INTRODUCTION

*Strongyloides stercoralis* is one of the most common human gastrointestinal parasites in the world. The Okinawa Prefecture of Japan is located in a subtropical region, which is endemic for *S. stercoralis*. With humid and warm soil, subtropical regions provide the preferred external environment for *S. stercoralis*. The filariform larvae, which inhabit the soil, usually infect humans via skin penetration. After infection, the larvae travel to the duodenum to become adult females. Rhabditiform larvae, hatched from eggs produced by the females, are excreted from the human host. However, some larvae reinfect the host through the intestinal mucosa or perianal skin, using a process called autoinfection, which is unique to *S. stercoralis* and HTLV-1 in the Okinawan population has been steadily decreasing over the past 24 years.

The diagnosis of cancer was based on histology, cytology, and radiological findings. Patients diagnosed with metastatic cancer were excluded because the source of primary cancer could not be determined within reasonable time constraints.

**Statistical analyses.** The $\chi^2$ test was used to compare the prevalence of *S. stercoralis* or HTLV-1 infection between
sexes. The \( \chi^2 \) test was also used to compare the prevalence of each cancer in a crude analysis with a history of \textit{S. stercoralis} or HTLV-1 infection. Logistic regression analyses adjusted for age and sex were used to examine the odds of developing each cancer considering the incidence of \textit{S. stercoralis} or HTLV-1 infection. All statistical analyses and graphical representations were performed using SPSS (version 21.0; IBM Corp., Armonk, NY) software packages. The \( P \) values reported here are two sided.

**RESULTS**

**Prevalence of \textit{S. stercoralis} and HTLV-1 infection.** The study population was composed of 3,154 men and 2,055 women, with a mean age of 56.4 ± 17.9 (standard deviation [SD]) years (range: 11–101 years). The total prevalence of \textit{S. stercoralis} infection in our study population was 5.2\% (Table 2, Figure 1A). The prevalence of \textit{S. stercoralis} in the male population (6.3\%) was significantly higher than that in the female population (3.6\%, \( P < 0.001 \)). There were no patients with a \textit{S. stercoralis} infection that were born after 1960. The total prevalence of HTLV-1 infection was 13.6\% (Table 2, Figure 1B). The prevalence of HTLV-1 infection in men and women was 12.3\% and 15.5\%, respectively. HTLV-1 infection was significantly more prevalent in women than in men (\( P < 0.001 \)). The number of \textit{S. stercoralis} and HTLV-1 infections steadily decreased for both sexes in each successive generation.

To evaluate the relationship between \textit{S. stercoralis} infection and HTLV-1 infection, we compared only patients born before 1960. The total number of patients born before 1960 was 4,056 (2,459 men and 1,597 women). Within this population, the prevalence of \textit{S. stercoralis} infection was significantly higher in patients with HTLV-1 infection compared with that in patients without HTLV-1 infection (Tables 3 and 4). The

### Table 1

| Birth year | Number of \textit{S. stercoralis}-positive patients/number of tested patients (%) | Number of HTLV-1-positive patients/number of tested patients (%) |
|------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|
| \( \leq 1919 \) | 24/168 (14.8)                                                                      | 31/168 (18.5)                                                   |
| 1920–1929 | 25/168 (14.8)                                                                      | 33/168 (18.5)                                                   |
| 1930–1939 | 36/168 (21.4)                                                                      | 49/168 (29.2)                                                   |
| 1940–1949 | 45/168 (26.8)                                                                      | 56/168 (33.6)                                                   |
| 1950–1959 | 54/168 (32.2)                                                                      | 64/168 (38.2)                                                   |
| 1960–1969 | 63/168 (37.1)                                                                      | 73/168 (43.5)                                                   |
| 1970–1979 | 72/168 (43.1)                                                                      | 82/168 (49.2)                                                   |
| 1980–1989 | 81/168 (48.4)                                                                      | 91/168 (54.1)                                                   |
| \( \geq 1990 \) | 90/168 (53.6)                                                                      | 100/168 (60.0)                                                  |
| Total     | 398/168 (23.5)                                                                     | 499/168 (29.8)                                                  |

