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Mortality among Inhabitants of an HTLV-I Endemic Area in Japan

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A community-based cohort study was conducted to clarify the risk of human T-cell leukemia virus type I (HTLV-I) infection for cause-specific deaths. A total of 1,997 individuals (751 men and 1,246 women) aged 30 or older in A-Island, Nagasaki Prefecture, Japan who had voluntarily attended annual mass health examinations, including serum HTLV-I antibody test, were followed up for a mean period of 5.3 years. In a Cox proportional hazards analysis adjusted for age at baseline, the HTLV-I seropositivity was found to be associated with mortality from all causes in men (hazard ratio (HR) 1.89; 95% confidence interval (CI) 1.01–3.54) and women (HR 1.94; 95% CI 1.16–3.22). When the effects of 2 deaths (1 man and 1 woman) from adult T-cell leukemia/lymphoma (ATL) were excluded, the mortality risk decreased slightly but was still significantly or marginally significantly greater than 1 in both men (HR 1.77; 95% CI 0.93–3.37) and women (HR 1.87; 95% CI 1.12–3.12). Further analysis of cause-specific deaths revealed a significant increase in the risk for non-neoplastic diseases but not for neoplasms excluding ATL. These findings suggest that long-term HTLV-I infection represents a health hazard greater than just that for the development of ATL. It was difficult, however, to draw a conclusion regarding the association between HTLV-I infection and cancer risk, because the number of cancer deaths was small and the incidence of cancer was not investigated.

Key words: HTLV-I carrier — Mortality — Prospective cohort study

Human T-cell leukemia virus type-I (HTLV-I),[1] the etiological agent of adult T-cell leukemia/lymphoma (ATL),[2] is endemic in several regions of the world, including southwestern Japan,[3] the Caribbean basin[4] and central African countries.[5] In Japan, it is estimated that more than one million adults are infected with the virus and that approximately 50% of these people are clustered in the Kyushu region.[6]

HTLV-I has been shown to be etiologically linked to several clinical entities other than ATL: tropical spastic paraparesis (TSP)/HTLV-I associated myelopathy (HAM),[7,8] arthritis,[9] bronchitis[10] and uveitis.[11] Furthermore, it has been suggested that individuals infected with HTLV-I are immunosuppressed[12,13] and thus susceptible to infectious diseases.[14–16] Associations between HTLV-I infection and increased risk of cancer[17,18] and renal diseases[19] have also been hypothesized.

Whether or not HTLV-I infection increases mortality from causes other than ATL is an important public health issue. However, few cohort studies have explored this problem,[20] and most epidemiologic studies addressing the health hazard caused by HTLV-I have focused on the risk estimation of ATL alone.[4,21–24]

The objective of the present investigation was to estimate by means of a prospective cohort study the risk of death from all causes, neoplasms and non-neoplastic diseases, among HTLV-I carriers.

MATERIALS AND METHODS

Area and population for baseline data The study area consisted of 26 villages in B-town, located on A-Island, Nagasaki Prefecture, Japan where HTLV-I is endemic.[22] As part of community-based measures to prevent HTLV-I infection and ATL, serum antibodies to HTLV-I were checked at least once between 1984 and 1990 in 751 men and 1,246 women over 30 years of age who had voluntarily participated in annual mass health examinations. This group of 1,997 subjects, which covered 42% of men and 50% of women living in the area, was used as the study population. Information on occupation, drinking and smoking habits, and history of blood transfusions was obtained through interviews.

Assay of serum HTLV-I antibody Serum antibody to HTLV-I was tested by the gelatin particle agglutination (PA) method (Serodia ATLA, Fujirebio, Tokyo).[25] We did not re-examine positive samples by other methods because the high reliability of the PA tests in these

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HTLV-I endemic areas was confirmed by the indirect immunofluorescence (IF) assay and/or the enzyme-linked immunosorbent assay (ELISA) in our preliminary validation study. For example, 72 (36.0%) of 200 examined sera were PA-positive and 71 of these were IF-positive.

