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Human papillomavirus infection associated with increased risk of new-onset psoriasis: a nationwide population-based cohort study

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Abstract

Background: This study investigated whether patients with a history of human papillomavirus (HPV) infection are at increased risk of developing psoriasis.
Methods: We enrolled 66 274 patients with HPV infection between 1997 and 2013 from the Taiwan National Health Insurance Research Database, and compared them with control individuals who had never been diagnosed with HPV infection (at a 1:4 ratio matched by age, sex and index year) in relation to the risk of developing psoriasis. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with the control group as reference.
Results: The adjusted hazard ratio (aHR) was 1.177 (95% CI, 1.010–1.373) after adjusting for demographic characteristics, comorbidities, dermatology-related outpatient visits and medications. The HPV group had an increased risk of psoriasis compared with the control group in all of the different age groups. The *P*-value for interaction between age and exposure of HPV is 0.009 in our sub-group analysis.
Conclusions: A higher risk of psoriasis was found after HPV infection, and age acted as an effect modifier between the HPV infection and risk of psoriasis.

Key words: Papillomavirus infection, psoriasis, cohort study

Key Messages

- We used a nationwide population-based cohort study to investigate the risk of psoriasis in patients with incident human papillomavirus (HPV) infection.
- We found that the patients with HPV infection exhibited a 1.177 times greater risk of subsequently developing new-onset psoriasis than did those in the general population.
- A stratified analysis revealed that the effects of HPV infection were significant in both sexes and all age groups.
- A prominent interaction effect between age and HPV infection of developing psoriasis diseases was also observed in this study.

Introduction

Psoriasis is a chronic inflammatory dermatosis which affects 0.5–4.6% of the world's population,[1] leading to substantial detriment to patients' quality of life and contributing to the global burden of diseases.[2–4] Psoriasis can be provoked by genetic or environmental factors, particularly drugs and infections. Previous studies have shown that infections with viruses [such as human immunodeficiency virus (HIV), herpes simplex virus (HSV) and Zika virus], bacteria (such as streptococcal and staphylococcus infections), fungi (such as malassezia and *Candida albicans* infections), and infestations with parasitic mites such as *Sarcoptes scabiei* may trigger psoriasis.[5–10] Medications such as beta-blockers, lithium, antimalarial drugs and even oral corticosteroids are also usually referred to as contributors to the onset of psoriasis.[11–15] The pathophysiology of psoriasis usually requires inflammatory cellular reactions. Patients also often experience systemic autoimmune disorders in their lifetime, such as psoriatic arthritis. The association between psoriasis and autoimmune diseases is commonly believed to exist, but the exact mechanism has not been extensively studied so far. More long-term follow-up studies in infection-linked psoriasis are still required.

The role of the adaptive immune system, particularly of Th1 and Th17 lymphocytes and possible decreased Tregs function, has been regarded as prominent in the immunopathogenesis of psoriasis.[16] The complex interplay of proinflammatory cytokines, chemokines, growth factors and chemical mediators initiated by Th17 cells may well be critical for inducing the keratinocyte hyperplasia, angiogenesis and influx of neutrophils that ultimately culminate in excess keratinocyte proliferation and characteristic features of psoriatic plaques.[17,18] Human papillomaviruses (HPV) are small double-stranded DNA viruses among which specific types are known as distinct risk factors for multiple cancers,[19,20] and which have been found in head, neck, breast, cervical, lung, oral, oesophageal and anogenital lesions.[6,21–28]

Several researchers have observed that an HPV infection predominantly stimulates systemic interleukin 17 (IL-17) production in HPV-induced carcinogenesis and that HPV infection provides better conditions for IL-17 secretion in the development of cervical cancer.[29,30] Plaque psoriasis is the most common presentation of the disease. A previous case report has shown that a plaque type psoriasis might be triggered by HPV infection.[24] This case report also illustrated the role of nerve growth factor (NGF) in HPV-induced psoriasis. NGF not only influenced the pathological features of new-onset psoriasis, but was also found in increased amounts in psoriatic-prone skin.[24] All of these observations have made larger scale of investigation of the association between HPV infection and newly diagnosed psoriasis warranted.

In this study, we hypothesized that HPV infection might provide better conditions for the IL-17-producing T cells and then induce the immunopathogenesis of psoriasis. As no previous studies on the epidemiological relationship between HPV infection and the subsequent development of psoriasis had been proposed, we conducted this original longitudinal nationwide cohort study to explore this important issue.

Methods

Data source

The data in this study were obtained from the Taiwan's National Health Insurance Research Database (NHIRD) which contains health care data of more than 95% of residents in Taiwan since 1995. Within Taiwan's universal National Health Insurance (NHI) scheme, all medical claims are mandatorily sent to the Bureau of National Health Insurance (BNHI) for validation and reimbursement. The NHIRD collects beneficiaries' registration files regarding demographics, all types of medical visits, laboratory tests codes, procedure codes, prescriptions codes and diagnostic codes based on the International Classification

of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) system. The Longitudinal Health Insurance Database 2000 (LHID 2000), a subset of NHIRD, was used in this study. LHID 2000 is composed of all the original claim data of 1 000 000 people randomly sampled from the year 1997 registry for beneficiaries of the NHIRD. There are no statistically significant differences in the distribution of age, sex or health care costs between the 1 000 000 people from the LHID 2000 and the original NHIRD. The original identification number of each patient in this dataset was encrypted to protect privacy. The Institutional Review Board of Chung Shan Medical University in Taiwan approved this study (IRB permit number CS15134) and waived the need for informed consent since the data were used anonymously and de-identified before analysis.