**FIGURE 1.** The study included 5,209 patients who were admitted to the First Department of Internal Medicine for Infectious, Respiratory, and Digestive Medicine at the University of Ryukyus Hospital in Okinawa, Japan, between 1991 and 2014. \( (A) \) The prevalence of \textit{Strongyloides stercoralis} infection in men (circles) and women (squares) by age. \( (B) \) The prevalence of human \textit{T}-cell lymphotropic virus type 1 infection in the men (circles) and women (squares) by age.
for each cancer. Although our data suggest that S. stercoralis mean age of 61.8 ± 12.9 (SD) years.

With a mean age of 67.0 ± 10.2 (SD) years. The cancer-free identified 1,352 patients with diagnostically confirmed cancer. Patients are more likely to develop cancer (P < 0.001), respectively. Using a logistic regression model adjusted for age and sex, we calculated the OR stratified for each cancer. Although some publications report younger patients with S. stercoralis infection who have never traveled outside of Japan,15,16 the overall prevalence of S. stercoralis infection has markedly decreased since 1960. This change is most attributed to improvements in public health and sanitation. After World War II, intestinal parasitic infections were common in Okinawa because of poverty, poor sanitation, the use of human waste as fertilizer, and the common practice of barefoot agricultural work.15 At that time, public health centers also lacked the ability to detect, treat, or provide prevention for parasites.17 At that time, public health centers also lacked the ability to detect, treat, or provide prevention for parasites.17 After implementation of the “Zero Parasite Campaign” from 1965 to 1969, the infection rate of parasites was drastically reduced and soil sanitation was improved. Our study also shows that the prevalence of HTLV-1 infection is decreasing steadily, which supports existing literature from Japan and Okinawa.18,19 Satake and others suggested this reduction might be called the “birth cohort effect” whereby the high-prevalence cohort (those born 1930–1960) ages while younger cohorts (those born after 1960) have lower prevalence rates.20 These findings may be the result of increased knowledge regarding HTLV-1 and its transmission routes.18 In Japan, the transmission of virus via transfusion has been eliminated since the implementation of HTLV-1 screening of donated blood in 1986. Japanese mothers have increased the number of bottle-fed babies,21 thereby decreasing the vertical infection of HTLV-1. In 2011, the Japanese Ministry of Health, Labour and Welfare initiated a nationwide program to prevent mother-to-child infection by screening all pregnant women for HTLV-1 infection and recommending bottle feeding for women with positive results.24

The data suggest a strong correlation between S. stercoralis and HTLV-1 infections. The prevalence of S. stercoralis infection was significantly higher (P < 0.001) in patients with HTLV-1 infection compared with that in patients without HTLV-1 infection. Patients infected with HTLV-1 developed S. stercoralis infection 2.4 times more often than noninfected patients. Multiple studies in Okinawa have showed an increased risk for S. stercoralis infection when the host is immuno-compromised,19,25,26 and similar findings were reported in studies conducted in other regions, such as South America.27–30 Furthermore, when the data were stratified for sex, we also found that females were more likely to have concurrent infections of S. stercoralis and HTLV-1. This altered susceptibility is most likely due to the difference in effectiveness of HTLV-1 transmission. It has been documented that

### Table 3

|          | HTLV-1 |
|----------|--------|
|          | Positive | Negative | Total |
| Strongyloides stercoralis | 82 (2.0%) | 190 (4.7%) | 272 |
|          | 575 (14.2%) | 3,209 (79.1%) | 3,784 |
| Total    | 657 | 3,399 | 4,056 |

HTLV-1 = human T-cell lymphotropic virus type 1.

Odds ratio = 2.41 (95% confidence interval = 1.83, 3.17; P < 0.001) by χ² analysis.

