THE ROLE OF HUMAN PAPILLOMAVIRUS IN SCREENING FOR
CERVICAL CANCER

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To the faculty of Washington State University:

The members of the committee appointed to examine the ICNE Research requirements and manuscript of Susan E. McFadden find it satisfactory and recommend that it be accepted.

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THE ROLE OF HUMAN PAPILLOMAVIRUS
IN SCREENING FOR CERVICAL CANCER

Abstract

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Chair: Lorna Schumann

Cervical cancer is the second most common type of cancer found in women worldwide. It is the leading form of cancer death in most developing countries. In 1998, over 12,000 women in the United States were diagnosed with uterine cervical cancer, and 4,800 women died of the disease. Cervical cancer is a preventable disease caused by certain forms of the human papillomavirus (HPV). Current screening protocols center on the use of the Papanicolaou (Pap) smear, which was developed in the 1940’s. In areas where this test is routine and available, morbidity and mortality rates have dropped dramatically. Many women throughout the world and in underserved regions of the United States do not have adequate access to the Pap smear technology. As long as women worldwide and in the U.S. continue to die needlessly of cervical cancer, more comprehensive and accessible screening methods must be explored.

Because the Pap smear is a screening tool, not a diagnostic tool, further studies must be done to identify the actual nature of discovered abnormalities. Of particular concern is the classification of atypical squamous cells of undetermined significance (ASCUS), which may simply indicate inflammation, or may be the first indicator of serious pathology. The follow-up of ASCUS Pap smears with HPV screening will allow for a clarification of the best approach to treatment.
This article will explore the options for effectively screening for cervical cancer. Screening options include HPV identification, cytological screening, or a combination approach, including the use of visual examination with the use of colposcopy. The advantages and disadvantages of each of these three approaches have been analyzed, including their accuracy, cost, and benefit. Current pathophysiology, diagnostic criteria, treatment approaches, and patient preparation and education related to cervical cancer screening and prevention are also included. A screening algorithm, supported by a review of the literature, has been proposed.
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Introduction

Cervical cancer is the second most common type of cancer found in women worldwide. It is the leading form of cancer death in most developing countries (Richart, 1995). With the advent of strong screening protocols which center on the use of the Papanicolaou (Pap smear) test, the cervical cancer death rate in comparison to other cancer deaths in the United States has dropped from over 30% in 1930 to less than 8% in 1994 (Cancer Statistics, 1998). Similar drops have been seen in other developed countries where the Pap smear is readily available.

Since the development of the Pap smear in the 1940’s, screening has centered on the use of the Pap smear for identification of abnormal pre-invasive cells, known as dysplasia, which are the precursor cells to cervical cancer. Where Pap smear screening has been properly implemented, cervical cancer death rates have dropped 50 to 70% (Cuzick, 1998). However, in a retrospective review of 312 labs, Montes, Cibas, DiNisco, and Lee (1999) found that false-negative Pap smears in women with subsequent pathology were identified in 19.7% of the cases reviewed.

Despite formal national screening programs, over 12,000 women in the United States were diagnosed with cancer of the cervix in 1998, and 4,800 women died of the disease (Cancer Statistics, 1998; Canavan, 2000). Many women throughout the world and in underserved regions of the United States do not have adequate access to the Pap smear technology, and it is not a perfect diagnostic tool for those with access. As long as women continue to die needlessly of
cervical cancer, more comprehensive and accessible screening methods must be explored.

Because the Pap smear is a screening tool, rather than a diagnostic tool, further studies must be done to identify the actual nature of discovered abnormalities. Of particular concern is the classification of atypical squamous cells of undetermined significance (ASCUS). This cytological abnormality may simply indicate inflammation, or it may be the first indicator of serious pathology (Apgar & Botzman, 1999). Because of the potential for underlying malignancy, many experts recommend following all ASCUS results with a colposcopy. This approach is often impractical and expensive, as many of these early irregular smears are benign (Jones, 1995). Other approaches to dealing with minor Pap abnormalities include serial repeat Pap smears and testing for the human papillomavirus (HPV), the virus that has been implicated in the evolution of cervical cancer.

Although a variety of factors may cause cervical dysplasia, the primary risk of dysplasia advancing to cervical cancer is human papillomavirus (Kjellberg et al., 1998). Van Muyden et al., (1999) identified HPV in 100% of their study population of women with invasive cervical cancer. However, Tabrizi et al., (1999) found HPV DNA in only 90% of cases of cervical cancer. Those women with HPV-negative carcinoma had a better prognosis, leaving Tabrizi et al., to conclude that HPV-negative cancers are different from those with detectable HPV-DNA. Van Muyden et al., theorize that the failure to find HPV in cervical carcinoma simply indicates a lack of sensitivity of the HPV testing method. This
strong correlation between HPV and cervical cancer opens the door for new methods of screening, namely through the identification of high-risk HPV.

