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ORIGINAL RESEARCH

Association Between Human Papillomavirus and Thymic Cancer: A Population-Based Cohort Study

Peng-Tzu Liu[1–4], Wan-Lun Hsu[5,6], Tzu-I Chen[6], Chung-Ju Chiang[7], Mei-Hung Pan[8], Hui-Ling Lee[9], Chia-Chuan Wang[3], Chien-Jen Chen[8], Vinchi Wang[3,10], Yong-Chen Chen[6,11]

[1]Graduate Institute of Chemistry, Fu Jen Catholic University, New Taipei City, 242, Taiwan; [2]Graduate Institute of Biomedical and Pharmaceutical Science, Fu Jen Catholic University, New Taipei City, 242, Taiwan; [3]School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, 242, Taiwan; [4]Department of Family Medicine, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, 111, Taiwan; [5]Master Program of Big Data in Biomedicine, College of Medicine, Fu Jen Catholic University, New Taipei City, 242, Taiwan; [6]Data Science Center, College of Medicine, Fu Jen Catholic University, New Taipei City, 242, Taiwan; [7]Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, 100, Taiwan; [8]Genomics Research Center, Academia Sinica, Taipei, Taiwan; [9]Department of Chemistry, Fu Jen Catholic University, New Taipei City, 242, Taiwan; [10]Department of Neurology, Cardinal Tien Hospital, New Taipei City, 231, Taiwan; [11]Post-Baccalaureate Program in Nursing, Fu Jen Catholic University, New Taipei City, 242, Taiwan

Correspondence: Vinchi Wang, School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, 242, Taiwan, Tel +886-2-2905-3468, Fax +886-2-2905-2096, Email vwneur@yahoo.com.tw; Yong-Chen Chen, Post-Baccalaureate Program in Nursing, Fu Jen Catholic University, New Taipei City, 242, Taiwan, Tel +886-2-2905-2046, Fax +886-2-2905-2095, Email 137159@mail.fju.edu.tw

Background: Thymic carcinoma is an uncommon malignancy with unclear etiology. Although human papillomavirus (HPV) has been implicated in multiple cancers, its potential association with thymic cancer remains poorly studied in large population-based cohorts. This study aimed to investigate the role of HPV in developing thymic cancer and the risk of different HPV genotypes on thymic cancer.

Methods: We examined the longitudinal relationship between HPV infection and thymic cancer in a cohort of 10,558 women aged 30 to 65 years who were enrolled in 1991 or 1992 in Taiwan. Cervical cells collected at the beginning of this study were tested for 39 types of HPV. The incidence of newly developed thymic cancer was determined through a computerized linkage with the National Cancer Registry by using the topography code 164 for thymic cancer in the International Classification of Diseases, Ninth Edition.

Results: An increased risk of thymic cancer was associated with HPV infection, with an HR (95% CI) of 2.42 (0.62 to 9.38) after adjustment for age and body mass index. The level of risk was higher for infections with HPV types classified in the International Agency for Research on Cancer group 3, with an adjusted HR (95% CI) of 11.82 (2.51 to 55.70).

Conclusion: This population-based cohort study provides longitudinal evidence that HPV infection may be associated with an increased risk of thymic cancer. While no significant overall association was observed, subgroup analysis revealed a notable association with HPV genotypes classified as IARC group 3. Additional studies are necessary to confirm the role of HPV in thymic carcinogenesis.

Keywords: human papillomavirus, thymic cancer, cohort study

Introduction

According to the fifth edition of World Health Organization's classification system, thymic epithelial tumors are divided into thymoma, thymic carcinoma, and thymic neuroendocrine tumor (NET).[1–4] Thymic carcinoma, which is relatively rare, accounts for 5–36% of all thymic epithelial tumors.[4,5] Moreover, thymic carcinoma exerts a more severe clinical impact than does thymoma primarily because of its higher tendency to metastasize, resulting in poorer prognosis overall. Thymoma has the highest 5-year survival rate among the aforementioned thymic cancer subtypes, approaching 90%.[6] By contrast, thymic NETs, which account for 2–5% of all thymic epithelial tumors, have a more variable 5-year survival rate, ranging from 28 to 75%.[4,6]

