Abstract

Objectives: The association between viral hepatitis (B and C) and oral cavity cancer has been widely debated. This nationwide, population-based cohort study assessed the subsequent risk of oral cavity cancer among patients with chronic viral hepatitis infection.

Materials and Methods: Data were retrieved from insurance claims data of 1,000,000 randomly sampled individuals covered under the Taiwan National Health Insurance system. We identified a total of 21,199 adults with chronic viral hepatitis infection (12,369 with HBV alone, 5,311 with HCV alone, and 3,519 with HBV/HCV dual infections) from 2000–2005. Comparison group comprised 84,796 sex- and age-matched subjects without viral hepatitis during the same study period. Incidence and risk of subsequent oral cavity cancer were measured until 2008.

Results: The incidence of oral cavity cancers was 2.28-fold higher among patients with HCV alone than non-viral hepatitis group (6.15 versus 2.69 per 10,000 person-years). After adjusting for sociodemographic covariates, HCV alone was significantly associated with an increased risk for oral cavity cancer (hazard ratio (HR) = 1.90, 95% confidence interval (CI) = 1.20–3.02). This positive association was highest among individuals in the 40–49-year age group (HR = 2.57, 95% CI = 1.21–5.46). However, there were no significant associations between HBV alone or HBV/HCV dual infections and risk for oral cavity cancer.

Conclusion: Our data suggest that HCV but not HBV infection is a risk factor for oral cavity cancer. In addition, subjects with HCV infection tend to be at early onset risk for oral cavity cancer. This finding needs to be replicated in further studies.

Introduction

Oral cavity cancer comprises of 2% to 3% of all malignancies (reviewed in Kademenos) [1]. Oral squamous cell carcinoma (OSCC) is the most common type of oral carcinoma and accounts for approximately one ninth of oral malignancies. The identified risk factors of oral cavity cancer include tobacco use, alcohol consumption, race, chewing of betel leaves and areca nuts, and low socioeconomic status (SES). Recently, the role that viruses play in the development of oral cavity cancer has also received tremendous interest [1,2,3].

Overall, 12% of the global cancer burden is conservatively estimated to be virus-attributable [4]. Currently, six human viruses have been classified by the International Agency for Research on Cancer (IARC) as being carcinogenic to humans based on sufficient evidence supporting their etiologic association with human cancers, namely Epstein-Barr virus, hepatitis B virus.
Data Sources

Materials and Methods

Study Sample

Statistical Analysis
Results

Baseline Characteristics and Comorbidities of the Study Subjects

In our study, the patients with HCV infection were more likely to be older, blue collar workers, living in lower urbanization level areas in southern Taiwan, as well as to have lower income levels than the 84,769 non-viral hepatitis comparison subjects (Table 1). They also were more likely to have DM, hypertension, and hyperlipidemia. On the contrary, patients with HBV tended to be younger and to have a lower prevalence of CAD and hypertension than subjects in the non-viral hepatitis comparison group.

Incidence Densities and HR of Oral Cancer among Viral Hepatitis

In total, we observed 198 cases of oral cavity cancer (174 males and 24 females) among 682,647 person-years, with an incidence density of 2.90 per 10,000 person-years (Table 2). The univariate Cox proportional hazard regression analysis revealed that the risk of developing oral cavity cancer among men with hepatitis was more than 5-fold higher than among women with hepatitis (HR = 5.88, 95% CI = 3.84–9.01). The highest age-specific HR was observed in the 50–59-year age group (HR = 15.9, 95% CI = 6.36–39.5). People residing in eastern Taiwan and those residing on offshore islands had 2.99-fold higher risk (95% CI = 1.45–4.27) among the income groups. The incidence of oral cavity cancer was approximately 2.3-fold higher in the cohort of patients with HCV infection than subjects in the non-viral hepatitis group (6.15 versus 2.69 per 10,000 person-years) (HR = 2.28, 95% CI = 1.44–3.60). There was no significant association between patients with HBV alone or patients with HBV+HCV dual infections and risk of developing oral cavity cancer. In addition, baseline comorbidities, including DM, CAD, hyperlipidemia, and hypertension were not significant risk factors for developing oral cavity cancer.

