Role of the human papilloma virus in the development of cervical intraepithelial neoplasia and malignancy

A M Jastreboff, T Cymet

Human papilloma virus (HPV) is a public health problem as a sexually transmitted disease and as a critical factor in the pathogenesis of various cancers. The clinical manifestations, epidemiology, and virology that are critical to understanding the process of cervical dysplasia and neoplasia are reviewed. A discussion of the cervical transformation zone and the classification of cervical dysplasia and neoplasia leads into the importance of the Papanicolaou smear in prevention of potentially devastating sequelae of this virus. The role of the immune system in the progression of the disease and how it relates to vaccines, as well as treatment and prevention of HPV, are reviewed.

Viruses, from the Latin “slime” or “poisonous juice” were not understood as unique entities until the 19th century. The major development that lead to understanding viruses occurred in 1884 when Chamberland created a filter with pores small enough to retain bacteria, yet large enough for viruses to pass through. A century later, in the 1950s, a variety of viral particles were documented by electron microscopy.

Papilloma virus was initially isolated from cottontail rabbits in 1933. In 1935 it was discovered that papillomas induced by papilloma virus had the potential to transform into malignant processes. Squamous cells that developed from human papilloma virus (HPV) lesions were noted in 1956. The authors called these cells koilcytotic atypia or koilocytosis, meaning “hollow”, from the Greek word koilos. Before the invention of cloning techniques in the 1970s, investigation of HPV was difficult since the virus does not grow in culture. Zur Hausen cloned the potentially malignant HPV 16 in the 1980s. By the end of the 20th century, over 100 types of HPV were identified.

HPV is recognised as a public health problem for its role as a sexually transmitted disease and also as a critical factor in the pathogenesis of various cancers. HPV is a crucial element in the development of cervical cancer, the third most common malignancy in women. The cause and effect relationship between HPV and cervical cancer is compelling. HPV DNA has been found in 90% of cervical cancer and 50% of vulvar cancer. Fifty percent of young, sexually active women are infected with HPV types that may promote the development of cancer. In fact, HPV 16 and 18 have been classified as “carcinogenic” by the World Health Organisation International Agency for Research on Cancer.

CLINICAL PRESENTATION
HPV infection is initially asymptomatic and transmission between people occurs before overt expression of the virus is seen or felt. Clinically, HPV infects the basal cells of the epithelium of skin and mucous membranes. Because HPV may affect sites where there are epithelial cells, infections have been documented in the oral mucosa, oesophagus, larynx, trachea, conjunctiva, as well as genital and anal areas. HPV has not been identified in gastrointestinal mucosa.

Infection may present in various ways. Latent HPV may be asymptomatic identified only by molecular biology techniques, or subclinical, seen on colposcopy. The virus may present as hyperplastic, hyperkeratotic warts or dysplastic lesions that may undergo neoplastic transformation.

Non-genital warts may be passed on by fomites or direct contact with even a small area of broken skin. Alternatively, genital warts are passed on through direct contact with the lesion. Genital warts in females appear initially on the posterior introitus and adjacent labia; the warts then spread to the vulva, and eventually to the vagina and cervix. Genital warts can cause intense discomfort with associated pruritis, bleeding, and secondary infection caused by superficial injury due to scratching.

Perhaps more important than the initial wart lesions that recur over the years, are the consequences of the latent infection with this virus—that is, dysplasia, neoplasia, and cervical cancer that occurs in a significant portion of these women. Important questions to ask include: Why do some women carry HPV for years with minimal sequelae while others are afflicted with carcinoma in situ? How can we prevent the spread of this potentially fatal virus? What is the role of the Papanicolaou (PAP) smear in the prevention of the more detrimental outcomes of this virus?

EPIDEMIOLOGY
Just under half of the 100 HPV types identified infect the genital tract. Of these viral types only a small number have been detected in malignant lesions—that is, HPV 16, 18, 26, 27, 30, 31, 33–35.

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; HSIL, high grade squamous intraepithelial lesions; LSIL, low grade squamous intraepithelial lesions; PAP, Papanicolaou (smear)
CERVICAL DYSPLASIA

The cervical transformation zone is of particular significance as it is the location where cervical dysplasia most often occurs. 

The cervix is made up of two histologically unique parts. The endocervix, which is predominantly comprised of columnar cells, and the exocervix, which is made up of squamous cells.