In the United States, data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program database indicate that the age-standardized incidence rates are between 0.13 and 0.15 per 100,000 people for thymoma

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and 0.02 per 100,000 people for thymic NET.[1,6–8] Furthermore, according to the findings of the RARECARE project, the age-standardized incidence rate for thymic epithelial tumors in Europe is 0.17 per 100,000 people.[9] Previous studies conducted in Europe and the United States have reported slightly higher incidences of thymic epithelial tumors in men than in women.[6,10] Among ethnic groups, Asian Americans and Pacific Islanders have the highest incidence rates of thymic epithelial tumors, followed by African Americans.[6] Regarding age, the incidence of thymic cancer is highest in individuals aged between 70 and 74 years.[6]

In Asia, data obtained from a hospital-based cancer registry and the National Cancer Center in Japan revealed an incidence rate of 0.29 cases per 100,000 person-years for thymic carcinoma.[11] The incidence rate of thymic carcinoma in men is approximately twice that in women. The highest incidence rates were observed in men aged between 75 and 79 years and in women aged between 70 and 74 years.[11] Furthermore, according to the National Cancer Registry Annual Report 2020, in Taiwan, the age-standardized incidence rate of thymic cancer in men is approximately 1.46 times higher than that in women (2.1 vs 1.44 per 100,000 people).[12]

Human papillomavirus (HPV) is the primary causative agent of cervical cancer.[13] HPV is a small, non-enveloped, circular DNA virus classified under the Papillomavirus genus of the Papovaviridae family.[14] Over 200 HPV genotypes have been identified, with significant differences in infection rates and carcinogenicity among different types. According to global epidemiological data, HPV accounts for 31.1% of pathogen-related cancers, ranking second only to *Helicobacter pylori*, which accounts for 36.3%.[15] Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, affects multiple organs including the kidneys, heart, liver, pancreas, and immune system. Immunosuppression is a shared risk factor for both HPV and COVID-19, increasing the risk of persistent HPV infection and severe COVID-19 outcomes.[16] Previous studies have demonstrated that HPV is implicated in not only cancers of the female reproductive system but also urogenital, oropharyngeal, breast, colorectal, esophageal, and lung cancers.[17–22] In particular, 70% to 80% of cases of oropharyngeal squamous cell carcinoma (OPSCC) in the United States and Europe are associated with HPV. By contrast, in Taiwan, HPV-related OPSCC accounts for only 25–30% of cases.[23,24] In addition, HPV is implicated in 50% to 84% of colorectal, rectal, and anal cancers.[18,25,26] Furthermore, HPV genotypes 16 and 18 are the primary causative agents of cervical cancer in Western countries, whereas HPV genotypes 52 and 58 are the main causative agents in Taiwan.[27–29] In North America and Europe, approximately 85% of OPSCC cases are attributable to HPV genotypes 16 and 18.[30] However, a retrospective cohort study conducted at a single medical center in Taiwan revealed that HPV genotype 16 alone and HPV genotype 58 alone accounted for 76.9% and 7.5% of cases, respectively.[31,32]

Although previous studies have suggested that age and ethnicity lead to differences in incidence rates, some studies have proposed that infection or chronic inflammation is associated with the development of thymoma or thymic carcinoma.[5,6,33,34] Malcolm et al observed that thymic hypertrophy, characterized by an increase in the numbers of all types of thymocytes and enhanced cellularity of the cortex and medulla, increased with age in transgenic mice expressing the E7 protein of HPV16 from the keratin 14 promoter.[35] However, currently, evidence remains limited to establishing only a correlation between thymic cancer and viral infection, largely because of a lack of large-scale cohort prospective studies. Thus, in the present study, we used a large-scale community-based database to investigate the potential association between HPV and thymic cancer. In addition, we explored whether specific HPV genotypes are linked to thymic cancer.