This article will explore the options for effectively screening for cervical cancer. Screening options include HPV identification, cytological screening, or a combination approach, including the use of visual examination with the use of colposcopy. This article will analyze the advantages and disadvantages of each of the three approaches with an emphasis on their efficacy, cost, and benefit. A brief review of the current treatment recommendations for cervical cancer and patient preparation information is also included.

Pathophysiology

In contrast to most cancers that are treatable only after the cancer has been identified, cervical cancer is a preventable disease. Cervical cancer can be prevented either through avoidance of HPV, the causative agent, or through the identification and treatment of pre-invasive lesions. The dysplastic precursor lesions to cervical carcinoma are frequently referred to as cervical intraepithelial neoplasia (CIN) or, more specifically, squamous intraepithelial lesions (SIL), a term that identifies the area where abnormal cells proliferate.

Most cervical dysplasia occurs in the area of the squamocolumnar junction of the cervix, an area of active squamous cell proliferation. Until puberty, this junction is located on the exposed vaginal portion of the cervix and is relatively stable. At puberty, with the accompanying increase in estrogen, the squamous margin encroaches on the single-layered, mucous-secreting epithelium--the columnar epithelium--forming an area of metaplasia known as the transformation
zone (MacKay, 1999). In young women and in women on oral contraceptives, this transformation zone is visible surrounding the cervical os and is called ectopy. Ectopy recedes into the endocervical canal with age and with the onset of sexual intercourse (Celum, Wilch, Fennell, & Stamm, 1998). Dysplasia is most commonly identified within the transformation zone, thus requiring that cell samples be collected from this area when a Pap smear is obtained.

As noted above, various types of human papillomavirus have been identified as the cause of cervical cancer (Van Muyden et al., 1999). Studies indicate that specific HPV types infect the squamous epithelium of the cervix. A number identifies each type of HPV. Human papillomavirus DNA can be identified in more than 80% of women with biopsy-confirmed SIL, with HPV types 6 and 11 predominating in low-grade SIL. High-grade lesions are most frequently associated with type 16. (Park, Fujiwara, & Wright, 1995). The HPV DNA incorporates itself into the cellular DNA, activating oncogenes and suppressing the host cell’s immune response. Cervical cells are particularly prone to this type of damage during puberty and pregnancy, when the high levels of estrogen are promoting rapid change (Cothran & White, 1995). The cervix of women who use oral contraceptives is also vulnerable, as the constant infusion of estrogen may prevent the natural recession of the ectopy into the cervical canal (Kruger-Kjaer et al., 1998).

Papillomaviruses are epithelialtrophic, often causing focal epithelial proliferation, commonly known as warts. More than 70 different types of human papillomaviruses have now been identified (Schiffman & Brinton, 1995). These
variations, although similarly structured, are anatomically specific, with lesions always located in the same epithelial region and with a consistency in the type of lesion that they produce. Research has identified 23 different types of HPV that infect the female and male anogenital tract. These 23 types are thus passed sexually. These various HPV types are associated with a range of anogenital diseases, from the common genital wart, Condyloma acuminata, to invasive squamous cell carcinoma (Park et al., 1995).

Human papillomaviruses associated with the anogenital region include HPV 6, 11, 16, 18, 30, 31, 33, 35, 39, 40, 42-45, 51-58, and 61 (van Muyden et al., 1999). These HPV types are also classified according to their oncogenic risk. Most are classified as low-oncogenic-risk and are associated with Condyloma acuminata and low-grade squamous intraepithelial lesions (CIN 1), but are rarely found in association with invasive cancer. Intermediate-risk HPV includes types 33, 35, 39, 51, 52, and 59. Intermediate types are uncommonly detected in invasive anogenital cancers, but are associated with high grade SIL (CIN 2, 3). Types 16, 18, 31, 45, 56, and 58 are the high-oncogenic-risk types and are commonly found in women with high grade SIL (CIN 3) and with invasive cancer of the cervix and vulva. Type 16 is the most commonly found high-risk virus, detected in 30-77% of women with high grade SIL (Park et al., 1995). However, HPV 16 is also common in minor grade lesions and in atypical squamous cells of undetermined significance (ASCUS). High-risk HPV types, particularly type 16, are commonly detected in ASCUS smears and in condyloma (Autillo-Touati et al., 1998). Lin et al., (2000) found that ASCUS samples that were high-risk HPV-
positive were significantly more likely to have high-grade dysplasia or cancer. Therefore, when facing a confusing ASCUS Pap smear, screening for the presence of high-risk HPV may provide a strong prognostic barometer, indicating the need for further diagnostic testing.

