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Trends in the Seroprevalence of HTLV-1 in Japanese Blood Donors in Nagasaki Prefecture, 2000-2006

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Abstract

Human T-cell leukemia virus type-1 (HTLV-1) is the established cause of adult T-cell leukemia/lymphoma. Monitoring time trends in HTLV-1 seroprevalence in blood donors is important to assess the safety of the blood supply in the viral endemic area. We analyzed changes in HTLV-1 seroprevalence in 48,415 first-time blood donors who donated blood from 2000 to 2006 in Nagasaki prefecture, an endemic area in Japan. The donors were divided into 10-year birth cohorts: before 1950, 1951-1960, 1961-1970, 1971-1980, and 1981-1990. Among the first-time blood donors, 622 were tested positive for HTLV-1 (overall seroprevalence: 1.28%, [95%CI: 1.19-1.39]). Seroprevalence was significantly high in the birth cohort of before 1950 (6.22%) and declined with birth-year. The time trend of the birth-cohort specific seroprevalence showed almost no change within each birth cohort, except for the birth cohort of 1981-1990 that showed a significantly declining trend (P for trend = 0.006). Among the birth cohort of 1981-1990, the seroprevalence was stable among those born during 1981 to 1986 (0.66-0.83%), but was lower among those born during 1987 to 1990 (0-0.38%). Detail analyses showed that HTLV-1 seroprevalence among blood donors clearly declined in those born after 1987.

Keywords: HTLV-1, blood donors, seroprevalence, birth cohort analysis

1 Introduction

Human T-cell leukemia virus type-1 (HTLV-1) is the etiological agent for adult T-cell leukemia/lymphoma (ATLL) and other HTLV-1-associated diseases [1-3]. The virus is transmitted through three routes: mother-to-infant, sexual contact, and blood transfusion [4-7]. In mother-to-infant transmission, breast-feeding has been reported to be the dominant route [8]. To prevent milk-borne transmission, a prefecture-wide intervention program named the ATLL Prevention Program (APP) started in August 1987 in Nagasaki prefecture, an HTLV-1 endemic area in Japan [9-11]. The APP involved the screening of pregnant women for HTLV-1 and the intervention to instruct the virus carrying mothers to refrain from breast-feeding. To prevent blood-borne transmission, a nationwide routine serological screening for HTLV-1 of donated blood was launched in 1986 all over Japan [4].

Monitoring time trends in HTLV-1 infection rates in blood donors is important to assess the safety of the blood supply and to estimate population risks in the viral endemic area. Previous studies of Japanese blood donors reported that the age-specific HTLV-1 seroprevalence steadily declined over the decades [12-15]. Birth-cohort effects, changing the length of breast-feeding, sanitary improvement, and the dilution effect caused by HTLV-1-negative immigrants have been discussed as reasons for the declining trend [15-17]. Although such an age-specific analysis is commonly used for epidemiological studies, it sometimes obscures important trends that can occur within people born at different times. An alternative method of analyzing trends in viral seroprevalence is to examine birth-cohort specific trends [18]. As the HTLV-1 virus mainly infects infants, a birth-cohort specific analysis is more useful for understanding trends of HTLV-1 seroprevalence than an age-specific analysis that is strongly affected by the birth cohort effect.

In the present study, we analyzed the time trends of the birth-year specific seroprevalence of HTLV-1 among first-time blood donors to examine whether the seroprevalence changed over time within the same birth cohort.

2 Materials and methods

Breakdown data on demographic characteristics (sex, birth year, age at donation) and serological test results were obtained from two blood centers, the Nagasaki Red Cross Blood Center and the Sasebo Red Cross Blood Center, where blood donors were voluntary or directed, non-remunerated, and gave written informed consent to be tested for infectious diseases. Both Blood Centers cover blood donation and supply all over the Nagasaki prefecture, the population of which is estimated to be approximately 1,461,000. We used a dataset of first-time donations from April 1, 2000 to December 31, 2006. A donation was defined as “first-time” if the donor specified that this was the first time that they had given blood at any center and there was no history of prior donations. A serological assay and the subsequent confirmatory tests were performed according to the standard protocol of Japanese Red Cross. The donors were divided into 5 birth-cohorts depending on their year of birth: before

1950, 1951 to 1960, 1961 to 1970, 1971 to 1980, and 1981 to 1990. Seroprevalence was defined as the number of HTLV-1 positive first-time donations divided by the total number of first-time donations in each category, and the exact binomial 95% confidence intervals (CIs) for each seroprevalence were calculated. A trend test was performed using the Cochran-Armitage test. Comparisons of seroprevalence among categories were performed by calculating seroprevalence ratios (PR) and the 95% CI via the log-binomial regression model [19]. All statistical analyses were performed using SAS version 8.02 (SAS Institute Japan, Tokyo, Japan) [20] with a two-tailed significance level of 0.05.