Materials and Methods

Study Design and Cohort Recruitment

This study used data from the 1991 to 1992 Community-Based Cancer Screening Program in Taiwan. A total of 11,923 women aged 30 to 39 years from 7 townships in Taiwan were enrolled. Because the primary aim of this study was to investigate the effect of HPV on cervical cancer development, individuals with inadequate cervical cell specimens and those with a history of hysterectomy were excluded from the sampling. This process resulted in a final cohort of 10,615 individuals who underwent the Papanicolaou (Pap) smear test (Cervex Brush, Rovers, Netherlands) and HPV DNA testing (ViraPap Kit, Digene Diagnostics, Silver Spring, MD, USA). To examine the correlation between HPV and thymic cancer development in women, individuals with any known history of cancer at the time of screening were further

excluded, resulting in a final cohort of 10,558 individuals. Given the community-based design, no formal sample size calculation was performed; all eligible individuals were enrolled without sampling.

Subsequently, well-trained public health nurses administered standardized individual questionnaires to these participants. These questionnaires covered sociodemographic characteristics, dietary habits, cigarette smoking, alcohol consumption, betel nut chewing, history of menarche, menopause, pregnancy, delivery, and oral contraceptive or intrauterine device usage. Cells collected for HPV testing were preserved at −80°C. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board by the institutional review board (IRB) of Fu Jen Catholic University (no. C112033). All participants provided written informed consent before enrollment, and all data were de-identified prior to analysis.

Methods of HPV DNA Extraction, HPV Polymerase Chain Reaction Assay, and HPV Genotyping

One milliliter of a frozen cervical cell sample was aliquoted into 100-μL volumes before DNA extraction. The methods for DNA extraction and polymerase chain reaction (PCR) employed in this study have been described in previous studies.[13,34,36,37] For HPV genotyping, we used the EasyChip HPV blot kit (King Car, Taiwan), which can detect 39 genotypes of HPV [6, 11, 16, 18, 26, 31, 32, 33, 35, 37, 39, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, CP8061 (71), 72, 74, CP8304 (81), 82, MM4 (82), MM7 (83), MM8 (84), and L1AE5 (85)] through reverse-blot hybridization.[36,37]

A specimen was considered HPV-positive if it showed positive results in both the EasyChip kit and PCR assays. For specimens initially EasyChip kit testing positive, reconfirmation through additional PCR for genotyping was performed. If a specimen exhibited a consistent gel electrophoresis pattern of HPV DNA but inconsistent genotyping results, it was classified as an equivocal type. Specimens exhibiting consistent positive gel electrophoresis of HPV DNA but a negative result in the EasyChip assay were categorized as other types and not included among the 39 detected genotypes; they were then directly sequenced from the L1 region. Both equivocal and other types were included in the positive group. Each batch of experiments contained 96 samples, namely 89 cervical tissue samples and 7 control samples, to maintain a contamination-free environment, to facilitate reproducibility, and to ensure the accuracy of the results as described previously.[13]

We classified the HPV genotypes detected using the EasyChip kit in accordance with the classification system established by the International Agency for Research on Cancer (IARC).[38] HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 were categorized as IARC group 1. HPV genotype 68 (2A) and HPV genotypes 26, 53, 66, 67, 70, 73, and 82 (2B) were categorized as IARC group 2. HPV genotypes 6 and 11 were categorized as IARC group 3. Other types that were not considered to be carcinogenic and are unspecified by the IARC but were detected using the EasyChip kit included HPV 32, 37, 42, 43, 44, 54, 55, 61, 62, 69, CP8061 [71], 72, 74, CP8304 [81], MM7 [83], MM8 [84], and L1AE5 [85].

Identification of Patients with Newly Diagnosed Common Female Cancers During Follow-up

We linked data from the National Cancer Registry, National Death Certification Registry, and National Health Insurance database in Taiwan, tracking records up to December 31, 2020. Newly diagnosed primary cancers have been registered in the National Cancer Registry since 1996. Thymus malignant tumors are coded as 164 in the *International Classification of Diseases, Ninth Edition*. Thymic cancers were diagnosed through histological analysis and further classified in accordance with the *International Classification of Diseases for Oncology, Third Edition*. Confirmatory cytology and tissue morphology were available for 91.5% to 99.6% of all diagnosed thymic cancers from 1991 to 2020.