Significant predictors in the univariate analysis were included in a multivariate Cox hazard model to identify the most important risk factors for oral cavity cancer (Table 2). Because occupation and monthly income were highly correlated, we selected monthly income for multivariate analysis. In the multivariate Cox hazard model, we found that men had a 6.7-fold greater risk of developing oral cavity cancer than women (HR = 6.70, 95% CI = 4.34–10.3). The highest age-specific HR still remained in the 50–59-year age group (HR = 17.9, 95% CI = 7.11–45.0). Individuals living in eastern Taiwan and islands had significantly highest risk of developing oral cavity cancer (HR = 2.92, 95% CI = 1.58–4.03), whereas monthly income levels were not related to the disease risk. The multivariate Cox model also showed that the risk of developing oral cavity cancer was significantly higher among subjects with HCV infection than among individuals with no collar workers (HR = 1.65, 95% CI = 1.20–2.27). Subjects with a monthly income ranging from 1–15841 NT dollars were at the highest of developing oral cavity cancer (HR = 2.49, 95% CI = 1.45–4.27) among the income groups. The incidence of oral cavity cancer was approximately 2.3-fold higher in the cohort of patients with HCV infection than subjects in the non-viral hepatitis group (6.15 versus 2.69 per 10,000 person-years) (HR = 2.28, 95% CI = 1.44–3.60). There was no significant association between patients with HBV alone or patients with HBV+HCV dual infections and risk of developing oral cavity cancer. In addition, baseline comorbidities, including DM, CAD, hyperlipidemia, and hypertension were not significant risk factors for developing oral cavity cancer.

