

The association between human papillomavirus infection and head and neck cancer

A population-based cohort study

Stella Chin-Shaw Tsai, MD, PhD^a, Jing-Yang Huang, PhD^b, Chuck Lin^c, Yung-Po Liaw, PhD^b, Frank Cheau-Feng Lin, MD, PhD^{d,e,*}

Abstract

Human papillomavirus (HPV) has been linked with development of oropharyngeal squamous cell carcinoma, a subset of head and neck cancer (HNC). This study aimed to evaluate the association between HPV infection and subsequent development of HNC and to report epidemiological information in Taiwan.

This population-based cohort study retrieved patient data from the longitudinal health insurance database (LHID) of Taiwan's National Health Insurance Research Database (NHIRD) from 2005 to 2010 and analyzed it retrospectively. The crude incidence rate and incidence rate ratios with 95% confidence intervals of HNC were estimated in patients with and without HPV infection. A time-to-event analysis was conducted and multiple regression analysis was performed to identify factors associated with HNC in HPV-infected patients, including age at baseline, sex, and comorbidities.

This study included the data of 25,520 HPV-infected and 1,061,817 noninfected patients. The HPV-infected group had a significantly higher proportion of females than the noninfected group (55.80% vs 50.66%, respectively; $P < .0001$). The incidence rate of HNC was 11.49 (males) and 5.83 (females) per 10^5 person-months versus 11.38 (males) and 3.90 (females) per 10^5 person-months in the infected and noninfected groups, respectively. HPV was significantly associated with cancer in females (hazard ratio = 1.520, 95% confidence interval 1.166–1.981), but not in males (hazard ratio = 1.000, 95% confidence interval 0.815–1.228). No significant differences were found in age between the HPV-infected and noninfected patients (49.20 ± 14.34 years vs 49.09 ± 13.82 years, respectively); and a slightly higher percentage of HPV-infected patients had a specific comorbidity than did noninfected patients 12.54% versus 9.43%, ischemic heart disease 14.22% versus 10.51%, hypertension 22.40% versus 19.54%, liver disease 22.88% versus 16.17%, and renal disease 7.14% versus 5.39%, respectively.

Results of this study may help clinicians in the diagnosis, prognosis, and treatment of head and neck cancer.

Abbreviations: CI = confidence intervals, HNC = head and neck cancer, HPV = human papillomavirus, HR = hazard ratios, IRR = incidence rate ratios, LHID = longitudinal health insurance database, NHIRD = National Health Insurance Research Database, OPSCC = oropharyngeal squamous cell carcinoma.

Keywords: head and neck cancer, human papillomavirus, National Health Insurance Research Database, population-based cohort study

Editor: Ziyuan Zhou.

Y-PL and FC-FL contributed equally to this work.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

Supplementary figure. Age-adjusted Kaplan–Meier survival curves. The age-adjusted survival curves show significant difference in the cumulative probability of long-term-survival of female between the group with HPV infection and the group without HPV infection, <http://links.lww.com/MD/C812>.

the authors of this work have nothing to disclose.

^a Department of Otolaryngology, Tungs' Taichung MetroHarbor Hospital, Wuchi, ^b Department of Public Health and Institute of Public Health, Chung Shan Medical University, ^c Department of Medical Research, Tungs' Taichung MetroHarbor Hospital, Wuchi, ^d School of Medicine, Chung Shan Medical University, ^e Department of Surgery, Chung Shan Medical University Hospital, Taichung, Taiwan.

* Correspondence: Frank Cheau-Feng Lin, Department of Surgery, Chung Shan Medical University Hospital, 110 Sec.1 Jian-Guo North Road, Taichung 40201, Taiwan (e-mail: fmklin@gmail.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:7(e14436)

Received: 22 February 2018 / Received in final form: 24 November 2018 / Accepted: 16 January 2019