When cervical cancer develops, the disease generally progresses over the course of several years from initial exposure to HPV, to low-grade SIL, to high-grade SIL, to carcinoma in situ, to invasive cervical carcinoma. Spontaneous regression of this process back to cytologically normal cervical tissue typically occurs at or before the low-grade SIL level. Low-grade SIL is common, usually benign and self-limiting; high-grade SIL, contrastingly, is quite rare, but, if left untreated, will generally progress to neoplasia. For this reason, when screening is dependent exclusively on Pap smear technology, high-grade SIL is considered the only true precursor to cervical cancer (Adam et al., 2000). High-oncogenic risk HPV types 16 and 18 are also considered cervical cancer precursors. These high-risk HPV positive lesions are the most at risk for eventual advancement to cervical cancer.

Clinical Features and Risk Factors

Cervical dysplasia is essentially an asymptomatic condition that may result from previous exposure to HPV. A majority of women who are diagnosed with HPV will develop low-grade SIL within 4 years of infection (Schiffman & Brinton, 1995). Other causes of dysplasia include other infectious or inflammatory agents or exposure to other reactive irritants. Most low-level dysplasia spontaneously regresses to cytologic normalcy. However, there is a 15-
25% risk of low-grade SIL progressing to high-grade within two to four years. The asymptomatic nature of cervical dysplasia requires recognition of risk factors for likely exposure and contraction of HPV, particularly the HPV of high oncogenic nature, types 16, 18, 31, 45, 56, and 58.

All sexually active women are at risk for HPV (Reed et al., 1993). HPV is the single most common sexually transmitted disease, with detection rates as high as 65% of the general population (Adam et al., 2000). HPV peak prevalence occurs in women between 16 and 25 years of age. The prevalence rate drops sharply in women over the age of 30, possibly because of immunologic clearance or suppression of existing infection, or because of less exposure to new HPV types, as women in this older age category typically have fewer new sexual partners (Schiffman and Brinton, 1995). Women over 30 may also have a maturational protection, as the vulnerable transformation zone regresses on the face of the cervix as women age. HPV levels remain high in women with high-grade lesions. Adam et al., (2000) found that 38% of HPV-positive women aged 35 to 39 have high-grade SIL, while only 13.4% of those subjects less than 19 years old had similar results. HPV infection and low-grade SIL are usually diagnosed in women in their late teens and early twenties, high-grade SIL in 25 to 35 year-olds, and invasive cervical cancer after the age of 35. On average, approximately 15% of HPV positive cases will progress to high-grade SIL or carcinoma in situ within nine years (Daley, 1998).

Since most HPV infections disappear within months of the initial diagnosis, other factors must also play a role in its potential advancement to
cervical cancer. High-oncogenic type HPV is the single most predictive co-factor for cancer progression (Schiffman and Brinton, 1995; Adam et al., 2000). High levels of HPV and the length of time since the initial infection are also linked to higher-grade lesions. A higher degree of dysplasia is often seen with a longer duration of infection. Immune-compromised women have a much greater likelihood of developing progressive SIL. In a study of HIV-positive women with no documented cervical disease, Ellerbrock et al., (2000) diagnosed dysplasia in 20% of the study participants within three years of their HIV diagnosis. Invasive cervical cancer is a definitive diagnosis for AIDS in women who are HIV positive (Hollander & Katz, 1999).

Other risks associated with the sexually transmitted nature of HPV include women who have known their current sexual partner less than 24 months, women with multiple sexual partners or non-monogamous partners, and women who began sexual activity at a younger age (Reed et al., 1993). Svare et al., (1998) compared the HPV prevalence between Danish women, where cervical cancer rates are extremely low, and Greenlandic women, where rates are nearly 4 times higher. Overall, the HPV rates were similar. However, in Greenland, HPV infections tended to be peak in women less than 19 years of age, followed by a dramatic drop in infection rates in their early 20s. HPV rates for Danish women were significantly lower in the first decades of life. The primary difference between the two groups was the age at initial onset of intercourse, indicating that exposure to HPV in a woman's teen years increases the risk of the eventual development of cervical cancer.
Independent risk factors for the progression to cervical cancer include smoking, low income, and the use of oral contraceptives (Adam et al., 2000). Nicotine, a potential carcinogen, is concentrated in the cervical tissue of women who smoke. Smoking also presumably lowers the immune response, increasing the likelihood of progressive damage. Sanjose et al., (1996) confirmed the correlation between low-income level and a higher incidence of invasive cervical cancer. These researchers postulate that the difference is related to a lower use of preventive care, lack of appropriate screening, and a higher incidence of HPV. Kruger-Kjaer et al., (1998) explored the relationship of long-term oral contraceptive (OC) use and the progression of dysplasia. In this study, they found correlation with OC use and the development of high-grade lesions; there was no relationship to the development of low-grade SIL. The estrogenized state of OC users may prevent the ectopy of the cervix from receding into the cervical canal, leaving the vulnerable area exposed.