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| Variables                  | Viral hepatitis |          |          |          |          |          |
|---------------------------|----------------|----------|----------|----------|----------|----------|
|                           | No             | HBV alone| HCV alone| HBV+HCV  |
|                           | N = 84796      | N = 12369| N = 5311 | N = 3519 | p-value  |
| Sex                       | Women          | 37444 (44.2) | 5145 (41.6) | 2653 (50.0) | 1563 (44.4) | <0.0001  |
|                           | Men            | 47352 (55.8) | 7224 (58.4) | 2658 (50.1) | 1956 (55.6) |
| Age, years                | 18–29          | 18200 (21.5) | 3472 (28.1) | 527 (9.9)   | 551 (15.7)  | <0.0001  |
|                           | 30–39          | 17556 (20.7) | 3113 (25.2) | 668 (12.6)  | 608 (17.3)  |
|                           | 40–49          | 19068 (22.5) | 2842 (23.0) | 1120 (21.1) | 805 (22.9)  |
|                           | 50–59          | 13760 (16.2) | 1619 (13.1) | 1113 (21.0) | 708 (20.1)  |
|                           | 60–69          | 10316 (12.2) | 883 (7.1)   | 1105 (20.8) | 591 (16.8)  |
|                           | 70–79          | 5032 (5.9)   | 380 (3.1)   | 660 (12.4)  | 218 (6.2)   |
|                           | ≥80            | 864 (1.0)    | 60 (0.5)    | 118 (2.2)   | 38 (1.1)    |
| Geographic region         | Northern       | 40020 (47.2) | 5468 (44.2) | 1540 (29.0) | 1126 (32.0) | <0.0001  |
|                           | Central        | 16791 (19.8) | 2672 (21.6) | 1153 (21.7) | 729 (20.7)  |
|                           | Southern       | 21349 (25.2) | 3297 (26.7) | 2196 (41.4) | 1401 (39.8) |
|                           | Eastern and Islands | 6635 (7.8) | 932 (7.5)   | 422 (8.0)   | 263 (7.5)   |
| Occupation                | Public         | 8132 (9.6)   | 1490 (12.1) | 419 (7.9)   | 339 (9.6)   | <0.0001  |
|                           | Labor          | 27421 (32.3) | 3671 (29.7) | 2522 (47.5) | 1488 (42.3) |
|                           | Business       | 37891 (44.7) | 5802 (46.9) | 1611 (30.3) | 1268 (36.0) |
|                           | Low income     | 371 (0.4)    | 46 (0.4)    | 49 (0.9)    | 19 (0.5)    |
|                           | Retired and others | 10981 (13.0) | 1360 (11.0) | 710 (13.4)  | 405 (11.5)  |
| Urbanization level        | 1              | 25896 (30.5) | 3627 (29.3) | 1069 (20.1) | 804 (22.9)  | <0.0001  |
|                           | 2              | 24648 (29.1) | 3712 (30.0) | 1530 (28.8) | 1001 (28.5) |
|                           | 3              | 15623 (18.4) | 2327 (18.8) | 888 (16.7)  | 625 (17.8)  |
|                           | 4              | 18621 (22.0) | 2702 (21.9) | 1823 (34.3) | 1089 (31.0) |
| Monthly income, NT$       | 0              | 18817 (22.2) | 2560 (20.7) | 1147 (21.6) | 722 (20.5)  | <0.0001  |
|                           | 1–15840        | 10378 (12.2) | 1280 (10.4) | 637 (12.0)  | 353 (10.0)  |
|                           | 15841–25000    | 36597 (43.2) | 5043 (40.8) | 2743 (51.7) | 1752 (49.8) |
|                           | >25000         | 19004 (22.4) | 3486 (28.2) | 784 (14.8)  | 692 (19.7)  |
| Diabetes mellitus         | No             | 78312 (92.4) | 11364 (91.9) | 4320 (81.3) | 2991 (85.0) | <0.0001  |
|                           | Yes            | 6484 (7.7)   | 1005 (8.1)  | 991 (18.7)  | 528 (15.0)  |
| Coronary artery disease   | No             | 37983 (44.8) | 6495 (52.5) | 2468 (46.5) | 1757 (49.9) | <0.0001  |
|                           | Yes            | 46813 (55.2) | 5874 (47.5) | 2843 (53.5) | 1762 (50.1) |
| Hypertension              | No             | 69159 (81.6) | 10479 (84.7) | 3463 (65.2) | 2575 (73.2) | <0.0001  |
|                           | Yes            | 15637 (18.4) | 1890 (15.3) | 1848 (34.8) | 944 (26.8)  |
| Hyperlipidemia            | No             | 76023 (89.7) | 10797 (87.3) | 4289 (80.8) | 2905 (82.6) | <0.0001  |
|                           | Yes            | 8773 (10.4)  | 1572 (12.7) | 1022 (19.2) | 614 (17.5)  |

Urbanization level: 1 indicate the highest level of urbanization and 4 the lowest.

Chi-square test.

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hepatitis group (HR = 1.90, 95% CI = 1.20–3.02). Further data analysis showed that HCV was a significant risk factor for oral cavity cancer even after excluding individuals with diagnoses of smoking-related cancers (including ICD-9-CM: 146–150, 157, 160–162, and 189) during the follow-up period (HR = 1.92, 95% CI = 1.21–3.04) (not shown in the tables).

