A Follow-Up Study of Morbidity and Mortality Associated with Hepatitis C Virus Infection and Its Interaction with Human T Lymphotropic Virus Type I in Miyazaki, Japan

Cynthia Boschi-Pinto, Sherri Stuver, Akihiko Okayama, Dimitrios Trichopoulos, E. John Orav, Hirohito Tsubouchi, and Nancy Mueller

Hepatitis C virus (HCV) has been reported to be associated with the development of chronic hepatitis in 50%–85% of cases of acute hepatitis [1–3], of which ~20% progress to cirrhosis [4–6] in a long-lasting, indolent process. Furthermore, there is strong evidence linking HCV infection to the risk of developing hepatocellular carcinoma [7, 8]. The risk of hepatocellular carcinoma has been estimated to be 3%–7.8% per year among patients with HCV-associated liver cirrhosis [5, 8].

HCV also has been associated with the occurrence of several extrahepatic diseases [1, 4], such as mixed essential cryoglobulinemia [9], porphyria cutanea tarda [10], polyarteritis nodosa [11], sicca-like syndrome [12], and lichen planus [13]. The general pathologic mechanisms for such diseases are suggested to be either immunologically mediated or directly related to viral injury [14]. Renal disease, mainly glomerulopathy, has been associated with HCV infection as well [15, 16]. The postulated mechanisms by which HCV may cause kidney damage are likely also to be immune mediated, involving deposition of immune complexes containing the virus within the glomeruli [15]. In addition, some studies have linked HCV to the development of diabetes [17–20]. Recently, HCV has been associated with several lymphoproliferative disorders, such as B cell non-Hodgkin's lymphoma [21, 22]. It also has been hypothesized that HCV infection could cause immunosuppression [23], and HCV has been reported to infect peripheral blood mononuclear cells [24].

Human T lymphotropic virus type I (HTLV-I) is known to be causally associated with the development of adult T cell leukemia/lymphoma [25] and HTLV-I–associated myelopathy [26, 27]. In addition to its direct pathogenic role in these diseases, HTLV-I infection is postulated to be associated with a number of other diseases as a result of its immune-modulating effects, including uveitis, polymyositis, chronic inflammatory arthropathy, and chronic renal failure [28, 29]. There is also some evidence that HTLV-I produces a functional impairment of the cellular immune response among carriers [30–32]. Because of the postulated role of cellular immunity in the development and progression of HCV-associated liver disease [33–36], it is reasonable to expect that the interaction between HTLV-I and HCV may contribute to and change the natural history of such disease. Furthermore, it has been shown that HCV-infected persons who are immunosuppressed because of coinfection with human immunodeficiency virus (HIV) seem to have more-rapid progression of HCV-associated liver disease.
Thus, it is possible that coinfection with HCV and HTLV-I may affect the development of other diseases and may lead to increased mortality among those with dual infection. In our analysis, we examined the effect of HCV infection and its interaction with HTLV-I infection on the incidence and mortality patterns among adults from a village in Japan that has been found to have endemic levels of both viruses.

Methods

Study population. The Miyazaki Cohort Study is an ongoing, prospective cohort study in which the adult populations of 2 villages in southern Japan have been followed since November 1984. All village residents who attend the free, government-sponsored health examinations offered annually to those ≥40 years old are asked to participate; younger adults also may take part. The Miyazaki Cohort Study was originally established to evaluate the natural history of HTLV-I infection in a population in which it is endemic; ~27% of the study subjects are positive for antibodies to HTLV-I (anti-HTLV-I) at baseline. Recently, the prevalence of HCV infection was found to be relatively high in 1 of the study villages, village A. Thus for the present analysis we studied cohort members from village A. As of November 1994, 969 village residents were enrolled in the study; for 965 of these, there was complete data on antibodies to HCV (anti-HCV).

Morbidity and mortality data. Data on self-reported disease history, clinical test results, and physical examination findings are collected at every health screen. A questionnaire is administered to participants at their baseline entry screen, by public health nurses from the local city health department who have no knowledge of the participants’ virus status. This baseline questionnaire includes questions on alcohol consumption and smoking habits as well as on health history and symptoms. An additional, shorter questionnaire is completed at each follow-up attended, updating information on smoking and drinking habits and on health history. A complete blood cell count and liver-enzyme measurements are obtained from a fresh blood specimen by a commercial laboratory in Miyazaki City.