Physical symptoms associated with cervical dysplasia are rare, but include complaints of vaginal itching, odor, swelling, or visible lesions. These symptoms may be related to other sexually transmitted diseases, such as chlamydia trachomatis, which may be present concomitantly. Concomitant sexually transmitted infections are another significant risk factor (Reed et al., 1993; Schiffman & Brinton, 1995; Koskela et al., 2000). Women or their male partners may present with visible condyloma, typically of the low-oncogenic risk type, most often types 6 and 11. However, often multiple HPV types are present, requiring further typing if diagnosed visually (Cothran & White, 1995).
The most common clinical sign of actual cervical carcinoma is a visible lesion appearing as a tumor or ulceration. Women may present with irregular or excessive vaginal bleeding, post-coital spotting, and cervical ulceration. Bloody or purulent, odorous, non-pruritic discharge may appear, if invasive lesions are present. Late invasive symptoms may include bladder and rectal dysfunction or fistulas and pain in the lower pelvic region (MacKay, 1999).

**Differential Diagnosis—The Bethesda System**

In an effort to clearly delineate the various possible cytological findings associated with the Pap smear, thus strengthening its value as a screening tool, a 1988 National Cancer Institute panel developed a standardized classification and diagnostic system known as the Bethesda System (Lunberg, 1988) (see Table 1). This classification system, although modified in 1991, continues to provide a useful, standardized format for the differentiation of Pap smears and the accompanying clinical diagnosis (Kurman, Henson, Herbst, Noller, & Schiffman, 1994). The Bethesda System utilizes the following descriptive diagnoses: benign cellular changes associated with infection, reactive changes, epithelial cell abnormalities, and finally, other malignant neoplasms. Evaluation of benign changes of infection include fungal, bacterial, protozoan, and viral, such as HPV. Definitive diagnoses of infectious etiology often require further confirmatory studies, such as cultures, or in the case of HPV, DNA hybrid screening. Reactive changes occur in response to inflammation, atrophy, or exposure to irritants such as chemotherapeutic agents, intrauterine contraceptive devices (IUDs), or the effects of treatment therapy.
Epithelial cell abnormalities are related to the advancement of cervical cancer. These cellular abnormalities include squamous and glandular cell changes. Squamous cell changes are classified in the Bethesda System as atypical squamous cells of undetermined significance (ASCUS), squamous intraepithelial lesion (SIL), or squamous cell carcinoma. Squamous intraepithelial lesions are further classified as low-grade or high-grade. Low-grade SIL encompasses mild dysplasia or cervical intraepithelial neoplasia grade 1 (CIN 1) and HPV. High-grade SIL includes moderate dysplasia (CIN 2), or severe dysplasia or carcinoma in situ (both graded CIN 3). Glandular cells are similarly differentiated between atypical glandular cells of undetermined significance (AGCUS), endometrial cells present when not histologically expected, adenocarcinoma, or other epithelial malignant neoplasm. Nonepithelial malignant neoplasms require a specification as to the type of malignancy (Lunberg, 1988).

The Bethesda system also includes a statement as to the adequacy of the specimen, with a recommendation for repeating the smear if it is deemed unsatisfactory. A hormonal evaluation confirms if the hormonal pattern is compatible with the woman’s age and history, requiring that the clinician provide this historical information to the pathologist.

The Bethesda system has led to greater clarity and differentiation of the diagnosis of Pap smears. However, since its inception, the number of equivocal Pap smears—the ASCUS category—has grown. The potential for morbidity associated with over-read Pap smears has led some to question the value of using the Pap smear as an end-stage screening tool (Jones, 1995).
The optimal screening protocol for the prevention of cervical cancer remains controversial. However, because of the typically slow nature of the advancement from initial HPV infection to advancing dysplasia, and because low-grade lesions often regress without treatment, a reasonable and safe protocol would involve recognizing women at higher risk of dysplastic advancement and screening those women aggressively, while monitoring lower risk women with a conservative, watchful waiting approach. Women with high-grade lesions, CIN 2 or 3, require more aggressive follow-up with immediate colposcopic evaluation. If a woman has a normal Pap smear, it is reasonable to forgo HPV screening and monitor her with serial smears.