### Table 3: Adjusted HRs of Oral Cavity Cancer with Viral Hepatitis by Age and Sex Stratification

|               | Cases | PY     | I*  | HR (95% CI) | HR (95% CI) |
|---------------|-------|--------|-----|-------------|-------------|
| **Sex**       |       |        |     |             |             |
| Women         | 24    | 305111 | 0.79| 1.00        | (reference) |
| Men           | 174   | 377536 | 4.61| 5.88        | (3.84–9.01)*** |
| **Age, years**|       |        |     |             |             |
| 18–29         | 5     | 150172 | 0.33| 1.00        | (reference) |
| 30–39         | 33    | 143684 | 2.30| 6.91        | (2.70–17.7)*** |
| 40–49         | 65    | 155956 | 4.17| 12.5        | (5.05–31.2)*** |
| 50–59         | 58    | 110782 | 5.24| 15.9        | (6.36–39.5)*** |
| 60–69         | 28    | 81639  | 3.43| 10.4        | (4.01–26.9)*** |
| 70–79         | 8     | 35840  | 2.23| 6.92        | (2.26–21.1)** |
| ≥80           | 1     | 4572   | 2.19| 7.24        | (0.85–62.0)  |
| **Geographic region** | | | | | |
| Northern      | 53    | 309978 | 1.71| 1.00        | (reference) |
| Central       | 45    | 137697 | 3.27| 1.91        | (1.28–2.84)*** |
| Southern      | 73    | 182033 | 4.01| 2.34        | (1.64–3.34)*** |
| Eastern and island | 27  | 52932  | 5.10| 2.99        | (1.88–4.75)*** |
| **Occupation**|       |        |     |             |             |
| Public        | 17    | 67960  | 2.50| 1.10        | (0.65–1.87)  |
| Labor         | 85    | 226777 | 3.75| 1.65        | (1.20–2.27)** |
| Business      | 68    | 299509 | 2.27| 1.00        | (reference) |
| Low income    | 1     | 2916   | 3.43| 1.53        | (0.21–11.0)  |
| Retired and others | 27 | 85484  | 3.16| 1.39        | (0.89–2.18)  |
| **Monthly income, NTS** | | | | | |
| 0             | 23    | 146869 | 1.57| 1.00        | (reference) |
| 1–15840       | 31    | 79023  | 3.92| 2.49        | (1.45–4.27)** |
| 15841–25000   | 107   | 298236 | 3.59| 2.27        | (1.45–3.56)** |
| >25000        | 37    | 158519 | 2.33| 1.47        | (0.88–2.48)  |
| **Viral hepatitis** | | | | | |
| No            | 147   | 546846 | 2.69| 1.00        | (reference) |
| HBV alone     | 21    | 78803  | 2.66| 1.00        | (0.63–1.58)  |
| HCV alone     | 21    | 34150  | 6.15| 2.28        | (1.44–3.60)** |
| HBV+HCV       | 9     | 22848  | 3.94| 1.46        | (0.75–2.86)  |

PY, person-years; I, incidence; HR, hazard ratio; CI, confidence interval.

*P<0.05, **P<0.01, ***P<0.0001.
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Adjusted HRs of Oral Cavity Cancer with Viral Hepatitis by Age and Sex Stratification

Table 3 shows the age-specific and sex-specific HRs of oral cavity cancer for hepatitis cohorts compared to the comparison cohort. The adjusted HRs of oral cavity cancer among subjects infected with HCV alone were highest in those aged 40–49 years (HR = 2.57, 95% CI = 1.21–5.46) followed by those <40 years old (HR = 2.48, 95% CI = 0.75–8.19). However, no significant associations appeared for those with HBV alone or those with HCV/HBV dual infections. Furthermore, the sex-specific adjusted HRs of oral cavity cancer associated with HCV were 1.69 (95% CI = 0.49–5.83) for women and 1.88 (95% CI = 1.14–3.09) for men. On the contrary, there were no significant risks of oral cavity cancer in those with sole HBV infection or those with HBV/HCV dual infections. The interaction between HCV status and age of developing oral cavity cancer was moderately significant (P = 0.078). In the contrast, the interaction between HCV status and sex was not statistically significant (P = 0.97).
**Table 3. Adjusted HRs and 95% CIs of oral cavity cancer associated with viral hepatitis compared with non-viral hepatitis by age and sex stratification.**