Study subjects and study design

The study subjects were sampled from LHID 2000 data. Those missing demographic data and who died before January 2003 were excluded. We identified newly diagnosed patients with HPV infection (ICD-9 codes 079.4, 078.1, 078.10–078.12, 078.19, 759.05, 795.09, 795.15, 795.19, 796.75 and 796.79) in the period of January 1997 to December 2013 from both outpatient and inpatient visits (Figure 1). The index date was defined as the first date that HPV was diagnosed. For further ascertainment, only patients with at least one inpatient admission or two outpatient visits during 1 year after first being diagnosed with HPV were selected. To increase the likelihood of identifying newly diagnosed HPV infection, the exclusion criteria for the study subjects were: (i) patients diagnosed with HPV infection before January 2003 ($n = 20\ 366$); (ii) patients with a history of psoriasis (ICD-9-CM codes 696.0, 696.1) before the index date ($n = 550$); (iii) patients with no HPV infection treatment procedure code: 'Electrocauterization for condyloma (50 005)', 'Condyloma, excision and electrocauterization (55 008)', 'CO_2 laser operation (62 020)', 'Chemosurgery, condyloma (50 015)', 'Electro cauterization, simple (51 005)', 'Electro cauterization, complicated (51 006)', 'Liquid nitrogen cryosurgery (51 017)', 'Cryotherapy, simple, including CO_2 freezing and liquid nitrogen (51 021C)' or 'Cryotherapy, complicated, including CO_2 freezing and liquid nitrogen (51 022))' during the 3 months after the index date ($n = 5392$). As a result, a total of 66 274 psoriasis-free subjects with newly diagnosed HPV infection were identified from the LHID 2000 for the study based on the criteria above.

The control group was selected from LHID 2000, randomized and matched at a ratio of 1:4 by age, sex and the index date. The age of each study subject was measured by the difference in time between the index date and the date of birth. Subjects with a history of psoriasis diagnosed before the index date were excluded. Finally, 265 096 subjects were enrolled as a comparison cohort (non-HPV group) in this study. Individuals in both the study group and the control group were followed up until there was a psoriasis event, death event or until December 2013. The death of an individual was defined by a record in the death certificate database of Taiwan.

Outcomes and covariates

All ambulatory medical care and inpatient records for each subject in the two groups were tracked from their index visit till the end of 2013. The date of the first principal diagnosis of psoriasis during the follow-up period was defined as the primary endpoint. Both cohorts were followed up until psoriasis was diagnosed, or patients withdrew from the NHI programme or until the end of 2013, whichever occurred first. To ensure that only patients with a correct diagnosis of psoriasis (ICD-9-CM codes 696.0, 696.1) were included, only patients with at least one inpatient admission or three or more ambulatory visits with the diagnosis of psoriasis were eligible. The comorbidities analysed in this study were hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidaemia (ICD-9-CM code 272), coronary artery disease (CAD, ICD-9-CM codes 410–414), cerebrovascular accident (ICD-9-CM codes 430–438), chronic kidney disease (CKD, ICD-9-CM code 585), chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 490–492, 493–496), systemic lupus erythematosus (SLE, ICD-9-CM code 710.0), ankylosing spondylitis (AS, ICD-9-CM code 720.0), rheumatoid arthritis (RA, ICD-9-CM code 714.0), Sjögren's syndrome (SS, ICD-9-CM code 710.2), urticaria (ICD-9-CM code 708), allergic rhinitis (ICD-9-CM codes 477), atopic dermatitis (ICD-9-CM code 691), chronic liver diseases (ICD-9-CM code 571.4), hepatitis B virus infection (ICD-9-CM codes 070.2, 070.3, V02.61), hepatitis C virus infection (ICD-9-CM codes 070.44, 070.51, 070.54, 070.7, V02.62), streptococcal tonsillitis (ICD-9-CM code 034.0), herpes simplex virus (ICD-9-CM code 054.9), candidiasis (ICD-9-CM code 112.1) and HIV infection (ICD-9-CM codes 042–044, 795.8, V08). Information on comorbid medical disorders was obtained by tracing all the ambulatory medical care and inpatients records in the NHI database within 2 years before the index date. As an active health-care-seeking individual will probably have a higher chance of being visible as being positive for both HPV and psoriasis, we also adjusted the frequency of dermatology-related outpatient visits identified within 1 year before the index date, in order to control the potential selection bias. The medication confounders in this study were oral