Our results were different from those of other investigators, who reported high percentages of false-positive reactions by the PA method in some instances.[26,27] The reason for this difference may be explained as follows: the predictive value of a diagnostic test depends not only on its efficacy but also on the prevalence of a disease among the study population[28,29]; the false-positive rates for the PA method may be lower in areas with a higher prevalence of true HTLV-I carriers. Furthermore, Kinoshita *et al.*[29] recently reported that the presence of HTLV-I proviral DNA in peripheral blood mononuclear cells, as detected by the polymerase chain reaction, correlated closely with serum antibody to HTLV-I tested by PA, IF and ELISA in inhabitants of an endemic area of HTLV-I. We came to the conclusion, therefore, that the false-positive reactions resulting from the PA method did not pose a serious problem in the present study.

Multiple participations of approximately 50% of the study population allowed us to evaluate the correlation among repeated assays of serum HTLV-I antibody. The phi coefficients ranged from 0.895 to 1.000, showing a fairly good assay reproducibility (Table I). However, 30 (3.0%) of the 998 subjects who had been evaluated twice or more yielded inconsistent results in at least two of the repeated examinations. Confirmation by the IF method suggested a seroconversion in some of these 30 subjects. But we used the initial data for all subjects because exclusion of the above 30 individuals would have produced another potential source of bias.

Follow-up Between April and September 1992, we investigated the vital status of the 1,997 individuals by referring to the residence registry. The follow-up period extended from the date of the initial health examination to the date of death or movement, or April 1, 1992. One hundred and twenty of the 1,997 subjects had died and 41 had moved to other towns. By reviewing death certificates in the 2 main hospitals and 3 private clinics located in the study area, we ascertained the cause of death in all subjects who had died, and categorized these according to the 9th Revision of the International Classification of Diseases (ICD) as being due either to neoplasms or non-neoplastic diseases. The neoplasms included both malignant and benign types (ICD 140–239), while the term non-neoplastic disease referred to all remaining conditions other than injury or poisoning (ICD E800–E999). Examination of previous diseases for approximately 75% of the deceased suggested that misclassification of cause of deaths had occurred very seldom.

In addition, we reviewed the pathological reports of the 2 and the medical records of the 4 individuals in whom ATL or malignant lymphoma was listed as the underlying cause of death. Subjects satisfying all of the following 4 conditions were diagnosed as having ATL: description of ATL or malignant lymphoma on death certificates; the presence of serum antibody to HTLV-I; histological evidence showing the presence of atypical lymphoid cells (flower cells) in peripheral blood or lymphoid tissues; and exclusion of pre- or smoldering ATL. Consequently, the cause of death in the 1 pre- or smoldering ATL case who had died from opportunistic infection was reclassified into the category of non-neoplastic diseases (see "Results").

Statistical analysis The association between serum HTLV-I antibody status and sex, age, occupation, smoking and drinking habits, and history of blood transfusions was assessed by use of the chi-square test or Student's *t* test. The relationship between HTLV-I seropositivity and mortality was examined by the Kaplan-Meier method. The log rank test was used to determine whether or not the mortality differed significantly according to serum HTLV-I antibody status. We used the Cox proportional hazards model[30] in the age-adjusted multivariate analysis. The hazard ratios (HR), their 95% confidence intervals (CI) and the probability of statistical significance (two-tailed) were computed. On the basis of the regression coefficient, the age-adjusted survival probabilities for HTLV-I carriers and non-HTLV-I carriers were also calculated.

Table I. Correlation among Repeated Assays of Serum HTLV-I Antibody in Subjects with Multiple Participations

Year of examination	1984	1985	1986	1987
1985	1.000 (57)[a]			
1986	1.000 (54)	0.956 (561)		
1987	0.964 (61)	0.976 (575)	0.960 (662)	
1988	— —	0.919 (257)	0.895 (248)	0.930 (304)

a) Phi coefficient = $\sqrt{\text{chi square}/N}$ (number of subjects in parentheses).

RESULTS

HTLV-I seroprevalence in men and women was 20.4% and 28.1%, respectively, showing a significantly higher rate in women ($P<0.01$). In men, HTLV-I seropositivity was virtually stable in the over-30 year age group (14.9–22.1%). In women, on the other hand, HTLV-I seroprevalence increased with age from 20.8% in the 30–39 year age group to 39.4% in the 80–89 year age group (data not shown).