| Viral hepatitis          | HBV alone | HCV alone | HBV + HCV |
|--------------------------|-----------|-----------|-----------|
|                          | aHR (95% CI) | aHR (95% CI) | aHR (95% CI) |
| Age, years*              |           |           |           |
| <40                      | 1.01 (0.39–2.63) | 2.48 (0.75–8.19) | 1.86 (0.44–7.84) |
| 40–49                    | 0.85 (0.36–1.98) | 2.57 (1.21–5.46)* | 0.93 (0.22–3.82) |
| 50–59                    | 1.24 (0.53–2.92) | 1.67 (0.70–3.95) | 1.55 (0.55–4.34) |
| ≥60                      | 1.86 (0.65–5.33) | 1.20 (0.42–3.45) | 0.65 (0.09–4.76) |
| Interaction              | p = 0.16 | p = 0.078 | p = 0.61 |
| Sex*                     |           |           |           |
| Women                    | 1.18 (0.27–5.12) | 1.69 (0.49–5.83) | 1.18 (0.16–8.92) |
| Men                      | 1.08 (0.66–1.75) | 1.88 (1.14–3.09)* | 1.28 (0.63–2.62) |
| Interaction              | p = 0.83 | p = 0.97 | p = 0.90 |

aHR: adjusted hazard ratio.  
a: adjusted for sex, region, and income.  
b: adjusted for age, region, and income.  
*p<0.05, **p<0.01.  
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**Discussion**

In this nationwide, population-based cohort study conducted in an area where both viral hepatitis and oral cavity cancer are endemic, significant risk of developing oral cavity cancer was observed in patients with HCV but not HBV infection. We also found that, in the general Taiwanese population, male subjects tended to have a 6.7-fold higher risk of developing oral cavity cancer than female counterparts. This finding is compatible with the finding reported in the Taiwan government cancer registry report [14]. The age of developing oral cavity cancer among HCV carriers (peak age group: 40–49 years) also tended to be younger than that of the general population (peak age group: 50–59 years). We also observed that subjects residing in the eastern Taiwan and islands had significantly highest risk of developing oral cavity cancer, followed by those living in the southern part of Taiwan.

HCV infection predisposes patients to extrahaemoplastic disorders involving renal, dermatologic, hematologic, and rheumatologic systems as well as autoimmune abnormalities [18,19]. Extrahaemoplastic manifestations may result from immunologic trigger mechanisms as well as viral invasion and replication that affect extrahaemoplastic tissues and organs [20].

The association between HCV infection and oral cavity cancer is still controversial [11,12,13]. HCV is a virus with triple tissue tropism – hepatotropism, lymphotropism, and sialotropism [21]. HCV RNA has been detected in saliva and salivary tissue in patients with chronic salivary gland disorders, a finding that suggests that HCV, a sialotropic virus, can reside within salivary gland cells [22]. Other studies, however, have shown that HCV detection in saliva and in salivary glands is not related to oral health conditions [23,24,25]. Grossmann et al. suggest that HCV might play an indirect role in causing diseases of the oral cavity and salivary glands by stimulating an immune response [21]. In addition, one of the most frequently reported oral extrahaemoplastic manifestations of HCV infection is lichen planus [26,27,28]. This premalignant condition is associated with the development of OSCC [29]. In a Brazilian cross-sectional study, there was a significant association between oral lichen planus and hepatitis C in their cohort of 215 patients with chronic HCV infection [21]. The progression of lichen planus into OSCC in patients with hepatitis C has been described in two case reports [29,30]. Several studies have shown that the transformation rate of oral lichen planus to OSCC is approximately 0.04% to 1.74% [31,32]. Interestingly, Nobles et al. demonstrated no predilection for the development of oral cavity cancers in patients infected with HCV [12]. Therefore, the role that HCV and its viral proteins play in the pathogenesis of oral diseases remains unclear.