3 Results

Between 2000 and 2006, 48,415 first-time blood donors (males: 29,887, females: 18,528) underwent screening tests for HTLV-1. Most first-time donations were given by men (61.7%) and the birth-cohort of 1981-1990 (55.3%). Among the first-time donors, 622 tested positive for HTLV-1, indicating that the overall seroprevalence was 1.28% (95%CI, 1.19-1.39). Seroprevalence was significantly higher in females (1.52%) than males (1.14%) (PR; 1.34, 95%CI; 1.14-1.57) and was significantly higher in those born earlier: 6.22% in the birth cohort of before 1950, 3.83% in the birth cohort of 1951-1960, 1.87% in the birth cohort of 1961-1970, 0.81% in the birth cohort of 1971-1980, and 0.65% in the birth cohort of 1981-1990 (**Table 1**). The overall time trend in HTLV-1 seroprevalence was stable during the year of donation from 2000 to 2006 (P for trend: 0.84 for all donors, 0.47 in males, and 0.85 in females) (**Table 2**). The trends in the birth-cohort specific seroprevalence during the year of donation from 2000 to 2006 showed almost no change over time within any of the birth-cohorts, except for the birth-cohort of 1981-1990 (**Figure 1**), among which a significantly declining trend of seroprevalence was observed (P for trend = 0.006). Among the birth cohort of 1981-1990, the seroprevalence was 0.83% in the 1981 birth-cohort, 0.92% in the 1982 cohort, 0.53% in the 1983 cohort, 0.71% in the 1984 cohort, 0.82% in the 1985 cohort, 0.66 in the 1986 cohort, 0.38 in the 1987 cohort, 0.20 in the 1988 cohort, and 0 in the 1989 and the 1990 birth cohorts (P for the trend = 0.001) (**Figure 2**). We performed additional trend analyses by categorizing the cohort into two groups, those who were born 1981-1986 and those born 1987-1990. There was no significant trend in the seroprevalence among those born during 1981 to 1986 (P for trend = 0.49), whereas there was a declining trend in those born during 1987 to 1990 with a marginal statistical significance (P for trend = 0.08). Furthermore, when we narrowed donors to those born in 1985-1990 and compared the seroprevalence by categorizing those in 1985-1986 and 1987-1990, the seroprevalence was significantly lower in the latter than the former group (PR: 0.36, 95% CI: 0.21-0.65, $P=0.0005$). Thus, the seroprevalence of HTLV-1 clearly declined in those born after 1987.

4 Discussion

The present analyses demonstrate two important trends of HTLV-1 seroprevalence in blood donors during the

donation period from 2000 to 2006 in Nagasaki prefecture, an HTLV-1 endemic area in Japan: a decreasing trend of the seroprevalence in those born after 1987, and a sustained high rate of the seroprevalence in those born before 1987, especially those born before 1960.

Time trend analyses for any viral seroprevalence are conventionally evaluated using age-specific methods, whereas birth-cohort methods are rarely documented. However, birth-cohort patterns of the disease prevalence are sometimes more useful for understanding a real time trend of a disease rate than age-specific patterns [21]. For example, the seroprevalences of *Helicobacter Pylori* and human immunodeficiency virus-1 have often been evaluated by birth-cohort specific analyses, and these analyses provided unique patterns [22-23]. As for the seroprevalence trends of HTLV-1 among blood donors, most of the previous Japanese studies from endemic areas reported a clear decline in the age-specific positive rate, especially in the younger generation [12-15]. Our age-specific analysis also showed a declining trend pattern of the seroprevalence in all age-specific groups during the same donation period of 2000-2006 (data not shown), which was different from that of the birth-cohort specific analyses that showed a stable seroprevalence within almost cohorts, except for those born between 1981 and 1990 in the present report. This suggests that not only age-specific but also birth-cohort specific analyses are necessary to understand the real time trend of virus prevalence in blood donors.