The transformation zone, also called the squamocolumnar junction, is the area of the cervix where the exocervix and endocervix meet. Starting during puberty, the columnar cells of the endocervix slowly transform into squamous cells, thus it is said that the exocervix "moves in" towards the cervical os.

Classification of dysplastic lesions is also an important issue. Depending on the time of publication, various sources use different descriptions and classification systems. In the 1940s, cervical abnormalities were described by Papanicolaou who devised a five class system (I to V), which included mild, moderate, and severe dysplasia, carcinoma in situ, and cancer. In the late 1960s, Richart created a new classification of dysplasia where changes were termed cervical intraepithelial neoplasia (CIN) I, II, and III.

It was thought that a progression of events occurred as patients advanced sequentially through these stages on a continuum from CIN I to carcinoma in situ.

As cervical dysplasia was studied more closely it became evident that it did not follow a straightforward progression. With a diagnosis of CIN I, about 1% progress to invasive carcinoma. The transformation from CIN I to CIN II occurs very quickly, with about 5% on CIN II progressing to invasive cancer. Evidence indicates that CIN III does in fact have a significant risk (12%) of progressing to invasive carcinoma if left untreated. The treatment for CIN II and III is essentially the same and, therefore, clinically did not warrant separate categories. In addition, this system of classification was not utilised uniformly throughout academic institutions and other more descriptive classifications continued to be used. A uniform classification system was needed for algorithms of treatment protocols and for groupings in scientific studies.

Table 1  The Bethesda system for rating cytology

<table>
<thead>
<tr>
<th>Bethesda system</th>
<th>Description</th>
<th>Papanicolaou classification</th>
<th>Cervical intraepithelial neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>Atypical squamous cells of undetermined significance Low grade squamous intraepithelial lesions</td>
<td>Squamous atypia</td>
<td>CIN I</td>
</tr>
<tr>
<td>LSIL</td>
<td>Mild dysplasia, koilocytic or condylomatous atypia</td>
<td>Papanicolaou class II</td>
<td>CIN I</td>
</tr>
<tr>
<td>HSIL</td>
<td>Moderate to severe dysplasia</td>
<td>Papanicolaou class III</td>
<td>CIN II</td>
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<td></td>
<td></td>
<td>Papanicolaou class IV</td>
<td>CIN III</td>
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<tr>
<td></td>
<td></td>
<td>Papanicolaou class IV</td>
<td>Carcinoma in situ</td>
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</table>
(ASCUS), low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL), and carcinoma in situ (see table 1).\(^{1,2,10}\)

**ROLE OF THE PAP SMEAR**

The Papanicolaou smear is based on the work of a Greek physician, George N Papanicolaou.\(^{19}\) Papanicolaou first began to study normal and abnormal vaginal cytology in the late 1920's.\(^{19}\) He published his findings with Herbert Traut, a gynecological pathologist, in 1941 in *The diagnostic value of vaginal smears in carcinoma of the uterus.*\(^{20}\) Named after its creator, today the vaginal smear is known as the PAP smear.

Unfortunately, there has never been an evaluation of PAP smear screening in a randomised control trial.\(^{21}\) The data regarding screening is based on differences seen geographically over the time that the PAP smear has been used.\(^{22}\) Over-all, the PAP has decreased the rate of stage II squamous cell carcinoma in women that are regularly screened but has not been shown to decrease the rate of adenocarcinoma or adenocarcinoma.\(^{16}\) The American College of Obstetrics and Gynecology recommends that PAP smear screening should start at age 18 or when the woman becomes sexually active.\(^{23}\) The recommendation is to continue annual screening until three normal PAP smears have been obtained; at this time, if the physician prefers, the women may be tested less frequently.\(^{24}\) There is no consensus as of yet to what age to stop PAP smear screening, but since cervical cancer may be diagnosed postmenopausally, individual risk factors must be taken into consideration.\(^{24}\) The American Academy of Family Physicians recommends discontinuation of PAP smear screening after age 65 if the woman does not have a history of positive PAP smears.\(^{24}\) In women who have had hysterectomies the incidence of cervical cancer is extremely low. Therefore if the uterus was removed for benign reasons, the cervical epithelium was completely removed, and the woman had no previous abnormal PAP smear findings, screening may be discontinued.\(^{25}\)

