Human T Lymphotropic Virus Type 1 Infection and Gastric Cancer Development in Japan

Satohiro Matsumoto,1 Kazumi Yamasaki,2 Kenichiro Tsuji,1 and Satoshi Shirahama1
1Department of Internal Medicine, Kamigoto Hospital, and 2Department of Internal Medicine, Narao Hospital, Nagasaki, Japan

(See the editorial commentary by Blaser and Valentine, on pages 1–3.)

Background. The rate of human T lymphotropic virus type 1 (HTLV-1) positivity among residents of Kamigoto, Japan, is extremely high (15%). Although the rate of Helicobacter pylori positivity in Kamigoto is almost the same as that in other areas of Japan, the incidence of gastric cancer in Kamigoto is lower. This study examined whether HTLV-1 infection affects H. pylori infection and the development of gastric cancer.

Methods. The study involved 5686 patients >40 years of age who provided serum specimens for HTLV-1 antibody testing during 1989–1992. A total of 1812 patients underwent gastric endoscopy during the follow-up period. Of these, 497 were HTLV-1 seropositive. Data for these patients were compared with those for 497 HTLV-1–seronegative control patients matched for age, sex, and follow-up duration. We followed these groups until 2003 and determined the cumulative incidence rate of gastric cancer.

Results. The rate of H. pylori positivity was 61.7% in the HTLV-1–positive group and 71.6% in the HTLV-1–negative group (P = .07). Fourteen HTLV-1–positive patients (2.8%) had gastric cancer, compared with 35 patients (7.0%) in the HTLV-1–negative group (odds ratio, 0.38; 95% confidence interval, 0.21–0.70; P = .0028).

Conclusion. HTLV-1 infection likely reduces the risk of H. pylori infection and proliferation and, thereby, the risk of gastric cancer.

Human T lymphotropic virus type 1 (HTLV-1) is etiologically linked to adult T cell leukemia/lymphoma (ATL). Several studies and reports have suggested that HTLV-1 infection is associated with an increased risk of malignancies other than ATL. Asou et al. [1] reported that 5 of 18 smoldering-type ATL cases were complicated by other malignancies, such as cancer of the vagina, skin, stomach, and liver. By contrast, Arisawa et al. [2] reported that HTLV-1 carriers did not have an increased risk of cancer in general but did have a reduced risk for gastric cancer.

In Nagasaki Prefecture, Japan, in 2000, the incidence of gastric cancer was 91.6 cases per 100,000 population, compared with a mean incidence of 74.6 cases per 100,000 population in Kamigoto, Nagasaki Prefecture, for the 6-year period from 1998 through 2003. The incidence of gastric cancer in Kamigoto is less than that in Nagasaki Prefecture. On the other hand, the rate of HTLV-1 positivity in Kamigoto is extremely high, reaching 15% and >30% among subjects in age groups that are associated with a risk of gastric cancer, compared with 6% in other areas of Japan where the prevalence of HTLV-1 positivity is high [3]. A few reports showed a significantly low prevalence of Helicobacter pylori infection among patients infected with HTLV-1 [4, 5]. The aim of this retrospective cohort study was to assess the relationship between serological evidence of HTLV-1 infection, serological evidence of H. pylori infection, and the development of gastric cancer, to examine whether HTLV-1 infection affects H. pylori infection and the development of gastric cancer.

PATIENTS, MATERIALS, AND METHODS

Study population and design. We examined the serum HTLV-1 antibody status in 5686 patients aged >40 years at their initial visit to Kamigoto Hospital during 1989–1992 (rate of HTLV-1 antibody positivity, 29.3%). A total of 2630 were men, and 3056 were...
women (mean age, 59 years [range, 40–98 years]), and all were followed up through March 2003. A total of 1812 patients (771 men and 1041 women; mean age, 57 years [range, 40–91 years]) underwent upper gastrointestinal endoscopy during the follow-up period (rate of HTLV-1 antibody positivity, 27.4%). Of these patients, 497 were HTLV-1 seropositive (183 men and 314 women; mean age, 59 years [range, 40–91 years]) and did not have gastric cancer detected at entry. These data were compared with those for 497 HTLV-1–seronegative control subjects matched for age, sex, and follow-up duration who also did not have gastric cancer detected at entry (figure 1). The primary end point was the date of gastric cancer detection or the date of final endoscopic examination during the follow-up period. For patients with gastric cancer, the secondary end point was the date of death due to gastric cancer.

