Hasegawa H, Komoda M, Yamada Y, Yonezawa S, Tsutsumida H, Nagai K, Atogami S, Tsuruda K, Osaka A, Sasaki D, Yanagihara K, Imaizumi Y, Tsukasaki K, Miyazaki Y, Kamihira S.	Aberrrant Expression of membrane Mucin contributes in tumor progression in ATL.	Leak & Lym	52	1108-17	2011
Hasegawa H, Yamada Y, Tsukasaki K, Mori N, Tsuruda K, Sasaki D, Usui T, Osaka A, Atogami S, Ishikawa C, Machijima Y, Sawada S, Hayashi T, Miyazaki Y, Kamihira S.	LBH589, a deacetylase inhibitor, induces apoptosis in adult T-cell leukemia/lymphoma cells via activation of a novel RAIDD-caspase-2 pathway.	Leukemia	25(4)	575-87	2011
Uchimaru K.	Current problems on the management of HTLV-1 asymptomatic carriers and ATL patients.	Rinsho Ketsueki	52(10)	1432-8	2011
Watanabe T.	Current status of HTLV-1 infection.	Int J Hematol	94(5)	430-4	2011
Tian Y, Kobayashi S, Ohno N, Isobe M, Tsuda M, Zaike Y, Watanabe N, Tani K, Tojo A, Uchimaru K.	Leukemic T cells are specifically enriched in a unique CD3(dim) CD7(low) subpopulation of CD4(+) T cells in acute-type adult T-cell leukemia.	Cancer Sci	102(3)	569-77	2011

Umino A, Nakagawa M, Utsunomiya A, Tsukasaki K, Taira N, Katayama N, Seto M.	Clonal evolution of adult T-cell leukemia/lymphoma takes place in the lymph nodes.	Blood	117(20)	5473-8	2011
Kozako T, Akimoto M, Toji S, White Y, Suzuki S, Arima T, Suruga Y, Matsushita K, Shimeno H, Soeda S, Kubota R, Izumo S, Uozumi K, Arima N.	Target epitopes of HTLV-1 recognized by class I MHC-restricted cytotoxic T lymphocytes in patients with myelopathy and spastic paraparesis and infected patients with autoimmune disorders.	J Med Virol	83(3)	501-9	2011
Ogata M, Satou T, Kawano R, Yoshikawa T, Ikewaki J, Kohno K, Ando T, Miyazaki Y, Ohtsuka E, Saburi Y, Kikuchi H, Saikawa T, Kadota J.	High incidence of cytomegalovirus, human herpesvirus-6, and Epstein-Barr virus reactivation in patients receiving cytotoxic chemotherapy for adult T cell leukemia.	J Med Virol	83(4)	702-9	2011
Sasaki D, Imaizumi Y, Hasegawa H, Osaka A, Tsukasaki K, Choi YL, Mano H, Marquez VE, Hayashi T, Yanagihara K, Moriwaki Y, Miyazaki Y, Kamihira S, Yamada Y.	Overexpression of Enhancer of zeste homolog 2 with trimethylation of lysine 27 on histone H3 in adult T-cell leukemia/lymphoma as a target for epigenetic therapy.	Haematologica	96	712-9	2011

Koh H, Nakamae H, Hagihara K, Nakane T, Manabe M, Hayashi Y, Nishimoto M, Umemoto Y, Nakamae M, Hirose A, Inoue E, Inoue A, Yoshida M, Bingo M, Okamura H, Aimoto R, Aimoto M, Terada Y, Koh KR, Yamane T, Ohsawa M, Hino M.	Factors that contribute to long-term survival in patients with leukemia not in remission at allogeneic hematopoietic cell transplantation.	J Exp Clin Cancer Res	30	36	2011
Kannagi M, Hasegawa A, Kinpara S, Shimizu Y, Takamori A, Utsunomiya A.	Double control systems for human T-cell leukemia virus type 1 (HTLV-1) by innate and acquired immunity.	Canter Sci	102(4)	670-6	2011
Oka T, Satou H, Ouchida M, Utsunomiya A, Yoshino T.	Cumulative epigenetic abnormalities in host genes with viral and microbial infection during initiation and progression of malignant lymphoma/leukemia.	Cancers	3	568-81	2011

Waki F, Masuoka K, Fukuda T, Kanda Y, Nakamae M, Yakushijin K, Togami K, Nishiwaki K, Ueda Y, Kawano F, Kasai M, Nagafuji K, Hagihara M, Hatanaka K, Taniwaki M, Maeda Y, Shirafuji N, Mori T, Utsunomiya A, Eto T, Nakagawa H, Murata M, Uchida T, Iida H, Yakushiji K, Yamashita T, Wake A, Takahashi S, Takaue Y, Taniguchi S.	Feasibility of reduced-intensity cord blood transplantation as salvage therapy for graft failure: results of a nationwide survey of adult patients.	Biol Blood Marrow Transplant	17(6)	841-51	2011
Uota S, Dewan MZ, Saitoh Y, Muto S, Itai A, Utsunomiya A, Watanabe T, Yamamoto N, Yamaoka S.	An IκB kinase 2 inhibitor IMD-0354 suppresses the survival of adult T-cell leukemia cells.	Cancer Sci	103(1)	100-6	2011
Nakai A, Minakami H, Unno N, Saito S, Morikawa M, Yoshimura Y, Terao T.	Characteristics of pregnant Japanese women who required hospitalization for treatment of pandemic (H1N1) 2009.	J Infect	62	232-3	2011

齋藤 滋.	HTLV-I母子感染対策のために助産師が知っておきたい知識	ペリネイタルケア	31	65-71	2012
山野嘉久、佐藤知雄、安藤仁、新谷奈津美、八木下尚子.	HTLV-1関連脊髄症（HAM）の治療法を確立していくために―その現状と展望―	日本臨牀			2011 in press
山野嘉久.	HTLV-1キャリアー，HTLV-1-associated myelopathy(HAM)患者診療の現状と問題点	血液内科	63(1)	81-6	2011
安藤仁、八木下尚子、新谷奈津美、佐藤知雄、山野嘉久.	HTLV-1関連脊髄症（HAM）の病態と治療	医療と検査機器・試薬 別冊 機器・試薬	34(4)	472-7	2011
上平 憲.	HTLV-1感染の特性と成人T細胞白血病－ウイルス母子感染対策－	宝函32(2)	32(2)	13-23	2011
高崎由美、岩永正子、塚崎邦弘.	話題：くすぶり型・慢性型成人T細胞白血病リンパ腫に対する無治療経過観察は適切な選択か?	血液内科（科学評論社）	63	40-5	2011
山野嘉久、佐藤知雄、新谷奈津美、安藤仁、八木下尚子.	HAM専門外来の取り組み	神経内科	75(4)	387-92	2011
武清孝弘、宇都宮與、村山芳博、内田綾子、中野伸亮、竹内昇吾、高塚祥芝、三石敬之、堂園浩一朗.	自家末梢血幹細胞移植患者の体力とQOL変化	総合リハビリテーション	39(6)	563-8	2011
宇都宮與.	One Point Advice 日和見感染症	M.P. Medical Practice 8	28(8)	1477	2011
宇都宮與、石田高司、鵜池直邦、瀬戸加大.	Round Table Discussion 成人T細胞白血病研究の進歩と今後の展望	Trends in Hematological Malignancies	3(2)	8-15 (64-71)	2011

齋藤 滋.	母子免疫	日本輸血・細胞治療学会認定医制度カリキュラム			2011
種部恭子、 齋藤 滋、 佐竹紳一郎、 澤木 勝、 十二町明、 中山哲規、 長谷川徹、 布施秀樹.	富山県における性感染症全数調査および定点の適正性に関する検討	日本性感染症学会誌	22	62-72	2011
齋藤 滋.	HTLV-I 感染症.	周産期医学	41	1099-103	2011
齋藤 滋、 杉浦真弓、 丸山哲夫、 田中忠夫、 竹下俊行、 山田秀人、 小澤伸晃、 中塚幹也、 木村正、 藤井知行、 下屋浩一郎、 山本樹生、 佐田文宏、 康東天、 早川智、 一瀬白帝、 柳原格、 秦健一郎、 勝山博信、 堤康央、 中野有美、 福井淳史、 杉俊隆.	不育症 over view	産婦人科の実際	60	1401-8	2011
齋藤 滋.	妊婦健診における感染症スクリーニング検査	ロシュ・ダイアグノスティックス株式会社.（リーフレット）			2011
齋藤 滋.	座長のまとめ 教育講演10：「HTLV-I母子感染防止―長崎県における24年間の取り組み―」増崎英明	日本周産期・新生児医学会雑誌	47	772	2011

