Incidence of Adult T-Cell Leukemia/Lymphoma among Human T-Lymphotropic Virus Type I Carriers in Saga, Japan

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ABSTRACT

Using a population-based cancer registry, we tabulated 69 definite adult T-cell leukemia/lymphoma cases (36 males and 33 females) and 2.20 expected cases (0.95 for males and 1.25 for females) diagnosed from 1981 to 1983 in Saga, Japan. The number of human T-lymphotropic virus type I carriers was computed by applying sex- and age-specific anti-human T-lymphotropic virus type I antibody positive rates among blood donors at the blood center in 1986 to the whole population of Saga Prefecture in 1982. The age-specific incidence rates among male human T-lymphotropic virus type I carriers from 40 to 79 yr of age per 100,000 were significantly higher than those of female carriers (P < 0.05), and the rates from 60 to 69 yr of age were the highest in both sexes. The annual crude incidence rates among carriers were 115.9 for males and 66.4 for females. The summary incidence rates with 95% confidence intervals were 115.9 (58.4 to 193.0) for males and 65.9 (30.0 to 115.9) for females. The cumulative risks were 4.5% (0.8 to 11.0) for males and 2.6% (0.3 to 7.0) for females. These morbidity figures were assumed to be underestimated partly due to the newly proposed clinical entity of adult T-cell leukemia/lymphoma.

INTRODUCTION

ATL or ATLL is a new clinical entity proposed by Takatsuki et al. in 1977 (1). By using the cell lines established beforehand (2), the associated virus was detected by means of the passive immunofluorescence method (3). Later the DNA sequences were clarified (4), and the ATL virus was verified to be identical to the one isolated from the lymphocytes of a patient with cutaneous T-cell lymphoma in the United States (5). In the meantime, the virus was named HTLV-I, and it was proved that the virus is directly associated with ATL. However, the precise carcinogenesis of ATLL is still unknown.

There are several epidemiological studies dealing with the morbidity of (or mortality from) ATLL in Japan (6–9); however, we considered it to be important to calculate more accurate and reliable incidence rates and cumulative risks of ATLL by sex with confidence intervals among HTLV-I carriers in an area with moderate endemicity of the virus by using a population-based local cancer registry in Saga Prefecture, located in Kyushu, the southern part of Japan with a population of 880,000.

PATIENTS AND METHODS

Patients. We first abstracted 256 reports of malignant lymphomas and other lymphoid malignancies (including case reports submitted by physicians, abstracted information from medical records at major hospitals by the registry staff, and death certificates whose addresses are located in Saga) newly diagnosed between 1981 and 1983 from the data of the Prefectural Cancer Registry (or Annual Cancer Survey, formerly).

Next we reviewed 121 autopsy cases described in the Annual of the Pathological Autopsy Cases in Japan, which were reported from the institutes in Saga and in the neighboring prefectures from 1981 to 1984. Definite ATLL cases whose addresses were located in Saga were tabulated into our study. Possible and/or suspected cases were referred to respective pathologists to obtain final diagnoses.

On the basis of the formation above, we compiled 69 definite incident ATLL cases (36 males and 33 females) diagnosed between 1981 and 1983 (Table 1). For a male case with probable ATLL based upon microscopic diagnosis and with positive T-cell marker but without confirmation of proviral DNA, the case was judged as probable and counted as 0.75. This inference was also based on the proportion of lymphoid T-cell versus B-cell malignancies in Kyushu (12). For one male case with possible ATLL based upon microscopic diagnosis with positive T-cell marker but without other diagnostic procedures, it was regarded as possible and counted as 0.5. For one male case and six female cases described as malignant lymphoma, not otherwise specified, the estimated number of ATLL patients was calculated by applying the number of these cases to the proportion of the number of definite ATLL cases to definite non-ATLL patients among malignant lymphomas in the respective age groups. In all, 36.95 ATLL patients among males and 34.25 cases among females were tabulated in the present study.

