Incidence and Cofactors of Hepatitis C Virus-related Hepatocellular Carcinoma: A Prospective Study of 12,008 Men in Taiwan

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In a community-based prospective study, the authors examined the independent and interactive effects of hepatitis C virus (HCV) infection and cofactors, including hepatitis B virus (HBV) infection and lifestyle habits, on the incidence of hepatocellular carcinoma (HCC) in Taiwan. At baseline recruitment, subjects were evaluated with regard to second-generation HCV antibody (anti-HCV), hepatitis B surface antigen, and serum alanine aminotransferase, as well as cigarette smoking, alcohol drinking, and betel quid chewing habits. A total of 12,008 male residents aged 30–64 years without a history of HCC were included in the study. Between July 1990 and June 2001, 112 incident cases of HCC were identified among the subjects and included in the analysis. Persons with anti-HCV positivity alone had a 20-fold increased risk of developing HCC in comparison with those who were negative for anti-HCV. In statistical assessment of additive interaction, HCV and HBV tended to act independently in the pathogenesis of HCC. The results of this study suggest that HCV plays a significant role in hepatocarcinogenesis in an area endemic for chronic HBV infection.

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world (1). Although chronic infection by hepatitis B virus (HBV) is a major cause of HCC, there is wide variation in the proportion of HCC attributable to HBV in different populations, ranging from 10 percent to 90 percent (1). Ever since hepatitis C virus (HCV) was cloned and a serologic assay for antibodies to HCV (anti-HCV) became available, a number of studies have implicated HCV infection as an important risk factor for HCC in populations with diverse degrees of HCC risk, ranging from low-risk non-Asians in the United States (2) to intermediate-risk Japanese (3) and Greeks (4) to high-risk Chinese (5) and Africans (6). Indeed, the role of HBV in human HCC is steadily declining, while HCV is gaining importance in the pathogenesis of HCC in many geographic areas (7–9). Of particular note, HCV infection, caused mostly by injection drug use, accounts for a significant increase in the occurrence of HCC and for a shift in peak incidence toward a younger age group in the United States over the past two decades (10). It is unclear, however, what proportion of
HCV-infected persons will develop HCC during their lifetime, especially among those living in HBV-endemic areas.

In addition to persistent hepatitis virus infection, cigarette smoking, alcohol drinking, and betel quid chewing have also been observed to be associated with an increased risk of HCC (11–13). However, there have been relatively few investigations of the effect of interaction between HCV infection and other viral and nonviral risk factors on the risk of HCC. In this study, we used long-term follow-up data to estimate the cumulative risk of developing HCC among HCV-infected persons in Taiwan, an area endemic for HBV infection (14). The potential joint effects of HCV infection and other risk factors on the incidence of HCC were also evaluated.

MATERIALS AND METHODS

Study population and recruitment

From July 1990 to June 1992, a community-based cancer screening program was carried out in seven townships in Taiwan, including Sanchi, Chutung, Potzu, and Kaohsu, located on Taiwan Island, and Makung, Huhsi, and Pahuwa, located on Penghu Islets. The potential screening population consisted of persons aged 30–64 years who were residing in the above townships. Initially, records of persons within the above age range were obtained from the local housing offices. There were 47,079 eligible males and 42,263 eligible females who were invited by letter to participate. Among those eligible subjects, eight males died before being contacted. A total of 12,016 male and 11,917 female adults were recruited; approximately 25 percent agreed to participate. Among those eligible subjects, eight males died before being contacted. A total of 12,016 male and 11,917 female adults were recruited; approximately 25 percent agreed to participate. Nonsmokers, the elderly, and those with a higher level of education showed higher rates of response (15). Only male subjects were included in the present study, because men are more frequently afflicted with HCC than women (16) and the prevalences of cigarette smoking (1.0 percent), alcohol drinking (0.6 percent), and betel quid chewing (0.2 percent) were remarkably lower among our female subjects. Among these 12,016 male subjects, eight had HCC detected at enrollment and were excluded from the study. Thus, a total of 12,008 male adults participated in this study.