IV. 研究成果の刊行物・印刷

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Current Prevalence of HTLV-1 in Japan as Determined by Screening of Blood Donors

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Human T-cell leukemia virus type-1 (HTLV-1), a major source of adult T-cell leukemia and related diseases, is endemic to southwestern Japan. Mother-to-infant transmission via breast milk is an important route of infection, and establishing programs to prevent such transmission requires exact figures on the HTLV-1 prevalence rate and the number of carriers. Therefore, the seroprevalence of HTLV-1 among 1,196,321 Japanese first-time blood donors from 2006 to 2007 was investigated. A total of 3,787 of such donors were confirmed to be positive for anti-HTLV-1 antibody. By applying a fitness curve to the age ranges outside the blood donor age range, the present number of HTLV-1 carriers covering ages from 0 to 99 years was estimated to be at least 1.08 million in Japan; this value was 10% lower than that reported in 1988. The adjusted overall prevalence rates were estimated to be 0.66% and 1.02% in men and women, respectively. The peak in carrier numbers was found among individuals in their 70s, which is a shift from the previous peak observed in the 1988 database among individuals in their 50s. Carriers were distributed not only in the endemic southwestern region of Japan, but throughout the country, particularly in the greater Tokyo metropolitan area. By applying population projections, it was calculated that the carrier number will decrease by half in the next two decades; however, the carrier population will age over that interval, meaning that the age of patients with adult T-cell leukemia will also be higher. ***J. Med. Virol. 84:327–335, 2012.*** © 2011 Wiley Periodicals, Inc.

KEY WORDS: HTLV-1; seroprevalence; blood donors

INTRODUCTION

The human T-lymphotropic virus type 1 (HTLV-1; *Retroviridae, Deltaretrovirus, Simian T lymphotropic virus*) is a pathogenic retrovirus that causes adult T-cell leukemia, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), and uveitis [Takatsuki et al., 1977; Hinuma et al., 1981; Gessain et al., 1985; Osame et al., 1986; Mochizuki et al., 1992]. HTLV-1 prevalence shows a peculiar geographical distribution pattern, with virtually exclusive concentration in southwestern Japan, the Caribbean islands, regions of South America, and tropical Africa [Manns and Blattner, 1991; Mueller, 1991]. The high endemicity of the virus and the seriousness of the resulting diseases have prompted epidemiological research on the mode of viral transmission. Three major routes of viral transmission have been established: (1) mother-to-infant transmission, mainly via breast-feeding [Yamanouchi et al., 1985; Kinoshita et al., 1987]; (2) sexual transmission, predominantly male to female [Tajima et al., 1982; Murphy et al., 1989]; and (3) transfusion by cellular blood components [Okochi et al., 1984]. Transmission of the virus via transfusion has virtually been eliminated since the implementation of viral screening of donated blood in 1986 [Ikeda et al., 1984; Inaba et al., 1989]; thus, transmission today is mostly confined to the mother-to-infant and sexual routes. Carriers of the virus are readily identified by screening for the anti-HTLV-1 antibodies, and the most effective measure for the prevention of mother-to-infant transmission is apparent (i.e., bottle feeding). Hence, the implementation of strategies to prevent transmission is considered a matter of both public health and public policy in endemic areas [Hino, 2003]. Although several local governments in

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southwestern Japan have implemented a screening and consultation system, national guidelines for HTLV-1 screening have not been created; the screening of pregnant women for the virus has been left to individual gynecologists. The establishment of a program for carrier management would be facilitated by data on HTLV-1 prevalence rates and carrier numbers. To determine the current status of HTLV-1 infection in Japan, the HTLV-1 carriage rate among first-time blood donors during 2006 and 2007 was investigated, and the results were used to deduce the number of carriers in the entire country. In combination with published data on population projections, the results permitted an estimate of future changes in the number of carriers.

MATERIALS AND METHODS

Screening for Anti-HTLV Antibodies

In Japan, blood centers of the Japanese Red Cross (JRC) are the sole facilities authorized to handle blood collection, testing, processing, and distribution. In 1986, the JRC implemented an agglutination assay to screen for the presence of anti-HTLV-1 antibodies [Inaba et al., 1989]; use of this test continued until 2008. Prior to donation, all blood donors were informed that donated blood would be tested for anti-HTLV-1 antibodies. Blood donors examined in the current study were first-time donors (i.e., donors who have no record of blood donation for approximately the preceding 10 years) who donated blood during the 2 years from January 1, 2006 to December 31, 2007. Enrolling only first-time donors for the present study precluded the recounting of seronegative donors. Samples that were positive by the agglutination assay were subjected to a confirmatory test that employed immunofluorescence staining of the target MT-2 cell line [Miyoshi et al., 1981]. Only donors who were positive by the confirmatory test were included in the present study.

Estimation of Number of Carriers

Current and prospective population statistics for Japan were obtained from the vital statistics [National Statistics Center, 2009a] published by the Japanese Ministry of Health, Labour, and Welfare. The HTLV-1 prevalence rate among the first-time donors was obtained for each category defined by age, sex, and Prefecture. The number of HTLV-1 carriers in each category was estimated by projecting the detected prevalence rate to the population of that category. The ages of blood donors were categorized by intervals of 10 years. To deduce the carrier number for combined larger categories, the estimated carrier numbers were summed for the respective categories. Figures thus obtained are equivalent to those that are adjusted for age, sex, and Prefecture.

For most of the analyses, the 47 Prefectures of Japan were grouped into seven districts: Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku/Shikoku, and Kyushu. However, the number of carriers in Hokkaido and Tohoku were combined for the purpose of comparing changes in carrier numbers over the past two decades. To assess the distribution of the mean prevalence rates among Prefectures, the seven districts were grouped further into three larger regions, as follows (see also the map in Figure 4): eastern and central Japan (consisting of the Hokkaido, Tohoku, Kanto, and Chubu districts); western Japan (consisting of the Kinki and Chugoku/Shikoku districts); and southwestern Japan (consisting of the Kyushu district).

In Japan, the age of eligibility for blood donation was 16–64 years during the study period. For simplicity, the prevalence rate in the population in the 16–19 age category was assumed to correspond to that of the population in the 15–19 age category. The prevalence rates in the populations in the 0–4, 5–9, and 10–14 age categories were estimated by assuming that the prevalence rates in these cohorts form an exponential series with those of the 15–19, 20–29, 30–39, and 40–49 age categories. The corresponding curve was defined by the equation $R_a = R_0 \times e^{ba}$, where R_a and R_0 indicate the seropositivity rates at ages a and 0, respectively. The prevalence rate for the 10–19 age category was derived by combining the prevalence for the 15–19 age category with the estimated rate for the 10–14 age category. Similarly, the rate for the 0–9 age category was deduced by combining the rates for the 0–4 and 5–9 age categories.

The prevalence rate for the population in the 60–64 age category was assumed to correspond to that of the population in the 60–69 age category. The prevalence rates for the populations in the 70–79, 80–89, and 90–99 age categories were estimated based on the observation (1988 data) that prevalence rates increased in an essentially linear fashion between 30 and 64 years of age [Hashimoto et al., 1991]. Two decades later, prevalence rates in the population aged 50- to 84-year old are expected to be equal to or higher than that in the population aged 30–64 years observed in 1988.