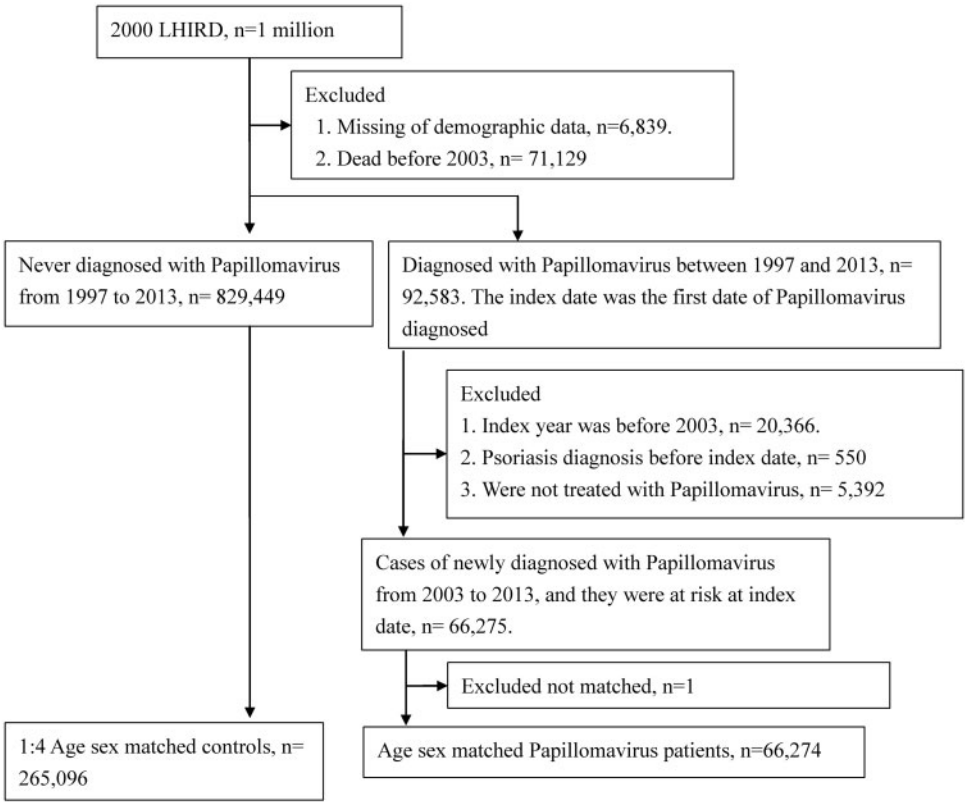

Figure 1 Flowchart of enrolment of subjects from the Longitudinal Health Insurance Database 2000 database, 1997–2013.

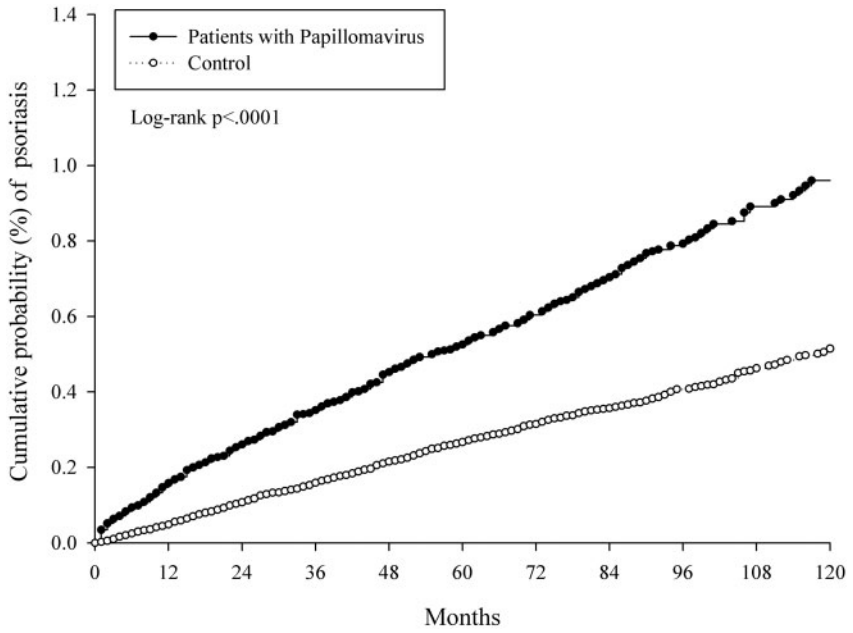

Figure 2 Kaplan-Meier curves of incidence of psoriasis in subjects with and without human papillomavirus infection.

corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), H_2 receptor antagonists, aspirin, oral antihypertensive drugs (including alpha-blockers, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs), oral antihypoglycaemic agents (including biguanides, sulphonylureas, alpha glucosidase inhibitors, thiazolidinediones) and statins. Drug use was defined as use of a drug for 30 days or more within 180 days before and after the index date.