Using a logistic regression model adjust for age and sex, we calculated the OR stratified for each cancer. HTLV-1 infection was not shown to significantly increase the odds of developing most types of cancer, except for liver cancer and lymphomas other than ATLL. Patients with an HTLV-1 infection in our cohort were approximately twice as likely to develop liver cancer (OR: 1.91, 95% confidence interval [CI]: 1.24, 2.95) and approximately three times more likely to develop lymphoma other than ATLL (OR: 2.76, 95% CI: 1.36, 5.62) compared with patients without HTLV-1.

### DISCUSSION

Our results show that there were no patients born after 1960 with S. stercoralis infection in our cohort. Although some publications report younger patients with S. stercoralis infection who have never traveled outside of Japan,15,16 the overall prevalence of S. stercoralis infection has markedly decreased since 1960. This change is most attributed to improvements in public health and sanitation. After World War II, intestinal parasitic infections were common in Okinawa because of poverty, poor sanitation, the use of human waste as fertilizer, and the common practice of barefoot agricultural work.15 At that time, public health centers also lacked the ability to detect, treat, or provide prevention for parasites.17 At that time, public health centers also lacked the ability to detect, treat, or provide prevention for parasites.17 After implementation of the “Zero Parasite Campaign” from 1965 to 1969, the infection rate of parasites was drastically reduced and soil sanitation was improved. Our study also shows that the prevalence of HTLV-1 infection is decreasing steadily, which supports existing literature from Japan and Okinawa.18,19 Satake and others suggested this reduction might be called the “birth cohort effect” whereby the high-prevalence cohort (those born 1930–1960) ages while younger cohorts (those born after 1960) have lower prevalence rates.20 These findings may be the result of increased knowledge regarding HTLV-1 and its transmission routes.18 In Japan, the transmission of virus via transfusion has been eliminated since the implementation of HTLV-1 screening of donated blood in 1986. Japanese mothers have increased the number of bottle-fed babies,21 thereby decreasing the vertical infection of HTLV-1. In 2011, the Japanese Ministry of Health, Labour and Welfare initiated a nationwide program to prevent mother-to-child infection by screening all pregnant women for HTLV-1 infection and recommending bottle feeding for women with positive results.24

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### Table 4

| Gender-stratified analyses | HTLV-1 |
|---------------------------|--------|
|                           | Positive | Negative | Total |
| Men*                      |          |          |       |
| Strongyloides stercoralis | Positive | 48 (2.0%) | 151 (6.1%) | 199 |
|                          | Negative | 311 (12.6%) | 1,949 (79.3%) | 2,260 |
|                          | Total    | 359 | 2,100 | 2,459 |
| Women†                    |          |          |       |
| S. stercoralis            | Positive | 34 (2.1%) | 39 (2.4%) | 73 |
|                          | Negative | 264 (16.5%) | 1,260 (78.9%) | 1,524 |
|                          | Total    | 298 | 1,299 | 1,597 |

HTLV-1 = human T-cell lymphotropic virus type 1.

*Odds ratio (OR) = 1.99 (95% confidence interval [CI] = 1.41, 2.82; P < 0.001) by χ² analysis.

†OR = 4.16 (95% CI = 2.58, 6.72; P < 0.001) by χ² analysis.
male-to-female sexual transmission is more efficient than female-to-male sexual transmission.\textsuperscript{29,30} Sexual transmission requires intimate and prolonged contact between partners.\textsuperscript{31} Several studies have also suggested a correlation between older age and risk of infection, particularly for women, whose increased susceptibility may be due to the thinning of vaginal epithelia tissue after menopause.\textsuperscript{30,32,33} However, some studies have shown that there are no correlations between the prevalence of \textit{S. stercoralis} and HTLV-1 infections.\textsuperscript{27,34} Carvalho and others suggested that the controversial results were due to the type of technique used to determine \textit{S. stercoralis} infection: stool examination or serological test.\textsuperscript{27} In our study, results show a strong correlation between \textit{S. stercoralis} and HTLV-1 infections because only stool examinations were used for determining \textit{S. stercoralis} infection.