At baseline recruitment, well-trained research assistants personally interviewed participants to solicit information on sociodemographic characteristics, habitual cigarette smoking, alcohol drinking, and betel quid chewing, and family history of cirrhosis and HCC. Information on injection drug use was not obtained, because this practice is infrequent in the Taiwanese adult population (17). Blood specimens, including samples of serum, plasma, and white blood cells, were also obtained from participants and were frozen at −70°F until subsequent analysis. All subjects gave informed consent for both the interview and blood collection. In addition, the anonymity of the subjects was maintained through numerical coding of questionnaires and blood samples. This community-based cancer screening program was supported and approved by the Department of Health, Executive Yuan.

Subjects were screened initially by the use of serologic markers, including alanine aminotransferase (ALT), aspartate aminotransferase, α-fetoprotein, hepatitis B surface antigen (HBsAg), and anti-HCV. Any subject with an elevated level of ALT (≥45 IU/liter), aspartate aminotransferase (≥240 IU/liter) or α-fetoprotein (≥20 ng/ml), who was positive for HBsAg or anti-HCV, or who had a family history of cirrhosis or HCC among immediate family members was then referred for upper abdominal ultrasonographic examination. In Taiwan, real-time ultrasonography is routinely performed, primarily for screening for HCC because it is most sensitive in detecting small HCCs (18). The abdominal ultrasonography was performed by board-certified gastroenterologists experienced in conducting ultrasonographic examinations using Toshiba SAL-38B and SSA-240A ultrasonographic apparatuses with 3.75-MHz real-time linear and sector probes (Toshiba, Tokyo, Japan).

In Taiwan, interferon (or other antiviral or immune therapy) is rarely used to treat chronic hepatitis C or chronic hepatitis B, because treatment with interferon is expensive and has severe side effects that are difficult to tolerate (19). For this reason, we did not refer our subjects with HCV or HBV infection to a hospital for treatment after enrollment.

Follow-up for vital status and HCC incidence

Subjects were followed up from cohort entry to June 30, 2001, for vital status and HCC incidence through computerized linkage with information obtained from the National Cancer Registry and the National Death Certification System in Taiwan (20, 21). In Taiwan, if a patient is diagnosed with or treated for cancer in a hospital with 50 or more beds, that hospital has a legal obligation to report the case to the National Cancer Registry. The data are evaluated on a yearly basis for completeness and accuracy. Case ascertainment by the registry through the hospital system is estimated to be 85 percent complete (22). In addition, it is mandatory to register any vital event, including migration and death, with the local housing office in Taiwan. All deceased residents in Taiwan are included in the computerized national death certificate data file. Thus, even if subjects emigrated to other areas in Taiwan, their vital status was completely followed up through data linkage with the household registration and death certification systems. Accordingly, we also linked data with information obtained from the National Death Certification System to trace vital status and to identify deaths from HCC among subjects who were not included in the National Cancer Registry. We considered follow-up of subjects in the present study to be quite complete with regard to vital status and the occurrence of HCC.

During the follow-up period, 112 subjects were diagnosed with HCC. When a case of HCC was identified, permission was sought from the hospital where the diagnosis had been made to obtain the subject’s medical charts and pathology reports. We ascertained that the diagnosis of HCC was established according to the following criteria, as described previously (20, 21): either positive findings upon cytologic or pathologic examination (58 cases, 51.8 percent) or an elevated serum α-fetoprotein level (≥400 ng/ml) combined with a lesion in the liver detected by imaging (computerized tomography or digitally substruded angiogram) (54 cases, 48.2 percent). Comparison of risk factors associated with
HCC showed similar distributions in these factors between HCC cases diagnosed by these two criteria.