Statistical analysis

The demographic characteristic data, including the distributions of categorical age, sex, urbanization level, income level, medical care utilization level, comorbidities and medications between the HPV study group and non-HPV comparison group were analysed by chi square (χ^2)tests. The incidence density of psoriasis per 100 000 person-months was calculated in both groups. To investigate the effect of HPV, a Cox proportional hazard regression analysis was conducted to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for covariates. The Kaplan-Meier method was used to describe the cumulative incidence of psoriasis in the two groups; differences between the two groups were evaluated using the log-rank test. Four statistical models were fitted to evaluate the effect of HPV on the risk of psoriasis. The first models just assessed the crude effect of HPV infection on the risk of incidental psoriasis. In the second model, we used demographic variables, including sex, age, urbanization and low income at baseline. In the third model, we examined the temporal relationship between HPV exposure and the risk of developing psoriasis diseases for both cohorts, adjusted for demographic variables, length of hospital stay, dermatology-related outpatient visits and comorbidities at baseline. Finally our full model (Model 4) adjusted for demographic variables, length of hospital stay, dermatology-related outpatient visit, comorbidities and comedications at baseline. Figure 2 showed the Kaplan-Meier curves of incidence of psoriasis in subjects with and without HPV infection. All the data and statistics were processed and analysed by the SAS software Version 9.3 (SAS Institute, Inc., Cary, NC), and a *P*-value less than 0.05 was considered to indicate statistical significance. The statistical power of this study, given the sample size, alpha error and the hypothesized difference between the two groups, is about 0.7.

Results

The baseline characteristics of the two groups are listed in Table 1. Patients with HPV had a higher frequency of dermatology-related outpatient visits. The HPV group also had a higher proportion of comorbidities except for diabetes and cerebrovascular accident. Table 2 shows the comedications in the two groups within 180 days before or after index date. A slightly higher proportion of the patients with HPV infection in this study used NSAIDs (4.59%), and an even higher proportion used antihypertensive drugs (11.38%).

Table 3 shows the incidence and adjusted HRs (aHRs) for all statistical models. The crude hazard ratio of HPV was 1.989 (95% CI, 1.760–2.249) (Model 1); the aHR after adjusting for demographic variables, including sex, age, urbanization and low income at baseline, was 1.990 (95% CI, 1.760–2.250) (Model 2); the aHR after adjusting for demographic variables, length of hospital stay, dermatology-related outpatient visits and comorbidities at baseline was 1.188 (1.019–1.384) (Model 3); the aHR after adjusting for demographic variables, length of hospital stay, dermatology-related outpatient visit, comorbidities and comedications at baseline was 1.177 (95% CI, 1.010–1.373) (Model 4). In Table 3, we used the Akaike information criterion (AIC) to compare Models 1–4. In Table 3, we found the smallest AIC in Model 4. Furthermore, we conducted the Schoenfeld residual plot of psoriasis for HPV exposure (in Supplementary Figure S1, available as Supplementary data at *IJE* online) in each model, which showed the effect of HPV exposure was under the assumption of proportional hazard. Supplementary Figure S2, available as Supplementary data at *IJE* online, present graphs of overall fit for each of the models. This analysis showed that infection with HPV had an independent effect on the development of new-onset psoriasis.

Table 4 shows the results of univariate and multivariate Cox regression analyses. Among all relevant variables, a history of HPV infections, age >20, male sex, having some comorbidities and using comedications showed a higher risk of developing psoriasis. The subjects who had histories of HPV infections had a crude HR of 1.989 (95% CI, 1.760–2.249) of developing psoriasis compared with the non-HPV control group; and after adjusting for all covariates listed in Table 1, the aHR was 1.177 (95% CI, 1.010–1.373). Compared with subjects aged less than 20 years, those aged 20–39 years had a higher risk of developing psoriasis (aHR = 1.905; 95% CI, 1.577–2.302) than those in the reference age group; for those aged 40–59 years and 60 years and older, the aHRs were 2.319 (95% CI, 1.901–2.830) and 2.970 (95% CI, 2.330–3.785), respectively. Also, compared with women, men had a slightly higher risk of psoriasis (aHR = 1.653; 95% CI, 1.464–1.866). Higher risks of psoriasis had been shown in subjects with some comorbidities, such as Sjögren's syndrome (aHR = 1.754; 95% CI, 1.049–2.933), hyperlipidaemia (aHR = 1.224; 95% CI, 0.991–1.513), cerebrovascular accident (aHR = 1.381; 95% CI, 1.033–1.845), chronic liver disease (aHR = 1.293; 95% CI, 1.049–1.595), urticarial (aHR = 1.250; 95% CI, 1.055–1.481), atopic dermatitis (aHR = 1.386; 95% CI, 1.056–1.819) and hepatitis C virus infection (aHR = 1.744; 95% CI, 1.072–2.839). For medication confounders, use of systemic corticosteroids was associated with an increased risk of psoriasis (aHR = 2.257; 95% CI, 1.676–3.038).