Statistical Analysis

For each participant, person-years of follow-up were calculated from the date of recruitment. The cumulative incidence of thymic cancers was determined using the Kaplan–Meier method, with censoring occurring at the date of diagnosis for new thymic cancer cases. Multivariate-adjusted HRs and their corresponding 95% CIs were computed using Cox proportional hazards models for patients who developed thymic cancers to analyze data on the basis of different

IARC groups for HPV-positive cases. The HPV genotypes present in patients with thymic cancer during the follow-up period were analyzed and categorized. A P value of <0.05 indicated statistical significance. All statistical analyses were performed using SAS version 9.1.4 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

In the CBCS-HPV study, 1170 participants were excluded because of missing data from either Pap smear or HPV testing, and an additional 138 individuals were excluded because they had previously undergone hysterectomy. As a result, 10,615 participants who met the eligibility criteria were enrolled. After the exclusion of individuals with a history of cancer, the final cohort for this longitudinal study contained 10,558 individuals (Figure 1). The mean age of these participants was 46.3 ± 9.7 years, and the prevalence rate of any type of HPV in the cohort was 15.5% (Table 1). Genotype analysis conducted on the participants who tested positive for HPV revealed the following distribution in accordance with the IARC classification system: 64.15%, 21.22%, and 13.05% for IARC groups 1, 2, and 3, respectively (Table S1). In addition, among specific HPV genotypes, the 5 most common were types 52 (2.47%), 16 (2.05%), 11 (1.85%), 18 (1.62%), and 58 (1.34%) (Table S1).

Association Between HPV Infection Status and Thymic Cancer

Table 1 lists the basic characteristics of the participants stratified by their HPV infection status. We noted significant differences in alcohol consumption and cigarette smoking between the HPV-positive and HPV-negative groups. Regardless of HPV status, no significant difference in mean age, oral contraceptive use, or betel nut chewing was observed between the HPV-positive and HPV-negative groups. In the follow-up analysis, in addition to the already known relationship between cervical cancer and HPV infection, a slightly increased HR for thymic cancer was observed in the HPV-positive group compared with the HPV-negative group (HR = 2.42, 95% CI = 0.62 to 9.38; Table 2). However, we noted no significant differences in the cumulative incidence rates of thymic cancer between the HPV-positive and HPV-negative groups (Figure 2).

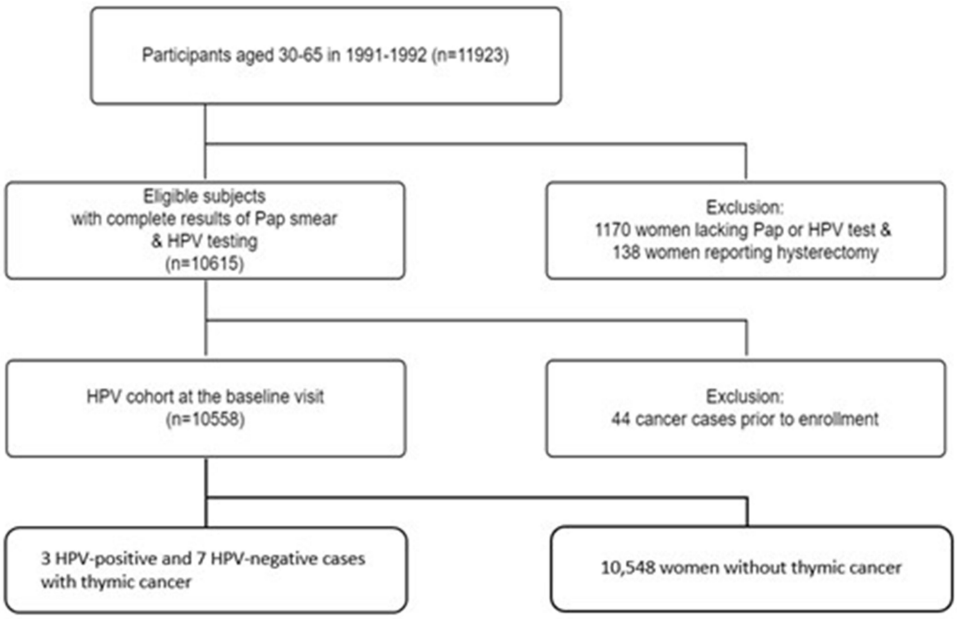

Figure 1 Flowchart for the selection of eligible participants from the CBCSP-HPV study.