Table II shows the characteristics of the study population with regard to serum HTLV-I antibody status. In men, there was no significant difference in the mean age at baseline between HTLV-I carriers and non-carriers, while in women, the carriers were an average of 3.1 years older than non-carriers ($P<0.01$). With regard to occupation, in men, the proportion of farmers was lower, and conversely, that of fishermen was higher, among carriers than among non-carriers. In women, the percentage of individuals engaged in farming was somewhat lower, and that of unemployed persons (or housewives) was higher, among carriers than among non-carriers. There was no significant difference in levels of cigarette smoking or alcohol consumption between carriers and non-carriers. The percentage of those who had received blood transfusions was less than 7% in both carriers and non-carriers, with no statistically significant difference, suggesting that blood transfusion was not a major route of HTLV-I infection in this study population.

During the follow-up period, the entire cohort underwent 10,503.6 person-years of observation, with a mean follow-up of 5.3 years. Among the 120 subjects who had died, malignant lymphoma or ATL was listed as the underlying cause of death in 4 subjects, 2 (1 man and 1 woman) of whom met the diagnostic criteria of ATL used in this study. The expression of T-cell surface markers had been established in one, and characteristic symptoms of ATL such as hepatosplenomegaly and hypercalcemia were present in the other subject. One male subject was considered to have pre- or smoldering ATL. In this case, skin eruption and atypical lymphocytes in peripheral blood (2–4%) were noted. But the direct cause of death was diagnosed as herpes simplex encephalitis and no evidence of ATL was found at autopsy. One woman with serum antibody to HTLV-I, whose pathology diagnosis was gastric malignant lymphoma, was not considered as having ATL. Using the 2 deaths as numerator and the person-years at risk (2,581.2) as denominator, the crude death rate from ATL was estimated at 0.77/1000 person-years, which is in close agreement with the incidence rates of ATL reported previously (0.6–1.3/1000 a year).[4, 21–24] There was no death from HAM/TSP. Finally, 35 of the 120 deaths were attributed to neoplasms, 73 to non-neoplastic diseases, and 12 to injury or poisoning (Table III).

The association between HTLV-I seropositivity and mortality was evaluated by survival analysis. The 7 men and 5 women who had died from injury or poisoning were regarded as censored cases in all subsequent analyses. In multivariate analysis, neither smoking nor drinking habits were included as covariates because there were no significant differences in these habits between HTLV-I carriers and non-carriers. Using the Kaplan-Meier method, we found that HTLV-I seropositivity was significantly or marginally significantly associated with mortality in both men ($P=0.0779$) and women ($P=$

Table II. Characteristics of Study Population According to Serum HTLV-I Antibody Status[a]

Characteristics		Men			Women		
		Non-carriers	Carriers	*P*-value[b]	Non-carriers	Carriers	*P*-value
No. of subjects		598	153		896	350	
Age (years)		57.2±11.9	57.6±10.9	0.67	55.6±12.4	58.7±12.6	<0.01
Occupation	farming	174 (29.1)	28 (18.3)	0.02	333 (37.2)	111 (31.7)	0.02
	fishery	165 (27.6)	62 (40.5)		43 (4.8)	11 (3.1)	
	individual business	37 (6.2)	8 (5.2)		63 (7.0)	16 (4.6)	
	salaried	41 (6.9)	9 (5.9)		36 (4.0)	14 (4.0)	
	others	66 (11.0)	20 (13.1)		114 (12.7)	48 (13.7)	
	unemployed	105 (17.6)	23 (15.0)		291 (32.5)	149 (42.6)	
Smoking	non-smokers	152 (25.4)	41 (26.8)	0.78	825 (92.1)	318 (90.9)	0.22
	current or ex-smokers	440 (73.6)	112 (73.2)		63 (7.0)	32 (9.1)	
Drinking	non-drinkers	188 (31.4)	47 (30.7)	0.81	783 (87.4)	306 (87.4)	0.72
	current or ex-drinkers	404 (67.6)	106 (69.3)		105 (11.7)	44 (12.6)	
Blood transfusion	+	29 (4.8)	4 (2.6)	0.22	52 (5.8)	24 (6.9)	0.51
	−	563 (94.1)	149 (97.4)		836 (93.3)	326 (93.1)	

a) Plus-minus values are means±SD. Values in parentheses are percentages.
b) By Student's *t* test or chi-square test. Unknown subjects were excluded.