Reasons for the declining trend of HTLV-1 seroprevalence in the birth cohort of 1981-1990 may include social changes during the long period from 1981 to 1990, such as decreasing duration of breastfeeding, an increase in the use of artificial feeding, decreasing number of siblings, and increasing migration rate in Nagasaki prefecture, as discussed previously [15-17]. Moreover, we presume another possible reason that the APP intervention in Nagasaki prefecture may affect the significantly declining trend in those born after 1987 because the APP started in the year 1987 in Nagasaki prefecture. A preliminary analysis reported that the APP intervention blocked approximately 80% of mother-to-child HTLV-1 transmission [10, 24], which suggest that an increasing number of seronegative children born from carrier mothers who had participated in the APP would become blood donors, and also suggest that seropositive children born from carrier mothers who had participated in the APP would abstain from blood donation. However, no data has been reported about the seroprevalence of HTLV-1 among children born from the virus carrying mothers who participated in the program. We obtained personally the estimated participation rate of pregnant mothers in the APP and then plotted the participation rate and the seroprevalence in blood donors born from 1985-1990 by calendar year. There was a possible inverse relation between the participation rates of pregnant mothers in the program (around 20% in 1987, 52.5% in 1988, 88.3% in 1989, and 87.8% in 1990) and the HTLV-1 seroprevalence in blood donors (0.82% in 1985, 0.66% in 1986, 0.38% in 1987, 0.20% in 1988, and 0 % in 1989 and 1990). Although our presumption has a limitation that a lack of information on blood donors born from the participant mothers, the low seroprevalence among those born after 1987 and the inverse relationship with the participation rate of pregnant mothers in the APP may support our presumption that APP intervention started in 1987 affect the decline of the virus seroprevalence in blood donors.

In our analyses, the HTLV-1 seroprevalence in blood donors born before 1950 and in those born in 1951-60 were stable at the high seroprevalence, 4 - 6% and 2 - 4%, respectively. These suggest that people born earlier would have been still at a higher risk of ATLL and other HTLV-1 related diseases. Furthermore, the overall seroprevalence rate of HTLV-1 was around 1.2%, which is higher than in other countries. For example, the seroprevalence in the US in 1991 was about 0.04% [25], in Eastern Saudi Arabia it is 0.06% [26], and in Taiwan it is 0.058% [27]. Even though the majority of HTLV-1 carriers rarely develop any HTLV-1-associated diseases and previous age-specific studies have emphasized the steadily declining number of HTLV-1 carriers in Japan, our results suggest that preventing the transmission of the virus is still an important public health issue in Nagasaki prefecture, an endemic area in Japan.

The present study has some limitations. We did not take into consideration potential sexual transmission, the window period, or the false-positive rate. It was impossible to adjust social changes such as decreasing duration of breastfeeding, an increase in the use of artificial feeding, decreasing number of siblings, and increasing migration rate. Furthermore, we have no information on how many children born from carrier mothers participating in the APP became blood donors. The strength of the present study is that this is the first report of a birth-cohort specific time trend for HTLV-1 seroprevalence in Japanese blood donors in Nagasaki prefecture where the intervention to instruct the virus carrying mothers to refrain from breast-feeding. Usually people donate blood at any ages among those with same birth year; therefore age-specific seroprevalence may be affected by the diversity of age at donation beyond the birth-cohort effect. We believe that our birth-year-specific seroprevalence trend provide a real trend of the virus prevalence because the infection mostly occurs during infancy in endemic areas, and because it is not influenced by the diversity of age at donation.

In conclusion, the present study demonstrated a decreased seroprevalence of the virus in people born after 1987 and a stable high seroprevalence of HTLV-1 in people born before 1960. Continuous evaluation of the seroprevalence of this virus in both blood donors and the general population is needed for public health safety in this endemic area.

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Figure Legends

Figure 1. HTLV-1 seroprevalence (%) in first-time blood donors by birth year group (before 1950, 1951-1960, 1961-1970, 1971-1980, and 1981-1990) and the year of donation (2000 to 2006). Temporal changes in seroprevalence in each birth-cohort during the year of donation was estimated using the Cochran-Armitage trend test.

Figure 2. Birth-year-specific HTLV-1 seroprevalence (%) in first-time blood donors born 1981-1990. Trend analysis for the seroprevalence by birth year from 1981 to 1990 shows a significantly declining pattern ($P < 0.001$). Among the birth cohort of 1981-1990, the seroprevalence was stable among those born during 1981 to 1986, whereas there was a declining trend in those born during 1987 to 1990 with a marginal statistical significance (P for trend = 0.08). Error bars represent 95% CIs.