No statistically significant associations between \textit{S. stercoralis} infection and the development of any specific types of cancer were found in our data. One study from Okinawa shows a significantly high prevalence of \textit{S. stercoralis} infection in patients with biliary tract cancer.\textsuperscript{35} Adult \textit{S. stercoralis} persist in human duodenum and upper jejunum, and the nematodes often migrate via the biliary tract. The resulting damage could cause cholangitis or pancreatitis or it could initiate and promote carcinogenesis.\textsuperscript{36–39} Although our study shows that patients with biliary tract cancer may be almost twice as likely to have evidence of \textit{S. stercoralis} infection as control patients (OR: 1.90, 95% CI: 0.93, 3.87), the evidence for this association is not statistically significant ($P = 0.08$). This result may be due to low statistical power, as only 69 cases of biliary tract cancers were included in our cohort.

Some studies suggest that HTLV-1 infection is associated with many types of cancer, mainly liver and other blood cancers.\textsuperscript{12,40–42} Other reports showed that HTLV-1 infection may have a protective effect against gastric cancers.\textsuperscript{10,11,43}

Our data show that HTLV-1 infection is not associated with cancer development apart from liver cancer and lymphomas other than ATLL. In addition, although our study found that patients with gastric cancer might be less likely to have evidence of HTLV-1 infection than patients with other types of cancer (OR: 0.75, 95% CI: 0.50, 1.12), the data are not statistically significant ($P = 0.16$). Similarly, we saw a trend that patients with esophageal cancer might be less likely to have evidence of HTLV-1 infection than patients with other types of cancer (OR: 0.56, 95% CI: 0.29, 1.11), but this difference also failed to reach statistical significance ($P = 0.10$). A report from Iran also described a trend toward an association of HTLV-1 infection and esophageal squamous cell carcinoma, but their data similarly failed to reach statistical significance.\textsuperscript{44}

This study found that HTLV-1 infection is associated with the development of liver cancer (OR: 1.91, 95% CI: 1.24, 2.95, $P = 0.003$). Similarly, a previous report showed a high association of HTLV-1 infection with the incidence of liver

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**Table 5**

| Cancer Type          | S. stercoralis infection rate | $P$ value | OR  | 95% CI         | $P$ value |
|----------------------|------------------------------|-----------|-----|----------------|-----------|
| Control              | 5.7% (147/2,596)             |           |     |                |           |
| Total cancer         | 8.7% (117/1,352)             | $<0.001^*$| 1.28| 0.98–1.66      | 0.06§     |
| Esophagus            | 6.4% (71/1,091)              | 0.48†     | 0.65| 0.29–1.45      | 0.29§     |
| Stomach              | 9.9% (24/242)                | 0.45†     | 1.22| 0.76–1.97      | 0.42§     |
| Biliary tract        | 14.5% (10/69)                | 0.05†     | 1.90| 0.93–3.87      | 0.08§     |
| Liver                | 6.4% (9/140)                 | 0.43†     | 0.72| 0.35–1.47      | 0.37§     |
| Colon and rectum     | 7.7% (15/194)                | 0.68†     | 0.94| 0.53–1.66      | 0.82§     |
| Lung                 | 9.6% (40/418)                | 0.46†     | 1.09| 0.73–1.64      | 0.68§     |
| Pancreas             | 5.4% (2/37)                  | 0.77†     | 0.83| 0.19–3.55      | 0.80§     |
| Lymphoma without ATLL| 2.7% (1/37)                  | 0.37†     | 0.28| 0.28–2.08      | 0.21§     |

