

Incidence and outcome of acquisition of human papillomavirus infection in women with normal cytology—a population-based cohort study from Taiwan

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Little is known about acquisition of human papillomavirus (HPV) and its outcome among older women with negative HPV testing and normal cytology. A longitudinal 3-yr follow-up of nested-cohort subjects ($n = 8825$) from a population-based cervical cancer screening study whose Pap and HPV tests were negative at baseline were conducted. Every active HPV-negative ($n = 413$) participant had 12-mo follow-ups of Pap smear and HPV testing. Colposcopy was performed if either HPV-positive or cytology was abnormal. The cytology and histology information of the remaining subjects (passive HPV-negative, $n = 8412$) was obtained from national registry database. Median age of participants was 45 yr (range, 30–73 yr). The incidence of new acquisition was 4.2/100 woman-years. The 3-yr cumulative total HPV acquisition rate was 11.1% (95% confidence interval [CI]: 8.1–14.1). Increased number of sexual partners (≥ 2 vs. 1) of the participant was associated with risk of acquisition (odds ratio [OR]: 5.0, 95% CI: 2.0–12.6) by multivariate analysis. Three cases of \geq cervical intraepithelial neoplasia (CIN) 2 were identified in 3-yr follow-up in active HPV-negative subjects. HPV genotypes in the dysplastic tissue were actually present at baseline samples after reanalysis. From the passive HPV-negative group, only 1 case progressed to CIN2 probably after HPV acquisition. Negative Pap and HPV tests assured a very low risk of developing \geq CIN2 within 3 yr despite incident HPV infection.

Human papillomavirus (HPV) is a causative factor of cervical intraepithelial neoplasia (CIN) and subsequent invasive carcinomas.^{1,2} HPV infection is common in female population, with many women at some age having been infected with HPV.² It is now widely accepted that persistent HPV infection is a prerequisite for progression into CIN and invasive carcinoma.^{3,4} The time from acquisition to development of cervical neoplasia is important for selecting an appropriate screening interval. However, the time lag from infection to disease is not easily determined, because a woman whose test

is positive in her first sample could have been infected long before that sample is taken. Natural history of HPV infection can be best studied from longitudinal cohort studies starting before sexual debut.⁵

Several previous studies, mostly targeted on young women, report incident HPV infection in women with negative HPV tests and normal Pap smears.^{6–9} In a Korean study of 171 university students (mean age, 18.4 yr), the acquisition rates of those starting sexual intercourse or had a new sex partner during study were 30 and 29.4% vs. 12.7% of those remained virginal at a median follow-up of 18 mo.⁶ Winer *et al.*⁷ and Moscicki *et al.*⁸ found that incidence and prevalence of HPV infection among young women (mean age, 20.0 and 19.2 yr, respectively) were usually high. However, these young women usually clear incident HPV in a short time without developing high-grade CIN. A Columbian cohort study found that incidence of HPV infection was 6.2 cases/100 woman-years in older women (aged 15–85 yr), with negative HPV and normal cytology. The study population was still relatively young with an interquartile range of 26–39.2 yr old (median 32.3 yr).⁹ Hence, we need to know more about acquisition of HPV and its outcome among older women.

The aims of this prospective cohort study are (i) to follow up women with normal cytology and negative HPV infection at baseline in a population-based study¹⁰; (ii) to investigate the host and viral factors in relation to incidence and

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