**Laboratory analyses**

Serum samples were assayed for HBsAg and α-fetoprotein by enzyme immunoassay with commercial kits (Abbott Laboratories, North Chicago, Illinois) and for anti-HCV by enzyme immunoassay with second-generation commercial kits (Abbott Laboratories, North Chicago, Illinois). In addition, both ALT and aspartate aminotransferase levels were determined by serum chemistry autoanalyzer (Hitachi model 736; Hitachi Company, Tokyo, Japan) using commercial reagents (Biomerieux, Mercy l’Etoile, France).

**Statistical methods**

Relative risks (RRs) and their 95 percent confidence intervals were estimated in a Cox proportional hazards model using the SAS statistical package (SAS Institute, Inc., Cary, North Carolina). The period of observation used in calculating incidence rate and relative risk began from the date of enrollment to the date of one of the following events, listed in descending order of priority: the date of diagnosis of HCC, the date of death, or the date of the last linked data available from the National Cancer Registry (June 30, 2001). Subjects who remained unaffected by HCC before death during the follow-up period or by the end of follow-up were considered censored at the date of death or the last date of follow-up. Cumulative incidence of HCC by year of follow-up was estimated for subjects who were seronegative for both anti-HCV and HBsAg, seropositive for anti-HCV alone, seropositive for HBsAg alone, and seropositive for both anti-HCV and HBsAg, respectively, by means of the Nelson-Aalen method, a nonparametric method of calculating cumulative hazards (the Kaplan-Meier estimator may be used when the interest is in survival function) (23, 24).

Estimation of cumulative risk of HCC and creation of the resultant figure (figure 1) were performed with Stata statistical software (Stata Corporation, College Station, Texas). In the data analysis, testing results for anti-HCV and HBsAg were missing for 110 and 40 subjects, respectively. In addition, the result of combined analysis of both anti-HCV and HBsAg was not available for 136 persons. Subjects with missing data on viral infections were excluded from the respective statistical analyses. Statistical assessment of interaction between HCV infection and other cofactors of interest in the risk of HCC was made on the basis of an additive scale by estimating the synergy index (25, 26). The synergy index \( S = \frac{RR(AB) - 1}{[\frac{1}{RR(AB)} - 1]} + [\frac{1}{RR(ab)} - 1] \), where \( A \) and \( B \) denote the presence of the two risk factors and \( a \) and \( b \) the absence of the two risk factors, respectively. Rothman (25) noted that in the absence of an additive interaction, \( S = 1 \). The 95 percent confidence interval of \( S \) was established using Rothman’s modified regression model (26). The additive model was used in this study because Kleinbaum et al. (27) have argued that deviations from additivity should be the focus whenever there are public health issues regarding a reduction in disease frequency. To assess the relation between serial ALT results and risk of HCC among HCV-infected subjects, a subset \( n = 417 \) of 553 anti-HCV-positive subjects, for whom repeated ALT measurements were made, was included in the analysis. Comparisons of baseline characteristics showed similar distributions in age, HBsAg carrier status, family history of cirrhosis and/or liver cancer, and habitual cigarette smoking and betel quid chewing between 417 anti-HCV-positives with serial testing of ALT and members of the entire cohort, although the former group had a lower frequency of alcohol drinking than the latter group (data not shown).

**RESULTS**

**Baseline characteristics**

Table 1 shows the characteristics of the subjects at enrollment, including age group, seropositivity for HBsAg and anti-HCV, history of cigarette smoking, alcohol consumption, and betel quid chewing, and family history of cirrhosis and/or liver cancer. More than 50 percent of the subjects were less than 50 years old when they enrolled. HBsAg positivity and anti-HCV positivity were 20 percent and 4.6 percent, respectively. Fifty-six percent of the subjects were cigarette smokers, 20 percent were alcohol drinkers, 12 percent were betel quid chewers, and 4.4 percent had a family history of cirrhosis and/or liver cancer among immediate family members.

