Human Papillomavirus:
Prevention and Treatment

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Presented at Bug Day, October 2007.

Interest in infection caused by the human papillomavirus (HPV) has arisen as it is now considered a vaccine-preventable infection. The media have raised concern as to whether mass vaccination strategies of young girls is warranted to prevent cervical cancer. However, HPV has also been implicated in a broad spectrum of disease processes in humans. Its manifestations range from common skin warts to cervical neoplasms and squamous cell carcinoma of the anogenital tract.

Infection with the HPV is common, manifesting as common warts (verruca vulgaris) in approximately 10% of children and young adults. The HPV is also considered to be the most common sexually transmitted infection (STI), with a prevalence in Canada of 10.8% to 29% among selected female populations and as high as 42% among adolescents and young adults. While most genital HPV infections are asymptomatic, they still carry a heavy burden of illness due to their potential to develop into genital warts (*Condyloma acuminatum*) and their oncogenic potential.

What is HPV?

Over 100 HPV types have been described. They consist of noneveloped virus particles consisting of double-stranded circular DNA, wrapped in a protein shell. These viruses infect differentiating epithelial cells of skin or mucosae. The cutaneous group infects only the skin and individual types are associated with specific clinical manifestations. The mucosal group infects the body's mucous membranes, such as the anogenital tract, the oral cavity and the respiratory tract. There are at least 40 HPV types able to infect the genital tract. Types 16 and 18 are estimated to account for 70% of cervical cancers worldwide and are considered to be the most prevalent high-risk oncogenic strains of the virus. Strains considered low risk for oncogenic potential, such as HPV Types 6 and 11, are associated with the development of external genital disease.

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What is the connection between HPV and cervical cancer?

Immunosuppression increases the risk of persistent infection with the HPV. Persistent (> 12 months with the same HPV type) infection with high risk HPV types is considered a necessary factor for invasive cervical cancer. Although necessary, persistent infection does not appear to be a sufficient condition and co-factors include:

- smoking,
- multiparity,
- long-term (greater than five years) use of oral contraceptives,
- coinfection with other STIs and
- inflammation.

Progression from dysplasia to invasive cancer averages 10 years, although high-risk types (HPV Types 16, 18, 31 and 45) progress in as little as three-to-six years.

How is HPV diagnosed?

Visible on routine exam, genital warts can be single or multiple and appear as soft, moist, flesh-coloured swellings of the skin. They can vary in size and may be raised, flat, or have the appearance of cauliflower. They can also be found internally on the vulva, perineum, perianal skin, penis and scrotum or internally in the vagina, urethra, anus and mouth. Colposcopy is required to assess vaginal and cervical lesions. Pap smears prepared from cervical scrapings are examined for cytologic evidence of a HPV infection and should include comments on:

- The adequacy of the sample
- A general categorization statement
- A descriptive diagnosis addressing:
  - Benign or reactive changes
  - Low- or high-grade intraepithelial cell abnormalities
  - Glandular cell abnormalities
  - Presence of malignant cells

Polymerase chain reaction, hybridization *in situ* and hybridization assay are techniques that have been used to diagnose and type HPV infection in the laboratory. These can be used in combination with pap smear screening to increase sensitivity, to help evaluate the significance of atypical smears of undetermined significance and to guide further evaluation or treatment.

How are infection with HPV and its sequelae managed?

Since up to 90% of anogenital HPV infections will resolve spontaneously after two years, expectant treatment is appropriate. However, cryotherapy or imiquimod 5% cream can also be utilized for quicker results. With regards to cervical dysplasia, low-grade lesions have a 60% regression rate and a 15% progression rate to high-grade abnormality; thus, they can be treated conservatively or with surgical excision. High-grade lesions should be treated aggressively with destruction or excision of the transformation zone of the cervix.

HPV is considered to be the most common STI.

Can HPV infection and its sequelae be prevented?

Currently, avoidance of contact with infectious lesions is the only effective preventive measure available. While this can include the use of barrier method contraceptives to reduce the risk of contracting genital warts and other HPV-related diseases of the genital tract, this method has limited effectiveness. Although not preventative of the HPV infection, screening for cervical dysplasia by regular pap smears remains an excellent method for reducing HPV-related morbidity. Comparative studies have shown up to a 10-fold decrease in cervical cancer mortality in populations undergoing regular screening.

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The guidelines for screening are:

- Initiation of pap smear screening at 18-years-of-age or at onset of sexual activity and continuing until menopause
- Annual screening for high-risk patients (*i.e.*, smoking, multiparity, early first intercourse, multiple and/or high-risk partners, immunosuppression)
- Two-to-five year interval screening for low-risk patients with three consecutive negative annual pap smears
- Patients with pap smears showing atypical cells of undetermined significance should undergo HPV testing
- Patients with smears showing low-grade or high-grade quamous intraepithelial lesions, carcinoma *in situ* or positive HPV testing should be referred to a gynecologist for colposcopy

Participation of Canadian women in pap screening appears to be relatively high. In the 2003 Canadian Community Health Survey, 79% of eligible Canadian women aged 18 to 69 years reported having had a pap test in the previous three years.

However, screening does have limitations, even for those regularly screened. Conventional cytology is limited, as it depends on the abilities of both the clinician and the cytologist to collect an adequate specimen and interpret it correctly. Thereafter, follow-up and management need to be sufficient and appropriate.

HPV vaccinations

A quadrivalent HPV vaccine is now approved for use in Canada. It contains the L1 capsid protein of four HPV strains (Types 6, 11, 16 and 18). The vaccine is given as three separate 0.5 mL doses. It should be administered as an intramuscular injection in the deltoid muscle or the anterolateral upper thigh using a zero, two and six month schedule.

The efficacy of this HPV vaccine was studied in four clinical trials in women 16- to 26-years-of-age. These were randomized, double-blind, placebo-controlled studies. The study populations were geographically widespread; subjects were enrolled in North America, Latin America, Europe and the Asian-Pacific regions. A recent model estimated that the number of 12-year-old females that needed to be vaccinated in order to prevent an episode of genital warts was eight and 324 would need to be vaccinated to prevent a case of cervical cancer. However, this was the most generous estimate of the vaccine based on the assumption that the vaccine's efficacy is 95% and that it provides life-long protection. Because these are estimates, it may be likely that a booster dose will be required at some time in the future.

Canadian guidelines from the National Advisory Committee on Immunization recommend the following regarding the HPV vaccination:

- Females between the ages of nine and 26 should be vaccinated, regardless of prior sexual activity or HPV infection
- Females > 26-years-of-age may still receive benefit, but no recommendations have been made at this time
- Not recommended for females less than nine-years-of-age
- The efficacy of the vaccine in males is unknown and therefore not recommended
- Not recommended in pregnant females
- There are no specific recommendations for those who are immunocompromised as it may not be effective

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