

Oncogenic Human Papillomavirus Infection: Epidemiology in Local High-Risk Women

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ABSTRACT

Human papillomavirus (HPV) is a common cause of viral infection of the epithelial tissues of skin and mucous membranes. While cutaneous wart is the commonest clinical manifestation of HPV infection, it is also known to cause genital tract malignancies. Lately, 48.3% of female sexually transmitted disease (STD) clinic attendees were found to have HPV and 24.0% of them were infected by oncogenic types. Identification of associated risk factors for oncogenic HPV is an important area in future studies.

Keywords: High-risk HPV, high-risk women, human papillomavirus, oncogenic, STD

INTRODUCTION

Human papillomavirus (HPV) has a wide disease spectrum ranging from benign common warts to cervical malignancies. Over 100 types of HPVs have been identified so far. The viruses cause specific diseases at their favourite sites of infection. HPV types 1, 2 and 4 cause common warts, while HPV types 16, 18, 31, 33 and 58 tend to affect lower genital tracts and are more persistent,¹ possessing moderate to high malignant potential.² This group of HPV is considered to be oncogenic.

In Hong Kong, genital wart is the third commonest sexually transmitted disease (STD) with a total of 3,316 cases reported by the government Social Hygiene Service in 2001. Its incidence remained high in the past ten years.³ Although cervical smear examination is offered to all new cases of genital wart at the female STD clinics in Hong Kong, and repeated annually for those with high-risk sexual behaviours, the epidemiology of oncogenic HPV among the STD clinics attendees is unknown.

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This article presents an update of the epidemiology of oncogenic HPV infection in local high-risk women. Virology, pathogenesis and diagnosis of oncogenic HPV are also discussed.

VIROLOGY

HPVs are small deoxyribonucleic acid (DNA) viruses containing approximately 7,900 base pairs. Recent molecular biology techniques using polymerase chain reaction (PCR) and DNA probes have facilitated HPV typing and characterization. By definition, each type is defined by having less than 90 percent DNA base-pair homology with any other identified HPV type.⁴

As mentioned earlier, several types of HPVs with different phenotypes have been associated with specific types of cancer. The so-called high-risk HPV types 16 and 18 are more frequently isolated in cervical cancer tissue than either intermediate (31, 33, 35, 39, 45, 51, 52, 58) or low-risk types (6, 11, 42, 43, 44).⁵ However, not all infections with HPV type 16 or 18 progress to cervical cancer. Within the single HPV type 16, specific variants are associated with different oncogenic potential.⁶

MOLECULAR PATHOGENESIS OF HPV

The HPV genome encodes DNA sequences for six early (E) proteins associated with viral gene regulation

and cell transformation, two late (L) proteins which form the shell of the virus, and one region of regulatory DNA sequences.^{7,8} Our understanding on the pathogenesis of malignant cells is incomplete, but the two most important HPV proteins in this process are E6 and E7. The continued expression of both of these proteins appears to be required to sustain a malignant phenotype.⁹ E6 and E7 act synergistically to transform cells, although E7 is capable of transforming cells in isolation.¹⁰

The different HPV types are characterized by genotypic variations in the DNA base-sequences of E6 and E7. It is these genotypic differences that permit stratification of the virus oncogenic phenotype into high-, intermediate-, and low-risk types. For example, the E7 protein of HPV 16 is more oncogenic than the E7 protein of HPV 6.

Both E6 and E7 proteins are consistently expressed in HPV-carrying anogenital malignant tumours, and they act in a cooperative manner to immortalize a wide variety of cell types.¹¹ At the molecular level, the ability of E6 and E7 proteins to transform cells relates in part to their interaction with two intracellular proteins, *p53* and retinoblastoma (*Rb*), respectively. In brief, these proteins suppress abnormal cell growth and proliferation.

Co-infection with HIV may directly promote HPV-associated oncogenesis at the molecular level. For example, in vitro studies suggest that the HIV-encoded Tat protein may enhance expression of the HPV E6 and E7 proteins.¹²

DIAGNOSIS

Because of the malignant association of some HPV types, early diagnosis is crucial. However, the diagnosis of oncogenic infection is usually not that straightforward and clinical diagnosis is often too late. Before the development of HPV typing technology, the diagnosis of oncogenic HPV infection can only be reflected by the identification of koilocytes.

The detection of HPV is facilitated by recent advances in molecular biology. There are now several methods for detecting the presence, quantity and type of HPV infection including in-situ hybridization (ISH), southern transfer hybridization (STH), hybrid capture (HC), dot blot (DB), filter hybridization (FH), and PCR.

These tests can be grouped according to their method of detection of DNA. PCR works by target amplification, HC by signal amplification and ISH/FH/DB and STH require no amplification. The principles of these tests are briefly discussed here.

In-situ hybridization

ISH is performed directly on tissue, which allows localization of the target sequences and correlation with the clinical appearance. DNA probes are applied directly to the permeabilized cells. However, this method is less sensitive than PCR or HC and is more labour intensive. There is currently no clear clinical indication for the routine use of ISH.