All 787 individuals who were enrolled in the cohort by November 1994 and who participated in at least 2 screens between November 1984 and November 1995 were included in the morbidity study. On average, these subjects attended 6 annual health screens. The incident diseases studied were those known or postulated to be associated with HCV infection (i.e., liver disease, diabetes, and renal disease) as well as cardiovascular disease, since heart disease has been linked to chronic infections [39]. Persons who reported having a history of a particular disease of interest at their baseline screen were excluded from the follow-up analysis for that specific disease. Those who did not report having the disease of interest at baseline were considered free of the disease and were followed over time until they reported occurrence of the disease, at which point they were considered as having incident disease as of the reported age at onset.

The public health nurses involved in the annual health examinations are also responsible for monitoring mortality, and they collect data on the time and cause of death. If there was no reported information that a subject had died, we assumed that she or he is alive. All 965 villagers who were enrolled in the cohort through November 1994 and for whom there was anti-HCV data were included in the mortality analysis. Mortality end points consisted of all causes of death, as well as the broad subgroups of death due to malignancy and death due to nonmalignant diseases. Liver cancer and cardiovascular disease as specific causes of death also were examined. There was only 1 death due to a liver disease other than hepatocellular carcinoma and 1 due to renal disease; thus, these causes of death were not investigated.

Serologic assays. We detected of anti-HCV was done at the Miyazaki Medical College and using a second-generation particle agglutination assay (Serodia-HCV; FujiRebio, Tokyo). Positivity was judged on the basis of specific agglutination patterns, according to the manufacturer’s instructions. All positive samples were confirmed at the Division of Transfusion Transmitted Diseases of the US Food and Drug Administration, by a second-generation recombinant immunoblot assay (RIBA 2.0; Chiron, Emeryville, CA). Specimens positive by recombinant immunoblot assay were considered positive for the presence of anti-HCV; of the subjects initially positive by particle agglutination assay, 3 were indeterminate and 1 negative by recombinant immunoblot assay. The specimens were tested retrospectively to ascertain anti-HCV serostatus at the first screen attended by the individual and to determine whether seroconversion occurred over the period of follow-up. Testing for anti-HTLV-I was done by use of a particle agglutination assay kit (Serodia-HTLV; FujiRebio), with positivity confirmed by Western blot [40]. All samples collected from study subjects were stored at −30°C.

Statistical methods. To examine the magnitude of the association between exposure to HCV and adverse health effects, rate ratios (RRs) for the univariate effects of this virus were first obtained by univariate Cox regression. RRs for the association of anti-HCV with incident diseases or with causes of death were then estimated after controlling for age, sex, smoking and drinking habits, and HTLV-I status, through Cox proportional hazards modeling [41]. Possible effect modification by the 2 viruses also was evaluated.

For the incidence data analysis, person-time at risk was accrued for each subject, beginning with the first screen attended through the development of the disease or through the most recent screen as of November 1995, whichever came first. For the mortality data analysis, person-time at risk was accumulated from the same starting point as that for the incidence study through the date of death or May 1997, whichever came first. For those who moved out of the study area, person-time was accrued until the last screen they attended, at which point they were censored. For those with an unknown date of death (n = 6), a date was assigned that was the midpoint between the last time that person was seen at a study screen and the date the death was recorded by the public health nurses.

Age was categorized either by approximate quartiles (16–44, 45–54, 55–64, and ≥65 years) or by tertiles (16–49, 50–64, and ≥65 years) when the limited number of outcome events required the use of fewer categories. Information on smoking and alcohol drinking habits were obtained from the baseline questionnaire, and both were assessed as “ever” (i.e., current or past) or “never.” Anti-HCV and anti-HTLV-I status were considered as time-varying covariates, because changes in serologic status occurred over the fol-
low-up period. Among the subjects analyzed, there were 14 confirmed seroconverters to anti-HCV and 11 to anti-HTLV-I seropositivity.

Statistical significance and estimate stability were assessed from the 95% confidence intervals (CIs). Effect modification was evaluated on an additive scale—that is, by examining whether the joint effect of the 2 viruses was greater than the simple sum of their individual effects. Therefore, the measure of interaction used was the synergy index (SI) [42]. The SI measures departures from the null value of 1, indicating whether there is synergism (>) or antagonism (< 1) between the factors under study. SIs with their respective 95% CIs were calculated [43, 44].