Reevaluation of the Number of Carriers Surveyed in 1988

In 1988, a nationwide survey was carried out among blood donors to estimate the number of HTLV-1 carriers in the entire country [Hashimoto et al., 1991]. That study screened for seropositivity among all donors, not just first-time donors. However, data were collected only for donations made during a 1-month interval, which should have precluded data from repeated donations. In addition, at the time of that study, donors were not yet being notified of their HTLV-1 status, meaning that seropositive donors could continue donating blood. Prevalence rates obtained under these conditions (Table I) were regarded as equivalent to the rates expected for first-time blood

TABLE I. HTLV-1 Prevalence Rate Among Blood Donors in 1988 [Hashimoto et al., 1991]

Age categories	16–19	20–29	30–39	40–49	50–64
Hokkaido					
Male	0.17	0.47	0.63	0.83	0.83
Female	0.26	0.29	0.68	1.35	1.25
Tohoku					
Male	0.29	0.23	0.52	0.97	0.93
Female	0.23	0.33	0.59	0.84	1.17
Kanto					
Male	0.16	0.28	0.5	0.65	0.83
Female	0.15	0.29	0.59	0.84	1.21
Chubu					
Male	0.16	0.29	0.31	0.46	0.48
Female	0.19	0.36	0.57	0.86	0.84
Kinki					
Male	0.16	0.43	0.8	1.05	1.14
Female	0.35	0.52	1.13	1.47	1.84
Chugoku					
Male	0.08	0.39	0.53	0.87	0.88
Female	0.22	0.3	0.71	0.91	1.36
Shikoku					
Male	0.26	0.5	0.61	0.68	1.23
Female	0.29	0.46	1.29	1.03	1.82
Kyushu					
Male	0.75	1.44	2.69	3.71	5.21
Female	0.93	1.38	2.99	5.05	7.65
Whole country					
Male	0.23	0.44	0.8	1.03	1.37
Female	0.29	0.48	1.01	1.43	2.1

The 50–59 years category is combined with 60–64 years category in the 1991 study. Prevalence rates for the Chugoku and Shikoku districts are shown separately. Values are shown as percentages.

donors. Therefore, the 1988 survey estimated the total number of carriers at approximately 1.2 million for the entire country [Tajima et al., 1990]. There were, however, no published estimates on the number of carriers outside the eligible age range for blood donation. To address this issue, the numbers of carriers under 16 and over 64 years were re-examined and the analysis incorporated the assumptions described above, namely an exponential rate increase under 16 years, and a linear rate increase over 64 years.

Statistical Analysis

Differences in the mean prevalence rates in Prefectures among the three large regions were assessed using the Mann–Whitney *U*-test. Differences in prevalence rates between sexes and between 1988 and 2006–2007 were assessed using the chi-squared test. Unless otherwise indicated, a *P*-value of <0.05 was considered significant.

RESULTS

From 2006 to 2007, the JRC blood centers accepted 1,196,321 blood donations from first-time donors. Of the samples that tested-positive by agglutination assay, 3,787 (0.317% of all the first-time donors) were confirmed to be positive for anti-HTLV-1 antibody using the immunofluorescence test. The prevalence rates adjusted for age and sex were obtained for each Prefecture, and the maximum, minimum, and median were derived for each of the three large regions described above (eastern and central Japan, western Japan, and southwestern Japan; Table II). The prevalence rates for Prefectures were significantly different among the three large regions. As expected, prevalence rates were highest in southwestern Japan (where HTLV-1 is endemic); additionally, prevalence rates in western Japan were significantly higher than those in eastern and central Japan (Table II).

The nationwide prevalence rate, adjusted for district, is shown as a function of age in Figure 1. The observed rate increased sharply with the age of the donor. The difference in prevalence rate between sexes was significant for donors in their 20s, 30s, 50s, and 60s, and there was a trend toward increasing differences between sexes in the elderly. For example, the absolute prevalence rate differences between sexes were 0.29% and 0.37% for donors in their 50s and 60s, respectively; compare these values to differences of 0.05% and 0.06% for those in their 30s and 40s, respectively. Table III shows the age distribution of prevalence rate for each district. As expected, the highest rate was observed in the Kyushu districts (southwest Japan). The two Prefectures with the highest prevalence rates in the country were both located in the Kyushu district; the corresponding rates are shown in Figure 2. Notably, in both these Prefectures, the prevalence rates among under 40 donors were <2%, with large increases among older donors. For example, in one of the Prefectures (Fig. 2A), the mean rate for all donors was 1.95%, and the rates in the 60–64 age category were 14.0% and 8.7% for females and males, respectively. Thus, almost 1 out of 50 first-time donors were positive for the anti-HTLV-1 antibody in this Prefecture. For the entire nation, the total number of carriers aged 15–64 years in the Japanese population was calculated to be 510,000; this value was obtained by summing the total number of carriers from all districts.

The prevalence rates and the numbers of carriers in the populations under 15 years and over 64 years of age were estimated on the basis of the assumptions described above. The distribution of the estimated prevalence rate also is included in Table III; these estimates are indicated in italics. The overall prevalence rates covering all age categories from 0 to 99 years were calculated as 0.66% and 1.02% for males and females, respectively (data not shown). By summing up the projected carrier numbers within the blood donor age categories and the estimated carrier numbers outside the donor age categories, the total number of carriers aged 0–99 in Japan was calculated to be 1.08 million. This value was 10% lower than that derived in the 1988 study. The nationwide distribution of the number of carriers as a function of age is shown in Figure 3 (closed triangles). According to our analysis, carrier numbers are highest among individual in their 70s, followed by those in their 60s and 50s.

TABLE II. Mean Prevalence Rates Among Blood Donors (2006–2007) by Region

Region	Districts included (number of Prefectures included)		Min.	Max.	Med.
Eastern and Central Japan[a]	Hokkaido (1), Tohoku (6), Kanto (9), Chubu (8)	Male	0.04	0.26	0.11
		Female	0.04	0.32	0.15
		Total	0.06	0.26	0.13
Western Japan[a]	Kinki (6), Chugoku/Shikoku (9)	Male	0.05	0.41	0.25
		Female	0.09	0.53	0.30
		Total	0.10	0.45	0.27
Southwestern Japan[a]	Kyushu (8)	Male	0.48	2.01	0.93
		Female	0.83	2.43	1.29
		Total	0.62	1.95	1.07

Regional minimum (Min.), maximum (Max.), and median (Med.) of prevalence rates in Prefectures are shown (%), with the whole country divided into three regions as indicated. Note that the Niigata and Yamanashi Prefectures are included in the Kanto district.
[a]Statistically significant differences in prevalence rate among the three regions (Eastern/Central vs. Western vs. Southwestern; $P < 0.05$; Mann–Whitney U-test).

Comparison of country-wide prevalence rates between 2006 and 2007 and 1988 (bottom rows of Tables I and III) revealed that the 1988 rates were significantly higher than the 2006–2007 rates for both sexes in all donor age categories, that is, for donors aged 16–19, 20–29, 30–39, 40–49, and 50–64 years of age ($P < 0.01$; chi-squared test). The 1988 prevalence rates for those under 15 years and over 64 years of age were estimated using the methods described above, and the numbers of carriers in 1988 were deduced for all age categories. In Figure 3, the carrier numbers derived from the 1988 data (open circles) are overlaid with those derived from the 2006 to 2007 data. For the 1988 values, the carrier numbers form a roughly symmetrical curve, with values peaking for individuals in their 50s. Over the course of the subsequent two decades, the curve shifted to the right (i.e., skewed older). By 2006–2007, the number of carriers over 70 years of age had increased by 69% (178,000), whereas the number of carriers under 60 years of age had decreased by 50% (405,000).

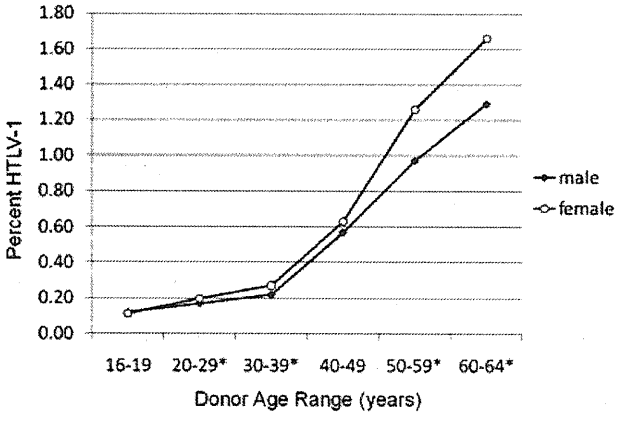

Fig. 1. Anti-HTLV-1 antibody prevalence rate among Japanese blood donors as a function of donor age. Prevalence rate was normalized by district population. Prevalence rates (%) of the anti-HTLV-1 antibody are plotted as a function of donor age range in males (closed diamonds) and females (open circles). Exact figures for the prevalence rates in each age and sex categories are derived from the bottom row of Table III. *Statistically significant difference between sexes ($P < 0.05$; chi-squared test).