<http://dx.doi.org/10.1097/MD.00000000000014436>

1. Introduction

Human papillomavirus (HPV) has a causal role in the development of oropharyngeal squamous cell carcinoma (OPSCC).^[1,2] HPV-associated OPSCC is an etiologically distinct subset of head and neck cancer (HNC) that is differentiated by unique clinical, epidemiological, and molecular characteristics, as well as diagnostic and prognostic factors that differ from cancers not associated with HPV.^[1,3–5] Patients with HPV-associated HNC were reported to be usually younger and male and present with later-stage tumors than those with tumors not associated with HPV infection.^[1] Although the natural disease course of HPV-related HNC is not yet clear, investigators have postulated that a subclinical HPV infection may be present in the oral cavity for decades before cancer develops.^[3]

Associations have been shown between HPV genotypes and abnormal cytology. An investigation of HPV genotypes in Thai women with high-grade squamous intraepithelial lesions and invasive cervical cancer found that HPV-58, a unique high-risk genotype, was most prevalent and that HPV-16, -18, -33, and -68 genotypes were all high-risk and with high distribution in women with these cancer types.^[6] In northern Taiwan, HPV-52 was the most frequent type in all age groups and over 56% of HPV-positive patients had 1 or more of the 4 most common HPV genotypes: HPV-52, -16, 58, and -56.^[7] Also in Taiwan, high-risk HPV 16/18 was more frequently detected in association with lung tumors in females compared with males.^[8] A study among African women showed that 67.7% of HPV-16 and -18 were associated with abnormal cytology, especially cervical neoplasias.^[9] Potent carcinogenicity has also been associated with HPV subtypes 16 and 18 as well as p16 expression in oropharyngeal cancer, with possible racial/ethnic differences.^[10–12] Results of these studies suggest that differences in geography, culture, or both may affect the local epidemiology of HPV infection and subsequent risk of acquiring HNC.^[1,13] The epidemiology of HPV-related oral squamous cell carcinomas is said to be evolving and studies are needed to explore the natural history of HPV infection, especially oral HPV, and associations with HPV-associated HNC, so that strategies for prevention can be developed.^[14]

Taiwan has one of the highest incidences of HNC worldwide.^[15] While central European countries and Latin American countries are shown to have a low prevalence of HPV-associated HNC,^[16] studies in Western countries show a decline in overall HNC incidence but an increase in cases of HPV-related HNC.^[15] In Taiwan, however, both the overall incidence of HNC and HPV-associated HNC are reported to be rising continuously.^[15] Considering the high incidence of both HNC and HPV-associated HNC in Taiwan, we hypothesized that population-based analysis may reveal epidemiological trends between age, gender, and other factors and the development of HNC in HPV-infected individuals in Taiwan. Therefore, the present study aimed to evaluate associations between HPV infection and subsequent HNC and to report HPV- and HNC-related epidemiological information in Taiwan.

2. Methods

2.1. Study design and ethical considerations

We conducted a population-based cohort study using patient data from Taiwan's National Health Insurance Research Database (NHIRD) from 2005 to 2010 to explore the association between HPV and subsequent HNC development and to collect HPV- and HNC-related epidemiological information in Taiwan. The study protocol was reviewed and approved by the Internal

Review Board of Tungs' Taichung MetroHarbor Hospital (#TTMHH-R0001). All patient data from the NHIRD were deidentified and therefore signed informed consent was waived.

2.2. Study sample and data collection

All patient data for this study were retrieved from the national longitudinal health insurance database (LHID) of the NHIRD from 2005 to 2010. The NHIRD in Taiwan provides insurance coverage for 23 million registered patients, representing 99% of the entire national population. Other studies in Taiwan have used the NHIRD to explore associations between various factors and certain disease states.^[17,18]

A total of 1,091,307 patients were enrolled in this study, of which 25,653 HPV infected patients and 1,065,654 noninfected patients were divided into an HPV exposure group and a control cohort and were followed from 2005 to 2010 until the occurrence of HNC or death. Initially, we excluded patients who were younger than 30 years of age in 2005 ($n = 868,600$) and who were missing demographic data ($n = 20$). We then excluded patients who had been previously diagnosed with HNC from January 2001 to December 2004. Finally, 25,520 HPV-infected and 1,061,817 non-HPV-infected patients were included in the analysis (Fig. 1). Patients diagnosed with HPV were identified using the following International Classification of Disease Clinical Modification (ICD-9-CM) codes: 079.4, 078.1, 078.10 to 078.12, 078.19, 759.05, 795.09, 795.15, 795.19, 796.75, and 796.79. HNC was identified by the ICD-9-CM codes 140 to 149. During the follow-up period, 741 HPV patients (2.90%) and 49,952 (4.70%) controls were considered withdrawn from the study due primarily to death or termination of insurance coverage.