Table III. Causes of Death According to Serum HTLV-I Antibody Status

Causes of death (ICD Codes)	Men		Women	
	Non-carriers	Carriers	Non-carriers	Carriers
Total	41	14	34	31
All neoplasms (140–239)	15	5	8	7
ATL	0	1	0	1
Malignant lymphoma excluding ATL (200–202)	0	0	0	1
All non-neoplastic diseases	19	9	23	22
Infectious diseases (001–139)	0	0	2	0
Heart disease (390–429)	7	3	8	8
Cerebrovascular disease (430–438)	4	3	6	5
Respiratory disease (460–519)	2	1	1	1
Renal disease (580–589)	2	0	2	5
Others	4	2[a]	4	3
Injury or poisoning (E800–E999)	7	0	3	2

a) A patient with pre- or smoldering ATL who died from herpes simplex encephalitis was included.

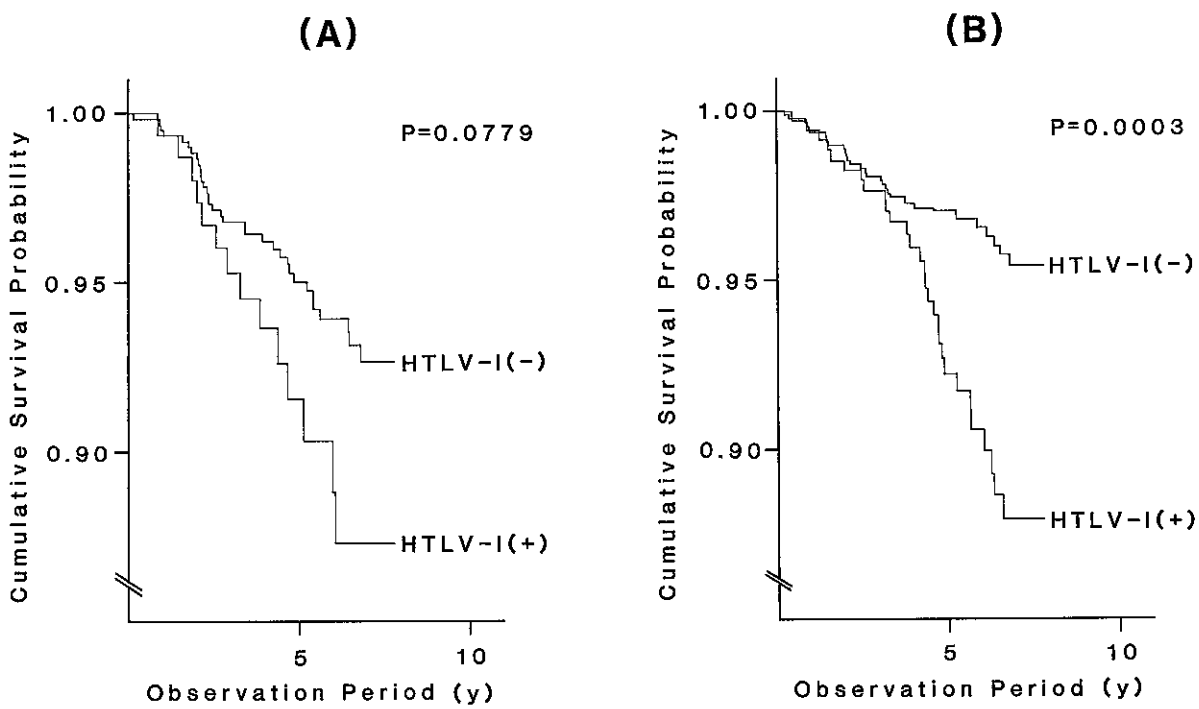

Fig. 1. Cumulative survival probability in (A) 751 men and (B) 1,246 women according to serum HTLV-I antibody status. Twelve deaths from injury or poisoning were regarded as censored cases.

0.0003, Fig. 1). After adjustment for age using the Cox regression model, the association between HTLV-I seropositivity and mortality was statistically significant in both sexes (Table IV). The hazard ratio associated with HTLV-I infection for death from all causes was 1.89 (95% CI 1.01–3.54) for men and 1.94 (95% CI 1.16–3.22) for women. The hazard ratio corresponding to a yearly age increase was 1.11 (95% CI 1.08–1.15) for men and 1.12 (95% CI 1.09–1.15) for women. Therefore, the mortality risks associated with HTLV-I infection were almost equivalent to that caused by a 5.9-year age increase. When the 2 deaths from ATL were censored, the association was slightly weakened but remained significant or marginally significant in both men and women.

