Geographic Distribution of the Incidence of Adult T-cell Leukemia/Lymphoma and Other Malignancies in Nagasaki Prefecture, Japan

Kokichi Arisawa¹,², Midori Soda², Satoshi Shirahama³, Hiroshi Saito¹, Noboru Takamura¹, Maki Yamaguchi⁴, Kazumasa Odagiri¹, Tohru Nakagoe⁵, Akihiko Suyama² and Hiroshi Doi⁶

Departments of ¹Preventive Medicine and Health Promotion and ⁴Obstetrics and Gynecology and ⁵First Department of Surgery, Nagasaki University School of Medicine, Nagasaki, ²Department of Epidemiology, Radiation Effects Research Foundation, Nagasaki, ³Kamigoto Hospital, Minamimatsuura-gun and ⁶Department of Health and Welfare, Nagasaki Prefecture, Nagasaki, Japan

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Background: It remains unclear whether human T-cell lymphotropic virus type-I (HTLV-I) infection is associated with an increased risk of malignancies other than adult T-cell leukemia/lymphoma.

Methods: The authors investigated the geographic distribution of the incidence of adult T-cell leukemia/lymphoma and other malignancies in Nagasaki Prefecture, Japan, where HTLV-I is endemic. The world age-standardized incidence rates of adult T-cell leukemia/lymphoma and five cancers of other sites were calculated in 15 areas, using the data from the Nagasaki Prefectural Cancer Registry (1985–97).

Results: The incidence of adult T-cell leukemia/lymphoma was found to be positively correlated with that of biliary tract cancer in men (person-years-weighted \( r = 0.49, P = 0.06 \)) and liver cancer in women (\( r = 0.56, P = 0.03 \)), but not with cancer of the stomach, lung or cervix uteri.

Conclusions: The results may not support the hypothesis that HTLV-I infection is strongly associated with an increased risk of cancer of the stomach, lung or cervix uteri. The association between HTLV-I infection and cancer of the biliary tract and the possible interaction between hepatitis C virus and HTLV-I in the development of liver cancer should be evaluated by prospective cohort studies.

Key words: biliary tract cancer – ecological study – HTLV-I – liver neoplasms – lymphoma

INTRODUCTION

No definite conclusion has been reached on whether human T-cell lymphotropic virus type-I (HTLV-I) infection is associated with an increased risk of malignancies other than adult T-cell leukemia/lymphoma (ATL). In 1986, Asou et al. (1) reported that the prevalence of HTLV-I seropositivity was 2–15 times higher in cancer patients without a history of blood transfusion than in control subjects of the same age. Since then, several case reports and case-control studies have suggested an association between HTLV-I infection and cancers of the cervix uteri (2,3), lung (small cell type) (4), liver (5) and other sites (6). More severe atrophy of the gastric mucosa, a precursor lesion of stomach cancer, has also been reported in patients with ATL and HTLV-I-associated myelopathy and asymptomatic HTLV-I carriers than in HTLV-I negative controls (7). On the other hand, except for liver cancer (8,9), no significantly increased risk of cancer has been reported in cohort mortality studies of HTLV-I carriers (9–11). If HTLV-I infection has strong effects on the occurrence of other cancers, the geographic pattern of ATL may be correlated with that of other malignancies. In this paper, the geographic distribution of the incidence of ATL and other malignancies was examined in Nagasaki Prefecture, Japan.

SUBJECTS AND METHODS

STUDY AREA AND POPULATION

The study area comprised the whole of Nagasaki Prefecture, Japan, the total population of which included 736,729 men and 826,230 women in 1990 (12). In this prefecture, a population-based cancer registry (Nagasaki Prefectural Cancer Registry) has been operating since 1985 (13). In the present study, we excluded Iki Island (total population in 1990 = 17,827 men and
Table 1. Age-standardized incidence rates of adult T-cell leukemia/lymphoma and other malignancies according to area in Nagasaki Prefecture, Japan (men, 30–79 years of age, 1985–97)*