2.3. Statistical analysis

A 2-tailed t test was used to compare differences between continuous variables, and a χ^2 test was used to compare nominal variables. The crude incidence rate (per 1000 person-months) was computed, and the incidence rate ratios (IRR) with 95% confidence intervals (CI) were estimated in a univariate Poisson regression model. A time-to-event analysis was conducted for the long-term follow-up that included the date of HNC onset if such occurred. All individuals received follow-up from January 2005. Follow-up was deemed to be concluded if a patient had withdrawn, in the case of death, or at the end of the study (December 2010). Kaplan–Meier survival curves and multiple Cox proportional hazard regression models were used to estimate the risk of HNC.

For the Cox multiple regression analysis conducted to estimate risk of HNC after HPV exposure, the model was adjusted for confounding factors, including age at baseline, sex, income, the area of residence, and comorbidities such as chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 492–496), ischemic heart disease (ICD-9-CM codes 411, 413, and 414), hypertension (ICD-9-CM code 401), diabetes mellitus (ICD-9-CM code 250), ischemic stroke (ICD-9-CM codes 433, 434, and 436), liver disease (ICD-9-CM code 571), and renal disease (ICD-9-CM codes 580–589). All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC). A 2-tailed P of $< .05$ was considered statistically significant.

3. Results

This study included 25,520 HPV-infected individuals in the patient cohort and 1,061,817 non-HPV-infected patients in the

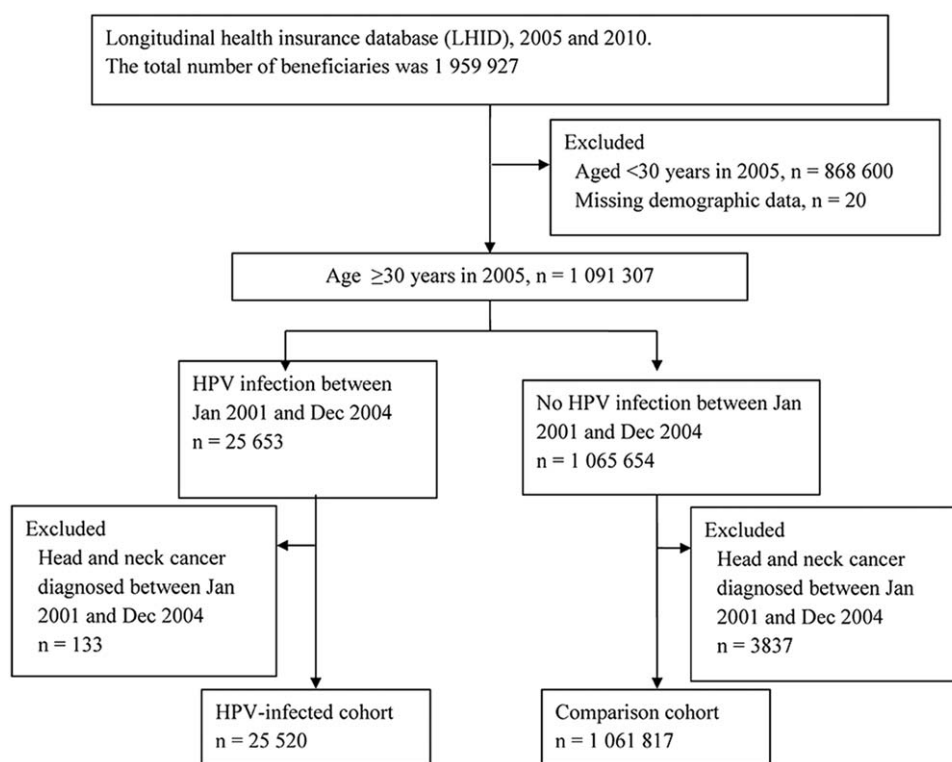


Figure 1. A flow chart of study participants.