Results

Baseline characteristics. Forty-three percent of the 965 subjects in village A were infected at baseline with at least 1 of the viruses; 16% were anti-HCV–positive only, and 20% were anti-HTLV-I–positive only. Coinfection was present in 63 subjects, ~28% of all anti-HCV–positive subjects (table 1). Most subjects were >54 years old (65% of those anti-HCV–positive and 53% of those HCV-negative), nondrinkers (>70%, regardless of anti-HCV serostatus), and nonsmokers (~64%) at baseline; 60% were women (table 1). Alcohol drinking and smoking were more frequent behaviors among men (66% and 73%, respectively) than among women (2.5% and 10%, respectively). Similar distributions for demographic and lifestyle characteristics were observed for the subgroup of subjects included in the analysis of incident disease (data not shown).

Morbidity analysis. To evaluate the possible confounding effects of variables such as age, sex, and smoking and drinking habits, we performed Cox proportional hazards regression analyses. The results for incident disease are shown in table 2, with both the unadjusted and adjusted RRs. A strong, significant effect of HCV on self-reported incident liver disease (RR, 3.5) was observed in these data. Positive associations with incident diabetes (RR, 2.2) and with cardiovascular disease (RR, 1.8) were present, although they did not reach statistical significance. Only the unadjusted effect of HCV infection on reported renal disease could be examined, and even that estimate was very unstable because of the sparseness of the data (RR, 2.0).

Mortality analysis. Among the 965 subjects in village A, 130 deaths occurred over the follow-up period. Malignancies accounted for 38% (49/130) of all deaths. Of these 49 deaths due to malignancies, 8 (16%) were from liver cancer, 8 (16%) from lung cancer, 7 (14%) from stomach cancer, and 5 (10%) from colon cancer. Among the other causes of death (n = 81), 24 (30%) deaths were due to respiratory disease, 20 (25%) to cardiovascular disease, 15 (19%) to stroke, 1 (1%) to renal disease, and 1 (1%) to liver disease.

Data in table 3 indicate that anti-HCV seropositivity increased the adjusted rate of dying from any cause by only 20% and that of dying from causes other than malignancy by only 30%; neither association was statistically significant. Anti-HCV seropositivity was strongly associated with death from liver cancer (RR, 8.2). Being male was also an important predictor of death from liver cancer (RR, 8.5; 95% CI, 1.1–65.3). No association of anti-HCV seropositivity with death due to cancer or death due to any malignancy other than liver cancer was observed. A positive association was not found for anti-HCV positivity and death from cardiovascular disease (RR, 0.8).

Combined effect of HCV and HTLV-I. We also investigated the dual effect of HCV and HTLV-I coinfection, to determine whether there was any effect modification by the 2 viruses on morbidity and mortality from liver disease. Synergy between the 2 infections was present for liver disease, as reflected by the RR of 5.9 for the joint exposure to HCV and HTLV-I, in

| Table 1. Baseline demographic and lifestyle characteristics of studied subjects (n = 965), by hepatitis C virus (HCV) serostatus. |
| --- | --- | --- |
| Characteristic | Anti-HCV-positive | Anti-HCV-negative |
| Age, years | | |
| 16–44 | 26 (11.7) | 167 (22.5) |
| 45–54 | 51 (23.0) | 182 (24.5) |
| 55–64 | 77 (34.7) | 216 (29.1) |
| >65 | 68 (30.6) | 178 (24.0) |
| Sex | | |
| Male | 89 (40.0) | 300 (40.0) |
| Female | 133 (60.0) | 443 (60.0) |
| Smoking status* | | |
| No | 142 (64.2) | 478 (64.7) |
| Yes | 79 (35.8) | 261 (35.3) |
| Alcohol drinking status* | | |
| No | 158 (73.2) | 516 (71.8) |
| Yes | 58 (26.8) | 203 (28.2) |
| Anti-HTLV-I serostatus | | |
| Positive | 63 (28.4) | 194 (26.1) |
| Negative | 159 (71.6) | 549 (73.9) |

NOTE. Data are no. (%). Anti-HCV, antibody to HCV; anti-HTLV-I, antibody to human T lymphotropic virus type I.