Table 1 Basic Characteristics of Patients with and without HPV Infection

	Entire Cohort (N=10558)		HPV Any Type (–)* (N=8918)		HPV Any Type (+)† (N=1640)		*p* value‡
	N	%	N	%	N	%	
Age, (years)							
(Mean ± SD)	46.3±9.7		46.0±9.6		47.5±9.9		0.16
Oral contraceptives							
Yes	3237	30.66	2715	30.44	522	31.83	0.28
No	7251	68.68	6142	68.87	1109	67.62	
Unknown	70	0.66	61	0.68	9	0.55	
Cigarette smoking							
Yes	108	1.02	80	0.90	28	1.71	<0.05
No	10405	98.55	8797	98.64	1608	98.05	
Unknown	45	0.43	41	0.46	4	0.24	
Alcohol consumption							
Yes	67	0.63	48	0.54	19	1.16	<0.05
No	10447	98.95	8831	99.02	1616	98.54	
Unknown	44	0.42	39	0.44	5	0.3	
Betelnut chewing							
Yes	18	0.17	15	0.17	3	0.18	0.90
No	10494	99.39	8862	99.37	1632	99.51	
Unknown	46	0.44	41	0.46	5	0.3	

Notes: *HPV any type (–), indicates no detectable infection with any HPV genotype. †HPV any type (+), indicates the presence of infection with any HPV genotype. ‡p <0.05 indicates statistical significance.

Table 2 Baseline HPV Infection and Subsequent Development of Thymic Cancer

	HPV DNA Status	HPV Genotype	Age of Enrollment (Years)	Age at Diagnosis (Years)	Histology of Thymic Tumor (ICD-O-3)	Follow-up HPV Status
Case 1	+	52	45	55	Metaplastic thymoma (85803)	No data
Case 2	+	11, 18	30	51	Thymoma, type AB (85823)	–
Case 3	+	11, 71	36	61	Thymoma, type B3 (85853)	18, 33
Case 4	–	–	44	46	Diffuse large B-cell lymphoma (96803)	–
Case 5	–	–	52	58	Leiomyosarcoma (88903)	–
Case 6	–	–	58	69	Thymoma, type C (85863)	No data
Case 7	–	–	63	81	Thymoma, malignancy (80003)	No data
Case 8	–	–	42	60	Thymoma, type B2 (85843)	–
Case 9	–	–	50	73	Thymoma, type A (85813)	–
Case 10	–	–	32	61	Thymoma, type B2 (85843)	–

Association Between Different Category of HPV Genotypes and Thymic Cancer

Further analysis of the HPV-positive group revealed that those with HPV genotypes classified as IARC group 3 had a higher HR (11.82, 95% CI = 2.51 to 55.7; Table 2) for thymic cancer incidence. Moreover, we noted a significant difference in the cumulative incidence rates of the participants with HPV genotypes classified as IARC group 3 and the other participants (ie, those who tested negative for HPV and those who tested positive for HPV genotypes not classified in IARC group 3; Figure 3). We comprehensively analyzed the demographic data of 10 participants with thymic cancer (Table 3). None of these participants had a history of tobacco, alcohol, or betel nut use. Moreover, except for thymic cancer, no organ malignancies were identified during the follow-up period. Among 3 participants with HPV positivity,