comparison cohort. No significant differences were found in age between the HPV-infected and noninfected patients (49.20 ± 14.34 years vs 49.09 ± 13.82 years, respectively). The HPV-infected group had a significantly higher proportion of females than the noninfected group (55.80% vs 50.66%, respectively; $P < .0001$). A slightly higher percentage of patients had a specific comorbidity in the infected group than in the noninfected group, including COPD (12.54% vs 9.43%, respectively), ischemic heart disease (14.22% vs 10.51%, respectively), hypertension (22.40% vs 19.54%, respectively), liver disease (22.88% vs 16.17%, respectively), and renal disease (7.14% vs 5.39%, respectively). The significance of some factors may be attributed to the large sample size of both groups (Table 1).

Table 2 shows the incidence rates (per 10^5 person-months) for HNC and the IRR for the HPV-infected and noninfected individuals stratified by sex. For males, the incidence rate of HNC was 11.49 and 11.38 per 10^5 person-months in the HPV-infected and uninfected groups, respectively, and the IRR was 1.01 (95% CI 0.81–1.26) for HPV infection. For females, the incidence rate of HNC was 5.83 and 3.90 per 10^5 person-months in the HPV-infected and noninfected groups, respectively, and the IRR was 1.50 (95% CI 1.15–1.95) for HPV infection. Figures 2 and 3 show the cumulative incidence rates for HNC in males and females, respectively.

Estimations of hazard ratios (HR) for HNC were conducted using multiple Cox proportional hazard regression models. After adjusting for age, low income, the area of residence, and comorbidities, HPV infection was significantly associated with HNC in females (HR = 1.520, 95% CI 1.166–1.981), (Supplemental Figure, <http://links.lww.com/MD/C844>). However, no significant associations were found between HPV infection and HNC for males (HR = 1.000, 95% CI 0.815–1.228). Other

potential risk factors for HNC included the area of residence for both sexes, diabetes mellitus for males, liver disease for males, and COPD for females (Table 3).

4. Discussion

This study aimed to evaluate associations between HPV infection and subsequent HNC development and found significantly more females with HNC in the HPV-infected group than in the noninfected group. Regression analysis identified a significant association between HPV infection and subsequent HNC in Taiwanese females but the same association was not found in males. Both similar and contrasting results have been found in other studies in Taiwan. In a study by Lin et al^[19] involving patients with lung cancer in Taiwan, a difference between males and females was also observed for the risk of HPV infection and Taiwanese women who were exposed to HPV had a higher risk of lung cancer. However, in another study involving patients with lung cancer in Taiwan, Cheng et al^[8] found a higher HPV6 prevalence in male patients than in female patients. Moreover, a previous study by de Martel et al^[20] assessing data from the GLOBOCAN 2012 and Cancer of Five Continents databases found that the attributable fraction of all HPV-associated cancers in China, including HNC, cervical, uterine, and anal cancer, was 5.4% for females and 0.5% for males. In addition, one of the most extensive continuous population-based studies worldwide was conducted in the United States (the National Health and Nutrition Examination Survey) and analysis of data from that study demonstrated a prevalence of 6.9% (range, 5.7%–8.3%) for oral HPV, with significant differences between males (10.1%; range, 8.3%–12.3%) and females (3.6%; range, 2.6–5.0%).^[3] In a Canadian study of 460 HNC patients from 4 different hospitals and 458 controls, Farsi et al^[11]

Table 1**Distribution of demographic characteristics in the HPV-infected and noninfected groups.**