HTLV-I Carriers. In order to calculate population at risk or the number of HTLV-I carriers in Saga Prefecture, sex- and age-specific anti-HTLV-I antibody positive rates among blood donors at the Saga Red Cross Blood Center during the fiscal year of 1986 (April 1986 to March 1987) were tabulated. At the blood center, the antibody to HTLV-I was screened at the final serum dilution (or titer) of 2 by the gelatin particle agglutination test (14), which is highly sensitive but less specific. In other words, there is little false negative but moderate false positive at this titer. Because the population seropositive rate at the titer of 2 or over by the gelatin particle agglutination method is reported to be practically equivalent to that by the passive immunofluorescence method (14), this cutoff titer was utilized to calculate the number of HTLV-I carriers. As the seropositive rates for the elderly groups (aged 65 or over) were not available from the center, the seroconversion rates (or hazard functions) in these age groups surveyed among the general population in a neighboring prefecture (10) were used for extrapolating the prevalence curves in Saga. Applying these HTLV-I prevalence rates to the whole population in 1982, we computed the sex- and age-specific number of HTLV-I carriers (Table 2).
The crude incidence rates were computed by the number of ATLL cases and lymphoma, not otherwise specified. ATL (or pre-ATL) with positive antibody were not included.

### Table 1 Number of definite, probable, possible, and estimated ATLL cases by sex and age by using cancer registry in Saga Prefecture from 1981 to 1983

<table>
<thead>
<tr>
<th>Age</th>
<th>Male Definite</th>
<th>Male Probable</th>
<th>Male Possible</th>
<th>Male Estimated</th>
<th>Female Definite</th>
<th>Female Probable</th>
<th>Female Possible</th>
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<tbody>
<tr>
<td>16-19</td>
<td>0.86</td>
<td>23,893</td>
<td>205</td>
<td>1.01</td>
<td>24,129</td>
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<td>50-59</td>
<td>6.02</td>
<td>52,736</td>
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* One male anti-HTLV-I antibody negative ATLL and one female smoldering ATL (or pre-ATL) with positive antibody were not included.

* Numbers in parentheses, number of cases described as a priori, malignant lymphoma, not otherwise specified.

### Table 2 Sex- and age-specific HTLV-I prevalence rate, whole population as of October 1, 1982, and number of HTLV-I carriers in Saga Prefecture in 1982

<table>
<thead>
<tr>
<th>Age</th>
<th>Male HTLV-I prevalence rate (%)</th>
<th>Male Whole population carriers</th>
<th>Male HTLV-I carriers</th>
<th>Female HTLV-I prevalence rate (%)</th>
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* The HTLV-I seropositive rates at the titer of 2° or over by the gelatin particle agglutination method.

### Calculation of Rates and Risks, and Statistical Test

Using the number of ATLL cases as numerator and the whole population and number of HTLV-I carriers as denominator, we calculated sex- and age-specific incidence rates, crude incidence rates, and summary incidence rates with 95% confidence intervals. It was our assumption that the number of cases under 40 yr, or 80 yr of age or over was small and unstable, both the incidence rates and the cumulative risks were computed from 40 to 79 yr of age. The crude incidence rates were computed by the number of ATLL cases and HTLV-I carriers. In the calculation of the summary incidence rates and their confidence intervals, the variations in both numerators and denominators were simultaneously taken into account by applying the Poisson approximations, and the incidence rates throughout the age strata, estimated by the method of maximum likelihood, were assumed common (15). This procedure is considered a refinement and extension of the method of indirect standardization (16). The cumulative risks with 95% confidence intervals were obtained by using sex- and age-specific incidence rates and their respective upper and lower confidence limits (17). The Mantel-Haenszel test (18), stratified by age group, was applied to examine the difference in the age-specific rates with 95% confidence intervals. Since the number of cases under 40 yr, or 80 yr of age or over was small and unstable, both the incidence rates and their confidence intervals, the variations in both numerators and denominators were simultaneously taken into account by applying the Poisson approximations, and the incidence rates throughout the age strata, estimated by the method of maximum likelihood, were assumed common (15). This procedure is considered a refinement and extension of the method of indirect standardization (16). The cumulative risks with 95% confidence intervals were calculated by using the number of HTLV-I carriers as denominator, it is conceivable that those figures are underestimated rather than overestimated. That is, it seems unlikely that cases of Hodgkin’s disease, B-cell lymphomas, non-ATLL T-cell lymphomas, and other lymphoid malignancies unrelated to HTLV-I were diagnosed as ATLL. Rather, since ATLL is a newly proposed disease entity and diagnostic information and techniques are not yet fully known by every physician, some ATLL cases may have been overlooked. In addition, the quality of the local cancer registry does not seem to be thorough, because the cancer registration system in Saga depends in part on voluntary reporting by physicians. Definite ATLL patients registered only by death certificates were 25% (9 cases) for males and 3% (1 case) for females, which suggests that there is underreporting on such a level. There are two factors, however, which counterbalance the above. The first is the well-known fact that the prognosis of ATLL is very poor. Indeed, all patients with ATLL, with two exceptions (chronic type of ATLL), died by the end of 1987. Second, the number of undisclosed cases may be regarded as small since the cancer registry routinely collects all death certificates.

