Recent Prevalence of Human T-cell Leukemia Virus Type 1 Carrier Associated with Horizontal Transmission in Pregnant Japanese Women

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Recent Prevalence of Human T-cell Leukemia Virus Type 1 Carrier

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**Short title:** HTLV-1 due to horizontal transmission

**Key words:** human T-cell leukemia virus type 1, pregnancy, horizontal transmission, Japan
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SUMMARY: The current study was conducted to examine the number of human T-cell leukemia virus type 1 (HTLV-1) carrier and how horizontal transmission affects the prevalence of HTLV-1 carrier in pregnant Japanese women in 2019. We requested 2,214 obstetrical facilities to provide information of HTLV-1 tests in pregnant women who delivered in 2019. The estimated number of HTLV-1 carrier in pregnant Japanese women was 952. At least 10% or more of the HTLV-1 carriers were those due to horizontal transmission.
Japan, especially Kyushu islands, has been reported to be one of the areas of highest prevalence of human T-cell leukemia virus type 1 (HTLV-1) infection in the world \((1, 2)\). Since September 2010, in Japan the serological screening for the detection of HTLV-1 antibodies can be performed for all women during pregnancy with the public funds for strategies to prevent HTLV-1 vertical transmission. Confirmation tests for the screening positives have been covered by insurance for all.

Vertical transmission is most important route of HTLV-1 infection; however, horizontal (sexual) transmission may be also generally accepted as an important route of infection in adults \((3-6)\). Although transmission had been confirmed in infancy through breastfeeding, little was known about the epidemiological aspects of new HTLV-1 infections later in life. The transmission rate in exclusively formula-fed infants has been reported to be approximately 2-3\%, indicating the possibility of alternative routes \((7,8)\). Based on a retrospective cohort analysis in 2016, there may be about 4,000 people infected with HTLV-1 who experienced seroconversion (called 'seroconverters') per year in Japan \((9)\).

Therefore, the current study was conducted to examine how horizontal transmission affects the prevalence of HTLV-1 carrier in pregnant Japanese women in 2019.

The protocol for this study was approved by the Ethics Committee of the Japan Association of Obstetricians and Gynecologists (JAOG) \((2017-5)\).

On December 2020, we requested 2,214 obstetrical facilities that are members of the JAOG to provide information of HTLV-1 tests in pregnant women.
who delivered at ≥ 22 weeks’ gestation in 2019. A total of 1,468 (66.3%) of 2,214 obstetrical facilities responded and information on a total of 568,626 women, accounting for approximately or more than 66% of all pregnant women analyzed with the report by the Ministry of Health, Labour and Welfare (Japan) in 2019 (865,324 women) was provided (10). In this study, we requested the number of HTLV-1 ‘seroconverters’ whose HTLV-1 tests were negative at their previous pregnancies.

The $\chi^2$ or Fisher’s exact test was used for categorical variables. Differences with $p < 0.05$ were considered significant.

**Table 1** shows the prevalence of HTLV-1 carrier and the rate of HTLV-1 ‘seroconverter’ by area in Japan. In pregnant Japanese women, the prevalence of HTLV-1 carrier was 0.11%, while the rate of HTLV-1 ‘seroconverter’ of the carriers was 10.7%. Considering the response rate, the number of HTLV-1 carrier in pregnant Japanese women in 2019 was estimated to be 952.

**Table 2** shows the rate of HTLV-1 ‘seroconverter’ of the carriers in each region of Japan. There were no significant differences in the rate in the 6 regions of Japan.

In 2019, the estimated number of HTLV-1 carrier in pregnant Japanese women was 952. In addition, at least 10% or more of the HTLV-1 carriers were those due to horizontal transmission.

Based on the results of confirmation tests in 2011-2013, the prevalence and number of HTLV-1 carrier in pregnant Japanese women were estimated to be 0.16-0.18% and 1,560-1,780, respectively (11,12). Although the number of delivery in Kyushu islands was only 13-14% of Japanese deliveries, 51-53% of
HTLV-1 carrier of pregnant Japanese women was present in Kyushu islands (11,12). The prevalence of HTLV-1 carrier in Kyushu islands and the other areas were 0.60-0.66 and 0.08%, respectively (11,12). Therefore, in 2019 the estimated number of HTLV-1 carrier in pregnant Japanese women decreased to 55-60% of those 6-8 years ago. However, there was no change in the distribution of HTLV-1 carriers centered on Kyushu islands.