	HPV infection (n=25,520)*	No HPV infection (n=1,061,817)*	P value
Age in 2005 (mean±SD; y)	49.20±14.34	49.09±13.82	.2194
Sex			<.0001
Female	14,240 (55.80)	537,873 (50.66)	
Male	11,280 (44.20)	523,944 (49.34)	
Low income			<.0001
No	25,400 (99.53)	1,054,662 (99.33)	
Yes	120 (0.47)	7155 (0.67)	
Area of residence			<.0001
Taipei area	10,243 (40.14)	387,096 (36.46)	
Northern	3058 (11.98)	144,785 (13.64)	
Central	4964 (19.45)	188,405 (17.74)	
Southern	2820 (11.05)	152,912 (14.40)	
Kaohsiung area	3934 (15.42)	163,387 (15.39)	
Eastern	501 (1.96)	25,232 (2.38)	
Comorbidity			
COPD	3201 (12.54)	100,161 (9.43)	<.0001
Ischemic heart disease	3629 (14.22)	111,586 (10.51)	<.0001
Hypertension	5717 (22.40)	207,502 (19.54)	<.0001
Diabetes mellitus	3268 (12.81)	118,964 (11.2)	<.0001
Ischemic stroke	844 (3.31)	32,291 (3.04)	.0145
Liver disease	5839 (22.88)	171,742 (16.17)	<.0001
Renal disease	1821 (7.14)	57,271 (5.39)	<.0001

COPD=chronic obstructive pulmonary disease, HPV=human papillomavirus, SD=standard deviation.

*Categorical data are summarized as n (%).

reported that patients with HPV-associated HNC are usually younger and male and that these patients present with smaller, later-stage tumors with a better prognosis than those with tumors not associated with HPV.^[11] Gender differences may be associated with HPV status and type, route of HPV infection, and regional prevalence of HPV. Another study suggested that HPV-related tumors appear to affect certain ages, genders, and racial/ethnic groups disproportionately, which may indicate different disease processes for the HPV-associated tumors than in non-HPV-associated tumors.^[21] Clearly, further investigation of possible associations between HPV-associated HNC and these variable factors of HPV are warranted in the future.

This study found no significant differences in age between the HPV-infected and noninfected groups. However, this finding differs from those in other published studies where age differences were shown to be associated with HPV-associated HNC development. In an article by Gillison et al,^[22] HPV-related HNCs were generally more prevalent in younger patients. Further, Farsi et al^[11] also determined that patients with HPV-related HNC are usually younger and male.

In the present study, the cumulative incidence of HNC was significantly higher for females with HPV than those without HPV and risk was also higher. However, no significant difference in cumulative incidence was determined for males with or without HPV. Development of HNC also appears to differ according to individual lifestyle habits, area of residence, and other factors in addition to the presence or absence of HPV. Farsi et al^[11] demonstrated that the effects of heavy smoking and drinking by individuals with HPV16 infection significantly increased the risk of HNC. However, the incidence of HNC has been increasing worldwide despite a decline in tobacco use that has been attributed to the growing prevalence of oncogenic strains of HPV in the oral cavity.^[4] Udager and McHugh^[4] reported that tobacco and alcohol-associated HNC is generally seen in older males. Registry-based studies from Western countries show that HPV incidence has decreased along with the decline in tobacco use; however, the overall incidence of HPV-related HNC has increased.^[21] In Taiwan, Hwang et al^[15] used data from the Taiwan Cancer Registry to show that the overall incidence of HNC has continued to climb, and the greatest increase was observed in HPV-related HNC.

Table 2**Incidence of HNC in the HPV-infected and noninfected groups from 2005 to 2010.**

	HPV infection	No HPV infection	IRR (95% CI)	P value
Males				
Follow-up person-months	722,339	34,564,264		
Mean±SD	67.60±12.19	67.76±11.98		
Event of head and neck cancer (crude incidence rate/10 ⁵ person-months)	83 (11.49)	3933 (11.38)	1.01 (0.81–1.26)	.9299
Females				
Follow-up person-months	977,793	36,732,216		
Mean±SD	68.69±10.12	68.35±10.95		
Event of head and neck cancer (crude incidence rate/10 ⁵ person-months)	57 (5.83)	1431 (3.90)	1.50 (1.15–1.95)	.0028

HPV=human papillomavirus, IRR=incidence rate ratio, SD=standard deviation.