**HCC development in relation to baseline features**

Overall, the mean duration of follow-up was 9.2 years (standard deviation, 1.4). In 110,038.8 person-years of follow-up, HCC was detected in 112 subjects. Therefore, the incidence density of HCC was 101.8 per 100,000 person-years. As is shown in table 1, the incidence rate of HCC increased significantly with advancing age. The development of HCC was observed significantly more frequently in subjects who were positive for HBsAg (RR = 16.1, 95 percent confidence interval (CI): 10.1, 25.7), subjects who were positive for anti-HCV (RR = 3.6, 95 percent CI: 2.1, 6.2), and subjects with a family history of cirrhosis and/or liver cancer among immediate family members (RR = 2.6, 95 percent CI: 1.4, 4.8). There was a borderline-significant relation between history of alcohol consumption and risk of HCC (RR = 1.5, 95 percent CI: 1.0, 2.3). However, no significant association with HCC was found for a history of cigarette smoking or betel quid chewing.

**Interaction between HCV and HBV infection**

Among the 11,872 persons studied, 9,007 subjects (75.9 percent) were seronegative for both anti-HCV and HBsAg, 2,312 (19.5 percent) were positive for HBsAg alone, 441 (3.7 percent) were positive for anti-HCV alone, and 112 (0.9 percent) were positive for both anti-HCV and HBsAg. The independent and interactive effects of anti-HCV- and HBsAg-positive status on the incidence of HCC are shown in table 2. In comparison with subjects who were seronegative for both anti-HCV and HBsAg, the age- and family
history-adjusted relative risks of developing HCC for subjects positive for HBsAg alone, subjects positive for anti-HCV alone, and subjects positive for both anti-HCV and HBsAg were 38.5 (95 percent CI: 19.9, 74.5), 21.5 (95 percent CI: 9.3, 49.9), and 30.4 (95 percent CI: 9.5, 96.9), respectively.

To evaluate HCC risk, we further assessed the cumulative incidences of HCC by year of follow-up for the four groups. As is shown in figure 1, the 10-year cumulative incidence of HCC for subjects positive for anti-HCV alone, subjects positive for HBsAg alone, and subjects positive for both anti-HCV and HBsAg was 2.98 percent, 3.63 percent, and 4.46 percent, respectively. These cumulative risks of HCC were higher than the risk of 0.13 percent observed among subjects who were seronegative for both anti-HCV and HBsAg.

Interaction of anti-HCV with lifestyle factors

Further analyses were carried out to assess joint effects between anti-HCV and the habits of cigarette smoking, alcohol drinking, and betel quid chewing on development of HCC. As table 3 shows, anti-HCV positivity tended to interact additively with cigarette smoking, alcohol drinking, and betel quid chewing in risk of HCC, although the synergy indices were not statistically significant. In comparison with that for nonsmokers who were negative for anti-HCV, the age-, HBsAg-, and family history-adjusted relative risk of HCC development was 1.1 (95 percent CI: 0.7, 1.7) for smokers who were negative for anti-HCV, 2.1 (95 percent CI: 0.8, 5.3) for nonsmokers who were positive for anti-HCV, and 3.9 (95 percent CI: 2.0, 7.7) for smokers who were positive for anti-HCV. The corresponding S was 2.45 (95 percent CI: 0.41, 14.69). In comparison with that for nondrinkers who were negative for anti-HCV, the adjusted relative risk of developing HCC was 1.6 (95 percent CI: 1.0, 2.6) for drinkers who were negative for anti-HCV, 3.1 (95 percent CI: 1.7, 5.7) for nondrinkers who were positive for anti-HCV, and 4.1 (95 percent CI: 1.3, 13.0) for drinkers who were positive for anti-HCV. The corresponding S was 1.11 (95 percent CI: 0.21, 5.77). In comparison with that for persons who did not consume betel quid and were negative for anti-HCV, the adjusted relative risk of HCC development was 0.8 (95 percent CI: 0.4, 1.6) for anti-HCV-negative subjects who consumed betel quid, 2.6 (95 percent CI: 1.5, 4.6) for anti-HCV-positive subjects who did not consume betel quid, and 6.8 (95 percent CI: 1.7, 28.2) for anti-HCV-positive subjects who consumed betel quid. The corresponding S was 4.23 (95 percent CI: 0.58, 30.72).