**ROLE OF THE IMMUNE SYSTEM IN THE PROGRESSION OF HPV TO CERVICAL DYSPLASIA**

Why does cervical dysplasia undergo a malignant transformation in some women but not others? It appears that the immune system plays a significant part in the regression or progression of cervical dysplasia. One study suggested that CD8 cells against HPV antigen were more prevalent in women without cervical dysplasia than in women with cervical dysplasia.\(^{26}\) Also antibody levels in persistent HPV are increased in chronic HPV infection and there is evidence of T-cell recruitment to the site of HPV infection.\(^{27}\) In addition, CD8 tumour infiltrating lymphocytes have been found in cervical cancer.\(^{28}\) To examine the role of the immune system in HPV, scientists have examined immunocompromised women with HIV. One such study, published in March 2001, confirmed that women infected with HIV had an increased incidence of squamous intraepithelial lesion due to an increased risk of infection with HPV as well as due to the depressed immune states.\(^{29}\) In this study, in women infected with HIV the prevalence of ASCUS was found to be 1.8 times greater and squamous intraepithelial lesion was 3.9 times greater than that of women who did not have HIV.\(^{30}\) It is evident in this patient population that there is in fact a more rapid and increased incidence of HPV caused cervical dysplasia and therefore, a depressed immune system may lead to decreased ability to suppress the progression to dysplastic lesions.

**TREATMENT**

The treatment of cervical dysplasia may be complicated, reflecting differences in algorithms used at various institutions and distinct treatments for varied degrees of dysplasia. For example, in a compliant patient with ASCUS and minimal risk factors it may be suggested to repeat the PAP smear with-in three to six months.\(^{31}\) If the repeat PAP smear is positive the patient should undergo colposcopy.\(^{32}\) If compliance is questionable in a patient with ASCUS, the patient may undergo colposcopy with an endocervical biopsy without obtaining the repeat PAP smear beforehand.

LSIL may be observed or excised, where as HSIL should be biopsied using colposcopy.\(^{33}\) Further treatment of HSIL includes various procedures to obliterate the potentially malignant cells. Cryosurgery is the ablation of the dysplastic lesion, using cold in the form of liquid nitrogen. Laser ablation is the use of heat to burn away the dysplasia. Surgical excision is the process of making a cone biopsy and actually removing a wedge of the cervix. There are also medical treatments that include the use of topical antimetabolites (5-fluorouracil) or interferon. It is important to understand that each of these forms of treatment may at best prevent the progression of cervical dysplasia to cancer but none of these treatments are a cure for the virus itself. Therefore, it is important to discuss prevention, the only known “cure” for HPV infection.

**PREVENTION**

First, it is important to counsel patients on the environmental risk factors that may predispose them to becoming infected with the HPV virus. If a patient decreases the number of sexual partners she has, she will then decrease the probability of becoming infected with HPV. In addition, although HPV may be spread even if a barrier method is used, the use of barrier contraceptives decreases the probability that the patient will become infected. Annual PAP smears have become a crucial tool in decreasing mortality from cervical cancer. Mortality from cervical cancer has decreased by over 40% since the start of PAP smear screening in the United States.\(^{34}\) This decrease in mortality occurs because the lesions are detected early on when they are still treatable.

Promising future forms of treatment are various HPV vaccines. There are several forms of HPV vaccines/cervical cancer vaccines that are currently under investigation. The transfer of cytotoxic T-lymphocytes has been successful in eliminating certain tumours in mice.\(^{35}\) Peptide based vaccines have been shown to activate antigen specific cytotoxic T-cells.\(^{36}\) Virus-like particles, for example containing only the major capsid protein, may potentially be used as a prophylactic vaccine and have shown to produce humoral immunity in mice.\(^{36}\) Vaccine with a vector encoding for HPV has produced humoral and cell mediated responses in mice which DNA vaccines have shown a similar response in rabbits.\(^{36}\) Of these studies are still at the level of animal based models therefore it may be years before scientists create what would be the ideal HPV vaccine; one which would have preventative as well as therapeutic faculties.

**CONCLUSION**

In conclusion, HPV is a significant public health problem as a sexually transmitted disease and more importantly as a crucial contributing factor to the development of cervical cancer. Consequently, PAP smear screening has become a crucial part of women’s health as early detection of cervical dysplasia has significantly reduced the morbidity and mortality of cervical cancer in the United States. Therefore, it is not only necessary for physicians to continue PAP smear screening on women who present for the “annual well women exam”; but it is also vital to target women who present to the clinic for other health problems; women who would otherwise not be screened for potentially devastating sequelae.

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