Table IV. Age-adjusted Relative Risks of Death from All Causes, Neoplasms and Non-neoplastic Diseases Associated with HTLV-I Infection in 751 Men and 1,246 Women[a]

Variable	Men			Women		
	No. of events	Hazard ratio (95% CI)	*P*-value	No. of events	Hazard ratio (95% CI)	*P*-value
All causes	48	1.89 (1.01–3.54)	0.0457	60	1.94 (1.16–3.22)	0.0109
All causes[b]	47	1.77 (0.93–3.37)	0.0802	59	1.87 (1.12–3.12)	0.0171
Neoplasms	20	1.43 (0.52–3.95)	0.4878	15	2.12 (0.76–5.90)	0.1518
Neoplasms[b]	19	1.16 (0.39–3.52)	0.7868	14	1.78 (0.61–5.18)	0.2907
Non-neoplastic diseases	28	2.30 (1.04–5.12)	0.0409	45	1.95 (1.09–3.50)	0.0255

a) Cox proportional hazards analysis was used. Twelve deaths from injury or poisoning were regarded as censored cases.
b) One man and one woman who died from ATL were regarded as censored cases.
CI, confidence interval.

At the end of the follow-up, the values of age-adjusted cumulative survival probability of HTLV-I seronegative and seropositive women, computed regarding the 1 death from ATL as a censored case, were 0.944 and 0.899, respectively. Further analysis of cause-specific mortality revealed a significantly increased risk for non-neoplastic diseases in both sexes. Because of the small number of deaths, the risk estimates of the neoplasms were unstable, with no significant increase in the risk for all neoplasms or neoplasms excluding ATL in either sex.

DISCUSSION

In this study, we found that HTLV-I infection was associated with an approximately 1.9-fold increased risk of mortality. When the effects of the 2 deaths from ATL were excluded, the relative risk decreased slightly, but it still remained statistically or marginally significantly greater than 1 in both sexes. Furthermore, bias due to differences in occupation was unlikely because the economic status in the study population was rather uniform and similar results were obtained even after adjustment for the differences in occupation (data not shown). These findings point to adverse effects of HTLV-I infection other than ATL on the health status of virus carriers. Our results are contrary to those reported by Tokudome *et al.*,[20] who followed 3,991 healthy HTLV-I carriers in the Kyushu region for an average of 2.7 years. They found no excess mortality from any cause or from cancers other than ATL. However, the seropositive subjects selected in their study were voluntary blood donors, and the standardized mortality ratios were computed using mortality data derived from the entire Japanese population. Therefore, the possibility of selection bias, i.e., healthy donor effect, could not be excluded.[20] Interestingly, a recent case-control study reported a higher probability of early death in the mothers of HTLV-I carriers than in those of non-carriers in Miyazaki Prefecture.[31]

On the basis of case-control studies, several researchers have hypothesized an increased risk of cancer among HTLV-I carriers. Asou *et al.*[17] reported that HTLV-I seroprevalence was higher in patients with cancers of various organs who had not had blood transfusions than in the general population in Kumamoto Prefecture, Japan. Miyazaki *et al.*[18] reported a similar finding in patients with cervical and vaginal carcinoma. In the present study, we found a significant increase in the risk for death from non-neoplastic diseases but not from neoplasms. However, it was difficult to draw a firm conclusion regarding the association between HTLV-I infection and cancer risk, because the number of cancer deaths was small and the incidence of cancer was not investigated.