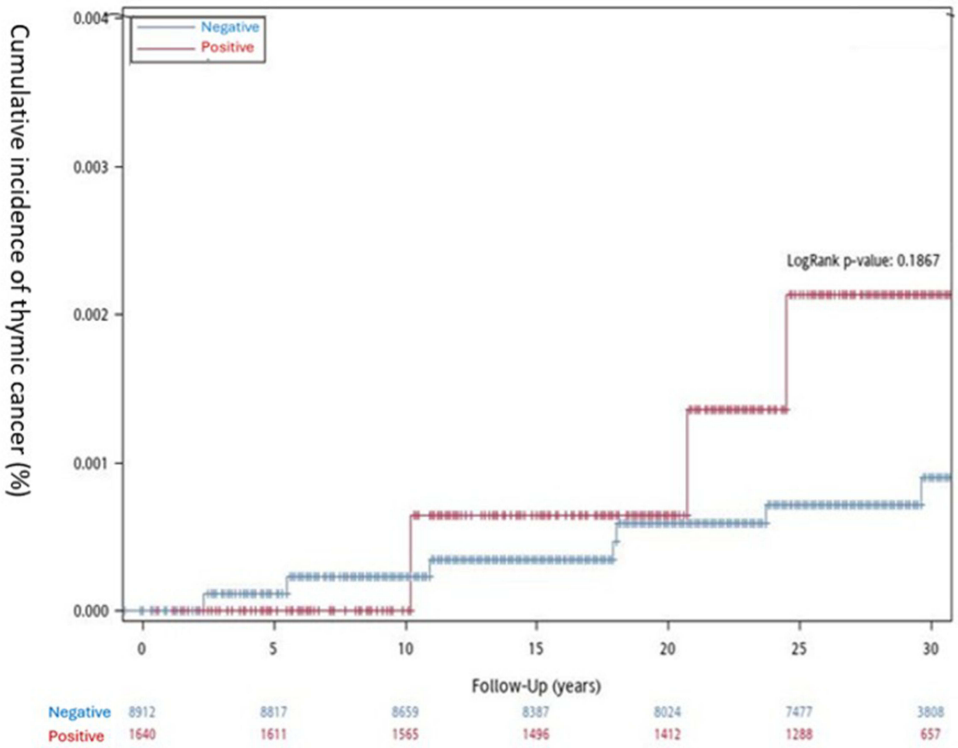

Figure 2 Cumulative incidence of thymic cancer by HPV status at study entry.

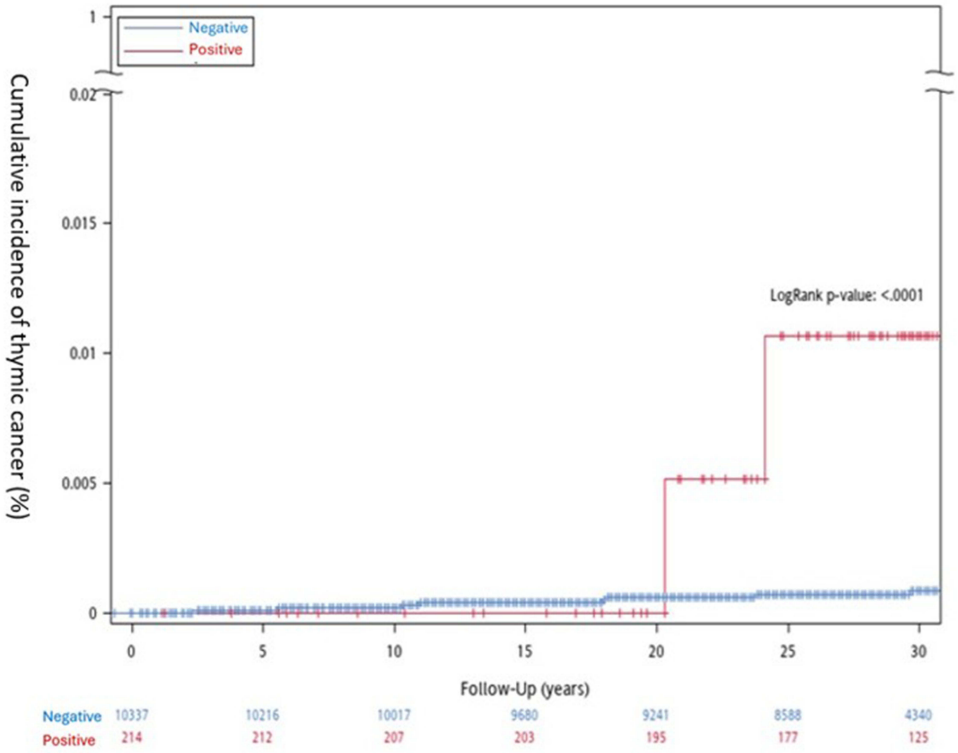

Figure 3 Cumulative incidence of thymic cancer in HPV-positive cases classified as IARC group 3 versus other participants.