Dot blot, filter hybridization and Southern transfer hybridization

DB, FH, and STH all require binding of target DNA to filter supports before hybridizing with DNA probes. STH differs from the other methods by the addition of an electrophoretic separation step that increases the specificity of the test by the use of restriction endonucleases for each HPV type before applying the probe. All of these tests produce qualitative results. These tests are occasionally used in research settings and are not used for clinical indications.

Hybrid capture

HC requires long single-stranded, or multiple oligonucleotide RNA probes to hybridize with the whole HPV genome in solution. RNA-DNA antibodies conjugated to alkaline phosphatase are then added to the hybrid, which bind in a non-sequence dependent fashion. The detection method uses a chemiluminescent reaction to provide a semi-quantitative result.

HC is the only contemporary method for HPV testing of the cervix approved by the Food and Drug Administration (FDA).

Polymerase chain reaction

Target DNA is selectively amplified by the action of DNA polymerase on specific primers that can then be detected by DB or STH. PCR can detect between 10 to 100 DNA molecules in a specimen and is the most sensitive method available. By combining the sensitivity of PCR with the use of specific primer sequences,

individual HPV types can be isolated from a variety of clinical specimens and correlated with the disease process present. Like the other HPV detection methods, it is not used in clinical settings.

Others

Serologic techniques to diagnose HPV infection are available only in research laboratories and have been utilized primarily to conduct epidemiological studies.

HOW COMMON IS ONCOGENIC HPV IN LOCAL HIGH-RISK WOMEN?

Since the transmission of oncogenic HPV is mainly through sexual contact, it is expected that the prevalence of oncogenic HPV in those who practise high risk sexual behaviour such as commercial sex workers, and human immunodeficiency virus-1 (HIV-1) infected individuals should be high. Nevertheless, there is a lack of local data.

In a cross-sectional study conducted by Ngan et al nine years ago,¹³ 207 women attending a local STD clinic were tested for cervical HPV infection. Twenty-six (12.6%) patients were found to have HPV (types 6, 11, 16, 18, 31, 33, 35) from the cervical smear by DNA filter in-situ-hybridization. The prevalence of the high- and low-risk HPV types was not further elaborated.

Recently, an epidemiological study was conducted in two local STD clinics and one HIV clinic under the Department of Health (the author's unpublished data). Two hundred and forty-five female attendees were tested for HPV. Twenty-nine different HPV types were identified. Some patients were infected with multiple types of HPV. Types 16, 18, 52 were the first three most common oncogenic HPV found. The low-risk HPV types detected were 6, 11, 42, 53, 54, 66 and 84. Some rare HPV types: 61, 62, 70, 72, CP8304, JC9710 and L1AE9, with unknown clinical significance were noted. Overall, 48.3% of them had HPV infection. Oncogenic and low-risk HPV types were 24.0% and 12.8% respectively. Eleven of 58 oncogenic HPV positive cases were co-infected with HIV-1, but no low-risk HPV was detected in this group of patients. HIV-1 was found to significantly increase the risk of oncogenic HPV positivity.

Although the tests involved in both studies were different and direct comparison could not be made, the

latest findings were actually alarming as they indicated a rising trend of HPV infection in local high-risk women. In fact, this phenomenon seems to parallel to the increasing incidence of other STDs in the past few years in Hong Kong.³ This may be secondary to the fact that in our more westernized society, people start to have sex at an early age, have more casual sex and a greater number of sexual partners.¹⁴

Interestingly, low-risk HPV types were less commonly found than high-risk HPV types in these high-risk women. It is postulated that because oncogenic HPV types are less infectious while causing more persistent infection than their low-risk counterparts; repeated exposure is needed for the infection to occur.

Age was inversely associated with HPV infection. Young females were more likely to harbour HPVs, and all oncogenic HPVs were found below the age of 61 in the recent study. This phenomenon reflects the natural self-limiting course of the disease. It is of note that the number of low-risk and oncogenic HPV cases peaked between age 31 and 60. This may be due to re-infection as a result of continuing high-risk sexual behaviour in this group of patients.

DISCUSSION

The utmost importance of oncogenic HPV infection is its association with lower genital tract malignancies, and among them cervical malignancy has the strongest aetiological link.^{1,2,15} As molecular diagnosis of HPV has become available, we are now equipped with another powerful tool in cervical cancer screening. However, the interpretation of asymptomatic oncogenic HPV infection in young females is difficult. And the cost of the test is also a major obstacle to its wider use.

As it is not feasible to adopt HPV typing as a primary screening test for cervical dysplasia for every individual attending the STD clinics, a better understanding of local situation is the first essential step to define the best strategic role of HPV testing. High-risk sexual behaviour, genetic background, concurrent genital tract infections and environmental factors may have significant bearing on HPV infection and its outcome. Thus identification of risk factors associated with oncogenic types infection, in order to select patients for secondary screening would be a more cost-effective

strategy, and this is an interesting aspect of ongoing research.

Lastly, the detection of such oncogenic HPVs may guide us towards monitoring the disease closely and provide prompt intervention once cytological abnormality is found.

Learning points:

Oncogenic HPVs are associated with anogenital malignancies, but its prevalence varies widely in different cohorts and places. 24% of local female STD clinic attendees were found to have this infection. HIV-1 seropositivity significantly increases the risk of occurrence of oncogenic HPV. At present, HPV testing is used as an adjunct for cervical cancer screening.

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