There are several possible biological mechanisms by which HTLV-I infection could increase mortality. The first is through mild immunosuppression caused by the virus.[12–15] Suppressed cellular immunity[13] might increase the susceptibility to infectious agents in elderly HTLV-I carriers who have various underlying diseases. This explanation may be difficult to support because there was no death from infectious diseases among HTLV-I carriers. It should be noted, however, that common infections, e.g., pneumonia, are not usually selected as the primary cause of death. The second mechanism is through renal diseases. High HTLV-I seroprevalence in chronic hemodialysis patients without history of blood transfusions[19] and glomerular deposition of HTLV-I antigen/antibody immune complex in a patient with ATL[32] have been reported. In the current study, renal disease was listed as the underlying cause of death in 5 female HTLV-I carriers. However, the latter mechanism does not fully explain the higher mortality among HTLV-I carriers, because the significant association between HTLV-I seropositivity and mortality in women did not disappear even after

the effect of renal diseases was excluded (HR 1.72; $P=0.0500$). The mechanism through HAM/TSP[7, 8] seems unlikely, since the lifetime risk of developing HAM is extremely low — approximately 0.25%.[33] The incidence rates of other HTLV-I associated syndromes in symptom-free HTLV-I carriers are not known.

One problem that should be considered when interpreting the results of this study is the accuracy of information on exposure. A small number of measurement errors, false-positive reactions, and the occurrence of seroconversion may have led to the misclassification of serum HTLV-I antibody status. Measurement errors usually lead to the underestimation of relative risks.[34] On the other hand, the possibility remains that the false-positive reactions by the PA assay, which result from the cross reactivity of cellular proteins and other infectious viruses with HTLV-I p19 core protein,[35] are associated with increased risk of mortality. However, from the proportion of inconsistency in repeated assays of serum HTLV-I antibody (3.0%) and the false-positive rates found by the PA method among the general population (less than 3%),[29] the misclassification of HTLV-I serostatus was estimated to be less than 6% and therefore should exert little effect in this study. With regard to the outcome variable, it is unlikely that the results were seriously distorted by the 2.1% of the study subjects lost to follow-up, and there is no reason to believe that any substantial mortality difference existed between those who had moved to other towns and those who had not.

In conclusion, our results suggest that long-term HTLV-I infection is associated with an excessive risk of mortality and that the risk is greater than that caused only by the development of ATL. However, we believe that further investigations in other HTLV-I endemic areas and critical analysis are needed before a conclusion about the cause-effect relationship can be reached. Larger follow-up studies or incidence studies may be required to determine whether or not HTLV-I infection is associated with increased risk of cancer.

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REFERENCES

1) Poiesz, B. J., Ruscetti, F. W., Gazdar, A. F., Bunn, P. A., Minna, J. D. and Gallo, R. C. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc. Natl. Acad. Sci. USA*, **77**, 7415–7419 (1980).
2) Hinuma, Y., Nagata, K., Hanaoka, M., Nakai, M., Matsumoto, T., Kinoshita, K., Shirakawa, S. and Miyoshi, I. Adult-T-cell leukemia: antigen in an ATL cell line and the detection of antibodies to the antigen in human sera. *Proc. Natl. Acad. Sci. USA*, **78**, 6476–6480 (1981).
3) Hinuma, Y., Komoda, H., Chosa, T., Kondo, T., Kohakura, M., Takenaka, T., Kikuchi, M., Ichimaru, M., Yunoki, K., Sato, I., Matsuo, R., Takiuchi, Y., Uchino, H. and Hanaoka, M. Antibodies to adult T-cell leukemia-virus-associated-antigen (ATLA) in sera from patients with ATL and controls in Japan: a nationwide sero-epidemiologic study. *Int. J. Cancer*, **29**, 631–635 (1982).
4) Murphy, E. L., Hanchard, B., Figueroa, J. P., Gibbs, W. N., Lofters, W. S., Campbell, M., Goedert, J. J. and Blattner, W. A. Modeling the risk of adult T-cell leukemia/lymphoma in persons infected with human T-lymphotropic virus type I. *Int. J. Cancer*, **43**, 250–253 (1989).
5) Delaporte, E., Dupont, A., Peeters, M., Josse, R., Merlin, M., Schrijvers, D., Hamono, B., Bedjabaga, L., Cheringou, H., Boyer, F., Brun-Vezinet, F. and Larouze, B. Epidemiology of HTLV-I in Gabon (western equatorial Africa). *Int. J. Cancer*, **42**, 687–689 (1988).
6) Tajima, K., The T- and B-cell Malignancy Study Group and Co-authors. The 4th nation-wide study of adult T-cell leukemia/lymphoma (ATL) in Japan: estimates of risk of ATL and its geographical and clinical features. *Int. J. Cancer*, **45**, 237–243 (1990).
7) Gessain, A., Barin, F., Vernant, J. C., Gout, O., Maurs, L., Calender, A. and de Thé, G. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet*, **ii**, 407–410 (1985).
8) Osame, M., Usuku, K., Izumo, S., Ijiri, N., Amitani, H., Igata, A., Matsumoto, M. and Tara, M. HTLV-I associated myelopathy, a new clinical entity. *Lancet*, **i**, 1031–1032 (1986).
9) Nishioka, K., Maruyama, I., Sato, K., Kitajima, I., Nakajima, Y. and Osame, M. Chronic inflammatory arthropathy associated with HTLV-I. *Lancet*, **i**, 441 (1989).
10) Sugimoto, M., Nakashima, H., Watanabe, S., Uyama, E., Tanaka, F., Ando, M., Araki, S. and Kawasaki, S. T-lymphocyte alveolitis in HTLV-I-associated myelopathy. *Lancet*, **i**, 1220 (1987).
11) Nakao, K., Ohba, N. and Matsumoto, M. Noninfectious anterior uveitis in patients infected with human T-lymphotropic virus type I. *Jpn. J. Ophthalmol.*, **33**, 472–481 (1989).
12) Katsuki, T., Katsuki, K., Imai, J. and Hinuma, Y. Immune suppression in healthy carriers of adult T-cell