Table 5 demonstrates the association of risks of psoriasis between sex subgroups and age subgroups. In the sex subgroup analysis, females with HPV showed a higher risk

Table 1. Baseline characteristics of the study group and matched cohort

	Control $n = 265\,096$	Papillomavirus patients $n = 66\,274$	*P*-value
Age at index date (years)			0.999
<20	65 652 (24.77%)	16 413 (24.77%)	
20–39	97 404 (36.74%)	24 351 (36.74%)	
40–59	70 008 (26.41%)	17 502 (26.41%)	
>=60	32 032 (12.08%)	8008 (12.08%)	
Sex			0.999
Female	137 544 (51.88%)	34 386 (51.88%)	
Male	127 552 (48.12%)	31 888 (48.12%)	
Urbanization			<0.0001
Urban	159 429 (60.14%)	42 234 (63.73%)	
Suburban	80 091 (30.21%)	19 004 (28.67%)	
Rural	25 576 (9.65%)	5036 (7.60%)	
Low income	1631 (0.62%)	316 (0.48%)	<0.0001
Length of hospital stay (days)			<0.0001
0	235 643 (88.89%)	58 700 (88.57%)	
1–6	18 294 (6.90%)	5107 (7.71%)	
7–13	5773 (2.18%)	1381 (2.08%)	
>=14	5386 (2.03%)	1086 (1.64%)	
Frequency of all outpatient visit			<0.0001
0	27 108 (10.23%)	3 (0.00%)	
1–10	122 526 (46.22%)	23 601 (35.61%)	
>10	115 462 (43.55%)	42 670 (64.38%)	
Frequency of dermatology-related outpatient visits			<0.0001
0	213 915 (80.69%)	5364 (8.09%)	
1–2	36 179 (13.65%)	46 111 (69.58%)	
>2	15 002 (5.66%)	14 799 (22.33%)	
Comorbidities			
SLE	371 (0.14%)	144 (0.22%)	<0.0001
Ankylosing spondylitis	625 (0.24%)	257 (0.39%)	<0.0001
RA	1816 (0.69%)	576 (0.87%)	<0.0001
Sjögren's syndrome	1286 (0.49%)	559 (0.84%)	<0.0001
Hypertension	29 714 (11.21%)	8349 (12.60%)	<0.0001
Diabetes mellitus	14 710 (5.55%)	3773 (5.69%)	0.1482
Hyperlipidaemia	19 629 (7.4%)	6668 (10.06%)	<0.0001
Coronary artery disease	10 387 (3.92%)	3364 (5.08%)	<0.0001
Cerebrovascular accident	6498 (2.45%)	1628 (2.46%)	0.9373
CKD	1872 (0.71%)	533 (0.80%)	0.0078
COPD	15 543 (5.86%)	5028 (7.59%)	<0.0001
Chronic liver diseases	12 248 (4.62%)	4436 (6.69%)	<0.0001
Urticarial	22 869 (8.63%)	7943 (11.99%)	<0.0001
Atopic dermatitis	6446 (2.43%)	2473 (3.73%)	<0.0001
Allergic rhinitis	38 137 (14.39%)	13 748 (20.74%)	<0.0001
Hepatitis B virus infection	4171 (1.57%)	1729 (2.61%)	<0.0001
Hepatitis C virus infection	1480 (0.56%)	414 (0.62%)	0.0426
Streptococcal tonsillitis	536 (0.20%)	157 (0.24%)	0.0803
HIV	84 (0.03%)	62 (0.09%)	<0.0001
Herpes simplex	3004 (1.13%)	1623 (2.45%)	<0.0001
Candidiasis	5532 (2.09%)	2189 (3.30%)	<0.0001

The length of hospital stay and frequency of outpatient visits were identified within 1 year before the index date. Comorbidities were identified within 2 years before the index date.

CAD, coronary artery disease; SLE systemic lupus erythematosus; RA, rheumatoid arthritis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Table 2. Medication among groups within 180 days before or after index date

	Control $n = 265\,096$	Papillomavirus patients $n = 66\,274$	*P*-value
Corticosteroids	2945 (1.11%)	1169 (1.76%)	<0.0001
NSAIDs	9646 (3.64%)	3043 (4.59%)	<0.0001
PPI	2371 (0.89%)	914 (1.38%)	<0.0001
H_2 receptor antagonist	3390 (1.28%)	1084 (1.64%)	<0.0001
Aspirin	7626 (2.88%)	2129 (3.21%)	<0.0001
Oral antihypertensive drugs	25 836 (9.75%)	7545 (11.38%)	<0.0001
Oral antihyperglycaemic agents	8960 (3.38%)	2001 (3.02%)	<0.0001
Statin	6747 (2.55%)	2232 (3.37%)	<0.0001

Use of medication was defined as the prescription for at least 30 days of drug use within 180 days before or after the index date. Oral antihypertensive drugs include alpha-blockers, beta- blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and calcium channel blockers (CCB). Oral antihyperglycaemic agents include biguanides, sulphonylureas, alpha glucosidase inhibitors, thiazolidinediones.

NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Table 3. Time to event analysis

	Control $n = 265\,096$	Papillomavirus patients $n = 66\,274$	*P*-value of aHR for HPV patients	AIC for model fit
Follow-up person-months	17 443 784	4 398 431		
Event of psoriasis	766	384		
Incidence rate[a] (95% CI)	4.39 (4.09–4.71)	8.73 (7.9–9.65)		
Model 1: Crude hazard ratio (95% CI)	Reference	1.989 (1.760–2.249)	<0.0001	28 094.719
Model 2: aHR (95% CI)	Reference	1.990 (1.760–2.250)	<0.0001	27 843.758
Model 3: aHR (95% CI)	Reference	1.188 (1.019–1.384)	0.0279	27 597.834
Model 4: aHR (95% CI)	Reference	1.177 (1.010–1.373)	0.0370	27 584.160

Model 1: crude hazard ratio. Model 2: adjusted for demographic variables, including sex, age, urbanization and low income at baseline. Model 3: adjusted for demographic variables, length of hospital stay, frequency of dermatology-related outpatient visits and comorbidities at baseline. Model 4: adjusted for demographic variables, length of hospital stay, frequency of dermatology-related outpatient visits, comorbidities and comedications at baseline.

AIC, Akaike information criterion; HPV, human papillomavirus; aHR, adjusted hazard ratio; CI, confidence interval.

[a]Per 100 000 person-months.

of developing psoriasis (aHR = 1.312; 95% CI, 1.045–1.649) than males with HPV (aHR = 1.072; 95% CI, 0.871–1.319). Males with HPV had the highest incidence rate of psoriasis among all sex subgroups (10.20; 95% CI, 8.93–11.66). However, the *P*-value for interaction by sex subgroup was not significant (0.2138). In the age subgroup analysis, compared with matched non-HPV age subgroups, those aged below 20 had the lowest risk of developing psoriasis (aHR = 0.993; 95% CI, 0.640–1.542) and those aged over 60 had the highest risk of developing psoriasis (aHR = 1.649; 95% CI, 1.177–2.311). The risk increased with age in both the HPV and the non-HPV subgroup. The *P*-value for interaction in the age subgroup was significant (0.0092).

Discussion

In this first retrospective cohort study using nationwide population-based data over 12 years, we found that persons with HPV had a nearly 2-fold increase in incident psoriasis compared with the general population. Furthermore, stratified analysis revealed that the effects of HPV infection were significant in both sexes and in patients of all age groups. A prominent interaction effect between age and HPV infection on the risk of developing psoriasis diseases was also observed in this study. As age increased, the patients with HPV infection manifested higher risk of developing psoriasis in comparison with the control groups. Although the subjects in the HPV infection group had a significantly higher rate of comorbid diseases compared with the comparison cohort, HPV infection remained an independent risk factor for developing psoriasis in terms of baseline characteristics, comorbidities and comedications.

The underlying mechanism by which HPV infection increases the risk of developing psoriasis remains unclear. However, a case of plaque-type psoriasis triggered by genital warts after HPV infection has been reported. It also indicated that a high level of nerve growth factor (NGF) was provoked by the inflammatory status of the lesions.[21] The association of psoriasis and other virus infections such as HIV was well established in the previous studies, with the CD4+ T-cells depleted in HIV leading to psoriasis onset.[5]

Table 4. Estimation the hazard ratio of psoriasis by using Cox proportional hazard regression

	Univariate modelling		Multivariate modelling	
	HR	95% CI	aHR	95% CI
Exposure of HPV (ref: non HPV)	1.989	1.760–2.249	1.177	1.010–1.373
Age at index date (ref: <20)				
20–39	2.030	1.685–2.446	1.905	1.577–2.302
40–59	2.554	2.111–3.091	2.319	1.901–2.830
>=60	4.145	3.376–5.089	2.970	2.330–3.785
Sex male (ref: female)	1.502	1.336–1.688	1.653	1.464–1.866
Urbanization (ref: urban)				
Suburban	0.985	0.864–1.122	1.012	0.888–1.154
Rural	1.224	1.013–1.479	1.235	1.020–1.494
Low income	0.585	0.219–1.561	0.627	0.235–1.675
Length of hospital stay (days) (ref: 0)				
1–6	1.046	0.835–1.310	0.830	0.660–1.043
7–13	1.913	1.410–2.596	1.254	0.915–1.717
>=14	2.048	1.462–2.869	1.060	0.740–1.520
Frequency of all outpatient visit (ref: 1–10)				
0	0.548	0.396–0.758		
>10	1.702	1.506–1.924		
Frequency of dermatology-related outpatient visits (ref: 1–2)				
0	0.586	0.511–0.672	0.633	0.537–0.747
>2	2.441	2.085–2.858	2.108	1.793–2.478
Comorbidities				
SLE	3.509	1.573–7.827	1.612	0.697–3.731
Ankylosing spondylitis	2.066	0.927–4.605	1.396	0.623–3.127
RA	2.447	1.573–3.808	1.344	0.848–2.131
Sjögren's syndrome	3.122	1.906–5.114	1.754	1.049–2.933
Hypertension	1.980	1.702–2.303	0.872	0.678–1.122
Diabetes mellitus	1.799	1.457–2.222	0.879	0.635–1.215
Hyperlipidaemia	2.188	1.849–2.588	1.224	0.991–1.513
Coronary artery disease	2.051	1.645–2.558	0.910	0.700–1.183
Cerebrovascular accident	2.680	2.071–3.469	1.381	1.033–1.845
CKD	1.730	0.928–3.225	0.737	0.391–1.392
COPD	1.878	1.561–2.260	1.234	1.011–1.505
Chronic liver diseases	2.082	1.720–2.521	1.293	1.049–1.595
Urticaria	1.705	1.448–2.008	1.250	1.055–1.481
Atopic dermatitis	1.913	1.466–2.496	1.386	1.056–1.819
Allergic rhinitis	0.951	0.807–1.121	0.854	0.722–1.012
Hepatitis B virus infection	1.243	0.823–1.879	0.722	0.472–1.104
Hepatitis C virus infection	3.325	2.088–5.294	1.744	1.072–2.839
Streptococcal tonsillitis	1.903	0.791–4.579	2.004	0.832–4.831
HIV	–	–		
Herpes simplex			0.859	0.561–1.314
Candidiasis			1.433	1.027–1.999
Medications				
Oral corticosteroids	4.624	3.527–6.062	2.257	1.676–3.038
NSAID	1.849	1.459–2.344	0.901	0.697–1.167
PPI	2.270	1.458–3.532	1.161	0.737–1.829
H_2 receptor antagonist	1.835	1.215–2.773	0.883	0.576–1.354
Aspirin	2.281	1.769–2.941	1.015	0.747–1.379