* Some smoking and drinking data were missing.

| Table 2. Unadjusted and adjusted rate ratios (RRs) and 95% confidence intervals (CIs) for association between specific diseases and hepatitis C virus (HCV) serostatus. |
| --- | --- | --- |
| Disease, HCV serostatus | No. of cases | Unadjusted RR (95% CI) | Adjusteda RR (95% CI) |
| Liver disease | | | |
| Anti-HCV–seropositive | 26 | 3.5 (1.9–6.4) | 3.5 (1.9–6.5) |
| Anti-HCV–seronegative | 16 | 1.0 | 1.0 |
| Renal disease | | | |
| Anti-HCV–seropositive | 4 | 2.0 (0.5–9.1) | ND |
| Anti-HCV–seronegative | 3 | 1.0 | 1.0 |
| Cardiovascular disease | | | |
| Anti-HCV–seropositive | 12 | 1.7 (0.8–3.5) | 1.8 (0.8–3.8) |
| Anti-HCV–seronegative | 18 | 1.0 | 1.0 |
| Diabetes | | | |
| Anti-HCV–seropositive | 5 | 2.4 (0.7–7.9) | 2.2 (0.7–7.3) |
| Anti-HCV–seronegative | 6 | 1.0 | 1.0 |

NOTE. Anti-HCV, antibody to HCV; ND, not done.

a Adjusted for 4 age groups, sex, smoking, drinking, and human T lymphotropic virus type I serostatus.

b Adjusted for 3 age groups, sex, smoking, drinking, and human T lymphotropic virus type I serostatus.
contrast with the RR of 2.8 for exposure only to HCV (table 3). Boschi-Pinto et al. JID 2000;181 (January)

4). The SI for this interaction was 2.7 (95% CI, 0.7–10.5). There was also an important impact of the interaction between the 2

Also, as of November 1995, only 4% (39/965) of the cohort

viruses on death due to liver cancer, as shown by an RR of

subjects in village A had been lost to follow-up, all because

they had moved out of the study area. Therefore, loss to follow-

dup does not likely represent a major problem for the analysis

Discussion

This study is unique because it involves a community-based
cohort in which both HCV and HTLV-I infections were found
to be endemic. Moreover, >70% of the target population is

enrolled in the study, demonstrating a high participation rate.
Also, as of November 1995, only 4% (39/965) of the cohort

subjects in village A had been lost to follow-up, all because

they had moved out of the study area. Therefore, loss to follow-

up does not likely represent a major problem for the analysis

of these data. Another important strength of this analysis is

cohort in which both HCV and HTLV-I infections were found

to be endemic. Moreover,

that the use of second-generation assays reduced the likelihood

of false-positive results for anti-HCV serostatus. In addition,
because the analysis only includes data reported through No-

vember 1996, knowledge of anti-HCV serostatus could not have affected self-reporting of disease.

However, there are some limitations to these data. Misclas-
sification may have occurred in the assessment of the exposures

of interest, but, because errors in the virus antibody test results

are likely to be random, the effect would be to bias the RR

estimates toward the null. Information on incident disease is

self-reported, and cause of death is based on data collected, by

the local public health nurses, from next of kin rather than

from medical records. These facts may have led to some sub-

notification of death as well as to misclassification of both
disease and cause of death. In the case of an underascertainment

despite a higher RR, there is no reason to think that it would be different

for those exposed and not exposed to HCV, in which case the RR

measure would be unaffected [42]. Misclassification of mor-

bidity and mortality data also would likely be nondifferential.

An additional important limitation of our study is the lack of

power to quantify increased risks of developing or dying from

the diseases of interest, particularly with regard to the assess-

ment of an effect due to the interaction of HCV and HTLV-I

infections.

The association between HCV and liver disease is well rec-

ognized [4, 7, 8]. Not surprisingly, incident hepatic disease was

significantly associated with anti-HCV positivity in the current

study. It has been hypothesized that the natural progression

of HCV-associated liver disease proceeds from acute hepatitis to

chronic persistent hepatitis to chronic active hepatitis to liver

cirrhosis in ~20% of those with chronic active hepatitis [1–3].

The most severe outcomes among the spectrum of liver diseases

in which HCV infection has been implicated are liver failure

and hepatocellular carcinoma [1–3]. The process of hepatocar-

cinogenesis in HCV-infected persons is believed to occur mainly

through the development of liver cirrhosis [1, 8, 45], although

HCV-associated liver cancer in the absence of such disease has

been reported [46]. The strong association between anti-HCV

and liver cancer was confirmed in the present study, albeit on

the basis of mortality data.