Table 3 Multivariable Cox Proportional Hazards Regression Model Analysis of the Associations of IARC HPV Groups with Thymic Cancer Risk

HPV Genotype	HR*	95% CI	*p* value†
Any type (−)‡	1.00	Ref.	
Any type (+)§	2.42	0.62–9.38	0.201
IARC group 1 (−)	1.00	Ref.	
IARC group 1 (+)	2.36	0.50–1.16	0.277
IARC group 3 (−)	1.00	Ref.	
IARC group 3 (+)	11.82	2.51–55.70	0.002

Notes: *Adjusted for age. †$p < .05$ indicates statistical significance. ‡Any type (–), indicates no detectable infection with any HPV genotype. §Any type (+), indicates the presence of infection with any HPV genotype.
Abbreviations: CI, confidence interval; HR, hazard ratio; IARC, International Agency for Research on Cancer; Ref., reference.

2 had dual-genotype infections, including one case where HPV genotype 11 was present. Specifically, Case 2 had concurrent infections with IARC group 1 (type 18) and group 3 (type 11) genotypes, whereas Case 3 was infected with an IARC group 3 genotype (type 11) and a non-IARC-classified genotype (type 71). Histologically, Cases 2 and 3 were diagnosed with mixed-type thymoma, whereas Case 1 was diagnosed with an unspecified type of thymic carcinoma. The time from the initial Pap smear to the diagnosis of cancer varied. Case 1 was diagnosed with thymic cancer after a decade of follow-up, whereas Cases 2 and 3 were diagnosed after more than 20 years of follow-up.

Discussion

This large-scale, community-based cohort study investigated the potential association between HPV infection and thymic cancer development in women. Cervical tissue samples were tested using PCR and gene chip technology to identify HPV exposure and genotype distribution. While no significant overall association was observed between HPV infection and thymic cancer, subgroup analysis revealed a noteworthy link with HPV genotypes classified as IARC group 3.

Importantly, this observed association with IARC group 3 HPV genotypes (HR=11.82) should be interpreted with caution, as it was based on only one case (HPV11 in Case 2). This result should be interpreted as exploratory and hypothesis-generating only, and should be validated in larger studies.

The HPV prevalence in our cohort was 15.5%, slightly lower than the 19.85% reported by Jeng et al in a Taiwan-based urban population using similar molecular detection methods.[39] This difference may be attributable to variations in age distribution and geographic settings. Nevertheless, the consistency with contemporary epidemiological trends reinforces the validity of our findings.

Although the present study did not observe a significant association between any type of HPV and thymic cancer development, a subanalysis of HPV genotypes revealed that those categorized in IARC group 3 had a relatively high risk of thymic cancer. Previous studies have reported HPV has been implicated in cervical and various anogenital and oropharyngeal cancers. To the best of our knowledge, this is the first study to indicate a possible association between specific HPV genotype classifications and thymic cancer. Although age and ethnicity are considered as potential risk factors, the number of large cohort studies confirming the relationships of other risk factors with thymic cancer remains lacking. Thus, the present study provides limited evidence for understanding these associations.

Among thymic cancer cases, patients who were HPV-positive were younger (mean age 55.8 years) than their HPV-negative counterparts (mean age 64.0 years), suggesting a potential age-related susceptibility. In the previous study, Cufi et al observed decreased expression of p53, a tumor suppressor, and increased expression of $p16^{CDKN2A}$, a surrogate marker for HPV infection, in 11 cases of thymoma-associated MG. However, subsequent tests using real-time PCR for HPV DNA yielded negative results.[33] The discrepancy may reflect differences in detection methods (immunohistochemistry vs PCR), sample types (thymoma vs thymic carcinoma), or population characteristics. Thus, the relationship

between viral infections and thymoma or thymic carcinoma remains inconclusive. Although neither the previous study nor the present study directly detected HPV DNA in thymic tissue, the former suggested a potential association between thymoma, and HPV infection based on $p16^{CDKN2A}$ overexpression identified by immunohistochemistry. In contrast, our study demonstrated a possible association through cohort-based follow-up of HPV infection identified in cervical samples. This limitation underscores the need for tissue-based molecular analysis to validate potential viral involvement in thymic tumorigenesis.