Figure 4 depicts the changes in the total carrier numbers over the past two decades in relation to geography (district). Nationwide, the carrier number had decreased by 10% since 1988. The largest decreases were seen in the Hokkaido/Tohoku, Kyushu, and Kinki districts, which exhibited decreases of 44%, 19%, and 16%, respectively. Together, these three districts were calculated to have 208,000 fewer carriers by 2006–2007. On the other hand, the number of carriers increased by 46% (60,000 more carriers) in the Kanto district and by 41% (24,000 more carriers) in the Chubu district.

By using published data for population forecasts, and assuming that the Japanese population will age while maintaining its current HTLV-1 prevalence rate, both carrier number and the age distribution of carriers in the future was predicted. The analysis suggested that the number of carriers will decrease by approximately 2.5% each year, potentially reaching as low as 560,000 (a twofold decrease) by 2027. The projected age distribution of carriers is shown in Figure 5. It is predicted that the peak of the number of carriers will continue to be observed among individuals in their 70s, whereas the number of carriers in their 50s and 60s will decrease markedly.

DISCUSSION

Japan is one of the few developed countries with a high prevalence rate for HTLV-1 carriage. The country is thus in a unique position to establish the scientific basis for medical intervention and public policy for prevention and cure of HTLV-1-related diseases. There has, however, been no nationwide survey of HTLV-1 carriage in Japan since 1988, although several intensive screening tests have been performed for local residents and patients or pregnant women at medical facilities [Tajima et al., 1990; Morofuji-Hirata et al., 1993; Mueller et al., 1996; Taylor et al., 2005]. Our data not only clarify the current status of HTLV-1 in Japan but also reveal epidemiological changes in the carrier status over the past two decades.

HTLV-1 prevalence rate and the number of HTLV-1 carriers often have been deduced from the results of

TABLE III. HTLV-1 Prevalence Rate in 2006–2007 in All Age Categories

Age categories	0–9	10–19	16–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99
Hokkaido											
M	*0.04*	*0.08*	0.09	0.17	0.15	0.49	0.54	0.70	*0.72*	*0.82*	*0.92*
F	*0.02*	*0.04*	0.04	0.18	0.10	0.46	0.79	1.13	*1.14*	*1.37*	*1.62*
Tohoku											
M	*0.03*	*0.05*	0.06	0.11	0.10	0.29	0.38	1.52	*1.13*	*1.33*	*1.53*
F	*0.02*	*0.04*	0.05	0.13	0.12	0.41	0.48	1.20	*1.22*	*1.47*	*1.72*
Kanto											
M	*0.03*	*0.05*	0.06	0.10	0.09	0.28	0.61	0.67	*0.90*	*1.06*	*1.22*
F	*0.02*	*0.05*	0.05	0.09	0.14	0.37	0.65	0.80	*1.22*	*1.53*	*1.84*
Chubu											
M	*0.03*	*0.06*	0.07	0.13	0.13	0.35	0.43	0.51	*0.55*	*0.64*	*0.72*
F	*0.03*	*0.05*	0.06	0.13	0.28	0.39	0.80	0.39	*0.97*	*1.10*	*1.24*
Kinki											
M	*0.05*	*0.10*	0.12	0.15	0.24	0.52	1.11	1.38	*1.46*	*1.63*	*1.80*
F	*0.05*	*0.08*	0.10	0.19	0.27	0.65	1.51	1.73	*2.16*	*2.51*	*2.86*
Chugoku/Shikoku											
M	*0.05*	*0.10*	0.11	0.21	0.17	0.40	0.66	1.00	*1.15*	*1.37*	*1.59*
F	*0.04*	*0.07*	0.09	0.19	0.22	0.32	0.87	0.98	*1.21*	*1.37*	*1.53*
Kyushu											
M	*0.19*	*0.35*	0.41	0.55	1.00	2.32	3.40	5.04	*6.23*	*7.49*	*8.75*
F	*0.20*	*0.37*	0.44	0.74	0.95	2.18	4.28	7.34	*9.44*	*11.77*	*14.10*
Whole country											
M	*0.06*	*0.10*	0.12	0.17	0.22	0.57	0.97	1.29	*1.59*	*1.92*	*2.19*
F	*0.05*	*0.09*	0.11	0.20	0.27	0.63	1.26	1.66	*2.36*	*2.96*	*3.48*

Figures for the 16–19 age category were derived from screening data and are indicated in non-italicized font; figures for the 10–19 age category were derived from the combination of screening data (for 16–19 years) and deduced data (10–15 years), and are indicated in italicized font. For the prevalence rate for the 60–69 age category, values for the 60–64 age category were used. Figures are shown as percentages; italics indicate estimated figures.

screening of local residents or patients. However, such surveys are of limited use for estimating figures for a larger population, either because of small population size, geographic focus, or skewing due to the underlying health status of the population examined. In this regard, the population of voluntary blood donors has been an appealing alternative for the estimation of the prevalence rate of asymptomatic diseases or carriage status; a large amount of data could be obtained from otherwise healthy individuals and from almost all areas of the country with a relatively even sampling rate. It is essential in a blood donor-based study to obtain data from first-time donors who have not been screened for the disease marker, thus

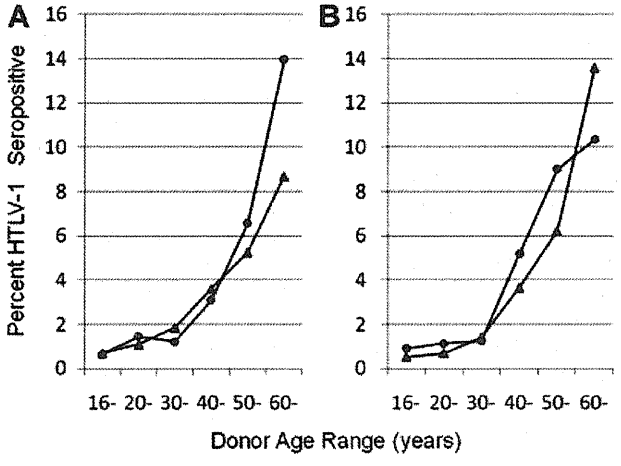

Fig. 2. Age distribution of HTLV-1 prevalence rate in Prefectures A and B in Kyushu district. Prevalence rates (%) of the anti-HTLV-1 antibody are plotted as a function of donor age range in males (closed triangles) and females (closed circles). Prefectures A and B were selected because these Prefectures have the highest mean prevalence rates in Japan.

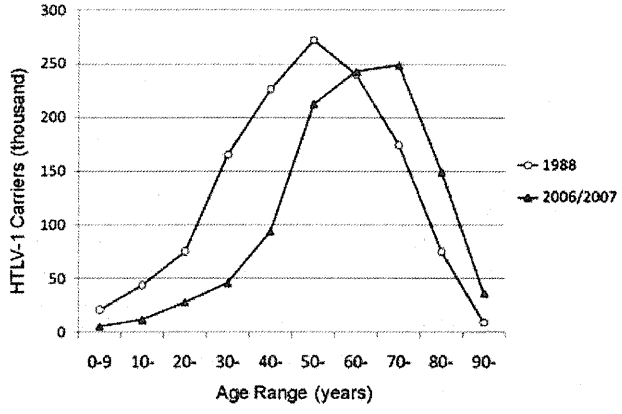

Fig. 3. Age distribution of HTLV-1 carriers estimated for 1988 and 2006–2007. Number of HTLV-1 carriers are shown for the respective age ranges in 1988 (open circles) and 2006–2007 (closed triangles). For the age categories between 20 and 59 years, carrier numbers were based on the results of blood donor screening; for the age categories 0–9 and 70–99 years, numbers were deduced from the assumed prevalence curve; for the age categories 10–19 and 60–69, numbers were derived from a combination of screening data and deduced data.