<table>
<thead>
<tr>
<th>Area</th>
<th>ATL</th>
<th>Stomach</th>
<th>Liver</th>
<th>Biliary tract and intrahepatic bile duct</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagasaki</td>
<td>7.0 (5.7–8.3)</td>
<td>167.7 (161.4–173.9)</td>
<td>90.9 (86.3–95.6)</td>
<td>20.7 (18.5–22.8)</td>
<td>94.4 (89.9–99.0)</td>
</tr>
<tr>
<td>Sasebo</td>
<td>7.6 (5.9–9.3)</td>
<td>169.6 (161.5–177.8)</td>
<td>65.0 (60.0–70.1)</td>
<td>20.2 (17.5–23.0)</td>
<td>93.5 (87.6–99.4)</td>
</tr>
<tr>
<td>Shimabara</td>
<td>1.9 (0–4.0)</td>
<td>137.9 (120.7–155.0)</td>
<td>55.0 (44.1–65.8)</td>
<td>15.7 (10.2–21.2)</td>
<td>76.3 (63.8–88.7)</td>
</tr>
<tr>
<td>Ishaya</td>
<td>5.7 (3.1–8.3)</td>
<td>155.3 (141.9–168.8)</td>
<td>59.7 (51.4–68.1)</td>
<td>16.3 (12.0–20.6)</td>
<td>91.2 (81.0–101.4)</td>
</tr>
<tr>
<td>Omura</td>
<td>7.2 (4.1–10.4)</td>
<td>133.0 (119.3–146.7)</td>
<td>58.0 (48.9–67.1)</td>
<td>22.0 (16.4–27.5)</td>
<td>86.3 (75.5–97.2)</td>
</tr>
<tr>
<td>Fukue</td>
<td>19.0 (10.9–27.1)</td>
<td>110.8 (92.2–129.3)</td>
<td>95.4 (77.5–113.3)</td>
<td>27.8 (18.7–36.9)</td>
<td>94.2 (77.4–110.9)</td>
</tr>
<tr>
<td>Hirado</td>
<td>25.3 (15.6–35.1)</td>
<td>163.3 (140.0–186.7)</td>
<td>73.8 (57.8–89.7)</td>
<td>19.4 (11.7–27.1)</td>
<td>84.0 (68.2–99.8)</td>
</tr>
<tr>
<td>Matsuura</td>
<td>19.2 (10.2–28.3)</td>
<td>138.2 (115.1–161.3)</td>
<td>43.5 (30.5–56.4)</td>
<td>15.7 (8.3–23.0)</td>
<td>93.2 (74.9–111.6)</td>
</tr>
<tr>
<td>Nishisonogi</td>
<td>8.5 (6.3–10.7)</td>
<td>154.5 (145.0–164.1)</td>
<td>74.4 (67.8–81.1)</td>
<td>18.6 (15.3–21.8)</td>
<td>95.1 (87.8–102.4)</td>
</tr>
<tr>
<td>Higashisonogi</td>
<td>6.3 (2.5–10.0)</td>
<td>126.5 (109.4–143.6)</td>
<td>44.9 (34.6–55.3)</td>
<td>17.2 (11.1–23.4)</td>
<td>87.5 (73.6–101.3)</td>
</tr>
<tr>
<td>Kitatakaki</td>
<td>3.6 (0.4–6.9)</td>
<td>150.0 (129.0–171.0)</td>
<td>54.7 (41.7–67.8)</td>
<td>13.0 (6.7–19.3)</td>
<td>97.4 (80.9–113.9)</td>
</tr>
<tr>
<td>Minamitakaki</td>
<td>6.1 (3.9–8.2)</td>
<td>148.3 (138.2–158.4)</td>
<td>45.7 (40.1–51.3)</td>
<td>13.7 (10.8–16.7)</td>
<td>86.0 (78.7–93.3)</td>
</tr>
<tr>
<td>Kitamatsuura</td>
<td>15.0 (10.9–19.0)</td>
<td>156.4 (143.2–169.6)</td>
<td>73.4 (64.2–82.6)</td>
<td>22.9 (18.0–27.9)</td>
<td>91.2 (81.6–100.8)</td>
</tr>
<tr>
<td>Minamimatsuura</td>
<td>25.1 (19.0–31.3)</td>
<td>163.1 (147.3–178.8)</td>
<td>118.6 (105.0–132.1)</td>
<td>32.9 (26.0–39.8)</td>
<td>114.7 (102.1–127.3)</td>
</tr>
<tr>
<td>Tushima</td>
<td>21.5 (14.8–28.3)</td>
<td>165.0 (147.1–182.9)</td>
<td>47.6 (37.8–57.3)</td>
<td>14.5 (9.3–19.8)</td>
<td>78.1 (65.9–90.3)</td>
</tr>
<tr>
<td>Prefecture (total)</td>
<td>9.7 (9.0–10.5)</td>
<td>155.4 (152.3–158.5)</td>
<td>72.0 (69.9–74.1)</td>
<td>19.4 (18.4–20.5)</td>
<td>91.7 (89.4–94.0)</td>
</tr>
</tbody>
</table>

DCO, proportion of cases registered by death certificate only; I/D ratio, incidence/death ratio. *World population was used as the reference population. Iki Island was omitted because of an exceptionally high proportion of cases registered by death certificate only. 'Cases per 100 000 person-years. Numbers in parentheses are 95% confidence intervals.