The low-grade Pap smears, CIN 1 and ASCUS, remain the most confusing clinically. HPV screening in the setting of a marginal Pap smear provides objective data for further recommendations. Current FDA approved screening for HPV involves the use of the Digene Hybrid Capture II test. The Hybrid Capture II utilizes a DNA probe to identify fourteen different high-oncogenic risk types of HPV and reports a positive result if any of the 14 types is found in the testing mix. Low-risk HPV may be present in a sample that is reported back as negative. The Digene Hybrid Capture II is strictly utilized for cancer risk screening. Clinicians must remain alert for other signs of HPV, which while not likely to cause cancer, may have other clinical sequelae. (Information related to the clinical identification of HPV obtained through personal communication with pathovirology lab technician, Harborview Medical Center, Seattle, Washington,
Figure 1 is an author-developed algorithm, supported by a review of the literature, which outlines the above screening strategy and specifies when HPV screening is of value.

**Sensitivity/Specificity**

Table 2 lists the sensitivities and specificities of cervical cancer screening methods, including the Pap smear, HPV testing, and a combination approach. The slow nature of dysplastic advancement is well suited to a conservative monitoring of ambiguous or low-grade SIL (ASCUS, CIN 1). Repetitive Pap screening and/or confirmation of irregularities with HPV-typing allows for accurate diagnosis over time. The high-degree of sensitivity associated with a combination of Pap and HPV testing (96.9 %) provides a viable alternative to widespread colposcopic examinations.

**Cost Analysis**

Table 3 is an estimate of the costs for procedures related to cervical cancer screening and the time frame for receiving the results of these procedures. Colposcopies typically are scheduled shortly after an irregular Pap smear is identified, meaning that the cost of the colposcopy is additive to that of the Pap smear. Therefore, slowing decisions while monitoring dysplasia with serial screening, rather than immediate colposcopic treatment, will often allow the body to heal itself and save money. The Thin-prep Pap method is significantly more expensive than the standard slide. This added cost is offset by the advantage of collecting the HPV sample at the same time as the Thin-prep. If the HPV sample is not needed, it may be discarded without further expense; if it is needed, a
second collection fee will not be incurred. Forgoing annual screening in women who are at low-risk of cervical cancer would be an effective cost-control measure.

**Patient Education and Preparation**

Women need to understand that the Pap smear and HPV testing are screening tools used to identify pre-cancerous and cancerous cervical lesions. Table 4 is an information sheet, outlined in a question and answer format, designed to help women understand how best to prevent HPV contraction and how to prepare for screening tests and treatment procedures.

**Treatment Plan**

Invasive cervical cancer is a preventable disease. Advanced invasive cervical cancer has only a 14% five-year survival rate (Wolff, 1996); prevention is the key to effective treatment. The five-year survival rate is 99% for women with localized cervical cancer, also known as cancer in situ (CIS). On average, carcinoma in situ will advance to invasive disease within two to ten years (MacKay, 1999). This slow progression allows for identification and treatment before the cancer advances.

The method of treatment is dependent upon the results of cervical screening. Cervical intraepithelial neoplasia 1 (CIN 1) may be monitored for progression. These lesions often regress back to normalcy without treatment (Schiffman & Brinton, 1995). As the primary prognostic indicator of cervical carcinoma, a CIN 2 or 3 diagnosis requires colposcopic evaluation, and if abnormal cells are visualized, biopsy (Daley, 1998).
Small, high-grade dysplastic lesions may be treated with ablative therapies, such as cauterization or cryotherapy (MacKay, 1999). Visible lesions may also be excised using a wire loop, known as a “large loop excision”. For this excision procedure to be successful, clear healthy margins surrounding the removed tissue must be present (Paraskevaidis et al., 2000). The treatment of choice for pre-invasive cancer, CIN 3 or carcinoma in situ, is complete surgical removal of the transformation zone, known as conization of the cervix. Ablative therapies must be followed with regular screening, especially the first 2 years after treatment, to quickly identify recurrence (MacKay, 1999).

The treatment for advanced cervical carcinoma is dependent upon the grade of the carcinoma lesion. A total hysterectomy is the recommended treatment for carcinoma in situ (stage 0) for women who have completed childbearing. Ablative therapies as outlined above may be appropriate for women who wish to retain the uterus. Regular follow-up with Pap smears every 4 months for 1 year, every 6 months for the second, and annually thereafter is vital to quickly identify recurrence in women who still have a uterus (MacKay, 1999).

Micro-invasive carcinoma (stage IA) is treated with a simple hysterectomy. Lesions extending past the cervix but not yet invading the pelvic wall (stages IB and IIA) may be treated with radical hysterectomy or radiation. Cancerous lesions that have extended past the pelvic wall (stages IIB, III, and IV) require radiation treatment (MacKay, 1999).
Conclusion

Invasive cervical cancer is a needlessly deadly disease. Effective measures exist to prevent the unnecessary morbidity and mortality associated with cervical cancer. In developed countries, where established screening and treatment protocols exist, the incidence of cervical cancer has been dramatically reduced (Cuzick, 1998). However, cervical cancer remains the leading cause of cancer death in women in most developing countries (Richart, 1995). Even in the United States, a significant portion of the population is left unscreened or inadequately screened, leading to thousands of cervical cancer deaths each year (Cancer Statistics, 1998).