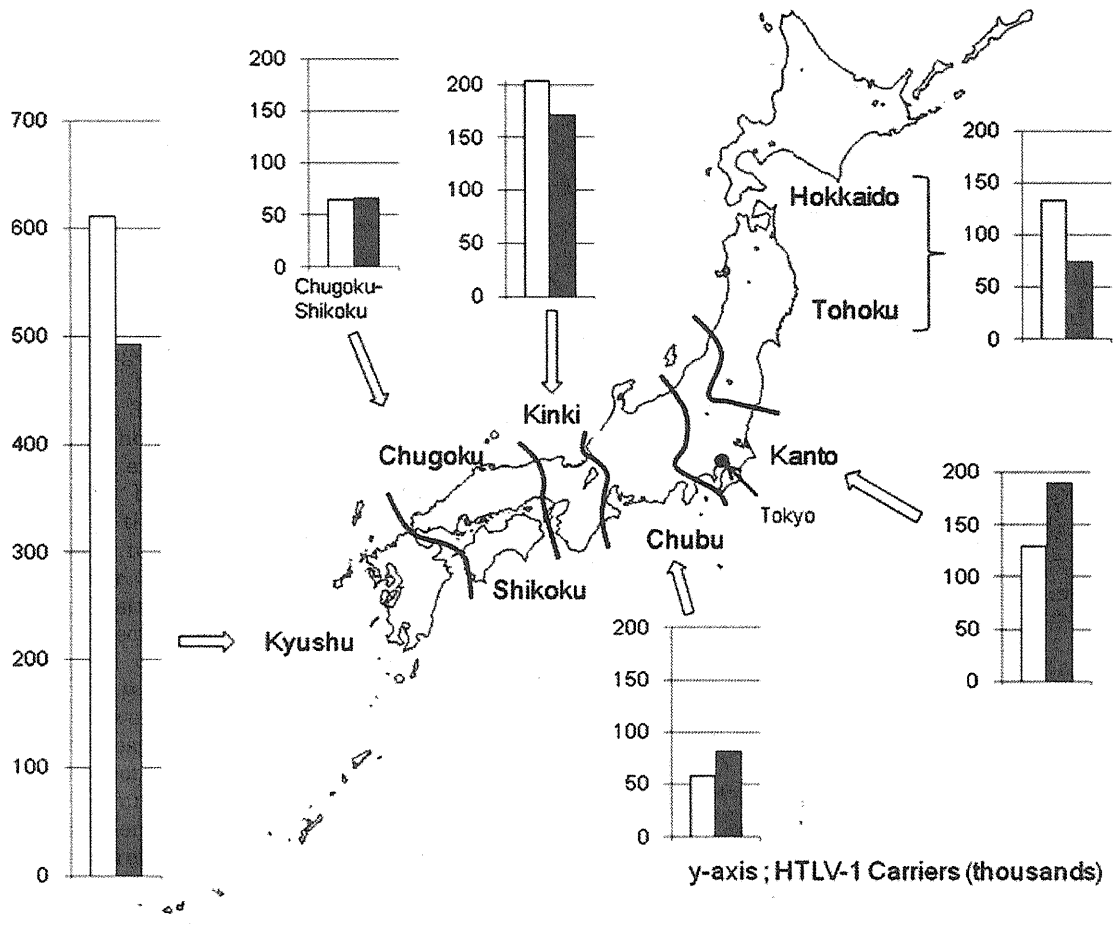

Fig. 4. Changes in the total number of carriers aged (0–99) in six districts of Japan over past two decades. Carrier numbers (thousands) are indicated for 1988 (white bars) and 2006–2007 (black bars). For this analysis, Japan was divided into six districts, such that the Hokkaido and Tohoku districts were combined, and the Niigata and Yamanashi Prefectures were included in the Kanto district.

reducing the chances of bias (e.g., repeated donation by marker-negative donors). This strategy makes it possible to project the obtained data to the general population.

Despite the exclusive use of first-time donors, our data set may still provide skewed conclusions, particularly in the study of HTLV-1. First, people diagnosed with HTLV-1-related diseases, and HTLV-1 carriers identified during the screening of pregnant women, are unlikely to be blood donors, but nonetheless should be counted as seropositives. Second, family members of patients with HTLV-1-related diseases and of HTLV-1 carrier women are less likely themselves to be blood donors. Third, blood donors are typically healthier than the general population, including a reduced likelihood of HTLV-1-associated illnesses [Atsma et al., 2011]. All of these factors would render the observed (donor) HTLV-1 prevalence rate lower than the actual value. Thus, the results of this study represent a lower estimate of HTLV-1 prevalence. Indeed, most studies on HTLV-1 prevalence rates obtained from the screening of local inhabitants, pregnant women, or hospital patients suggest higher prevalence rates than those seen in blood donor-based studies [Hlela et al., 2009; Koga et al., 2010]. In addition, although young first-time donors may be representative of their age group, the first-time donors in older cohorts are less likely to be representative, because older individuals donate blood after self-selection and medical exclusion as described above; the motives for blood donation also will differ between such groups. These distinctions make it difficult to evaluate prevalence rates evenly between younger and older donors. Nonetheless, our analysis provides key prevalence data in terms of sample size and geographic range, potentially permitting regional and even international comparisons.

Combining the prevalence rate deduced from donor measurement and the rate estimated from the theoretical curve, the overall prevalence rates covering all age categories were calculated to be 0.66% and 1.02% for men and women, respectively. The total number of HTLV-1 carriers in Japan was estimated to be 1.08 million, of which 0.51 million were derived from the

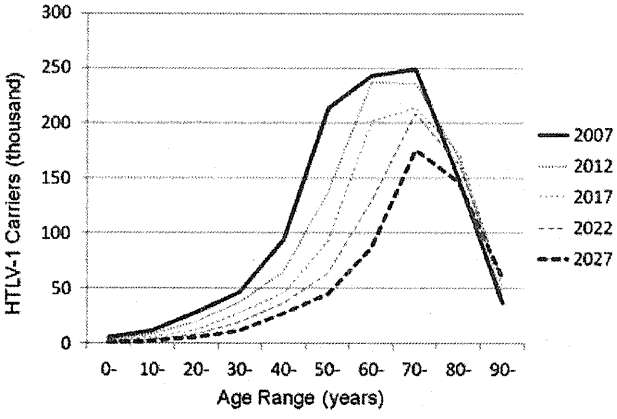

Fig. 5. Projected age distribution of HTLV-1 carriers over the next two decades. Age distribution for HTLV-1 carriage is projected at 5-year intervals for the next 20 years, from 2007 (bold solid line) through 2027 (bold broken line).

blood donor age categories. As noted above, these values are likely to represent lower limits: while the prevalence rate among people over 64 years of age was estimated based on the assumption that the rate increases linearly from 40 years of age, empirical results indicate that the increase in the rate becomes greater as the population ages.

Aside from transfusion-related transmission, horizontal transmission of HTLV-1 is believed to occur predominantly from men to women through sexual contact [Kajiyama et al., 1986; Murphy et al., 1989]. In fact, it may be possible to estimate horizontal transmission rates based on our data, by comparing the prevalence rates between the first-time donors in an age category in 1988 to those in the respective (20-year older) age category for 2006–2007. Such an analysis, however, risks the drawing of a skewed conclusion because of multiple assumptions needed to calculate the rate. Indeed, discordant results about sexual transmission have been reported even within cohort studies [Iga et al., 2002; Roucoux et al., 2005]. In the setting of blood donation, determination of the horizontal transmission rate would require following a large number of blood donors for several decades so as to track HTLV-1 seroconversion.

Most women under 30 years of age, and a considerable proportion of women in their 30s, are potential childbearers. The analysis suggests the existence of approximately 30,000 carriers among Japanese women in these age categories. Assuming that the total fertility rate in Japan is 1.32 [National Statistics Center, 2009b] and that the mother-to-infant HTLV-1 transmission rate is 20% [Nakano et al., 1986; Sugiyama et al., 1986; Wiktor et al., 1993], it is calculated that 7,900 children born to carrier mothers will be infected with HTLV-1 in the absence of future interventions to prevent mother-to-infant transmission.

Although the number of carriers 0–99 years of age decreased by 10% over the past two decades, the most remarkable change during that time was the aging of the carriers, as revealed by the rightward shift of the curve in Figure 3. Particularly noteworthy was the increase in the number of carriers over 70 years of age: this age category constituted 258,000 (22% of all carriers) in 1988, as opposed to 436,000 (40% of all carriers) in 2006–2007. Most likely, this aging of HTLV-1 carriers was a "birth cohort effect," whereby the high-prevalence cohort (those born 1930–1960) ages, while younger cohorts (those born after 1960) have lower prevalence rates. In addition, the extension of Japanese lifespan seems to have augmented the trend toward the carrier aging; the average lifespan of the Japanese has extended by 4 and 5 years for men and women, respectively, over the past two decades [Ministry of Health, Labour, and Welfare, 2009].