The ATLL incidence rates were approximately 1 of 860 among male and 1 of 1500 among female HTLV-I carriers. The cumulative risks were 4.5% (0.8 to 11.0) for males and 2.6% (0.3 to 7.0) for females.

### DISCUSSION

This is the first report to show the rates and the risks of ATLL among HTLV-I carriers according to sex by using a population-based cancer registry. It must be noted, however, that while every effort was made to compile an accurate number of ATLL cases as numerator, it is conceivable that those figures are underestimated rather than overestimated. That is, it seems unlikely that cases of Hodgkin’s disease, B-cell lymphomas, non-ATLL T-cell lymphomas, and other lymphoid malignancies unrelated to HTLV-I were diagnosed as ATLL. Rather, since ATLL is a newly proposed disease entity and diagnostic information and techniques are not yet fully known by every physician, some ATLL cases may have been overlooked. In addition, the quality of the local cancer registry does not seem to be thorough, because the cancer registration system in Saga depends in part on voluntary reporting by physicians. Definite ATLL patients registered only by death certificates were 25% (9 cases) for males and 3% (1 case) for females, which suggests that there is underreporting on such a level. There are two factors, however, which counterbalance the above. The first is the well-known fact that the prognosis of ATLL is very poor. Indeed, all patients with ATLL, with two exceptions (chronic type of ATLL), died by the end of 1987. Second, the number of undisclosed cases may be regarded as small since the cancer registry routinely collects all death certificates.

As mentioned earlier, the number of HTLV-I carriers was calculated by using the positive rates of antibody to HTLV-I among blood donors. This number of carriers was assumed to be underestimated partly due to the healthy donor effect, because blood used for transfusions is solely procured by voluntary donation in Japan. This factor as denominator may overestimate the risk; however, the calculated rates were almost equivalent to or rather higher than those reported thus far (6–9). The age-specific incidence rates from 60 to 69 yr of age were the highest in both sexes, but the sex difference in the risk was found to be apparent. It is claimed that the individuals infected horizontally by blood transfusion (19) or by sexual contacts (9, 20) are not at risk of ATLL, partly because a long latency
period is needed for the onset of ATLL. In this connection, the seroconversion through transfusion would overestimate the denominator, and thus, underestimate the risk; however, it would not upset the comparison of the morbidity rates between males and females, as long as the frequency of transfusion is not much different between sexes. Furthermore, in order to eliminate the seroconversion rates between sexes. Furthermore, in order to eliminate the seroconversion by sexual transmission, the seroconversion rates among females over 20 yr of age were assumed to be equivalent to those among males, and the population at risk among females was calculated. As a result, the risk of ATLL among males was still higher than that of females with statistical significance at the 5% level. Further research is required to distinguish the effects of factors (such as age, period or cohort, infection via transfusion, or sex) associated with the cross-sectional HTLV-I prevalence curve and to identify the true population at risk of ATLL.

The series of ATLL studies led us to a new idea and/or model of carcinogenesis in humans. The HTLV-I is the first retrovirus which has been proved to be causally related to human cancer, but the precise role of the virus in the leukemogenesis remains to be disentangled. Recently another disease related to HTLV-I was proposed, that is, HAM (21), which is a neurological disease characterized by spastic spinal paraparesis, similar to tropical spastic paraparesis (22) with positive anti-HTLV-I antibody. Contrary to ATLL, there are HAM cases contracted by horizontal infection of HTLV-I as well as by vertical transmission, but the pathogenesis as to how the lymphotrophic virus causes such neurological symptoms in humans is still unclear. Currently, there are neither case reports of HAM patients subsequently incurring ATLL nor patients simultaneously suffering HAM and ATLL. A case-referent study is now under way to compare the cases of ATLL or HAM with HTLV-I carriers in terms of host and environmental factors which might be related to the promotion and/or manifestation of either ATLL or HAM.

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