Table 1. The overall seroprevalence of HTLV-1 infection in first-time blood donors, 2000 - 2006

	No. Donors	No.HTLV-1 positive	Seroprevalence % (95%CI)	PR (95%CI)
Total	48415	622	1.28 (1.19-1.39)	
Sex				
Male	29887	340	1.14 (1.02-1.26)	1
Female	18528	282	1.52 (1.35-1.71)	1.34 (1.14-1.57)
Birth year groups				
1981-1990	26794	175	0.65 (0.56-0.76)	1
1971-1980	11143	90	0.81 (0.65-0.99)	1.2 (1.0-1.6)
1961-1970	4764	89	1.87 (1.50-2.29)	2.9 (2.2-3.7)
1951-1960	3657	140	3.83 (3.23-4.50)	5.9 (4.7-7.3)
Before 1950	2057	128	6.22 (5.52-7.35)	9.5 (7.6-12)

Abbreviations: HTLV-1: human T-cell leukemia virus type-1, PR: prevalence ratio, CI: confidence interval.

Table 2. HTLV-1 seroprevalence in first-time blood donors by sex and year of donation 2000 - 2006

	Year of Donation							P for trend*
	2000	2001	2002	2003	2004	2005	2006	
Male								
No. Donors	4020	3430	3747	4046	4529	5219	4896	
No. HTLV-1 positive	42	37	44	49	42	70	56	
Seroprevalence (%)	1.04	1.08	1.17	1.21	0.93	1.34	1.14	0.84
Female								
No. Donors	2951	2444	2383	2476	2875	3009	2390	
No. HTLV-1 positive	47	45	36	28	36	46	44	
Seroprevalence (%)	1.59	1.84	1.51	1.13	1.25	1.53	1.84	0.47
Total								
No. Donors	6971	5874	6130	6522	7404	8228	7286	
No. HTLV-1 positive	89	82	80	77	78	116	100	
Seroprevalence (%)	1.28	1.40	1.31	1.18	1.05	1.41	1.37	0.85

Abbreviations: HTLV-1: human T-cell leukemia virus type-1.

*P for trend in the seroprevalence from 2000-2006 was evaluated using the Cochran-Armitage test.

Figure 1

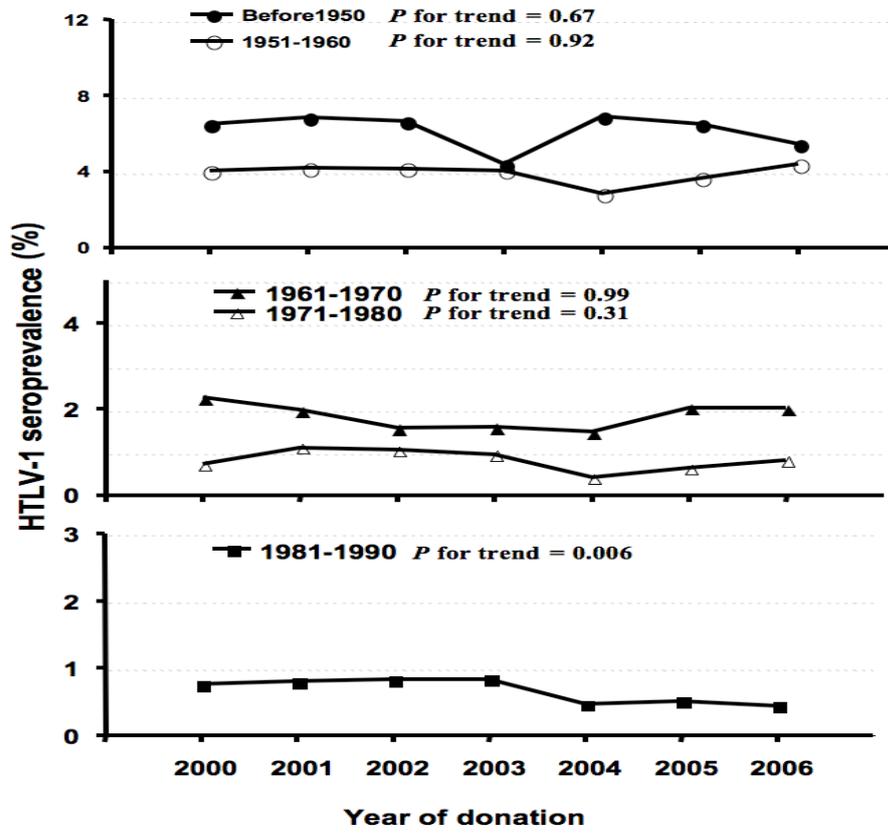


Figure 2