Screening has historically centered upon the Papanicolaou smear. However, Pap smear technology is not perfect. In a study of over 300 labs, nearly 20% of women who were later found to have cervical pathology, originally had false-negative Pap smears (Montes et al., 1999). False-positive Pap smears are also common, leading to unnecessary worry, expense, and excessive, often invasive, treatment. Women may not be adequately screened for a number of reasons, including lack of access to care, personal distaste for the invasive nature of the procedure, and a general misunderstanding of the preventive nature of the screening tool and the risk factors associated with cervical cancer.

Human papillomavirus is the primary cause of cervical cancer. HPV DNA has been identified in 90 to 100% of cervical cancer lesions (Van Muyden et al, 1999; Tabrizi et al., 1999). The identification of high-oncogenic risk HPV in the setting of a questionable Pap smear result (ASCUS or CIN 1) supports aggressive
treatment. Conversely, a negative HPV result provides objective evidence that a conservative watchful-waiting approach to treatment is appropriate. HPV screening, utilized as an adjunct to the traditional Pap smear, assists in the determination of an appropriate, cost-effective treatment plan.

When available, the standard Pap smear remains the best first option for screening. Pap smears, however, have a considerable false negative rate, are not always readily available, and require women to submit to an invasive procedure, which many refuse to do. Identification of human papillomavirus is a valuable option as an addition to the existing screening tools. HPV identification is valuable both with borderline Pap smears and with negative smears in relatively at-risk individuals.

HPV screening may also provide a first-line approach to screening for women when the Pap smear is not a feasible option. Wright, Denny, Kuhn, Pollack, and Lorincz (2000) explored this option in a study in which they compared the accuracy of self-collected HPV samples to that of Pap smears for cervical cancer screening. They concluded that the HPV screening is less specific, but just as sensitive as the Pap smear. This demonstration that HPV self-collection may be a viable alternative to screening opens public health doors to the successful screening of women who were previously neglected. The future of cervical cancer screening lies in the continued advancement of HPV testing. The key for the practitioner is to identify women at risk of cervical cancer, counsel them on measures to lower that risk, and screen appropriately.
Table 1

**Bethesda System for Reporting Cervical/Vaginal Cytological Diagnoses**

**Adequacy of the Specimen**
- Satisfactory for evaluation
- Satisfactory for evaluation but limited by: (specify reason)
- Unsatisfactory for evaluation: (specify reason)

**General Categorization (optional)**
- Within normal limits
- Benign cellular changes: See descriptive diagnosis
  - Epithelial cell abnormality: See descriptive diagnosis

**Descriptive Diagnosis: Benign Cellular Changes**

**Infection**
- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* sp
- Predominance of coccobacilli consistent with shift in vaginal flora
- Bacteria morphologically consistent with *Actinomyces* sp
- Cellular changes associated with Herpes simplex virus
- Other

**Reactive Changes**—cellular changes associated with:
- Inflammation (Includes typical repair)
- Atrophy with inflammation ("atrophic vaginitis")
- Radiation
- Intrauterine Contraceptive Device (IUD)
- Other

**Descriptive Diagnosis: Epithelial Cell Abnormalities**

**Squamous Cell**
- Atypical squamous cells of undetermined significance (ASCUS): Qualify
- Low-grade squamous intraepithelial lesion (SIL): HPV, mild dysplasia/CIN 1
- High-grade SIL: Moderate and severe dysplasia, CIS/CIN 2 and CIN 3
- Squamous Cell Carcinoma

**Glandular Cell**
- Endometrial cells, cytologically benign, in a postmenopausal woman
- Atypical glandular cells of undetermined significance (AGUS): Qualify
- Endocervical adenocarcinoma
- Endometrial adenocarcinoma
- Extrauterine adenocarcinoma
- Adenocarcinoma, not otherwise specified

**Descriptive Diagnosis: Other Malignant Neoplasms**

**Descriptive Diagnosis: Hormonal Evaluation:** (Applies to vaginal smears only)
- Hormonal pattern compatible with age and history
- Hormonal pattern incompatible with age and history: Specify
- Hormonal pattern not possible due to: Specify