(Continued)

Table 4. Continued

	Univariate modelling		Multivariate modelling	
	HR	95% CI	aHR	95% CI
Oral antihypertensive drugs	2.163	1.852–2.526	1.227	0.945–1.594
Oral antihyperglycaemic agents	1.821	1.392–2.382	1.002	0.673–1.494
Statin	2.481	1.896–3.247	1.255	0.911–1.727

The length of hospital stay and frequency of outpatient visit were identified within 1 year before the index date. Comorbidities were identified within 2 years before the index date. Oral antihypertensive drugs include alpha-blockers, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and calcium channel blockers (CCB). Oral antihyperglycaemic agents include biguanides, sulphonylureas, alpha glucosidase inhibitors, thiazolidinediones. Use of medication was defined as the prescription for at least 30 days of drug within 180 days before or after index date. The covariates included exposure of HPV, age at index date, sex, urbanization, low income, length of hospital stay, frequency of dermatology-related outpatient visits, comorbidities and medications in the multivariate modelling.

HPV, human papillomavirus; aHR, adjusted hazard ratio; CI, confidence interval; CAD, coronary artery disease; SLE systemic lupus erythematosus; RA, rheumatoid arthritis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors.

Table 5. Incidence and hazard ratios of psoriasis for the patients stratified by gender and age

	Non-HPV		HPV		
Sub-group	*n*	Incidence rate[a] (95% CI)	*n*	Incidence rate[a] (95% CI)	aHR[b] (95% CI)
Sex-subgroup					
Female	137 544	3.46 (3.10–3.86)	34 386	7.38 (6.34–8.58)	1.312 (1.045–1.649)
Male	127 552	5.41 (4.94–5.94)	31 888	10.20 (8.93–11.66)	1.072 (0.871–1.319)
P for interaction					0.2138
Age-subgroup					
<20	65 652	2.23 (1.85–2.7)	16 413	3.55 (2.63–4.79)	0.993 (0.640–1.542)
20–39	97 404	4.47 (3.99–5.02)	24 351	7.60 (6.37–9.06)	1.054 (0.819–1.357)
40–59	70 008	5.52 (4.87–6.26)	17 502	10.08 (8.37–12.13)	1.089 (0.816–1.453)
>=60	32 032	7.21 (6.06–8.59)	8008	23.18 (19.16–28.04)	1.649 (1.177–2.311)
P for interaction					0.0092
Frequency of dermatology-related outpatient visits					
0	213 915	3.61 (3.31–3.94)	5364	4.31 (2.64–7.04)	1.115 (0.677–1.837)
1–2	36 179	5.97 (5.05–7.06)	46 111	6.37 (5.54–7.33)	1.069 (0.856–1.335)
>2	15 002	12.33 (10.28–14.8)	14 799	17.89 (15.41–20.76)	1.382 (1.090–1.752)
P for interaction					0.2578

HPV, human papillomavirus; aHR, adjusted hazard ratio.

[a]Per 100 000 person-months.

[b]Adjusted for demographic variables, length of hospital stay, frequency of dermatology-related outpatient visits, comorbidities and comedications at baseline.