The geographical distribution of HTLV-1 seroprevalence among blood donors was highly variable, ranging from 0.06% in a Prefecture in eastern Japan up to 1.95% in a Prefecture in Kyushu. The carriers in the Kyushu district accounted for 45.7% of all carriers deduced for all age categories (0–99) in Japan. Changes in the distribution of carriers (0–99) over the past two decades revealed increasing numbers of carriers in the Kanto district, which includes the greater metropolitan Tokyo area, and in the Chubu district. In part, this pattern can be explained by the movement of population from northeastern and western Japan to the metropolitan and central areas. Over the past two decades, nationwide population rose 4.1%. During this interval, the population rose by 9.2% and 5.6% in the Kanto and Chubu districts, respectively, whereas population has decreased by 1.8% in the Hokkaido/Tohoku district or increased only marginally (1.1%) in the Kyushu district [National Statistics Center, 2009c]. Clearly, the carrier population has redistributed along with the movement of the general population. These results reveal that the prevention of HTLV-1 transmission is not an issue limited to the Kyushu district, but is now a challenge for the entire country.

On the basis of population projections, the changes in the number of HTLV-1 carriers were estimated for the next two decades. Although the number of carriers is expected to decrease by 50% in the next two decades, the age-based skew of the carriers is expected to become more prominent, with the peak number of carriers continuing to be those in their 70s. Accordingly, the population of adult T-cell leukemia patients is expected to become older. Since the conventional treatment strategy is inapplicable for these patients [Hermine et al., 1998; Tsukasaki et al., 2009; Tanosaki and Tobinai, 2010], this shift will represent a new medical challenge.

In conclusion, the study indicated that the number of HTLV-1 carriers in Japan is currently 1.08 million at the minimum, and that the carriers are distributed throughout the country. Intensive discussion and nationwide surveys will be needed to identify carriers, to educate seropositive individuals on the prevention

of mother-to-infant transmission, and to establish a consultation system for these people. Although the carrier number is expected to decrease by half in the next two decades, carrier population will age along with the general population. It is essential to establish a novel consensus regimen for the care and treatment of elderly patients with HTLV-1-associated diseases.

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REFERENCES

Atsma F, Veldhuizen I, Verbeek A, de Kort W, de Vegt F. 2011. Healthy donor effect: Its magnitude in health research among blood donors. Transfusion 51:1820–1828.

Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A, de Thé G. 1985. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 2:407–410.

Hashimoto S, Funamoto T, Yamanaka R, Nishioka K. 1991. Study of the HTLV-I carrier status (distribution of carrier rate by districts). Report on the study of the prevention of mother-to-infant transmission of ATL. Tokyo, Japan: Ministry of Health, Labour and Welfare, pp 39–43.

Hermine O, Wattel E, Gessain A, Bazarbachi A. 1998. Adult T cell leukaemia: A review of established and new treatments. BioDrugs 10:447–462.

Hino S. 2003. Primary prevention of adult T cell leukemia (ATL) in Nagasaki, Japan by refraining from breast-feeding. In: Sugimura K, Uchiyama T, Matsuoka M, Kannagi M, editors. Gann Monograph on Cancer Research No. 50. Tokyo, Japan: Japan Science Societies Press, pp 241–251.

Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto M, Kinoshita KI, Shirakawa S, Miyoshi I. 1981. Adult T-cell leukemia: Antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci USA 78:6476–6480.

Hlela C, Shepperd S, Khumalo NP, Taylor GP. 2009. The prevalence of human T-cell lymphotropic virus type 1 in the general population is unknown. AIDS Rev 11:205–214.

Iga M, Okayama A, Stuver S, Matsuoka M, Mueller N, Aoki M, Mitsuya H, Tachibana N, Tsubouchi H. 2002. Genetic evidence of transmission of human T cell lymphotropic virus type 1 between spouses. J Infect Dis 185:691–695.

Ikeda M, Fujino R, Matsui T, Yoshida T, Komoda H, Imai J. 1984. A new agglutination test for serum antibodies to adult T-cell leukemia virus. Gann 75:845–848.

Inaba S, Sato H, Okochi K, Fukada K, Takakura F, Tokunaga K, Kiyokawa H, Maeda Y. 1989. Prevention of transmission of human T-lymphotropic virus type 1 (HTLV-1) through transfusion, by donor screening with antibody to the virus: One-year experience. Transfusion 29:7–11.

Kajiyama W, Kashiwagi S, Ikematsu H, Hayashi J, Nomura H, Okochi K. 1986. Intrafamilial transmission of adult T cell leukemia virus. J Infect Dis 154:851–857.

Kinoshita K, Amagasaki T, Hino S, Doi H, Yamanouchi K, Ban N, Momita S, Ikeda S, Kamihira S, Ichimaru M. 1987. Milk-borne transmission of HTLV-I from carrier mothers to their children. Jpn J Cancer Res 78:674–680.

Koga Y, Iwanaga M, Soda M, Inokuchi N, Sasaki D, Hasegawa H, Yanagihara K, Yamaguchi K, Kamihira S, Yamada Y. 2010. Trends in HTLV-1 prevalence and incidence of adult T-cell leukemia/lymphoma in Nagasaki, Japan. J Med Virol 82:668–674.

Manns A, Blattner WA. 1991. The epidemiology of the human T-cell lymphotrophic virus type I and type II: etiologic role in human disease. Transfusion 31:67–75.

Ministry of Health, Labour, Welfare. Annual report on life span. Available from: http://www.mhlw.go.jp/toukei/saikin/hw/life/life09/sankou02.htm.

Miyoshi I, Kubonishi I, Yoshimoto S, Akagi T, Ohtsuki Y, Shiraishi Y, Nagata K, Hinuma Y. 1981. Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T cells. Nature 294:770–771.

Mochizuki M, Yamaguchi K, Takatsuki K, Watanabe T, Mori S, Tajima K. 1992. HTLV-I and uveitis. Lancet 339:1110.

Morofuji-Hirata M, Kajiyama W, Nakashima K, Noguchi A, Hayashi J, Kashiwagi S. 1993. Prevalence of antibody to human T-cell lymphotropic virus type I in Okinawa, Japan, after an interval of 9 years. Am J Epidemiol 137:43–48.

Mueller N. 1991. The epidemiology of HTLV-I infection. Cancer Causes Control 2:37–52.

Mueller N, Okayama A, Stuver S, Tachibana N. 1996. Findings from the Miyazaki Cohort Study. J Acquir Immune Defic Syndr Hum Retrovirol 13:S2–S7.

Murphy EL, Figueroa JP, Gibbs WN, Brathwaite A, Holding-Cobham M, Waters D, Cranston B, Hanchard B, Blattner WA. 1989. Sexual transmission of human T-lymphotropic virus type I (HTLV-I). Ann Intern Med 111:555–560.

Nakano S, Ando Y, Saito K, Moriyama I, Ichijo M, Toyama T, Sugamura K, Imai J, Hinuma Y. 1986. Primary infection of Japanese infants with adult T-cell leukaemia-associated retrovirus (ATLV): Evidence for viral transmission from mothers to children. J Infect 12:205–212.

National Statistics Center. 2009a. Vital statistics of Japan 2009. Available from: http://www.e-stat.go.jp/SG1/estat/GL32020101.do?method=extendTclass&refTarget=toukeihyo&listFormat=hierarchy&statCode=00450011&tstatCode=000001028897&tclass1=000001035021&tclass2=000001038360& tclass3=000001038362&tclass4=000001038371&tclass5=.

National Statistics Center. 2009b. Special report of vital statistics, trends in live births, live birth rates (per 1,000 population), sex ratio of live births, total fertility rates, mean interval of occurrence, 1899–2009. Available from: http://www.e-stat.go.jp/SG1/estat/GL32020101.do?method=extendTclass&refTarget=toukeihyo&listFormat=hierarchy&statCode=00450013&tstatCode=&tclass1=&tclass2=&tclass3=&tclass4=&tclass5=.

National Statistics Center. 2009c. Vital statistics of Japan 2009. Available from: http://www.e-stat.go.jp/SG1/estat/GL08020103.do?_toGL08020103_&tclassID=000001007702&cycleCode=0&requestSender=search.

Okochi K, Sato H, Hinuma Y. 1984. A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: Seroconversion in recipients. Vox Sang 46:245–253.

Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, Matsumoto M, Tara M. 1986. HTLV-I associated myelopathy, a new clinical entity. Lancet 1:1031–1032.

Roucoux DF, Wang B, Smith D, Nass CC, Smith J, Hutching ST, Newman B, Lee TH, Chafets DM, Murphy EL, HTLV Outcomes Study Investigators. 2005. A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. J Infect Dis 191:1490–1497.