leukemia retrovirus (HTLV-I): impairment of T-cell control of Epstein-Barr virus-infected B-cells. *Jpn. J. Cancer Res.*, **78**, 639–642 (1987).
13) Tachibana, N., Okayama, A., Ishizaki, J., Yokota, T., Shishime, E., Murai, K., Shioiri, S., Tsuda, K., Essex, M. and Mueller, N. Suppression of tuberculin skin reaction in healthy HTLV-I carriers from Japan. *Int. J. Cancer*, **42**, 829–831 (1988).
14) Nakada, K., Kohakura, M., Komoda, H. and Hinuma, Y. High incidence of HTLV antibody in carriers of strongyloides stercoralis. *Lancet*, **i**, 633 (1984).
15) Yamaguchi, K., Kiyokawa, T., Nakada, K., Lee, S. Y., Asou, N., Ishii, T., Sanada, I., Seiki, M., Yoshida, M., Matutes, E., Catovsky, D. and Takatsuki, K. Polyclonal integration of HTLV-I proviral DNA in lymphocytes from HTLV-I seropositive individuals: an intermediate state between the healthy carrier state and smoldering ATL. *Br. J. Hematol.*, **68**, 169–174 (1988).
16) Khono, S., Koga, H., Kaku, M., Yasuoka, A., Maesaki, S., Tanaka, K., Mitsutake, K., Matsuda, H., Araki, J. and Hara, K. Prevalence of HTLV-I antibody in pulmonary cryptococcosis. *Tohoku J. Exp. Med.*, **167**, 13–18 (1992).
17) Asou, N., Kumagai, T., Uekihara, S., Ishii, M., Sato, M., Sakai, K., Nishimura, H., Yamaguchi, K. and Takatsuki, K. HTLV-I seroprevalence in patients with malignancy. *Cancer*, **58**, 903–907 (1986).
18) Miyazaki, K., Yamaguchi, K., Tohya, T., Ohba, T., Takatsuki, K. and Okamura, H. Human-T-cell leukemia virus type I infection as an oncogenic and prognostic risk factor in cervical and vaginal carcinoma. *Obstet. Gynecol.*, **77**, 107–110 (1991).
19) Lee, S. Y., Matsushita, K., Machida, J., Tajiri, M., Yamaguchi, K. and Takatsuki, K. Human T-cell leukemia virus type I infection in hemodialysis patients. *Cancer*, **60**, 1474–1478 (1987).
20) Tokudome, S., Maeda, Y, Fukada, K., Teshima, D., Asakura, T., Sueoka, E., Motomura, Y., Kusumoto, Y., Imamura, Y., Kiyokawa, T., Ikeda, M. and Tokunaga, O. Follow-up of asymptomatic HTLV-I carriers among blood donors in Kyushu, Japan. *Cancer Causes Control*, **2**, 75–78 (1991).
21) Tajima, K. and Kuroishi, T. Estimation of rate of incidence of ATL among ATLV (HTLV-I) carriers in Kyushu, Japan. *Jpn. J. Clin. Oncol.*, **15**, 423–430 (1985).
22) Tajima, K., Kamura, S., Ito, S., Ito, M., Nagatomo, M., Kinoshita, K. and Ikeda, S. Epidemiological features of HTLV-I carriers and incidence of ATL in an ATL-endemic island: a report of the community-based cooperative study in Tsushima, Japan. *Int. J. Cancer*, **40**, 741–746 (1987).