Furthermore, Nagao et al. reported a higher prevalence of HCV antibody and RNA in patients with oral cavity cancer [11]. However, in 2002, Takata et al. reported, after age adjustment, a significantly decreased prevalence of HCV antibody in their patients with oral cavity cancer [13]. Using logistic regression analysis to eliminate the influence of age, Takata and colleagues suggested that the increased prevalence of HCV antibody in oral cavity cancer patients is more likely due to age differences rather than to carcinogenic action of HCV [11,27,28]. In addition, Nobles et al. observed that HCV patients present with an earlier age of onset of squamous cell carcinoma of the head and neck (SCCHN) than controls [12]. The age difference between these two groups may reflect differences in risk factors for the development of hepatitis C. The increased prevalence of intravenous drug abuse among younger populations, and socioeconomic differences between young and old age groups may also explain the age difference. Nobles and his colleagues also suggested HCV is considered a cofactor instead of a comorbid condition in relation to the development of head and neck cancer [12]. The localization of HCV RNA in oral lichen planus and OSCC tissue derived from patients with hepatitis C may provide one possible explanation to oral carcinogenesis of HCV [29]. In this prospective cohort study, we demonstrated that HCV is a risk factor for the development of oral cavity cancer (HR = 2.57, 95% CI = 1.21–5.46 in the 40–49-year age group). The risk of developing oral cavity cancer among patients with HCV is 10 years earlier than the general population. This finding is unlike the finding reported in the retrospective case study by Takata and his colleagues [13]. In addition, multivariate Cox regression analysis revealed that males had a 6.7-fold greater risk of developing oral cavity cancer than females. The discrepancy between men and women in the general population can be explained by the fact that men tend to be engaged in riskier lifestyle behaviors than women, such as cigarette smoking (46.8% vs. 4.3%), frequent alcohol consumption (15.1% vs. 2.6%), and betel quid chewing (14.4% vs. 1.5%) [33,34,35]. However, among the HCV infected subjects, female carriers are at similar risk of developing oral cavity cancer to their male counterparts (HRs were 1.69 and 1.88, respectively). Cacoub et al. suggested that female sex is one of the risk factors associated with developing extrahaemoplastic manifestations of HCV infection [36]. Although another possibility to explain the stronger association of HCV with oral cancer for females compared to males might be due to the small number of female oral cancer subjects in our cohort, this finding provided an interesting observation. Further studies with larger female samples are needed to verify this observation.

In this study, infection with HBV alone and HBV/HCV coinfection were not correlated with oral cavity cancer. Our finding is consistent with that reported in a Japanese study, which showed that high levels of HBV surface antigen were observed in patients with benign oral tumors but not in patients with oral cavity cancer requiring dental surgery [13]. Their finding suggests that HBV infection is unlikely to play a major role in oral tumor formation. A study by Bokor-Bratic also suggested that oral
leukoplakia was not associated with HBV infection in Serbia [37]. In addition, only HCV has the lymphatrophic character that is assumed to be the cause of HCV-associated extrahepatic manifestations [38]. Therefore, this HCV’s lymphatrophic character may explain why we found that HCV, but not HBV, was associated with oral cavity cancer. HBV and HCV are both hepatotropic viruses. Their coinfection is associated with clinically and histologically more severe liver disease and higher risk for the development of hepatocellular carcinoma [15,39]. Cho et al. have recently demonstrated in a meta-analysis study that co-infection of HBV and HCV has a subadditive risk for HCC [40]. Other clinical studies suggested a reciprocal interference of one virus on the replication of the other or both [41,42]. Some other clinical studies also showed co-infected cases with the phenomenon of the replication of the other or both [43,44]. This reciprocal interference between HBV and HCV may also explain the lack of increasing incidence of oral cavity cancer among our HBV+HCV infected population as one or both viruses were inhibited for their replication. Further prospective cohort studies are required to verify this finding.