19 481 women) from the correlation analysis because of an exceptionally high proportion of cases registered by death certificate only (DCO, 55.1% for six malignancies examined). In addition, the analysis was restricted to those of 30–79 years of age, since the number of patients under 30 years of age was small and the DCO% was relatively high among those aged 80 years or older.

**CASES OF ATL AND OTHER MALIGNANCIES**

All cases of ATL diagnosed between January 1985 and December 1997 were selected from the file of the Nagasaki Prefectural Cancer Registry. The diagnostic criteria used were (i) T-cell malignancy with seropositivity to HTLV-I or (ii) clinical diagnosis of ATL. The validity of the diagnosis and the potential source of bias have been reported elsewhere (14). Briefly, the diagnosis of ATL was considered to be generally valid, but it was speculated that a precise differential diagnosis between ATL and other non-Hodgkin’s lymphoma had not always been performed for patients aged 70 years or older.

Similarly, all incident cases of gastric cancer (International Classification of Diseases for Oncology-Topography 1510–1519, C160–C169), liver cancer (1550, C220), biliary tract cancer (including cancers of the intrahepatic bile duct, extrahepatic bile duct and gall bladder) (1551, 1560–1569, C221, C239, C240, C241, C248, C249), lung cancer (1620–1629, C339, C340–C349) and cervical cancer (1800–1809, C530–C539) were also selected from the file of the Cancer Registry.

**STATISTICAL ANALYSIS**

The gender- and 10-year age-specific person-years at risk were calculated by summing the population from 1985 to 1997 (12). The incidence of ATL and other malignancies was calculated by dividing the number of cases by person-years at risk. The age-standardized incidence rates and their confidence intervals (CI) were calculated by the direct method, using as weights the world population. Spearman rank correlation and weighted least-squares analyses (15) were used to examine the association between the incidence of ATL and that of other malignancies. All statistical analyses were performed using the SAS software package (Version 6.12) (16).

**RESULTS**

Age-standardized incidence rates of ATL and other malignancies among men and women are shown in Tables 1 and 2, respectively. In the whole of Nagasaki Prefecture, the proportion of DCO ranged from 1.2% (cervical cancer in women) to 23.3% (liver cancer in women). The incidence/death ratio
ranged from 1.28 (liver cancer in men) to 5.16 (cervical cancer in women). The age-standardized incidence of ATL (cases/100,000 person-years) was 9.7 (95% CI 9.0–10.5) for men and 5.6 (95% CI 5.1–6.1) for women. Among men, the incidence of ATL in each area varied by a factor of 13.3, ranging from 1.9 in Shimabara to 25.3 in Hirado (Fig. 1a). Among women, there was also a large variation in the incidence (2.2 in Kitatakaki to 11.9 in Hirado, Fig. 1b). The age-standardized incidence rates of stomach, liver and lung cancers in Nagasaki Prefecture were 2.4–4.4 times higher in men than women, which was similar to that reported from the 10 population-based cancer registries in Japan (17). The regional variations in the incidence rates were smaller for cancers of the stomach, liver, biliary tract, lung and cervix uteri than for ATL. Among 2034 patients with histologically confirmed liver cancer, 1890 (92.9%) were hepatocellular carcinoma, 25 (1.2%) were hepatocellular carcinoma + cholangiocarcinoma and 48 (2.4%) were hepatocellular carcinoma + cholangiocarcinoma and 48 (2.4%) were adenocarcinoma.

Table 3 summarizes the correlation between the incidence rates of ATL and those of other malignancies. The incidence of ATL was found to be positively correlated with that of biliary tract cancer in men (Spearman \( r = 0.45 \), \( P = 0.09 \), person-years-weighted \( r = 0.49 \), \( P = 0.06 \), Fig. 2a) and liver cancer in women (Spearman \( r = 0.67 \), \( P = 0.007 \), weighted \( r = 0.56 \), \( P = 0.03 \), Fig. 2b). When biliary tract cancer was classified into subsites, among men, the association with ATL was stronger for extrahepatic bile duct cancer [number of cases (\( n \) = 713, weighted \( r = 0.48 \), \( P = 0.07 \)] than for gall bladder cancer (\( n =
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Regarding the cancers of the intrahepatic bile duct, the number of cases was too small to calculate the region-specific incidence rates \( n = 193 \). There was no significant positive correlation between ATL and cancer of the stomach, lung or cervix uteri. When lung cancer was classified into histological subtype, the person-years-weighted \( r \) between ATL and small cell lung cancer \( n = 723 \) was 0.40 \( (P = 0.14) \) for men. There were only 158 patients with small cell lung cancer among women. These results of correlation analyses were essentially similar when the 1985 Japanese model population was used as a reference (data not shown). There was no positive correlation between the DCO% of ATL and

Figure 1. Age-standardized incidence of ATL (cases/100,000 person-years) in each area among (a) men and (b) women. Iki Island was excluded because of an exceptionally high proportion of cases registered by death certificate only.
that of bile duct cancer in men (Spearman $r = 0.16$, $P = 0.57$) or liver cancer in women (Spearman $r = -0.10$, $P = 0.72$).