Serial variations in ALT level and HCC risk

Among the 417 anti-HCV-positive subjects with serial measurements of ALT, 62.1 percent (n = 259) had persistently normal values for ALT, 31.7 percent (n = 132)
possessed intermittently elevated levels of ALT, and 6.2 percent (n = 26) demonstrated persistently elevated levels of ALT. In contrast, of the 6,118 anti-HCV- and HBsAg-negative subjects with serial ATL evaluations (a subset of 9,007 persons who were seronegative for both anti-HCV and HBsAg, as shown in Table 2), 95.8 percent (n = 5,863) had persistently normal values for ALT, 3.9 percent (n = 239) possessed intermittently elevated levels of ALT, and 0.3 percent (n = 16) demonstrated persistently elevated levels of ALT. During the follow-up period, three cases of HCC were detected among the 259 subjects with a persistently normal ALT level (group A), nine cases were detected among the 132 subjects with an intermittently elevated ALT level (group B), and four cases were detected among the 26 subjects with a persistently elevated ALT level (group C). The corresponding HCC incidence rates for groups A, B, and C were 12.1, 387.9, and 302.6 per 100,000 person-years, respectively. When the variables of age and HBsAg-positive status were adjusted and group A was used as the referent group, the incidence rate of HCC was significantly higher for subjects with intermittently elevated ALT levels (adjusted RR = 6.1, 95 percent CI: 1.6, 22.4) and those with persistently elevated ALT levels (adjusted RR = 16.0, 95 percent CI: 3.5, 74.2) (Table 4). The Mantel $\chi^2$ test for trend indicated...
DISCUSSION

This large-scale community-based prospective study revealed that the incidence density and cumulative risk of HCC were 20-fold higher in subjects with anti-HCV alone than in those who were seronegative for anti-HCV. To the best of our knowledge, this is the first report on HCC incidence among HCV-infected persons in an area endemic for chronic HBV infection. This is also the first study to have used long-term follow-up data to evaluate the joint effect of chronic HCV and HBV infections on the risk of developing HCC. The results of the current study are in agreement with previous findings that HCV infection is a significant predictor of HCC development in Taiwan (5, 28, 29).

Previous studies have indicated that progression from chronic hepatitis to cirrhosis and HCC was accelerated by dual infection with HCV and HBV (2, 30, 31). In addition, HCV and HBV have been reported to have an interacting role in the origin of HCC (2, 28, 32). The results of the present long-term follow-up study contradict previous findings of a synergistic effect of coinfection with HCV and HBV.

### TABLE 2. Independent and interactive effects of hepatitis C virus and hepatitis B virus infections on the development of hepatocellular carcinoma in a cohort of 12,008 male adults, Taiwan, 1990–2001

<table>
<thead>
<tr>
<th>Anti-HCV†</th>
<th>HBsAg†</th>
<th>No. of subjects‡</th>
<th>Hepatocellular carcinoma</th>
<th>Relative risk</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>9,007</td>
<td>10</td>
<td>12.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>2,312</td>
<td>81</td>
<td>387.9</td>
<td>32.2</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>441</td>
<td>12</td>
<td>302.6</td>
<td>25.1</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>112</td>
<td>4</td>
<td>388.1</td>
<td>32.5</td>
</tr>
</tbody>
</table>

* Synergy index ($S_i$) = 0.56 (95% confidence interval: 0.18, 1.46).
† Anti-HCV, antibodies to hepatitis C virus; HBsAg, hepatitis B surface antigen; CI, confidence interval.
‡ One hundred thirty-six subjects with missing data on hepatitis virus markers were not included in the analysis.
§ Per 10⁵ person-years.
¶ Adjusted for age and family history of cirrhosis and/or liver cancer in first-degree relatives.

