THE HONG KONG COLLEGE OF PATHOLOGISTS
SCIENTIA ILLUMINAT MEDICINAM
香港病理學專科學院

Topical Update – The Hong Kong College of Pathologists

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

Volume 8, Issue 2 **July 2013**

Editorial note:

Human papillomavirus (HPV) infection is of much current interest, with the availability and increasing use of the vaccines in different localities including Hong Kong. In this issue of the Topical Update, Prof. Paul Chan shares the local epidemiology of cervical HPV infection, in aid of formulating strategies to maximize the clinical benefits and cost-effectiveness of HPV-based diagnostic tests and vaccines. We welcome any feedback or suggestion. Please direct them to Dr. Janice Lo (e-mail: janicelo@dh.gov.hk), Education Committee, The Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Epidemiology of Cervical Human Papillomavirus Infection in Hong Kong: Implications on Preventative Strategy

Prof. Paul KS Chan
Professor, Department of Microbiology, Prince of Wales Hospital
The Chinese University of Hong Kong

Introduction

The family *Papillomaviridae* is comprised of a large group of viruses found in many mammalian species. Infection with papillomaviruses can be asymptomatic or results in the development of benign or malignant neoplasia. Cervical cancer is the most important consequence, in terms of disease burden, of human papillomavirus (HPV) infection. To date, the genomic sequences of more than 150 HPV types have been characterized. Of these, more than 40 types can infect the female genital tract, and at least 15 types are epidemiologically linked to cervical cancer. Over the last few years, there has been a vast increase in using HPV DNA detection as an adjunctive or primary tool in cervical cancer screening programmes. Primary prevention of cervical cancers associated with the two most common types (HPV16 and HPV18) can now be achieved by vaccination. A thorough understanding on the epidemiology of cervical HPV infection is essential to maximize the clinical benefits and cost-effectiveness of HPV-based diagnostic tests and vaccines. In this review, some key epidemiological features of HPV infection in Hong Kong are presented to assist the formulation of strategies applicable to Hong Kong.

Prevalence of infection

"How common is cervical HPV infection?" This is always the first question to ask before any advice on vaccination can be made.

Local studies on "well-women" self-referred for cervical screening showed that the prevalence of

cervical HPV infection (defined as having an HPV DNA-positive cervical scrape sample) was around 8% among adult women aged 26-45 years.[1,2] The figure "1 in 12" is recommended for public education. While the studies reported a significant association between number of life-time sexual partners and smoking exposure, the prevalence among those without any recognizable risk factors is high enough to recommend vaccination in general for everyone.

Our patients with systemic lupus erythematosis (SLE) were found to have a higher prevalence of HPV compared to age-matched controls (12% vs 7%); and among those infected, the chance of carrying high-risk types was also higher (11% vs 4%).[3,4] The impaired immunity associated with SLE might have hindered the clearance of high-risk HPV infection and allow progression to cervical intraepithelial neoplasia, which occurred 6 times more frequent in SLE patients compared to controls.[4] Protection against HPV infection is certainly needed for SLE patients. However, safety and efficacy data specific for SLE patients are very limited for the two available vaccines. Maintaining regular cervical screening is therefore very important for SLE patients regardless of their history of vaccination.

Two age-related peaks of infection

Of note, two age-related peaks of infection were observed in Hong Kong (Figure 1). The first peak occurring in young women 26-30 years is expected for a sexually transmitted infection like HPV. The second peak occurring at age 46-50 years could be due to new infections, reactivation of latent infections, or cohort effect. Nevertheless, the phenomenon of having a second infection peak has also been observed in many other countries. This age-related distribution of infection has a few implications to our local practice.

Firstly, the first peak of infection in Hong Kong appears later than those observed in other countries. This "later" peak indicates that the catch-up vaccination programme in Hong Kong should cover a wider age range, say up to 25 years. Secondly, cervical cancer prevention programmes in Hong Kong should target both peaks of infection as each of them is followed by a peak of cancer about 15-20 years later (Figure 1). Offering vaccination to women beyond the age of the first peak of infection (26-30 years) needs more consideration. From the public health point of view, this may not be cost-effective, and the efficacy is expected to be not as good as those clinical trial data collected from young subjects. However, individuals may feel that even some degree of decrease in cancer risk may be worth paying. So far, both vaccines are registered in Hong Kong for women aged up to 45 years. After all, vaccinating adolescent girls before their sexual debut is the best way to achieve maximum clinical benefit.

Thirdly, the fact that the first peak of infection in Hong Kong occurs "later" should be considered when formulating strategy of using HPV-based screening test. Most HPV-positive women who are within the age range of the first peak are having transient HPV infection that will soon be cleared by itself within 1-2 years. At the same time, the chance of having high-grade CIN and invasive cancers within this age group is relatively low. Thus, most HPV positive results are "false-positives", i.e. background noise. The clinical value of HPV test can be increased by restricting the test for women beyond the "background noise", i.e. age above 35 years based on local data.