**DISCUSSION**

In the present study, we used the incidence of ATL in each area as the exposure variable because data on the prevalence of HTLV-I seropositivity in the whole of Nagasaki Prefecture were not available. There was no positive correlation between the incidence of ATL and that of other malignant lymphomas (men, $n = 1090$, Spearman $r = 0.17$, $P = 0.54$, person-years-weighted $r = 0.05$, $P = 0.87$; women, $n = 702$, Spearman $r = 0.12$, $P = 0.68$, weighted $r = 0.07$, $P = 0.82$, data not shown). This suggested that the misclassification of ATL as other malignant lymphomas was not serious. However, the use of ATL incidence instead of the HTLV-I seroprevalence may become a limitation as well as an advantage of the study. Because it is considered that HTLV-I infection acquired after adolescence does not lead to ATL (18), the large variation in the incidence of ATL may reflect the difference in the proportion of persons infected with HTLV-I early in life. Therefore, if HTLV-I infection after adulthood has strong effects on the development of other cancers, misclassification bias may become an issue, the direction of which is not necessarily towards the null (19). This problem may be more serious for women than men, because sexual transmission of HTLV-I occurs more frequently from male to female than vice versa (20). On the other hand, if vertical transmission is biologically relevant, the use of ATL incidence as the exposure variable may be justified and it may reduce the possibility of confounding by other oncogenic viruses caught mainly through blood transfusion (hepatitis C virus) or sexual transmission (human papilloma viruses 16 and 18).

There are several explanations for the significant association between ATL and liver cancer, over 90% of which may be hepatocellular carcinoma. The first is the simple coincidence of the distribution of HTLV-I and hepatitis C virus (HCV), both of which are endemic in remote islands, such as the Goto Islands in Nagasaki Prefecture. The second is the possible effect of HTLV-I to promote progression from HCV infection to chronic hepatitis, liver cirrhosis and liver cancer. One study suggested that infection with HTLV-I inhibited the elimination of HCV in interferon-treated and non-treated individuals (21). It has also been reported that co-infection with HCV and HTLV-I had a synergistic effect on mortality from liver cancer in Miyazaki Prefecture, Japan (8). The influence of hepatitis B virus (HBV) may be smaller than HCV, because after 1985 the prevalence of the HBV surface antigen became much lower than that of HCV antibody in patients with hepatocellular carcinoma in Nagasaki Prefecture (22). Confounding by the completeness of cancer registration seems unlikely, since there was no positive correlation between the DCO% of ATL and that of liver cancer.

A characteristic clustering of mortality from biliary tract cancer has been reported in Japan (23), suggesting the involvement of environmental factors in the etiology. Case-control studies in Japan and the USA consistently suggested that cholelithiasis is a risk factor for bile duct cancer (24,25). Intriguingly, an increased prevalence of HTLV-I infection and IgE antibody to roundworm has been reported in patients with hepatolithiasis in the Kamigoto Islands, where HTLV-I is endemic (26, 27). It is of concern whether HTLV-I infection leads to a more severe roundworm infection (such as migration to the biliary tract) and thereby increases the risk of cholelithiasis and biliary tract cancer. Spurious association because of the completeness of registration seems unlikely, as was the case for liver cancer among women.

There was a weak positive but not significant correlation between the incidence of ATL and that of small cell lung cancer among men ($r = 0.40$, $P = 0.14$). However, the possibility of confounding by smoking habit could not be precluded, because one case-control study suggested that smoking was a risk co-factor of ATL among HTLV-I carriers (28).

An association between HTLV-I infection and cancer of the cervix uteri (2,3) and stomach (7) has been hypothesized and...
as a biological mechanism, mild immune suppression by HTLV-I has been proposed (2,7). In the current study, we could find no evidence to support this hypothesis at the population level. However, it should be recognized that ecological study is not a strong study design in terms of causal inference (19). In particular, this type of study cannot eliminate the confounding effects of other factors, such as smoking and dietary habits. In addition, it was difficult to find a plausible explanation for the gender difference found in cancers of the liver and biliary tract. Thus, analyses at the level of the individual, e.g. prospective cohort studies, are required to evaluate in more detail whether HTLV-I infection is associated with an increased risk of developing cancers of other sites.

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References