(National Cancer Institute, 2000)
<table>
<thead>
<tr>
<th>Types of Tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear--ASCUS (~5% of all Paps)</td>
<td>77.7% (Schiffman et al., 2000)</td>
<td>94.2% (Schiffman et al., 2000)</td>
</tr>
<tr>
<td>Repeat Pap smears</td>
<td>85% (Bergeron et al., 2000)</td>
<td>64.1% (Manos et al., 1999)</td>
</tr>
<tr>
<td>ASCUS Pap+ HPV--CIN 2, 3</td>
<td>66% (Cox, 1998)</td>
<td>89.0% (Schiffman, 2000)</td>
</tr>
<tr>
<td>HPV (Digene Capture II)--CIN 2, 3</td>
<td>76.2% (Manos et al., 1999)</td>
<td>89.0% (Schiffman, 2000)</td>
</tr>
<tr>
<td>Pap smear + HPV testing</td>
<td>89.2% (Manos et al., 1999)</td>
<td>64.1% (Manos et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>88.4% (Schiffman et al., 2000)</td>
<td>89.0% (Schiffman, 2000)</td>
</tr>
<tr>
<td></td>
<td>96.9% (Manos et al., 1999)</td>
<td>89.0% (Schiffman, 2000)</td>
</tr>
</tbody>
</table>
Table 3

Cost Analysis and Timing of Tests

*Pap smear slide:* Negative-- ~$25.00 plus office visit cost of ~$50.00-$75.00

Abnormal-- ~$28.00 plus office visit cost of ~$50.00-$75.00

*Thin-prep Pap smear:* ~$33.50 plus office visit cost of ~$50.00-$75.00

Evaluation of Pap smear takes approximately 5 days.

*HPV testing (Digene Hybrid Capture II):* ~$67.50 (Obtained from Thin-prep collection)

HPV results are obtained within 2 weeks of lab receiving specimen. The results are reported as positive if any of 14 high-oncogenic risk types of HPV are identified in the testing mix.

*Colposcopy:* ~$110.00 without biopsy

~$135.00 with biopsy

Results of colposcopy without biopsy are immediate. Most biopsy results are back in 2 to 3 days, although it may take up to 2 weeks to obtain results.

(Estimated costs and time frames obtained from personal communication with virology lab technician, Harborview Medical Center, Seattle, WA; senior coding analyst, Patient Accounting, Group Health Cooperative, Spokane, WA; & cytology technician, Pathology Associates, Spokane, WA, October, 2000).
Table 4

Patient Education and Preparation

What causes cervical cancer?

Cervical cancer is a progressive disease caused by the human papillomavirus (HPV). Because the cervix opens in the vagina, it is vulnerable to bacteria and viruses that may travel up the vagina and gather at the mouth of the cervix, sometimes causing sexually transmitted diseases. HPV is the most common of these diseases. Some types of HPV infection lead to cervical cell changes, called dysplasia. Dysplasia may eventually advance to cancer (Krames, 1993).

Am I at risk?

Almost all sexually active women run some risk of contracting HPV and, subsequently, cervical cancer. For this reason, all sexually active women should be screened periodically, particularly within the first two years after initiating a new sexual relationship. More frequent screening may be necessary if a routine exam reveals early cervical changes or if signs of inflammation are evident.

What is human papillomavirus (HPV)?

Human papillomavirus is the virus that causes warts. To date, more than 68 different types of human papillomaviruses have been identified. Twenty-three different types of HPV have been identified that infect the genital region of men and women. These various HPV types are associated with a range of genital diseases, from the common genital wart, condyloma, to invasive cancer of the cervix (Park et al., 1995).
How is genital HPV spread?

As with all warts, genital HPV is spread through direct skin-to-skin contact. It is not transmitted through blood or body fluids. Genital HPV targets the moist mucous membranes surrounding the genitals. The most common form of transmission is direct contact between the infected skin on the penis, scrotum, vagina, vulva, or anus and the uninfected skin in the genital or anal region of the partner’s body (ASHA, 1995).

How do I know if I have HPV?

Recognition of HPV can be difficult. Many people with HPV are asymptomatic, and the latency period for HPV (the time from date of infection to actual development of HPV) may be many months to years. Sometimes, you or your health-provider may see the HPV lesions. If your sexual partner has a definitive diagnosis, then you are likely to be carrying the virus as well. Without a visual confirmation of the disease, HPV may be identified through viral screening. Sometimes, the Pap smear will show changes indicative of HPV (ASHA, 1995).

What is a Pap smear?

The Pap smear is a part of the pelvic exam used to examine the cells of the cervix to screen for signs of pre-cancerous lesions and cancer. Incidentally, Pap smears may identify cellular changes associated with infection. If these problems are caught early, they can usually be treated successfully. The Pap is not a specific test for HPV, although sometimes the results suggest that HPV may be present (Krames, 1993).
How is a Pap smear obtained?