Information on the occurrence of gastric cancer and death due to gastric cancer was collected by the Kamigoto Hospital Cancer Registry, in cooperation with the Kamigoto town office. We examined the cumulative incidence and survival rates for gastric cancer. The follow-up duration (±SD) was 9.5 ± 3.4 years for the HTLV-1–positive group versus 9.6 ± 3.2 years for the HTLV-1–negative group (P = .71) (table 1). Patients who underwent gastrointestinal endoscopic examination for detection of gastric cancer or for investigation of gastrointestinal symptoms were included in both HTLV-1 populations. Gastric cancers were classified as either intestinal-type or diffuse-type carcinoma, according to the criteria of Lauren [6].

**Laboratory analysis.** Serum HTLV-1 antibody examination was performed using particle agglutination assays. The Serodia ATLA kit (Fujirebio) was used through April 1990, after which the Serodia HTLV-1 kit (Fujirebio) was used.

Stored serum samples collected from all patients who developed gastric cancer underwent EIA (SRL) for detection of IgG antibodies to *H. pylori*. An IgG antibody titer of ≥10 U/mL was considered indicative of *H. pylori*. The samples were collected before the development of gastric cancer and the initiation of *H. pylori* eradication therapy.

A total of 296 of 994 individuals underwent a histologic examination, a $^{13}$C urea breath test, and, as described above, EIA for IgG antibodies to *H. pylori*. One hundred twenty (55 men and 65 women) of 497 examined patients were in the HTLV-1–seropositive group, and 176 (71 men and 105 women) of 497 were in the HTLV-1–seronegative group. *H. pylori* positivity was defined as a positive result of any of these assays.

**Statistical analysis.** The demographic characteristics of the study subjects were compared using the Student t test (for age and duration of follow-up). The rate of *H. pylori* positivity was evaluated with the Fisher exact test. The cumulative incidence and survival rate for patients with gastric cancer were evaluated with the Kaplan-Meier method and were compared using the log-rank test. Odds ratios (ORs), their 95% confidence intervals (CIs), and statistical significance were computed. All analyses

**Table 1. Characteristics of men with and men without antibody to human T lymphotropic virus type 1 (HTLV-1).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HTLV-1 antibody status</th>
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<tbody>
<tr>
<td></td>
<td>Positive (n = 183)</td>
<td>Negative (n = 183)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at study entry, years</td>
<td>58 ± 10</td>
<td>58 ± 10</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>40–80</td>
<td>40–77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of <em>H. pylori</em> positivity, % of men</td>
<td>56.4</td>
<td>74.6</td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Follow-up duration, mean ± SD, years</td>
<td>9.2 ± 3.4</td>
<td>9.4 ± 3.4</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

* Comparisons were performed by means of the Student t test, except for the rate of *Helicobacter pylori* positivity, which was compared using the Fisher exact test.

Figure 1. Flowchart of the selection of patients with human T lymphotropic virus type 1 (HTLV-1) infection and matched control subjects without HTLV-1 infection.
were performed with StatView, version 5.0. Statistical significance was set at $P < .05$.

**RESULTS**

The rate of $H. pylori$ positivity was 61.7% in the HTLV-1–positive group, compared with 71.6% in the HTLV-1–negative group ($P = .07$). Among men, the rates were 56.4% in the HTLV-1–positive group and 74.6% in the HTLV-1–negative group ($P = .03$) (table 1), and among women, the rates were 66.2% and 69.5%, respectively ($P = .73$).

There were 14 cases of gastric cancer (incidence, 2.8% [3.0 cases/year per 1000 population]) among HTLV-1–positive patients and 35 cases (incidence, 7.0% [7.3 cases/year per 1000 population]) among HTLV-1–negative control patients (OR, 0.38; 95% CI, 0.21–0.70; $P = .0028$). There were 14 cases of gastric cancer (incidence, 2.8% [3.0 cases/year per 1000 population]) among HTLV-1–positive patients, compared with 35 (7.0%) of 497 HTLV-1–negative patients (odds ratio, 0.38; 95% confidence interval, 0.21–0.70; $P = .0028$).

For men, there were 8 cases in the HTLV-1–positive group and 19 cases in the HTLV-1–negative group (OR, 0.39; 95% CI, 0.17–0.90), and for women, there were 6 and 16 cases, respectively (OR, 0.36; 95% CI, 0.14–0.91) (figure 3). The mean age at the time of gastric cancer onset was 72 years (range, 49–96 years) in the HTLV-1–positive group, compared with 70 years (range, 42–77 years) in the HTLV-1–negative group. In the HTLV-1–positive group, there were 9 cases of intestinal-type carcinoma, 2 cases of diffuse type, and 3 cases of unknown type, compared with 14 cases of intestinal-type carcinoma, 15 cases of diffuse type, 1 case of mixed type, and 5 cases of unknown type in the HTLV-1–negative group. Eight (57.1%) of 14 patients in the HTLV-1–positive group had been infected with $H. pylori$, compared with 27 (77.1%) of 35 patients in the HTLV-1–negative group ($P = .18$). The mean observation period ($\pm SD$) was 6.8 ± 3.3 years in the HTLV-1–positive group and 5.7 ± 3.1 years in the HTLV-1–negative group ($P = .27$) (table 2).