Previous studies have categorized HPV genotypes into high risk (group 1), intermediate risk (group 2), and low risk (group 3) on the basis of the IARC's risk assessment for cervical cancer. However, the contributions of individual genotypes to cancer risk vary.[31,40,41] Notably, 2 of 3 HPV-positive thymic cancer patients carried genotypes 18 and 52, both belonging to IARC group 1. However, a significant association was detected with group 3 genotypes, including HPV 6 and 11, traditionally considered low risk and more commonly linked to benign lesions such as warts. These genotypes have also been sporadically detected in lung as well as head and neck cancers, prompting investigation into possible oncogenic mechanisms.[42–44]

The observed association with group 3 HPV types raises the question of how low-risk genotypes may contribute to the thymic epithelial tumorigenesis. Several hypotheses have been proposed to explain HPV-driven carcinogenesis in non-mucosal sites. The first theory suggests that HPV is transmitted through mononuclear white cells via the bloodstream or lymphatic system to the target organ, resulting in infection.[45,46] Second, the "hit and run" hypothesis posits that HPV initiates carcinogenesis in thymic epithelial tumors, even without the histological evidence of persistent viral infection.[47] Thus, even if the virus is cleared by the immune system or remains at a very low viral load in the tissue, it can still lead to the development of cancer in the future. The third theory involves extracellular vesicles containing nucleic acids, proteins, and noncoding RNA, potentially originating from another site of initial infection. These vesicles may transfer to tissues that lack HPV receptors, leading to abnormal cell proliferation.[48]

The present study had some limitations that should be considered. First, HPV detection was limited to cervical samples at baseline, without direct HPV testing of thymic tissues or longitudinal follow-up for persistent infection. However, these participants who tested positive for HPV were aged between 51 and 64 years. Previous studies have been suggested that, due to immune suppression occurring after the age of 50, the likelihood of transient HPV infection is considered low. Second, the rarity of thymic cancer and small number of cases (n = 10) limited the statistical power of genotype-specific analyses. Third, potential confounding factors such as environmental exposures (eg, radiation) or hereditary predispositions could not be adjusted due to data limitations. Finally, in the absence of direct thymic testing, the possibility of contamination or non-local HPV presence cannot be excluded, and causal inference requires further mechanistic validation.

Conclusions

In this cohort study of adult women, HPV infection was confirmed using cervical DNA analysis, and younger age was observed among thymic cancer patients with HPV positivity. Although no significant increase in overall cancer risk was detected, a potential association between thymic cancer and IARC group 3 HPV genotypes was identified. Given the rarity of thymic cancer and the novelty of these findings, additional multicenter studies and molecular investigations are warranted to clarify the biological plausibility and clinical relevance of this association.

Abbreviations

CI, confidence interval; HR, hazard ratio; NET, thymic neuroendocrine tumor; HPV, human papillomavirus; IRB, institutional review board; OPSCC, oropharyngeal squamous cell carcinoma; Pap, Papanicolaou; PCR, polymerase chain reaction.

Data Sharing Statement

Data is unavailable due to privacy or ethical restrictions.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board by the institutional review board (IRB) of Fu Jen Catholic University (no. C112033).

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Author Contributions

Peng-Tzu Liu: Conceptualization, Formal acquisition, Writing-original draft, Writing-review & editing. Wan-Lun Hsu: Conceptualization, Methodology. Tzu-I Chen: Data curation, Formal analysis, Software. Chung-Ju Chiang: Methodology, Resources, Validation. Mei-Hung Pan: Investigation. Hui-Ling Lee: Supervision. Chia-Chuan Wang: Conceptualization, Supervision. Chien-Jen Chen: Investigation, Supervision. Vinchi Wang: Conceptualization, Supervision. Yong-Chen Chen: Conceptualization, Formal acquisition, Project administration, Writing-review & editing.

All authors made a significant contribution to the work reported, whether in conception, design, data acquisition, analysis, interpretation, or in all these areas. All authors participated in drafting or critically revising the article; gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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