activity and defective T-cell activity in HCL (35, 36).

There are many case reports in the literature documenting instances of multiple primary cancers in HCL patients. The rate of multiple primary cancers in the large case series of 172 HCL patients being followed at the University of Chicago was 8.7% after 10 years of follow-up with all but one of the second malignancies diagnosed concurrently with or after the HCL diagnosis (37).

Because HCL and chronic lymphocytic leukemia, both chronic lymphoproliferative malignancies primarily of B-cell origin, have similar clinical presentations, one might expect similar patterns of incidence. Neither disease occurs in the young. However, the incidence rate of chronic lymphocytic leukemia rapidly rises in late middle age and continues to increase with age, whereas the incidence rate of HCL appears to plateau after late middle age. In addition, the incidence rate of chronic lymphocytic leukemia are similar in blacks and whites, and the overall male:female rate ratio is less than 2. In fact, none of the four major types of leukemia show the unique racial/ethnic pattern of HCL or the extreme male:female rate ratio observed for HCL.

Although the age-specific and race-specific incidence patterns of classic Kaposi's sarcoma (i.e., Kaposi's sarcoma that is not related to the AIDS epidemic) differ from those of HCL, there are some striking similarities between the two diseases (38). In Los Angeles County, Jewish men of European (especially Eastern and Southern European) origin have excess risk of classic Kaposi's sarcoma (38). Furthermore, the male:female rate ratio for classic Kaposi's sarcoma is greater than 3 for Spanish-surnamed whites, non-Spanish surnamed whites, and blacks. Kaposi's sarcoma patients also appear to have increased risk of second primary malignancies, although in contrast to HCL, the majority of these cancers are lymphoreticular neoplasms (39, 40). Further studies in other geographic locations are necessary to confirm the epidemiological features of HCL observed here. Although difficult to conduct due to the rarity of HCL, analytic studies will be required to explore the reasons for the marked...
excess of HCL in males and among Jews, in particular, and to identify possible nondemographic risk factors for the disease.

REFERENCES