Chronic hepatitis B virus infection is known also to be

strongly associated with liver cancer [7, 47]. Chronic carrier

status, as measured by hepatitis B virus surface antigen, was

not evaluated in the present study. However, a previous case-

control analysis of the same cohort population found hepatitis

B virus surface antigen in 2% of the control subjects studied

and in only 1 subject among those who died from liver cancer

[48]. Therefore, it is unlikely that positivity for hepatitis B virus

surface antigen would greatly confound these data.

The exact mechanism for HCV-associated liver damage has

not been established. HCV may be directly cytotoxic to the

infected hepatocytes, or immune-mediated mechanisms related
to immune complex formation or to the stimulation of a rapid

lymphocyte response to HCV may indirectly lead to liver damage [4]. Some authors speculate that the presence

of cytotoxic T lymphocytes reactive to HCV in liver tissue is

suggestive of T cell–mediated hepatocyte lysis [33, 34]. In acute

hepatitis C, strong T lymphocyte responses and low or absent

antibody levels have been shown to be present in those patients

who clear the virus; in contrast, patients who develop chronic

hepatitis have high antibody titers and poor T cell proliferative

responses [35, 36].

<table>
<thead>
<tr>
<th>Cause of death, HCV serostatus</th>
<th>No. of deaths</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV–seropositive</td>
<td>41</td>
<td>1.3 (0.9–1.9)</td>
<td>1.2 (0.8–1.7)</td>
</tr>
<tr>
<td>Anti-HCV–seronegative</td>
<td>89</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>All cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV–seropositive</td>
<td>14</td>
<td>1.2 (0.6–2.2)</td>
<td>1.0 (0.5–1.9)</td>
</tr>
<tr>
<td>Anti-HCV–seronegative</td>
<td>35</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Liver cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV–seropositive</td>
<td>6</td>
<td>9.0 (1.8–44.5)</td>
<td>8.2 (1.6–41.4)</td>
</tr>
<tr>
<td>Anti-HCV–seronegative</td>
<td>2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Other malignancyb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV–seropositive</td>
<td>8</td>
<td>0.7 (0.3–1.5)</td>
<td>0.6 (0.3–1.3)</td>
</tr>
<tr>
<td>Anti-HCV–seronegative</td>
<td>33</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>All other nonmalignant causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV–seropositive</td>
<td>27</td>
<td>1.4 (0.9–2.2)</td>
<td>1.3 (0.8–2.2)</td>
</tr>
<tr>
<td>Anti-HCV–seronegative</td>
<td>54</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV–seropositive</td>
<td>5</td>
<td>0.9 (0.3–2.6)</td>
<td>0.8 (0.3–2.2)</td>
</tr>
<tr>
<td>Anti-HCV–seronegative</td>
<td>16</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

NOTE. Anti-HCV, antibody to HCV.

* Adjusted for 3 age groups, sex, smoking, drinking, and human T lympho-

tropic virus type I serostatus.

b Includes malignancies other than liver cancer.

Table 3. Unadjusted and adjusted rate ratios (RRs) and 95% confidence intervals (CIs) for association of hepatitis C virus (HCV) sero-

status with overall and cause-specific mortality.
HTLV-I carriers have been shown to have an impaired cellular immune response [30–32]. HTLV-I infection has also been associated with the presence of opportunistic infections and with some autoimmune conditions, as well as with an increased risk for the development of malignancies [28, 29]. Moreover, HTLV-I has been suggested to interact with HCV in the progression of liver disease [49, 50]. In our study, we found a strong positive interaction between HCV and HTLV-I infections in the most extreme HCV-associated outcome—death from liver cancer. However, the confidence interval around the SI for the interaction was rather wide and included the null value of 1, indicating the statistical uncertainty of the synergistic effect of HTLV-I on the progression of HCV-associated liver disease is biologically plausible, and there are correlated findings in the literature about HIV and HCV coinfection. Some studies have shown that those infected with both HIV and HCV have a higher risk of developing liver disease than do those infected with HCV alone [37, 38, 51, 52]. Furthermore, HIV seems to modify the natural progression of HCV infection by leading to a more severe and rapid progression of liver damage [37, 38]. Other studies of patients coinfected with both HCV and HIV have suggested that the high HCV viremia observed in HIV-positive patients could be due to the immunosuppression induced by HIV [53, 54]. More specifically, it has been reported that HCV replication increases when the immune system is impaired by HIV [52, 55] and that HCV load increases over time as HIV-associated immunodeficiency progresses [51].