Sugiyama H, Doi H, Yamaguchi K, Tsuji Y, Miyamoto T, Hino S. 1986. Significance of postnatal mother-to-child transmission of human T-lymphotropic virus type-I on the development of adult T-cell leukemia/lymphoma. J Med Virol 20:253–260.

Tajima K, Tominaga S, Suchi T, Kawagoe T, Komoda H, Hinuma Y, Oda T, Fujita K. 1982. Epidemiological analysis of the distribution of antibody to adult T-cell leukemia-virus-associated antigen: possible horizontal transmission of adult T-cell leukemia virus. Gann 73:893–901.

Tajima K, The T- and B-cell Malignancy Study Group. 1990. 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.

Takatsuki K, Uchiyama T, Sagawa K, Yodoi J. 1977. Adult T cell leukemia in Japan. In: Seno S, Takaku F, Irino S, editors. Topics in HemJTology. Amsterdam: Excerpta Medica, pp 73–77.

Tanosaki R, Tobinai K. 2010. Adult T-cell leukemia–lymphoma: Current treatment strategies and novel immunological approaches. Expert Rev Hematol 3:743–753.

Taylor GP, Bodéus M, Courtois F, Pauli G, Del Mistro A, Machuca A, Padua E, Andersson S, Goubau P, Chieco-Bianchi L, Soriano V, Coste J, Ades AE, Weber JN. 2005. The seroepidemiology of human T-lymphotropic viruses: Types I and II in Europe: A prospective study of pregnant women. J Acquir Immune Defic Syndr 38:104–109.

Tsukasaki K, Hermine O, Bazarbachi A, Ratner L, Ramos JC, Harrington W, Jr., O'Mahony D, Janik JE, Bittencourt AL, Taylor GP, Yamaguchi K, Utsunomiya A, Tobinai K, Watanabe T. 2009. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia–lymphoma: A proposal from an International Consensus Meeting. J Clin Oncol 27:453–459.

Wiktor SZ, Pate EJ, Murphy EL, Palker TJ, Champegnie E, Ramlal A, Cranston B, Hanchard B, Blattner WA. 1993. Mother-to-child transmission of human T-cell lymphotropic virus type I (HTLV-I) in Jamaica: Association with antibodies to envelope glycoprotein (gp46) epitopes. J Acquir Immune Defic Syndr 6:1162–1167.

Yamanouchi K, Kinoshita K, Moriuchi R, Katamine S, Amagasaki T, Ikeda S, Ichimaru M, Miyamoto T, Hino S. 1985. Oral transmission of human T-cell leukemia virus type-I into a common marmoset (*Callithrix jacchus*) as an experimental model for milk-borne transmission. Jpn J Cancer Res 76:481–487.

4

Host Immune System Abnormalities Among Patients with Human T-Lymphotropic Virus Type 1 (HTLV-1)-Associated Disorders

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1. Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a human retrovirus that causes persistent infection in the host. While most infected persons remain asymptomatic carriers (ACs), 3–5% develop a T-cell malignancy termed adult T-cell leukemia (ATL) (Uchiyama et al., 1977), and another 0.25–3% develop a chronic progressive inflammatory neurologic disease known as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Gessain et al., 1985; Osame et al. 1986). Although HTLV-1-associated disorders have been extensively studied, the exact mechanism by which they are induced by HTLV-1 is not completely understood. The proviral load of HTLV-1 could contribute to the development of these disorders, since the circulating number of HTLV-1-infected T cells in the peripheral blood is associated with the risk of developing HAM/TSP and ATL (Iwanaga et al., 2010; Nagai et al. 1998). However, more detail on the precise immune mechanisms controlling HTLV-1-infected cells is still needed.

HTLV-1 preferentially infects $CD4^+$ T cells, the central regulators of the acquired immune system (Richardson et al., 1990). This is known to induce a variety of abnormalities, such as proliferation, cellular activation, and proinflammatory changes (Boxus et al., 2009; Satou et al., 2010; Yamano et al. 2009). These abnormalities, in turn, may deregulate the balance of the host immune system.

HTLV-1 also causes abnormalities among uninfected immune cells. Patients with HTLV-1-associated disorders demonstrate abnormalities in both the amount and function of CD8+ cytotoxic T lymphocytes (CTL), an important component of host immune response against HTLV-1 (Bangham 2009; Kannagi et al., 2011; Matsuura et al., 2010). Patients with ATL and HAM/TSP may also experience reductions in the amount and efficacy of cellular components of innate immunity, which is vital in regulating the immune response against general viral infections and cancers (Azakami et al., 2009; Matsuura et al., 2010). In this chapter, we have summarized the host immune system abnormalities that are associated with HTLV-1 infection.

2. Abnormality of HTLV-1-infected $CD4^+$ T cells

2.1 $CD4^+CD25^+CCR4^+$ T Cells are a major reservoir of HTLV-1-infected T cells, which increase in HAM/TSP and ATL patients

HTLV-1 mainly infects $CD4^+$ T helper (Th) cells, which play a central role in adaptive immune responses (Richardson et al., 1990). $CD4^+$ Th cells recruit and activate other immune cells, including B cells, CD8 T cells, macrophages, mast cells, neutrophils, eosinophils, and basophils (Zhu et al., 2010). Based on their function, their pattern of cytokine secretion, and their expression of specific transcription factors and chemokine receptors, $CD4^+$ Th cells, differentiated from naïve $CD4^+$ T cells, are classified into 4 major lineages: Th1, Th2, Th17, and T regulatory (Treg) cells. To understand the effects of HTLV-1 infection on the function of CD4 Th cells, it is necessary to know which Th population HTLV-1 infects.

It was recently shown that the chemokine receptor CCR4 is expressed on HTLV-1-infected leukemia cells in ATL patients (Yoshie et al., 2002). CCR4 is selectively expressed on suppressive T cell subsets, such as Treg and Th2 cells, in HTLV-1-seronegative healthy individuals (Yoshie et al., 2001). Using molecular and immunological techniques, we also demonstrated that $CD4^+CD25^+CCR4^+$ T cells were the predominant viral reservoir in both ACs and HAM/TSP patients, and that this T cell subset was increased in HAM/TSP patients (Yamano et al., 2009). Thus, $CD4^+CD25^+CCR4^+$ T cells are a major population of HTLV-1-infected T cells, which increase in number in both HAM/TSP and ATL patients.

The molecular mechanism of HTLV-1 tropism to CCR4 expressing $CD4^+$ T cells was recently uncovered (Hieshima et al., 2008). HTLV-1 Tax, a transcriptional regulator encoded by the HTLV-1 genome, does not induce expression of CCR4, but it does induce expression of CCL22, the ligand for CCR4. Because HTLV-1-infected T cells selectively interact with $CCR4^+CD4^+$ T cells, this results in preferential transmission of HTLV-1 to $CCR4^+CD4^+$ T cells.

2.2 Differences in the fates of $CD4^+CD25^+CCR4^+$ T cells in HAM/TSP and ATL patients

Among $CD4^+$ Th cells, the major reservoir of HTLV-1 is $CD4^+CD25^+CCR4^+$ T cells, including suppressive T cell subsets such as Treg and Th2 under healthy conditions. The exact mechanism by which HTLV-1 induces the deregulation of the host immune system is not completely understood. However, the recent discovery of Treg cells has provided new opportunities and generated increased interest in this issue. In healthy individuals, Treg cells suppress the proliferation of, and cytokine production by, pathogenic T cells, and thereby plays a key role in the maintenance of immune system homeostasis (Sakaguchi et al., 1995). Treg cells can be identified *ex vivo* by the intracellular expression of the transcriptional regulator Foxp3 (Hori et al., 2003), which is critical for the development and function of Treg cells in both mice and humans.