During this period, the number of deliveries in Japan has decreased by 10-20%; however, the prevalence and number of pregnant HTLV-1 carriers has decreased further. The migration of Japanese people from Kyushu to the metropolitan area may have contributed to the decrease in HTLV-1 carriers in Kyushu islands (13); however it seems unclear. In addition, the change in the main method of confirmation tests for HTLV-1 infection from western blot (WB) test followed by polymerase chain reaction (PCR, WB/PCR) to line immunoassay (LIA, LIA/PCR) during the period may be a large bias in comparing the prevalence (14). HTLV-1 carrier is diagnosed only after a confirmation tests shows a positive result. In indeterminate case, PCR is used as a final test to diagnose HTLV-1 infection. LIA was developed for the serological confirmation and discrimination of HTLV-1 infection (15). This assay performs well in confirming HTLV-1 seropositivity by exhibiting a low incidence of indeterminate results. In addition, the results of LIA are in good agreement with PCR results. However, the changes in the prevalence of HTLV-1 carrier may be the effect of HTLV-1 vertical transmission prevention projects since about 30 years ago in Japan (7,16,17). For example, a prefecture wide intervention at Nagasaki Prefecture, one of the hot endemic foci of HTLV-1, by refrain from breast-feeding blocked approximately
80% of mother-to-child transmission of HTLV-1 (16).

Unfortunately, in this study we did not request the answers regarding the number of delivery and/or the intervals from the previous pregnancies. However, at least 10% or more of the HTLV-1 carriers were those due to horizontal transmission. The rate of HTLV-1 seroconversion due to sexual contact in pregnant women in Japan may be considered to be influenced greatly by the rate of HTLV-1 infection in men in their 20s to 40s in the respective geographical areas of Japan. The rate of HTLV-1 infection in men has been reported to be higher in the Kyushu islands than in other regions (9). Therefore, it has been expected that the rate of HTLV-1 seroconversion due to sexual contact in pregnant women would be higher in the Kyushu islands. However, in the current study regional differences were not observed in the rate. These mothers may have been infected during a period of childcare, and vertical transmission to former infant/child may have occurred depending on the feeding methods. In considering with the total fertility rate in Japan (= about 1.4; the number of children the couple actually has and those actually intends to have: 1.71 and 2.07), the estimated HTLV-1 transmission risk in pregnant women may almost double to about 20% including the number of nulliparous women (18).

Based on the current results, horizontal transmission of HTLV-1 may have increased compared to the decrease in vertical transmission of HTLV-1. New HTLV-1 infections in adults may be an important public health concern in Japan, and preventive strategies may be needed to reduce the new transmission.

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30, 2020).


Table 1. Prevalence of human T-cell leukemia virus type 1 (HTLV-1) carrier and the rate of HTLV-1 ‘seroconverter’ in pregnant women who delivered at ≥ 22 weeks’ gestation in 2019 by area in Japan

<table>
<thead>
<tr>
<th>Areas of Japan</th>
<th>Obstetric institutes</th>
<th>Total pregnant women</th>
<th>HTLV-1 carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Except Kyushu islands</td>
<td>1,221</td>
<td>485,826</td>
<td>361 (0.07)</td>
</tr>
<tr>
<td>Kyushu islands</td>
<td>247</td>
<td>82,800</td>
<td>245 (0.30)</td>
</tr>
<tr>
<td>Total</td>
<td>1,468</td>
<td>568,626</td>
<td>606 (0.10)</td>
</tr>
</tbody>
</table>

Data are presented as number (%).
HTLV-1, human T-cell leukemia virus.
‘Seroconverter’, subjects whose HTLV-1 tests were negative at their previous pregnancies.
LIA, line immunoassay.
PCR, polymerase chain reaction.
**Table 2.** Rate of human T-cell leukemia virus type 1 (HTLV-1) ‘seroconverter’ in pregnant women who delivered at ≥ 22 weeks’ gestation in 2019 by region in Japan

<table>
<thead>
<tr>
<th>Region of Japan</th>
<th>HTLV-1 carrier</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>‘Seroconverters’</td>
<td></td>
</tr>
<tr>
<td>Hokkaido-Tohoku</td>
<td>34</td>
<td>3 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Kanto (Tokyo)</td>
<td>128</td>
<td>12 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Hokuriku-Chubu</td>
<td>60</td>
<td>8 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Kansai</td>
<td>81</td>
<td>10 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Chugoku-Shikoku</td>
<td>58</td>
<td>6 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Kyushu</td>
<td>245</td>
<td>26 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>606</td>
<td>65 (10.7)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number (%).
HTLV-1, human T-cell leukemia virus.
‘Seroconverter’, subjects whose HTLV-1 tests were negative at their previous pregnancies.