In persons coinfected with HTLV-I and HCV, it is possible that infection of T cells by HTLV-I interferes with the cytotoxic T lymphocyte response to HCV-infected hepatocytes. A weak cytotoxic T lymphocyte response in HTLV-I carriers could be responsible for an ineffective resolution of HCV infection, leading to persistent liver damage and, thus, exacerbating the progression of liver disease and promoting the process of hepatocarcinogenesis. In a separate analysis of the Miyazaki Cohort Study [56], a positive interaction between anti-HCV and anti–HTLV-I positivity associated with diminished skin reactivity to purified protein derivative was found, which suggests that coinfection may increase host cellular immune suppression.

HCV infection also has been linked to a number of extrahepatic manifestations [1, 4]. In our analysis of incident disease, we were able to explore HCV’s effect on diabetes, cardiovascular disease, and renal disease. Liver injury has been associated with the presence of diabetes, in which its pathology is similar to that associated with liver disease from alcoholism [57]. Some studies also have postulated a direct association between HCV infection and diabetes [17–20]. However, these studies were based either on hospitalized patients and clinic populations or on blood donors as the control group. In our follow-up study of population-based data, we found a positive, although not significant, association between HCV infection and incident diabetes, which was independent of the effect of alcohol consumption. Of interest, a recent study detected negative-strand viral RNA in the pancreases of 5 of 8 HCV-infected patients who died of AIDS-related complications, suggesting the presence of possible HCV replication in the pancreases of these patients [58].

Coronary heart disease has been linked to chronic infections, including those by certain herpesviruses, particularly cytomegalovirus [39]. However, there have been no reports of an effect of HCV on cardiovascular disease. No significant association was shown for HCV and cardiovascular disease in the present analysis. The sparseness of data on reported incident renal disease enabled us to perform only a univariate analysis. The association found was positive, although not statistically significant. In an additional study of prevalent data on baseline clinical serologic information from this same population, an adjusted odds ratio of 2.8 (95% CI, 1.1–7.1) was calculated for the association of proteinuria with anti-HCV positivity (unpublished data, C.B.-P., S.S., A.O., Edward Tabor, H.T., N.M.). Elevated proteinuria may indicate the presence of glomerulopathy, which is the type of renal injury commonly reported in HCV-infected persons [15, 16]. Of the subjects in the present study who attended a health screen at their reported age of development of renal disease, none had elevated proteinuria, although they may have had renal diseases other than those indicated by proteinuria. Thus, the weaker, nonsignificant association found in our prospective analysis could be due to the fact that the renal diseases analyzed were not related to glomerulopathy.

In conclusion, HCV plays an important role in the natural progression of liver disease in this Japanese population in which levels of infection are highly endemic. We also have observed a possible positive association between HCV infection and self-reported incident diabetes. Furthermore, our findings suggest that coinfection with HTLV-I may interfere with HCV infec-

### Table 4. Evaluation of interaction between hepatitis C virus (HCV) and human T lymphotropic virus type I (HTLV-I) infections on liver disease and death from liver cancer.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HCV-negative/HTLV-I-negative</th>
<th>HCV-positive/HTLV-I-negative</th>
<th>HCV-negative/HTLV-I-positive</th>
<th>HCV-positive/HTLV-I-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
<td>1.0</td>
<td>2.8 (1.3–5.9)</td>
<td>1.0 (0.4–2.9)</td>
<td>5.9 (2.5–13.9)</td>
</tr>
<tr>
<td>Death from liver cancer</td>
<td>1.0</td>
<td>8.5 (0.9–82.5)</td>
<td>2.7 (0.2–44.2)</td>
<td>21.9 (2.2–221.8)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are rate ratio (95% confidence interval). Models were adjusted for 3 age groups, sex, smoking, and drinking.

* Reference group.
tion, leading to more-severe liver disease progression, possibly through the immune-deregulating effects of HTLV-I infection.

Acknowledgments

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