### TABLE 3. Joint effects of hepatitis C virus infection and lifestyle habits on the risk of hepatocellular carcinoma in a cohort of 12,008 male adults, Taiwan, 1990–2001

<table>
<thead>
<tr>
<th>Lifestyle habit and anti-HCV† status</th>
<th>Engaged in lifestyle habit?</th>
<th>No. of cases</th>
<th>HCC*</th>
<th>Relative risk</th>
<th>S*</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td>No.</td>
<td>Incidence rate†</td>
<td>Crude</td>
<td>Adjusted‡</td>
<td>95% CI</td>
</tr>
<tr>
<td>Negative</td>
<td>No</td>
<td>4,950</td>
<td>39</td>
<td>84.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Negative</td>
<td>Yes</td>
<td>6,382</td>
<td>53</td>
<td>91.4</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Positive</td>
<td>No</td>
<td>220</td>
<td>5</td>
<td>244.6</td>
<td>2.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>333</td>
<td>11</td>
<td>372.6</td>
<td>4.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td></td>
<td>No.</td>
<td>Incidence rate†</td>
<td>Crude</td>
<td>Adjusted‡</td>
<td>95% CI</td>
</tr>
<tr>
<td>Negative</td>
<td>No</td>
<td>8,968</td>
<td>65</td>
<td>78.7</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Negative</td>
<td>Yes</td>
<td>2,352</td>
<td>27</td>
<td>127.1</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Positive</td>
<td>No</td>
<td>461</td>
<td>13</td>
<td>309.7</td>
<td>3.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>90</td>
<td>3</td>
<td>384.9</td>
<td>4.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Betel quid chewing</td>
<td></td>
<td>No.</td>
<td>Incidence rate†</td>
<td>Crude</td>
<td>Adjusted‡</td>
<td>95% CI</td>
</tr>
<tr>
<td>Negative</td>
<td>No</td>
<td>9,944</td>
<td>84</td>
<td>92.1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Negative</td>
<td>Yes</td>
<td>1,384</td>
<td>8</td>
<td>63.2</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Positive</td>
<td>No</td>
<td>480</td>
<td>14</td>
<td>321.9</td>
<td>3.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>71</td>
<td>2</td>
<td>319.2</td>
<td>3.4</td>
<td>6.8</td>
</tr>
</tbody>
</table>

* Anti-HCV, antibodies to hepatitis C virus; HCC, hepatocellular carcinoma; S, synergy index; CI, confidence interval.  
† Per 10⁵ person-years.  
‡ Adjusted for age, hepatitis B surface antigen-positive status, and family history of cirrhosis and/or liver cancer in first-degree relatives.
HBV on the development of HCC obtained from cross-sectional or case-control studies. Instead, our data suggest an independent effect between HCV and HBV infections on the risk of developing HCC. Different pathogenetic insights in hepatozellcarcinogenesis may exist between HCV and HBV. The genome of HBV has been found to integrate in the genomic DNA of the host, which induces carcinogenic processes, such as HBV DNA integration into the hepatocyte genome and modification of cellular gene expression caused by insertion mutations, chromosomal rearrangement, or the transcriptional transacting activity of the X and pre-S-S regions of the HBV genome (33). In contrast, HCV is an RNA virus and is not integrated in genomic DNA. Insertional mutation is therefore unlikely to be a mechanism responsible for HCV-related hepatocarcinogenesis. HCV has been shown to be strongly associated with chronic liver disease and cirrhosis. This suggests that the hepatocarcinogenesis of HCV may be a process of progression from unresolved viral hepatitis, chronic hepatitis, or liver cirrhosis to HCC (33). However, HCV infection may also be associated with HCC without cirrhosis (34). The mechanism through which HCV may contribute to the development of HCC requires further investigation.