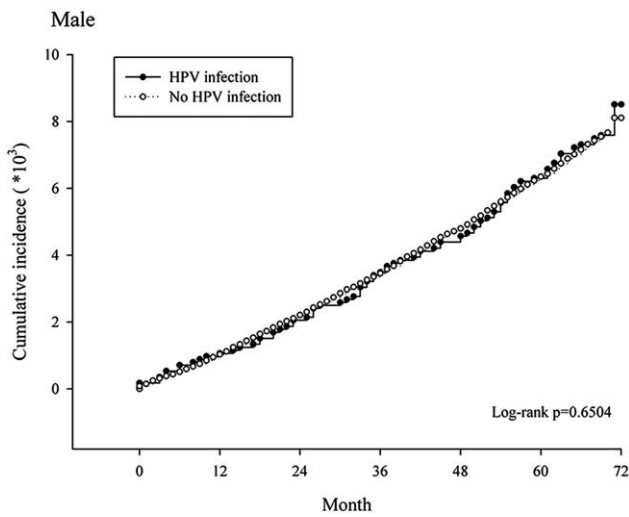


Figure 2. A Kaplan–Meier curve of the cumulative incidence of HNC in the HPV-infected and noninfected groups, males. HNC = head and neck cancer, HPV = human papillomavirus.

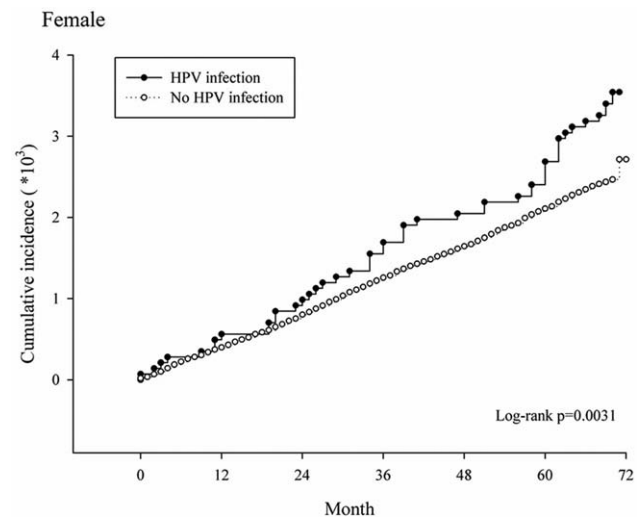


Figure 3. A Kaplan–Meier curve of the cumulative incidence of HNC in the HPV-infected and noninfected groups, females. HNC = head and neck cancer, HPV = human papillomavirus.

The clinical value of this study is its focus on obtaining epidemiological information on the subsequent development of HNC in patients with HPV infection in Taiwan, and the knowledge gained through our results, particularly about gender differences, may be of use in diagnosing and treating HPV-associated HNC in Taiwan as well as predicting outcomes. Our results suggest that HPV testing may provide useful predictive information and, along with other demographic and clinical information, may help to identify individuals at risk of developing HNC. In an epidemiological study of Taiwanese patients with oral cancer, HPV16, pathological stage T3/T4 and N1/N2, and extracapsular tumor spread were independent factors for overall survival; and patients infected with HPV had a

shorter 5-year overall survival than patients without HPV infection (49% vs 80%; $P < .021$).^[23]

5. Limitations

This study used the NHIRD to collect data on patients with HPV infection in Taiwan who developed subsequent HNC but several inherent limitations are noted. The NHIRD does not report data pertaining to individual direct clinical laboratory data such as virus type or known risk factors such as smoking status, alcohol use, or family history. This is an essential limitation as a decrease in smoking and alcohol use has led to a reduction of smoking-related HNC in some countries where public health-related

Table 3
Multiple cox regression analysis of HPV and HNC stratified by sex.