23) Tokudome, S., Tokunaga, O., Shimamoto, Y., Miyamoto, Y., Sumida, I., Kikuchi, M., Takeshita, M., Ikeda, T., Fujiwara, K., Yoshihara, M., Yanagawa, T. and Nishizumi, M. Incidence of adult-T-cell leukemia/lymphoma among human T-lymphotropic virus type I carriers in Saga, Japan. *Cancer Res.*, **49**, 226–228 (1989).
24) Kondo, T., Kono, H., Miyamoto, N., Yoshida, R., Toki, H., Matsumoto, I., Hara, M., Inoue, H., Inatsuki, A., Funatsu, T., Yamano, N., Bando, F., Iwao, E., Miyoshi, I., Hinuma, Y. and Hanaoka, M. Age- and sex-specific cumulative rate and risk of ATLL for HTLV-I carriers. *Int. J. Cancer*, **43**, 1061–1064 (1989).
25) Ikeda, M., Fujino, R., Matsui, T., Yoshida, T., Komoda, H. and Imai, J. A new agglutination test for serum antibodies to adult T-cell leukemia virus. *Gann*, **75**, 845–848 (1984).
26) Maeda, Y., Imai, J., Kiyokawa, H., Kanamura, M. and Hino, S. Performance certification of gelatin particle agglutination assay for anti-HTLV-I antibody: inconclusive positive results. *Jpn. J. Cancer Res.*, **80**, 915–919 (1989).
27) Kwon, K. W., Ikeda, H., Yano, M. and Sekiguchi, S. Evaluation of the human T-cell leukemia virus type I seropositivity of blood donors by the particle agglutination inhibition test. *Jpn. J. Cancer Res.*, **80**, 833–839 (1989).
28) Ransohoff, D. F. and Feinstein, A. R. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N. Eng. J. Med.*, **299**, 926–930 (1978).
29) Kinoshita, T., Imamura, J., Nagai, H., Ito, M., Ito, S., Ikeda, S., Nagatomo, M., Tajima, K. and Shimotohno, K. Absence of HTLV-I infection among seronegative subjects in an endemic area of Japan. *Int. J. Cancer*, **54**, 16–19 (1993).
30) Harrell, F. E. The PHGLM procedure. *In* "Supplementary User's Guide," pp. 267–294 (1983). SAS Institute, Cary, North Carolina.
31) Stuver, S. O., Tachibana, N. and Mueller, N. Case-control study of factors associated with human T-cell leukemia virus type-I infection in southern Miyazaki, Japan. *J. Natl. Cancer Inst.*, **84**, 867–872 (1992).
32) Miyoshi, I., Yoshimoto, S., Ohtsuki, Y., Fujishita, M., Akagi, T., Yoshiki, T. and Koike, T. Adult T-cell leukemia antigen in renal glomerulus. *Lancet*, **i**, 768–769 (1983).
33) Kaplan, J. E., Osame, M., Kubota, H., Igata, A., Nishitani, H., Maeda, Y., Khabbaz, R. F. and Janssen, R. S. The risk of development of HTLV-I-associated myelopathy/tropical spastic paraparesis among persons infected with HTLV-I. *J. Acquired Immune Defic. Syndr.*, **3**, 1096–1101 (1990).
34) Willet, W. C. Correction for the effects of measurement error. *In* "Nutritional Epidemiology," pp. 272–291 (1990). Oxford University Press, New York.
35) Fujino, R., Kawato, K., Ikeda, M., Miyakoshi, H., Mizukoshi, M. and Imai, J. Improvement of gelatin particle agglutination test for detection of anti-HTLV-I antibody. *Jpn. J. Cancer Res.*, **82**, 367–370 (1991).