The cumulative incidence of gastric cancer was 1.1% during the first 5 years of follow-up (1994–1998) and 3.0% during the entire (i.e., ~10-year) follow-up period (1999–2003) in the HTLV-1–positive group, compared with 2.7% and 8.0%, respectively, in the HTLV-1–negative group ($P = .0028$). The incidence of gastric cancer in the HTLV-1–positive group was lower than that in the HTLV-1–negative group ($P = .0028$). Among men, the cumulative incidence of gastric cancer was 1.8% during the first 5 years of follow-up and 4.8% during the overall follow-up period in the HTLV-1–positive group, compared with 4.6% and 11.1%, respectively, in the HTLV-1–negative group ($P = .04$). Among women, the cumulative incidence of gastric cancer was 0.7% for the 5-year period and 1.9% for the

**Figure 2.** Kaplan-Meier analysis of the cumulative incidence of gastric cancer, by serum human T lymphotropic virus type 1 (HTLV-1) antibody status. During follow-up, gastric cancer developed in 14 (2.8%) of 497 HTLV-1–positive patients, compared with 35 (7.0%) of 497 HTLV-1–negative patients (odds ratio, 0.38; 95% confidence interval, 0.21–0.70; $P = .0028$). The cumulative incidence, % of patients

**Figure 3.** Kaplan-Meier analysis of the cumulative incidence of gastric cancer among 366 men (A) and 628 women (B) by serum human T lymphotropic virus type 1 (HTLV-1) antibody status. Among men, gastric cancer developed in 8 of 183 HTLV-1–positive patients and in 19 of 314 HTLV-1–negative patients (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.17–0.90; $P = .04$), whereas among women, gastric cancer developed in 6 and 16 patients, respectively (OR, 0.36; 95% CI, 0.14–0.91; $P = .03$).

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The cumulative survival rate during the first 5 years of follow-up among the 49 patients with gastric cancer was 28.6% (4 of 14 patients) in the HTLV-1–positive group, compared with 34.3% (12 of 35 patients) in the HTLV-1–negative group (P = .74) (figure 4).

DISCUSSION

We found that the incidence of gastric cancer in the HTLV-1–positive group was lower than that in the HTLV-1–negative group. Iwata et al. [7] reported that the hazard ratio associated with HTLV-1 infection for death from all causes, excluding ATL, was 1.77 (95% CI, 0.93–3.37) for males and 1.87 (95% CI, 1.12–3.12) for females, although analysis of cause-specific mortality revealed a significantly increased risk for nonneoplastic disease in each group. Arisawa et al. [2] reported that HTLV-1-seropositivity was associated with increased mortality from all causes, excluding ATL (risk ratio [RR], 1.3; 95% CI, 1.0–1.7), and that HTLV-1 infection was not associated with an increased risk of any cancer other than ATL, colorectal cancer, liver cancer, and lung cancer but was associated with a reduced risk of gastric cancer (RR, 0.42; 95% CI, 0.17–0.99). In addition, Asou et al. [1] and Kozuru et al. [8] reported that HTLV-1 infection was associated with an increased risk of various cancers.

There is increasing evidence to suggest that gastric infection with H. pylori is a risk factor for gastric cancer. Stored serum samples collected from individuals without gastric cancer were tested for IgG antibodies to H. pylori by ELISA. The mean time between serum collection and diagnosis of gastric carcinoma was 14.2 years. Of the 109 patients with confirmed gastric cancer, 84% had been infected previously with H. pylori, compared with 61% of matched control subjects (OR, 3.6; 95% CI, 1.8–7.3) [9]. The Eurogast Study Group demonstrated a significant correlation between the gastric cancer mortality rate and the prevalence of H. pylori seropositivity. It can be predicted that mortality from gastric cancer in a population with a 100% prevalence of H. pylori infection would be ~6 times that in a population with a