	Males		Females	
	HR (95% CI)	P value	HR (95% CI)	P value
HPV infection (ref: uninfected)	1.000 (0.815–1.228)	.9984	1.520 (1.166–1.981)	.0020
Age in 2005 (per year)	1.011 (1.009–1.014)	<.0001	1.013 (1.008–1.017)	<.0001
Low income (ref: No)				
Yes	1.199 (0.867–1.659)	.2732	1.278 (0.723–2.257)	.3983
Residence area (ref: Taipei area)				
Northern	1.036 (0.929–1.155)	.5285	1.227 (1.029–1.463)	.0227
Central	1.654 (1.516–1.804)	<.0001	1.546 (1.333–1.792)	<.0001
Southern	1.788 (1.635–1.956)	<.0001	2.045 (1.770–2.364)	<.0001
Kaohsiung area	1.537 (1.402–1.686)	<.0001	1.242 (1.053–1.466)	.0100
Eastern	1.615 (1.342–1.943)	<.0001	1.494 (1.079–2.068)	.0156
Comorbidity (ref: No)				
COPD	1.057 (0.956–1.168)	.2805	1.442 (1.245–1.671)	<.0001
Ischemic heart disease	0.900 (0.812–0.999)	.0474	1.175 (1.006–1.372)	.0416
Hypertension	1.071 (0.985–1.164)	.1097	1.101 (0.956–1.267)	.1808
Diabetes mellitus	1.222 (1.115–1.340)	<.0001	1.009 (0.865–1.177)	.9082
Ischemic stroke	1.142 (0.979–1.332)	.0903	0.930 (0.703–1.231)	.6112
Liver disease	1.351 (1.255–1.454)	<.0001	1.166 (1.019–1.333)	.0251
Renal disease	0.986 (0.869–1.119)	.8302	1.088 (0.888–1.333)	.4176

CI=confidence interval of HR, HPV=human papillomavirus, HR=hazard ratio; ref=reference.

antismoking campaigns have been published.^[24] However, the present analysis did include immunodeficiency-related comorbidities, diabetes mellitus, and liver and renal diseases. In addition, the prevalence of cases identified in our study using ICD-9 cases recorded in the LHID was lower than that found in other studies, suggesting that the present study may have the problem of misclassification; in particular, most HPV cases cannot be defined and such misclassification may result in underestimating correlations. We also grouped patients according to their baseline HPV status, which also may result in underestimating risk. We did not evaluate changes in diagnosis and treatment during the study period, which would be useful information when studying HNC in HPV-infected patients and remains to be explored in future studies.

6. Conclusions

Results of the present study reveal that significantly more females with HNC are present among HPV-infected individuals than among those without HPV infection in Taiwan, although no significant differences in age are found. Knowledge that a greater number of females develop HNC after HPV infection may help clinicians in the diagnosis, prognosis, and treatment of HPV-associated HNC in Taiwan.

Author contributions

Stella Chin-Shaw Tsai: definition of intellectual content; literature research; data acquisition; manuscript preparation

Jing-Yang Huang: data analysis; statistical analysis

Chuck Lin: literature research; data acquisition; statistical analysis

Yung-Po Liaw: study concepts; definition of intellectual content; statistical analysis

Frank Cheau-Feng Lin: guarantor of integrity of the entire study; study concepts; study design; manuscript editing; manuscript review

All authors agree to be accountable for all aspects of the work.

Conceptualization: Yung-Po Liaw, Frank Cheau-Feng Lin.

Data curation: Stella Chin-Shaw Tsai, Jing-Yang Huang, Chuck Lin.

Formal analysis: Jing-Yang Huang, Chuck Lin, Yung-Po Liaw.

Writing – original draft: Stella Chin-Shaw Tsai.

Writing – review & editing: Frank Cheau-Feng Lin.