This study has 2 main strengths. First, our study is the very first one used complete nationwide population-based data to assess the association between chronic viral hepatitis infection and oral cavity cancer. The sample size is large to differentiate risk difference between those with HBV and HCV infections. Second, selection and nonresponse biases may have been minimized by the comprehensive coverage of the NHI system (>96% of the islanders) and the large sample size.

This study had several limitations. First, some patients with hepatitis infection do not have obvious clinical symptoms and, therefore, might not seek medical attention. Claims for medical services would, therefore, not be available for those patients. As a result, some patients with asymptomatic hepatitis infection were most likely included in the comparison group. However, if viral hepatitis infection is associated causally with oral cavity cancer, this misclassification may lead the estimated HRs toward the null and further strengthen our findings. In addition, the overall seroprevalence of antibody to HCV (anti-HCV) in Taiwan has been estimated approximately <3% [45,46]. The prevalence of chronic HCV infection identified in our cohort was approximately 2.2%. Therefore, the positive association between HCV and oral cavity cancer in our cohort is accountable. Second, some oral cavity cancer risk factors, such as chewing of betel nut, smoking, and alcohol consumption were unavailable in the insurance claims database. Therefore, we cannot rule out some of the potential confounding effects associated with these factors. Ko et al. suggested that betel quid chewing is the most potent risk factor for oral cavity cancer in Taiwan, followed by cigarette smoking and alcohol drinking [47]. In Taiwan, the prevalence of cigarette smoking and betel quid chewing is highest in the eastern region, followed by the southern region [33]. Betel nut chewers in Taiwan are who tend to be poorly educated, low income earners, and blue collar workers [33]. We, hence, included monthly income and geographical regions in our multivariate Cox hazard model to reduce confounding effects caused by betel quid chewing, cigarette smoking, and alcohol consumption. In addition, in Taiwan, almost all betel quid chewers are smokers [33]. After excluding smoking-related cancers among our subjects, we found that the HR of oral cavity cancer for HCV alone infection increased from 1.90 to 1.92.

Therefore, these lifestyle factors may not significantly confound our results as we thought. Third, the diagnoses of oral cavity cancer, HBV infection, HCV infection, and other comorbidities based on International Classification of Disease codes may be less accurate than those obtained through a standardized procedure. However, the NHI Bureau of Taiwan randomly samples a fixed percentage of claims from every hospital and randomly interviews patients and reviews charts each year to verify the diagnosis validity and quality of care [40]. Patients with confirmed oral cavity cancer deserve medical cares as the “Catastrophic Illness” with minimum co-payment under the Taiwan NHI plan. All cancers are histology confirmed. The diagnoses of oral cavity cancer are likely accurate and are representative of all oral cavity cancer in Taiwan. Fourth, the vast majority of the residents in Taiwan are of Chinese ethnicity. Hence, the ability to generalize the results to other racial/ethnic groups is unclear given that the transmission route of viral hepatitis infection in Chinese might not be the same as that in other ethnic groups. Fifth, there is some plausibility for the association of lichen planus (one of the most frequently reported oral extrahepatic manifestations of HCV infection) and oral cavity cancer [29]. However, the incidence of lichen planus in our subjects was not indexed on the insurance records.

In summary, in this nationwide population-based cohort study conducted in a country in which both viral hepatitis and oral cavity cancer are endemic, we found a positive association between oral cavity cancer and HCV infection. Male subjects were at higher risk of developing oral cavity cancer than their female counterparts. Patients with HCV presented at an earlier age of onset of oral cavity cancer than subjects in the viral hepatitis-free control group. More perspective cohort studies are needed to determine the association between oral cavity cancer and HCV infection.

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Author Contributions

Conceived and designed the experiments: FHS SFH FCS HYC CCY. Performed the experiments: FHS CCY CTS PCC SNC. Analyzed the data: SNC PCC FCS HYC. Contributed reagents/materials/analysis tools: CCL SFH. Wrote the paper: FHS FCS CCY.

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