Figure 4. Kaplan-Meier analysis of the cumulative survival rate among 49 patients with gastric cancer, by serum human T lymphotropic virus type 1 (HTLV-1) antibody status. During follow-up, 4 of 14 HTLV-1–positive patients and 12 of 35 HTLV-1–negative patients died (P = .74).
0% prevalence [10]. The World Health Organization and the International Agency for Research on Cancer consensus group stated in 1994 that there was sufficient epidemiologic and histologic evidence to classify *H. pylori* as a definite carcinogen [11]. In 1998 Huang et al. [12] reported results of a meta-analysis of the relationship between *H. pylori* seropositivity and gastric cancer, Asaka et al. [13] and Kikuchi et al. [14] reported an association between *H. pylori* infection and the development of gastric cancer, and in 2001 Uemura et al. [15] reported that gastric cancer developed in 4.7% of persons infected with *H. pylori* but in no uninfected persons during a mean follow-up duration of 7.8 years. It has thus become clear that *H. pylori* infection is associated with the development of gastric cancer [15].

In the present study, conducted during a follow-up period of ~10 years, HTLV-1 infection was associated with a 3-fold reduction in the risk of gastric cancer, suggesting that HTLV-1 infection plays a role in reducing the risk for gastric cancer. We therefore looked at whether HTLV-1 infection may reduce the risk of *H. pylori* infection. Isomoto et al. [4] and Walker [5] demonstrated that patients infected with HTLV-1 had a low prevalence of *H. pylori* infection. Tachibana et al. [16] showed that healthy carriers of HTLV-1 exhibited significant diminution of delayed-type hypersensitivity, suggesting the existence of subclinical immunosuppression even among healthy carriers of HTLV-1. It is possible that, during long-term infection with HTLV-1, progression of immunosuppression provides a less suitable intragastric environment for *H. pylori* colonization and that the organism may gradually be eliminated from the stomach [4]. Stuver et al. [17] reported that significantly fewer HTLV-1–positive patients had a past history of peptic ulcer, with odds ratios of 0.49 (95% CI, 0.27–0.89) and 0.81 (95% CI, 0.42–1.6) for male and female patients, respectively.

In this study, the rate of *H. pylori* positivity in the HTLV-1–positive group was lower than that in the HTLV-1–negative group overall and for men and women; furthermore, the frequencies of gastric cancer among men, women, and both groups combined were greater among HTLV-1–negative patients than among HTLV-1–positive patients, although the differences were not significant. These findings suggest that HTLV-1 infection may reduce the risk of *H. pylori* infection and proliferation. Among all men and HTLV-1–positive women with gastric cancer, the number of patients with intestinal-type carcinoma was greater than the number with diffuse-type carcinoma. In contrast, among HTLV-1–negative women, the number with diffuse-type carcinoma was greater than the number with intestinal-type carcinoma. The reason for the latter finding remains unclear.

Yamashita et al. [18] determined the prevalence of *H. pylori* infection in healthy children from the Kyushu region in Japan. The prevalences of *H. pylori* seropositivity were 3% among children aged <1 year, 10% among those aged 1–4 years, 19% among those aged 5–9 years, 25% among those aged 10–14 years, and 29% among those aged 15–19 years. *H. pylori* infection is known to be acquired early during childhood [19, 20]. Infection frequently occurs before 10 years of age, and two-thirds of individuals become infected before 7 years of age [21]. Furthermore, family structure during early life (i.e., sibship size and birth order) is associated with a risk of future development of gastric cancer among *H. pylori*–positive males [22]. On the other hand, invasion by infected lymphocytes, which occurs via vertical infection (in 70% of cases), horizontal infection (in 20%), or transmission through blood (in 10%), is required for HTLV-1 infection in vivo. A relatively high proportion of babies born to women positive for HTLV-1 test positive for anti–HTLV-1 antibody, although this antibody disappears within the first 9 months of life in many cases and by 2 years of age in nearly all cases. Among children with infection transmitted from their mother, there were no cases of seroconversion after the age of 3 years [3]. These findings suggest that HTLV-1 infection is frequently acquired before *H. pylori* infection. Early infection with HTLV-1 may weaken gastric mucosal immune responses and thereby affect *H. pylori* infection and proliferation. In this study, we did not adjust for *H. pylori* infection, smoking, drinking habits, and salt intake, which could be related to the etiology of gastric cancer. Further studies of gastric cancer associated with HTLV-1 seropositivity with adjustment for these factors are needed.

In conclusion, the incidence of gastric cancer in the HTLV-1–positive group was lower than that in the HTLV-1–negative group. HTLV-1 infection likely reduces the risk of *H. pylori* infection and proliferation and, thereby, the risk of gastric cancer.

### References