References

- [1] Farsi NJ, Rousseau MC, Schlecht N, et al. Aetiological heterogeneity of head and neck squamous cell carcinomas: the role of human papillomavirus infections, smoking, and alcohol. *Carcinogenesis* 2017; 38:1188–95.
- [2] Karbalaie NMH, Safarnezhad TF, Panahi M, et al. Human papillomavirus investigation in head and neck squamous cell carcinoma: initial report from the low risk HPV types associations. *Asian Pac J Cancer Prev* 2017;18:2573–9.
- [3] Serrano B, Brottons M, Bosch FX, et al. Epidemiology and burden of HPV-related disease. *Best Pract Res Clin Obstet Gynaecol* 2018;47:14–26.
- [4] Udager AM, McHugh JB. Human papillomavirus-associated neoplasms of the head and neck. *Surg Pathol Clin* 2017;10:35–55.
- [5] Ou D, Garberis I, Adam J, et al. Prognostic value of tissue necrosis, hypoxia-related markers and correlation with HPV status in head and neck cancer patients treated with bio- or chemo-radiotherapy. *Radiother Oncol* 2018;126:116–24.
- [6] Sukasem C, Pairoj W, Sackang N, et al. Molecular epidemiology of human papillomavirus genotype in women with high-grade squamous intraepithelial lesion and cervical cancer: will a quadrivalent vaccine be necessary? *J Med Virol* 2011;83:119–26.
- [7] Wang CH, Garvilles RG, Chen CY. Characterization of human papillomavirus infection in North Taiwan. *J Med Virol* 2010;82:1416–23.
- [8] Cheng YW, Chiou HL, Chen JT, et al. Gender difference in human papillomavirus infection for non-small cell lung cancer in Taiwan. *Lung Cancer* 2004;46:165–70.
- [9] Ogembo RK, Gona PN, Seymour AJ, et al. Prevalence of human papillomavirus genotypes among African women with normal cervical cytology and heoplasiz: a systematic review and meta-analysis. *PLoS One* 2015;10:e0122488.
- [10] Ragin C, Liu JC, Jones G, et al. Prevalence of HPV infection in racial-ethnic subgroups of head and neck cancer patients. *Carcinogenesis* 2016; [Epub ahead of print].
- [11] Husain N, Neyaz A. Human papillomavirus associated head and neck squamous cell carcinoma: controversies and new concepts. *J Oral Biol Craniofac Res* 2017;7:198–205.
- [12] Anderson S, Isaac A, Jeffery CC, et al. Practices regarding human papillomavirus counseling and vaccination in head and neck cancer: a Canadian physician questionnaire. *J Otolaryngol Head Neck Surg* 2017;46:61.
- [13] Combes JD, Franceschi S. Role of human papillomavirus in non-opharyngeal head and neck cancers. *Oral Oncol* 2014;50:370–9.
- [14] Gooi Z, Chan JY, Fakhry C. The epidemiology of the human papillomavirus related to head and neck cancer. *Laryngoscope* 2016; 126:894–900.
- [15] Hwang TZ, Hsiao JR, Tsai CR, et al. Incidence trends of human papillomavirus-related head and neck cancer in Taiwan, 1995–2009. *Int J Cancer* 2015;137:395–408.
- [16] Ribeiro KB, Levi JE, Pawlita M, et al. Low human papillomavirus prevalence in head and neck cancer: results of large case-control studies in high-incidence regions. *Int J Epidemiol* 2011;40:489–502.
- [17] Chang CH, Lin JW, Chen HC, et al. Non-steroidal anti-inflammatory drugs and risk of lower gastrointestinal adverse events: a nationwide study in Taiwan. *Gut* 2011;60:1372–8.
- [18] Chen PL, Lee WJ, Sun WZ, et al. Risk of dementia in patients with insomnia and long-term use of hypnotics: a population-based retrospective cohort study. *PLoS One* 2012;7:e49113.
- [19] Lin FC, Huang JY, Tsai SC, et al. The association between human papillomavirus infection and female lung cancer: a population-based cohort study. *Medicine (Baltimore)* 2016;95:e3856.
- [20] de Martel C, Plummer M, Vignat J, et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer* 2017;141:664–70.
- [21] Cole L, Polfus L, Peters ES. Examining the incidence of human papillomavirus-associated head and neck cancer and ethnicity in the U.S., 1995–2005. *PLoS One* 2012;7:e32657.
- [22] Gillison ML, Chaturvedi AK, Anderson WF, et al. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. *J Clin Oncol* 2015;33:3235–42.
- [23] Lee LA, Huang CG, Tsao KC, et al. Human papillomavirus infections are common and predict mortality in a retrospective cohort study of Taiwanese patients with oral cavity cancer. *Medicine (Baltimore)* 2015;94:e2069.
- [24] Faraji F, Zaidi M, Fakhry C, et al. Molecular mechanisms of human papillomavirus-related carcinogenesis in head and neck cancer. *Microbes Infect* 2017;19:464–75.