Age-distribution of intraepithelial neoplasia and invasive cancer

A retrospective study on the age distribution of cervical intraepithelial neoplasia (CIN) and invasive cancers diagnosed in Queen Elizabeth Hospital and Prince of Wales Hospital showed that while there were two age-related peaks of cervical cancer as expected from the two age-related peaks of HPV infection, only one peak of CIN was observed (Figure 1). The absence of a second peak of CIN that one would expect to observe among women aged 51-65 years was most likely to be a consequence of poor screening uptake in this group of women who may perceive that their risk of cervical cancer ceases when they have reached menopause. HPV DNA test which

offers a higher sensitivity and longer lasting negative predictive value is a better choice for this hard-to-reach group.[5] A certain portion of the screening resource in Hong Kong should focus at this group, and the normal upper age limit (65 years) should not be applied to those who have not received a sensitive screening test in the last few years.

HPV type distribution

"What proportion of cervical cancers can be prevented by vaccination?" This is an important question from public health as well as personal perspective, as the current HPV vaccines only contain the two most common high-risk types (HPV16 and HPV18). It is very common to have multiple HPV types detected from a specimen of CIN or invasive cervical cancer. It is believed that only one of the multiple HPV types is the true culprit, but it is difficult to differentiate them in a cross-sectional study. The concept of "attribution" is used, which put a best estimated weight on each HPV type identified. Based on this approach, the estimated attribution of HPV16 and HPV18 among cervical lesions in Hong Kong was found to be: 59.5% for squamous cell carcinoma, 78.6% for adenocarcinoma, 35.9% for CIN3, 18.4% for CIN2, and 7.4% for CIN1.[6] Since adenocarcinoma accounts for about 15% of invasive cervical cancers in Hong Kong, one could expect about 62% of cervical cancers in Hong Kong are covered by the current HPV vaccines. In fact, the overall protection could be higher as there is evidence showing cross-protection for other non-HPV16/18 high-risk types. This portion of additional protection is difficult to estimate, and the bivalent vaccine seems to perform better in this aspect.[7-10]

Unique features in Hong Kong

The fact that HPV16 and HPV18 are the two most common types found in cervical cancers and high-grade CIN is consistently observed across the world. However, the distribution of other high-risk types shows some degree of geographical variation. For instance, the pooled attribution rates of HPV52 and HPV58 to cervical cancer were about 3-5 folds higher in East Asia compared to elsewhere.[11] In Hong Kong, HPV52 and HPV58 ranked the second and third among CIN and invasive cancers.[6] The unusual high disease burden attributed to HPV58 was found to be associated with the circulation of a variant (E7 T20I, G63S) with higher oncogenicity in Hong Kong and the region around.[12,13]

The higher disease attribution of HPV52 and HPV58 in East Asia, including Hong Kong, has important implications. Firstly, HPV-based screening assay should include these two types. Secondly, it is more important for East Asian countries to verify and quantify cross-protection to these two types as conferred by current HPV16/18 vaccines. Thirdly, should any type replacement occur after wide-spread administration of HPV16/18 vaccines, it is easier to detect in East Asian countries provided that comprehensive data on HPV type distribution in pre-vaccine era are available.

Final remarks

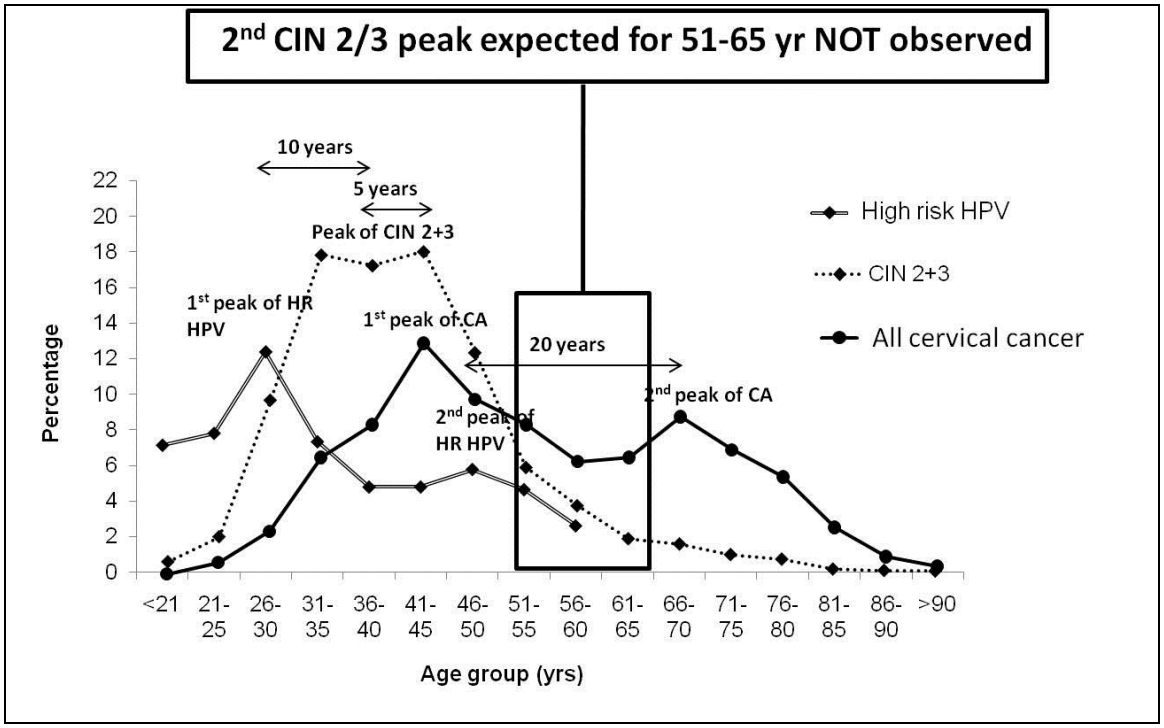
The association between HPV and cervical cancer stands an excellent example how the prevention of a cancer can be enhanced by understanding its root cause. To date, at least 20% of human cancers are etiologically link to viruses, and there could be more to come. Human tumour virology is a rapidly growing research field that deserves attention.