**Table 6**

| Cancer Type          | HTLV-1 infection rate | $P$ value | OR  | 95% CI         | $P$ value |
|----------------------|-----------------------|-----------|-----|----------------|-----------|
| Control              | 12.9% (467/3,612)     |           |     |                |           |
| Total cancer         | 15.2% (219/1,437)     | 0.03*     | 0.90| 0.75–1.09      | 0.28§     |
| Esophagus            | 8.8% (10/114)         | 0.06†     | 0.56| 0.29–1.11      | 0.10§     |
| Stomach              | 12.2% (32/262)        | 0.15†     | 0.75| 0.50–1.12      | 0.16§     |
| Biliary tract        | 16.9% (12/71)         | 0.73†     | 0.96| 0.53–1.84      | 0.90§     |
| Liver                | 22.3% (32/143)        | 0.01†     | 1.91| 1.24–2.95      | 0.003§    |
| Colon and rectum     | 15.0% (30/200)        | 1.00†     | 0.91| 0.60–1.40      | 0.68§     |
| Lung                 | 13.5% (60/444)        | 0.23†     | 0.81| 0.58–1.12      | 0.19§     |
| Pancreas             | 7.8% (7/338)          | 0.26†     | 0.45| 0.14–1.49      | 0.19§     |
| Lymphoma without ATLL| 28.5% (12/42)         | 0.03†     | 2.76| 1.36–5.62      | 0.005§    |

\textsuperscript{ATLL = adult T-cell leukemia/lymphoma; CI = confidence interval; OR = odds ratio.}

\textsuperscript{A χ\textsuperscript{2} analysis was used to compare \textit{S. stercoralis} infection between patients with cancer (total cancer) and control patients (control).}

\textsuperscript{A logistic regression analysis, adjusted for age and sex, was used to compare \textit{S. stercoralis} infection between patients with each type of cancer and patients with other types of cancer.}
cancer. Here, we also showed that HTLV-1 infection in patients with non-ATLL lymphoma was significantly higher than that in patients with other types of cancer (OR: 2.76, 95% CI: 1.36, 5.62, P = 0.005). Although HTLV-1 has not been previously associated with the occurrence of lymphoma other than ATLL, some reports have suggested that HTLV-1 carriers with B-cell lymphoma tend to have worse prognosis or that the frequency of primary malignant neoplasms in HTLV-1 carriers is higher than that in seronegative cases. Another report also suggested that the interaction between Epstein–Barr virus and HTLV-1 could promote T- and B-cell dysfunctions and cell proliferation and inhibit apoptosis, favoring lymphomagenesis.

Some limitations exist in this study. First, only the patients that were admitted to the Department of Infectious, Respiratory, and Digestive Medicine University of the Ryukus Hospital and tested for HTLV-1 or S. stercoralis were included. The use of this population may introduce a selection bias in our results. Second, we did not examine the effect of confounding variables in our logistic regression, including other known carcinogens, such as smoking, drinking, parasitic infections other than S. stercoralis, and viral infections other than HTLV-1 (hepatitis B/C virus, Epstein–Barr virus, etc.). All patients with HTLV-1 carrier status were included in this study regardless of age. The number of young patients that were included in the HTLV-1-associated cancer development sub-analysis may have skewed the results in the opposite direction. To help normalize the results, age and sex were included in the logistic regression model to eliminate those biases.

CONCLUSIONS

Our study indicates that the prevalence of S. stercoralis and HTLV-1 infections have been decreasing in recent years. Strongyloides stercoralis infection was 2.4 times more likely in patients with HTLV-1 infection than in patients without it. Diligence toward the prevention of these diseases through decreased poverty and increased sanitation has proven effective. Continued improvements in education, testing, and treatment could easily eliminate S. stercoralis infections and drastically reduce the prevalence of HTLV-1 infections. In addition, HTLV-1 infection in patients with hepatic cancer or lymphomas other than ATLL appears to be significantly higher than that in patients with other types of cancer. Further investigation regarding the possible mechanisms behind these associations is needed.

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