A previous study found an increased prevalence of HPV in hairs plucked from patients with psoriasis who were treated with psoralen-UV-A. The finding suggested that this psoriasis treatment might have increased the expression of the tumourigenic agent HPV in skin by stimulating HPV virus activation directly.[31] Although the cellular pathomechanism of psoriasis triggered by all types of infections was not extensively understood, it was postulated that the inflammatory state after HIV infection led to the upregulation of NGF synthesis, and that NGF influenced the pathological features of psoriasis, followed by keratinocyte proliferation, angiogenesis and T-cell activation.32–36 A high level of NGF was reported in the psoriatic-prone skin compared with normal skin.[24,32,34]

The subgroup analysis of our study showed that subjects with HPV infection in all age groups had an increased risk of psoriasis and, as age increased, the effect of HPV infection became more prominent in developing psoriasis. Though psoriasis was more common in the 15–30-year age group,[37,38] we found that the risk was the highest in the age group of 60 years and over, with an aHR of 1.649 (95% CI, 1.177–2.311). Generally, it is considered that immune reactions to infections are usually more intense in younger than older people. Nevertheless, we hypothesized that older women could be infected with the highly pathogenic HPV subtypes more easily than younger women.[39] New data published recently from a 2-year, semi-annual follow-up study suggested that HPV reactivation risk may

increase in women aged approximately 50 years—adding to an overall increased rate of HPV detection at older ages.[40]

Another finding that deserves attention in this study is that the prominent risk of developing psoriasis was noted in the patients with a previous diagnosis of Sjögren's syndrome, with an aHR of 1.754 (95% CI, 1.049–2.933). Sjögren's syndrome affected 0.2% to 3.0% of the population by 2014,[41,42] and usually presents as a primary disease itself, or as a secondary syndrome of autoimmune diseases.[43–46] However, individuals affected by primary Sjögren's syndrome still have an increased risk of being diagnosed with new-onset additional autoimmune diseases or life-threatening systemic disorders.[47–51] Therefore, clinicians should be aware of the increased risk of psoriasis in the patients with Sjögren's syndrome, who should be educated and monitored.

The strength of our study was the use of nationwide population-based data to evaluate new-onset psoriasis risk in patients with HPV infection.[52] Advantages of using our NHIRD in research have been previously described,[37] including an enormous sample size, population-based data and long-term comprehensive follow-up. Conducting a population-based prospective cohort study is the best way to investigate risk factors, although a retrospective population-based cohort study using insurance data is a suitable and economical alternative. In addition, we also put the frequency of dermatology-related outpatient visits into the multivariate modelling to minimize selection bias, and included the confounding factors of a variety of different infections and drugs. Furthermore, our subgroup analysis illustrated the interaction effect of different age groups.

Several limitations should be considered when interpreting our findings. First, the ICD-9-CM codes for the diagnoses of HPV infection and psoriasis were based on administrative claims data recorded by physicians and hospitals rather than a prospective clinical setting. Inaccuracy may have resulted in misclassification, despite the fact that the Bureau of NHI uses an auditing mechanism to minimize diagnostic uncertainty and misclassification. In addition, the diagnosis of HPV infection in this study was strictly defined by the HPV infection treatment procedure code, thus yielding better diagnostic validity. Only patients with the diagnosis code of HPV infection and receiving cryotherapy treatment for condyloma concurrently would be classified as HPV cohorts. The definition will enhance the accuracy of diagnosis of HPV infection. However, condylomas were recurrent in nature and these patients would have more frequent medical visits than matched controls, so they would be more likely to be diagnosed with psoriasis early. This would result in surveillance bias. However, we have included dermatology-related outpatient visits in our regression models as a confounder, to minimize such bias. Second, data on alcohol, smoking, socioeconomic status and family history were unavailable in the NHIRD, all of which are potential confounding factors.[53–55] Consequently, further analysis in relation to these variables could not be conducted, although chronic obstructive pulmonary disease was used as a proxy variable for cigarette smoking, as has been done in several previous studies.[56–58] Third, almost all the enrollees were Taiwanese. Thus, our findings may not be pertinent to non-Asian ethnic groups. Further studies should therefore be verified in other ethnic groups, in view of possible ethnic and geographical differences in the incidence of HPV and psoriasis. Moreover, HPV vaccination may alter the immune system of the host. However, there are no data about HPV vaccination in our NHIRD database because HPV vaccination is a self-paid service, not covered by NHI, and is therefore not included in NHIRD. Nevertheless, our findings suggested the possible role of HPV infection in the pathogenesis of psoriasis, which increased the understanding of the diseases and led to better care of the patients.

In conclusion, this 12-year population-based cohort study demonstrated a higher risk of psoriasis in patients with previous HPV infection, among both sexes and all ages of patients. The risk was more prominent with increased age. Further studies are required to clarify the underlying biological mechanisms of these associations. We suggest that clinicians be aware of the increased risk of psoriasis in patients with HPV infection and provide appropriate monitoring of the high-risk groups, in addition to treating their HPV infection.

Supplementary Data

Supplementary data are available at *IJE* online.

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Author Contributions

Study concept and design: M-L.C., W-M.K., J-Y.H., Y-M.H., J.C-C.W. Acquisition of data: J-Y.H. Analysis and interpretation of data: M-L.C., W-M.K., J-Y.H., Y-M.H.g, J.C-C.W. Writing (original draft preparation): M-L.C., Y-M.H. Writing (review and editing): M-L.C., Y-M.H, J.C-C.W. All authors were involved in drafting the article or revising it, and all authors approved the final version to be published.

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