You will need to undress from the waist down, lie on the exam table, and place your legs in the table stirrups. Your health-care provider will then open your vagina with an instrument called a speculum. She will then obtain samples from your cervix with a small spatula or swab, placing them on a slide to be sent to the lab for evaluation. She may also obtain samples for other testing, such as HPV or other infections (Your Pap Exam, 1993).

When should I have a Pap smear?

All women should begin having Pap screening when they become or are preparing to become sexually active. After the initial screen, you and your provider will need to determine the frequency of future smears. Usually, yearly exams are recommended for three to four years, followed by screening every three to five years. Generally, women who have had a history of sexually transmitted infections should continue to have yearly screening. If abnormal cells are identified, more frequent screening, more in-depth testing to obtain a definitive diagnosis, or treatment may be necessary (Apgar & Brotzman, 1999).

How should I prepare for the Pap smear?

1. Schedule the Pap smear between menstrual cycles. Menstrual blood may obscure any cells obtained, making them impossible to evaluate.

2. Avoid vaginal creams, foams, or suppositories for a week before the exam. Do not douche, use tampons, or have sexual intercourse the day before the exam.
3. Follow-up the results of your Pap smear with your health-care provider. Most offices will have a system of results notification. However, if you do not hear from the health-care office, call your provider; do not assume that no news is good news.

4. Discuss how frequently you should return for screening. The answer will probably depend on your medical history (A patient guide, 1995).

Can I prevent HPV?

If you are sexually active, HPV can be difficult to prevent because it is often difficult to identify, and it is quite prevalent. HPV is contracted through body-to-body contact. Therefore, because a condom does not adequately cover the entire genital region, it is not an effective barrier to HPV. Use of the condom or the diaphragm may protect the cervix, because it is completely covered with these barrier methods. Obviously, condom usage remains extremely important as a tool for the prevention of most other sexually transmitted infections. The female condom, which covers the entire vulva, may be more protective (Cothran & White, 1995).

The best protection against HPV is to limit your number of sexual partners and to know your partner’s sexual history. Women who begin sexual activity at an older age are statistically less likely to develop problems associated with HPV. As the cervix matures, the vulnerable area becomes smaller.

Is there a cure for HPV?

No. It may be possible for your body’s own immune system to clear the virus. However, most often HPV is a virus that stays in your body once you have
contracted it. Treatment can destroy the lesions, and for most women, the immune system will help keep the HPV under control. Over time, the chance of recurrent abnormalities from the HPV lessens.

Is there anything else that I can do to protect myself?

Yes. The best protection is to keep your immune system as healthy as possible. This means not smoking, eating well, and protecting yourself against other sexually transmitted infections by limiting your number of sexual partners and by using condoms. Women who smoke have a higher rate of cervical cancer; smoking may inhibit the immune system, preventing or slowing repair of abnormal tissue.
Figure 1

Cervical Cancer Screening Algorithm

Woman presents to clinic for routine gynecologic exam

Has woman ever been or is she planning to become sexually active? (1)

No

Deter Pap

May get baseline after 18 years

Normal Pap Smear

Evaluate for HPV risk

Low risk?

High risk? (6)

Repeat yearly for 3 years, then every 3 years. Reinitiate yearly screening if begins new sexual relationship (2)

Yes

Obtain Thin-prep Pap with Specimen for HPV

ASCUS/CIN 1 Pap

Perform HPV testing (4)

Negative HPV

Repeat Pap in 6 months

Normal smear

Abnormal smear

Positive HPV

(5)

Refer for colposcopic exam

CIN 2 or 3

Refer for colposcopic exam

Repeat to routine screening
Footnotes to algorithm: This algorithm is referenced and supported with the numbers in parentheses at the end of key sections:

(1) Cervical cancer is caused by HPV, a sexually transmitted virus (Van Muyden et al., 1999). Therefore, women who are not sexually active are not at risk. Note: The practitioner must maintain a high level of suspicion and recommend the Pap smear if the sexual history is ambiguous.

(2) Women who receive screening every 3-5 years are not at significantly greater risk for invasive cervical cancer than are women who are tested annually (Wolff, 1996; Richart, 1995).

(3) High-grade SIL, CIN 2 or 3, is considered the only true precursor to cervical cancer (Adam et al., 2000; Daley, 1998).

(4) Testing of low-grade SIL and ASCUS Pap smears for HPV is a cost-effective and safe approach to avoid unnecessary colposcopic examinations (Apgar & Brotzman, 1999).

(5) Positive HPV results will be identified through the use of the Digene Hybrid Capture II test. DNA recognition of any of 14 high-oncogenic risk types will be included as positive.

(6) Risk factors for HPV include onset of sexual activity as an adolescent, multiple partners, other sexually transmitted infections, smoking, low income, and the use of oral contraceptives (Adam et al., 2000).
References