Reference

1. Chan PK, Chang AR, Cheung JLK, Chan DP, Xu LY, Tang NLS, Cheng AF. Determinants of cervical human papillomavirus infection: differences between high and low oncogenic risk types. Journal of Infectious Diseases 2002; 185: 28-35.
2. Chan PK, Ho WC, Wong MC, Chang AR, Chor JS, Yu MY. Epidemiologic risk profile of infection with different groups of human papillomaviruses. Journal of Medical Virology 2009; 81: 1635–1644.
3. Tam LS, Chan AY, Chan PK, Chang AR, Li EK. Higher prevalence of squamous

intraepithelial lesion in Systemic Lupus Erythematosus - association with human papillomavirus infection. Arthritis and Rheumatism 2004; 11: 3619-3625.
4. Tam LS, Chan PK, Ho SC, Yu MM, Yim SF, Cheung TH, Wong MC, Li EK. Natural history of cervical papilloma virus infection in systemic lupus erythematosus – a prospective cohort study. Journal of Rheumatology 2010; 37: 330-340.
5. Chan PK, Picconi MA, Cheung TH, Giovannelli L, Park JS. Laboratory and clinical aspects of human papillomavirus testing. Critical Reviews in Clinical Laboratory Sciences 2012; 49: 117-136.
6. Chan PK, Cheung TH, Li WH, Yu MY, Chan MY, Yim SF, Ho WC, Yeung AC, Ho KM, Ng HK. Attribution of human papillomavirus types to cervical intraepithelial neoplasia and invasive cancers in Southern China. International Journal Cancer 2012; 131: 692-705.
7. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsagué X, Skinner SR, Apter D, Naud P, Salmerón J, Chow SN, Kitchener H, Teixeira JC, Hedrick J, Limson G, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, De Carvalho NS, Germar MJ, Peters K, Mindel A, De Sutter P, Bosch FX, David MP, Descamps D, Struyf F, Dubin G; HPV PATRICIA Study Group. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncology 2012; 13: 89-99.
8. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. New England Journal Medicine 2007; 356: 1915-1927.
9. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, Hedrick J, Jaisamrarn U, Limson G, Garland S, Szarewski A, Romanowski B, Aoki FY, Schwarz TF, Poppe WA, Bosch FX, Jenkins D, Hardt K, Zahaf T, Descamps D, Struyf F, Lehtinen M, Dubin G; HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009; 374: 301-314.
10. Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, Koutsky LA, Tay EH, Garcia P, Ault KA, Garland SM, Leodolter S, Olsson SE, Tang GW, Ferris DG, Paavonen J, Steben M, Bosch FX, Dillner J, Joura EA, Kurman RJ, Majewski S, Muñoz N, Myers ER, Villa LL, Taddeo FJ, Roberts C,Tadesse A, Bryan J, Lupinacci LC, Giacoletti KE, Sings HL, James M, Hesley TM, Barr E. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. Journal of Infectious Diseases 2009; 199: 926-935.
11. Chan PK. Human papillomavirus type 58: the unique role in cervical cancers in East Asia. Cell and Bioscience 2012; 2: 17.
12. Chan PK, Lam CW, Cheung TH, Li WWH, Lo KWK, Chan MYM, Cheung JLK, Cheng AF. Association of human papillomavirus type 58 variant with the risk of cervical cancer. Journal of the National Cancer Institute 2002; 94: 1249-1253.
13. Chan PK, Zhang C, Park JS, Smith-McCune KK, Palefsky JM, Giovannelli L, Coutlée F, Hibbitts S, Konno R, Settheetham-Ishida W, Chu TY, Ferrera A, Alejandra Picconi M, De Marco F, Woo YL, Raiol T, Piña-Sánchez P, Bae JH, Wong MC, Chirenje MZ, Magure T, Moscicki AB, Fiander AN, Capra G, Young Ki E, Tan Y, Chen Z, Burk RD, Chan MC, Cheung TH, Pim D, Banks L. Geographical distribution and oncogenic risk association of human papillomavirus type 58 E6 and E7 sequence variations. International Journal of Cancer 2013; 132: 2528-2536.

Figure 1. Age distribution of cervical HPV infection, cervical intraepithelial neoplasia and invasive cancers in Hong Kong.



The details of this study can be found in reference 6.