Considerable evidence indicates that the evolution of HCC is a multistage, multifactorial process. Either HCV or HBV may not be a sufficient cause for the development of HCC. A moderate excess risk of HCC associated with alcohol drinking (11, 35), cigarette smoking (11, 36, 37), and betel quid chewing (13) has been documented, although the relative importance of these lifestyle factors varies among populations. In addition, an additively synergistic effect between HBsAg carrier status and alcohol drinking and cigarette smoking has also been demonstrated (11). Similarly, the results of our analysis tend to suggest a more-than-additive effect of HCV infection and lifestyle factors, including cigarette smoking, alcohol drinking, and betel quid chewing, on hepatocarcinogenesis. Acknowledging the notion that chronic HCV infection causes chronic phasic necroinflammation and regenerative proliferation in the liver, our findings suggest that the sustained proliferation of new liver cells may render subjects with HCV infection more susceptible to the effects of environmental carcinogens.

Another important parameter that influenced the risk of HCC among patients with HCV infection was the behavior of ALT during follow-up. Those patients with persistently elevated or fluctuating ALT levels during the observation period in this study demonstrated a significantly higher rate of HCC development compared with patients in whom ALT remained normal during follow-up. The ALT level is presumed to be a marker of hepatic inflammation. However, histologically mild disease has been recognized in HCV-infected persons with elevated ALT values, and histologically advanced disease has been demonstrated in those with normal or minimally elevated ALT measures (38, 39). Thus, the activity of liver disease represented by ALT measurements in this study might have been subject to potential errors in validity because of the lack of histologic data. However, since our study used a prospective design, biased assessment of the activity of liver disease might not be associated with the incidence of HCC. In other words, any misclassification of the activity of liver disease in this study was likely to have been random and would have caused us to underestimate any true association. Overall, our observation suggests that the activity of liver disease, which is characterized by inflammation, necrosis, and regeneration, plays an important role in promoting HCC development among persons infected with HCV.

Certain limitations of this study should be noted. In the present study, follow-up of the subjects was carried out using passive surveillance via linkage with national databases. This could have resulted in overestimation of the person-years contributed by subjects who were lost to follow-up. Subsequently, the incidence rates of HCC may have been underestimated. In addition, there is evidence suggesting that interferon therapy, when associated with response, delays progression to cirrhosis and reduces the incidence of HCC among patients with HCV infection (40). Unfortunately, we did not obtain therapeutic data on subjects and could not take this variable into account in the analysis. Nevertheless, this disadvantage may have had minimal influence on our results because of the rarity of receipt of interferon therapy for HCV or HBV infection among the Taiwanese. Whether virologic factors such as level of viremia and genotype contribute to the risk of HCC among persons infected with HCV is also relevant in HCV-related hepatocarcinogenesis. However, these viral characteristics were not elucidated in this population-based follow-up study because of logistic considerations. Indeed, the influence of viral load and HCV genotype on the development of HCC has been a subject of controversy. Some inves-
tigations have shown that serum HCV titers were positively correlated with the clinical stage of liver disease (41, 42), and there was a difference in pathogenicity according to HCV genotype; genotype 1b was associated with more severe liver disease than other genotypes (43–45). However, some studies have failed to establish correlations between level of viremia and HCV genotype and the incidence of HCC (46–48). In Taiwan, the predominant HCV genotype in patients with HCC is 1b (49). Patients with HCV-1b were older, had a longer duration of infection, and had higher serum HCV titers than those with other genotypes (50). If these findings were applied to our subjects, HCV-1b may have been present longer than other HCV types, thus being able to generate a cohort of infected patients with a longer and more advanced form of chronic liver disease.

In conclusion, persistent liver inflammation and ongoing liver disease may play an important role in the development of HCC among patients with chronic HCV infection. In addition, the sustained proliferation of new liver cells may also render HCV-infected persons more susceptible to the effects of environmental carcinogens. Although preventing the transmission of hepatitis viruses is the most important strategy for reducing HCC risk, our putative finding of an additive interactive effect between HCV infection and lifestyle factors, including cigarette smoking, alcohol drinking, and betel quid chewing, in the causation of HCC may increase public health awareness of the necessity for reducing the prevalence of these lifestyle habits to prevent HCC among persons infected with HCV.

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