Significant reductions in Foxp3 expression and/or Treg cell function have been observed in several human autoimmune diseases (Sakaguchi et al., 2008), suggesting that defects in Foxp3 expression and/or Treg function may precipitate the loss of immunologic tolerance. Recently, significant reductions in Foxp3 expression and Treg cell function have also been observed in $CD4^+CD25^+$ T cells and/or $CD4^+CD25^+CCR4^+$ T cells from patients with HAM/TSP (Hayashi et al., 2008; Michaelsson et al., 2008; Oh et al., 2006; Ramirez et al., 2010; Yamano et al., 2005). Furthermore, decreased expression levels of the Treg-associated immune suppressive molecules CTLA-4 and GITR were also observed on $CD4^+CD25^+$ T cells in HAM/TSP patients (Ramirez et al., 2010; Yamano et al., 2005). Notably, overexpression of HTLV-1 *tax* can reduce

Foxp3 expression and inhibit the suppressive function of Treg cells (Yamano et al., 2005). Furthermore, because of a Tax-induced defect in TGF-β signaling, HAM/TSP patients experience reductions in Foxp3 expression and impairment of Treg function (Grant et al., 2008). Moreover, a significant reduction in $CD4^+CD25^+Foxp3^+$ Treg cells was demonstrated in HTLV-1-*tax*-expressing transgenic mice, which develop an inflammatory arthropathy (Ohsugi et al., 2011). Thus, HAM/TSP patients display a decreased ratio of $Foxp3^+$ Treg cells within HTLV-1-infected $CD4^+CD25^+CCR4^+$ T cells.

Importantly, a more detailed flow cytometric analysis of Foxp3 expression in $CD4^+CD25^+CCR4^+$ T cells demonstrated that the frequency of "$Foxp3^-$ population" was extraordinary high in HAM/TSP patients (Yamano et al., 2009). Moreover, an analysis of proinflammatory cytokine expression in this $Foxp3^-CD4^+CD25^+CCR4^+$ T cell subset demonstrated that these cells were unique because, in healthy individuals, they produced multiple proinflammatory cytokines such as IL-2, IL-17, and few interferon (IFN)-γ, while $Foxp3^+CD4^+CD25^+CCR4^+$ T cells (Treg cells) did not. Furthermore, HAM/TSP patients were found to exhibit only a few $Foxp3^+CD4^+CD25^+CCR4^+$ T cells that did not produce such cytokines. Rather, these patients had an increased number of $Foxp3^-CD4^+CD25^+CCR4^+$ T cells, which were found to overproduce IFN-γ. Further, given the increase of clinical diseases and severity of HAM/TSP observed in these patients, it appears likely that the frequency of these IFN-γ-producing $Foxp3^-CD4^+CD25^+CCR4^+$ T cells may have a functional consequence (Yamano et al., 2009). Thus, while the $CD4^+CD25^+CCR4^+$ T cell population in healthy patients mainly comprises suppressive T cell subsets such as Treg and Th2, HAM/TSP patients possess an increased proportion of IFN-γ-producing $Foxp3^-CD4^+CD25^+CCR4^+$ T cells, which are rarely encountered in healthy individuals and lead to an overproduction of IFN-γ (Figure 1).

Although Foxp3 expression is decreased by $CD4^+CD25^+$ ($CCR4^+$) T cells in HAM/TSP patients (Hayashi et al., 2008; Michaelsson et al., 2008; Oh et al., 2006; Ramirez et al., 2010; Yamano et al., 2005), it is increased by $CD4^+CD25^+(CCR4^+)$ ATL cells in most ATL patients (Karube et al., 2004; Roncador et al., 2005) (Figure 1). Therefore, it has been hypothesized that ATL cells may be derived from Treg cells (Kohno et al., 2005). Interestingly, some ATL cells exhibit immunosuppressive functions similar to those of Treg cells, which may contribute to the cellular immunodeficiency that has been clinically observed in ATL patients (Chen et al., 2006; Kohno et al., 2005; Matsubar et al., 2006); however, some ATL cells lose this regulatory function (Shimauchi et al., 2008).

2.3 HTLV-1 may induce plasticity of Foxp3+ cells into exFoxp3+ cell

In HTLV-1-seronegative healthy individuals, $CD4^+CD25^+CCR4^+$ T cells mainly include suppressive T cell subsets such as Treg and Th2 (Yoshie et al., 2001). In ATL patients, most of this subset develops leukemogenesis by maintaining the $Foxp3^+$ Treg phenotype (Figure 1). However, as mentioned above, T cells of this subset become Th1-like cells that overproduce IFN-γ in HAM/TSP patients (Figure 1). Since HTLV-1 may preferentially transmit to $CCR4^+CD4^+$ T cells, these findings suggest that HTLV-1 may intracellularly induce T-cell plasticity of Treg cells into $IFN\text{-}\gamma^+$ T cells. Indeed, one recent report indicated that loss of Foxp3 in Treg cells and acquisition of IFN-γ may result in the conversion of suppressor T cells into highly autoaggressive lymphocytes ($exFoxp3^+$ cells), which can favor the development of autoimmune conditions (Tsuji et al., 2009; Zhou et al., 2009). Importantly, Toulza et al. (2008) demonstrated that the rate of CTL-mediated lysis was

negatively correlated with the number of HTLV-1-Tax$^-$ CD4$^+$Foxp3$^+$ cells, but not with the number of Tax$^+$ CD4$^+$Foxp3$^+$ cells, suggesting that HTLV-1-infected Treg cells lose their regulatory function, while HTLV-1-uninfected Treg cells contribute substantially to immune control of HTLV-1 infection. Additionally, functional impairment of CD4$^+$Foxp3$^+$ Treg cells was observed in mice that were transgenic mice for the *HTLV-1 bZIP factor* (*HBZ*) gene, which encodes the minus strand of HTLV-1 (Satou et al., 2011). These findings support the hypothesis that HTLV-1 may be one of the exogenous retrovirus genes responsible for immune dysregulation through interference of CD4$^+$CD25$^+$ Treg cell function. This hypothesis is currently under investigation to elucidate the precise molecular mechanisms by which HTLV-1 influences the fate and function of CD4$^+$CD25$^+$CCR4$^+$ T cells, especially Foxp3$^+$ Treg cells.

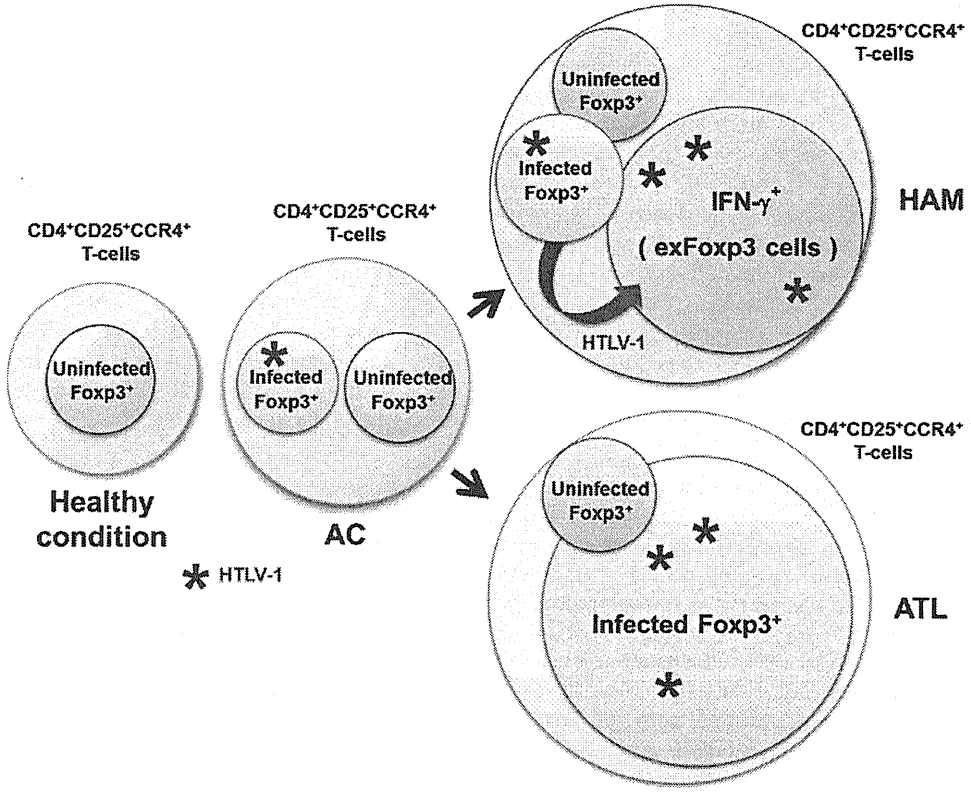

Fig. 1. Cellular components of CD4$^+$CD25$^+$CCR4$^+$ T cells in healthy individuals, asymptomatic carriers, ATL, and HAM/TSP patients.

3. Abnormality of cytotoxic T lymphocyte (CTL) response

CD8$^+$ Cytotoxic T lymphocyte (CTL) responses are an effective host defense system against all virus infections and malignancies. CTLs act by killing autologous cells that express viral